DOI: 10.53469/jcmp.2025.07(06).30

Exosome-based Cannabidiol Formulation Demonstrates Superior Anti-glioma Activity by Boosting Cellular Uptake and Cytotoxicity

Shiying Feng[1], Wei Zhu[2,*]

[1]Baotou Medical College, Baotou 014040, China
[2]Department of Oncology, Baotou Central Hospital, Baotou 014040, China
**Correspondence Author*

Abstract: ***Background:*** *Cannabidiol (CBD) exhibits potential anti-tumor properties, but its clinical application against aggressive brain tumors such as glioma is severely limited by poor bioavailability and low cellular uptake. Therefore, developing advanced drug delivery systems to unlock its therapeutic potential is urgently needed.* ***Methods:*** *In this study, we developed and characterized an exosome-based CBD formulation (CBD-exos) derived from human umbilical cord mesenchymal stem cells (hUC-MSCs). We systematically evaluated its drug-loading capacity, cellular uptake efficiency, and compared its anti-glioma effects directly with those of free CBD in the U87MG and U251 human glioma cell lines.* ***Results:*** *CBD-exos presented as typical ~140 nm vesicles and were efficiently loaded with CBD (25 μg per mg of exosomal protein). Critically, fluorescence tracing confirmed that CBD-exos were rapidly internalized by glioma cells. Consequently, CBD-exos demonstrated dramatically enhanced cytotoxicity, with IC50 values of 0.9 μM in U87MG and 0.5453 μM in U251 cells—representing a 7.8-fold and 4.4-fold increase in potency compared to free CBD, respectively. This superior activity was further validated by a more potent inhibition of cell migration (P<0.001) and a more pronounced induction of S-phase cell cycle arrest.* ***Conclusion:*** *Our findings indicate that utilizing exosomes as a nanocarrier is a highly effective strategy for overcoming the limitations of CBD. The resulting CBD-exos formulation significantly enhances anti-glioma activity by greatly boosting cytotoxicity, highlighting its potential as a highly promising novel therapeutic agent for glioma.*

Keywords: Glioma, Cannabidiol, Exosome, Drug Delivery System, Nanomedicine.

1. Introduction

Glioma is the most common and aggressive primary malignant tumor of the central nervous system (CNS), particularly glioblastoma (GBM), which is associated with a dismal prognosis and a five-year survival rate of less than 5% [1-3]. The current standard of care, the Stupp protocol, which combines surgery with concurrent radiochemotherapy, faces significant challenges, including resistance to temozolomide (TMZ) and the formidable blood-brain barrier (BBB) [4, 5]. The BBB acts as a natural physiological fortress, severely restricting the entry of most chemotherapeutic agents into the brain parenchyma. This results in drug concentrations at the tumor site that are far below therapeutically effective levels. Therefore, developing novel therapeutic strategies that can efficiently penetrate the BBB and precisely target tumors represents a critical and unresolved challenge in the field of neuro-oncology.

In recent years, cannabidiol (CBD), a non-psychoactive phytocannabinoid, has garnered significant attention for its multi-faceted anti-cancer activities. Moreover, studies have confirmed that CBD can inhibit the proliferation and migration of glioma cells while inducing apoptosis, demonstrating its considerable therapeutic potential [6-11]. However, the clinical translation of CBD is not straightforward. Its key bottleneck lies in its intrinsic physicochemical properties: CBD's high lipophilicity results in poor water solubility and low oral bioavailability. More importantly, it struggles to effectively penetrate the BBB, failing to achieve and maintain therapeutically effective anti-tumor concentrations within the brain tissue [12, 13]. This delivery efficiency challenge is the single greatest obstacle preventing CBD's transition from a "promising molecule" to an "effective drug."

To overcome this delivery hurdle, nanotechnology offers a promising solution. Among the various nanocarriers, exosomes derived from mesenchymal stem cells (MSCs) exhibit unparalleled advantages. As natural nanoscale vesicles (30–150 nm), exosomes possess excellent biocompatibility, low immunogenicity, and an intrinsic ability to cross the BBB and target the tumor microenvironment [14-16]. Compared to artificially synthesized nanoparticles, exosomes represent a 'smarter' and more natural delivery vehicle. We theorized that leveraging this advanced natural carrier to load CBD could simultaneously address the dual challenges of CBD's poor water solubility and inefficient targeted delivery.

Against this backdrop, the present study aimed to construct a CBD delivery system based on exosomes from human umbilical cord mesenchymal stem cells (hUC-MSCs), termed CBD-exos, and to systematically investigate whether this strategy could significantly enhance the anti-glioma efficacy of CBD. We hypothesized that through effective encapsulation and delivery by exosomes, CBD-exos would exhibit cellular uptake efficiency, cytotoxicity, and inhibitory effects on malignant glioma phenotypes far superior to those of free CBD. This research provides crucial experimental evidence and an innovative technological pathway for the development of novel, highly effective, and low-toxicity therapeutics for glioma.

