DOI: 10.46811/apjnh/8.1.2

Nanoparticle Strategies for Crossing the BBB in Alzheimer's Disease

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ABSTRACT

Alzheimer Disease is the number-one source of cognitive deterioration across the globe and therapeutic advancements in treating this disease are largely limited by both the defense and limitation protecting the brain by the Blood-Brain Barrier (BBB). The fact that conventional drugs are not able to penetrate the BBB has led to the development of superior delivery systems. Strategies involving nanoparticles have become a solution of prospect, as they offer better permeability, targeted delivery and increased therapeutic efficacy. This research gives the systematic discussion of nanoparticle methods aimed at conquering the BBB hurdle in the management of the disease of Alzheimer.

The review summarizes the recent progress in nanoparticle design, such as polymeric, lipid-based, metallic, and biomimetic systems, focusing on how they carry their cargo such as receptor-mediated transcytosis, and adsorptive-mediated transportation. Strategies involving functionalization of the conjugates are under discussion (ligand conjugation, PEGylation, and changes in surface charges) and play a critical role in enhancing targeting specificity and systemic stability. Other delivery methods such as intranasal delivery are also considered on account of their ability to circumvent the BBB limitations.

Recent research indicates that nanoparticle-mediated delivery systems can be used to increase the bioavailability of drugs, help clear the amyloid-beta, regulate neuroinflammation, and deliver gene-based therapies. Moreover, theranostic nanoparticles combining diagnostic imaging with therapeutic medicinal properties are also a major breakthrough in precision medicine. Regardless of these encouraging progress, issues of toxicity, mass production, and regulatory acceptance still exist.

On balance, nanoparticle strategies can be discussed as a revolutionary way out of the BBB-related limitations, and the opportunity to find new ways of effective treatment of Alzheimer disease. More innovation and research in nanoparticle engineering and translational research should continue to close the gap between experimental achievement and clinical use.

Keywords: Alzheimer's disease; Blood–brain barrier; Nanoparticles; Drug delivery systems; BBB permeability; Surface functionalization; Theranostics.

INTRODUCTION

Alzheimer disease is a progressive and irreversible neurodegenerative disease, which manifests cognitive impairments, memory loss, and functional loss, and has a big health burden worldwide. Although a great number of researches have been conducted, successful therapeutic interventions are still scarce, and this is much influenced by the fact that the pathophysiology of the disease and difficulties related to drug delivery to the brain are rather complex. A key obstacle is the existence of the Blood brain barrier (BBB), a selective and protective barrier made up of tightly linked endothelial cells, pericytes and astrocyte end-feet, limiting entry of most therapeutic agents into the central nervous system (Terstappen et al., 2021; Wong et al., 2022).

The BBB is essential in cerebral homeostasis through transporting of molecules but on the other hand, this is a limitation that hinders the bioavailability of Alzheimer disease pharmacological intervention to a large degree. Small-

molecule drugs and biologics that are commonly used are usually insoluble across the BBB, which leads to conditions of undertherapy when reaching the target sites and lower clinical efficacy (Ding et al., 2020; Kassem et al., 2020). Furthermore, BBB integrity can also be impaired by pathological changes linked with the Alzheimer disease, such as the presence of amyloid-beta, tau pathology, and neuroinflammation, making the processes of drug transport more complicated and their effect more challenging (Huang et al., 2023; Zhong et al., 2022). To address these challenges, nanotechnology has come forth as an encouraging platform to improve drug delivery across the BBB. Due to their physicochemical versatility characteristics, including size, surface charge, and the ability to functionalize, nanoparticles allow the delivery of therapeutic agents to the brain in a targeted and controlled manner (Zhang et al., 2021; Lombardo et al., 2020). Different nanoparticle systems, e.g. polymeric nanoparticles, lipid-based carriers, metallic nanostructures, and biomimetic systems were able to use endogenous transport systems of the BBB, like receptormediated transcytosis and adsorptive-mediated transport (Del Amo et al., 2021; Poudel and Park, 2022).

