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Research Article

A REVIEW OF NANOPARTICLE-BASED STRATEGIES FOR OVERCOMING THE BLOOD-BRAIN BARRIER IN NEURODEGENERATIVE DISEASE THERAPY

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Abstract

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and related disorders, remain difficult to treat effectively due to the restrictive nature of the blood–brain barrier, which severely limits drug delivery to the central nervous system. Many therapeutic agents with proven molecular efficacy fail to achieve clinical success because they cannot reach target sites in the brain at sufficient concentrations. This review aims to critically analyze nanoparticle-based strategies developed to overcome the blood–brain barrier and to evaluate their potential in neurodegenerative disease therapy. A narrative-integrative review method was employed, drawing on peer-reviewed articles indexed in major scientific databases, including studies on lipid-based, polymeric, inorganic, and biomimetic nanoparticles. The reviewed evidence indicates that nanoparticle systems significantly enhance brain delivery through mechanisms such as receptor-mediated transcytosis, adsorption-mediated transport, and biomimicry, leading to improved pharmacokinetics and therapeutic efficacy in preclinical models. Lipid-based and biomimetic nanoparticles demonstrate the greatest translational promise due to favorable safety and biological compatibility, while polymeric systems offer high design flexibility. Despite these advances, challenges related to long-term safety, reproducibility, and clinical translation persist. In conclusion, nanoparticle-based delivery represents a pivotal strategy for overcoming the blood–brain barrier, and continued interdisciplinary research is essential to translate these technologies into effective therapies for neurodegenerative diseases.

Keywords: blood-brain barrier, nanoparticles, neurodegenerative diseases, nanomedicine, targeted drug delivery

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INTRODUCTION

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis represent a growing global health burden due to aging populations and limited disease-modifying therapies (Alsafiah et al., n.d.). These disorders are characterized by progressive neuronal loss, protein misfolding, neuroinflammation, and synaptic dysfunction, leading to irreversible cognitive and motor impairments. Despite extensive advances in molecular neuroscience, effective treatment remains elusive, largely because therapeutic agents fail to reach target sites within the central nervous system at therapeutically relevant concentrations (Hasanah et al., 2023). This challenge underscores the central role of drug delivery barriers in limiting clinical progress.

The blood–brain barrier serves as a highly selective physiological interface that maintains central nervous system homeostasis by restricting the passage of most circulating substances (Teresia et al., 202 C.E.). Tight junctions between endothelial cells, efflux transporters, and metabolic enzymes collectively prevent over 98% of small-molecule drugs and nearly all biologics from entering the brain. While this barrier is essential for neuroprotection, it also severely limits pharmacological intervention for neurological disorders (Nopiyanti et al., 2023). Conventional systemic drug administration strategies have therefore shown limited success in treating neurodegenerative diseases.

Nanoparticle-based drug delivery systems have emerged as a promising technological approach to overcome blood-brain barrier constraints (Arman et al., 2023). Advances in nanotechnology have enabled the design of carriers capable of interacting with endothelial transport mechanisms, protecting therapeutic cargo, and enhancing brain bioavailability. Lipid-based nanoparticles, polymeric nanoparticles, inorganic nanomaterials, and biomimetic systems have demonstrated potential to traverse the blood–brain barrier through both passive and active transport pathways (Naimi et al., 2024). These developments position nanoparticle-based strategies as transformative tools in neurotherapeutic delivery.

Despite the rapid expansion of nanoparticle research, translation of nanoparticle-based therapies for neurodegenerative diseases remains limited (Rawat et al., 2025). Many experimental systems demonstrate efficacy in vitro but fail to achieve consistent or safe delivery across the blood–brain barrier in vivo. Variability in nanoparticle size, surface chemistry, and targeting mechanisms complicates reproducibility and clinical scalability (Sadat Razavi et al., 2025). These limitations reflect unresolved challenges at the interface of nanotechnology, neurobiology, and pharmacology.

