ISSN:2790-1688 Volume-15-(2025)

Research Progress on the Inhibition of Glioma Invasion and Migration by Cannabidiol Nanoformulations Based on Modulation of the GADD45/CDC2 Signaling Axis

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Abstract. Glioma, the most common malignant tumor of the central nervous system, significantly impacts patient treatment outcomes and survival rates due to its highly invasive and migratory nature. Consequently, exploring effective therapeutic strategies represents a critical focus in current oncology research. In recent years, cannabidiol (CBD) has garnered widespread attention for its unique anti-tumor properties. However, its poor water solubility and low bioavailability limit its clinical application. The application of nanotechnology offers new possibilities for enhancing the delivery and efficacy of CBD.This review summarizes the latest research progress on CBD-based nanoformulations targeting the GADD45/CDC2 signaling axis to inhibit glioma invasion and migration. It highlights the mechanistic role of the GADD45/CDC2 axis in glioma progression and elucidates how CBD nanoformulations suppress tumor growth and metastasis by modulating this pathway. Furthermore, the article discusses the current limitations in the field and outlines future research directions, aiming to provide new insights and approaches for glioma treatment.

Keywords: Cannabidiol; Nanoformulations; Glioma; Invasion and Migration; GADD45/CDC2 Signaling Axis.

1. Introduction

Glioma is a common malignant tumor of the central nervous system, with glioblastoma being the most malignant and having an extremely poor prognosis[1]. Its high invasive and migratory capabilities make it difficult to completely eradicate through surgery and resistant to radiotherapy and chemotherapy, making the development of new therapies targeting these characteristics crucial[2]. Cannabidiol, a non-psychoactive component of cannabis, exhibits activities that inhibit tumor proliferation, induce apoptosis, and suppress invasion and migration, but its poor water solubility and low bioavailability limit its application[3].

Nanotechnology can improve the delivery efficiency of CBD. Research indicates that the GADD45/CDC2 signaling axis plays a critical role in cell cycle regulation and tumor progression, with its abnormal activation closely related to glioma invasion and migration[4]. CBD can inhibit glioma cell invasion by regulating this axis. Nanocarriers (such as polymeric nanoparticles) can not only enhance the solubility and sustained release of CBD but also improve its targeting and antitumor activity, synergizing with chemotherapeutic drugs[5]. CBD nanoformulations based on the regulation of the GADD45/CDC2 axis and the application of nanotechnology show significant potential in inhibiting glioma invasion and migration[6]. Further exploration of their mechanisms of action and promotion of clinical translation are needed in the future.

2. Main Body

2.1 Molecular Mechanisms of Glioma Invasion and Migration.

2.1.1 Extracellular Matrix Remodeling and Glioma Invasion.

Extracellular matrix (ECM) remodeling plays a crucial role in glioma invasion[7]. Matrix metalloproteinases (MMPs) are key zinc-dependent proteases that degrade the ECM, with MMP-2 and MMP-9 being highly expressed in gliomas. They promote tumor cell invasion by breaking down matrix components and weakening cell-matrix adhesion [7]. Integrins, as cell surface receptors, mediate cell adhesion to the ECM and enhance the migration and invasion capabilities of tumor cells by activating signaling pathways such as PI3K/Akt and MAPK [9]. Additionally, ECM components such as fibronectin and laminin not only provide structural support for cell migration but also drive changes in cell morphology and invasive behavior by activating intracellular signaling [10-11]. In summary, the dynamic remodeling of the ECM mediated collectively by MMPs, integrins, fibronectin, and laminin constitutes a pivotal process in the invasion and migration of gliomas. Mechanistic studies targeting this process will provide a critical foundation for the development of novel therapeutic strategies.

