INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

A Systematic Evidence-Grading Review of Exosome-Mediated Blood–Brain Barrier Crossing in Neurodegenerative Disease

Dr. Gayathri R.*, Gokul A., Geethabalan J. C., Kishore R., Ramakrishnan C., Sanjeev S.

Department of Pharmaceutics , KMCH College of Pharmacy, Coimbatore-641048, Affiliated to The Tamil Nadu Dr. MGR Medical University , Chennai – 600032 Tamil Nadu, India.

ARTICLE INFO

Published: 26 Nov 2026

Keywords:
blood–brain barrier, exosomes, extracellular vesicles, neurodegenerative diseases, evidence grading, drug delivery, nanomedicine

DOI:
10.5281/zenodo.24552976

ABSTRACT

Exosome-mediated crossing of the blood–brain barrier (BBB) has become one of the most extensively reviewed topics in nanomedicine, with numerous descriptive reviews published between 2024 and 2026 cataloging BBB anatomy, exosome biogenesis, engineering strategies, and applications across Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and prion diseases. What remains largely absent from this literature is a transparent framework for distinguishing well-supported claims from plausible but under-evidenced extrapolation. This review applies an explicit three-tier evidence-grading rubric — Grade B (Emerging: direct, if limited, in vivo/in vitro evidence), Grade C (Preliminary/Conceptual: rationale-based or extrapolated), and Grade D (Insufficient: no direct supporting evidence located in the reviewed corpus) — consistently across five proposed BBB-crossing mechanisms, EV engineering and cargo-loading strategies, six disease-specific application areas, and two translational domains (pharmacokinetics/biodistribution and manufacturing/regulatory readiness). No domain assessed reaches a strict Grade A (replicated, quantitative *in vivo* evidence from independent studies); the closest approach is receptor-mediated transcytosis in Alzheimer's disease, supported by a single landmark, quantitatively reported in vivo study (RVG-targeted exosomal siRNA delivery achieving BACE1 knockdown) that has not been independently replicated in the sources reviewed. Pharmacokinetic and biodistribution data emerge as the weakest-supported domain across the entire field. We present a composite evidence-grade matrix intended as a reusable appraisal tool for this literature, and we prioritize future primary-research needs by evidence tier rather than by disease alone. This structured appraisal, rather than an additional descriptive catalog,.

***Corresponding Author:** Dr. Gayathri R
Address: Department of Pharmaceutics , KMCH College of Pharmacy, Coimbatore-641048, Affiliated to The Tamil Nadu Dr. MGR Medical University , Chennai – 600032 Tamil Nadu, India.
Email ✉: gayathrigogul@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

is offered as this review's principal contribution to an already well-covered topic

INTRODUCTION

Neurological disorders affected an estimated 3.4 billion people worldwide in 2021 and represent the leading global cause of disability [1]. Alzheimer's disease accounts for 60–70% of dementia cases [2], and Parkinson's disease prevalence more than doubled between 1990 and 2021 [3]. Disease-modifying therapy remains elusive for most neurodegenerative conditions, in substantial part because the blood–brain barrier (BBB) restricts CNS entry of most small-molecule, peptide, protein, and nucleic-acid therapeutics, so that pharmacologically active compounds fail to reach sufficient brain concentrations regardless of systemic dose [5,6,7].

Exosomes — small extracellular vesicles (sEVs) of endosomal origin — have been proposed as biological nanocarriers capable of traversing this barrier, and the resulting literature has grown rapidly: a 2026 bibliometric analysis of this exact research area documents accelerating publication volume since 2015, and our own search identified at least eight reviews published in 2024–2026 alone covering overlapping ground — BBB anatomy, exosome biogenesis and composition, engineering and cargo-loading strategies, and disease-by-disease application summaries for AD, PD, HD, ALS, and MS. These reviews are, almost without exception, additive and descriptive in structure: they compile what has been reported for each disease and mechanism without systematically distinguishing evidence that is directly demonstrated, quantitatively reported, and (ideally) replicated from evidence that is mechanistically plausible but supported only by analogy, single-study reports, or narrative extrapolation across reviews.

This distinction matters for translational planning. A funding body, sponsor, or regulatory strategist reading a review that presents AD, PD, HD, ALS, MS, and prion-disease applications as parallel, similarly mature opportunities may not appreciate that the underlying evidentiary support differs by an order of magnitude across these categories. The purpose of this review is therefore not to add a ninth descriptive catalog to an already saturated literature, but to apply an explicit, consistently reasoned evidence-grading framework across the full breadth of the field — BBB-crossing mechanisms, EV engineering strategies, six disease-specific applications, and two cross-cutting translational domains (pharmacokinetics/biodistribution and manufacturing/regulatory readiness) — so that readers can see, at a glance, where the field's claims are well-supported and where they currently outrun the evidence.