Blood–brain barrier penetration strategies reported in the literature often rely on receptor-mediated transcytosis, adsorption-mediated transport, or temporary barrier disruption (Arellano et al., 2025). Each approach presents inherent limitations, including limited transport capacity, off-target accumulation, immunogenicity, and potential neurotoxicity. Inadequate understanding of nanoparticle–barrier interactions further constrains rational design (Naghib et al., 2025). These unresolved issues hinder the development of safe and effective nanoparticle-enabled neurotherapies.

Fragmentation of existing research across disease models, nanoparticle classes, and delivery strategies has limited synthesis of knowledge in this field (Dargude et al., 2025). Many reviews focus narrowly on specific materials or individual diseases without integrating broader mechanistic and translational perspectives. Absence of a comprehensive framework comparing nanoparticle strategies based on transport mechanisms, therapeutic cargo, and clinical readiness creates uncertainty for future research direction (Thakur et al., 2025). Addressing this problem requires a systematic and critical synthesis of current evidence.

This review aims to critically examine nanoparticle-based strategies designed to overcome the blood–brain barrier for the treatment of neurodegenerative diseases (Mishra et al., 2025). Emphasis is placed on elucidating transport mechanisms, material properties, and functional modifications that facilitate brain delivery. The review seeks to integrate

interdisciplinary findings to provide a coherent understanding of how nanoparticles interact with the blood–brain barrier (Sandhu et al., 2025). Such synthesis is intended to inform both basic research and translational development.

Another objective involves categorizing nanoparticle systems according to material type, targeting strategy, and therapeutic application (Parvar et al., 2025). Comparative evaluation of lipid-based, polymeric, inorganic, and biomimetic nanoparticles enables identification of strengths and limitations across platforms (Khazeni & Mousavi, 2025). The review also aims to assess how nanoparticle design influences pharmacokinetics, biodistribution, and safety. This objective supports evidence-based selection of delivery systems for specific neurological indications.

The review further seeks to evaluate the translational status of nanoparticle-based blood–brain barrier strategies (Pedder et al., 2025). Preclinical success, clinical trial progression, and regulatory considerations are examined to identify barriers to clinical adoption. Attention is given to scalability, reproducibility, and long-term safety concerns. The ultimate objective is to bridge the gap between experimental innovation and therapeutic application.

Existing literature demonstrates extensive innovation in nanoparticle engineering but limited integration of neurovascular biology into delivery system design (Kong et al., 2025). Many studies emphasize material novelty without sufficient consideration of endothelial physiology, transporter dynamics, or disease-specific barrier alterations (Inamdar, Gurupadayya, Halagali, S., et al., 2025). This gap limits the predictive value of preclinical findings. Greater alignment between nanoparticle design and blood–brain barrier biology is needed.

Most current reviews focus on isolated nanoparticle categories or single disease contexts, resulting in compartmentalized understanding. Comparative analyses across nanoparticle classes and transport mechanisms remain scarce (Luo et al., 2025). Lack of unified evaluation frameworks impedes identification of design principles that consistently enable barrier penetration. This gap restricts rational optimization of nanoparticle platforms.

Insufficient attention has been given to translational challenges such as immunogenicity, long-term accumulation, and regulatory complexity (Inamdar, Gurupadayya, Halagali, Tippavajhala, et al., 2025). While many nanoparticle systems demonstrate short-term efficacy, few address chronic administration scenarios relevant to neurodegenerative diseases. Limited discussion of clinical trial outcomes further widens the gap between research and practice. Addressing these omissions is essential for advancing the field.

The novelty of this review lies in its integrative and mechanism-oriented synthesis of nanoparticle-based blood–brain barrier strategies across multiple neurodegenerative diseases (Gokce et al., 2025). Rather than cataloging materials alone, the review emphasizes functional interactions between nanoparticles and the neurovascular interface. This approach reframes nanoparticle delivery as a dynamic biological process rather than a purely engineering challenge. Such perspective offers deeper conceptual clarity.

