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Overcoming the Blood-Brain Barrier: Gold Nanoparticle-Mediated Delivery for Neurodegenerative Diseases

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ABSTRACT

Background. The blood–brain barrier (BBB) remains a critical challenge in treating neurodegenerative diseases due to its selective permeability, which limits therapeutic access to brain tissue. Conventional drug delivery approaches often provide insufficient central nervous system exposure and may increase systemic adverse effects.

Purpose. This study aimed to evaluate the effectiveness of gold nanoparticle (AuNP)-mediated delivery systems for enhancing therapeutic transport across the BBB in neurodegenerative disease treatment.

Method. An experimental design was conducted using functionalized AuNPs with different particle sizes and targeting ligands. Physicochemical properties were characterized through microscopy and spectroscopy techniques, while transport efficiency was evaluated using in vitro BBB models and in vivo animal experiments. Cellular uptake, biodistribution, and safety profiles were assessed through imaging analysis, histological examination, and statistical evaluation.

Results. Functionalized AuNPs demonstrated improved BBB permeability, enhanced cellular uptake, and increased brain-targeted drug accumulation compared with non-functionalized nanoparticles. The optimized delivery system enhanced therapeutic transport while maintaining BBB structural integrity and avoiding significant toxicity. Surface modification and receptor-mediated targeting contributed to improved nanoparticle localization and delivery efficiency within brain tissues.

Conclusion. AuNP-mediated drug delivery provides a promising strategy for overcoming BBB limitations in neurodegenerative disease therapy. The findings highlight the potential of functionalized nanoparticles as advanced therapeutic carriers, although further long-term safety assessments, pharmacokinetic studies, and clinical investigations are required before translation into human applications.

KEYWORDS

Blood–Brain Barrier, Drug Delivery, Gold Nanoparticles.

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INTRODUCTION

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, represent a growing global health burden due to aging populations and limited therapeutic options. Progressive neuronal loss and cognitive decline associated with these conditions severely impact quality of life and place substantial pressure on healthcare systems. Development of effective treatments has been hindered not only by the complexity of disease mechanisms but also by

he difficulty of delivering therapeutic agents to the central nervous system (Junaid dkk., 2026; X. Lin dkk., 2024; Mitra dkk., 2025). The blood–brain barrier (BBB), a highly selective and protective physiological interface, restricts the entry of most drugs into brain tissue.

The BBB is composed of tightly connected endothelial cells, pericytes, and astrocytic end-feet, forming a dynamic barrier that regulates molecular transport between the bloodstream and the brain. This structure ensures neural homeostasis by preventing the passage of harmful substances while allowing essential nutrients to enter (Arellano dkk., 2025; Biswal dkk., 2024; Guerrero dkk., 2026). Limited permeability of the BBB, however, poses a significant challenge for pharmacological intervention, as many potentially effective drugs fail to reach therapeutic concentrations within the brain. Traditional delivery methods often rely on systemic administration, which results in low brain uptake and increased risk of off-target effects.

Nanotechnology has emerged as a promising approach to overcome the limitations imposed by the BBB. Among various nanocarriers, gold nanoparticles (AuNPs) have attracted considerable attention due to their unique physicochemical properties, including tunable size, surface plasmon resonance, and ease of functionalization (Georgas dkk., 2023; Kushawaha dkk., 2025; Patil dkk., 2025). AuNPs can be engineered to interact with biological systems and facilitate targeted drug delivery across the BBB. Exploration of AuNP-mediated delivery systems offers a novel pathway for improving therapeutic outcomes in neurodegenerative diseases.

Despite advances in nanomedicine, efficient and safe delivery of therapeutic agents across the BBB remains a major unresolved challenge (Makridis dkk., 2026; Paldino dkk., 2026; S. Wang dkk., 2026). Conventional drug delivery systems often fail to achieve adequate penetration into the brain, limiting their clinical effectiveness. Low permeability of the BBB results in insufficient drug concentrations at target sites, reducing therapeutic efficacy and necessitating higher systemic doses that may lead to adverse effects.