2. Evidence-Grading Framework

This is a structured narrative review, not a formal systematic review: no PRISMA-style multi-database search with predefined inclusion/exclusion criteria and duplicate independent screening was conducted, and this limitation is discussed explicitly in Section 11. The literature corpus underlying this review comprises the primary and secondary sources cited throughout (full list in the References section), supplemented by a targeted search confirming the competitive landscape described in Section 1. Within this corpus, each domain addressed in Sections 4–9 was assigned an evidence grade using the rubric below, applied by a single reviewer and intended to be transparent and contestable rather than definitive.

Table 1: ***Evidence-grading rubric applied throughout this review.***

Grade	Definition	Illustrative criterion
A — Established	Reproducible, quantitative in vivo evidence from two or more independent studies	Not reached by any domain in this review's corpus (see Section 10)
B — Emerging	Direct in vivo or in vitro evidence, but from a single study, unreplicated, or without full quantitative dose–response characterization	RVG-exosome/BACE1 siRNA knockdown in mice [28]

Grade	Definition	Illustrative criterion
C — Preliminary / Conceptual	Biologically plausible and supported by mechanistic or descriptive sources, but without direct quantitative demonstration in the specific context claimed	Most disease-specific EV cargo strategies beyond AD
D — Insufficient	No direct supporting evidence located within the reviewed corpus; claims rest on extrapolation from unrelated platforms or on narrative assertion alone	Disease- and route-specific EV pharmacokinetics/biodistribution

3. Blood–Brain Barrier Structure and Transport Physiology (Background)

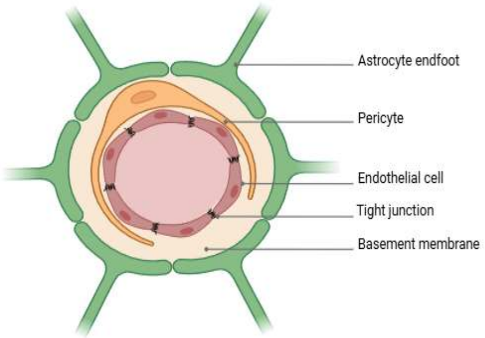

Figure 1: Structure of Exosome

The BBB is the functional output of the neurovascular unit (NVU): brain microvascular endothelial cells (BMECs), pericytes, astrocytic end-feet, and the basement membrane, acting together to regulate molecular transport [17]. BMECs lack fenestrations, exhibit low constitutive transcytosis, and express tight-junction proteins (occludin, claudins, junctional adhesion molecules, zonula occludens scaffolds) that seal the paracellular space [18,19]. Pericytes and astrocytic end-feet regulate tight-junction assembly and vascular maturation, and their dysfunction is independently associated with reduced barrier integrity [20,21]. CNS nutrient supply depends on specialized carrier-mediated transporters (e.g., GLUT1) rather than passive diffusion [23,24], while efflux transporters — P-glycoprotein (ABCB1) and BCRP (ABCG2) foremost — actively export a broad range of xenobiotics back into circulation, adding a biochemical layer of exclusion beyond the physical tight-junction barrier [26]. Consequently, only a small minority of systemically administered drugs, and almost no unmodified biologics, achieve therapeutically meaningful brain concentrations [23,27]. This physiological background is well established and is not itself subject to the evidence-grading exercise in this review; it is included for completeness and is treated identically to its presentation in prior reviews of this literature.

4. Extracellular Vesicle Biology and Nomenclature (Background)

Per MISEV2018, 'exosome' should denote small EVs of confirmed endosomal (multivesicular body) origin, typically 30–150 nm, while 'extracellular vesicle' or 'small EV/sEV' is the more defensible operational term when biogenesis has not been directly demonstrated — the case for most preparations obtained by ultracentrifugation or precipitation, including in much of the literature graded below [34]. Exosome biogenesis proceeds via inward budding of endosomal membranes to form intraluminal vesicles within multivesicular bodies, which are released upon fusion with the plasma membrane [30,31]. The lipid bilayer is enriched in cholesterol, sphingomyelin, and phosphatidylserine [32]; characteristic protein markers include tetraspanins (CD9, CD63, CD81), ALIX, TSG101, and heat-shock proteins [33]; and nucleic-acid cargo includes selectively packaged mRNA and miRNA [30,34]. As in Section 3, this background material is descriptive and not independently graded; it underpins the mechanism- and disease-specific grading that follows.