2. Materials and Methods

2.1 Cell Lines and Culture

Human umbilical cord mesenchymal stem cells (hUC-MSCs,

passages P3-P7) were generously provided by the Chinese PLA General Hospital and were cultured in serum-free medium for mesenchymal stem cells (Youkang, Cat. No. NC0107) at 37°C in a humidified atmosphere with 5% CO_2. The human glioma cell lines U87MG (Cat. No. 06.0133) and U251 (Cat. No. 06.0130) were purchased from EallBio and authenticated by Short Tandem Repeat (STR) profiling. Glioma cells were routinely cultured in high-glucose Dulbecco's Modified Eagle Medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS, Gibco) and 1% penicillin/streptomycin (Gibco).

2.2 Preparation and Characterization of CBD-loaded Exosomes (CBD-exos)

2.2.1 Preparation of CBD-exos

hUC-MSCs at 80% confluency were co-cultured with 40 μM cannabidiol (Lukemei, Shenzhen; dissolved in DMSO) for 12 h. The conditioned medium was collected and subjected to differential centrifugation (300 × g for 10 min; 2000 × g for 20 min) to remove cells and debris. Subsequently, exosomes were isolated and purified using the EXODUS-H600 system (Hui-Xin Biotech, Shenzhen), which is based on ultrasonic nanofiltration. This process yielded empty exosomes (exos) and CBD-loaded exosomes (CBD-exos). The protein concentration of exosomes was determined using the Qubit Protein Assay Kit (Thermo Fisher).

2.2.2 Transmission Electron Microscopy (TEM)

The exosome suspension was dropped onto a copper grid, negatively stained with 2% uranyl acetate, and then observed and imaged using a transmission electron microscope (JEOL) at an accelerating voltage of 100 kV.

2.2.3 Nanoparticle Tracking Analysis (NTA)

The size distribution and particle concentration of diluted exosome samples were analyzed using a ZetaView NTA analyzer (Particle Metrix).

2.2.4 Western Blot Analysis

A total of 20 μg of exosomal protein was separated by SDS-PAGE and subsequently transferred to a PVDF membrane. After blocking with 5% non-fat milk, the membrane was incubated overnight at 4°C with primary antibodies against human CD63 (1:1000, Solarbio), CD81 (1:1000, abinScience), and TSG101 (1:1000, Solarbio). The next day, the membrane was incubated with an HRP-conjugated goat anti-rabbit IgG secondary antibody (1:5000, Solarbio). Finally, the protein bands were visualized using an ECL (enhanced chemiluminescence) detection method.

2.3 Analysis of Exosomal Drug Loading

The CBD content in CBD-exos was quantified using an Ultra-Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry system (UPLC-QTOF, Waters ACQUITY I-Class & Xevo G2-XS). Separation was performed on an ACQUITY UPLC HSS T3 column (2.1 × 100 mm, 1.8 μm). The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). Mass spectrometry was operated in electrospray negative ionization (ESI^-) mode, scanning over a mass range of m/z 50–1500. The CBD concentration was calculated by comparison with a standard curve generated from CBD standards (12.5–100 μg/mL), and the drug loading content was expressed as μg of CBD per mg of exosomal protein.

2.4 Cellular Uptake Assay

Exosomes (100 μg) were incubated with 2 μM of the near-infrared fluorescent dye DiR (Aladdin) at 37°C for 30 min in the dark. Free dye was removed by ultracentrifugation (100,000 × g, 70 min, twice) to obtain DiR-labeled exosomes. For mitochondrial staining, a 100 nM working solution of MitoTracker Green (MedChemExpress) was prepared. U87MG and U251 cells (5×10^4 cells/well) were seeded in 24-well plates. After 24 h, cells were stained with 100 nM MitoTracker Green for 30 min at 37°C, followed by washing with PBS. Then, cells were co-incubated with DiR-labeled exosomes (100 μg/mL) for 24 h. Nuclei were counterstained with Hoechst 33342 (5 μg/mL, Aladdin). Cellular internalization of exosomes was observed using a laser scanning confocal microscope (Zeiss).

2.5 Cytotoxicity Assay (MTT Assay)

U87MG and U251 cells (5×10^3 cells/well) were seeded in 96-well plates. After 24 h, cells were treated with serially diluted concentrations (0–20 μM) of free CBD or an equivalent concentration of CBD-exos for 48 h. For the time-dependent experiment, cells were treated with 4 μM of CBD or equivalent CBD-exos for 0–120 h. Following treatment, MTT solution (5 mg/mL) was added to each well and incubated for 4 h. The formazan crystals were then dissolved in DMSO, and the absorbance was measured at 570 nm using a microplate reader. Cell viability was calculated using the formula: (OD of experimental group / OD of control group) × 100%. The IC50 values were determined using GraphPad Prism 7.0 software with a non-linear regression model (log(inhibitor) vs. response).