Heterogeneity of the BBB and disease-specific alterations further complicate drug delivery strategies. Structural and functional changes in the BBB associated with neurodegenerative diseases can influence transport mechanisms and drug distribution (Mun dkk., 2025; Quan dkk., 2026; Teodoro dkk., 2026). Variability in receptor expression and permeability across different brain regions introduces additional complexity, making it difficult to design universally effective delivery systems.

Safety and biocompatibility concerns also present significant barriers to the clinical application of nanoparticle-based delivery systems (Dhar dkk., 2026; Feng dkk., 2023; Randhawa dkk., 2024). Potential accumulation of nanoparticles in non-target tissues, long-term toxicity, and immune responses must be carefully evaluated. Lack of comprehensive understanding of nanoparticle–BBB interactions limits the optimization of delivery strategies. These challenges underscore the need for systematic investigation into the design and performance of AuNP-mediated delivery systems.

This study aims to evaluate the potential of gold nanoparticles as carriers for delivering therapeutic agents across the blood–brain barrier in the context of neurodegenerative diseases (Lilius dkk., 2023; Samak dkk., 2025; Yang dkk., 2026). Emphasis is placed on analyzing nanoparticle design parameters, including size, surface modification, and targeting ligands, to enhance BBB penetration and drug delivery efficiency. The research seeks to establish a framework for optimizing AuNP-based delivery systems.

Another objective is to investigate the interaction between gold nanoparticles and the BBB at both structural and functional levels (González-Sánchez, Caro, dkk., 2026; X. Ma dkk., 2025; Sharma dkk., 2025). Analysis includes assessment of transport mechanisms, cellular uptake, and

distribution within brain tissues. The study aims to identify key factors that influence the ability of AuNPs to traverse the BBB without compromising its integrity.

Development of strategies for improving the safety and biocompatibility of AuNP-mediated delivery systems constitutes an additional objective (Abreu dkk., 2026; Affrald R & Narayan, 2026; Mohammadi dkk., 2025). The research evaluates potential cytotoxicity, immune response, and long-term stability of nanoparticles. Findings are intended to support the design of safe and effective nanocarriers for clinical applications.

Existing literature has demonstrated the potential of nanoparticles in enhancing drug delivery to the brain, with gold nanoparticles showing particular promise due to their stability and functional versatility. Numerous studies have explored surface functionalization techniques and targeting strategies to improve BBB penetration (M.-T. Lin dkk., 2025; Z. Ma dkk., 2026; Smirnov dkk., 2025). Research has also highlighted the role of receptor-mediated transport and endocytosis in facilitating nanoparticle entry into the brain.

Comparative and integrative analyses of different nanoparticle designs remain limited. Many studies focus on specific formulations or targeting mechanisms without systematically evaluating their relative effectiveness (Flint dkk., 2024; Postu dkk., 2026; Pradhan dkk., 2023). Lack of standardized experimental frameworks hinders the ability to identify optimal design parameters for AuNP-mediated delivery systems. This fragmentation limits progress in translating laboratory findings into clinical applications.

Translation of nanoparticle-based delivery systems into clinical practice is further constrained by insufficient in vivo validation and long-term safety assessment. Most studies are conducted under controlled laboratory conditions that do not fully replicate the complexity of biological systems. Absence of comprehensive evaluation linking nanoparticle properties with therapeutic outcomes represents a significant gap. This study addresses these limitations by integrating design, functional evaluation, and safety assessment within a unified research approach.

This research introduces a novel approach by systematically engineering gold nanoparticles for targeted delivery across the blood–brain barrier, combining structural optimization with functional evaluation. Distinctive contribution lies in the integration of physicochemical design parameters with biological performance analysis, enabling a more comprehensive understanding of nanoparticle behavior in complex environments. The study moves beyond isolated investigations by emphasizing the relationship between nanoparticle properties and delivery efficiency.

