DOI: 10.53992/njns.v11i2.331 NUST Journal of Natural Sciences, Vol. 11, Issue 2, 2026

Review Article

Emerging nanoparticles for glioblastoma: Engineering precision across the blood-brain barrier

Huzaifa Shoaib*, Arfa Khan

Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan.

***Corresponding author's email:** huzaifashoaib137@gmail.com

Abstract

Glioblastoma (GBM) remains one of the most lethal brain malignancies, characterized by aggressive invasion, therapeutic resistance and poor prognosis. Conventional treatment approaches are limited by systemic toxicity, poor blood–brain barrier (BBB) penetration and lack of tumor specificity. Nanoparticle-based therapeutics offer a transformative paradigm redefining drug delivery, diagnostics and multimodal strategies in GBM. In this review, we critically explore a diverse variety of advanced nanocarrier platforms designed for anti-proliferative, radiosensitizing and immunomodulatory interventions. These systems enhance BBB penetration, tumor localization and enable co-delivery of chemotherapeutics, gene therapies and imaging agents with high precision. Innovative approaches show efficacy against glioma stem cells, modulate the tumor microenvironment and address resistance mechanisms. Integration with radiotherapy and immunotherapy yields synergistic tumor suppression and immune activation, advancing personalized nanomedicine. Despite these advancements, translational hurdles remain nanogenotoxicity, long-term biosafety, immune responses and regulatory barriers. This review emphasizes such challenges while identifying opportunities for strategic innovation in GBM nanotherapy. By uniquely bridging preclinical advances with emerging clinical perspectives, we highlight its distinct contribution within the field. By bridging nanotechnology, molecular oncology and bioengineering, we highlight how rational nanoparticle design can shift GBM management toward targeted, multimodal precision therapy, offering renewed hope against one of oncology's most intractable diseases.

Keywords: Glioblastoma, Nanoparticles, Blood-Brain Barrier, Nanotechnology, Nanomedicine, Nanotherapeutics.

Article History: **Received:** 13 Jan 2026, **Revised:** 09 Feb 2026, **Accepted**: 10 Feb 2026, **Published:** 10 Jul 2026.

Introduction

Glioblastoma is the most common and aggressive malignant brain tumor in adults [1]. The World Health Organization (WHO) recently updated its classification of central nervous system tumors to reflect a deeper understanding of molecular pathophysiology. This revised framework identifies diffuse gliomas as the most prevalent and aggressive type of adult glioma, subdivided into: (1)

oligodendroglioma, IDH-mutant and 1p/19q co-deleted (WHO grade 2 and 3); (2) astrocytoma, IDH-mutant (WHO grade 2–4); and (3) glioblastoma, IDH–wild type (WHO grade 4) [2]. Brain tumors are broadly categorized as benign (non-cancerous) or malignant (cancerous). GBM is a high-grade (grade 3 or 4), malignant tumor characterized by rapid progression, recurrence after treatment and poor prognosis. In contrast, benign tumors are typically low-grade (grade 1 or 2), grow slowly and have a lower likelihood of recurrence [3]. GBM arises from glial cells, the supportive elements of the central nervous system [4], and most frequently affects the brainstem, cerebellum and spinal cord [5]. While the exact etiology remains unclear, high-dose exposure to ionizing radiation is a recognized risk factor of GBM. However, no consistent associations of GBM have been established with lifestyle factors such as alcohol consumption, smoking or drug use [6 - 7]. The clinical manifestations of GBM include neurological deficits, memory impairment, headaches, personality changes and cognitive dysfunction. Although GBM primarily affects adults, it accounts for approximately 3% of pediatric brain tumors as well [8 - 10]. The diagnosis typically involves neurological examination and advanced neuroimaging techniques, often at a late stage due to the tumor's insidious onset and the brain's ability to compensate for structural abnormalities [11 - 13]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are standard tools for assessing tumor location, size and progression. Moreover, several molecular biomarkers such as isocitrate dehydrogenase (IDH) mutation status, epidermal growth factor receptor (EGFR) amplification, O6-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation, p53 mutations, telomerase reverse transcriptase (TERT) promoter mutations and neurofibromatosis type 1 (NF1) are increasingly being used for diagnostic and prognostic evaluations [14 - 16]. Despite substantial research efforts, current treatment options for GBM remain inadequate. Standard therapy involves maximal surgical resection followed by concurrent radiotherapy and chemotherapy with temozolomide (TMZ) [17 - 18]. A more recent innovation, Tumor Treating Fields (TTF), delivers low-intensity (1–2 V/cm), intermediate-frequency (100 kHz^{-1} MHz) electric fields to disrupt mitosis and promote tumor cell apoptosis [19]. Nonetheless, these interventions have only modestly extended patient survival, with median survival remaining around 14 months and tumor recurrence often occurring within seven months of initial diagnosis [20 - 21]. Various nanoparticle platforms have been extensively investigated for the targeted treatment of glioblastoma (GBM), as summarized in the graphical abstract (Figure 1).

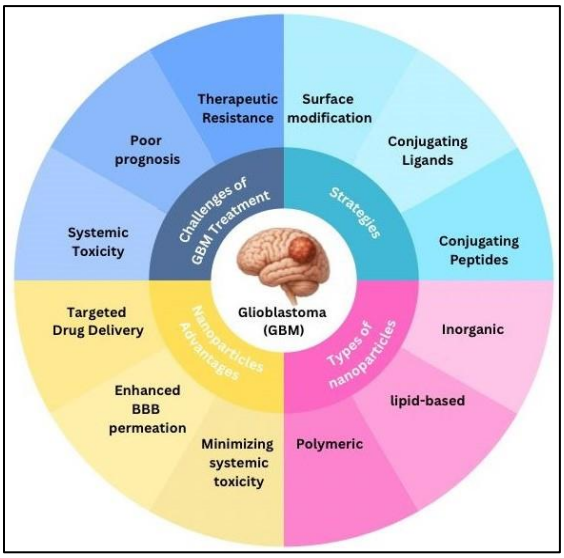

Figure 1: Graphical abstract illustrates the diverse nanoparticle platforms explored for glioblastoma (GBM) therapy.

One of the most significant obstacles in GBM therapy is the limited ability of therapeutic agents to penetrate the blood-brain barrier (BBB) and the blood–tumor barrier (BTB). These physiological barriers prevent over 98% of small-molecule drugs and virtually 100% of large-molecule drugs

from reaching the brain parenchyma, posing a major challenge for effective drug delivery [22 - 24]. While the BBB plays a crucial role in neuroprotection by restricting harmful substances, it simultaneously hinders the delivery of therapeutic agents to the tumor site, further complicating GBM management [25].

To overcome these limitations, nanotechnology has emerged as a promising strategy for enhancing drug delivery in GBM treatment [26]. Engineered nanoparticles (NPs) can improve drug solubility, protect therapeutic agents from degradation and facilitate targeted delivery across the BBB via passive or active transport mechanisms. These systems enable controlled release and reduce systemic toxicity, significantly improving drug localization at tumor sites [27 - 29]. Figure 2 demonstrates the comparison between conventional drug delivery systems and nanoparticle-based delivery for glioblastoma.

Nanoparticles, typically ranging in size from 1 to 100 nanometers, exhibit unique physicochemical properties such as high surface area-to-volume ratio, structural flexibility and enhanced permeability that make them highly effective carriers for anticancer agents [30 - 33]. Depending on the material, nanoparticles can be made from organic material, e.g., dendrimers, liposomes, polymers, and lipid nanoparticles, including solid nanoparticles; inorganic material, e.g., nanoparticles of metal oxides, silver, gold, nanodiamonds, nanotubes, and carbon dots; or a combination of two or more materials [34]. While clinical translation is still in its early stages, nanoparticle-based therapies hold immense potential to revolutionize GBM management. Various nanoparticle platforms including lipid-based carriers designed to traverse the BBB have shown promising results [35 - 37].