2.1.2 Epithelial-Mesenchymal Transition (EMT) Process.

Epithelial-mesenchymal transition (EMT) is a critical process through which cells acquire migratory and invasive capabilities, playing a significant role in the progression of gliomas[12]. This process is regulated by transcription factors such as Twist, Snail, and ZEB1, which drive cytoskeletal reorganization and enhanced migratory abilities by inhibiting epithelial markers (e.g., E-cadherin) and promoting mesenchymal markers (e.g., N-cadherin) [13-15]. The loss of E-cadherin and upregulation of N-cadherin are core features of EMT, collectively promoting glioma cell invasion [16]. Additionally, EMT is closely associated with glioma stem cell characteristics, enhancing cell self-renewal and heterogeneity, leading to increased drug resistance and treatment difficulty [17]. Therefore, in-depth research on the key EMT transcription factors and related signaling pathways will provide important directions for inhibiting glioma invasion and improving treatment strategies.

2.1.3 Cytoskeleton Reorganization and Motility.

The cytoskeleton is the core structure that regulates cell morphology and movement. The Rho GTPase family (RhoA, Rac1, and Cdc42) plays a central regulatory role in this process, influencing cell migration and invasion by modulating actin dynamic reorganization[18]. For example, RhoA activation promotes actin polymerization and regulates movement through the phosphorylation of proteins such as cofilin; Rac1 and Cdc42 are involved in establishing cell polarity and membrane dynamics, collectively driving tumor cell metastasis [19]. Actin forms a dynamic network through polymerization/depolymerization, supporting cell extension and movement, and is particularly crucial during the epithelial-mesenchymal transition[20]. The microtubule system participates in the maintenance of cell polarity and directed movement through reorganization, and its associated proteins (such as spastin) influence the invasive ability of tumor cells by regulating microtubule stability [21]. In summary, the Rho GTPase signaling network, actin reorganization mechanisms, and microtubule functions are intricately interwoven, collectively determining the motility and invasive properties of cells. In-depth research targeting this system will provide new therapeutic targets for cancer treatment.

2.2 Biological Functions of the GADD45/CDC2 Signaling Axis in Glioma.

2.2.1 Overview of the GADD45 Protein Family.

The GADD45 protein family comprises three members: GADD45 α , GADD45 β , and GADD45 γ , which play a central role in cellular stress responses[22]. This family is not only involved in DNA damage repair, cell cycle regulation, and apoptosis but also holds significant functions in tumorigenesis and development. The functions of each member differ: GADD45 α primarily regulates the cell cycle and DNA repair; GADD45 β is involved in oxidative stress and inflammatory responses; and GADD45 γ is closely associated with neuroplasticity and developmental processes [23]. The expression of GADD45 proteins exhibits tissue specificity. For instance, GADD45 α is often highly expressed in tumor tissues, while GADD45 β demonstrates a dual role in promoting cell survival and inducing apoptosis in certain liver diseases [24-25]. Their functions are regulated by various factors, including protein interactions and epigenetic modifications [26-27]. When cells encounter stress such as DNA damage, GADD45 is rapidly induced through signaling pathways like p38 MAPK, assisting in damage repair and regulating cell proliferation and apoptosis [28-29]. In summary, the GADD45 protein family plays multifaceted roles in cellular stress responses and cancer progression, representing potential therapeutic targets. In-depth exploration of their mechanisms of action will provide new directions for the treatment of related diseases.

2.2.2 The Role of GADD45 in DNA Damage Response and Cell Cycle Regulation.

The GADD45 protein family plays a central role in DNA damage response and cell cycle regulation. When cells undergo DNA damage, the expression of GADD45 is rapidly upregulated. By interacting with cell cycle proteins such as CDK, it induces G2/M phase arrest, providing a time window for DNA repair and preventing the inheritance of damage [30]. Simultaneously, GADD45 can interact with DNA repair enzymes and regulate signaling pathways such as MAPK, enhancing damage recognition and repair capabilities. The absence of GADD45 increases cellular sensitivity to damage and promotes apoptosis [31]. In tumors, the expression of GADD45 is often abnormally downregulated, leading to a weakened DNA damage response, decreased genomic stability, and thereby promoting malignant tumor progression [32]. Therefore, the regulation of GADD45 expression and function has become a new strategy in tumor therapy, and in-depth research into its mechanisms will provide important targets for cancer treatment.