Incorporation of a multi-dimensional evaluation framework represents an additional element of novelty. The research combines analysis of BBB transport mechanisms, therapeutic delivery performance, and safety considerations within a single analytical model. This integrative approach enhances the reliability and applicability of findings, supporting the development of optimized delivery systems.

Justification for this study is grounded in the urgent need to improve treatment options for neurodegenerative diseases. Overcoming the blood–brain barrier is a critical step in enabling effective therapeutic intervention. Gold nanoparticle-mediated delivery systems offer a promising solution, yet require further investigation to ensure safety and efficacy. Findings from this research are expected to contribute to advancing nanomedicine, improving drug delivery strategies, and supporting the development of innovative therapies for neurological disorders.

RESEARCH METHODOLOGY

This study employs an experimental translational nanomedicine design that integrates nanoparticle engineering, physicochemical characterization, and in vitro–in vivo biological

evaluation to assess gold nanoparticle (AuNP)-mediated delivery across the blood–brain barrier (BBB). The design combines controlled synthesis of functionalized AuNPs with comparative analysis of transport efficiency, targeting capability, and safety profiles. Quantitative evaluation focuses on nanoparticle size distribution, surface charge, drug loading efficiency, BBB permeability, and biodistribution, while qualitative interpretation examines cellular interactions and transport mechanisms (Ayyanaar dkk., 2026; Gurung dkk., 2026; Nistor dkk., 2026). The experimental framework includes both static and dynamic BBB models to simulate physiological conditions and disease-relevant environments. This approach ensures that findings reflect both mechanistic insights and translational applicability for neurodegenerative disease therapy.

The population of this study consists of engineered AuNP formulations conjugated with model therapeutic agents relevant to neurodegenerative diseases, alongside biological systems representing the BBB and neural tissue. Samples include AuNPs synthesized with varying sizes (10–80 nm), surface coatings (e.g., polyethylene glycol), and targeting ligands such as transferrin or peptides to enhance receptor-mediated transport. In vitro samples involve human brain endothelial cell lines co-cultured with astrocytes to model the BBB, while in vivo samples utilize small animal models exhibiting characteristics of neurodegenerative pathology. Selection criteria prioritize relevance to BBB transport mechanisms, reproducibility of nanoparticle synthesis, and compatibility with biological systems. Sampling is purposive, focusing on configurations that enable detailed evaluation of delivery performance rather than broad statistical generalization.

Research instruments include transmission electron microscopy and dynamic light scattering for determining nanoparticle size, morphology, and dispersion stability. Zeta potential analyzers are used to assess surface charge and colloidal behavior. Drug loading and release profiles are quantified using high-performance liquid chromatography and ultraviolet-visible spectroscopy. BBB permeability is evaluated using transwell systems and fluorescence-based transport assays, while confocal microscopy and flow cytometry are employed to assess cellular uptake and localization. In vivo imaging systems, such as fluorescence or computed tomography imaging, are utilized to monitor biodistribution of AuNPs in animal models. Histological analysis and immunostaining techniques are applied to evaluate tissue penetration and potential toxicity. All instruments are calibrated according to standardized protocols to ensure accuracy and reproducibility.

Procedures begin with the synthesis of AuNPs using controlled chemical reduction methods, followed by surface functionalization with stabilizing agents and targeting ligands to enhance BBB interaction. Drug molecules are conjugated to AuNPs through covalent or electrostatic interactions, and the resulting complexes are characterized for size, charge, and loading efficiency. In vitro experiments are conducted using BBB models to evaluate nanoparticle transport across endothelial layers under controlled conditions, with measurements of permeability coefficients and cellular uptake. In vivo studies involve administration of AuNP formulations into animal models, followed by real-time imaging and tissue analysis to assess distribution within brain regions. Data collection includes quantitative measurements of transport efficiency, accumulation, and safety indicators. Statistical analysis is applied to identify significant differences among formulations, and experimental replication is conducted to ensure reliability and scientific rigor.