In this review, we specifically aim to provide a comprehensive analysis of the evolving role of advanced nanoparticle formulations in GBM therapy. By critically examining the types, mechanisms and clinical applications of these nanoparticle-based formulations and delivery systems,

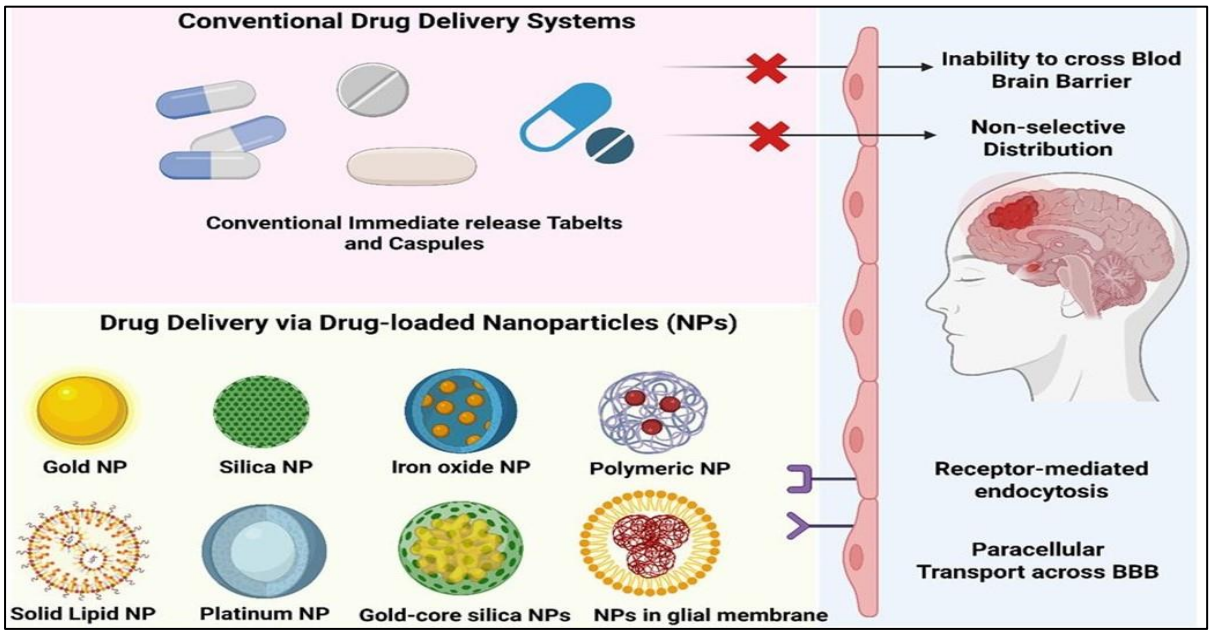

Figure 2: Comparison between conventional drug delivery systems and nanoparticle-based delivery for glioblastoma. Conventional formulations face major challenges like inability to cross the BBB and lack of selectivity, whereas nanoparticles utilize receptor-mediated endocytosis and parallel transport to achieve targeted brain delivery

We highlight their advantages, limitations and future potential. The review also emphasizes how nanotechnology can bridge the translational gap between laboratory findings and clinical outcomes, ultimately contributing to the advancement of personalized and precision medicine in GBM treatment.

Pathophysiology

In this section, we provide a concise yet comprehensive overview of GBM pathophysiology, as understanding its underlying mechanisms is crucial for appreciating how nanoparticles can be strategically applied in its therapy.

Glioblastoma (GBM) is a highly aggressive and complex brain tumor characterized by a multifaceted pathogenesis involving a wide spectrum of genetic, epigenetic and molecular alterations. These changes affect oncogenes, DNA repair mechanisms, tumor suppressor genes and critical cellular signaling pathways, ultimately driving tumor initiation, progression and resistance to therapy [38 - 40]. GBM is broadly classified into two main subtypes: primary (de novo) and secondary glioblastoma. Primary GBM accounts for approximately 80–90% of cases, arises without evidence of a pre-existing lower-grade glioma and typically affects older individuals (median age ~65 years). In contrast, secondary GBM represents 5–10% of cases, evolves from lower-grade astrocytomas and generally occurs in younger individuals (median age ~45 years) [41 - 42].

Cellular origin and cancer stem cell hypothesis

Recent investigations suggest that GBM may originate from neural stem cells or glial progenitor cells residing in the subventricular zone (SVZ). These precursor cells may undergo epigenetic reprogramming, giving rise to glioblastoma stem-like cells (GSCs) with self-renewing and multipotent capabilities, hallmarks that drive tumor growth, therapeutic resistance and recurrence [43 - 45]. Epidermal Growth Factor Receptor variant III (EGFRvIII) has been implicated in facilitating this transformation [44, 46 - 47]. Additionally, mesenchymal stromal cells within the perivascular niche have been proposed as potential glioblastoma-initiating cells, particularly in the mesenchymal subtype [48].

Key generic alterations

GBM is characterized by recurrent mutations in several critical genes, including TP53, PTEN, EGFR, IDH1 and NF1 [49]. Mutations in IDH1/2 disrupt normal cellular metabolism and lead to the production of the oncometabolite D-2-hydroxyglutarate (D-2-HG), which promotes tumorigenesis through epigenetic dysregulation [50 - 53]. EGFR amplification and mutations particularly EGFRvIII, are present in approximately 40% of primary GBM cases and result in constitutive activation of downstream signaling pathways such as PI3K/Akt and MAPK, promoting uncontrolled proliferation and resistance to therapy [54 - 67]. PTEN, a tumor suppressor gene, negatively regulates the PI3K/Akt/mTOR signaling axis. Loss-of-function mutations in PTEN lead to increased cell growth, invasiveness and drug resistance [68 - 69]. TP53 mutations, observed in around 35% of GBM cases, impair apoptosis, compromise genomic stability and enhance angiogenesis. Moreover, gain-of-function TP53 variants may further increase tumor aggressiveness [70 - 73]. TERT promoter mutations (TERTp) are found in roughly 80% of GBM cases and contribute to telomerase reactivation and cellular [74 - 75]. NF1, another tumor suppressor, acts as a negative regulator of the RAS/MAPK signaling cascade. Somatic NF1 mutations have been linked to sporadic GBM and other malignancies [76].

Dysregulated signaling pathways

GBM progression is driven by multiple dysregulated signaling pathways: Wnt/β-catenin signaling plays a crucial role in neurogenesis and stem cell maintenance and is implicated in glioma invasion and proliferation [77]. The PI3K/Akt/mTOR (PAM) pathway governs key cellular functions such as growth, metabolism, angiogenesis and therapeutic resistance [78]. The Notch signaling pathway supports tumor cell survival, self-renewal and resistance to conventional therapies [79]. These pathways represent important molecular targets for the development of next-generation GBM therapeutics.

Tumor microenvironment (tme) and hypoxia

The glioblastoma tumor microenvironment (TME) is a highly dynamic and complex network composed of tumor cells, brain-resident cells, immune infiltrates and extracellular matrix components. GBM cells actively modulate the TME to promote tumor proliferation, migration and resistance through direct cellular interactions and paracrine signaling80. Hypoxia is a defining feature of the GBM microenvironment and plays a pivotal role in tumor aggressiveness. It activates hypoxia-inducible factor-alpha (HIF-α), which upregulates the expression of genes involved in invasion, angiogenesis and metabolic reprogramming. Moreover, brain-resident glial cells such as astrocytes and microglia often adopt tumor-promoting phenotypes, further facilitating malignancy and treatment resistance [81].

