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PEPTIDE-LOADED NANOMATERIALS FOR ALZHEIMER'S DISEASE: MULTIFACETED THERAPEUTIC STRATEGIES WITH ADVANCED DRUG DELIVERY SYSTEMS

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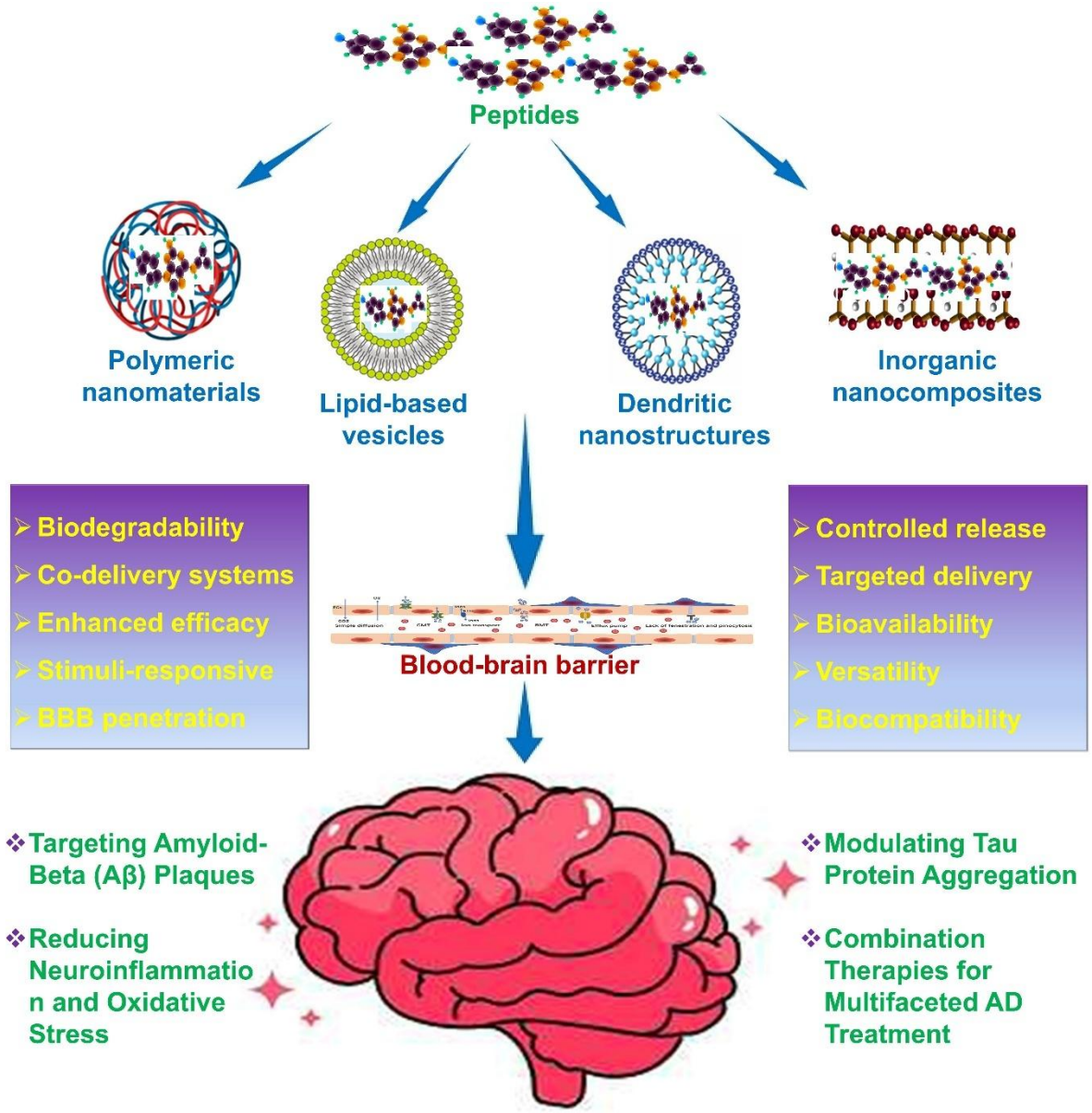
ABSTRACT
Alzheimer's disease (AD) is a gradually worsening neurodegenerative condition which is marked by the buildup of amyloid-beta (Aβ) plaques, neurofibrillary tangles caused by abnormal tau proteins, and sustained inflammation in the brain. Although advances in research, current treatments fail to efficiently slow or reverse disease progression which highlighting the critical necessity for innovative therapeutic approaches. Peptide-loaded nanomaterials represent a promising solution, combining the precision of peptides in targeting pathological markers with nanotechnology's delivery advantages. These systems particularly bind to Aβ and tau aggregates, while nanoscale platforms like liposomes, polymeric nanoparticles, and dendrimers improve blood-brain barrier (BBB) penetration and controlled drug release. Furthermore, they can co-deliver various therapeutics to address AD complicated pathology. While many preclinical studies demonstrate the potential of peptide-loaded nanomaterials to reduce Aβ/tau accumulation and improve cognition in animal models (e.g., KLVFF-gold NPs in APP/PS1 mice), outcomes vary due to factors such as off-target effects, inconsistent blood-brain barrier penetration, or material-specific toxicity (e.g., cationic dendrimers). Nevertheless, challenges like biocompatibility, scalable manufacturing, and clinical translation necessitate resolution. This review highlights recent advances in peptide-based nanocarriers for AD, expounds their therapeutic mechanisms, and identifies future significances to optimize efficiency. By merging peptide specificity with nanoscale versatility, these systems offer a transformative approach to treating AD and related neurodegenerative diseases.

KEYWORDS: Peptide-loaded nanomaterials; Alzheimer's disease; Drug delivery; Blood-brain barrier; Amyloid-beta plaques.

GRAPHICAL ABSTRACT



This review graphical abstract examines peptide-loaded nanomaterials as cutting-edge therapeutics for Alzheimer's disease (AD). It discusses polymeric, lipid-based, dendritic, and inorganic engineered nanocarriers for biodegradability, stimuli-responsive behaviour and blood-brain barrier penetration. These nanomaterials facilitate targeted peptide delivery to amyloid-beta plaques and tau aggregates, enhancing therapeutic efficacy through controlled release, co-delivery mechanisms, and reduced neuroinflammation and oxidative stress. Their biocompatibility and versatility enable combination therapies, addressing AD's multifaceted pathology.

1. INTRODUCTION

Alzheimer's disease (AD), recognized as the primary contributor to dementia cases worldwide, is a long-term neurodegenerative disorder concerning the gradual deterioration of cognitive functions[1, 2]. Symptoms like memory impairment, diminished problem-solving abilities, and shifts in behaviour progressively degrade over time, ultimately resulting in severe impairment and loss of independence[3, 4]. At a molecular level, the disease is characterized by the presence of extracellular amyloid-beta (Aβ) protein deposits, abnormal accumulations of hyperphosphorylated tau proteins within neurons (forming neurofibrillary tangles), and ongoing inflammatory processes in the brain that exacerbate neuronal damage[5, 6]. These abnormalities drive synaptic failure, neuronal death, and atrophy in brain regions like the hippocampus and cortex, which are vital for cognition[7].

Globally, AD affects over 50 million individuals, with projections estimating a tripling of cases by 2050 due to aging populations[8, 9]. Despite extensive research, the disease's origins remain elusive, and existing therapies—such as acetylcholinesterase inhibitors (e.g., donepezil) and NMDA receptor antagonists (e.g., memantine)—offer only transient symptom relief without altering disease progression. This gap underscores the critical demand for therapies targeting AD's root mechanisms[10, 11]. Developing treatments for AD is hindered by its complex, multifactorial pathology, involving Aβ aggregation, tau dysfunction, inflammation, oxidative stress, and synaptic loss[12, 13]. Conventional drugs often fail due to their inability to address these interconnected pathways. A major

obstacle is the blood-brain barrier (BBB), which blocks over 98% of potential therapeutics from reaching the brain[14]. Furthermore, the absence of robust biomarkers for early detection delays intervention until irreversible neuronal damage occurs[15].

Current FDA-approved drugs, including aducanumab—a controversial anti-Aβ antibody—highlight the field's limitations. While aducanumab reduces plaques, its modest efficacy and safety concerns emphasize the need for safer, more effective strategies. Therapies must evolve beyond symptom management to directly combat neurodegeneration[16, 17]. Recent advances in nanotechnology and peptide engineering have converged to create innovative therapeutic platforms. Peptides, with their high specificity, can be tailored to disrupt Aβ aggregation (e.g., KLVFF peptides) or inhibit tau hyperphosphorylation[18]. When integrated into nanocarriers like liposomes, polymer-based nanoparticles, or dendrimers, these peptides gain enhanced BBB permeability, targeted delivery, and controlled release[19].

Functionalization with ligands (e.g., transferrin, apolipoproteins) further improves brain targeting. Nanocarriers also enable combination therapies, simultaneously delivering anti-inflammatory agents, antioxidants, and peptide inhibitors to address AD's diverse pathology[20]. Preclinical success includes gold nanoparticle-peptide conjugates reducing Aβ plaques and improving cognition in AD mice, and tau-targeted nanoparticles diminishing tangles[21]. Challenges persist, such as optimizing biocompatibility, scaling production, and validating efficacy in humans[22]. However, peptide-loaded nanomaterials represent a transformative approach, merging precise molecular targeting with nanoscale engineering to potentially halt AD progression[23]. This strategy, by tackling both Aβ and tau pathways while mitigating secondary damage, could redefine treatment for AD and related neurodegenerative disorders[24].

This review explored the latest developments in peptide-loaded nanomaterials for AD therapy, examined their mechanisms of action, and discussed future directions for optimizing their therapeutic potential. Through a comprehensive analysis of preclinical and clinical advancements, this review aim to highlight the transformative potential of this emerging field and inspire further research and innovation.

2. Pathophysiology of AD

AD is a multifaceted neurodegenerative disorder driven by interconnected pathological processes that culminate in cognitive deterioration and structural brain damage (Figure 1). The disease's progression is marked by the accumulation of toxic protein aggregates, dysregulated immune responses, and cellular oxidative damage. Unravelling these mechanisms is vital for advancing therapeutic innovations, such as peptide-loaded nanomaterials, designed to intervene at multiple pathological nodes[25].