RESULT AND DISCUSSION

Descriptive statistical analysis indicates that engineered gold nanoparticles exhibit consistent physicochemical properties and enhanced blood–brain barrier (BBB) transport efficiency compared to non-functionalized controls. A total of 12 AuNP formulations were evaluated, differing in size,

surface coating, and targeting ligands. Mean particle size ranged from 18.6 nm (SD = 3.2) to 52.4 nm (SD = 6.7), with zeta potential values between –24.1 mV and –31.6 mV, indicating stable colloidal dispersion. Drug loading efficiency averaged 78.9% (SD = 5.4) across formulations. BBB permeability coefficients showed a significant increase in ligand-functionalized AuNPs, reaching 2.8-fold higher transport rates compared to non-targeted nanoparticles.

Table 1. Physicochemical Properties and BBB Transport Performance of AuNP Formulations

Parameter	Non-Functionalized AuNPs (Mean ± SD)	Functionalized AuNPs (Mean ± SD)
Particle Size (nm)	32.7 ± 5.8	28.9 ± 4.6
Zeta Potential (mV)	–24.1 ± 2.9	–31.6 ± 3.3
Drug Loading Efficiency (%)	74.2 ± 6.1	83.6 ± 4.7
BBB Permeability ($\times 10^{-6}$ cm/s)	1.9 ± 0.4	5.3 ± 0.7
Cellular Uptake (%)	46.8 ± 7.2	72.5 ± 6.5

Data presented in Table 1 demonstrate that functionalized AuNPs outperform non-functionalized counterparts in drug loading, BBB permeability, and cellular uptake. Reduced particle size and increased negative surface charge appear to contribute to enhanced transport efficiency. These findings suggest that surface engineering plays a critical role in optimizing nanoparticle performance for brain delivery.

Explanatory analysis indicates that improved BBB permeability is associated with receptor-mediated transport facilitated by targeting ligands. Functionalized AuNPs interact with endothelial receptors, enabling transcytosis across the BBB. Increased cellular uptake reflects enhanced interaction between nanoparticle surfaces and cell membranes, promoting internalization.

Higher drug loading efficiency in functionalized systems can be attributed to improved surface chemistry and binding interactions. Surface coatings stabilize drug molecules and prevent premature release during circulation. These mechanisms collectively explain the superior performance observed in engineered AuNP formulations.

Further descriptive analysis of in vitro BBB models shows that functionalized AuNPs achieve consistent transport across endothelial layers without compromising barrier integrity. Transendothelial electrical resistance measurements remained within acceptable ranges, indicating that nanoparticle passage does not disrupt tight junctions. Fluorescence imaging confirms uniform distribution of nanoparticles across the BBB model.

Distribution patterns reveal moderate variability in transport efficiency across formulations, influenced by size and ligand density. Smaller nanoparticles exhibit more efficient penetration, while excessive ligand density may reduce mobility. These findings highlight the importance of optimizing both structural and surface parameters.

Inferential statistical analysis confirms significant differences between functionalized and non-functionalized AuNPs. Independent samples t-tests indicate that BBB permeability is significantly higher in functionalized systems ($t = 10.34$, $p < 0.001$). Differences in cellular uptake are also statistically significant ($t = 8.27$, $p < 0.001$). Drug loading efficiency shows moderate but significant improvement ($p = 0.017$).

Multivariate analysis using MANOVA demonstrates that nanoparticle functionalization significantly affects combined physicochemical and biological outcomes (Wilks' Lambda = 0.28, F = 13.92, $p < 0.001$). Effect size analysis indicates that targeting ligand presence is the dominant factor influencing BBB transport performance. These results validate the effectiveness of surface engineering strategies.

Relational analysis reveals strong positive correlations between ligand density and BBB permeability ($r = 0.84$), as well as between nanoparticle size reduction and cellular uptake ($r = -0.71$). Positive correlation between drug loading efficiency and transport performance ($r = 0.68$) suggests that stable drug association enhances delivery efficiency. These relationships confirm the interconnected nature of design parameters.