In a nutshell, we highlighted the key pathophysiological hallmarks of GBM. GBM pathophysiology is defined by its complex cellular origins, cancer stem-cell driven growth, dysregulated signaling cascades, molecular alterations and a unique hostile tumor microenvironment marked by hypoxia. These interwoven processes collectively trigger the aggressive progression of tumor, therapeutic resistance and poor clinical outcomes, highlighting the hurdles of effective disease management. In the upcoming section, we explore how advanced nanoparticles are being leveraged in pharmacotherapy, not only in GBM therapy but also across a wide range of disorders.

Nano particles in pharmacotherapy

Recent advancements in nanotechnology have significantly reshaped modern medicine, especially in the domains of diagnostics, therapeutics and advanced drug delivery systems [82]. Nanoparticles (NPs), owing to their unique physicochemical properties including high surface area-to-volume ratio, structural flexibility, durability and functionalization potential have become valuable tools across a wide spectrum of medical applications, from cancer therapy to cardiovascular, dermatological and chronic disease management [83 - 84]. Nanoparticles are playing an increasingly pivotal role in early disease detection, particularly in identifying cancer biomarkers and hold promise in managing complex conditions such as Alzheimer's disease. Their utility is also being explored in autoimmune disorders, renal and dermatological diseases, infectious diseases and various cancers. With their capacity for surface modification and precise targeting, NPs support the development of personalized medicine, enabling both targeted therapies and pharmacogenetic approaches. Furthermore, they have demonstrated antimicrobial, antifungal and antiviral potential, expanding their relevance in infectious disease control [85]. Modern nanomedicine now encompasses innovative strategies such as vaccine development, gene therapy, immune modulation, and regenerative medicine. Nanocarriers are being engineered to simultaneously deliver therapeutic agents,

monitor treatment response and enable imaging, thereby facilitating real-time, patient-specific interventions [86]. Of particular importance is the ability of certain nanoparticles to traverse biological barriers, including the BBB, significantly enhancing drug delivery and therapeutic outcomes in neurological and chronic conditions [87]. Based upon the fundamental principles of nanomedicine, we next explore a series of novel nanoparticle-based strategies displaying their unique designs, mechanisms and therapeutic applications across diverse diseases.

Novel nanoparticle formulations

Another shows the design of a sprayable film containing nanocellulose and L-serine–modified silver nanoparticles, which showed not only effective antimicrobial and anti-inflammatory activity but also superior wound healing results in vivo. The novelty of this system lies in the dual role of L-serine, both as a nanoparticle precursor and as an antibacterial enhancer, while nanocellulose provided a porous, breathable, and drug-carrying matrix. This simple yet highly effective platform highlights the potential of multifunctional nanomaterials for clinical wound management and post-procedural care [88]. Parallel advances were seen in wound management, where a nanocomposite hydrogel dressing was developed using herbal extracts of *Ferula gummosa* and UIO-66-NH_2 nanoparticles incorporated into a chitosan–alginate hydrogel. These formulations showed strong antibacterial activity against *Pseudomonas aeruginosa*, antibiofilm efficacy, minimal cytotoxicity and significantly enhanced wound healing in vivo compared to free extract treatments. Their stability under refrigerated conditions further strengthens their translational potential for clinical wound care [89]. In a recent study, selenium nanoparticles encapsulated in niosomes were engineered to overcome stability and bioavailability limitations while targeting oral cancer cells (HSC-3). These nanocarriers displayed remarkable stability, uniformity, and sustained cytotoxicity over 72 hours, significantly outperforming free selenium. By combining biocompatible niosomes with selenium's inherent anticancer activity, the formulation achieved enhanced tumoricidal efficacy, showing how encapsulation strategies can enhance therapeutic durability and selectivity [90]. In another approach, Alectinib-loaded chitosan–alginate nanoparticles (ACANPs) were designed to address solubility and bioavailability challenges linked with non-small cell lung cancer therapy. Using an advanced emulsification and ionotropic gelation method, ACANPs demonstrated threefold improved drug release, markedly lower IC_{50} values in vitro, and nearly 80% higher oral bioavailability in vivo. These findings reinforce the value of polymeric nanoparticle systems in optimizing pharmacokinetics and maximizing therapeutic efficiency of existing drugs [91]. For cancer treatment, folate-targeted liposomal Bleomycin (FL-Bleomycin) demonstrated significant promise in oral cavity cancer (CAL27). By incorporating folic acid into nanoliposomes, this system enhanced tumor-specific uptake, improved cytotoxicity, and induced effective cell cycle arrest at the G2/M phase. The formulation also showed a controlled release profile and downregulated EGFR expression, highlighting its potential for precision therapy in folate receptor-positive tumors [92]. Hyaluronic acid-coated niosomes encapsulating α-terpineol (α-TN-HA) demonstrated strong anticancer potential through selective uptake and apoptosis induction. These particles not only achieved high encapsulation efficiency and stability but also triggered cell cycle arrest, upregulated apoptotic markers (BAX, P21, P53), and exhibited minimal toxicity toward normal cells, highlighting their promise as a targeted and safer cancer therapy [93]. Complementing

these advances, thermoresponsive lipid nanoparticles (TLNs) were developed for hyperthermia-triggered cancer therapy. By exploiting a eutectic fatty acid mixture with a phase transition temperature of ~41 °C, doxorubicin-loaded TLNs achieved burst release under mild hyperthermia while maintaining sustained release at physiological temperature. This design resulted in significantly enhanced cytotoxicity against breast cancer cells under hyperthermic conditions and superior cellular uptake compared to free drug or conventional carriers, offering a stable and practical approach for thermal-drug synergistic therapy [94]. Beyond oncology, nanoparticle systems are being used in organ protection. Investigations on virgin coconut oil (VCO) and glutathione (GSH) in nanoparticulate formulations revealed strong reno-protective effects in a rat model of gentamicin-induced acute renal failure. Compared to conventional formulations, the nanoparticle-based combinations more effectively restored renal function, reduced inflammatory cytokines, and improved histological outcomes. The enhanced protection highlights how nanoparticle delivery can potentiate natural compounds by improving tissue distribution and therapeutic impact [95]. In infectious disease management, a dual-functional nanoparticle system (MVNP-CA/IFN-γ) to remove persistent MRSA infections. This formulation integrated a PLGA core with a mannose-vancomycin lipid shell, enabling cascade targeting of intracellular bacteria within macrophages. By co-delivering the antibiotic chrysomycin A and the immune modulator interferon-γ, the nanoparticles both eliminated bacterial persisters and reprogrammed macrophages toward an M1 phenotype, thereby overcoming persistence and immune evasion. This innovative dual-therapy approach presents a powerful strategy against chronic and recurrent bacterial infections [96]. In neurodegenerative disorders, a chitosan-coated solid lipid nanoparticle (CS-SLN) platform was engineered to intranasally deliver carbenoxolone for Parkinson's disease. This system enhanced brain penetration and sustained release, resulting in enhanced motor coordination, restoration of dopaminergic balance and reduction in oxidative stress, neuroinflammation, and α-synuclein accumulation in a rat model. These findings underscore the potential of mucoadhesive nanocarriers in bypassing the blood-brain barrier and providing neuroprotection in Parkinson's disease [97]. In inflammatory bowel diseases such as ulcerative colitis, silica-coated calcium phosphate nanoparticles carrying siRNA against NF-κB p65 have shown marked efficacy in murine models. These nanoparticles effectively suppressed the NF-κB signaling pathway and demonstrated targeted accumulation in lymphoid-rich tissues, offering promise for the treatment of intestinal inflammation [98].