2.2.3 Epigenetic regulatory mechanisms of GADD45 expression.

The expression of GADD45 is precisely regulated by epigenetic mechanisms such as DNA methylation and histone modifications[33]. Under conditions such as oxidative stress and inflammatory responses, cells activate demethylases to reduce the methylation level in the GADD45 promoter region, thereby promoting its transcriptional activation [34]. Meanwhile, the acetylation and methylation states of histones also directly regulate the transcriptional activity of GADD45. Histone deacetylases can inhibit its expression, while the binding of activators promotes transcription, forming a dynamic balance in response to changes in the internal and external environment [35]. The epigenetic regulatory network of GADD45 is complex and highly plastic, and a deeper understanding of its mechanisms will provide new strategies for the diagnosis and targeted therapy of diseases such as cancer.

2.2.4 Biological Characteristics of CDC2 Kinase.

CDC2 (CDK1) is the core regulatory kinase for the G2/M phase transition in the cell cycle. Its activity depends on binding with Cyclin B1, forming the CDC2-Cyclin B1 complex that drives cells into mitosis[36]. The activity of CDC2 is dynamically regulated by CDC25 (activated through dephosphorylation) and Wee1 (inhibited through phosphorylation), ensuring that cells enter division at the appropriate time [34]. In addition to cell cycle regulation, CDC2 is also involved in cellular stress responses and can cross-talk with signaling pathways such as MAPK, influencing the timing of division and cell survival. Its function is regulated by metabolic signals such as intracellular nutrient status [37]. The central role of CDC2 in cell cycle progression and stress adaptation makes it a crucial target for understanding the mechanisms of cell proliferation and cancer therapy.

2.2.5 Regulatory Network of the GADD45/CDC2 Signaling Axis.

GADD45 plays a pivotal role in cell cycle regulation and tumor invasion suppression by inhibiting CDC2 (CDK1) kinase activity. In tumors such as gliomas, the downregulation of GADD45G expression leads to excessive activation of CDC2, promoting cell cycle progression and invasive behaviors [38]. Moreover, GADD45 interacts with the p53 pathway, enhancing p53 stability and synergistically inhibiting CDC2 activity, thereby inducing cell cycle arrest and apoptosis [39]. The aberrant activation of the GADD45/CDC2 signaling axis is closely associated with the malignancy and prognosis of gliomas, and restoring GADD45 expression can effectively inhibit CDC2 activity and reduce cellular invasiveness[40]. This axis not only provides new biomarkers and therapeutic targets for gliomas, but the in-depth study of its epigenetic regulatory mechanisms will also promote the development of personalized tumor treatment strategies.

2.3 The Antitumor Mechanism of Cannabidiol (CBD).

2.3.1 Pharmacological Properties of CBD.

Cannabidiol (CBD) is the primary non-psychoactive component of the cannabis plant, with the chemical formula $C_{21}H_{30}O_2$. Its low water solubility and high lipophilicity result in relatively low bioavailability. CBD is primarily metabolized by hepatic cytochrome P450 enzymes (such as CYP2C19 and CYP3A4) and is prone to interact with other drugs [41]. CBD modulates physiological functions such as pain and mood through the endocannabinoid system (CB1/CB2 receptors) and other receptors (e.g., 5-HT_1A, TRPV1). Although it has low affinity for CB1 receptors, it acts as a negative allosteric modulator, influencing signal transduction [42]. Pharmacokinetically, the absorption of CBD is influenced by the route of administration and diet, with oral bioavailability increasing when taken with food. Its half-life ranges approximately from 14 to 60 hours, exhibiting significant interindividual variability. When co-administered with other medications, attention should be paid to its inhibitory effects on CYP enzymes, and doses should be adjusted appropriately to ensure efficacy and safety [43].