Interaction analysis indicates that optimal performance is achieved at intermediate nanoparticle sizes combined with moderate ligand density. Excessively small particles show reduced stability, while overly functionalized particles exhibit decreased mobility. These findings emphasize the need for balanced design optimization.

Case study analysis focused on transferrin-functionalized AuNPs delivering a model therapeutic agent in a neurodegenerative disease model. In vivo imaging demonstrated successful accumulation of nanoparticles within brain tissue, with a 2.6-fold increase in signal intensity compared to non-functionalized controls. Drug concentration in brain regions reached therapeutically relevant levels within 6 hours of administration.

Histological analysis confirmed widespread distribution of nanoparticles in targeted brain regions without evidence of tissue damage. Control groups showed minimal penetration and lower drug concentration. These results illustrate the effectiveness of receptor-mediated targeting in enhancing BBB crossing.

Explanatory analysis of the case study indicates that transferrin receptors facilitate efficient nanoparticle transport through receptor-mediated endocytosis and transcytosis. Surface functionalization enables selective interaction with BBB endothelial cells, improving delivery specificity. These mechanisms explain the enhanced accumulation observed in brain tissue.

Comparative evaluation suggests that functionalized AuNPs achieve superior delivery efficiency while maintaining safety and structural integrity. Reduced off-target distribution indicates improved targeting precision. These findings support the application of engineered nanoparticles in neurological therapies.

Interpretation of the results suggests that gold nanoparticle-mediated delivery represents a highly effective strategy for overcoming BBB limitations. Enhanced permeability, targeted delivery, and stable drug association collectively contribute to improved therapeutic potential. Functionalization emerges as a critical determinant of nanoparticle performance.

Overall findings indicate that optimization of nanoparticle size, surface charge, and ligand density is essential for achieving efficient and safe brain delivery. Results provide a strong empirical basis for advancing AuNP-based systems and support their potential application in treating neurodegenerative diseases.

The findings demonstrate that gold nanoparticle (AuNP) functionalization substantially enhances blood–brain barrier (BBB) permeability, cellular uptake, and drug delivery efficiency without compromising barrier integrity. Quantitative results show that ligand-decorated AuNPs achieve markedly higher permeability coefficients and intracellular accumulation compared to non-functionalized counterparts. Drug loading efficiency also improves with optimized surface chemistry, indicating stronger drug–carrier interactions. These outcomes confirm that rational surface engineering can convert AuNPs into effective carriers for central nervous system delivery.

Performance differentials across formulations indicate that nanoparticle size and ligand density are critical determinants of transport efficiency. Intermediate particle sizes combined with moderate ligand coverage yield optimal BBB crossing, while extremes in either parameter reduce performance. Stability measurements further demonstrate that functionalized systems maintain colloidal integrity during transport, preventing premature aggregation or drug release. These findings highlight the importance of balancing physicochemical parameters to achieve reliable delivery.

Inferential analyses validate the robustness of observed improvements, with statistically significant differences in permeability, uptake, and loading between functionalized and control systems. Multivariate results indicate that ligand-mediated targeting is the dominant contributor to enhanced transport. Correlation patterns between size, surface charge, and uptake further support mechanistic coherence. These results collectively confirm that engineered AuNPs provide a measurable and reproducible improvement in BBB transport performance.

Case study observations corroborate these conclusions by demonstrating effective in vivo brain accumulation of transferrin-functionalized AuNPs. Imaging and histological analyses reveal widespread distribution within target regions without evidence of tissue disruption. Achieved drug concentrations reach therapeutically relevant levels within clinically meaningful timeframes. These findings provide compelling evidence for translational potential in neurodegenerative disease therapy.

The results align with existing literature that identifies receptor-mediated transcytosis as a viable pathway for nanoparticle transport across the BBB. Prior studies have shown that ligands such as transferrin and peptides facilitate interaction with endothelial receptors, enhancing transport efficiency. Agreement with these findings reinforces the validity of ligand-functionalization strategies. The present study extends this knowledge by providing a comparative and quantitatively validated framework.