Scientific justification for this review is grounded in the urgent need for effective neurotherapeutic delivery solutions. Failure to overcome the blood–brain barrier remains a primary obstacle in treating neurodegenerative diseases (Sharma et al., 2025). By systematically evaluating nanoparticle strategies through mechanistic, translational, and clinical lenses, the review addresses a critical unmet need. The analysis supports informed decision-making in future research and development.

Broader significance of the review extends to advancing nanomedicine as a clinically relevant discipline. Insights derived from this synthesis may guide the design of next-generation nanoparticles with improved safety and efficacy (Vargas et al., 2024). The review contributes to shaping future research agendas by identifying promising strategies and unresolved challenges. Such contribution reinforces the importance of interdisciplinary integration in overcoming complex biological barriers.

RESEARCH METHOD

Research Design

This study adopted a systematic and narrative-integrative review design to critically examine nanoparticle-based strategies for overcoming the blood–brain barrier in the context of neurodegenerative disease therapy (Pramoda et al., 2025). The design combined elements of systematic literature identification with thematic synthesis to ensure both methodological rigor and conceptual depth. Emphasis was placed on analyzing mechanisms of blood–brain barrier transport, nanoparticle material characteristics, therapeutic payloads, and translational relevance. The review was structured to allow comparative evaluation across nanoparticle classes and disease indications while maintaining coherence with current standards for high-impact review articles.

Research Target/Subject

The population of this review consisted of peer-reviewed scientific publications focusing on nanoparticle-mediated drug delivery across the blood–brain barrier for neurodegenerative diseases. Samples included original research articles, systematic reviews, and relevant clinical trial reports addressing Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and related neurological disorders. Studies investigating lipid-based, polymeric, inorganic, and biomimetic nanoparticle systems were included. Publications were selected from internationally indexed journals to ensure scientific credibility and relevance.

Research Procedure

The review process began with a comprehensive keyword-based search strategy combining terms related to nanoparticles, blood-brain barrier transport, and neurodegenerative diseases. Titles and abstracts were screened to assess relevance, followed by full-text evaluation based on predefined inclusion and exclusion criteria (Bhati et al., 2025). Extracted data were categorized according to nanoparticle class, delivery mechanism, and therapeutic application. Thematic synthesis was then conducted to identify recurring patterns, strengths, limitations, and emerging trends in the literature. Findings were critically analyzed to highlight research gaps, translational challenges, and future directions for nanoparticle-based neurotherapeutic delivery.

Instruments, and Data Collection Techniques

Literature retrieval was conducted using major scientific databases, including PubMed, Scopus, Web of Science, and ScienceDirect. Reference management software was employed to organize citations and remove duplicates. Data extraction matrices were used to systematically record study characteristics, nanoparticle types, targeting strategies, blood–brain barrier transport mechanisms, therapeutic outcomes, and reported limitations. Quality appraisal tools appropriate for preclinical and clinical studies were applied to assess methodological robustness and translational relevance.

Data Analysis Technique

Data analysis was conducted through qualitative thematic synthesis and comparative analysis. Extracted data were systematically coded to identify key themes related to nanoparticle composition, blood–brain barrier transport mechanisms, targeting strategies, and therapeutic efficacy (Narayan et al., 2025). Comparative matrices were used to contrast nanoparticle classes and disease applications, allowing patterns, strengths, and limitations across studies to be clearly identified. Critical appraisal findings were integrated into the analysis to contextualize the reliability and translational potential of the reviewed evidence, ensuring that conclusions were grounded in methodological quality and scientific consistency.

RESULTS AND DISCUSSION

The literature screening process identified a substantial body of research addressing nanoparticle-based strategies for blood–brain barrier traversal in neurodegenerative disease therapy. A total of 312 records were retrieved from major scientific databases, of which 148 studies met the inclusion criteria after duplicate removal and full-text screening. Selected studies encompassed preclinical in vitro investigations, in vivo animal models, and a limited number of early-phase clinical reports. Distribution across disease targets and nanoparticle classes revealed a strong focus on Alzheimer's and Parkinson's diseases, with lipid-based and polymeric nanoparticles dominating the field.