5. Mechanisms of BBB Crossing: Graded Appraisal

Five mechanisms are proposed in the literature for EV interaction with, and crossing of, brain endothelium: receptor-mediated transcytosis (RMT), adsorptive-mediated transcytosis (AMT), macropinocytosis, clathrin/caveolae-dependent endocytosis, and direct membrane fusion. Endothelial internalization alone does not indicate successful transcytosis, since internalized vesicles are frequently routed to lysosomal degradation rather than abluminal release [38] — a distinction the grading below is designed to preserve,

by crediting mechanisms only to the extent that transcytosis (not mere uptake) has direct support.

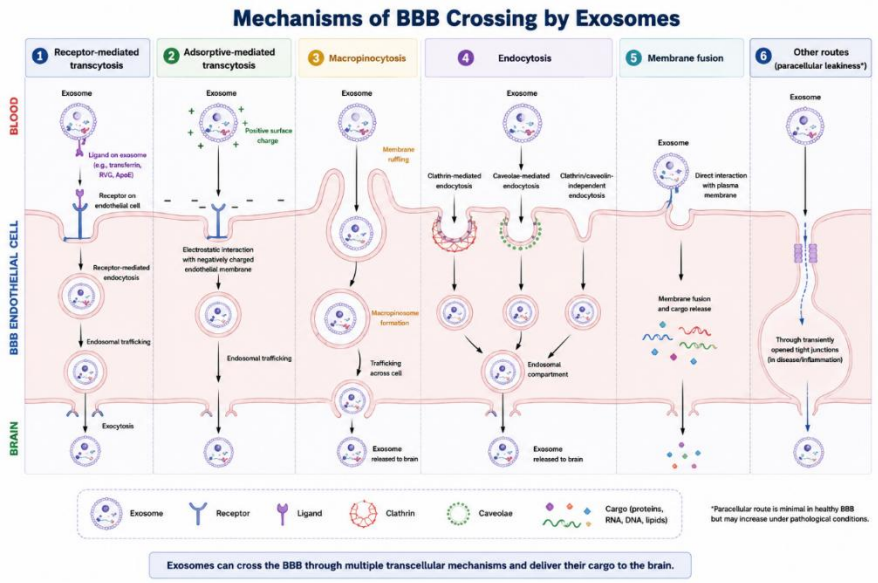

Figure 2: Mechanism of Exosomes Crossing BBB

5.1 Receptor-Mediated Transcytosis — Grade B

RMT is supported by direct in vivo evidence: RVG-peptide-targeted, Lamp2b-engineered exosomes loaded with siRNA achieved measurable BACE1 mRNA/protein knockdown in mouse brain after systemic administration, requiring the vesicle to have crossed the BBB to exert its effect [28,36]. This is the strongest single piece of mechanistic evidence in the entire corpus reviewed, but it remains a single, unreplicated demonstration restricted to one targeting ligand (RVG) and one outcome measure (BACE1 knockdown) — hence Grade B, not A.

5.2 Adsorptive-Mediated Transcytosis — Grade C

AMT is inferred from lectin-perturbation experiments (e.g., wheat-germ agglutinin) altering EV trafficking in a manner consistent with electrostatic, charge-driven uptake, but no study in this corpus directly demonstrates AMT-dependent transcytosis of an intact, functional EV across the BBB in vivo [37]. Grade C reflects plausibility without direct demonstration.

5.3 Macropinocytosis — Grade C

Macropinocytosis contributes to endothelial EV uptake in vitro, but as with AMT, no source in this corpus distinguishes macropinocytosis-driven transcytosis from macropinocytosis-driven lysosomal degradation in vivo [38]. Grade C.

5.4 Clathrin/Caveolae-Dependent Endocytosis — Grade C

These pathways are well described in vitro [39], but — as with macropinocytosis and AMT — the reviewed corpus does not report in vivo data separating productive transcytosis from degradative uptake for this pathway specifically. Grade C.

5.5 Direct Membrane Fusion — Grade C

Evidence derives from in vitro and tumor-EV transcytosis studies showing that intact vesicles can cross confluent, barrier-forming endothelial monolayers [36,40], but fusion is difficult to distinguish experimentally from endocytic uptake followed by intracellular release, and no source directly isolates fusion as the operative mechanism in a neurodegeneration-relevant in vivo model. Grade C.