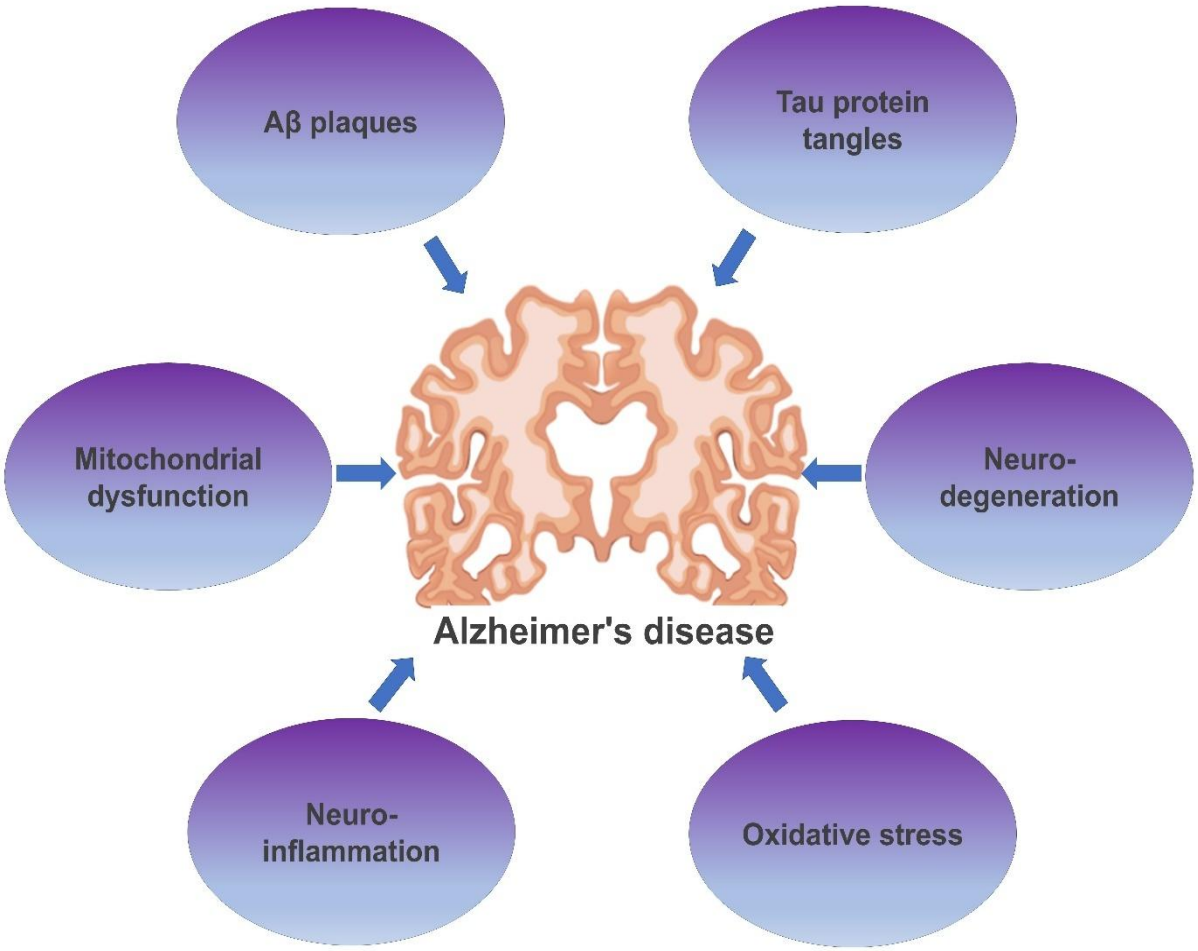


Figure 1: General pathophysiology of AD

2.1. Aβ plaques and their role in AD

Central to AD pathology is the amyloid cascade hypothesis, which posits that the abnormal buildup of Aβ peptides initiates a destructive chain of events. Aβ originates from the enzymatic processing of amyloid precursor protein (APP), a transmembrane protein cleaved sequentially by β-secretase and γ-secretase[26]. In healthy brains, Aβ is generated at low levels and efficiently cleared. However, in AD, disrupted clearance mechanisms or overproduction lead to Aβ accumulation, fostering its aggregation into insoluble extracellular plaques[27].

Notably, soluble Aβ oligomers small, soluble clusters of Aβ are more neurotoxic than mature fibrillar plaques. These oligomers bind to synaptic receptors, including NMDA and AMPA receptors, triggering calcium overload and excitotoxicity. This disrupts synaptic plasticity, the foundation of learning and memory, and induces dendritic spine loss, impairing neuronal communication[28]. Aβ oligomers also activate microglia, the brain's immune sentinels, initiating a cascade of chronic inflammation[29]. While microglia initially attempt to phagocytose Aβ, prolonged activation releases pro-inflammatory cytokines and reactive oxygen species (ROS), exacerbating neuronal damage[30]. Aβ further contributes to oxidative stress by interacting with metal ions like copper and iron, catalyzing ROS production. This oxidative milieu damages lipids, proteins, and DNA, accelerating cellular dysfunction[31]. Despite Aβ's central role, clinical trials targeting it—via antibodies or secretase inhibitors—have shown limited success, underscoring the need to address coexisting pathologies like tau tangles and inflammation[32].

2.2. Tau protein tangles and neurodegeneration

Tau, a protein critical for microtubule stabilization, becomes pathogenic in AD through hyperphosphorylation. In healthy neurons, tau binds to microtubules, maintaining cytoskeletal integrity and facilitating nutrient transport[33]. In AD, excessive phosphorylation causes tau to detach, destabilizing microtubules and impairing axonal transport[34]. The misfolded tau proteins then aggregate into paired helical filaments, forming intracellular neurofibrillary tangles (NFTs)[35].

NFTs propagate through the brain in a predictable pattern, beginning in the entorhinal cortex and hippocampus—regions essential for memory—before spreading to associative cortices. This spatial progression mirrors the clinical trajectory of cognitive decline, with tangle density correlating more strongly with dementia severity than Aβ plaque burden[36]. Tau's role extends beyond AD; it is implicated in other tauopathies, such as frontotemporal dementia, highlighting its broad impact on neurodegeneration[37]. Aβ and tau pathologies are interdependent. Aβ accumulation can induce tau hyperphosphorylation, while tau dysfunction amplifies Aβ toxicity[33]. For instance, Aβ-induced calcium influx activates kinases like GSK-3β, which phosphorylate tau. Conversely, tau pathology disrupts mitochondrial function, worsening Aβ-induced oxidative stress[38].

2.3. Neuroinflammation and oxidative stress in AD

Chronic Neuroinflammation: Neuroinflammation in AD involves the sustained activation of microglia and astrocytes. Initially, microglia engulf Aβ and cellular debris, but chronic exposure to Aβ and tau transforms them into a reactive state, releasing neurotoxic cytokines (e.g., IL-1β, TNF-α) and chemokines[39]. These molecules recruit additional immune cells, perpetuating inflammation and damaging synapses. Activated astrocytes, meanwhile, contribute to ROS production and fail to support neuronal health, exacerbating metabolic stress[40]. This inflammatory response is a double-edged sword. While acute inflammation aids pathogen clearance, chronic activation creates a hostile microenvironment, accelerating neuron loss. Targeting inflammation without compromising the brain's defense mechanisms remains a therapeutic challenge[41].

Oxidative Stress and Mitochondrial Dysfunction: The AD brain is a hotspot for oxidative stress, driven by ROS overproduction and compromised antioxidant defenses. Aβ oligomers and tau aggregates impair mitochondrial function, reducing ATP synthesis and increasing ROS leakage. Metal ions bound to Aβ further catalyze ROS generation via Fenton reactions. Oxidative damage manifests as lipid peroxidation, protein carbonylation, and DNA breaks, particularly in mitochondrial DNA, which lacks robust repair mechanisms[42].

Neurons, with their high metabolic demands and lipid-rich membranes, are especially vulnerable. Oxidative stress not only damages cellular structures but also activates pro-death signaling pathways, pushing neurons toward apoptosis. Antioxidant therapies, however, face hurdles in crossing the BBB and achieving effective concentrations in the brain[43].

2.4. Integrated pathogenic model and therapeutic implications

AD's pathophysiology is not linear but a web of interacting processes: Aβ and tau pathologies ignite neuroinflammation and oxidative stress, which in turn accelerate protein aggregation and neuronal death. This vicious cycle explains the disease's inexorable progression and the inadequacy of single-target therapies[44]. Peptide-loaded nanomaterials present a breakthrough by enabling multi-pronged interventions. For example, peptides targeting Aβ aggregation (e.g., Aβ-binding motifs) can be co-delivered with tau-inhibiting peptides and anti-inflammatory agents via nanocarriers[45, 46]. Nanomaterials like liposomes or dendrimers enhance BBB penetration, protect payloads from degradation, and allow controlled release. Functionalization with targeting ligands (e.g., transferrin receptors) further directs them to affected brain regions[47].

Preclinical models demonstrate promise: gold nanoparticles conjugated with Aβ-inhibiting peptides reduce plaque burden and improve cognition in transgenic mice[48]. Similarly, lipid-based nanocarriers delivering antioxidant enzymes mitigate oxidative damage. However, challenges persist in optimizing biocompatibility, scalability, and clinical translation[49].

Peptide-loaded nanomaterials offer a promising approach to targeting these pathological mechanisms. By delivering therapeutic peptides that disrupt Aβ aggregation, inhibit tau hyperphosphorylation, reduce neuroinflammation, and mitigate oxidative stress, these advanced systems hold the potential to transform the treatment landscape for AD[50]. Future research should focus on optimizing the design and delivery of peptide-loaded nanomaterials to enhance their therapeutic efficacy and ensure their safety and biocompatibility[51].

3. Peptide-based therapeutics for AD

AD presents a labyrinth of pathological challenges, necessitating therapies that precisely target its molecular drivers. Peptide-based therapeutics have risen as a compelling strategy, leveraging their molecular specificity to disrupt toxic protein aggregates, temper neuroinflammation, and counteract oxidative damage[52]. While their potential is immense, hurdles such as instability and delivery limitations underscore the need for innovative engineering to unlock their full clinical promise[53, 54].

3.1. Mechanisms action in AD

Peptides act through multifaceted pathways to counteract AD's core pathologies, including Aβ plaques, tau tangles, and inflammatory cascades. Aβ peptides, particularly Aβ42, self-assemble into neurotoxic oligomers and fibrils. Therapeutic peptides can block this process by binding to Aβ and preventing its aggregation. For instance, the KLVFF peptide, derived from Aβ's hydrophobic core, competitively inhibits oligomerization by occupying critical binding sites[52]. Similarly, D-enantiomeric peptides—mirror-image amino acid sequences resist enzymatic degradation while destabilizing Aβ assemblies[55]. Beyond inhibition, certain peptides enhance Aβ clearance. By tagging Aβ for microglial phagocytosis, peptides like those mimicking apolipoprotein E (ApoE) promote plaque degradation, offering a dual mechanism to reduce cerebral Aβ burden[56].

Hyperphosphorylated tau detaches from microtubules, forming NFTs that disrupt neuronal integrity[57]. Peptides targeting tau pathology operate via two strategies: 1. Kinase Inhibition: Peptides mimicking endogenous kinase inhibitors suppress enzymes like GSK-3β, reducing tau phosphorylation[58]. For example, a peptide derived from the protein kinase A inhibitor (PKI) attenuates tau hyperphosphorylation in preclinical models[59]. 2. Aggregation Blockade: Peptides designed to mimic microtubule-binding regions of tau compete with misfolded tau, preventing NFT formation[60]. The QHG peptide, for instance, stabilizes tau's native structure, curtailing its pathological aggregation[61].

Chronic inflammation and oxidative damage amplify neurodegeneration. Peptides can intercept these processes: 1. Anti-Inflammatory Peptides: Derivatives of resolvins or annexin A1 dampen microglial activation, lowering pro-inflammatory cytokines (e.g., IL-6, TNF-α)[62]. The peptide Ac2-26, mimicking annexin A1's N-terminal, reduces neuroinflammation in AD mice[63]. 2. Antioxidant Peptides: Sequences rich in cysteine (e.g., glutathione analogs) scavenge reactive oxygen species (ROS), protecting neurons from oxidative insults[64, 65]. The EUK-134 peptide, a synthetic superoxide dismutase mimic, has shown efficacy in mitigating mitochondrial oxidative stress[66, 67].

