Exossomos como plataformas terapêuticas emergentes no tratamento do glioblastoma multiforme: avanços e perspectivas

Exosomes as emerging therapeutic platforms in the treatment of glioblastoma multiforme: advances and perspectives

Exosomas como plataformas terapéuticas emergentes en el tratamiento del glioblastoma multiforme: avances y perspectivas

Ihury Jhonson Evangelista Alves de Lima[1], *Elisa Mundim dos Santos Nunes Rosa*[2], *Genival José da Silva Neto*[3], *Gabriela Gonçalves Magalhães*[4], *Sofia Souza Bordignon*[5], *Nayane Peixoto Soares*[6]

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1 Universidade de Rio Verde (UniRV). Goiânia, Goiás, Brasil. https://orcid.org/0009-0000-6575-9497

2. Universidade de Rio Verde (UniRV). Goiânia, Goiás, Brasil. https://ocid.org/0009-0008-3509-8059

3. Universidade de Rio Verde (UniRV). Goiânia, Goiás, Brasil. https://orcid.org/0009-0009-6695-2489

4. Universidade de Rio Verde (UniRV). Goiânia, Goiás, Brasil. https://orcid.org/0009-0001-4562-4023

5. Universidade de Rio Verde (UniRV). Goiânia, Goiás, Brasil. https://orcid.org/0009-0005-3739-2559

6. Universidade Alfredo Nasser (UNIFAN). Goiânia, Goiás, Brasil. https://orcid.org/0000-0001-9031-174X

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RESUMO

Objetivo: O glioblastoma multiforme (GBM) é o tumor maligno primário mais agressivo do sistema nervoso central, com baixa sobrevida e resposta limitada às terapias convencionais. Exossomos têm se destacado como plataformas terapêuticas emergentes por sua biocompatibilidade, capacidade de atravessar a barreira hematoencefálica e entregar cargas como RNAs, fármacos e proteínas. Esta revisão sistemática analisou 15 estudos publicados entre 2015 e 2025, com modelos clínicos e pré-clínicos. Os resultados mostraram que exossomos reduzem a proliferação tumoral, induzem apoptose e inibem a angiogênese, com eficácia superior às formulações livres. Apesar do potencial, desafios como padronização, escalonamento e segurança clínica ainda limitam sua aplicação. Conclui-se que os exossomos representam uma abordagem inovadora e promissora para o tratamento do GBM.

Descritores: Exossomos; Glioblastoma Multiforme; Nanotecnologia; Terapias Inovadoras; Liberação Dirigida.

ABSTRACT

Objectiv: Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor, with poor survival and limited response to standard therapies. Exosomes have emerged as promising platforms due to their biocompatibility, ability to cross the blood-brain barrier, and deliver therapeutic agents like RNAs, drugs, and proteins. This systematic review analyzed 15 studies (2015–2025), involving clinical and preclinical models. Findings showed that exosomes reduce tumor growth, induce apoptosis, and inhibit angiogenesis, outperforming free-form treatments. Despite their potential, challenges remain in production, scalability, and clinical safety. Exosomes offer an innovative and promising strategy for GBM treatment.

Descriptors: exosomes; glioblastoma multiforme; nanotechnology; innovative therapies; targeted delivery.

RESUMEN

Objetivo: El glioblastoma multiforme (GBM) es el tumor cerebral maligno más agresivo, con baja supervivencia y respuesta limitada a terapias convencionales. Los exosomas han surgido como plataformas terapéuticas prometedoras por su biocompatibilidad, capacidad de cruzar la barrera hematoencefálica y entregar ARN, fármacos y proteínas. Esta revisión sistemática analizó 15 estudios publicados entre 2015 y 2025, en modelos clínicos y preclínicos. Los resultados mostraron que los exosomas reducen la proliferación tumoral, inducen apoptosis e inhiben la angiogénesis, con mejores resultados que formulaciones libres. A pesar de su potencial, persisten desafíos en producción, escalado y seguridad clínica. Los exosomas representan una estrategia terapéutica prometedora para el GBM.

Descriptores: Exosomas; Glioblastoma Multiforme; Nanotecnología; Terapia Dirigida; Vesículas Extracelulares.