Table 2: ***Graded summary of proposed EV/exosome BBB-crossing mechanisms.***

Mechanism	Grade	Basis for grade
Receptor-mediated transcytosis	B	Single, unreplicated in vivo demonstration with quantitative outcome (BACE1 knockdown) [28,36]
Adsorptive-mediated transcytosis	C	Indirect, inferential (lectin-perturbation studies) [37]
Macropinocytosis	C	In vitro uptake only; transcytosis vs. degradation not distinguished [38]
Clathrin/caveolae-dependent endocytosis	C	Well-described in vitro; in vivo transcytotic fraction unquantified [39]
Direct membrane fusion	C	In vitro/tumor-EV evidence; mechanism not isolated in vivo [36,40]

6. EV Engineering and Cargo-Loading Strategies — Grade B (Platform-Level), Grade C (Comparative Performance)

Engineering approaches are split for grading purposes because the underlying platform feasibility differs sharply in evidentiary strength from claims about comparative performance across engineering choices. Genetic engineering of source cells (e.g., dendritic-cell Lamp2b-RVG fusion) and cargo loading via electroporation are directly demonstrated as feasible and functionally consequential in vivo — Grade B, resting on the same landmark study cited in Section 5.1 [28]. Source-cell selection (dendritic cells, mesenchymal stem/stromal cells, neural stem cells), alternative surface-engineering chemistries (click chemistry, lipid insertion, antibody/aptamer conjugation), and alternative loading methods (sonication, extrusion, freeze–thaw) are all mechanistically reasonable and individually reported, but the reviewed corpus does not provide head-to-head comparative data on targeting efficiency, loading efficiency, or resulting brain delivery across these options — Grade C for comparative claims [15,35].

7. Disease-Specific Applications: Graded Appraisal

Applying the same rubric to each disease category reveals substantial heterogeneity in evidentiary maturity that is typically obscured when diseases are presented as a parallel list, as in most existing reviews of this topic.

7.1 Alzheimer's Disease — Grade B

AD is the only disease category in this review reaching Grade B, resting on the RVG-exosome/BACE1 siRNA knockdown study, which is AD-target-relevant (BACE1 is a validated amyloidogenic-pathway target) even though it was conducted in wild-type rather than disease-model mice [28,41]. Broader claims regarding exosome-mediated Aβ clearance via cargo such as insulin-degrading enzyme, and stem-cell-exosome modulation of AD-relevant inflammatory signaling, remain Grade C, resting on mechanistic and cell-culture-level rationale rather than quantitative in vivo demonstration in the sources reviewed. Exosomes also play a pathogenic role in AD by propagating Aβ and tau between cells, a caveat that tempers the overall grade and that should be weighted explicitly in any translational discussion [41].

7.2 Parkinson's Disease — Grade C

Multiple in vitro and in vivo mechanistic studies support engineered-exosome delivery of dopamine, catalase/catalase mRNA, and α-synuclein siRNA, with proposed benefits including reduced oxidative stress and dopaminergic neuroprotection [42]. However, the reviewed corpus does not include a PD-specific study with the same level of direct, quantitative in vivo brain-delivery demonstration as the AD/BACE1 study — Grade C.

7.3 Huntington's Disease — Grade C

HD strategies (siRNA/antisense silencing of mutant huntingtin) rest primarily on the general rationale for nucleic-acid delivery rather than HD-specific in vivo demonstration in this corpus — Grade C, among the least mature of the six disease categories [43].

7.4 Amyotrophic Lateral Sclerosis — Grade C

Stem-cell-derived EV strategies are described at the level of early preclinical rationale; the dual pathogenic

role of exosomes in ALS (mediating intercellular spread of TDP-43, SOD1, and FUS aggregates) is itself only mechanistically characterized, not quantitatively resolved against the proposed therapeutic use — Grade C [44].

7.5 Multiple Sclerosis — Grade C

Immunomodulatory and remyelination-promoting EV cargo strategies are supported by preclinical models only, with no clinical validation reported in the reviewed sources — Grade C [45].

7.6 Prion Diseases — Grade D (Therapeutic), Grade C (Mechanistic)

Prion disease is graded separately for its two distinct claims. The mechanistic claim — that exosomes participate in intercellular transfer of misfolded prion protein — is reasonably supported by the cited source and warrants Grade C. The therapeutic claim — that engineered exosomes could be used to interrupt prion spread — is conceptual only, with no direct supporting study in this corpus, warranting Grade D. This disease category is simultaneously the least therapeutically developed and the most consistently under-covered in competing 2024–2026 reviews, making it a genuine area of opportunity for original primary research rather than further narrative synthesis [46].