2.6 Transwell Migration Assay

U87MG (4×10^4 cells/well) or U251 (3×10^4 cells/well) cells, previously starved for 12 h, were resuspended in serum-free medium and mixed with the respective treatments (Control, exos, CBD-exos) before being added to the upper chamber of a Transwell insert (8 μm pore size, Corning). The lower chamber contained complete medium with 10% FBS as a chemoattractant. After 24 h of incubation, non-migrated cells on the upper surface were removed. Migrated cells on the lower surface were fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, and then imaged under a microscope. The number of migrated cells was quantified using ImageJ software.

2.7 Cell Cycle Analysis

Synchronized U87MG or U251 cells (5×10^5 cells/well) were treated with the respective agents (Control, exos, CBD, CBD-exos) for 24 h. Cells were harvested and fixed overnight

at 4°C with pre-chilled 70% ethanol. After washing with PBS, cells were stained with a propidium iodide (PI) solution containing RNase A (BD Biosciences) for 30 min at 37°C in the dark. The cell cycle distribution (G0/G1, S, and G2/M phases) was analyzed using a flow cytometer (BD Biosciences) and FlowJo software.

2.8 Statistical Analysis

All data are presented as the mean ± standard deviation (SD) from at least three independent experiments. Comparisons between groups were performed using a t-test or one-way analysis of variance (ANOVA). A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 7.0 software.

3. Results

3.1 Preparation and Characterization of CBD-loaded Exosomes (CBD-exos)

We successfully isolated exosomes derived from hUC-MSCs (exos) and their CBD-loaded form (CBD-exos). TEM analysis revealed that both sample groups exhibited the typical cup-shaped, bilayer vesicle structure with intact morphology (Figure 1A). Nanoparticle tracking analysis (NTA) confirmed that their size distribution was consistent with the standard for exosomes, with a peak diameter in the range of 120–140 nm (Figure 1B). Furthermore, Western blot analysis verified that both preparations highly expressed the characteristic exosomal marker proteins CD63, CD81, and TSG101 (Figure 1C).

Critically, we precisely quantified the drug loading efficiency using liquid chromatography-mass spectrometry (LC-MS) against a standard curve. The analysis confirmed that CBD was successfully encapsulated within the exosomes, with a drug loading content of approximately 25 μg of CBD per mg of exosomal protein. In contrast, no CBD signal was detected in the control empty exosomes (Figure 2A-D). These results collectively indicate that we have successfully prepared CBD-exos with well-defined physical characteristics and a high drug loading efficiency.

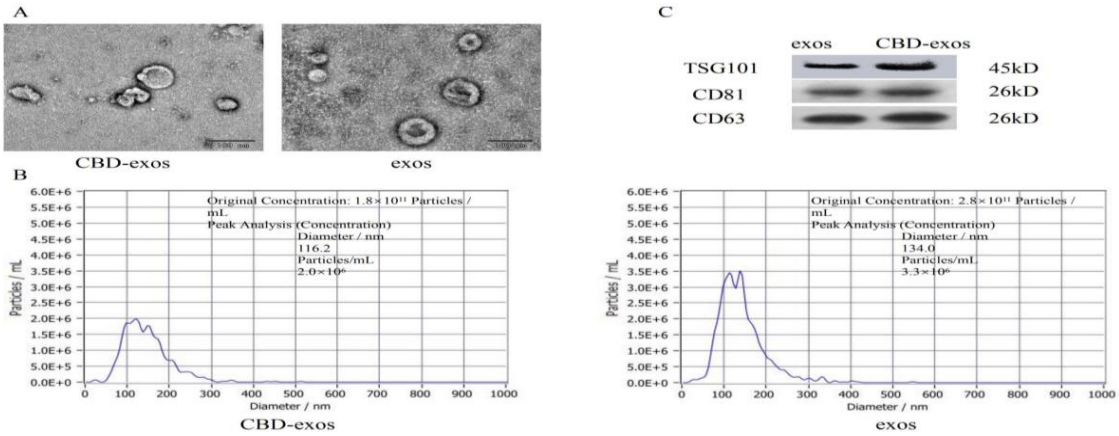

Figure 1: Characterization of exosomes derived from hUC-MSCs and CBD-loaded exosomes. (A) Representative transmission electron microscopy (TEM) images showing the morphology of exosomes. Scale bar, 100 nm. (B) Nanoparticle tracking analysis (NTA) showing the size distribution and concentration of exos and CBD-exos. (C) Western blot analysis of exosome-specific protein markers (CD63, CD81, and TSG101) in both exos and CBD-exos.