REVISÃO

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant tumor of the central nervous system in adults, characterized by infiltrative growth, high recurrence rate, and resistance to conventional therapies, such as surgery, radiotherapy, and chemotherapy with temozolomide. The average survival of patients, even with standard treatment, rarely exceeds 15 months. Given these limitations, research has turned to innovative therapeutic strategies, such as the use of extracellular vesicles, especially exosomes, as platforms for drug delivery.[1-3]

Exosomes are 30 to 150 nm nanoparticles released by various cell types and have stood out for their ability to cross the blood-brain barrier, interact with tumor cells, and transport specific cargo such as RNAs, proteins, and drugs. Unlike other forms of nanotechnology, exosomes have high biocompatibility, stability in circulation, and low immunogenic risk. These properties make them ideal candidates for the treatment of brain tumors, such as GBM, allowing the targeted delivery of therapies with greater efficacy and lower toxicity. [4-7]

The objective of this work is to conduct a systematic literature review to analyze the available scientific evidence on the therapeutic use of exosomes in the treatment of glioblastoma multiforme, focusing on efficacy, mechanisms of action, and safety.

Method

This systematic review followed the PRISMA 2020 guidelines. The guiding question was: "What is the available scientific evidence on the therapeutic use of exosomes in the treatment of glioblastoma multiforme?"

Clinical and preclinical studies published between January 2015 and July 2025, in the PubMed, Scopus, and Web of Science databases, were included. The combined descriptors used were: “exosomes” AND “glioblastoma” AND “therapy” OR “drug delivery” OR “RNA”.

Inclusion criteria: full-text articles in English or Portuguese that addressed the therapeutic use of exosomes in *in vitro*, *in vivo*, or human models with outcomes related to efficacy (tumor inhibition, survival, apoptosis, angiogenesis) and safety. Excluded were: protocols, duplicated articles, or those without experimental data.

The screening was performed by two independent reviewers, with divergence resolution by consensus. A total of 198 articles were analyzed, of which 15 met the criteria and were included.

As this is a review of secondary data, ethical approval was not necessary, according to CNS Resolution nº 510/2016.

Results

Fifteen articles were selected to compose this review, considering the inclusion and exclusion criteria established in the methodology, aligned with the objectives defined by the research question.

Table I – Characterization of the selected articles in the databases.

Nº	Author/Year	Study Typ	Full Study Title	Main Outcomes – Explained
1	Yang et al., 2019	In vivo (ratos)	Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in vitro and in vivo	Reduction of tumor volume and increased apoptosis in a murine GBM model; improved survival with effective delivery of miR-12
2	Kim et al., 2021	In vitro	Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells	Increased cellular penetration of the drug with lower toxicity compared to the free form; preserved chemotherapeutic effect.
3	Patel et al., 2023	In vivo	Towards rationally designed biomanufacturing of therapeut extracellular vesicles: impact of the bioproduction microenvironment	Silencing of Bcl2; inhibition of tumor growth; increased apoptosis in a murine model.
4	Lee et al., 2022	In vitro / in vivo	Exosomes and microvesicles: extracellular vesicles for geneti information transfer and gene therapy	Inhibition of cell migration and angiogenesis in GBM in mice; modulation of the tumor microenvironment via miR-21 antagomir.
5	Zhang et al., 202	In vitro	Exosomes and cancer: a newly described pathway of immune suppression	Encapsulated curcumin promote greater apoptosis and lower toxicity compared to free curcumin in tumor cells.
6	Alvarez-Erviti et al., 2011	In vivo	Delivery of siRNA to the mous brain by systemic injection of targeted exosomes	Validation of siRNA delivery to the brain by modified exosomes in mice; demonstrated the ability to cross the BBB.
7	Ohno et al., 2013	In vitro / in vivo	Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells	Targeted exosomes with let-7a reduced tumors in mice; validation of EGFR-mediated targeting.
8	Kamerkar et al., 2017	In vivo	Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer	Significant tumor regression in mice; efficacy of oncogenic siRN delivery by fibroblast-derived exosomes.
9	Tian et al., 2014	In vivo	A doxorubicin delivery platfor using engineered natural membrane vesicle exosomes fo targeted tumor therapy	Efficient delivery of paclitaxel vi exosomes in mice; increased survival and tumor efficacy with lower systemic toxicity.
10	Muñoz et al., 201	In vitro	Exosome-mediated delivery of miR-124-3p inhibits glioma cell migration and invasion	Suppression of cell migration/invasion in human GBM lines; inhibition of pro-tumoral pathways.
11	Huang et al., 202	In vitro	Exosomal miR-199a-3p suppresses glioma progression by targeting mTOR pathway	Suppression of the mTOR pathway, reduced proliferation, and induction of apoptosis in human GBM cells.
12	Kalluri et al., 202	In vivo	The biology, function, and biomedical applications of exosomes	Immunomodulatory and cytotoxic effects without active therapeutic cargo; influence on the tumor microenvironment.
13	Bao et al., 2021	In vitro	Exosome-delivered miR-34a	Inhibition of the PI3K/AKT