3.2. Advantages of peptides in targeting Aβ and tau

Peptides offer several advantages over traditional small-molecule drugs and antibody-based therapies in targeting Aβ and tau pathology in AD. Peptides can be engineered to bind specific epitopes on Aβ or tau with nanomolar affinity. For example, the Aβ-specific peptide PPI-1019 selectively neutralizes soluble oligomers, sparing physiological Aβ monomers. This precision minimizes off-target effects, a common drawback of small-molecule drugs[68]. AD hinges on aberrant protein interactions—Aβ oligomerization, tau-microtubule dissociation. Peptides excel at disrupting these events by mimicking interaction domains[69]. The tau-targeting peptide NAPVSIPQ (NAP), derived from activity-dependent neuroprotective protein (ADNP), stabilizes microtubules and blocks tau aggregation, preserving neuronal structure[70].

Composed of natural L-amino acids, peptides are inherently biocompatible and less likely to trigger immune reactions than monoclonal antibodies[71]. This is critical for chronic AD treatments requiring repeated dosing. Modifications like PEGylation further enhance stability without provoking immunity[72]. Peptides serve as versatile scaffolds for functional enhancements. Conjugation with cell-penetrating peptides (CPPs), such as TAT or penetratin, facilitates brain entry[73]. The TAT-KLVFF peptide hybrid demonstrates improved Aβ targeting in vivo[74]. Fusion peptides can merge Aβ/tau inhibitors with antioxidant motifs. A peptide combining KLVFF and a ROS-scavenging sequence (e.g., carnosine) addresses both aggregation and oxidative damage[46]. AD's complexity demands therapies that concurrently tackle Aβ, tau, inflammation, and oxidative stress. Peptide libraries allow for combinatorial designs. For instance, a bifunctional peptide with Aβ-binding and kinase-inhibiting domains (e.g., Aβ/GaK peptide) reduces plaques and tau phosphorylation synergistically[75].

3.3. Limitations of peptide-based therapies

Despite their advantages, peptide-based therapies face several limitations that must be addressed to achieve clinical success. Peptides are susceptible to enzymatic degradation in the body, leading to poor stability and short half-lives. This limits their therapeutic efficacy and necessitates frequent dosing. Strategies to improve peptide stability include the use of D-amino acids, cyclization, and conjugation to stabilizing molecules[76, 77]. The BBB is a major obstacle for delivering peptides to the brain. Most peptides have poor BBB permeability, limiting their ability to reach therapeutic concentrations in the brain. To overcome this challenge, peptides can be conjugated to BBB-targeting ligands, such as transferrin or cell-penetrating peptides, or encapsulated in nanocarriers designed to cross the BBB[78].

While peptides are generally less immunogenic than proteins, some peptides may still elicit immune responses, particularly if they are derived from non-human sequences or contain modifications. This immunogenicity can lead to adverse effects and reduce the therapeutic efficacy of peptides. Careful design and testing are required to minimize this risk[79]. The production of therapeutic peptides can be complex and costly, particularly for peptides that require extensive modifications or large-scale synthesis. Advances in peptide synthesis and manufacturing technologies are needed to reduce costs and improve scalability[80]. While preclinical studies have demonstrated the potential of peptide-based therapies for AD, clinical translation has been limited. Many peptide-based drugs fail in clinical trials due to issues such as poor bioavailability, lack of efficacy, or unexpected side effects. Rigorous preclinical testing and optimization are essential to improve the chances of clinical success[52].

3.4. Pathophysiology-Informed Nanomaterial Design

Designing nanomaterials for AD therapy requires a deep understanding of the disease's underlying pathophysiology. The hallmark features of AD—Aβ plaque formation, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, and impaired BBB integrity—inform the development of targeted nanotherapeutic strategies. Each pathological mechanism presents a unique therapeutic target that can be exploited through rational nanomaterial design, ensuring higher specificity, efficacy, and safety [50].

To counter Aβ aggregation, for example, nanocarriers can be engineered to display peptide ligands such as KLVFF, which specifically bind to Aβ sequences and inhibit fibril formation. These peptide-functionalized nanoparticles not only interfere with Aβ self-assembly but can also be used to deliver anti-amyloid drugs directly to affected brain regions, minimizing off-target effects. Similarly, in the context of tau pathology, nanomaterials can be conjugated with tau-recognizing sequences or kinase inhibitors that prevent tau hyperphosphorylation and tangle formation. Dendrimers and polymeric nanoparticles, due to their high surface functionality and controlled size, are particularly suited for multivalent targeting and co-delivery of multiple therapeutic agents [81].

Addressing oxidative stress and neuroinflammation, which are prominent in AD progression, involves integrating antioxidant or anti-inflammatory molecules within the nanocarrier system. Nanoparticles loaded with curcumin, resveratrol, or catalase-mimetic compounds have shown promise in scavenging ROS and reducing inflammatory cytokine expression in preclinical models. These functionalized carriers can be further modified with surface ligands such as transferrin or lactoferrin to enhance BBB crossing and promote selective uptake by neuronal or glial cells [82].

Moreover, considering the compromised BBB in AD patients, nanomaterials are increasingly being designed with surface modifications that facilitate receptor-mediated transcytosis. Strategies such as PEGylation for stealth properties, or attachment of ligands targeting LRP1, transferrin receptors, or insulin receptors, are employed to enhance nanocarrier transport into the brain. Lipid-based vesicles, polymeric micelles, and inorganic nanoparticles are all being tailored to navigate this physiological barrier effectively [83].

4. Nanomaterials as drug delivery systems

The advent of nanoscale delivery systems has transformed therapeutic administration by enabling site-specific, controlled, and effective transport of drugs to diseased cells. In AD, these systems hold exceptional promise, addressing the longstanding challenge of bypassing the BBB while shielding active compounds from enzymatic breakdown and systemic clearance. Their capacity for localized delivery to neurodegeneration-prone brain regions positions nanomaterials as pivotal tools in AD intervention[84].

4.1. Nanoscale platforms for AD intervention

Nanotechnology has become a cornerstone in advancing AD therapeutics, addressing critical limitations of conventional treatments through precision engineering. By leveraging unique physicochemical properties, nanomaterials enhance drug delivery, enable targeted interaction with pathological hallmarks, and amplify therapeutic impact[85]. These four major classes of nanomaterials—lipid-based vesicles, polymeric carriers, dendritic architectures, and inorganic composites—focusing on their design, applications, and translational challenges in AD management (Table 1).

Table 1: Comparative analysis of nanomaterial types for peptide delivery in AD

S. No	Nanomaterial	Key Properties	Advantages	Drawbacks	Clinical Stage
1.	**Liposomes**	Phospholipid bilayer, 50–200 nm	High biocompatibility, dual drug loading	Short circulation half-life, leakage	Phase II (e.g., Aducanumab-loaded)
2.	**Polymeric NPs (PLGA)**	Biodegradable, 10–100 nm	Controlled release, FDA-approved materials	Acidic degradation byproducts	Preclinical/Phase I
3.	**Dendrimers (PAMAM)**	Hyperbranched, ~5 nm	Multifunctional surface	Cationic toxicity at high doses	Preclinical optimization
4.	**Inorganic (AuNPs)**	Optical/magnetic properties	Theranostic capabilities	Non-degradable, metal accumulation	Preclinical (imaging focus)

As summarized in Table 1, liposomes offer high biocompatibility but limited stability, while polymeric nanoparticles (e.g., PLGA) enable sustained release yet face complex fabrication. Dendrimers provide precise functionalization but suffer from scalability challenges, whereas inorganic composites (e.g., gold NPs) combine imaging and therapy but pose long-term toxicity risks [86].

4.1.1. Lipid-based vesicles (liposomes)

Liposomes are spherical nanostructures composed of phospholipid bilayers that mimic biological membranes, offering high biocompatibility and versatility[87]. Their unique architecture allows simultaneous encapsulation of hydrophilic therapeutic agents within their aqueous core and hydrophobic compounds embedded within the lipid bilayer, making them adaptable carriers for AD therapeutics[88]. Liposomes are engineered to transport diverse therapeutic payloads, including peptides targeting Aβ aggregation, small molecules like curcumin with anti-inflammatory properties, and nucleic acids for gene-based interventions[89]. For example, liposomes functionalized with Aβ-binding peptides such as mAβ11 have demonstrated efficacy in reducing amyloid plaque burden in preclinical AD models. Additionally, co-loading liposomes with antioxidants like resveratrol enables dual-action therapy, simultaneously addressing Aβ pathology and oxidative stress[90].

A key advantage of liposomes lies in their capacity for targeted delivery. By modifying their surface with ligands such as transferrin receptors, liposomes achieve enhanced specificity for brain endothelial cells, improving transport across the BBB[78, 91]. While their bilayer structure protects encapsulated drugs from enzymatic degradation, liposomes face bioavailability challenges including premature drug leakage (up to 40% in serum within 24h) and rapid RES clearance ($t_{1/2} < 4h$ for conventional formulations). Strategies like PEGylation and cholesterol incorporation can mitigate these issues (Section 7.1), enabling moderate (~2-5 fold) bioavailability improvements over free drugs in optimized systems. Furthermore, the amphiphilic nature of liposomes enhances the solubility of hydrophobic drugs like rapamycin, expanding their therapeutic utility in AD[92]. Despite their promise, liposomes face limitations such as short circulation half-life due to rapid clearance by the reticuloendothelial system (RES)[93]. While PEGylation—coating liposomes with polyethylene glycol—extends circulation time, it can inadvertently reduce cellular uptake efficiency[94]. Another challenge is the risk of premature drug leakage caused by lipid membrane instability, particularly under physiological conditions. Addressing these stability and pharmacokinetic hurdles remains critical for optimizing liposomal formulations in clinical AD treatment[95].

4.1.2. Biodegradable polymeric nanoparticles

Biodegradable polymeric nanoparticles, such as those synthesized from poly(lactic-co-glycolic acid) (PLGA) or chitosan, are engineered to enable controlled drug release through gradual degradation of their polymer matrix. Their tunable physicochemical properties make them particularly suited for managing chronic conditions like AD, where sustained therapeutic intervention is critical[96]. These nanoparticles are tailored to address diverse aspects of AD pathology. PLGA-based systems, for instance, deliver anti-inflammatory agents such as methylene blue to suppress microglial overactivation, a key driver of neuroinflammation[97]. Chitosan nanoparticles, known for their mucoadhesive properties, enhance BBB permeability, facilitating the delivery of gene-editing tools aimed at modulating tau hyperphosphorylation. Advanced stimuli-responsive variants further refine therapeutic precision by releasing drugs in response to microenvironmental cues, such as the acidic pH prevalent in amyloid-rich brain regions[98].

A major advantage of polymeric nanoparticles is their capacity for sustained drug release, providing weeks-long therapeutic coverage through controlled polymer breakdown. They also support multidrug codelivery, enabling simultaneous encapsulation of amyloid-beta (Aβ) inhibitors like tramiprosate and neuroprotective agents such as brain-derived neurotrophic factor (BDNF) to tackle AD's multifactorial nature. Additionally, their biodegradability ensures minimal systemic toxicity, as polymers like PLGA degrade into biocompatible byproducts (e.g., lactic and glycolic acid) that are safely metabolized[99]. Despite their versatility, challenges persist. The fabrication complexity of these nanoparticles demands precise emulsion or nanoprecipitation techniques to achieve uniform drug encapsulation and particle size distribution. Furthermore, polymer-dependent toxicity can arise; for example, cationic polymers like polyethylenimine (PEI) may trigger inflammatory responses at higher doses. Addressing these limitations requires meticulous optimization of polymer composition and synthesis protocols to balance efficacy with safety[100].