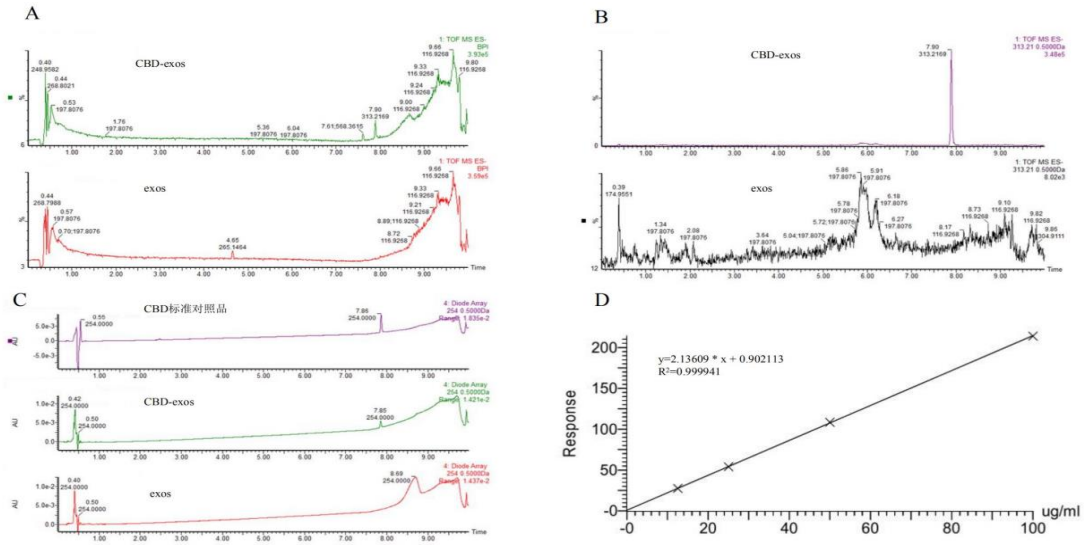

Figure 2: LC-MS analysis of CBD loading in exosomes. (A) Comparison of the Base Peak Ion (BPI) chromatograms of CBD-exos and exos in negative ion mode from UPLC-Q-TOF-MS. (B) Extracted Ion Chromatograms (EIC) for m/z 313.21, showing the signal intensity and retention time in CBD-exos versus exos in negative ion mode. (C) UV chromatograms at 254 nm for the CBD standard solution, CBD-exos, and exos. (D) The standard curve for CBD quantification.

3.2 Exosomes Mediate the Efficient Delivery of CBD into Glioma Cells

To validate the efficacy of exosomes as a delivery vehicle, we tracked their uptake by U87MG and U251 glioma cells. Exosomes were labeled with the near-infrared fluorescent dye DiR and then co-incubated with the cells for 24 hours. Confocal microscopy imaging clearly revealed that both empty exosomes and CBD-exos were extensively internalized by both cell lines, exhibiting significant fluorescent signals within the cytoplasm (Figure 3A-B). Furthermore, we stained the mitochondria of U87MG and U251 cells with MitoTracker Green and observed a co-localization phenomenon between the DiR-labeled exosomes and the mitochondria. This result directly demonstrates that the exosome formulation can effectively overcome the cell membrane barrier to successfully deliver its cargo into the cellular interior.