These advances highlight how novel nanocarriers are moving beyond conventional drug delivery to integrate multifunctional, targeted and stimuli-responsive strategies. By improving selectivity, overcoming biological barriers, and enhancing therapeutic precision, such nanoparticles represent a transformative step toward next-generation pharmacotherapy.

Nanoparticles for glioblastoma

Combinatorial approaches utilizing nanoparticle-based drug delivery systems have emerged as a pivotal advancement in glioblastoma (GBM) therapy. These nanoscale carriers enable targeted delivery of anticancer agents, facilitating enhanced intracellular drug accumulation, sustained release and improved permeation across the BBB. By increasing local drug concentration within tumor tissues, nanocarriers have demonstrated significant promise in suppressing GBM proliferation and overcoming pharmacological barriers to effective treatment [99].

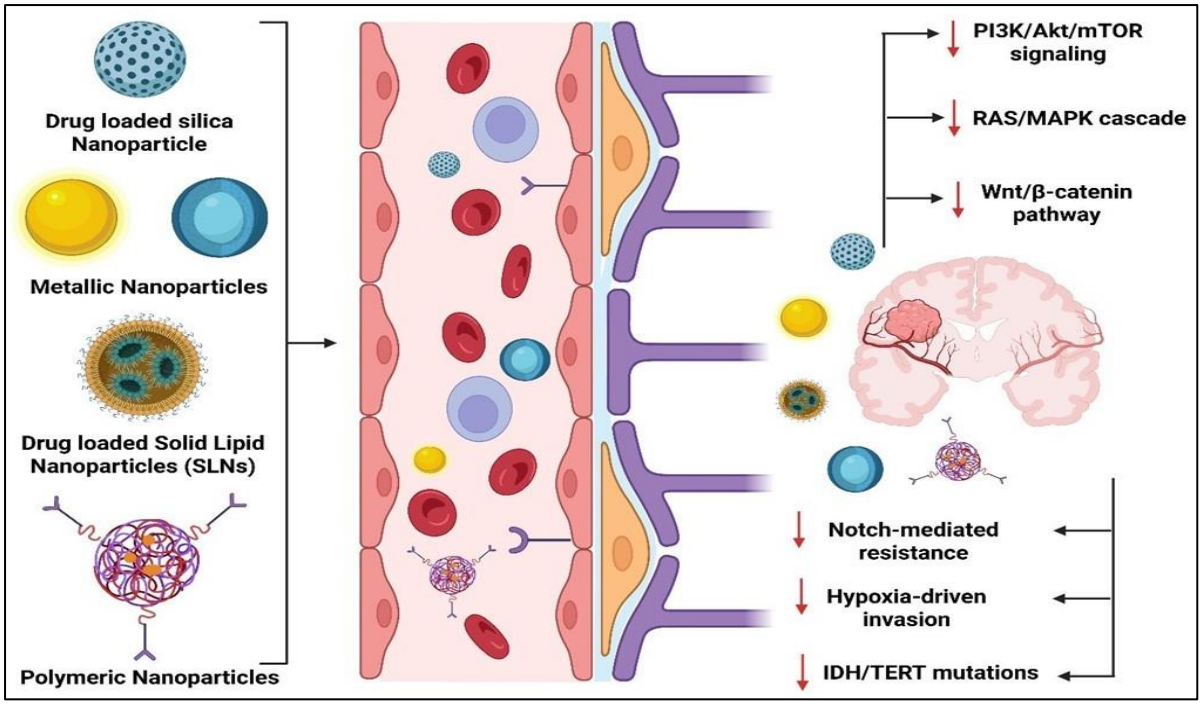

Figure 3: Schematic representation of drug loaded nanoparticles in attenuating brain tumors.

Figure 3 shows the schematic representation of drug loaded nanoparticles in attenuating brain tumors.

Nanoparticles not only enhance chemotherapy delivery but also serve as effective platforms for improving GBM immunotherapy, owing to their ability to modulate immune responses and optimize pharmacokinetics. Both natural and synthetic nanomaterials have been widely explored, with lipid- and polymer-based systems offering excellent biocompatibility and extended systemic circulation. Inorganic nanoparticles including silver, gold, magnetic and iron oxide types offer added functionality such as photothermal responsiveness, radiosensitization and imaging enhancement, reinforcing their role in integrated multimodal GBM therapy [100]. This section highlights the diverse types of nanoparticles studied for glioblastoma therapy.

Gold nanoparticles

Gold nanoparticles (GNPs) have emerged as highly promising candidates for glioblastoma therapy due to their promising physicochemical characteristics, comprising a large surface area-to-volume ratio, biocompatibility, ease of surface modification, and ability to cross the blood-brain barrier. These features make them valuable both as drug delivery vehicles and as enhancers of radiotherapy efficacy in combination treatment strategies [101 - 102].

One noteworthy innovation comprises gold nanoparticles (GNPs) conjugated with oligonucleotides targeting U87MG GBM cells. These constructs achieved over 75% inhibition of metabolic and proliferative activity, beside structural cell damage, validating their potential as key components in multi-pronged nanotherapeutic strategies [103]. PEGylated gold nanoparticles have also proved radiosensitizing and immunomodulatory effects. PEGylation enhanced DNA double-strand break formation following radiation and promoted cytokine-driven immune activation, highlighting their utility in integrative radio-immunotherapy regimens [101]. A synergistic platform combining gold-core silica-shell nanoparticles

(Au@SiO_2 NPs) with low-dose X-ray radiation significantly enhanced immune checkpoint blockade therapy (atezolizumab), boosting macrophage infiltration, increasing survival (up to 40%) and promoting apoptosis. This indicates potential for nanotechnology-enhanced immunoradiotherapy in GBM. In another innovative approach, Au@DTDTPA(Gd) nanoparticles were assessed under long-term cranial window imaging in U87 spheroids and organotypic brain slices. Joined with radiation (2× 5 Gy), they significantly suppressed tumor invasion, reduced malignancy and limited the persistence of stem-like cancer cells proving them to be effective radiosensitizers for GBM [104]. Additional experiments with Au@DTDTPA(Gd) showed these nanoparticles reduced glioma cell motility via altered mechanical properties traction forces, stiffness and adhesion strength rather than ECM degradation. Upregulation of talin-1 and β1 integrin supports their role in mechanical stabilization of glioma cells [105]. The role of gold nanoparticles (AuNPs) in enhancing radiotherapy-induced immunogenic cell death (ICD) has also been explored. In combination with radiotherapy, AuNPs boosted dendritic cell activation and raised the release of ICD-associated damage signals calreticulin (CRT), high-mobility group box 1 (HMGB1) and ATP. In preclinical GBM models, dying tumor cells subjected to the AuNP–radiotherapy combination acted as an autologous tumor vaccine, reducing tumor relapse. These findings support AuNPs as dual-function radiosensitizers with added immunostimulatory benefits [106]. Gold nanoparticles (AuNPs) continue to reap attention for GBM therapy due to their tunable physicochemical features and adaptable design. In one investigation, AuNPs functionalized with oligonucleotides were engineered to selectively target U87MG glioblastoma cells. These conjugates markedly suppressed metabolic activity, induced major morphological disruptions and reduced cancer cell viability by up to 75%. These findings support the potential of gold-based nanotherapeutics as a promising direction for multi-targeted and precision GBM interventions [103].