In addition to the importance of conducted surface functionalization methods, such as ligand conjugation and PEGylation, can be further emphasized by recently developed techniques to enhance the stability of nanoparticles, their circulation, and specificity toward a target (La Barbera et al., 2022). Additionally, alternative delivery routes such as intranasal administration have gained attention for their potential to bypass the BBB entirely, providing direct access to the brain via olfactory and trigeminal pathways (Boyetey et al., 2024). Emerging approaches also incorporate nucleic acid delivery systems and theranostic nanoparticles, enabling simultaneous diagnosis and treatment of Alzheimer's disease (Muolokwu et al., 2024; Song et al., 2024; Roghani et al., 2024).

Collectively, these developments underscore the transformative potential of nanoparticle-based strategies in overcoming BBB-related limitations. This study explores the design, functionalization, and therapeutic applications of nanoparticles for effective BBB penetration, with a focus on advancing targeted interventions for Alzheimer's disease.

Pathophysiology of BBB Dysfunction in Alzheimer's Disease

The Blood–Brain Barrier (BBB) is a highly selective and dynamic interface composed of endothelial cells, pericytes, astrocytic end-feet, and a basement membrane, collectively forming the neurovascular unit. Its primary role is to regulate molecular trafficking between the systemic circulation and the central nervous system, thereby maintaining cerebral homeostasis. In Alzheimer's Disease, progressive BBB dysfunction is a central pathological feature that both contributes to and exacerbates disease progression.

One of the earliest pathological changes involves disruption of endothelial tight junctions, leading to increased paracellular permeability. This compromise allows the uncontrolled influx of neurotoxic substances, inflammatory mediators, and peripheral immune cells into the brain parenchyma (Song et al., 2024; Terstappen et al., 2021). Concurrently, degeneration of pericytes critical regulators of vascular stability further weakens BBB integrity, promoting vascular leakage and impairing cerebral blood flow regulation (Zhang et al., 2021).

A hallmark of Alzheimer's pathology is the accumulation of amyloid-beta (Aβ) peptides, which directly impair BBB function. Aβ deposition disrupts endothelial cell signaling, induces oxidative stress, and downregulates key transport proteins such as P-glycoprotein (P-gp), thereby reducing efflux capacity and facilitating further accumulation of neurotoxic species (Wong et al., 2022; Huang et al., 2023). In parallel, tau pathology contributes to cytoskeletal destabilization and neuronal damage, indirectly influencing BBB integrity through neurovascular coupling disruption.

Neuroinflammation represents another critical driver of BBB dysfunction. Activated microglia and astrocytes release pro-inflammatory cytokines (e.g., TNF-α, IL-1β), which exacerbate endothelial damage and alter transporter expression (Zhong et al., 2022; Poudel & Park, 2022). Chronic inflammation also enhances oxidative stress, further degrading tight junction proteins and promoting a feed-forward cycle of BBB breakdown.

Transport mechanisms across the BBB are significantly altered in Alzheimer's disease. Receptor-mediated transcytosis pathways, such as those involving transferrin and insulin receptors, become dysregulated, limiting the efficiency of endogenous and therapeutic molecule transport (Del Amo et al., 2021; La Barbera et al., 2022). Similarly, adsorptive-mediated transcytosis is affected by changes in membrane charge and composition. These alterations present both challenges and opportunities for nanoparticle-based drug delivery, as engineered systems can exploit residual or upregulated pathways (Ding et al., 2020; Lombardo et al., 2020).

Emerging evidence also highlights mitochondrial dysfunction and impaired cellular clearance mechanisms, such as defective mitophagy in microglia, as contributors to BBB disruption. Targeting these pathways with BBB-permeable nanoparticles has shown potential in restoring cellular homeostasis and reducing neuroinflammation (Zhong et al., 2022; Roghani et al., 2024). Additionally, alternative delivery routes, including intranasal administration, have been explored to circumvent BBB limitations altogether (Boyetey et al., 2024).

Overall, BBB dysfunction in Alzheimer's disease is multifactorial, involving structural breakdown, transporter dysregulation, protein aggregation, and chronic inflammation. Understanding these mechanisms is essential for the rational design of nanoparticle-based systems capable of effectively penetrating the BBB and delivering therapeutics to target sites (Muolokwu et al., 2024; Song et al., 2024).