Differences emerge in the consistency and magnitude of delivery efficiency reported. Some earlier investigations demonstrate variable or limited transport due to suboptimal nanoparticle design. The current results indicate that precise control of size and surface chemistry can significantly reduce such variability. This refinement contributes to addressing reproducibility challenges in nanoparticle-based delivery systems.

Existing research often evaluates BBB transport and drug loading independently, resulting in fragmented understanding of system performance (Banerjee dkk., 2025; Mishra dkk., 2026; G. Wang dkk., 2023). The present study integrates these dimensions, demonstrating how physicochemical optimization influences both transport and therapeutic delivery. This integrated approach provides a more comprehensive evaluation of nanoparticle functionality. Findings therefore contribute to bridging gaps between design and application.

Inclusion of in vitro and in vivo validation further distinguishes this study from many previous reports that rely primarily on simplified models (Lapmanee dkk., 2026; Narayan dkk., 2025; Yue dkk., 2026). Observed alignment between model systems and biological outcomes strengthens translational relevance. This methodological integration enhances confidence in the applicability of findings to clinical scenarios.

The findings signal a shift in how BBB penetration is approached in neurotherapeutics. Passive diffusion and systemic dosing strategies are increasingly being replaced by targeted, carrier-mediated delivery systems. AuNPs exemplify this transition by enabling controlled and selective transport across the BBB (González-Sánchez, López-Lorente, dkk., 2026; Kerdtoob dkk., 2024; Thukral dkk., 2023). This shift reflects a broader movement toward precision nanomedicine.

Evidence from this study indicates that BBB impermeability is not an absolute barrier but a modifiable interface that can be navigated through engineered interactions. Receptor targeting transforms the BBB from a restrictive barrier into a selective gateway. This reconceptualization has significant implications for drug development strategies. The results highlight the potential of nanotechnology to redefine therapeutic accessibility to the brain.

Observed optimization of nanoparticle properties further suggests that effective delivery requires a systems-level understanding of transport mechanisms. Interplay between size, charge, and ligand density determines not only permeability but also biodistribution and retention. This complexity underscores the importance of integrated design approaches. The findings demonstrate that successful BBB crossing depends on coordinated tuning of multiple parameters.

The study also indicates that safety considerations must be integrated into design processes from the outset. Maintenance of BBB integrity and absence of tissue damage in the case study suggest that functionalized AuNPs can achieve targeted delivery without compromising physiological barriers. This balance between efficacy and safety is a critical indicator of clinical viability.

Implications of this study extend to the development of more effective treatments for neurodegenerative diseases. Enhanced delivery efficiency enables higher therapeutic concentrations in target regions, potentially improving treatment outcomes. Reduction in systemic exposure may also decrease adverse effects. These benefits align with the goals of precision and patient-centered therapy.

Pharmaceutical development processes can incorporate nanoparticle-based strategies to overcome longstanding limitations in central nervous system drug delivery. Integration of targeting ligands and controlled release mechanisms offers new avenues for therapeutic innovation. Findings provide a scientific basis for advancing AuNP-based platforms in drug design pipelines.

Regulatory implications include the need to establish evaluation frameworks for nanoparticle safety, efficacy, and long-term behavior in biological systems. Evidence from this study supports the feasibility of such systems but also highlights the importance of rigorous assessment. Standardization of characterization and testing protocols will be essential for clinical translation.

Healthcare systems may benefit from improved treatment options that address previously inaccessible neurological targets. Effective BBB penetration can expand therapeutic possibilities for conditions that currently lack adequate interventions. These implications underscore the broader societal relevance of nanoparticle-mediated delivery systems.

Observed results can be explained by the physicochemical and biological mechanisms governing nanoparticle transport. Ligand-functionalized AuNPs interact with specific endothelial receptors, triggering endocytosis and transcytosis pathways. This targeted interaction facilitates efficient crossing of the BBB. The mechanism explains the significant increase in permeability observed.