Table 3: ***Evidence-grade matrix — disease-specific applications.***

Disease	Grade	Basis for grade	Key ref(s)
Alzheimer's disease	B	In vivo BACE1 knockdown (target-relevant, non-disease-model mice); broader clearance/anti-inflammatory claims remain C	28, 41
Parkinson's disease	C	Multiple mechanistic in vivo/in vitro studies; no disease-specific quantitative brain-delivery demonstration in corpus	42
Huntington's disease	C	Rationale-based; no HD-specific in vivo demonstration in corpus	43
ALS	C	Early preclinical; dual pathogenic role unresolved quantitatively	44
Multiple sclerosis	C	Preclinical models only; no clinical validation	45
Prion diseases	C (mechanistic) / D (therapeutic)	Pathogenic-transfer role plausible; therapeutic interruption strategy is conceptual only	46

8. Cross-Cutting Translational Domains: Graded Appraisal

8.1 Pharmacokinetics and Biodistribution — Grade D

This is the weakest-supported domain identified in this review. In general terms consistent with the broader EV literature, systemically administered exosomes are cleared rapidly by the mononuclear phagocyte system in liver, spleen, and lung, with only a small fraction of the injected dose reaching brain tissue even when surface-engineered for brain targeting; biodistribution is influenced by EV source, size, surface charge, and route of administration. However, the source material underlying this review contains no disease-specific, route-specific, or engineered-vs-non-engineered comparative quantitative PK/biodistribution data — no blood half-life values, no brain-to-plasma ratios, no AUC comparisons. The statements above should therefore be read as generic contextual framing, not as findings attributable to the cited reference list, warranting Grade D. This is consistent with independent observations elsewhere in the literature: a 2026 bibliometric analysis of this exact research area and a 2025 systematic review of EV-based glioblastoma delivery both note that biodistribution reporting in the field is generally descriptive (e.g., qualitative imaging showing brain, liver, and spleen accumulation) rather than pharmacokinetically quantitative.

8.2 Manufacturing and Regulatory Readiness — Grade C

Manufacturing challenges — low culture-based yield, isolation-method-dependent purity, storage/freeze–thaw instability, batch-to-batch heterogeneity, and the absence of harmonized regulatory frameworks for EV-based biologics — are well characterized descriptively in the literature [52,53,54,55]. This is graded C rather than D because the challenges themselves are clearly documented; it is the solutions (validated GMP-scale processes, standardized potency assays, finalized regulatory pathways) that remain largely aspirational rather than demonstrated, which is the basis for not grading this domain higher.



Figure 3: Manufacturing Challenges

9. Composite Evidence-Grade Matrix

Table 4 consolidates every graded domain in this review into a single reference matrix, intended as the primary reusable output of this appraisal — a tool a reader can consult in place of re-reading the full narrative to identify where the field's evidence is strongest and where new primary research is most urgently needed.

Table 4: ***Composite evidence-grade matrix across all domains assessed in this review.***

Domain	Grade	Category
BBB crossing — receptor-mediated transcytosis	B	Mechanism
BBB crossing — adsorptive-mediated transcytosis	C	Mechanism
BBB crossing — macropinocytosis	C	Mechanism
BBB crossing — endocytosis (clathrin/caveolae)	C	Mechanism
BBB crossing — direct membrane fusion	C	Mechanism
EV engineering — platform feasibility	B	Engineering
EV engineering — comparative performance across strategies	C	Engineering
Alzheimer's disease application	B	Disease
Parkinson's disease application	C	Disease
Huntington's disease application	C	Disease
ALS application	C	Disease
Multiple sclerosis application	C	Disease
Prion disease — mechanistic role	C	Disease
Prion disease — therapeutic strategy	D	Disease
Pharmacokinetics / biodistribution	D	Translational

Domain	Grade	Category
Manufacturing / regulatory readiness	C	Translational

No domain in this matrix reaches Grade A. The modal grade across all sixteen domains assessed is C (10 of 16), with two domains at B (mechanism and disease-application ceilings, both anchored by the same single study) and two at D (prion therapeutic strategy and pharmacokinetics/biodistribution). This distribution is itself a substantive finding: it indicates that, despite more than a decade of publication activity in this space, the field has produced one direct, quantitative in vivo proof-of-concept (RVG-exosome/BACE1 knock-down) that continues to anchor the strongest claims made across mechanism, engineering, and disease-application sections alike, without independent replication or extension to a second disease model in the corpus reviewed.