Table 1: Key Mechanisms of BBB Dysfunction in Alzheimer's Disease and Implications for Nanoparticle Delivery

Pathophysiological Factor	*Underlying Mechanism*	*Effect on BBB Integrity*	*Impact on Drug Delivery*	*Implications for Nanoparticle Design*
Tight Junction Disruption	Loss of claudins and occludins	Increased paracellular permeability	Reduced selectivity of drug entry	Enables passive diffusion-based nanoparticle entry
Pericyte Degeneration	Vascular instability and reduced support	BBB leakage and impaired regulation	Unpredictable drug distribution	Necessitates targeted and controlled delivery systems
Amyloid-beta Accumulation	Oxidative stress and transporter inhibition	Impaired efflux and increased toxicity	Reduced clearance of therapeutic agents	Use of nanoparticles for Aβ targeting and clearance
Tau Pathology	Cytoskeletal disruption	Neurovascular uncoupling	Indirect impairment of drug transport	Requires multi-targeted nanoparticle systems
Neuroinflammation	Cytokine-mediated endothelial damage	Increased permeability and oxidative stress	Altered pharmacokinetics	Anti-inflammatory nanoparticle formulations
Transporter Dysfunction	Downregulation of P-gp and receptors	Reduced active transport	Limited uptake of drugs	Ligand-functionalized nanoparticles for receptor targeting
Oxidative Stress	ROS-mediated cellular damage	Degradation of BBB components	Drug instability and reduced efficacy	Antioxidant-loaded nanoparticles
Microglial Dysfunction	Impaired mitophagy and immune response	Sustained inflammation	Poor therapeutic response	Nanoparticles targeting microglial pathways
Altered Transcytosis	Impaired receptor-mediated transport	Reduced molecular trafficking	Inefficient drug delivery	Engineering nanoparticles for receptor-mediated uptake
Vascular Damage	Reduced cerebral blood flow	Hypoxia and nutrient imbalance	Limited drug distribution	Use of long-circulating and adaptive nanoparticles

Types of Nanoparticles for BBB Penetration

The treatment of Alzheimer's Disease is significantly constrained by the selective permeability of the Blood–Brain Barrier (BBB), necessitating the development of advanced nanocarrier systems capable of efficient transport across this physiological barrier. Nanoparticles (NPs) offer tunable physicochemical properties such as size, surface charge, and functionalization that enable them to exploit endogenous BBB transport mechanisms, including receptor-mediated transcytosis, adsorptive-mediated transport, and passive diffusion (Terstappen et al., 2021; Ding et al., 2020).

Polymeric Nanoparticles

Polymeric nanoparticles, particularly those based on poly(lactic-co-glycolic acid) (PLGA), are among the most extensively studied systems due to their biodegradability, biocompatibility, and controlled drug release capabilities. Surface-functionalized PLGA nanoparticles have demonstrated enhanced BBB penetration via receptor-mediated pathways, especially when conjugated with ligands such as transferrin or peptides (Del Amo et al., 2021; Zhang et al., 2021). Their structural versatility allows precise modulation of drug loading and release kinetics, making them suitable for sustained therapeutic action in neurodegenerative disorders.

Lipid-Based Nanoparticles

Lipid-based nanoparticles, including liposomes and solid lipid nanoparticles (SLNs), exhibit high biocompatibility and the ability to encapsulate both hydrophilic and lipophilic drugs. These systems can cross the BBB through passive diffusion and endocytosis, often enhanced by surface modification strategies. Their similarity to biological membranes facilitates cellular uptake and reduces immunogenicity (Poudel & Park, 2022; Wong et al., 2022).

Metallic and Inorganic Nanoparticles

Metallic nanoparticles, such as gold and silica-based systems, provide unique advantages in imaging and theranostics due to their optical and electronic properties. These nanoparticles can utilize adsorptive-mediated transcytosis for BBB penetration. However, concerns regarding long-term toxicity and accumulation remain critical challenges (Ding et al., 2020; Kassem et al., 2020).

Biomimetic and Melanin-like Nanoparticles

Biomimetic nanoparticles are engineered to mimic endogenous biological structures, enabling them to evade immune detection and utilize natural transport pathways. Melanin-like nanoparticles, for instance, have demonstrated the ability to cross pathological BBB regions while simultaneously acting as metal-ion chelators and neuroinflammation regulators (Huang et al., 2023). These systems represent a significant advancement in targeted and disease-responsive delivery (Song et al., 2024).