Influence of nanoparticle size and surface charge arises from their impact on cellular interaction and transport dynamics. Smaller particles exhibit enhanced mobility and penetration, while surface charge affects binding affinity and stability. Optimal combinations of these properties enable efficient transport without aggregation or rapid clearance. These factors explain the observed performance patterns.

Enhanced drug loading and retention can be attributed to strong interactions between AuNP surfaces and therapeutic molecules. Surface functionalization stabilizes drug attachment and prevents premature release during circulation. This stability ensures that therapeutic payloads

remain intact until reaching target sites. These mechanisms contribute to improved delivery efficiency.

Safety outcomes observed in the study are linked to controlled nanoparticle design that minimizes toxicity and immune activation. Biocompatible coatings and appropriate size ranges reduce the likelihood of adverse reactions. Preservation of BBB integrity further indicates that transport mechanisms do not disrupt physiological function. These explanations support the observed balance between efficacy and safety.

Future research should focus on optimizing nanoparticle formulations for specific neurodegenerative diseases, incorporating disease-specific targeting ligands and therapeutic agents. Exploration of multifunctional nanoparticles combining imaging and delivery capabilities may enhance diagnostic and therapeutic integration. Advances in material science can support these developments.

Interdisciplinary collaboration will be essential for advancing nanoparticle-based delivery systems. Integration of nanotechnology, neuroscience, pharmacology, and clinical research can accelerate innovation. Collaborative efforts can also facilitate translation from experimental models to clinical applications.

Expansion of research to include long-term safety studies and large-scale in vivo validation is necessary to ensure clinical readiness. Investigation of nanoparticle clearance, accumulation, and potential chronic effects will provide critical insights. These studies are essential for establishing regulatory approval pathways.

Policy and regulatory research should accompany technological development to address ethical, safety, and implementation challenges. Development of standardized guidelines for nanoparticle-based therapies can support clinical adoption. Future work should therefore address both scientific and institutional dimensions of advancing BBB-targeted drug delivery.

CONCLUSION

This study demonstrates that gold nanoparticle (AuNP) functionalization enables efficient and controlled transport across the blood–brain barrier, resulting in significantly enhanced drug delivery to brain tissue compared to non-functionalized systems. Distinctive findings reveal that receptor-targeted AuNPs achieve a substantial increase in BBB permeability and intracellular uptake while preserving barrier integrity and minimizing tissue damage. Evidence further indicates that optimal combinations of particle size, surface charge, and ligand density are critical for maximizing transport efficiency without compromising stability. The results challenge the traditional limitation of the BBB as an impermeable obstacle and establish it as a modifiable interface that can be navigated through rational nanomaterial engineering.

The contribution of this research lies in the development of an integrative framework that links nanoparticle physicochemical design with biological transport mechanisms and therapeutic performance. Conceptual advancement is reflected in redefining BBB drug delivery as a dynamic, receptor-mediated process rather than a passive diffusion limitation. Methodological value emerges from the combined use of controlled nanoparticle synthesis, comparative functionalization strategies, and both in vitro and in vivo validation supported by inferential statistical analysis. This approach enables systematic optimization of AuNP-based delivery systems and provides a reproducible model for evaluating nanoparticle-mediated transport in neurological applications.

Limitations of this study include the restricted range of nanoparticle formulations and targeting ligands examined, which may limit generalizability across diverse neurodegenerative disease contexts. Experimental models, although incorporating in vivo validation, may not fully

capture long-term physiological interactions, immune responses, and chronic accumulation effects. Variability in disease-specific BBB alterations also introduces complexity that was not fully addressed. Future research should expand nanoparticle design diversity, incorporate longitudinal safety and pharmacokinetic studies, and explore multifunctional and multi-targeted systems to enhance specificity, efficacy, and clinical translation potential in neurotherapeutic applications.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and improving the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHORS' CONTRIBUTION

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

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

Author 3: Data curation; Investigation.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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