4.1.3. Dendritic nanostructures (dendrimers)

Dendrimers are hyperbranched, nanoscale polymers characterized by radially symmetric layers and a high degree of structural precision[101]. Their unique architecture allows for dense surface functionalization, making them versatile platforms for drug delivery and targeting. Polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers are widely explored in AD research due to their tunable surface chemistry and ability to interact with pathological targets[102]. Dendrimers are engineered to address multiple facets of AD pathology. PAMAM dendrimers conjugated with tau-targeting peptides, such as PHF6, effectively inhibit neurofibrillary tangle (NFT) formation by blocking tau aggregation. Hydroxyl-terminated dendrimers, on the other hand, act as antioxidant scavengers, neutralizing reactive oxygen species (ROS) through surface functional groups. Their compact size (~5 nm) enhances BBB penetration and facilitates efficient uptake by neurons, enabling precise delivery to affected brain regions[103].

A key strength of dendrimers lies in their high payload capacity. Multiple surface functional groups allow simultaneous attachment of therapeutic agents, imaging probes, and targeting ligands, enabling multifunctional applications. Additionally, their monodisperse structure ensures uniformity across batches, a critical factor for reproducibility in preclinical and clinical studies[104]. Despite their advantages, dendrimers face significant hurdles. Cationic toxicity is a major concern—positively charged dendrimers, such as amine-terminated PAMAM, can disrupt mitochondrial membranes at higher concentrations, leading to cytotoxicity. Furthermore, synthesis complexity limits scalability, as traditional divergent or convergent growth methods require labor-intensive, multi-step processes. Advances in green synthesis and surface modification strategies are being explored to mitigate these challenges and enhance clinical viability[105].

4.1.4. Inorganic nanocomposites

Inorganic nanoparticles, such as gold (AuNPs), iron oxide (IONPs), and mesoporous silica nanoparticles (MSNs), leverage distinct optical, magnetic, and structural properties to serve dual diagnostic and therapeutic roles in AD. These materials are uniquely suited for theranostic applications, combining targeted drug delivery with real-time imaging capabilities[106]. AuNPs functionalized with thioflavin-T derivatives disrupt Aβ fibrillation through photothermal ablation, where near-infrared irradiation generates localized heat to dismantle plaques. IONPs, guided by external magnetic fields, deliver anti-TREM1 antibodies to microglial receptors, effectively suppressing neuroinflammatory cascades. MSNs, with their high surface area and porous structure, enable the co-delivery of acetylcholinesterase inhibitors like donepezil and imaging agents such as gadolinium, facilitating simultaneous treatment and MRI-based monitoring of disease progression[107].

A standout feature of inorganic nanoparticles is their multimodal functionality. For example, IONPs not only transport therapeutic payloads but also act as contrast agents for magnetic resonance imaging (MRI), allowing clinicians to track drug distribution and treatment efficacy in real time. Additionally, their stimuli-responsive behavior enhances precision—gold nanorods, for instance, release encapsulated drugs upon exposure to near-infrared light, enabling spatiotemporal control over therapy[107]. Despite their promise, inorganic nanoparticles face significant translational hurdles. Metallic toxicity remains a concern, as non-degradable materials like silica may accumulate in organs over time, posing long-term health risks. The complex synthesis protocols required for functionalization—such as the Stöber method for MSNs or ligand conjugation for AuNPs—demand specialized expertise and equipment, complicating large-scale production. Addressing these challenges requires innovations in biodegradable inorganic materials and streamlined fabrication techniques to ensure safety and scalability[108]. While each nanomaterial class offers distinct advantages, hybrid systems (e.g., liposome-polymer composites) are emerging to synergize benefits. Overcoming translational barriers—such as scalable manufacturing and rigorous biocompatibility testing—will determine their clinical viability. Innovations in surface engineering and stimuli-responsive design are poised to unlock next-generation nanotherapeutics for AD.

4.2. Properties of nanomaterials for brain delivery in AD

Delivering therapeutics to the brain remains a formidable challenge in treating AD, primarily due to the BBB—a selective membrane that blocks most drugs. Nanomaterials have emerged as innovative tools to bypass this barrier, leveraging distinct structural and functional attributes to enhance brain-targeted delivery[109]. Nanoparticle dimensions and geometry profoundly influence their capacity to cross the BBB. Particles in the 10–100 nm range strike a balance between avoiding rapid renal clearance (seen in sub-10 nm particles) and overcoming BBB resistance (a hurdle for those >100 nm). Smaller sizes provide a high surface-area-to-volume ratio, enhancing drug-loading efficiency and biological interactions[110]. Spherical nanoparticles dominate due to ease of synthesis and uniformity. However, anisotropic shapes (e.g., rods, discs) show unique advantages. For instance, rod-shaped particles exhibit improved cellular internalization via membrane interactions, potentially boosting brain uptake[96].

Surface charge, hydrophilicity, and functional groups dictate nanoparticle behavior in biological environments. Positively charged particles bind more readily to negatively charged cell membranes, enhancing uptake but risking toxicity and nonspecific binding. Neutral or mildly negative surfaces mitigate these risks while maintaining BBB penetration[111]. Hydrophobic particles often aggregate in blood, reducing efficacy. Coating with hydrophilic polymers like polyethylene glycol (PEGylation) enhances stability, prolongs circulation, and minimizes immune detection. Surface functionalization with ligands (e.g., transferrin, lactoferrin) enables receptor-mediated BBB transit. For example, transferrin-decorated nanoparticles exploit BBB endothelial receptors for targeted delivery[112]. Safety is paramount for brain-targeted nanomaterials. Biocompatible materials (e.g., lipids, PLGA, chitosan) minimize immune activation and neurotoxicity. Biodegradability ensures nanoparticles break into harmless byproducts, preventing long-term accumulation. PLGA, for instance, degrades into lactic and glycolic acids, metabolites safely processed by the body. Tailoring degradation rates aligns with therapeutic timelines, enabling sustained drug release[113].

Nanomaterials excel in multifunctionality. Surface modifications allow conjugation of targeting ligands (e.g., Aβ-binding peptides) for precise amyloid plaque engagement. Integration of imaging agents (e.g., iron oxide for MRI) supports real-time tracking of drug distribution. Co-loading diverse therapeutics (e.g., anti-inflammatory drugs + antioxidants) enables multitarget approaches to combat AD's complexity[24, 114]. Nanoparticle stability in circulation is vital. PEGylation shields against enzymatic degradation and opsonization, extending half-life. Prolonged circulation increases BBB interaction opportunities. However, overly stable particles may resist

payload release, necessitating balance. “Stealth” nanoparticles evade immune clearance, while stimuli-responsive designs (e.g., pH-sensitive release in acidic amyloid zones) ensure site-specific action[115].

Engineered release mechanisms optimize therapeutic impact. Polymeric matrices (e.g., PLGA) enable gradual drug elution over weeks, reducing dosing frequency. Stimuli-responsive systems activate under specific conditions: light-responsive gold nanoparticles release drugs upon near-infrared irradiation, while enzyme-triggered designs respond to amyloid-associated proteases[116]. Nanomaterials’ unique properties—size tunability, surface adaptability, biocompatibility, and multifunctional capacity—position them as transformative solutions for AD therapy. By addressing BBB challenges and enabling precise, sustained delivery, they offer a pathway to halt neurodegeneration. Future advancements in material science and bioengineering promise to refine these systems, accelerating their translation into clinical breakthroughs[110].

4.3. Functionalization strategies for enhanced targeting

Functionalization strategies are pivotal in refining the precision of nanomaterial delivery systems for AD. By engineering nanoparticle surfaces with specialized ligands, researchers enhance their capacity to traverse the BBB and selectively engage AD hallmarks like Aβ plaques, tau aggregates, and inflammatory pathways[117].

4.3.1. Ligand-driven targeting

Monoclonal antibodies, such as those targeting Aβ or phosphorylated tau, provide high specificity but face BBB penetration challenges due to their bulk. To mitigate this, smaller antibody fragments are conjugated to nanoparticles. Immunoliposomes decorated with Aβ-specific scFvs have demonstrated reduced plaque burden in preclinical models[84, 118]. Short-chain peptides, such as transferrin-mimetic sequences or Aβ-binding motifs (e.g., KLVFF), exploit receptor-mediated transport. Transferrin-coated nanoparticles hijack BBB endothelial transferrin receptors, while Aβ-targeting peptides direct cargo to amyloid deposits, enhancing localized therapy[119].

Synthetic oligonucleotides like DNA aptamers selective for tau oligomers fold into precise 3D conformations for high-affinity binding. Their modular design allows stability enhancements (e.g., phosphorothioate backbones) and easy conjugation to gold or silica nanoparticles[120]. Low-molecular-weight compounds, such as folate or nicotine analogs, leverage overexpressed receptors on BBB or neuronal cells. Folate-functionalized nanoparticles, for instance, target folate receptor-α on choroid plexus epithelial cells, facilitating brain entry[121].

4.3.2. Surface engineering for enhanced performance

Conjugation with polyethylene glycol (PEG) chains reduces opsonization and RES clearance, prolonging circulation. However, excessive PEGylation may hinder cellular uptake, necessitating balanced designs[122]. Zwitterionic polymers (e.g., polycarboxybetaine) or polysaccharides (e.g., heparin) create hydrophilic surfaces that evade immune detection. Hyaluronic acid-coated nanoparticles further target CD44 receptors on activated microglia[123]. Membrane-translocating peptides like penetratin or TAT facilitate BBB crossing and neuronal internalization. CPP-conjugated lipid nanoparticles efficiently deliver siRNA targeting BACE1, a key enzyme in Aβ production[124].

4.3.3. Stimuli-responsive drug release

Acidic microenvironments near Aβ plaques or inflamed tissues trigger payload release. Poly(histidine)-based nanoparticles destabilize at pH 6.5, releasing curcumin to suppress neuroinflammation[125]. Thermosensitive liposomes loaded with memantine rupture under localized hyperthermia (40–42°C), enabling controlled drug release in affected brain regions[126]. Nanoparticles incorporating MMP-9-cleavable linkers degrade in the presence of matrix metalloproteinases overexpressed in AD, ensuring site-specific release of tau aggregation inhibitors[127].

4.3.4. Multifunctional nanoplatforms

Iron oxide nanoparticles co-loaded with deferoxamine (chelator) and gadolinium enable simultaneous iron chelation and MRI monitoring of amyloid regression[128]. Nanocarriers decorated with both transferrin and tamibarotene (retinoic acid receptor agonist) achieve dual BBB penetration and neuronal differentiation, addressing synaptic loss[129]. Polymeric micelles co-encapsulating anti-inflammatory (e.g., dexamethasone) and antioxidant (e.g., NAC) agents synergistically mitigate oxidative stress and glial activation[130]. While functionalization enhances precision, challenges like intricate fabrication processes and ligand toxicity persist. Emerging solutions include biomimetic nanoparticles cloaked in macrophage membranes for innate BBB traversal and AI-driven ligand design to predict optimal binding motifs[131]. Strategic functionalization transforms nanomaterials into precision tools for AD therapy, enabling BBB penetration, targeted delivery, and combinatorial action. As innovations in bioengineering and nanotechnology converge, these systems herald a new era of personalized, disease-modifying treatments for Alzheimer’s and related neurodegenerative disorders[114].