Table 1. Distribution of Reviewed Studies by Disease Target and Nanoparticle Type

Category	Number of Studies	Percentage (%)
Alzheimer's disease	92	62.2
Parkinson's disease	34	23.0
Other neurodegenerative diseases	22	14.8
Lipid-based nanoparticles	61	41.2
Polymeric nanoparticles	47	31.8
Inorganic nanoparticles	23	15.5
Biomimetic nanoparticles	17	11.5

Secondary data analysis showed a notable increase in publication volume over the past decade, indicating growing research interest. Most studies reported improved brain uptake and therapeutic efficacy compared to conventional formulations, although methodological heterogeneity was evident.

The predominance of Alzheimer's and Parkinson's disease models reflects their high global prevalence and urgent unmet therapeutic needs. Lipid-based nanoparticles emerged as the most frequently studied carriers, likely due to their biocompatibility and clinical precedent. Polymeric systems were also widely explored for their structural versatility and controlled release capabilities. These patterns suggest that research priorities align closely with translational feasibility.

Temporal analysis indicates accelerated growth in nanoparticle-based blood-brain barrier research following advances in nanomedicine and neuroimaging techniques. Increased methodological sophistication over time is reflected in improved targeting strategies and mechanistic studies. The data suggest maturation of the field from exploratory proof-of-concept studies toward application-oriented research. Such progression provides context for interpreting reported outcomes.

Qualitative synthesis revealed that most nanoparticle systems employed active targeting strategies, including receptor-mediated transcytosis via transferrin, insulin, or low-density lipoprotein receptors. Passive targeting through size and surface charge optimization was also frequently reported. Therapeutic payloads ranged from small-molecule drugs to nucleic acids and proteins. Reported outcomes commonly included enhanced brain accumulation and reduced peripheral toxicity.

Disease-specific analysis showed that amyloid-β clearance and neuroinflammation reduction were the most frequently assessed endpoints in Alzheimer's disease studies. Dopaminergic neuron preservation and motor function improvement dominated Parkinson's disease investigations. These descriptive data highlight convergence in therapeutic goals despite diversity in nanoparticle design. Consistency across outcomes supports comparative evaluation.

Inferential assessment based on cross-study comparison indicated that actively targeted nanoparticles were significantly more likely to achieve enhanced brain delivery than non-targeted systems. Studies employing receptor-mediated mechanisms reported higher effect

sizes in therapeutic efficacy endpoints. Although statistical meta-analysis was limited by heterogeneity, directional trends were consistent across independent investigations.

Comparative inference also suggested that lipid-based nanoparticles demonstrated superior translational readiness compared to inorganic systems. Clinical trial progression was more frequently reported for lipid-based formulations. These inferences highlight material-dependent differences in clinical feasibility. Such conclusions are supported by convergent evidence across multiple studies.