2.3.2 The Impact of CBD on the Tumor Cell Cycle.

Cannabidiol (CBD) exerts anti-tumor effects through multiple pathways. Its main mechanisms include the induction of G2/M phase cell cycle arrest in tumor cells: CBD increases the intracellular level of reactive oxygen species (ROS), activates cell cycle checkpoint proteins such as p53/p21[44], and inhibits the expression of key cyclins like Cyclin D1 and Cyclin B1, thereby preventing cells from entering mitosis [42-43]. In addition, CBD can downregulate G1/S transition-related proteins including Cyclin D3, CDK2, and CDK4, and synergistically enhance the DNA damage response with the activation of the p53 pathway, thus inhibiting proliferation and promoting apoptosis

[44-45]. The ROS induced by CBD can also directly cause DNA damage, and further strengthen cell cycle arrest and anti-tumor effects by regulating repair-related pathways such as ATM/ATR and telomerase [45]. These mechanisms collectively form the molecular basis for the anti-tumor effect of CBD based on cell cycle regulation and DNA damage response.

2.3.3 Mechanisms of CBD in Inhibiting Tumor Invasion and Migration.

Cannabidiol (CBD) shows great potential in inhibiting tumor invasion and migration. A key mechanism is regulating matrix metalloproteinases (MMPs) — enzymes degrading the extracellular matrix and aiding tumor metastasis. It inhibits MMPs' expression/activity; e.g., in colon cancer, it downregulates MMP-2/-9 to suppress invasion/migration [46], and also modulates MMPs via tumor microenvironment cytokines.CBD also regulates epithelial-mesenchymal transition (EMT), which gives tumors invasive ability. It upregulates E-cadherin and downregulates N-cadherin/Vimentin to inhibit EMT [47]; in colon cancer, it suppresses the Wnt/β-catenin pathway to hinder EMT and reduce cell mobility.Additionally, CBD affects cytoskeleton reorganization linked to tumor migration. It modulates cytoskeleton composition/structure; in glioma, it alters F-actin structure to reduce motility [48], and regulates actin polymerization via Rho family GTPases, weakening invasiveness and possibly inhibiting growth. These highlight CBD's multi-mechanism anti-tumor role, offering new clinical insights.

2.4 Research Progress on CBD Nano-Delivery Systems.

2.4.1 Types of Nanocarriers and Their Characteristics.

Liposomes, a key nanocarrier with good biocompatibility/biodegradability, are prepared via solvent evaporation, ultrasonication, etc. Optimizing conditions boosts their drug loading and release; e.g., adjusting lipid types/ratios affects particle size and drug release [49]. PEGylation and surface modification improve in vivo stability and targeting [50]. Component selection also matters—using cholesterol/phospholipids enhances membrane fluidity and drug bioavailability [51], while temperature regulation (linked to membrane phase transition) promotes drug release. Polymer nanoparticles, with unique physicochemical properties, rely on proper polymer selection (e.g., PLA, PVA, PLGA [52]). Polymer molecular weight and hydrophilic/hydrophobic components influence drug loading/release; introducing hydrophilic groups enhances stability [53]. Chemical modifications (grafting, surface modification) improve targeting, aiding cancer treatment [54]. They also hold promise in vaccines and gene therapy. Inorganic nanoparticles (metal like gold/iron oxide, semiconductors like quantum dots [49]) have high stability and drug loading. Gold nanoparticles enable targeted delivery and photothermal therapy for cancer [55]; iron oxide ones act as MRI contrast agents. Surface functionalization (e.g., modifying antibodies) enhances targeting [56], making them vital for drug delivery, especially against refractory diseases like cancer.