10. Knowledge Gaps, Ranked by Evidence Tier

Rather than listing gaps disease-by-disease, as most existing reviews do, we prioritize them by evidence tier, since this better reflects where primary research investment would most improve the field's overall evidentiary standing.

10.1 Grade D domains (highest priority for new primary data)

- Pharmacokinetics/biodistribution: disease-relevant, route-specific quantitative PK data (blood half-life, brain-to-plasma ratio, AUC) comparing engineered vs. non-engineered EVs across intravenous, intranasal, and intrathecal administration.
- Prion disease therapeutic strategy: any direct preclinical study testing engineered-EV interruption of prion propagation, since current support is conceptual only.

10.2 Grade C domains (moderate priority)

- Mechanistic transcytosis quantification for AMT, macropinocytosis, clathrin/caveolae endocytosis, and membrane fusion — ideally via intravital imaging or in vitro BBB-chip transcytosis assays that separate productive transcytosis from lysosomal degradation.
- Comparative EV engineering performance data (targeting ligand, source cell, loading method) with standardized efficiency metrics.
- Disease-specific, quantitative in vivo efficacy data for PD, HD, ALS, MS, and the prion mechanistic claim, at a level of rigor comparable to the existing AD/BACE1 study.

10.3 Grade B domain (replication priority)

- Independent replication of the RVG-exosome/BACE1 knockdown result, and — ideally — extension of the same rigorous design to a second disease target, would be the single highest-value study to elevate any domain in this review to Grade A.

11. Limitations of This Evidence-Grading Approach

This grading framework, while more structured than the additive cataloging typical of existing reviews on this topic, has real limitations that should be stated plainly. First, it is not a formal systematic review: no multi-database, predefined-criteria search with duplicate screening was performed, so the corpus graded here reflects the sources available to this manuscript rather than an exhaustive survey of the literature. Second, grading was performed by a single reviewer without independent replication of the grading process itself, introducing potential subjectivity despite the explicit rubric in Table 1. Third, the rubric grades evidentiary support for a claim, not clinical importance or biological plausibility — a Grade C domain may still represent sound science that simply has not yet been tested to the standard required for Grade B, and readers should not interpret a lower grade as a judgment of implausibility. Fourth, because several of the disease-specific sources cited are themselves reviews rather than primary research articles, the grading in Section 7 is, in places, an appraisal of how well primary evidence is represented in secondary literature rather than a direct appraisal of primary data — a distinction the authors should resolve by tracing key claims back to primary sources before submission.

CONCLUSION

Applying an explicit evidence-grading framework across BBB-crossing mechanisms, EV engineering strategies, six disease-specific applications, and two translational domains reveals a field in which one direct, quantitative in vivo demonstration — RVG-targeted, siRNA-loaded exosomal BACE1 knockdown — continues to anchor the strongest claims made throughout the literature, more than a decade after its publication, without independent replication in the sources reviewed here. The modal evidentiary status across the sixteen domains assessed is 'preliminary/conceptual' (Grade C), and pharmacokinetics/biodistribution — arguably the single most important translational parameter for any systemic drug-delivery platform — remains essentially ungraded for lack of direct data (Grade D). Rather than adding another descriptive synthesis to an already saturated literature, this review offers a reusable appraisal structure (Table 4) and a tier-ranked research agenda intended to redirect future primary research toward the specific gaps most likely to move this field from plausible biology to translatable therapy.