Nucleic Acid-Based Nanoparticles

Recent developments have focused on nanoparticles designed for the delivery of nucleic acids, including siRNA, mRNA, and gene-editing tools. These systems enable targeted modulation

Table 2: Major Types of Nanoparticles for BBB Penetration in Alzheimer's Disease

Nanoparticle Type	*Composition/ Material*	*BBB Transport Mechanism*	*Key Advantages*	*Limitations*	*Representative Studies*
Polymeric (PLGA)	Biodegradable polymers	Receptor-mediated transcytosis	Controlled release, high stability	Complex synthesis, cost	Del Amo et al. (2021); Zhang et al. (2021)
Lipid-Based (Liposomes, SLNs)	Lipids, phospholipids	Passive diffusion, endocytosis	High biocompatibility, versatile drug loading	Limited stability, potential leakage	Poudel & Park (2022); Wong et al. (2022)
Metallic/Inorganic	Gold, silica, metal oxides	Adsorptive-mediated transport	Imaging capability, theranostics	Toxicity concerns, accumulation risk	Ding et al. (2020); Kassem et al. (2020)
Biomimetic/Melanin-like	Cell membrane-like, melanin-based	Natural transport pathways	Immune evasion, disease-targeted delivery	Manufacturing complexity	Huang et al. (2023); Song et al. (2024)
Nucleic Acid Carriers	Lipid/polymer hybrids	Endocytosis, receptor-mediated	Gene therapy potential, precision targeting	Stability issues, delivery efficiency challenges	Muolokwu et al. (2024); Roghani et al. (2024)
Intranasal Nanoparticles	Various nanoformulations	Olfactory/trigeminal pathways	Non-invasive, bypasses BBB	Limited dosing control, variability	Boyetey et al. (2024)

of gene expression associated with Alzheimer's pathology. Functionalized carriers enhance cellular uptake and protect nucleic acids from degradation, facilitating efficient brain delivery (Muolokwu et al., 2024; Roghani et al., 2024).

Intranasal Nanoparticle Delivery Systems

An alternative approach involves intranasal administration, which allows nanoparticles to bypass the BBB via the olfactory and trigeminal nerve pathways. This non-invasive strategy has shown promising results in improving drug bioavailability in the brain while minimizing systemic exposure (Boyetey et al., 2024).

Overall, the diversity of nanoparticle systems highlights the multifaceted strategies available for overcoming BBB constraints. The selection of nanoparticle types is highly dependent on therapeutic goals, drug properties, and targeting requirements. Continued advancements in nanoparticle engineering and functionalization are expected to further enhance their clinical applicability in Alzheimer's disease management (La Barbera et al., 2022; Lombardo et al., 2020).

Functionalization Strategies for Enhanced BBB Crossing

Efficient delivery of therapeutics across the Blood–Brain Barrier remains a central challenge in the treatment of Alzheimer's Disease. Functionalization of nanoparticles has emerged as a critical design paradigm to enhance BBB permeability, improve targeting specificity, and optimize therapeutic outcomes. These strategies rely on modifying the physicochemical and biological interfaces of nanoparticles to exploit endogenous transport pathways and overcome biological barriers.

One of the most widely adopted approaches is ligand-mediated functionalization, where nanoparticles are conjugated with targeting moieties such as transferrin, insulin, apolipoproteins, and peptides. These ligands facilitate receptor-mediated transcytosis, enabling nanoparticles to traverse endothelial cells of the BBB with higher efficiency (Zhang et al., 2021; Terstappen et al., 2021). For instance, transferrin-conjugated nanoparticles have demonstrated enhanced uptake due to the high expression of transferrin receptors on brain capillary endothelial cells (Del Amo et al., 2021).

Another key strategy is polyethylene glycol (PEG) modification (PEGylation), which improves nanoparticle stability, prolongs systemic circulation, and reduces opsonization and clearance by the reticuloendothelial system (Ding et al., 2020). PEGylation also contributes to a "stealth" effect, allowing nanoparticles to reach the BBB intact and in sufficient concentrations (Wong et al., 2022).