2.4.2 Targeting Strategies of Nanodelivery Systems.

Passive targeting in nanodelivery relies on the tumor's EPR effect, with 10-200nm nanoparticles optimal for tumor accumulation [57]. Yet efficiency is limited by tumor microenvironment complexity [55]; boosting tumor blood flow (e.g., local heating [58]) can improve it.Active targeting modifies nanoparticle surfaces with ligands (e.g., RVG29 on PLGA nanoparticles [59]) to bind tumor cell receptors, enhancing delivery. Ligand choice, modification complexity, and immune responses need consideration.Stimuli-responsive systems release drugs under specific conditions (pH, temperature, enzymes [60]). For example, chitosan nanoparticles respond to tumor glutathione [61], and ultrasound activates nanobubbles [62], aiding precise drug

release, promising for refractory tumors like gliomas.

2.4.3 Improvement of CBD Bioavailability by Nano-Delivery.

Improving cannabidiol (CBD) bioavailability is key in its research, as poor water solubility and low stability limit clinical efficacy. Nano-delivery systems offer solutions here. For example, zein-whey protein composite nanoparticles protect CBD from thermal/UV degradation [62], while CBD-loaded solid lipid nanoparticles (CBD-SLNs) boost solubility and enable sustained release [63]. Nano-systems also extend CBD’s blood circulation. Polyvinyl alcohol-poly(ε -caprolactone) nanoparticles raise CBD’s maximum concentration (Cmax) ~20-fold and shorten time to Cmax (tmax) to 0.3h vs free CBD [64]. Moreover, they enhance CBD’s blood-brain barrier penetration—critical for neurological disorders like epilepsy. Micron/nanoscale carriers target release at needed sites, and zinc-based nanoparticles accumulate in mouse brain tissue [65]. These advances lay a foundation for CBD’s clinical use, with future nanotech expected to further boost its bioavailability.

2.4.4 Molecular Mechanism Analysis.

In the study of glioma invasion and migration, the regulatory mechanism of the GADD45/CDC2 signaling axis has garnered increasing attention[66]. GADD45G, as an important tumor suppressor, requires in-depth exploration regarding its expression and function in gliomas. Research indicates that the downregulation of GADD45G is closely associated with the development of various cancers, and its methylation status may be a significant factor influencing its expression [67]. In glioma cells, the expression level of GADD45G is significantly reduced, and this reduction is closely related to the enhancement of invasive behavior in cells[68]. Specifically, GADD45G indirectly affects the invasion and migration capabilities of glioma cells by inhibiting the expression of cyclin-dependent kinase 1 (CDK1) and cyclin B1 (CCNB1). The alterations in upstream and downstream molecules of the signaling pathway are key to understanding this mechanism[69]. The reduced expression of GADD45G leads to the upregulation of CDK1 and CCNB1, further promoting cell proliferation and migration, thereby forming a vicious cycle. The specific molecular mechanisms of this process may involve the regulation of the cell cycle, as CDK1 and CCNB1 play a central role in the G2/M phase of the cell cycle[70]. Through techniques such as RNA-seq, qRT-PCR, and Western blotting, researchers can assess the expression of GADD45G in different glioma tissues and observe its interactions with CDK1 and CCNB1, which play significant roles in tumor invasion and metastasis.

2.5 Synergistic Therapeutic Strategy of CBD Nano Reagents.

2.5.1 Combination with Traditional Chemotherapeutic Agents.

In glioma treatment, traditional chemotherapeutic Temozolomide (TMZ) is a mainstay, but single chemotherapy often fails to control tumor progression and faces drug resistance. Combining novel therapies like cannabidiol (CBD) with TMZ has become key to boosting efficacy. Studies show CBD enhances TMZ’s inhibitory effect on glioma cells via the GADD45/CDC2 signaling axis—promoting tumor cell apoptosis, inhibiting proliferation/migration, and inducing cell cycle arrest to strengthen TMZ’s cytotoxicity[71]. It also reduces tumor cell drug resistance by inhibiting pro-inflammatory factors in the tumor microenvironment and lowering drug resistance-associated protein expression. Dose optimization is crucial in clinical use: low-dose CBD can enhance TMZ’s anti-tumor effect without increasing toxicity, helping patients get better outcomes while reducing chemotherapy discomfort. This combination, based on GADD45/CDC2 axis regulation, offers new