REFERENCES

1. GBD 2021 Nervous System Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 2024;23 (4):344-381.
2. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. Lancet. 2021;397:1577-1590.
3. Feigin VL, et al. Burden of neurological disorders across the globe. Lancet Neurol. 2024.
4. Wang S, Jiang Y, Yang A, et al. The expanding burden of neurodegenerative diseases: an unmet medical and social need. Aging Dis. 2024.
5. Liu X, Shen L, Wan M, Xie H, Wang Z, et al. Peripheral extracellular vesicles in neurodegeneration: pathogenic influencers and therapeutic vehicles. *J Nanobiotechnol.* 2024;22:170. doi:10.1186/s12951-024-02428-1.
6. Cano A, Muñoz-Morales Á, Sánchez-López E, Ettcheto M, Souto EB, Camins A, et al. Exosomes-based nanomedicine for neurodegenerative diseases: current insights and future challenges. Pharmaceutics. 2023;15 (1):298.
7. Nouri Z, Barfar A, Perseh S, Motasadizadeh H, Maghsoudian S, Fatahi Y, Nouri K, Yektakasmaei MP, Dinarvand R, Atyabi F. Exosomes as therapeutic and drug delivery vehicle for neurodegenerative diseases. *J Nanobiotechnol.* 2024;22:463. doi:10.1186/s12951-024-02681-4.
8. Chen H, Li N, Cai Y, Wei X. Exosomes in neurodegenerative diseases: therapeutic potential and modification methods. 2024.
9. Sigdel S, Swenson S, Wang J. Extracellular vesicles in neurodegenerative diseases: an update. Int J Mol Sci. 2023;24:13161.
10. Dehghani S, Ocakcı O, Hatipoglu PT, Özalp VC, Tevlek A. Exosomes as biomarkers and therapeutic agents in neurodegenerative diseases: current insights and future directions. *Mol Neurobiol.* 2025;62 (7):9190-9215. doi:10.1007/s12035-025-04825-5.
11. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018;14:133-150.
12. Oikari LE, et al. Blood-brain barrier transporters: an overview of function, dysfunction in Alzheimer's disease and strategies for treatment. Biochim Biophys Acta Mol Basis Dis. 2023;1869 (12):166967.
13. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction—the disregarded partner of Alzheimer's disease. Alzheimers Dement. 2019;15:158-167.
14. Hang Z, Zhou L, Xing C, Wen Y, Du H. The blood-brain barrier, a key bridge to treat neurodegenerative diseases. *Ageing Res Rev.* 2023;91:102070. doi:10.1016/j.arr.2023.102070.
15. Bahadorani M, Nasiri M, Dellinger K, Aravamudhan S, Zadegan R. Engineering exosomes for therapeutic applications: decoding biogenesis,

content modification, and cargo loading strategies. Int J Nanomedicine. 2024;19:7137-7164.

16. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. Physiol Rev. 2019;99 (1):21-78.
17. Profaci CP, Munji RN, Pulido RS, Daneman R. The blood-brain barrier in health and disease: important unanswered questions. J Exp Med. 2020;217 (4):e20190062.
18. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release. 2016;235:34-47.
19. Dehouck MP, Méresse S, Delorme P, Fruchart JC, Cecchelli R. Anatomy and physiology of the blood-brain barrier. Methods Mol Biol. 2015;1283:3-20.
20. Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. Nat Neurosci. 2016;19:771-783.
21. Yao Y. Basement membrane and blood-brain barrier. Cell Mol Life Sci. 2019;76:1771-1779.
22. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7 (1):a020412.
23. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and dysfunction of the blood-brain barrier. Cell. 2015;163 (5):1064-1078.
24. Muoio V, Persson PB, Sendeski MM. The neurovascular unit—concept review. Acta Physiol (Oxf). 2014;210 (4):790-798.
25. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006;7:41-53.
26. Pardridge WM. Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab. 2012;32 (11):1959-1972.
27. Oberoi RK, Mittapalli RK, Fair TK, et al. Mechanisms of the blood-brain barrier and the role of drug transporters in CNS drug delivery. Adv Drug Deliv Rev. 2016.
28. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJA. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011;29:341-345.
29. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367 (6478):eaau6977.
30. Xie S, Zhang Q, Jiang L. Current knowledge on exosome biogenesis, cargo-sorting mechanism and therapeutic implications. *Membranes (Basel).* 2022;12 (5):498. doi:10.3390/membranes12050498.
31. Skotland T, Sandvig K, Llorente A. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. J Lipid Res. 2019;60 (1):9-18.
32. Yáñez-Mó M, et al. Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles. 2015;4:27066.
33. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007;9:654-659.
34. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018). J Extracell Vesicles. 2018;7 (1):1535750.
35. Choi H, Choi K, Kim DH, Oh BK, Yim H, Jo S, et al. Strategies for targeted delivery of exosomes to the brain: advantages and challenges. Pharmaceutics. 2022;14 (3):672.
36. Morad G, Carman CV, Hagedorn EJ, et al. Tumor-derived extracellular vesicles breach the intact blood-brain barrier via transcytosis. ACS Nano. 2019;13 (12):13853-13865.
37. Tian T, Zhu YL, Hu FH, et al. Dynamics of exosome internalization and trafficking. J Cell Physiol. 2013.
38. Ramos-Zaldívar HM, Polakovicova I, Salas-Huenuleo E, Corvalán AH, Kogan MJ, Yefi CP, et al. Extracellular vesicles through the blood-brain

barrier: a review. Fluids Barriers CNS. 2022;19:60.