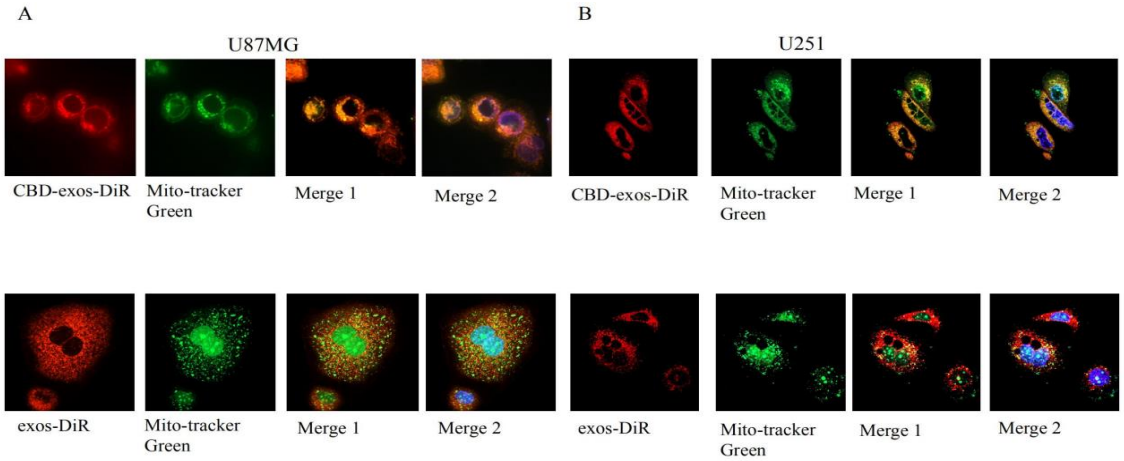

Figure 3: Cellular uptake and mitochondrial co-localization of exosomes in glioma cells. Confocal microscopy images of U87MG (A) and U251 (B) cells after a 24-hour incubation with DiR-labeled empty exosomes (exos) or CBD-loaded exosomes (CBD-exos). Exosomes are shown in red (DiR-labeled), mitochondria were stained with MitoTracker Green (green), and nuclei were counterstained with Hoechst (blue). The merged images indicate the co-localization of exosomes with mitochondria (yellow/orange signals).

3.3 CBD-exos Exhibit Superior Cytotoxicity Against Glioma Cells

We next evaluated the therapeutic efficacy of the formulation. MTT assay results revealed that CBD-exos exerted a dramatically more potent cytotoxic effect compared to free CBD. After 48 hours of treatment, the IC50 values for CBD-exos were 0.9 μM in U87MG and 0.5453 μM in U251 cells. These values were 7.8-fold and 4.4-fold lower, respectively, than those for free CBD (7 μM for U87MG; 2.379 μM for U251), indicating a substantial enhancement in potency (Figure 4A-B).

Furthermore, time-course experiments revealed that while both treatments exhibited time-dependent effects, the inhibitory effect of the CBD-exos group on cell proliferation became significantly stronger than that of an equivalent concentration of free CBD starting from 72 hours onwards ($P<0.001$ for U87MG; $P<0.05$ for U251). This suggests that exosomal delivery may lead to a more sustained intracellular drug effect.

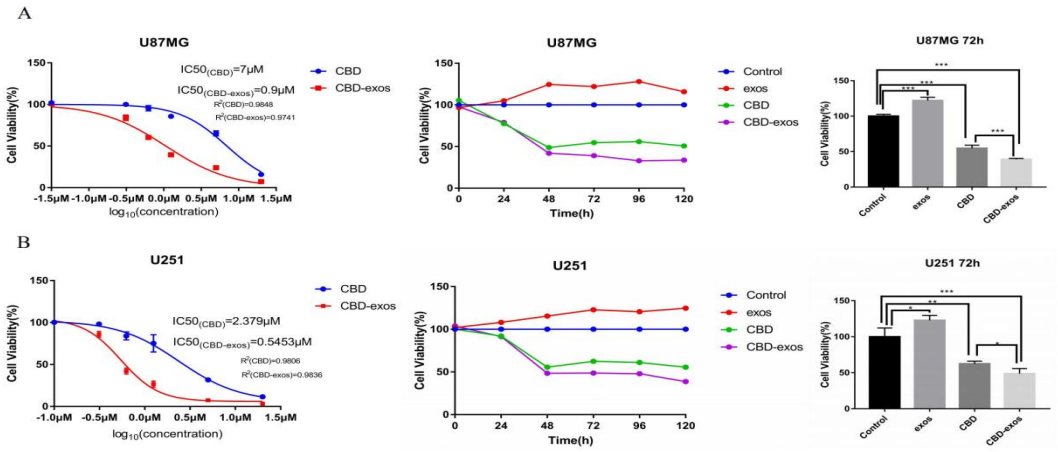

Figure 4: Enhanced anti-proliferative effect of CBD-exos on U87MG and U251 cells as determined by MTT assay. (A) For U87MG cells: (left) Dose-response curves used to determine IC50 values after 48 h of treatment with serially diluted CBD-exos and free CBD; (middle) Time-course analysis of cell viability under different treatments; (right) Comparison of cell viability at 72 h, showing significantly stronger inhibition by CBD-exos compared to the free CBD group ($P < 0.001$). (B) For U251 cells: (left) Dose-response curves for IC50 determination after 48 h of treatment; (middle) Time-course analysis of cell viability; (right) Comparison of cell viability at 72 h, showing enhanced inhibition by CBD-exos ($P < 0.05$). Data are presented as the mean ± SD (n=3). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

3.4 CBD-exos Potently Inhibit Key Malignant Phenotypes of Glioma Cells

To validate how this superior cytotoxicity translates into the inhibition of core tumorigenic functions, we next examined key malignant phenotypes. In Transwell migration assays, CBD-exos treatment drastically inhibited the migration of both U87MG and U251 cells, achieving inhibition rates as high as 85.7% (P<0.001) and 79.4% (P<0.001), respectively (Figure 5A-B).