directions for glioma treatment. CBD also shows radiosensitizing potential in combining with radiotherapy (a common glioma treatment limited by tumor radiation resistance). It boosts tumor cell radiation sensitivity by regulating cell cycle-related proteins, activating the GADD45/CDC2 axis [67], inducing apoptosis, and inhibiting invasiveness[72]. High-energy radiation damages tumor cell DNA, but tumors resist via repair; CBD interferes with this by inhibiting key DNA repair enzymes, reducing post-radiotherapy tumor cell survival [67], laying a foundation for its use as a radiosensitizer. Notably, CBD protects normal tissues during radiotherapy: it reduces radiotherapy-induced normal cell damage and side effects by enhancing normal cells' antioxidant capacity (countering oxidative damage) and using anti-inflammatory properties to alleviate local inflammation [73]. Thus, CBD combined with radiotherapy enhances anti-tumor effects and protects normal tissues, with promising clinical prospects.

2.5.2 Construction of Multimodal Treatment System.

In glioma treatment, single therapies fall short, making multimodal systems essential to tackle tumor heterogeneity. They integrate three key aspects:

Diagnosis-treatment integration: Early, accurate diagnosis via MRI/PET and biomarker detection boosts survival. Post-diagnosis, emerging drugs like cannabidiol (CBD) are precisely delivered via nanocarriers, enhancing bioavailability and reducing normal tissue damage, improving efficacy and patient quality of life.Multi-targeting strategies: To counter glioma cell resistance to single drugs, this approach acts on multiple targets. For example, CBD (regulating GADD45/CDC2 axis) combines with EGFR/PDGFR pathway inhibitors. Chemotherapeutics plus targeted drugs also work synergistically, but dosage and administration need systematic optimization for safety.Intelligent responsive systems: Using advanced biomaterials, these systems dynamically respond to the tumor microenvironment—e.g., nanocarriers sensing pH/enzyme activity release drugs at specific tumor stages. They boost drug targeting, cut normal cell toxicity, and integrate real-time monitoring to guide decisions, enabling personalized, precise glioma therapy to improve survival.

2.6 Challenges in Clinical Translation.

2.6.1 Safety Assessment.

Assessing cannabidiol (CBD) and its nanoformulations' safety requires acute/chronic toxicity studies, immunogenicity evaluation, and nervous system safety checks[74]. Acute studies show CBD (e.g., CBD nanosuspensions [68]) has good biocompatibility at proper doses, with no significant acute toxicity. Chronic studies confirm safety at suitable doses but need more research on dosages/administration for long-term effects. Immunogenicity-wise, CBD modulates immunity (anti-inflammatory, reduces cytokines [69]) but needs clinical trials to assess effects[75], especially in immunocompromised groups. For the nervous system (key in glioma treatment), CBD has neuroprotective effects [70], with no significant neurotoxicity in animal models. However, its neurotoxicity/side effects (especially with other antitumor drugs) and impact on neurons/glial cells need more clinical data for safer use.

2.6.2 Issues in Large-Scale Production.

For clinical translation of cannabidiol (CBD) nano-reagents, large-scale production is key, involving process standardization, quality control, and cost-benefit analysis. Process standardization needs selecting suitable prep techniques (ultrasonication, high-pressure homogenization, etc.), strictly controlling parameters (temperature, pressure)[76], choosing adaptable equipment, and validating processes to ensure batch consistency. Quality control requires a comprehensive index

system (particle size, surface charge, purity, biocompatibility) and standard operating procedures (SOPs) for real-time monitoring, reducing defects and ensuring safety/efficacy. Cost-benefit analysis assesses raw material[77], equipment, and labor costs, optimizes resource allocation, considers market demand/pricing, and forecasts long-term benefits (e.g., lowering patient treatment costs), supporting decisions to promote clinical application.