5. Peptide-loaded nanomaterials: Design and functional dynamics

Peptide-loaded nanomaterials represent a groundbreaking advancement in AD therapeutics, combining the molecular precision of peptides with the versatile delivery capabilities of nanotechnology (Table 2). These systems are engineered to overcome longstanding challenges such as BBB impermeability, rapid degradation of therapeutic agents, and off-target effects. By leveraging tailored synthesis methods and advanced characterization techniques, researchers optimize these nanomaterials for targeted brain delivery, controlled release, and enhanced stability, offering a transformative approach to AD treatment[132].

Table 2: Comparative analysis of peptide-loaded nanomaterials: efficacy, toxicity, and scalability

S. No	Parameter	Liposomes	Polymeric NPs	Dendrimers	Inorganic NPs
1.	Aβ Reduction (%)	40-60 (APP/PS1 mice)	50-70	30-50	60-80
2.	Tau Clearance	Moderate	High	Very High	Limited
3.	BBB Penetration	+++ (with targeting)	++	++++	++ (magnetic guid.)
4.	Immune Activation	Low (PEGylated)	Moderate	High (G4+)	Variable
5.	Scalability	Industrial scale	Pilot scale	Lab scale	Lab scale
6.	Clinical Stage	Phase II	Phase I	Preclinical	Preclinical

5.1. Fabrication and analytical profiling of peptide-loaded nanomaterials

The development of peptide-loaded nanomaterials begins with precise synthesis strategies to ensure optimal drug encapsulation or conjugation. Encapsulation methods, such as emulsion-solvent evaporation, embed hydrophilic peptides like Aβ inhibitors within the aqueous cores of liposomes or polymeric matrices like PLGA, while hydrophobic peptides integrate into lipid bilayers. Conjugation techniques, including thiol-maleimide coupling, covalently anchor peptides—such as tau-targeting sequences—to nanoparticle surfaces, ensuring stable presentation and interaction with pathological targets. Self-assembling amphiphilic peptides, such as EAK16-II, form nanostructures like micelles or nanofibers that inherently encapsulate therapeutic agents, capitalizing on their innate structural properties[133].

Characterization of these systems involves rigorous analysis of physicochemical and biological properties. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) quantify nanoparticle size (ideally 10–200 nm for BBB penetration) and visualize morphology, such as spherical or rod-like shapes. Surface charge, measured via zeta potential, is optimized to balance stability and cellular uptake, typically between +5 and −20 mV. Analytical methods like UV-Vis spectroscopy and high-performance liquid chromatography (HPLC) assess peptide encapsulation efficiency and release kinetics, ensuring >80% drug retention and controlled elution. Biocompatibility is validated through cytotoxicity assays on neuronal cell lines and hemolysis tests, confirming minimal toxicity at therapeutic doses[134].

5.2. Brain-targeting mechanisms of peptide-loaded nanomaterials

Peptide-loaded nanomaterials employ sophisticated mechanisms to traverse the BBB and engage AD-specific pathologies. Receptor-mediated transcytosis is a primary strategy, where nanoparticles functionalized with ligands like transferrin bind to BBB endothelial receptors, triggering vesicular transport into the brain. Adsorptive-mediated uptake leverages cationic cell-penetrating peptides (e.g., TAT) that interact electrostatically with the BBB's anionic surface, promoting membrane invagination and internalization. Additionally, nanoparticles mimicking nutrients like glucose exploit carrier-mediated transport via GLUT1 transporters, bypassing the BBB through endogenous pathways[135].

Once within the brain, these systems target pathological hallmarks with precision. For instance, gold nanoparticles conjugated with the KLVFF peptide selectively bind Aβ plaques via hydrophobic interactions, enabling localized disaggregation through photothermal therapy. Similarly, liposomes decorated with PHF6 peptides inhibit tau aggregation by blocking critical microtubule-binding domains. To mitigate neuroinflammation, dexamethasone-loaded dendrimers tagged with ICAM-1 antibodies target activated microglia, suppressing pro-inflammatory cytokine release. Intracellular delivery is enhanced by endosomal escape peptides (e.g., GALA), which facilitate lysosomal evasion, ensuring therapeutic cargo reaches the neuronal cytoplasm or organelles like mitochondria[136].

Beyond targeting and delivery, peptide-loaded nanomaterials play a direct role in interfering with Aβ and tau aggregation at the molecular level. For example, the KLVFF peptide, derived from the central hydrophobic core of Aβ42, exhibits high binding affinity (Kd ~ 0.7 μM) to Aβ monomers and oligomers, interrupting β-sheet formation and fibril elongation through steric hindrance and hydrogen bonding [81]. When conjugated to gold nanoparticles, this peptide forms multivalent interactions with fibrillar surfaces, enhancing disaggregation via local thermoplasmonic effects upon NIR irradiation. Similarly, PHF6 (VQIVYK), a tau aggregation motif, can be conjugated to nanocarriers to block pathological nucleation by competing for microtubule-binding sites, disrupting fibrillogenesis [137].

5.3. Controlled release and stability optimization

Achieving sustained therapeutic efficacy requires precise control over drug release kinetics and nanomaterial stability. Diffusion-controlled systems, such as porous silica nanoparticles, enable gradual peptide release through nanoscale channels, ideal for chronic AD management. Degradation-dependent mechanisms utilize biodegradable polymers like PLGA, which hydrolyze into nontoxic byproducts over weeks, synchronizing drug release with polymer breakdown. Stimuli-responsive designs, such as pH-sensitive poly(β-amino ester) nanoparticles, swell in the acidic microenvironment of amyloid plaques (pH ~6.5), accelerating drug release at disease sites[138].

Stability is enhanced through surface engineering and formulation strategies. PEGylation with PEG2000-DSPE coatings reduces immune recognition, extending circulation half-life beyond 12 hours. Crosslinking agents like glutaraldehyde stabilize chitosan nanoparticles against enzymatic degradation in the cerebrospinal fluid. Lyophilization with cryoprotectants such as trehalose preserves nanoparticle integrity during storage, ensuring >95% activity post-reconstitution. These strategies collectively improve bioavailability and therapeutic performance, critical for clinical translation[139].

Peptide-integrated nanosystems exemplify the synergy between nanotechnology and molecular biology, offering unparalleled precision in AD therapy. Future advancements will focus on scalable synthesis methods, such as microfluidics, and AI-driven peptide design tools like AlphaFold to predict optimal binding conformations. Emphasis on biodegradable materials and multifunctional theranostic platforms—combining therapy with real-time imaging—will further enhance clinical viability. As these innovations progress, peptide-loaded nanomaterials hold immense potential to revolutionize neurodegenerative disease treatment, transitioning from experimental models to patient-centered therapies[132].

6. Therapeutic applications of peptide-loaded nanomaterials in AD

Peptide-loaded nanomaterials have emerged as a groundbreaking strategy in AD therapy, offering precision targeting and multifunctional intervention (Figure 2). These advanced systems leverage nanotechnology to overcome the BBB, delivering therapeutic peptides directly to pathological sites while protecting them from degradation[23]. Their versatility enables simultaneous engagement with multiple AD hallmarks, including Aβ plaques, tau tangles, neuroinflammation, and oxidative stress, addressing the disease's complexity holistically [140].

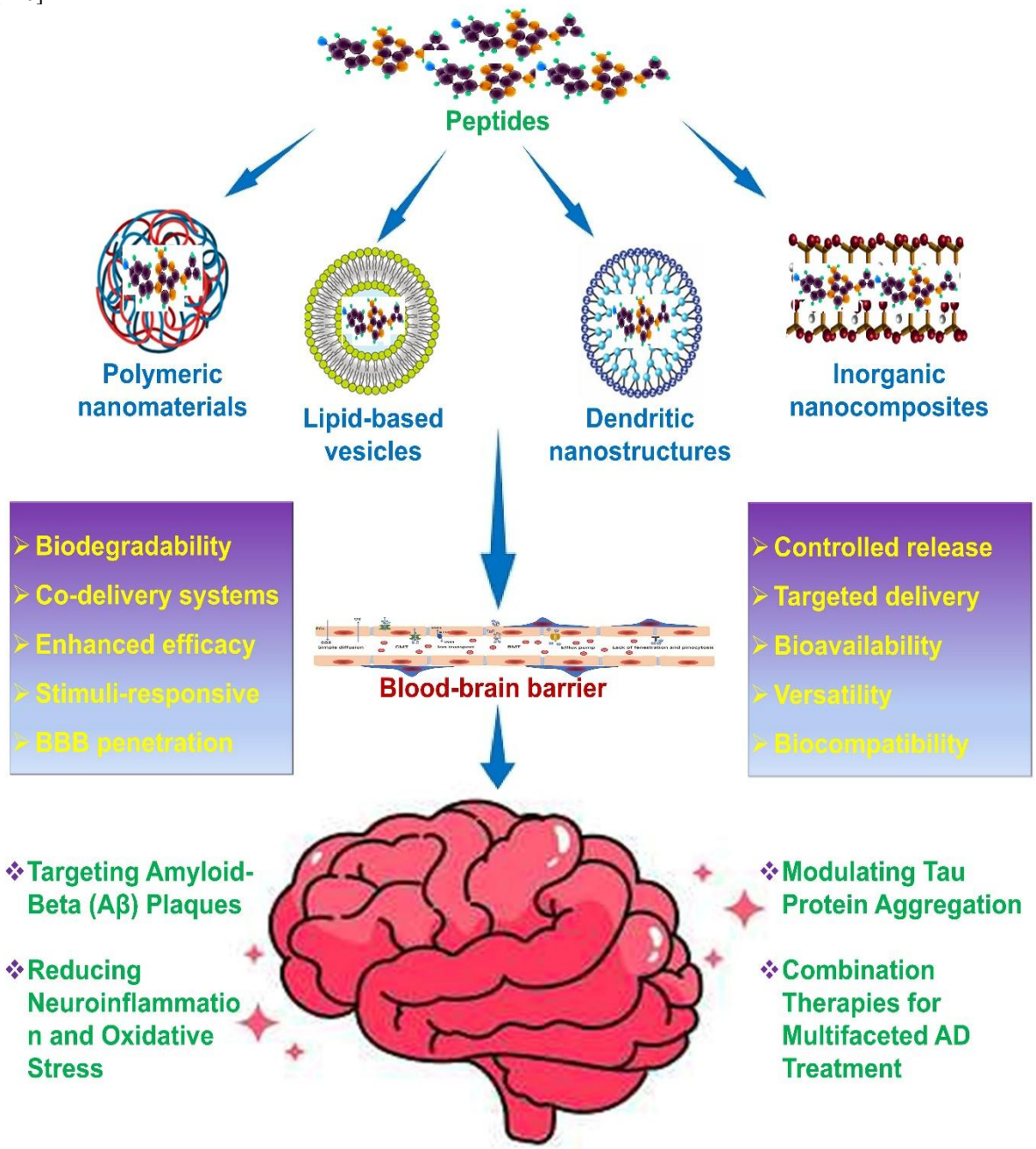


Figure 2: Novel therapeutic applications of peptide-loaded nanomaterials in AD

6.1. Targeting Aβ plaques

Aβ plaques, a hallmark of AD, disrupt neuronal communication and drive cognitive decline. Peptide-loaded nanomaterials combat this through strategies such as preventing Aβ aggregation, promoting clearance, and dissolving existing fibrils. For instance, gold nanoparticles conjugated with KLVFF peptides—derived from Aβ's hydrophobic core—bind to soluble Aβ, halting its assembly into toxic oligomers[141]. Preclinical studies in transgenic mice reveal that such systems reduce plaque burden and restore synaptic function. Additionally, polymeric nanoparticles functionalized with Aβ-specific antibodies act as molecular sponges, enhancing microglial clearance of amyloid deposits. Innovations like magnetic nanoparticles linked to Aβ-binding peptides apply mechanical forces to break down fibrils, showcasing their potential to reverse plaque pathology[61].