Lipid nanoparticles

Lipid nanoparticles (LNPs) have happened as striking candidates for brain tumor targeting owing to their desirable characteristics of biocompatibility, minimal toxicity, capacity for blood-brain barrier (BBB) traversal, and suitability for transporting both hydrophobic and hydrophilic drugs [107]. Lipid nanoparticles (LNPs) carrying doxorubicin and TLR agonists (CpG or pIpC) were studied as immunotherapeutic agents. PIpC-based LNPs induced stronger macrophage activation and phagocytic activity, while animal studies long-established better-quality survival and immune infiltration. Fascinatingly, the addition of doxorubicin did not significantly enhance efficacy, highlighting the individual potential of LNP-encapsulated TLR agonists [108]. In another study, a nanostructured lipid carrier (NLC) co-loaded with paclitaxel (PTX) and doxorubicin (DOX) was assessed for its efficacy against GSCs. The PTX–DOX–NLC formulation demonstrated superior inhibition of cellular proliferation and enhanced induction of apoptosis compared to single-drug or non-encapsulated treatments. Mechanistically, it downregulated the PI3K/AKT/mTOR signaling pathway, a key axis in gliomagenesis. Animal models further confirmed its potent anti-tumor efficacy, underscoring its promise as a co-delivery nanosystem for GBM therapy [109]. Additionally, a terpene-functionalized lipid nanocarrier was developed using soybean phospholipids and abietic acid analogues, co-loaded with temozolomide. These single-layer vesicles (~100 nm) exhibited enhanced cytotoxicity against T98G glioma

cells, high TMZ entrapment efficiency and minimized off-target toxicity toward hepatic cells. The incorporation of terpenes significantly improved therapeutic activity, highlighting the potential of nature-inspired nanocarriers in GBM management [110].

In a recent study, it was explored that Ionizable LNPs, already FDA-approved for RNA delivery, face challenges in brain targeting because of the BBB. A recent study employed focused ultrasound (FUS) with microbubbles to transiently interrupt the BBB, empowering efficient delivery of siRNA- and mRNA-loaded LNPs in a GBM mouse model. This approach accomplished 6–12-fold higher delivery proficiency compared to controls, demonstrating the potential of non-invasive, FUS-assisted LNPs for RNA-based therapies in GBM [111]. SLNs combine the benefits of biodegradability, stability, and controlled release. In preclinical models, ultrasmall SLNs co-loaded with paclitaxel, regorafenib, and nanoceria inhibited glioma proliferation, migration, and angiogenesis. Significantly, they accumulated selectively in tumor tissue without off-target toxicity, suggesting their feasibility as a safe, scalable, and cost-effective strategy for GBM therapy [112 - 114]. Additionally, solid lipid nanoparticles (SLNs) targeted toward monocarboxylate transporter-1 (MCT-1) and loaded with a dual-drug combination of carmustine and temozolomide, achieved receptor-specific uptake, gradual drug release and enhanced biocompatibility, marking a potent dual-agent nanotherapeutic strategy [115]. Lipid–polymer hybrid nanoparticles (LPHNPs), comprising a polymeric core enclosed within a lipid-PEG shell, integrate the benefits of both liposomes and polymeric carriers, enabling gene delivery, targeted imaging and combinatory treatment procedures with improved therapeutic indices [116]. Recent advances in nanotechnology have facilitated the design of highly specialized nanoparticles to overcome the therapeutic challenges associated with glioblastoma, particularly the BBB, drug resistance and systemic toxicity. One distinguished example includes thermoresponsive lipid nanoparticles (TLNs), which undergo a phase transition from solid to liquid at 39 °C, matching tumor microenvironment temperatures. This thermally triggered transformation enhances paclitaxel release, offering improved permeability and targeted delivery. Cytotoxicity assays revealed significantly reduced glioblastoma cell viability at 39 °C (69%) compared to 37 °C (82%), validating the TLNs' potential for site-specific chemotherapeutic release with minimal damage to surrounding healthy tissue [117].

Polymeric nanoparticles

Polymer-based nanotechnology has gained substantial courtesy in glioblastoma therapy, primarily due to its ability to deliver precise drug delivery, enhanced BBB penetration, and compliance to the tumor microenvironment (TME). Polymeric nanoparticles (NPs) such as poly(lactic-co-glycolic acid) (PLGA) or polylactic acid (PLA) offer tunable degradation rates, ensuring sustained and controlled drug release within the GBM environment [118]. Their biocompatibility reduces adverse immune responses, while their adaptability supports multifunctional designs capable of combining therapeutic payloads with imaging or synergistic agents. Common polymeric nanostructures include micelles, dendritic polymers, polymer vesicles, hydrogels, and metal-organic frameworks (MOFs), each contributing distinct advantages for drug delivery and tumor targeting [119]. Multifunctional polymeric nanodrugs further enhance therapeutic efficacy by integrating diverse functional modules, permitting multi-targeted combination approaches against tumor heterogeneity [120].

To attain selective delivery, polymeric nanodrugs are often engineered with ligand modifications that exploit receptors overexpressed in GBM cells, comprising transferrin (TfR), folate (FR), and epidermal growth factor receptor (EGFR) [121]. Such approaches diminish off-target effects while ensuring effective tumor accumulation. Recent studies represent this approach: temozolomide (TMZ)-loaded polyethyleneimine (PEI)-based polymeric NPs combined with macrophage membrane coating and low-frequency ultrasound demonstrated improved therapeutic activity compared to free TMZ [122]. Similarly, EGFR-targeted polymeric NPs loaded with gefitinib achieved higher tumor accumulation and enhanced antitumor efficacy in preclinical models [123]. Beyond chemotherapy, lipid–polymer hybrid NPs have been studied for CRISPR/Cas9 delivery, where a cationic ROS-responsive polymer core condensed sgRNA and Cas9, and a 4F-angiopep-2 lipid shell facilitated BBB penetration and glioma targeting. By knocking out STAT3, a central regulator of angiogenesis and immunosuppression, this system normalized tumor vasculature, suppressed pro-tumor cytokines (VEGF, IL-6, IL-10), and reprogrammed the immune microenvironment, ultimately reducing tumor burden and prolonging survival in orthotopic models [124].

Escalating the scope of polymer-based applications, semiconducting polymer systems have also been adapted for immunotherapy. A team of scientists developed a neutrophil-based “Trojan horse” nanosystem capable of co-delivering ferroptosis-inducing agents and immunomodulators, efficiently enhancing immune infiltration and antitumor responses in GBM models [125]. Collectively, these advances underscore the usefulness of polymeric nanoplatforms, which not only improve chemotherapeutic delivery but also enable genetic, targeted, and immunomodulatory strategies tailored to the complex pathology of GBM.

Silver nanoparticles

Silver nanoparticles (AgNPs) have recently attracted attention in oncology due to their broad antimicrobial and anticancer activities, as well as the likelihood of green synthesis approaches using plant extracts [126 - 127]. In glioblastoma therapy, methotrexate-conjugated silver nanoparticles (AgNPs@TEOS-MTX) have been explored as radiosensitizers to improve the efficacy of fractionated radiotherapy. These nanoparticles were thoroughly characterized, showing spherical morphology, nanometric size (~39.9 nm), and favorable zeta potential (−20.8 mV). Hemolysis assays confirmed their biocompatibility, while uptake studies demonstrated nearly complete internalization (99%) by U87 glioblastoma cells. Functionally, AgNPs@TEOS-MTX induced G2/M cell cycle arrest, apoptosis, inhibited proliferation, migration, and tumor sphere formation, with these effects being significantly amplified under 2 Gy X-ray exposure. Collectively, this establishes AgNPs@TEOS-MTX as a potent radiosensitizer with strong translational prospective for glioblastoma treatment [128].