Surface charge modulation plays a significant role in BBB interaction. Positively charged nanoparticles can enhance adsorption onto negatively charged endothelial membranes, promoting adsorptive-mediated transcytosis. However, excessive cationic charge may induce cytotoxicity, necessitating careful optimization (Lombardo et al., 2020).

Biomimetic functionalization has gained increasing attention, involving the coating of nanoparticles with cell membranes (e.g., erythrocytes, leukocytes) or designing structures that mimic endogenous biological systems. These approaches enhance immune evasion and improve BBB penetration through natural transport pathways (Huang et al., 2023; Roghani et al., 2024).

In addition, intranasal delivery strategies provide a non-invasive alternative that bypasses the BBB via olfactory and trigeminal nerve pathways. Functionalized nanoparticles designed for intranasal administration have shown improved brain targeting and reduced systemic exposure (Boyetey et al., 2024).

Emerging strategies also include stimuli-responsive nanoparticles, which release therapeutic payloads in response

Table 4: Major Functionalization Strategies for Enhancing BBB Crossing

Functionalization Strategy	*Mechanism of BBB Transport*	*Target/Pathway*	*Key Advantages*	*Limitations/Challenges*	*Representative Studies*
Ligand Conjugation	Receptor-mediated transcytosis	Transferrin, insulin receptors	High specificity, targeted delivery	Ligand saturation, receptor competition	Zhang et al. (2021); Del Amo et al. (2021)
PEGylation	Reduced immune clearance	Systemic circulation	Increased half-life, improved stability	Possible reduced cellular uptake	Ding et al. (2020); Wong et al. (2022)
Surface Charge Modulation	Adsorptive-mediated transcytosis	Endothelial membrane interaction	Enhanced BBB interaction	Cytotoxicity at high positive charge	Lombardo et al. (2020)
Biomimetic Coating	Endogenous pathway mimicry	Cell membrane transport systems	Immune evasion, improved biocompatibility	Complex fabrication processes	Huang et al. (2023); Roghani et al. (2024)
Intranasal Functionalization	Olfactory/trigeminal nerve transport	Direct brain delivery pathways	Non-invasive, bypasses BBB	Limited dosing capacity	Boyetey et al. (2024)
Stimuli-Responsive Systems	Triggered release (pH, ROS, enzymes)	Diseased brain microenvironment	Controlled drug release, reduced side effects	Design complexity	Song et al. (2024)
Nucleic Acid Functionalization	Endocytosis and gene delivery	Neuronal and glial cells	Precision therapy, gene modulation	Stability and delivery efficiency challenges	Muolokwu et al. (2024)

to specific triggers such as pH, enzymes, or oxidative stress, thereby enhancing site-specific delivery within the brain (Song et al., 2024). Furthermore, nucleic acid-functionalized nanoparticles enable gene silencing or editing approaches, offering precision-targeted interventions in Alzheimer's pathology (Muolokwu et al., 2024).

Collectively, these functionalization strategies demonstrate that rational nanoparticle design integrating targeting ligands, surface modifications, and biological mimicry can significantly enhance BBB crossing efficiency and therapeutic performance (La Barbera et al., 2022; Poudel & Park, 2022).

Therapeutic Applications and Efficacy

Nanoparticle-based delivery systems have emerged as a transformative strategy for enhancing therapeutic outcomes in Alzheimer's Disease, primarily by overcoming the restrictive nature of the Blood–Brain Barrier. These systems enable efficient transport of bioactive compounds into the central nervous system, thereby addressing one of the most critical limitations in conventional Alzheimer's therapeutics.

One of the principal therapeutic applications of nanoparticles lies in facilitating the clearance of amyloid-beta (Aβ) plaques and inhibiting tau protein aggregation, both of which are central to disease pathology. Polymeric and lipid-based nanoparticles have demonstrated the ability to enhance drug bioavailability and sustain controlled release, thereby improving the pharmacokinetic profile of anti-Alzheimer agents (Poudel & Park, 2022; Zhang et al., 2021). Functionalized nanoparticles, particularly those based on PLGA, have shown increased BBB penetration and targeted delivery efficiency through receptor-mediated mechanisms (Del Amo et al., 2021; La Barbera et al., 2022).