The study by Fan et al. (2018) underscores the potential of peptide-conjugated nanomaterials in AD therapy by designing curcumin-loaded PLGA-PEG nanoparticles functionalized with B6 peptide (PLGA-PEG-B6/Cur). The B6 peptide, targeting the transferrin receptor, enhances BBB permeability, addressing a critical challenge in central nervous system drug delivery. The PLGA-PEG matrix improves curcumin's bioavailability and enables sustained release, mitigating its rapid metabolism. In APP/PS1 transgenic mice, PLGA-PEG-B6/Cur significantly reduced amyloid-beta deposition and tau hyperphosphorylation while improving cognitive performance in Morris water maze tests. Notably, the nanoparticles demonstrated excellent hemocompatibility and low cytotoxicity, highlighting their translational potential. This study exemplifies how peptide-mediated targeting synergizes with nanocarriers to enhance therapeutic efficacy against AD pathologies. Future research could explore dose optimization, long-term safety, and combinatorial strategies with other neuroprotective agents. Such advancements may pave the way for clinical applications, offering a promising paradigm shift in AD treatment through precision nanomedicine[142].

The study by Al-azzawi et al. (2020) highlights the application of an ApoE-mimicking peptide (AEP)-functionalized nanocarrier to enhance flurbiprofen (FP) delivery across the BBB for AD therapy. By exploiting LDL receptor (LDLr)-mediated transcytosis, the AEP-conjugated system significantly improved FP permeability in an in vitro BBB model, achieving a six-fold increase over free FP. The nanocarrier retained FP's ability to modulate γ-secretase activity, reducing Aβ42 production in glial cells, while lysosomal hydrolysis enabled controlled drug release. Notably, the system demonstrated biocompatibility and low cytotoxicity, underscoring its potential for targeted Aβ plaque reduction. This work exemplifies how peptide-driven receptor targeting synergizes with nanocarriers to enhance therapeutic delivery, addressing Aβ pathology while minimizing off-target effects. Future studies could explore its integration with anti-tau or anti-inflammatory agents for combinatorial AD therapy[143].

Yin and colleagues (2015) investigated the potential of B6 peptide-conjugated, sialic acid-functionalized selenium nanoparticles (B6-SA-SeNPs) as a novel approach for AD treatment. Their research showed that these nanoparticles possess enhanced BBB penetration capabilities, positioning them as a potential therapeutic candidate. Experimental results indicated that B6-SA-SeNPs were successfully internalized by brain endothelial cells (bEnd.3) and efficiently transported through a lab-based BBB model. Crucially, the nanoparticles demonstrated a dual action against Aβ pathology: they blocked the formation of harmful fibrils by suppressing Aβ fibrillation and stimulated the breakdown of existing fibrils into non-toxic, unstructured aggregates. The study also documented the nanoparticles' protective role in neuronal cells, where B6-SA-SeNPs alleviated Aβ-induced toxicity in PC12 cells by lowering oxidative damage and programmed cell death. These observations underscore the nanoparticles' dual functionality—acting both as a targeted delivery platform and a direct intervention against AD's molecular mechanisms. While the findings highlight significant therapeutic promise, the authors emphasize the necessity of further animal-based research to validate the nanoparticles' safety and sustained effectiveness before advancing to human trials[144].

Zhang and collaborators (2019) engineered a zinc-binding peptide designed to counteract AD mechanisms by targeting zinc ion (Zn^{2+})-driven Aβ clumping and neuronal damage. Using phage display technology, the team isolated a seven-amino-acid sequence (H-M-Q-T-N-H-H) with strong selectivity for Zn^{2+}. To optimize therapeutic delivery, this peptide was integrated into chitosan nanoparticles coated with PEG, forming PEG/PZn-CS NPs—a formulation shown to improve structural durability and biological absorption. In laboratory tests, the engineered nanoparticles demonstrated notable efficacy in lowering Zn^{2+} concentrations and diminishing Aβ release in N2a-sw neuronal cells. This dual action mitigated Zn^{2+}-linked oxidative stress pathways and reduced programmed cell death triggered by Aβ toxicity. The findings underscore the potential of PEG/PZn-CS NPs as a dual-functional strategy, combining metal ion regulation with amyloid aggregation interference to address AD pathological processes[145].

Tiantian et al. (2016) synthesized penetratin (Pen) peptide-functionalized PEG-stabilized gold nanostars (AuNS) to enhance BBB permeability and facilitate near-infrared (NIR) photothermal therapy for AD. Their study demonstrated that Ru@Pen@PEG-AuNS effectively inhibited Aβ fibril formation and promoted the disaggregation of preformed fibrils under NIR irradiation. The inclusion of the Ru(II) complex improved real-time drug tracking while enhancing neuroprotection by reducing Aβ-induced cytotoxicity. More importantly, the conjugation of Pen peptide significantly improved the transport efficiency of nanoparticles across the BBB, overcoming a major limitation in AD drug delivery. In vivo studies confirmed increased nanoparticle accumulation in the brain, suggesting a promising nanotherapeutic approach. This multifunctional system offers

a dual mechanism—targeted Aβ inhibition and photothermal ablation—providing a potential breakthrough in AD therapy. However, further studies are required to evaluate long-term safety and clinical feasibility[146].

Li et al. (2017) developed a multifunctional peptide-conjugated gold nanorod (AuP) system for detecting Aβ aggregation and facilitating chemo-photothermal therapy for AD. Their study demonstrated that AuP nanorods, functionalized with Aβ15-20 peptide and polyoxometalates (POMs), exhibited strong near-infrared (NIR) absorption, allowing for precise photothermal ablation of Aβ fibrils. The AuP system not only inhibited Aβ aggregation but also successfully disassembled preformed fibrils under NIR irradiation. Additionally, in vitro and cerebrospinal fluid-based studies confirmed its ability to mitigate Aβ-induced cytotoxicity in neuronal cells. Notably, the AuP nanorods effectively crossed the blood-brain barrier, ensuring targeted therapeutic delivery. The integration of Aβ-targeting peptides, diagnostic capabilities, and therapeutic functionalities in a single nanoplatform represents a promising advancement in AD treatment. However, further in vivo studies are necessary to validate long-term efficacy, biocompatibility, and potential clinical translation of this approach[147].

Ruan et al. (2022) developed a multifunctional curcumin-conjugated nanotheranostic platform for AD that combines targeted Aβ detection with therapeutic intervention. The study demonstrated that curcumin-loaded superparamagnetic iron oxide (SPIO) nanoparticles, modified with CRT and QSH peptides, efficiently crossed the BBB and targeted Aβ plaques. These nanoparticles facilitated noninvasive monitoring of Aβ deposition via MRI and enabled precise quantification of plaque burden. Furthermore, their administration significantly improved cognitive function in APP/PS1 transgenic mice by reducing neuroinflammation through inhibition of the NLRP3 inflammasome. The dual functionality of this system—early diagnosis and therapeutic efficacy—highlights its potential as an advanced strategy for AD management. However, further in vivo investigations are needed to validate its long-term biocompatibility, optimize peptide modifications, and assess clinical translation for human applications. This approach presents a promising avenue for the early diagnosis and treatment of AD[148].

Khairnar et al. (2023) developed cyclic β-hairpin peptide-loaded PLGA nanoparticles as a novel anti-amyloid therapeutic for AD. Their study demonstrated that the designed peptide, BSBP8, effectively inhibited Aβ1–42 aggregation, reducing fibril formation by ~82% in a Thioflavin T assay. Additionally, BSBP8 disassembled preformed Aβ fibrils and exhibited neuroprotective effects by rescuing neuronal cells from Aβ-induced cytotoxicity. To enhance its BBB permeability, BSBP8 was encapsulated in PLGA nanoparticles, which showed efficient transport across an in vitro BBB model formed by MDCK cells. In vivo biodistribution studies revealed significant accumulation in the brain (~9%), liver (~52%), and kidney (~20%), with retention for at least seven days, highlighting its potential for sustained drug delivery. These findings underscore the promise of cyclic peptide-loaded nanoparticles as an effective therapeutic strategy for AD. However, further studies are needed to optimize dosage and assess long-term efficacy[149].

Sun et al. (2021) developed fluorescent cyclic peptide nanoparticles (c-PNPs) for detecting Aβ aggregation in cerebrospinal fluid (CSF) and serum, offering a novel diagnostic approach for AD. Their study demonstrated that c-PNPs exhibited strong affinity toward Aβ aggregates, leading to fluorescence intensity enhancements and wavelength shifts that correlated with disease severity. The negatively charged c-PNPs showed the highest sensitivity, effectively distinguishing between healthy individuals and AD patients at different stages. Furthermore, these nanoparticles exhibited inhibitory effects on Aβ fibril growth, suggesting their potential as both diagnostic and therapeutic agents. In vitro studies confirmed their biocompatibility and ability to mitigate Aβ-induced cytotoxicity in neuronal cells. The integration of real-time fluorescence detection with therapeutic functionality highlights the potential of c-PNPs as a dual-purpose nanoplatform. However, further in vivo studies are required to validate their long-term efficacy, biosafety, and clinical applicability in AD management[150].

Lee et al. (2019) developed an ultrasensitive fluorescence-based diagnostic system using a polyvalent directed peptide polymer (PDPP) coupled with a nanoporous ZnO nanoplatform for AD detection. Their study demonstrated that PDPP exhibited a 103-fold higher affinity toward Aβ42 compared to single peptides, enhancing specificity and sensitivity. The nanoporous ZnO platform further amplified fluorescence signals, allowing for the detection of Aβ42 at concentrations as low as 12 ag/mL, significantly surpassing conventional antibody-based assays. Moreover, PDPP successfully detected Aβ42 in cerebrospinal fluid (CSF) from AD patients, distinguishing between early and advanced stages of the disease. This novel approach not only improves early AD diagnosis but also provides a potential framework for detecting other neurodegenerative biomarkers. However, further in vivo studies are needed to validate long-term reliability, biocompatibility, and feasibility for clinical applications. The integration of PDPP with nanotechnology represents a promising advancement in AD diagnostics[151].

Ansari et al. (2024) highlighted the potential of peptide-loaded nanocarriers in overcoming the BBB and enhancing drug delivery for AD therapy. Their study emphasized the use of polymeric, lipid-based, and inorganic nanoparticles conjugated with bioactive peptides to improve targeting and bioavailability of therapeutic agents. Specifically, polymeric nanoparticles, such as chitosan-based carriers, demonstrated effective transport across the BBB, facilitating sustained release and improved neuroprotection. Metal-based nanoparticles, including selenium and iron oxide, were shown to exhibit antioxidant properties, reducing oxidative stress and mitigating Aβ aggregation. Furthermore, peptide-functionalized liposomes enhanced Aβ clearance, preventing its neurotoxic effects. These multifunctional nanocarriers not only serve as efficient drug delivery systems but also offer

neuroprotective and anti-inflammatory benefits. While promising, further in vivo validation and clinical trials are essential to establish their long-term safety and therapeutic efficacy in AD management[152].