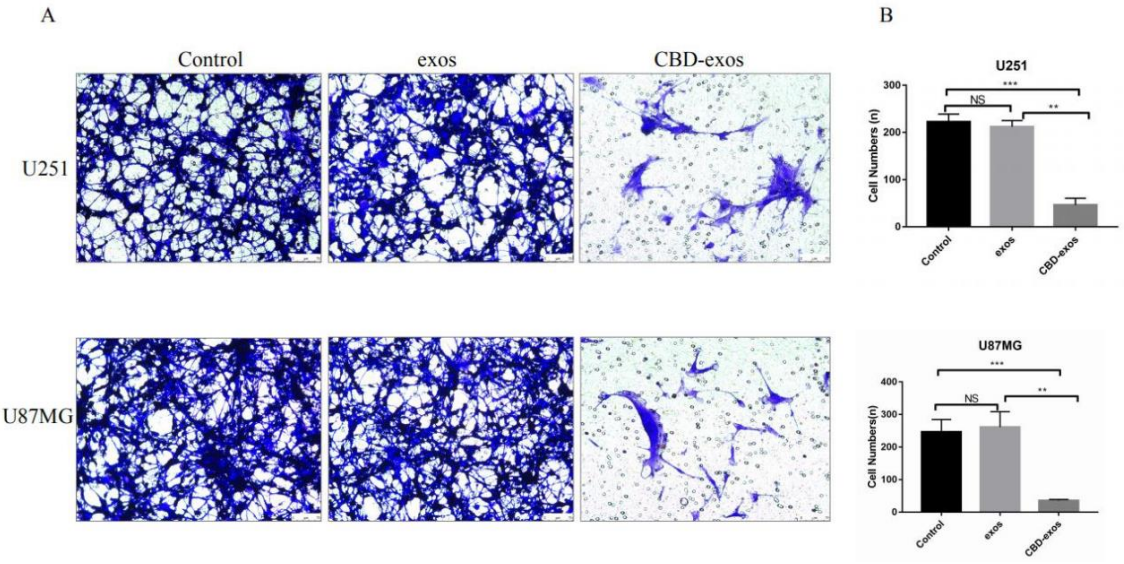

Figure 5: CBD-exos significantly inhibit the migration of glioma cells. (A) Representative microscopic images showing the migration of U87MG and U251 cells after 24 hours of different treatments. Migrated cells were fixed and stained with crystal violet. (B) Quantitative analysis of the number of migrated cells. Data are presented as the mean ± SD from three independent experiments. NS, not significant; **P < 0.01, ***P < 0.001. Scale bar, 75 μm.

Furthermore, cell cycle analysis by flow cytometry revealed that, compared to an equivalent dose of free CBD, CBD-exos induced a more potent S-phase arrest in both cell lines (Figure 6A-B). Taken together, the results from these functional assays consistently confirm that the enhanced cytotoxicity of CBD-exos effectively translates into a superior inhibition of key malignant behaviors, including proliferation and migration.

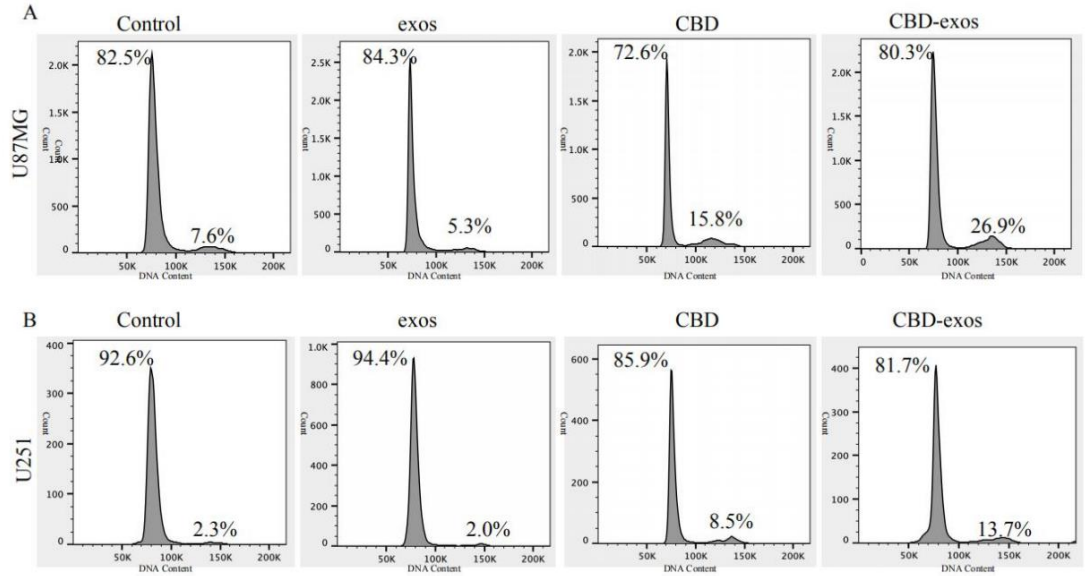

Figure 6: CBD-exos induce S-phase cell cycle arrest in U87MG and U251 glioma cells. Representative flow cytometry histograms and corresponding quantitative analysis of cell cycle distribution in (A) U87MG and (B) U251 cells. Cells were treated for 24 hours with CBD-exos, empty exosomes (exos), free CBD, or a vehicle control. While both CBD and CBD-exos caused an accumulation of cells in the S-phase, the proportion of S-phase arrested cells was significantly greater in the CBD-exos group.