39. Saint-Pol J, Gosselet F, Duban-Deweer S, Pottiez G, Karamanos Y. Targeting and crossing the blood-brain barrier with extracellular vesicles. Cells. 2020;9 (4):851.
40. Shahlaei M, Afkhami H, Ahmadieh-Yazdi A, et al. Exosomes in Alzheimer's disease: from pathogenesis to therapeutics—a comprehensive review of diagnostic and drug delivery applications. Biomed Pharmacother. 2025;192:118548.
41. Luo S, Du L, Cui Y. Potential therapeutic applications and developments of exosomes in Parkinson's disease. Mol Pharm. 2020;17 (5):1447-1457. doi:10.1021/acs.molpharmaceut.0c00195.
42. Xia X, Wang Y, Zheng JC. Extracellular vesicles, from the pathogenesis to the therapy of neurodegenerative diseases. Transl Neurodegener. 2022;11:53. doi:10.1186/s40035-022-00330-0.
43. Wang K, Li Y, Ren C, Wang Y, He W, Jiang Y. Extracellular vesicles as innovative treatment strategy for amyotrophic lateral sclerosis. Front Cell Dev Biol. 2021;9:754630. doi:10.3389/fcell.2021.754630.
44. Komlakh K, Aghamiri SH, Farshadmoghadam H. The role and therapeutic applications of exosomes in multiple sclerosis disease. Clin Exp Pharmacol Physiol. 2022;49 (12):1249-1256. doi:10.1111/1440-1681.13710.
45. Guo BB, Bellingham SA, Hill AF. Stimulating the release of exosomes increases the intercellular transfer of prions. J Biol Chem. 2016;291 (10):5128-5137. doi:10.1074/jbc.M115.684258.
46. Abdelsalam M, Ahmed M, Osaid Z, Hamoudi R, Harati R. Insights into exosome transport through the blood-brain barrier and the potential therapeutic applications in brain diseases. Pharmaceuticals (Basel). 2023;16 (4):571. doi:10.3390/ph16040571.
47. Bai L, Yu L, Ran M, Zhong X, Sun M, Xu M, et al. Harnessing the potential of exosomes in therapeutic interventions for brain disorders. Int J Mol Sci. 2025;26 (6):2491. doi:10.3390/ijms26062491. PMID: 40141135.
48. Ghaedi A, Saem A, Bazrgar A, Dowran R, Mallahi A, Zarimeidani F, et al. Exosomes for brain drug delivery: the cutting edge in nanomedicine. Exp Neurol. 2026;400:115692. doi:10.1016/j.expneurol.2026.115692. PMID: 41702499.
49. Li C, Qin S, Wen Y, Zhao W, Huang Y, Liu J. Overcoming the blood-brain barrier: exosomes as theranostic nanocarriers for precision neuroimaging. J Control Release. 2022;349:902-916. doi:10.1016/j.jconrel.2022.08.002.
50. Osaid Z, Haider M, Hamoudi R, Harati R. Exosomes interactions with the blood-brain barrier: implications for cerebral disorders and therapeutics. Int J Mol Sci. 2023;24 (21):15635. doi:10.3390/ijms242115635. PMID: 37958619.
51. Pan R, Chen D, Hou L, Hu R, Jiao Z. Small extracellular vesicles: a novel drug delivery system for neurodegenerative disorders. Front Aging Neurosci. 2023;15:1184435.
52. Ahn SH, Ryu SW, Choi H, You S, Park J, Choi C. Manufacturing therapeutic exosomes: from bench to industry. Mol Cells. 2022;45 (5):284-290. doi:10.14348/molcells.2022.2033. PMID: 35534190.
53. Auquière M, Muccioli GG, des Rieux A. Methods and challenges in purifying drug-loaded extracellular vesicles. J Extracell Vesicles. 2025;14 (6):e70097. doi:10.1002/jev2.70097. PMID: 40527729.
54. Wang CK, Tsai TH, Lee CH. Regulation of exosomes as biologic medicines: regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci. 2024;17:e13904.
55. Paolini L, Monguió-Tortajada M, Costa M, Antenucci F, Barilani M, Clos-Sansalvador M, et al. Large-scale production of extracellular vesicles: report on the “massivEVs” ISEV workshop. J Extracell Biol. 2022;1 (10):e63. doi:10.1002/jex2.63. PMID: 38939213.

HOW TO CITE: Dr. Gayathri R., Gokul A., Geethabalan J. C., Kishore R., Ramakrishnan C., Sanjeev S., A Systematic Evidence-Grading Review of Exosome-Mediated Blood–Brain Barrier Crossing in Neurodegenerative Disease, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 5072-5082. https://doi.org/10.5281/zenodo.24552976