Complementary *in vitro* evidence further supports the radio sensitizing and chemosensitizing role of metallic nanoparticles in GBM. A comparative study on U87MG cells evaluated AgNPs and TiO2NPs in combination with temozolomide (TMZ). Both nanoparticles enhanced TMZ activity by stimulating apoptotic (caspase-3 and 9 activation, DNA fragmentation via CAD) and inflammatory responses (TNF-α, IL-12), as well as increasing lipid peroxidation markers. Microscopic staining confirmed raised apoptosis in combined treatments versus TMZ alone. The observed effects were attributed to modulation of drug efflux transporters, improved drug delivery, and

enhanced intrinsic cytotoxic responses. These findings suggest that AgNPs and TiO2NPs may augment TMZ efficacy, offering a synergistic approach to overcome chemoresistance in glioblastoma [129]. In radiotherapy, silver nanoparticles (AgNPs) have emerged as effective neutron radiation sensitizers. Studies across diverse cancer models, including glioblastoma, have demonstrated sensitization ratios between 1.22 and 1.47, with maximum cytotoxicity (~96.2%) at elevated nanoparticle concentrations, signifying strong potential in neutron-assisted radiotherapy [130]. Biogenically synthesized Ag/AgCl nanoparticles, derived from yeast, exhibited superior antiproliferative activity against GBM02 glioblastoma cells up to 82% inhibition exceeding the efficacy of temozolomide (TMZ). These nanoparticles showed minimal cytotoxicity toward normal astrocytes and co-treatment with TMZ did not improve therapeutic effects, signifying selective tumor targeting and potential for safer monotherapy [131].

Liposomes

Liposomes, owing to their high biocompatibility and low toxicity, remain a valued drug delivery system for crossing the BBB [132]. A multifunctional liposome (Lpo@Cu2Se-GOx) demonstrated strong glioma inhibition by combining starvation therapy and ferroptosis induction. After uptake, GOx oxidized glucose into gluconic acid and H_2O_2, disrupting antioxidant defenses and triggering Cu^{2+}-mediated Fenton-like reactions. This cascade led to lipid peroxidation, ferroptosis, and immunogenic cell death, promoting dendritic cell maturation and T cell infiltration, with significant antitumor effects and no adverse reactions *in vitro* and *in vivo* [133]. Similarly, glucose oxidase–powered liposomal nanobot (lipoNbot) showed a 4.3-fold higher drug delivery efficiency by manipulating acidic, glucose-rich tumor microenvironments for chemotactic self-navigation. Its GOD-modified membrane and γ-glutamylated lipids permitted BBB penetration, lysosomal escape, and targeted chemotherapy against GBM [134]. An additional method employed Angiopep-2-modified liposomes co-loading resveratrol and α-melittin. These reduced α-melittin-associated hemolysis, enhanced BBB penetration, inhibited tumor growth, and prolonged survival in GB models. Mechanistically, they induced apoptosis, pyroptosis (via GSDMD, GSDME, caspase-3, NLRP3), and repressed EMT through Wnt/β-catenin pathway modulation, suggesting potential for GB treatment [135].

Silica nanoparticles

Mesoporous silica nanoparticles (MSNs), with large surface area, sponginess, and tunable surfaces, are promising “smart” carriers for tumor-targeted therapy [136-137]. A PTX-loaded MSN system topped with β-cyclodextrin via acid-cleavable hydrazone linkage, further upgraded with chlorotoxin (CHX), showed increased toxicity in U87 GBM cells despite lower uptake, representing tumor-environment–responsive release and receptor targeting potential [138]. To enhance chemodynamic therapy (CDT), a multifunctional hollow organosilicon nanosystem (HCTG-C) was designed, assimilating glucose oxidase (GOx), copper sulfide (CuS), and tirapazamine (TPZ) within CT2A glioma cell membrane coating. This platform allowed self-sustaining H_2O_2 production, GSH-triggered ferroptosis via Cu(I)-driven Fenton-like reactions, and hypoxia-activated chemotherapy, achieving powerful *in vitro* and *in vivo* antitumor efficacy with real-time MRI monitoring [139]. Additional approach established metformin-loaded Mn_3O_4@SiO_2@cRGD nanoparticles (MSMC NPs), which exhibited high loading, pH-responsive release (70% at pH 5.5), and enhanced uptake in U87/U251 cells. They reduced

viability, inhibited migration by 80% in spheroids, and significantly induced apoptosis, highlighting their theranostic potential for precise GBM treatment [140]. A study demonstrated a novel combinatory system integrating Au@DTDTPA(Gd) with PEGylated mesoporous silica nanoparticles (MSNs) modified with octyl chains (C8-MSNs) for transporting docetaxel (DTX) to TMZ-resistant GBM. These C8-MSNs were biocompatible, non-hemolytic and preserved their drug-carrying efficiency. In vivo imaging confirmed their selective accumulation in tumor tissues and effective traversal across the blood–brain tumor barrier (BBTB). In intracranial glioma models, DTX-loaded C8-MSNs improved survival by over 50%, reduced toxicity compared to free DTX and made considerable tumor regression. The treatment activated apoptosis markers such as cleaved caspase-3 and PARP, approving robust antitumor efficacy [141].

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) offer a theranostic platform for GBM due to their magnetic responsiveness, biocompatibility, and ease of functionalization [142]. A novel approach functionalized iron oxide nanoparticles (IONPs) with glucuronic acid to exploit GLUT1-mediated transcytosis, further improved by mild hypoglycemia. These IONPs empowered efficient BBB penetration and proceeded as magnetic hyperthermia mediators, with MRI-guided preclinical studies showing noteworthy tumor growth delay, highlighting their strong potential for targeted GBM therapy [143]. Similarly, magnetic nanoparticles such as transferrin-conjugated dextran-spermine systems showed pH-sensitive drug release, superparamagnetism, and high cytotoxicity in glioblastoma cells. In vivo biodistribution studies confirmed their ability to cross the BBB and preferentially accumulate in brain tissues, marking them as promising agents for precision-targeted theranostics [144]. Another promising system involves Angiopep-2-conjugated lipid magnetic nanocarriers encapsulating temozolomide (Ang-TMZ-LMNVs). These established synergistic effects with magnetic hyperthermia in vivo, showing strong tumor accumulation and suggestively extending survival in glioblastoma-bearing mice [145]. Oleylamine-functionalized Fe_3O_4 magnetic nanoparticles, encapsulating methotrexate in a micellar configuration, induced substantial pro-apoptotic effects (~10-fold increase vs. non-cancerous cells), with pH-sensitive release (85% at pH 5.0) and raised uptake by U87 cells (1.92-fold). These results highlight their suitability for magnetically targeted and controlled chemotherapeutic applications [146].

Polymeric nanoparticles loaded with cisplatin have addressed critical challenges like multidrug resistance and systemic toxicity by enhancing intracellular drug retention, triggering apoptosis and downregulating resistance-related transporters (ABCB1 and ABCG2). These features translate to improved therapeutic performance in GBM models [147]. A highly sophisticated platform employed triblock copolymer-derived macromolecular prodrugs with platinum-crosslinked cores and gadolinium coating. These nanoparticles provided dual functionality MRI contrast enhancement and potent anti-tumor activity through increased Pt DNA adduct formation and prolonged drug retention [148].

Metal oxide nanoparticles

Metal nanoparticles have gained attention for GBM therapy due to their roles in imaging, drug delivery, and radiosensitization [149]. A study shows that bovine serum albumin-coated copper oxide nanoparticles (BSA@CuO-NPs) improved stability and biocompatibility, and when combined with X-ray irradiation (2 Gy), significantly reduced clonogenic survival, induced apoptosis, and increased γ-H2AX

foci formation in U87 cells, confirming enhanced DNA damage and radio sensitization [150]. Similarly, sodium-doped zinc oxide nanoparticles synthesized via green chemistry with zingerone showed selective cytotoxicity against U87 cells while sparing normal HEK cells. Mechanistic analysis exposed apoptosis and TP53 pathway activation, with upregulation of PTEN, BAX, and P21 and downregulation of Bcl2, highlighting their promise as targeted anticancer agents [151]. Likewise, temozolomide-loaded superparamagnetic iron oxide nanoparticles (SPIONs), functionalized with folic acid and PEG, delivered superior outcomes in tri-modal therapy, integrating radiotherapy, thermal ablation and MRI-guided imaging. These systems achieved nearly twice the anti-proliferative effect compared to dual-modality treatments [152].