4. Discussion

The therapeutic efficacy against glioma is frequently constrained by the bottleneck of inefficient drug delivery. In this study, we successfully developed an exosome-based cannabidiol (CBD) nano-formulation (CBD-exos) and confirmed its potent anti-glioma efficacy in in vitro models. A central finding of our study is that exosome-mediated delivery enhanced the cytotoxic potency of CBD against U87MG and U251 glioma cells by 7.8-fold and 4.4-fold, respectively, as measured by IC50 values. This marked improvement in potency, coupled with a more pronounced inhibition of cancer

cell migration and proliferation, provides compelling evidence for the success of our strategy.

The superior anti-tumor activity of CBD-exos is fundamentally attributed to a revolutionary enhancement in delivery efficiency. Although CBD is a potent anticancer molecule, its therapeutic potential has been largely unrealized due to the physical barrier hindering its effective delivery to target sites. Our DiR fluorescence tracing results visually confirmed the efficient internalization of exosomes by glioma cells, suggesting they function as a "precision guidance system" for CBD. The phospholipid bilayer of the exosome not only encapsulates the highly lipophilic CBD, addressing the challenge of its poor aqueous solubility, but more critically, it facilitates cellular uptake via mechanisms such as endocytosis. This process bypasses the cell membrane barrier that often limits the entry of conventional drugs, effectively delivering the therapeutic payload directly into the intracellular space. This dramatic increase in intracellular drug concentration is the primary mechanism explaining the substantial reduction in IC50 values and the multi-fold enhancement in potency.

Previous studies have explored various nanocarriers, such as liposomes and polymeric nanoparticles, for anticancer drug delivery [17-19]. However, these synthetic vectors often present challenges related to biocompatibility and potential toxicity [20]. Our work innovatively employs natural exosomes derived from hUC-MSCs. Their intrinsic low immunogenicity and tumor-homing capabilities render them an ideal vehicle for drug delivery to brain tumors. Furthermore, while previous research has utilized exosomes for the delivery of conventional chemotherapeutics like doxorubicin and paclitaxel, our study is the first to integrate this advanced delivery platform with a natural product of immense potential, CBD. By systematically quantifying the resulting efficacy gain, our work addresses a significant gap in this research area.

While the findings of this study are encouraging, several avenues warrant further investigation. Preliminary evidence suggests that CBD profoundly impacts mitochondrial function and core metabolic pathways in glioma cells. However, the underlying molecular mechanisms require further systematic investigation. Moreover, the present study was conducted at the in vitro level. Future research must focus on validating the in vivo therapeutic efficacy, blood-brain barrier (BBB) penetration capacity, and overall safety profile of CBD-exos in animal models, particularly in orthotopic glioma models.

5. Conclusion

In conclusion, this study successfully developed a highly efficient exosome-based formulation of CBD (CBD-exos). We have demonstrated that this formulation enhances the in vitro anti-glioma activity of CBD by several-fold, an effect attributed to a substantial improvement in its cellular delivery efficiency. This work not only presents a highly promising solution to overcome the bottlenecks in the clinical application of CBD but also introduces a potentially safe and effective new strategy for the targeted therapy of glioma.

Funding

This work was supported by the Clinical Need Oriented Basic Research Project of Inner Mongolia Academy of Medical Sciences (No. 2023GLLH0229) to W.Z.

References

[1] GROCHANS S, CYBULSKA A M, SIMIŃSKA D, et al. Epidemiology of Glioblastoma Multiforme-Literature Review[J/OL]. Cancers, 2022, 14(10): 2412. DOI:10.3390/cancers14102412.

[2] KOSHY M, VILLANO J L, DOLECEK T A, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries[J/OL]. Journal of Neuro-Oncology, 2012, 107(1): 207-212. DOI:10.1007/s11060-011-0738-7.

[3] MILLER K D, OSTROM Q T, KRUCHKO C, et al. Brain and other central nervous system tumor statistics, 2021[J/OL]. CA: a cancer journal for clinicians, 2021, 71(5): 381-406. DOI:10.3322/caac.21693.