Israel and colleagues (2023) engineered a nanoscale therapeutic platform targeting β-amyloid pathology to enable neuron-specific nucleic acid delivery in AD research models. Their approach employed a synthetic copolymer—poly(β-L-malic acid-trileucine)—functionalized with a D-amino acid peptide, designed to exploit the Low-Density Lipoprotein Receptor-Related Protein-1 (LRP-1) transport mechanism. This modification enhanced the nanodrug's ability to traverse the BBB efficiently via receptor-mediated transcytosis. The system demonstrated successful delivery of miRNA and antisense RNA directly into neuronal cells, enabling precise modulation of disease-relevant genetic pathways. By combining β-amyloid-targeting specificity with enhanced BBB permeability, the nanodrug represents a dual-functional strategy to address both amyloid aggregation and dysregulated gene expression in AD. In vivo studies confirmed successful transport across the BBB, with nanodrug accumulation observed in neurons rather than astroglia, reducing Aβ plaque deposition. Further RNA-seq and PCR analysis validated significant alterations in AD-related gene expression, supporting the therapeutic potential of peptide-functionalized nanopolymers. This targeted approach offers a promising avenue for AD therapy by improving nucleic acid stability, reducing off-target effects, and enhancing neuronal uptake. However, additional long-term studies are necessary to assess clinical safety and optimize dosage parameters for effective human translation[153].

Zhou et al. (2022) developed a novel brain-targeted nanomedicine by functionalizing rifampicin-loaded poly(L-lactide) nanoparticles with RVG29 peptide to enhance BBB permeability for AD therapy. Their study demonstrated that RVG29-modified nanoparticles (RIF@PLA-PEG-Gd/Mal-RVG29) significantly improved rifampicin bioavailability by facilitating its transport across the BBB and enhancing neuronal uptake. In vivo imaging confirmed the targeted brain accumulation of these nanoparticles, while Morris water maze tests showed cognitive improvements in APP/PS1 transgenic mice. Additionally, immunofluorescence and histopathological analysis revealed that the nanomedicine reduced Aβ deposition in the hippocampus and cortex, improved synaptic integrity, and mitigated neuronal degeneration. The combination of brain-targeting ligands, anti-inflammatory effects, and MRI-based tracking highlights the potential of RVG29-functionalized nanocarriers as a promising therapeutic strategy for AD. However, further studies are needed to assess long-term safety and optimize dosing for clinical translation[154].

6.2. Modulating tau protein aggregation

Neurofibrillary tangles of hyperphosphorylated tau are central to neurodegeneration[155]. Nanomaterials address tau pathology by inhibiting kinase activity, disrupting aggregation, and promoting degradation. Lipid nanoparticles delivering peptides that block glycogen synthase kinase-3β (GSK-3β) reduce tau phosphorylation, curtailing tangle formation. Dendrimers conjugated with tau-mimetic peptides competitively inhibit self-assembly, decreasing tangle density in hippocampal neurons[156]. Furthermore, autophagy-inducing peptides encapsulated in biodegradable polymers like PLGA enhance pathological tau clearance through lysosomal pathways, improving cognitive outcomes in animal models[157].

6.3. Reducing neuroinflammation and oxidative stress

Chronic inflammation and oxidative damage exacerbate neuronal loss in AD. Peptide-loaded systems mitigate these processes by delivering anti-inflammatory agents to overactive glial cells and neutralizing ROS[158]. Chitosan nanoparticles loaded with interleukin-1β (IL-1β) inhibitors suppress microglial activation, lowering pro-inflammatory cytokine levels[159]. Antioxidant peptides, such as glutathione analogs stabilized in liposomal carriers, scavenge free radicals, protecting neurons from oxidative injury[82]. Hybrid platforms co-loaded with anti-inflammatory and antioxidant agents demonstrate synergistic neuroprotection, reducing hippocampal atrophy in preclinical studies[160].

This study elucidates the pivotal role of histidine in modulating the amyloid-like assembly of Fmoc-diphenylalanine (Fmoc-F-F) peptides into β-sheet-rich nanofilaments under aqueous conditions. These nanostructures exhibit peroxidase-like catalytic activity, driven by histidine's imidazole group, which facilitates ROS generation. Notably, a parallel investigation of Aβ1–42 aggregates revealed analogous enzyme-like behavior, correlating prolonged aggregation with heightened ROS production and neuronal toxicity. The discovery that Aβ filaments intrinsically mimic nanozymes provides a novel mechanistic link between amyloid aggregation and oxidative stress in AD pathogenesis. The findings underscore histidine's dual function as both a structural modulator and catalytic enhancer in peptide assemblies, offering insights into amyloid-mediated neurotoxicity. For therapeutic applications, targeting histidine's role in Aβ aggregation or engineering peptide-loaded nanomaterials to counteract ROS generation could mitigate AD progression. This work highlights the potential of amino acid-guided peptide nanomaterials in AD therapy, suggesting strategies to disrupt pathological aggregation or design functional nanostructures with antioxidative properties. Future research could explore histidine-modified nanomaterials as dual-purpose agents for amyloid inhibition and ROS scavenging, advancing precision nanomedicine for neurodegenerative disorders[161].

The study by Wu et al. (2024) demonstrates a promising bifunctional nanotherapeutic approach for AD by integrating halloysite nanotubes (HNTs) with the brain-targeting peptide RVG29 and Ripk1 siRNA. The RVG29-functionalized HNTs (SH-RVG) effectively cross the BBB, target Aβ plaques, and inhibit Aβ aggregation while promoting plaque clearance. This dual functionality addresses two critical AD hallmarks: amyloid pathology and Ripk1-mediated neuronal necroptosis. By loading Ripk1 siRNA into SH-RVG, the system silences Ripk1

expression around plaques, reducing necroptosis and neuronal loss, thereby rescuing cognitive deficits in AD mice. The study underscores the potential of peptide-guided nanomaterials to enhance targeted delivery and therapeutic efficacy in AD. The use of HNTs as both Aβ modulators and siRNA carriers highlights their versatility in multi-target strategies. Importantly, SH-RVG/siRipk1 exhibits favorable biosafety, a crucial consideration for clinical translation. These findings advance the development of peptide-nanomaterial hybrids for AD therapy, emphasizing the importance of combining BBB penetration, plaque targeting, and gene silencing to combat complex neurodegenerative mechanisms. Further studies should explore long-term safety and scalability for human applications[162].

6.4. Combination therapies for multifaceted AD treatment

The multifactorial nature of AD demands therapies that concurrently target Aβ, tau, inflammation, and oxidative stress. Peptide-loaded nanomaterials excel in co-delivering diverse agents, such as Aβ inhibitors paired with tau kinase blockers, to address multiple pathways. For example, silica nanoparticles simultaneously transport curcumin (anti-inflammatory) and rasagiline (neuroprotective), yielding superior cognitive outcomes compared to single-agent treatments. Functionalization with ligands like angiopep-2 enhances BBB penetration, ensuring therapeutic peptides reach effective concentrations in the brain[163].

The study by Silva et al. (2020) explores the use of nanostructured lipid carriers (NLCs) to enhance tacrine (TAC) delivery and its conjugation with the cell-penetrating peptide MAP for AD therapy. While TAC-loaded NLCs demonstrated reduced cytotoxicity and sustained release, the TAC-MAP conjugate exhibited significant toxicity in SH-SY5Y cells despite high encapsulation efficiency (>85.6%). The NLCs, with particle sizes <200 nm, improved TAC bioavailability and stability, addressing its short half-life and hepatotoxicity. However, the toxicity of TAC-MAP highlights challenges in balancing peptide-mediated delivery and biocompatibility. This work underscores the potential of peptide-functionalized nanomaterials in combination therapies to enhance drug efficacy and target multifactorial AD pathways. Future studies should optimize peptide conjugation strategies to mitigate toxicity while leveraging CPPs for brain-targeted delivery, aligning with the broader goal of developing safer, multifunctional AD therapeutics[164].

This study advances the application of peptide-loaded nanomaterials in AD therapy by targeting tau pathology, a key driver of neurodegeneration. The authors engineered a D-enantiomeric peptide, D-TLKIVWC (7-DP), which not only inhibits tau aggregation but also fragments preexisting tau fibrils derived from AD brains, neutralizing their prion-like seeding capacity. To overcome BBB limitations, 7-DP was conjugated to MNPs, enhancing stability and delivery. The MNPs-DP complex demonstrated dual functionality: preventing tau fibril propagation in biosensor cells and reducing neurotoxicity in neuronal cultures. In vivo, MNPs-DP treatment reversed cognitive deficits in PS19 tauopathy mice, correlating with reduced phosphorylated tau levels in the hippocampus. Notably, the formulation exhibited no significant toxicity, underscoring its biocompatibility. This work highlights the potential of combining protease-resistant D-peptides with nanocarriers to achieve targeted disaggregation of pathological tau, addressing both existing fibrils and preventing further spread. The findings provide a blueprint for developing multifunctional nanomaterials capable of disrupting tau pathology while ensuring safe, efficient CNS delivery, offering a promising therapeutic strategy for tauopathies like AD. Further optimization could explore dual therapeutic-imaging functionalities leveraging MNPs' magnetic properties[165].

The study by Wang et al. presents a multifunctional nanoprobe, CICe@M-K, designed to address two critical AD hallmarks: Aβ aggregation and oxidative stress. The system integrates mesoporous silica nanoparticles (MSNs) loaded with curcumin (Cur) and IR780, surface-modified with cerium oxide nanoparticles (CeO_2) and a targeting peptide (CKLVFFAED). The peptide enhances blood-brain barrier (BBB) penetration via RAGE receptor interaction and directs the probe to Aβ plaques. Cur and the peptide synergistically inhibit Aβ fibrillization through π-π stacking and hydrophobic interactions, while CeO_2 and Cur cooperatively scavenge ROS, mitigating oxidative damage. Near-infrared (NIR) irradiation triggers controlled Cur release, enhancing therapeutic precision. In vivo experiments in APP/PS1 mice demonstrated reduced Aβ plaques, decreased neuroinflammation (lower TNF-α/IL-1β levels), and improved cognitive performance in behavioral tests. The nanoprobe's biocompatibility and hemocompatibility further support its translational potential. This work underscores the efficacy of peptide-functionalized nanomaterials in dual-target AD therapy, combining BBB traversal, Aβ modulation, and ROS clearance. Such multifunctional platforms highlight the importance of addressing AD's multifactorial pathology through integrated nanomedicine approaches, offering a promising blueprint for future clinical development[166].

Peptide-loaded nanomaterials represent a paradigm shift in AD treatment, demonstrating preclinical success in reducing pathology and improving cognition. However, challenges such as scalable manufacturing, long-term biocompatibility, and clinical validation remain. Future research should prioritize biodegradable designs, personalized delivery systems, and theranostic platforms that combine therapy with real-time monitoring. By bridging these gaps, peptide-integrated nanosystems hold immense promise for transforming AD management, offering hope for effective, multifaceted interventions.