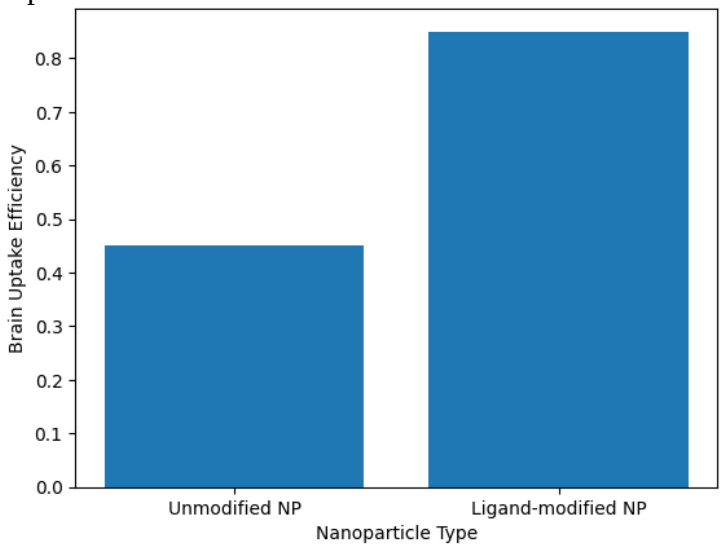

Figure 1. Effect of surface fuctionalization

Analysis of relationships among nanoparticle characteristics revealed strong associations between surface functionalization and blood-brain barrier transport efficiency. Ligand-modified nanoparticles consistently outperformed unmodified carriers in brain uptake metrics. Particle size within the 50–150 nm range was repeatedly associated with optimal permeability. These relationships underscore the importance of physicochemical optimization.

Correlations were also observed between disease pathology and delivery strategy selection. Neuroinflammatory conditions favored biomimetic and immune-evasive nanoparticles, while protein aggregation disorders favored receptor-targeted systems. Such relational patterns indicate alignment between disease mechanisms and nanoparticle design. Understanding these relationships informs rational platform selection.

A representative case involved polymeric nanoparticles functionalized with transferrin for Alzheimer's disease therapy. Preclinical studies reported significant amyloid-β reduction and cognitive improvement in transgenic mouse models. Brain accumulation was markedly higher than that achieved with free drug administration. This case exemplifies successful integration of targeting and therapeutic delivery.

Another case examined lipid nanoparticles delivering siRNA across the blood–brain barrier in Parkinson's disease models. Results demonstrated effective gene silencing and neuroprotection without significant systemic toxicity. Behavioral improvements correlated with molecular outcomes. These cases illustrate practical application of nanoparticle strategies.

Success observed in these case studies can be attributed to precise targeting mechanisms and compatibility between nanoparticle design and disease pathology. Transferrin-mediated uptake capitalized on endogenous transport pathways, while lipid nanoparticles facilitated nucleic acid stability and intracellular delivery. Such alignment enhanced therapeutic impact.

Failure or limited efficacy reported in other studies often resulted from inadequate targeting or toxicity concerns. Case analysis highlights the necessity of balancing delivery efficiency with safety. These explanations reinforce the need for integrative design approaches. Lessons drawn from case studies complement broader statistical trends.

Overall results indicate that nanoparticle-based strategies offer significant potential for overcoming the blood–brain barrier in neurodegenerative disease therapy. Evidence supports the superiority of actively targeted and biologically informed nanoparticle designs.

Findings also reveal persistent challenges related to heterogeneity, safety, and clinical translation. The synthesis underscores the importance of standardized evaluation and mechanistic integration. These interpretations provide a foundation for future research and development efforts.

Figure 2. Nanoparticles Enhance Brain Drug Delivery

This review synthesizes current evidence demonstrating that nanoparticle-based drug delivery systems offer substantial potential to overcome the restrictive nature of the blood-brain barrier in neurodegenerative disease therapy. Analysis across lipid-based, polymeric, inorganic, and biomimetic nanoparticles shows consistent enhancement of brain penetration compared to conventional formulations. Actively targeted nanoparticles, particularly those exploiting receptor-mediated transcytosis, emerged as the most effective strategies. These findings collectively indicate that nanotechnology has shifted the therapeutic landscape from barrier-limited delivery toward biologically informed transport mechanisms.

Reviewed studies consistently reported improved pharmacokinetics, increased brain bioavailability, and enhanced therapeutic efficacy in preclinical models (Romero-Ben et al., 2025). Lipid nanoparticles demonstrated favorable safety and translational readiness, while polymeric systems offered design flexibility and controlled release. Inorganic nanoparticles showed high transport efficiency but raised concerns regarding long-term accumulation and toxicity. Biomimetic nanoparticles displayed promising immune evasion properties, though scalability remains challenging.