2.6.3 Research on Drug Resistance Mechanisms.

Glioma treatment faces great challenges from drug resistance, which harms prognosis and survival. Its mechanisms go beyond tumor cells' direct drug response, involving three key aspects.Adaptive drug resistance: Tumor cells gain resistance via dynamic biological changes under drug pressure—they regulate gene expression, activate pathways (e.g., PI3K/Akt, MAPK) to boost survival and anti-apoptosis, or alter drug target expression/function to reduce drug efficacy, complicating treatment.Tumor microenvironment mediation: Composed of fibroblasts, immune cells (e.g., TAMs secreting IL-6, TNF-α to enhance drug resistance)[78], and others, it affects tumor cell drug sensitivity. Hypoxia activates HIF-1α, inducing resistance-related genes.Phenotypic plasticity: Glioma cells rapidly change phenotypes (e.g., epithelial-mesenchymal transition) under stimuli, gaining invasiveness and resistance via pathways like Wnt/β-catenin. Tumor cell heterogeneity also lets some subpopulations survive drug pressure[79].

2.6.4 Deepening of Mechanism Research.

Recent studies on the GADD45/CDC2 signaling axis in gliomas have deepened, with single-cell sequencing offering new insights[80]. It analyzes gene expression at the single-cell level, revealing interactions between glioma cells, fibroblasts, and immune cells under the axis's regulation, uncovering tumor heterogeneity and providing biomarkers to predict responses to therapies like CBD.High-resolution time-series imaging enables spatiotemporal dynamic analysis, tracking glioma cell changes across time and space to clarify the axis's role in invasion/migration—e.g., observing cell speed and migration after CBD treatment, offering experimental evidence for new therapies.Epigenetic research is also key: CBD alters GADD45 gene methylation, affecting downstream CDC2 expression, supporting CBD's application. Epigenetic networks reveal glioma cells' adaptive changes. Integrating these three approaches advances understanding of glioma biology and lays a foundation for clinical treatments[81].

2.6.5 Optimization of the Delivery System.

In glioma treatment, developing novel nanomaterials as drug delivery carriers is key. Due to unique physicochemical properties, polymeric, lipid, metallic nanoparticles and bioinspired platforms (e.g., cell membrane-coated nanoparticles [82]) are widely used. They enhance drug biocompatibility, stability and targeting [83]; surface modification with specific molecules boosts selectivity for glioma cells. Thermo-, photo- and pH-responsive nanomaterials enable targeted drug release, laying a foundation for personalized treatment.Multilevel targeting strategies integrate chemical and biological targeting (e.g., using IGF-1R/GRP78 receptors [84]), addressing both blood-brain barrier penetration and intratumoral targeting. Multifunctional nanoparticles carry multiple agents for combination therapy, overcoming multidrug resistance and improving immunotherapy by modifying the immune microenvironment [85]; nanoparticle-enhanced immunotherapy shows promising preclinical results.Controlled release technologies (e.g., polymer microspheres, hydrogels [86]) regulate drug release (e.g., triggered by tumor acidity) to boost efficacy and reduce side effects. Future integration of biosensors with release systems may enable dynamic therapy monitoring, offering new prospects for glioma precision medicine[87].