Carbon nanotubes

Carbon nanotubes (CNTs), particularly single-walled carbon nanotubes (SWCNTs), have emerged as highly promising nanomaterials in medicine and biotechnology due to their distinctive structural and physicochemical properties. Their ability to penetrate biological membranes, undergo surface functionalization, and facilitate targeted drug transport makes them suitable tools for both diagnostic and therapeutic applications in oncology, including glioblastoma multiforme (GBM) [153]. The exceptionally high surface area, tunable surface chemistry, and drug-loading capacity of CNTs enable efficient encapsulation and delivery of therapeutic molecules. Functionalization with targeting ligands further enhances tumor specificity, improving drug accumulation in GBM tissue while limiting systemic exposure. Advancements in CNT-based systems have confirmed their ability to transport chemotherapeutic drugs, nucleic acid-based therapies, and small molecules across the BBB, addressing one of the major limitations in GBM management. Multifunctional CNTs that integrate imaging probes with therapeutic payloads have also been developed, allowing simultaneous diagnosis, treatment, and real-time monitoring. Despite these advantages, challenges such as toxicity, biocompatibility, regulatory concerns, and the need for efficient clinical translation remain critical barriers that must be resolved before large-scale application [154]. In addition to drug delivery, CNT-based biosensing platforms have been explored for GBM cell detection. For instance, multi-walled CNTs (MWCNTs) functionalized with 4-aminothiophenol (4ATP) and subsequently electrodeposited on screen-printed gold electrodes provided a surface for conjugating arginyl–glycyl–aspartic acid (RGD) peptides. This engineered platform assisted the selective adhesion and monitoring of U-87MG glioblastoma cells through differential pulse voltammetry (DPV) and fluorescence imaging, demonstrating a linear detection range of 10^2–10^6 cells/mL [155]. Such platforms highlight the diagnostic potential of CNT-based nanostructures in GBM research.

Beyond delivery and detection, CNTs have also been shown to influence bioelectric signaling in glioblastoma. Studies reveal that CNT-polymers (CNTPs), in combination with externally applied electric fields, can alter transmembrane potential (Vmem) in GBM cells. Interestingly, Vmem modulation was more pronounced in invasive cancers, where it enhanced cellular responsiveness to stimuli, whereas in less invasive cancers, it predominantly increased metabolic activity. Significant changes in the cell cycle were observed approximately 48 hours post-treatment, underscoring the potential of CNTPs as modulators of tumor cell physiology [156].

Collectively, these findings emphasize the multifaceted role of CNTs in GBM research

ranging from drug delivery and biosensing to cellular modulation. While their unique properties make them strong candidates for next-generation nanomedicine, overcoming safety and translational challenges remains essential for their incorporation into clinical neuro-oncology.

Quantum dots (QDs)

Quantum dots (QDs) have shown considerable potential in oncology, offering targeted drug delivery, real-time imaging, and reduced systemic toxicity across multiple cancers, including glioblastoma [157]. Their small size, high photostability, and tunable emission properties make them effective tools for precise diagnostics and therapy.

Semiconductor QD biosensors, such as CdSe–CdS core–shell and carbon-based QDs, functionalized through EDC/NHS or thiol–maleimide chemistry, have been conjugated to antibodies and aptamers targeting biomarkers like EGFRvIII, IDH1/2 mutations, and MGMT promoter methylation. These systems translate biomarker recognition into quantitative optical signals using FRET or multiplex immunoassays, achieving sub-picomolar sensitivity in plasma and cerebrospinal fluid analyses. Beyond detection, QD-drug conjugates enable real-time tracking of personalized treatments. Despite these benefits, clinical progress is hindered by heavy-metal toxicity, nanoparticle aggregation, and regulatory concerns. Strategies such as PEGylation, silica encapsulation, and zwitterionic coatings are under development to improve in vivo stability and safety, with optimization of QD composition remaining crucial for clinical translation [158].

Experimental studies further highlight QD effects on glioblastoma biology. Cadmium–selenium QDs, at sub-toxic doses, significantly reformed the transcriptome of T98G glioblastoma cells after 72 hours of exposure. Key changes were noted in pathways related to neuroinflammation and hormonal regulation of the hypothalamus, with pro-inflammatory interleukins downregulated rather than upregulated. These conclusions suggest distinct immunomodulatory effects, though they raise concerns about potential impacts on fertility [159].

Functional applications of QDs in receptor targeting have also been explored. Transferrin-conjugated QDs (QD–Tf) were employed to quantify transferrin receptor (TfR) distribution in glioblastoma cell lines U87 and DBTRG-05MG, as well as HeLa cells. Flow cytometry and confocal microscopy revealed higher TfR labeling in DBTRG-05MG and HeLa cells compared to U87, with DBTRG-05MG showing enhanced receptor recycling. This supports the specificity and efficiency of QD–Tf bioconjugates in targeting TfR-mediated pathways [160].

Additionally, graphene quantum dots (GQDs) have appeared as biocompatible substitutes with superior electronic and optical properties and the ability to cross the BBB. A systematic review of 658 studies identified 10 key works focusing on GQDs in glioblastoma therapy. Applications included enhancing chemotherapy and photothermal therapy, as well as biosensing, bioimaging, and drug delivery. While research remains limited, these findings underscore the potential of GQDs as multifunctional platforms for glioblastoma treatment [161]. Collectively, QDs ranging from traditional semiconductors to graphene-based variants offer a versatile toolkit for glioblastoma therapy and diagnostics. However, addressing toxicity and stability challenges remains essential for their clinical advancement.

Nanodiamonds (NDs)

Nanodiamonds (NDs) have emerged as

promising nanomaterials for brain-targeted drug delivery due to their nanoscale size, high surface area, ease of functionalization, biocompatibility, and ability to cross the BBB. These properties enable them to bind multiple drugs and deliver bioactives with minimal side effects, making them valued candidates for treating neurological and infectious disorders such as Alzheimer's disease, Parkinson's disease, glioblastoma (GBM), HIV, amyotrophic lateral sclerosis, Huntington's disease, stroke, schizophrenia, epilepsy, encephalitis, sepsis, and meningitis [162]. In glioblastoma specifically, a reciprocal STAT3/IL-6 signaling loop between glioblastoma cells (GBCs) and astrocytes has been identified, driving tumor proliferation, invasion, and resistance to apoptosis. Doxorubicin-polyglycerol-nanodiamond conjugates (Nano-DOX), delivered via GBM-associated macrophages, were shown to suppress STAT3 activity in GBCs, reducing IL-6 secretion and disrupting this feedback loop. Nano-DOX also counteracted temozolomide-induced STAT3 activation, a key driver of chemoresistance, thereby offering a novel therapeutic approach for modulating the GBM microenvironment [163]. Beyond oncology, nanodiamonds have also shown promise in epilepsy management. To overcome poor BBB permeability of zonisamide (ZNS), a nose-to-brain (NTB) delivery system using carbon-based biocompatible nanodiamonds was established. An optimized intranasal ND-ZNS formulation (ND-ZNS F1) demonstrated favorable size (193.7 ± 19.3 nm), high loading efficiency (87.1%), and biphasic release suitable for both acute and chronic epilepsy treatment. *In vivo* studies demonstrated enhanced brain uptake, improved pharmacokinetics, and reduced systemic exposure compared to oral and intranasal free ZNS. In a temporal lobe epilepsy rat model, ND-ZNS F1 improved brain activity and histopathology while reducing epileptic biomarkers (NSE, NEFL, MMP-9) and modulating epigenetic pathways (miR-199/SIRT-1 and PVT-1/BDNF). These findings confirm ND-ZNS as a promising strategy for effective epilepsy management with lower dosing and fewer systemic side effects [164].