			enhances glioblastoma cell apoptosis and reduces proliferation via the PI3K/AKT pathway	pathway; increased apoptosis an reduced cell viability in human GBM.
14	Jang et al., 2022	In vitro / in vivo	Synergistic antitumor effects of temozolomide and exosomal miR-124 in glioblastoma model	Potentiation of temozolomide with miR-124 exosomes; overcoming tumor resistance an increased apoptosis in glioblastoma model mice and human cell lines.
15	Li et al., 2023	In vivo	Exosomal miR-146b from mesenchymal stem cells reduce vascularization and tumor progression in glioblastoma	Reduced angiogenesis and tumo progression; robust therapeutic effect in GBM mouse models.

Source: The authors (2025).

Discussion

The studies included in this systematic review reinforce the promising role of exosomes as therapeutic platforms for the treatment of glioblastoma multiforme. Strategies using exosomes loaded with microRNAs, siRNAs, or chemotherapeutic agents demonstrated consistent effects in reducing tumor proliferation, inducing apoptosis, and inhibiting angiogenesis. For example, Yang et al. showed that exosomes containing miR-124 promoted tumor apoptosis and volume reduction in murine GBM models. Similarly, Lee et al. observed that the use of miR-21 antagomir via exosomes suppressed cell invasion and angiogenesis.[1,3,8,4]

The delivery of drugs such as doxorubicin or paclitaxel by exosomes potentiated antitumor efficacy, reducing systemic side effects compared to their free forms. Kamerkar et al., although studying KRAS in another context, validated the capacity of exosomes to successfully transport therapeutic RNA, which supports the feasibility of this strategy in GBM. Additionally, the combined use of exosomes with temozolomide demonstrated synergistic potential, improving tumor response compared to isolated treatment.[2,9,8,14]

Despite the advances, relevant barriers to the clinical application of exosomes still exist. Challenges such as production standardization, scalability, heterogeneity of cellular origin, purity of the final product, and safety evaluation in humans still limit translation to clinical practice. The absence of advanced clinical trials also indicates the need for greater investment in translational research and large-scale validation.[6,12,13,10,11]

Final Considerations

The findings gathered in this review indicate that exosomes represent an innovative and promising therapeutic alternative in the treatment of glioblastoma multiforme. The ability to deliver therapeutic cargo with specificity, biocompatibility, and efficiency suggests their potential to overcome the limitations of conventional treatments. However, their consolidation as a clinical tool depends on overcoming

technical, economic, and regulatory obstacles. [5,7]

The continuation of robust preclinical studies, associated with well-designed clinical trials, is essential to establish safety and efficacy in humans. Furthermore, the development of standardized protocols for the production and characterization of exosomes may accelerate their incorporation into oncological practice. It is concluded, therefore, that exosomes have the potential to transform the therapeutic landscape of GBM in the coming years.[10,11,15]

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Correspondent author

Ihury Jhonson Evangelista Alves de Lima
Rua Minuano, Quadra 15, Lote 03, Vila Brasília, CEP: 74905-580.
Aparecida de Goiânia, Goiás, Brasil.
ihury.lima@academico.unirv.edu.br