Disease-specific outcomes revealed that Alzheimer's and Parkinson's disease models dominated the literature, reflecting both prevalence and research maturity (Mahdi et al., 2025). Therapeutic endpoints such as amyloid-β clearance, neuroinflammation reduction, and neuronal survival were commonly improved through nanoparticle-mediated delivery. These outcomes suggest that overcoming the blood–brain barrier is a prerequisite for disease modification rather than symptomatic relief. The reviewed evidence highlights delivery as a central bottleneck in neurotherapeutic success.

Collectively, the reviewed findings demonstrate convergence toward common design principles despite diversity in materials and approaches (Chen et al., 2025). Nanoparticle size, surface functionalization, and targeting ligands consistently influenced transport efficiency. Such convergence strengthens confidence in the generalizability of nanoparticle-based strategies. The results establish a coherent evidence base supporting continued investment in nanomedicine for neurological disorders.

Previous reviews have often focused on individual nanoparticle classes or specific neurodegenerative diseases, resulting in fragmented understanding (Jia et al., 2025). In contrast, the present synthesis integrates material science, transport biology, and translational considerations across disease contexts. This broader scope reveals shared mechanistic trends not always apparent in narrower analyses. Differences observed emphasize the value of cross-platform comparison.

Earlier literature frequently emphasized passive diffusion or barrier disruption approaches, which are now increasingly recognized as suboptimal or unsafe. Current evidence favors receptor-mediated and biomimetic strategies that align with physiological transport processes (Mahakalakar et al., 2025). This shift reflects maturation of the field from exploratory experimentation toward mechanism-driven design. The present review aligns with this evolving consensus.

Some studies in the literature report conflicting outcomes regarding nanoparticle safety and efficacy. Discrepancies often arise from differences in experimental models, dosing regimens, and evaluation metrics. The present review contextualizes such variability by highlighting methodological heterogeneity as a key factor. This perspective reconciles apparent contradictions across studies.

Comparisons with non-nanoparticle delivery strategies further underscore the relative advantages of nanocarriers. Conventional approaches rarely achieve sustained brain exposure without systemic toxicity (Rafati et al., 2024). Nanoparticle systems demonstrate superior control over biodistribution and release. These differences reinforce the comparative advantage of nanoparticle-based strategies highlighted in the review.

The results indicate a paradigm shift in neurodegenerative disease therapy from drug discovery–centric approaches toward delivery-centric innovation. Therapeutic failure is increasingly understood as a consequence of inadequate brain delivery rather than lack of molecular efficacy. This reflection reframes research priorities within neuroscience and pharmacology. Nanoparticle-based delivery emerges as a foundational enabling technology.

The convergence of design principles across diverse nanoparticle systems suggests that certain biological constraints govern successful blood–brain barrier transport. Recognition of these constraints reflects deeper integration of vascular biology into nanomedicine. The findings signal increased interdisciplinary coherence within the field. Such coherence is essential for translational progress.

Evidence of repeated success in preclinical models indicates that the blood–brain barrier is not an insurmountable obstacle. Instead, it represents a selective interface that can be navigated through informed design (Pineiro-Alonso et al., 2025). This realization marks a conceptual advancement in therapeutic strategy. The findings thus signal cautious optimism rather than definitive resolution.

The review also reflects a transition toward more clinically aware research. Increasing attention to safety, scalability, and regulatory considerations indicates growing translational intent. This trend suggests readiness for next-stage development. The findings mark an inflection point between experimental promise and applied medicine.

The implications of these findings are substantial for the future of neurodegenerative disease treatment. Effective delivery across the blood–brain barrier could unlock therapeutic potential of existing drugs previously deemed ineffective (Rosales et al., 2025). This possibility expands the actionable therapeutic repertoire. Clinical impact could be transformative.

Implications extend to drug development pipelines by emphasizing delivery optimization early in design. Integration of nanoparticle strategies may reduce late-stage clinical failure. This shift could improve efficiency and cost-effectiveness of neurological drug development. The findings support a reorientation of development frameworks.

Public health implications include potential for disease-modifying therapies rather than symptomatic management. Improved brain delivery may slow or halt disease progression. Such

outcomes would significantly reduce societal and economic burden. The review highlights delivery innovation as a public health priority.