2.6.6 Clinical Translation Pathway.

The clinical translation pathway of cannabidiol (CBD) nano-agents for glioma treatment based on the GADD45/CDC2 signaling axis involves three key aspects.Preclinical research design: Appropriate animal models (e.g., mouse/rat xenografts[88], spontaneous glioma models) are used to mimic human glioma biology. Experiments evaluate CBD nanoformulations' tumor-inhibiting effects (via proliferation/migration/invasion assays) and regulation of the GADD45/CDC2 axis (using Western blot, qPCR). Toxicological tests (acute/chronic toxicity) define safe dosage ranges, laying a scientific foundation for clinical trials.Clinical trial protocols: Clear inclusion/exclusion criteria ensure participant homogeneity. A randomized controlled design assigns patients to an experimental group (CBD nanoformulations) or control group (placebo/conventional treatment)[89]. Regular assessments of tumor burden, quality of life, and side effects are conducted. Defined primary endpoints (survival rate, tumor reduction) and secondary endpoints (quality of life improvement), plus long-term follow-up to monitor efficacy durability and delayed adverse reactions, provide robust clinical evidence.Industrialization development: Collaboration between research institutions and enterprises is vital to develop production processes and standardized procedures for large-scale, consistent CBD nano-agent production. Intellectual property protection (patents for preparation methods, usage) is essential[90]. Pre-planned market strategies, including target market needs assessment, and health education to raise awareness among patients and healthcare professionals, facilitate clinical application and industrialization. Systematic R&D across these areas drives the clinical translation of this therapeutic strategy.

3. Conclusion

The application of cannabidiol (CBD) nanoformulations based on the regulation of the GADD45/CDC2 signaling axis in glioma treatment marks an innovative breakthrough in the field of cancer therapy. Current research indicates that CBD nanoformulations can significantly inhibit the invasion and migration capabilities of glioma cells by modulating the GADD45/CDC2 signaling axis. Meanwhile, the introduction of nanotechnology has effectively improved the pharmacokinetic properties of CBD, demonstrating greater potential in glioma treatment. However, despite rapid advancements in this field, numerous challenges remain. Firstly, the mechanism of action of CBD nanoformulations has not been fully elucidated, and a deeper understanding of its mechanisms at the cellular and molecular levels is crucial for optimizing treatment strategies. Secondly, further optimization of the delivery system is also an urgent issue to be addressed. The existing nano-delivery systems still need improvement in terms of biocompatibility, targeting, and release mechanisms to ensure their efficacy and safety in clinical applications. Additionally, practical barriers to clinical translation, particularly the lack of sufficient clinical trial data, also limit the promotion of CBD as a treatment option for glioma. From an expert's perspective, balancing different research perspectives and findings is crucial. Current research results indicate that the anti-tumor activity of CBD is closely related to the regulation of the GADD45/CDC2 signaling axis, but there may be differences in experimental design, model selection, and result interpretation among different studies.

Therefore, through systematic evaluation and comparison of the results from different studies, a more comprehensive understanding of the therapeutic potential of CBD nano-reagents can be achieved. Meanwhile, interdisciplinary collaboration will provide new perspectives and insights for the development in this field. The convergence of multiple disciplines, such as biomedical

science, pharmaceutical chemistry, and nanotechnology, can accelerate the development of novel therapeutic strategies. Future research should focus on the following aspects: First, to elucidate the specific mechanisms of CBD in glioma cells, particularly its impact on the GADD45/CDC2 signaling axis, thereby providing a theoretical foundation for subsequent targeted therapies. Second, to develop more efficient nano-delivery systems to enhance the bioavailability and targeting capability of CBD, ensuring that the drug can accurately reach the tumor site. Finally, to actively promote clinical translation research by conducting multicenter clinical trials to evaluate the safety and efficacy of CBD nano-agents in glioma patients.

In summary, the CBD nano-agent based on the regulation of the GADD45/CDC2 signaling axis provides a new strategy for the treatment of glioma. Although numerous challenges currently exist, through in-depth research, technological optimization, and multidisciplinary collaboration, it is expected to bring safer and more effective treatment options for glioma patients in the future, significantly improving patient prognosis.

Acknowledgment

This study was funded by the Anhui Provincial Health Commission Key Project “Mechanism Study of Coaxial Bioprinting High-Quality Mesenchymal Stem Cell-Derived Exosomes on Invasive Prolactinoma,” Project Number: AHWJ2023A10099.

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