6.5. Comparative Evaluation of Peptide-Loaded Nanomaterials

In terms of **efficacy**, KLVFF-conjugated gold nanoparticles are highly effective in targeting and disaggregating amyloid-beta (Aβ) plaques, while also enabling photothermal therapy. However, their non-biodegradable nature raises concerns about long-term biocompatibility [167]. Tau-targeting dendrimers, such as PAMAM-PHF6, exhibit multifunctional properties, including kinase inhibition and antioxidant activity, but their cationic surface can cause toxicity at higher doses, which limits their safe application range [156].

Regarding **safety**, lipid-based vesicles like liposomes are well known for their biocompatibility and biodegradability. Nonetheless, they face limitations such as premature drug release and short circulation times. Inorganic nanomaterials like gold or iron oxide offer additional benefits for diagnostics, including MRI tracking, but carry risks of metal accumulation and require complex synthesis, potentially restricting their broader use.

In terms of **clinical potential**, many peptide-loaded nanomaterials show promise in preclinical models, with evidence of Aβ plaque reduction and cognitive improvement. However, translating these outcomes into clinical use remains difficult due to challenges like large-scale manufacturing, maintaining batch consistency, immune reactions, and effective delivery across the blood-brain barrier.

There are also **contradictions in the literature**, particularly in the reported efficacy of these nanomaterials. Variability in animal models, peptide conjugation methods, and dosing strategies contribute to inconsistent findings, such as differing Aβ clearance rates. Additionally, conflicting reports exist on the immunogenicity of PEGylated versus non-PEGylated systems, highlighting the need for standardized testing and long-term safety evaluations.

While KLVFF-gold nanoparticles demonstrate robust Aβ plaque reduction in transgenic mice [141], their clinical translation is hampered by unresolved concerns about gold accumulation in peripheral organs. In contrast, tau-targeting dendrimers (e.g., PAMAM-PHF6) mitigate neurofibrillary tangle formation but require optimization to reduce cationic cytotoxicity [156]. Lipid-based vesicles, though safer, exhibit lower drug-loading capacity compared to polymeric nanoparticles, underscoring the need for material-specific risk-benefit assessments [87].

7. Challenges and limitations in peptide-loaded nanomaterials for AD treatment

While peptide-loaded nanomaterials hold immense promise for the treatment of AD, several challenges and limitations must be addressed to realize their full potential. These challenges span biocompatibility and toxicity concerns, scalability and manufacturing hurdles, and translational barriers from preclinical to clinical studies. Addressing these issues is critical for ensuring the safety, efficacy, and clinical applicability of peptide-loaded nanomaterial-based therapies.

7.1. Biocompatibility and toxicity concerns

The advancement of peptide-loaded nanomaterials for AD therapy is hindered by critical biocompatibility and toxicity challenges. A primary concern is the immune response triggered when the body recognizes nanoparticles as foreign, activating inflammatory pathways. Strategies like PEGylation—coating nanoparticles with polyethylene glycol—help reduce immune detection by masking surface properties. Strategies like PEGylation—coating nanoparticles with polyethylene glycol—have traditionally been used to reduce immune detection and prolong systemic circulation by masking surface properties. However, recent evidence suggests that repeated administration can elicit anti-PEG antibodies, leading to immune-mediated clearance and potential hypersensitivity reactions, a phenomenon known as the accelerated blood clearance (ABC) effect (Zhou et al., 2022; Garay et al., 2020). Therefore, while PEGylation remains valuable, alternative stealth strategies such as zwitterionic coatings or glycosylation are being explored to mitigate immunogenicity concerns. Additionally, non-target tissue accumulation poses risks, particularly with inorganic materials such as gold nanoparticles, which resist biodegradation and may persist in organs like the liver or spleen. Enhancing specificity through targeted ligands can mitigate off-target effects, directing nanoparticles to brain tissue more efficiently[168].

Toxicity issues arise from cytotoxic materials, including certain metals and polymers. For instance, gold nanoparticles may release toxic ions under physiological conditions, necessitating rigorous dose optimization. Long-term safety remains uncertain, as chronic exposure could lead to oxidative stress or organ damage. Biodegradable materials like PLGA offer promise but degrade into acidic byproducts, potentially causing local inflammation. Solutions such as integrating buffering agents or modulating degradation rates are under investigation to enhance safety profiles[169].

7.2. Scalability and manufacturing hurdles

Scaling up production of peptide-loaded nanomaterials faces significant obstacles. The synthesis process involves intricate steps, including peptide conjugation and nanoparticle purification, requiring precise control to ensure consistency. Advanced characterization techniques like DLS and TEM add complexity and cost. To address scalability, automation technologies such as microfluidic systems are being adopted to standardize production. Natural polymers (e.g., chitosan) or lipid-based systems may simplify synthesis, reducing reliance on expensive or complex materials. Regulatory compliance, including Good Manufacturing Practices (GMP), further escalates costs, emphasizing the need for cost-effective, scalable solutions[132, 170].

7.3. Translational barriers from preclinical to clinical studies

Translating findings from animal models to human trials is fraught with challenges. Preclinical models, such as transgenic mice, inadequately replicate human AD pathology, particularly in BBB behavior and disease progression. Innovations like humanized mouse models and in vitro BBB systems aim to bridge this gap. Regulatory frameworks, governed by agencies like the FDA and EMA, demand extensive safety and efficacy data, yet lack tailored guidelines for nanomaterials. Collaborative efforts to establish standardized protocols are critical. Clinical trials must prioritize patient stratification using biomarkers (e.g., Aβ levels) and adaptive designs to refine endpoints dynamically. Incorporating patient feedback ensures trials address meaningful outcomes, enhancing relevance and success rates[132, 171].

Peptide-loaded nanomaterials represent a transformative approach to treating AD, but their successful development and clinical translation require overcoming significant challenges. Biocompatibility and toxicity

concerns must be addressed through rigorous testing and innovative design strategies. Scalability and manufacturing hurdles can be mitigated through automation, standardization, and the exploration of alternative materials. Translational barriers from preclinical to clinical studies necessitate improved models, regulatory collaboration, and robust clinical trial design. By addressing these challenges, researchers can unlock the full potential of peptide-loaded nanomaterials and bring effective, targeted therapies to patients with AD[172].

8. Future directions and opportunities

The realm of peptide-loaded nanomaterials for AD therapy is on the brink of transformative breakthroughs, driven by innovative strategies that promise to redefine treatment paradigms. As this field evolves, several key avenues—spanning molecular design, personalized approaches, diagnostic integration, and regulatory frameworks emerge as pivotal for advancing therapeutic outcomes and addressing the multifaceted nature of AD[173]. Advances in peptide engineering are revolutionizing the development of targeted therapies. Computational tools, such as machine learning and bioinformatics, enable the design of peptides with heightened specificity for AD-related proteins like Aβ and tau. For instance, computer simulations can model peptide interactions with pathological aggregates, guiding the creation of inhibitors with optimized binding and stability. Chemical enhancements, including structural modifications like cyclization or the incorporation of non-natural amino acids, bolster peptide resilience against enzymatic degradation and improve BBB penetration[174].

Peptide-loaded nanomaterials offer a promising platform for personalized AD therapy by targeting specific disease subtypes. For APOE ε4 carriers, nanoparticles conjugated with ApoE-mimetic peptides like COG1410 help restore lipid transport and reduce neuroinflammation. In sporadic late-onset AD, multifunctional systems co-targeting vascular damage (e.g., using angiopep-2 for BBB repair) and amyloid plaques can enhance therapeutic outcomes. Tau-predominant subtypes benefit from dendrimer-based delivery of kinase inhibitors (e.g., GSK-3β blockers) coupled with tau-specific cell-penetrating peptides to inhibit tau aggregation. For early-onset familial AD, CRISPR-loaded nanocarriers can correct APP or PSEN mutations, while simultaneously delivering Aβ-clearing peptides to address downstream pathology. This tailored approach enhances efficacy by aligning therapeutic mechanisms with subtype-specific disease drivers.

Concurrently, nanomaterial innovation is expanding therapeutic possibilities. Stimuli-responsive systems, such as pH- or temperature-sensitive nanoparticles, allow precise drug release in disease-specific microenvironments (e.g., acidic endosomes or inflamed brain regions). Hybrid platforms combining organic polymers with inorganic elements (e.g., gold or silica) integrate multifunctional capabilities, such as simultaneous drug delivery and imaging. Biomimetic designs, inspired by natural structures like cell membranes, enhance biocompatibility and targeting efficiency, exemplified by nanoparticles cloaked in BBB-mimicking coatings to improve brain uptake[23]. Personalized approaches aim to customize treatments based on genetic, molecular, and clinical data. Biomarkers like CSF Aβ42 or plasma tau levels enable patient stratification, ensuring therapies target specific pathological stages. Genomic insights into AD risk variants (e.g., APOE ε4) or tau mutations could inform the selection of peptide-loaded systems tailored to individual genetic profiles. For example, patients with aggressive tau pathology might receive nanomaterials delivering kinase inhibitors to curb hyperphosphorylation. Adaptive dosing regimens, informed by real-time biomarker monitoring, could further optimize efficacy while minimizing adverse effects[175].

The fusion of therapeutics with diagnostics (theranostics) offers unprecedented opportunities for early detection and treatment monitoring. Multimodal nanoparticles, equipped with contrast agents (e.g., gadolinium for MRI) and Aβ-targeting peptides, enable visualization of plaque reduction in real time. Non-invasive imaging techniques like PET scans can track nanoparticle distribution, providing insights into BBB traversal and target engagement. Additionally, nanosystems functionalized with probes for detecting soluble Aβ oligomers in blood or CSF could facilitate early diagnosis, allowing interventions before irreversible neuronal damage occurs[176]. Translating these advancements to the clinic demands robust regulatory frameworks and adaptive trial designs. Agencies like the FDA require comprehensive data on nanoparticle safety, including long-term biodistribution and toxicity profiles. Standardized protocols for manufacturing and quality control—ensuring batch consistency and stability—are critical for regulatory approval. Clinically, adaptive trial designs that adjust parameters based on interim results (e.g., modifying dosages or patient cohorts) can accelerate evaluation of multiple formulations. Patient-centric trials, incorporating feedback from individuals with AD, ensure endpoints like cognitive function or quality of life remain central to study goals. Peptide-loaded nanomaterials stand at the forefront of AD therapy innovation, offering precision, adaptability, and multifunctionality. By harnessing computational design, personalized strategies, diagnostic integration, and regulatory collaboration, these systems hold immense potential to transform AD care. As research progresses, the focus must remain on bridging laboratory discoveries with clinical needs, ultimately delivering hope and improved outcomes for patients navigating this complex disease[177].

9. CONCLUSION

Peptide-loaded nanomaterials embrace innovative potential in revolutionizing AD therapy, driven by strategic advancements across multiple domains. Novelties in molecular engineering are refining the precision and efficacy of these systems, enabling targeted delivery to pathological sites. Precision medicine approaches are progressing healthcare by designing treatments based on a patient's unique genetic, molecular, and biochemical characteristics. This tailored methodology improves treatment efficacy and reduces unintended side effects by aligning therapies

with individual biological markers and disease mechanisms. The combination of diagnostic imaging tools with therapeutic platforms facilitates real-time monitoring and early intervention, enhancing both detection and treatment responsiveness. Simultaneously, navigating regulatory landscapes and executing adaptive clinical trial designs are pivotal for translating laboratory breakthroughs into viable patient solutions. By listing these focal areas, the scientific community can fully leverage the capabilities of peptide-based nanosystems, escorting in a new era of Alzheimer's care characterized by hope, innovation, and transformative patient outcomes.

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