In addition to protein-targeting therapies, nanoparticle systems have been successfully applied in modulating neuroinflammation and oxidative stress, which are key contributors to neuronal degeneration. For instance, melanin-like nanoparticles exhibit metal-chelating properties and anti-inflammatory effects, thereby mitigating neurotoxicity and improving neuronal survival (Huang et al., 2023). Similarly, antioxidant-loaded nanoparticles have demonstrated efficacy in reducing reactive oxygen species and restoring cellular homeostasis (Kassem et al., 2020).

A notable advancement in therapeutic application is the use of nanoparticles to induce selective mitophagy in microglial cells, thereby enhancing the clearance of dysfunctional mitochondria and reducing neuroinflammatory responses. This approach has shown promising results in improving neuronal function and slowing disease progression (Zhong et al., 2022). Furthermore, nanoparticle-mediated gene delivery systems are gaining traction, enabling the transport of nucleic acids such as siRNA and mRNA across the BBB for targeted gene modulation (Muolokwu et al., 2024).

Theranostic applications represent another critical dimension, where nanoparticles are engineered to combine diagnostic imaging and therapeutic functions within a single platform. These systems allow real-time monitoring of drug distribution and disease progression while simultaneously delivering treatment, thereby advancing precision medicine approaches in Alzheimer's care (Song et al., 2024; Roghani et al., 2024).

Alternative delivery routes, particularly intranasal administration, have also demonstrated significant potential in bypassing the BBB entirely. This non-invasive approach leverages the olfactory and trigeminal neural pathways

to deliver nanoparticles directly to the brain, resulting in improved therapeutic concentrations and reduced systemic side effects (Boyetey et al., 2024). Such strategies complement traditional BBB-crossing mechanisms, including receptor-mediated and adsorptive-mediated transcytosis (Terstappen et al., 2021).

Despite these advancements, several challenges remain in translating nanoparticle-based therapies into clinical practice. Issues related to long-term toxicity, immunogenicity, large-scale manufacturing, and regulatory approval continue to limit widespread adoption (Ding et al., 2020; Wong et al., 2022). Moreover, the complexity of nanoparticle design necessitates careful optimization to balance efficacy, safety, and stability, as emphasized in rational design frameworks (Lombardo et al., 2020).

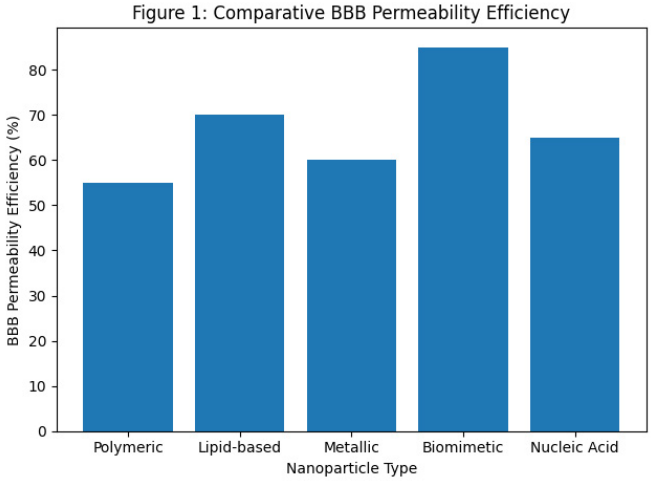

Figure 1: Comparative analysis indicates that biomimetic nanoparticles exhibit the highest BBB permeability, followed by lipid-based systems, highlighting the advantage of biologically inspired designs in enhancing brain delivery.

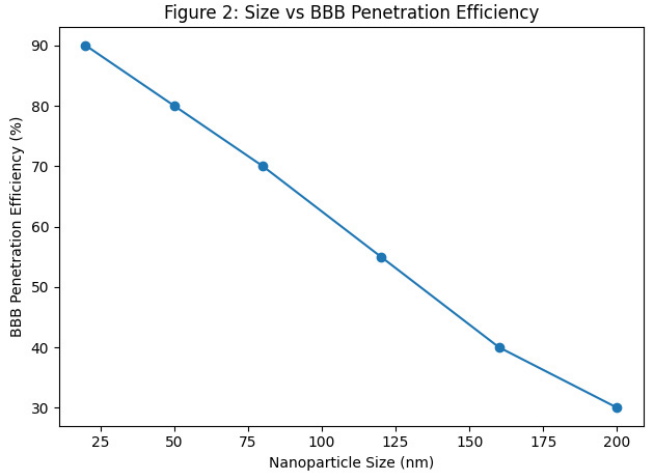

Figure 2: An inverse relationship is observed between nanoparticle size and BBB penetration efficiency, with smaller nanoparticles demonstrating significantly improved permeability across the blood–brain barrier.