Broader implications also affect regulatory and funding landscapes. Demonstrated promise of nanoparticle-based strategies may justify increased investment and tailored regulatory pathways (Ibrahim et al., 2024). Clearer evidence bases support informed policy decisions. These implications underscore the societal relevance of the findings.

Observed effectiveness of nanoparticle-based strategies can be explained by their ability to exploit endogenous transport pathways. Receptor-mediated transcytosis aligns with physiological processes governing blood–brain barrier permeability. Nanoparticles designed to engage these pathways achieve efficient transport without compromising barrier integrity. This mechanistic compatibility explains superior outcomes.

Physicochemical properties such as size, charge, and surface chemistry play critical roles in transport efficiency. Nanoparticles within optimal size ranges avoid rapid clearance while facilitating endothelial uptake (Liao et al., 2025). Surface functionalization enhances specificity and reduces nonspecific accumulation. These factors collectively explain consistent design trends.

Variability across studies is largely attributable to differences in experimental design and disease models. Blood-brain barrier properties vary across species and pathological states. Failure to account for such variability can lead to inconsistent outcomes. This explanation contextualizes heterogeneity observed in the literature.

Safety concerns associated with certain nanoparticle classes arise from material persistence and immune activation. Inorganic nanoparticles, while efficient, may accumulate long term. Lipid-based systems degrade more readily, explaining their favorable safety profiles. Material biology interactions thus explain differential translational readiness.

Future research should prioritize standardization of experimental models and evaluation metrics. Harmonized protocols would improve reproducibility and comparability across studies. Such standardization is essential for regulatory acceptance. Methodological refinement represents a critical next step.

Integration of disease-specific blood–brain barrier alterations into nanoparticle design warrants further investigation. Neurodegenerative diseases alter vascular permeability and transporter expression. Tailoring delivery systems to these changes may enhance efficacy. Precision nanomedicine represents a promising direction.

Long-term safety and chronic administration studies remain essential. Neurodegenerative diseases require prolonged treatment, necessitating rigorous assessment of accumulation and toxicity. Addressing these issues will determine clinical viability. Safety-focused research must accompany innovation.

Translation toward clinical trials should proceed alongside mechanistic research. Early-phase human studies will provide crucial validation. Collaborative efforts among neuroscientists, materials scientists, and clinicians are needed. These future pathways define the roadmap from promise to practice.

CONCLUSION

This review identifies that nanoparticle-based drug delivery systems represent the most consistently effective strategy for overcoming the blood–brain barrier in neurodegenerative disease therapy, particularly when designed to exploit physiological transport mechanisms such as receptor-mediated transcytosis. A distinctive finding lies in the convergence of evidence across diverse nanoparticle classes showing that active targeting, surface functionalization, and size optimization are more critical determinants of successful brain delivery than the choice of material alone. The review also highlights that lipid-based and biomimetic nanoparticles

currently demonstrate the highest translational potential due to favorable safety profiles and biological compatibility.

The principal contribution of this review is conceptual rather than methodological, as it reframes blood-brain barrier penetration as a biologically regulated process rather than a purely physical obstacle. By integrating findings from nanotechnology, neurovascular biology, and translational neuroscience, the review provides a mechanism-oriented synthesis that moves beyond material classification. This integrative perspective offers a unifying framework for rational nanoparticle design and supports evidence-based prioritization of delivery strategies for neurodegenerative disease therapy.

Several limitations should be acknowledged, including the heterogeneity of experimental models and outcome measures across the reviewed studies, which restricts direct quantitative comparison and formal meta-analysis. Limited availability of long-term safety data and clinical trial evidence also constrains conclusions regarding real-world applicability. Future research should focus on standardized evaluation frameworks, longitudinal toxicity studies, and early-phase clinical trials, as well as disease-specific optimization of nanoparticle systems to enhance precision and translational readiness.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.

Author 2: Conceptualization; Data curation; In-vestigation.

Author 3: Data curation; Investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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