[4] HOU X, DU H, DENG Y, et al. Gut microbiota mediated the individualized efficacy of Temozolomide via immunomodulation in glioma[J/OL]. Journal of Translational Medicine, 2023, 21(1): 198. DOI:10.1186/s12967-023-04042-5.

[5] ROH T H, KANG S G, MOON J H, et al. Survival benefit of lobectomy over gross-total resection without lobectomy in cases of glioblastoma in the noneloquent area: a retrospective study[J/OL]. Journal of Neurosurgery, 2020, 132(3): 895-901. DOI:10.3171/2018.12.JNS182558.

[6] AFRIN F, CHI M, EAMENS A L, et al. Can Hemp Help? Low-THC Cannabis and Non-THC Cannabinoids for the Treatment of Cancer[J/OL]. Cancers, 2020, 12(4): 1033. DOI:10.3390/cancers12041033.

[7] SREEVALSAN S, JOSEPH S, JUTOORU I, et al. Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent[J]. Anticancer Research, 2011, 31(11): 3799-3807.

[8] VELASCO G, SÁNCHEZ C, GUZMÁN M. Towards the use of cannabinoids as antitumour agents[J/OL]. Nature Reviews. Cancer, 2012, 12(6): 436-444. DOI:10.1038/nrc3247.

[9] LUCAS C J, GALETTIS P, SCHNEIDER J. The pharmacokinetics and the pharmacodynamics of cannabinoids[J/OL]. British Journal of Clinical Pharmacology, 2018, 84(11): 2477-2482. DOI:10.1111/bcp.13710.

[10] MUNSON A E, HARRIS L S, FRIEDMAN M A, et al. Antineoplastic activity of cannabinoids[J/OL]. Journal of the National Cancer Institute, 1975, 55(3): 597-602. DOI:10.1093/jnci/55.3.597.

[11] KHAN M I, SOBOCIŃSKA A A, CZARNECKA A M, et al. The Therapeutic Aspects of the Endocannabinoid System (ECS) for Cancer and their Development: From Nature to Laboratory[J/OL]. Current Pharmaceutical Design, 2016, 22(12): 1756-1766. DOI:10.2174/1381612822666151211094901.

[12] CALAPAI F, CARDIA L, SORBARA E E, et al. Cannabinoids, Blood-Brain Barrier, and Brain Disposition[J/OL]. Pharmaceutics, 2020, 12(3): 265. DOI:10.3390/pharmaceutics12030265.

[13] CHEVALIER M T, AL-WAEEL M, ALSHARABASY A M, et al. Therapeutic Polymer-Based Cannabidiol Formulation: Tackling Neuroinflammation Associated with Ischemic Events in the Brain[J/OL]. Molecular Pharmaceutics, 2024, 21(4): 1609-1624. DOI:10.1021/acs.molpharmaceut.3c00244.
[14] YANG T, MARTIN P, FOGARTY B, et al. Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio rerio[J/OL]. Pharmaceutical Research, 2015, 32(6): 2003-2014. DOI:10.1007/s11095-014-1593-y.
[15] SYN N L, WANG L, CHOW E K H, et al. Exosomes in Cancer Nanomedicine and Immunotherapy: Prospects and Challenges[J/OL]. Trends in Biotechnology, 2017, 35(7): 665-676. DOI:10.1016/j.tibtech.2017.03.004.
[16] YANG T, MARTIN P, FOGARTY B, et al. Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio rerio[J/OL]. Pharmaceutical Research, 2015, 32(6): 2003-2014. DOI:10.1007/s11095-014-1593-y.
[17] VERRICO C D, WESSON S, KONDURI V, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain[J/OL]. Pain, 2020, 161(9): 2191-2202. DOI:10.1097/j.pain.0000000000001896.
[18] MOMEKOVA D, IVANOV E, KONSTANTINOV S, et al. Nanocomposite Cryogel Carriers from 2-Hydroxyethyl Cellulose Network and Cannabidiol - Loaded Polymeric Micelles for Sustained Topical Delivery[J/OL]. Polymers, 2020, 12(5): 1172. DOI:10.3390/polym12051172.
[19] FRAGUAS-SÁNCHEZ A I, TORRES-SUÁREZ A I, COHEN M, et al. PLGA Nanoparticles for the Intraperitoneal Administration of CBD in the Treatment of Ovarian Cancer: In Vitro and In Ovo Assessment [J/OL]. Pharmaceutics, 2020, 12(5): 439. DOI:10.3390/pharmaceutics12050439.
[20] MÜLLER R H, GOHLA S, KECK C M. State of the art of nanocrystals--special features, production, nanotoxicology aspects and intracellular delivery[J/OL]. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V, 2011, 78(1): 1-9. DOI:10.1016/j.ejpb.2011.01.007.