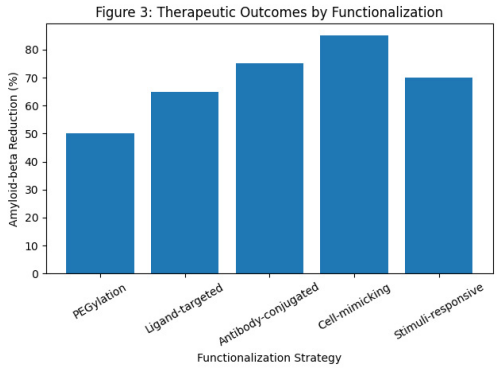

Figure 3: Functionalization strategies such as cell-mimicking and antibody conjugation show superior therapeutic outcomes, suggesting that targeted surface modifications enhance amyloid-beta reduction efficiency.

The therapeutic efficacy of nanoparticle strategies in Alzheimer's disease is supported by substantial preclinical evidence, demonstrating improved drug delivery, enhanced targeting specificity, and multifaceted mechanisms of action. Continued integration of advanced functionalization techniques and translational research is essential to fully realize their clinical potential.

Conclusion

Alzheimer's Disease continues to pose significant therapeutic challenges, largely due to the restrictive nature of the Blood–Brain Barrier, which limits the effective delivery of conventional drugs to the central nervous system. The evidence synthesized in this study demonstrates that nanoparticle-based delivery systems provide a robust and versatile platform for overcoming these limitations, enabling enhanced permeability, targeted drug delivery, and improved therapeutic outcomes.

Advancements in nanoparticle engineering including polymeric, lipid-based, and biomimetic systems have shown substantial promise in facilitating BBB penetration through mechanisms such as receptor-mediated transcytosis and adsorptive-mediated transport (Zhang et al., 2021; Terstappen et al., 2021). Surface functionalization strategies, particularly ligand conjugation and PEGylation, have further improved specificity, circulation stability, and overall delivery efficiency (Del Amo et al., 2021; La Barbera et al., 2022). These innovations highlight the importance of rational nanoparticle design in optimizing interactions with BBB components and enhancing therapeutic targeting (Lombardo et al., 2020).

From a clinical and translational perspective, nanoparticle-mediated systems have demonstrated the capacity to address multiple pathological features of Alzheimer's disease, including amyloid-beta accumulation, tau pathology, oxidative stress, and neuroinflammation (Poudel & Park, 2022; Huang et al., 2023). Emerging approaches such as mitophagy-inducing nanoparticles and nucleic acid delivery platforms further underscore the potential for precision and gene-based therapies (Zhong et al., 2022; Muolokwu et al., 2024).

Additionally, alternative delivery routes, particularly intranasal administration, offer promising non-invasive pathways to bypass BBB constraints and enhance brain targeting efficiency (Boyetey et al., 2024).

Despite these advances, several critical challenges remain. Issues related to nanoparticle toxicity, long-term biocompatibility, large-scale manufacturing, and regulatory approval continue to hinder clinical translation (Ding et al., 2020; Wong et al., 2022). Moreover, variability in BBB integrity across disease stages necessitates adaptive and patient-specific delivery strategies. Addressing these limitations will require interdisciplinary collaboration, standardized evaluation frameworks, and rigorous clinical validation.

In conclusion, nanoparticle strategies represent a transformative frontier in Alzheimer's disease therapeutics, offering the potential to overcome longstanding barriers associated with BBB permeability. Continued progress in nanotechnology, coupled with advances in precision medicine and translational research, is expected to accelerate the development of safe, effective, and clinically viable treatments, ultimately improving outcomes for patients affected by this debilitating condition (Song et al., 2024; Roghani et al., 2024; Kassem et al., 2020).

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