Together, these studies highlight the versatility of nanodiamonds in crossing the BBB, disrupting tumor-promoting pathways in GBM, and enabling targeted delivery for neurological diseases, supporting their development as multifunctional platforms in GBM.

Emerging nanoplatforms in glioblastoma

Nanomotors

Nanomotors signify an emerging active drug delivery platform for GBM, offering self-propelled motion that enables autonomous navigation across biological barriers. Unlike passive carriers, nanomotors can actively bypass the BBB, achieve deep tumor penetration, and enhance localized drug accumulation, thereby improving therapeutic efficacy while minimizing systemic toxicity. Recent advances have demonstrated different functionalized designs, including chemotactic nanomotors, near-infrared (NIR) light-driven nanomotors, and bubble-driven nanomotors, each tailored for precise GBM targeting and therapy [165].

A biomimetic hybrid cell membrane-modified dual-driven heterojunction nanomotor (HM@MnO_2-AuNR-SiO_2) was engineered to mimic glioma and macrophage surface traits, enabling BBB crossing and tumor targeting. Its heterojunction structure allowed dual propulsion by NIR-II light and oxygen bubbles, while AuNR-MnO_2 facilitated ROS generation, inducing immunogenic cell death. MnO_2 also released Mn^{2+} ions in the tumor microenvironment, activating the cGAS-STING pathway to enhance

antitumor immunity. *In vitro* and *in vivo* studies confirmed active targeting, M1 macrophage polarization, dendritic cell maturation, and effector T-cell activation, leading to improved GBM immunotherapy [166].

In a study scientists established biomimetic nanomotors with hollow openings camouflaged by hybrid cell membranes. Compared to Janus structures, the hollow design provided stronger propulsion and enabled efficient BBB crossing, tumor targeting, and deep diffusion against pressure gradients. These Bio-motors enhanced radiosensitivity, suppressed GBM growth, and prolonged survival in tumor-bearing mice, suggesting strong potential as modular carriers for combined therapy [167].

In a complementary approach, glucose-driven Janus nanomotors were fabricated by integrating platinum nanodendrites with mesoporous silica nanoparticles loaded with doxorubicin and capped by glucose oxidase (GOx). Propulsion occurred through a cascade reaction where GOx produced H_2O_2 from glucose, subsequently decomposed by PtNds into O2. GOx also served as a gatekeeper, releasing doxorubicin in response to intracellular proteases. Evaluations in cancer cells, spheroids, animal models, and patient-derived organoids demonstrated strong antitumor efficacy via synergistic drug release, ROS production, glucose depletion, and hypoxia reduction, marking a step toward clinical translation of endogenously fueled nanomotors [168].

Nanosponges

Nanosponges are porous, sponge-like nanocarriers with widespread cavities and a mesh-like network, enabling high drug, probe, or photosensitizer loading through encapsulation, conjugation, or absorption. They are broadly classified into polymer-, inorganic-, and bio-derived nanosponges, and their porous voids can be sealed with lipids or polymers to prevent premature leakage, protect therapeutic cargo, and sustain release. By overcoming limitations of conventional carriers, nanosponges have gained attention for cancer therapy and theranostics, including immunotherapy, targeted therapy, and chemotherapy [169].

A miR-nanosponge coated with BV2 cell membranes (BM@miR-nanosponge) was designed to cross the BBB and neutralize multiple oncogenic miRNAs (miR-9, miR-21, miR-215, miR-221). This multifunctional nanosponge significantly suppressed GBM progression, enhanced immune modulation, and extended the survival of GBM-bearing mice, outperforming temozolomide (TMZ), thereby offering a comprehensive miR-based therapeutic strategy [170]. In another study, hierarchical self-uncloaking CRISPR-Cas13a RNA nanococoons (RNCOs-D) were engineered, incorporating programmable RNA nanosponges (RNSs) for targeted delivery and controlled drug caging. The system enabled tumor-specific activation of Cas13a upon recognition of EGFRvIII mRNA, resulting in effective gene silencing and synergistic antitumor activity both in vitro and in vivo. This design underscores the promise of RNA-based nanosponges for precise and multimodal GBM therapy [171].

Hydrogels

Hydrogels have recently emerged as versatile nanoplatforms for GBM therapy and modeling, owing to their ability to mimic the extracellular matrix, encapsulate therapeutic agents, and provide sustained local drug delivery. Their tunable mechanical and biochemical properties make them attractive for both preclinical models and advanced treatment strategies. One study encapsulated U87 and patient-derived GBM spheroids in polyethylene glycol-based hydrogels of varying stiffness

(~1–7 kPa) to assess microenvironment effects on invasion and temozolomide (TMZ) response. Spheroids remained viable across all gels, with U87 cells infiltrating more in softer matrices and showing stiffness-dependent hypoxia responses. Patient-derived spheroids, however, exhibited no stiffness-related drug sensitivity, emphasizing the need to consider microenvironment mechanics in GBM models [172]. Another approach integrated liposome-like particles loaded with doxorubicin (LLP-DOX) into chitosan/hyaluronic acid/polyethyleneimine (CHI/HA/PEI) hydrogels for local therapy. This hybrid system ensured sustained drug release for up to 148 hours, demonstrated biocompatibility, and significantly reduced GBM spheroid viability compared to LLP-DOX alone, highlighting its potential for controlled local chemotherapy [173].

A biomimetic strategy combined brain-derived decellularized extracellular matrix (dECM) with hyaluronic acid methacrylate (HAMA), creating hydrogels that closely resembled native GBM tissue. These constructs supported adhesion, invasion, and tumor–stroma interactions, while coculture with microglia enhanced glioblastoma aggressiveness. The model offers a physiologically relevant platform for studying GBM progression and testing therapeutics [174]. To provide a consolidated overview, Table 1 summarizes the diverse novel nanoparticles explored for GBM therapy, highlighting their mechanisms, unique features and therapeutic outcomes.

Table 1: Novel nanoparticles in glioblastoma therapy.

No.	Nanoparticle	Size (nm)	Delivery Platform	Therapeutic Mechanism in GBM	Ref
1	Hybrid nanoparticles	50–300	Composite material-based	Multi-modal drug delivery systems with enhanced targeting accuracy	[175]
2	Solid lipid nanoparticles (SLNs)	50–1000	Fat-derived carriers	Encapsulate therapeutics, regulate release patterns, target tumor cells	[176]
3	Polymeric micelles	10–100	Self-assembled amphiphilic copolymers	Boost drug solubility, ensure selective delivery, increase uptake by cancer cells	[177]
4	Gold nanoparticles	15–50	Metallic-based	Amplify radiotherapy impact, facilitate precise drug transport	[178]
5	Lipid-core nanocapsules	50–200	Lipid-centered core–shell	Safeguard active drugs, improve bioavailability, directed delivery	[179]
6	Quantum dots	2–10	Semiconductor-based	Aid in tumor visualization, fluorescent targeting, and drug carriage	[180]
7	Magnetic nanoparticles	10–100	Magnetically navigable metals	Magnet-guided targeting, concurrent imaging support	[181]
8	Liposomes	50–200	Phospholipid vesicles	Encapsulate drugs for improved stability, minimize systemic toxicity	[182]
9	Dendrimers	1–10	Highly branched polymers	Precision delivery with high drug-loading capacity	[183]
10	Mesoporous silica nanoparticles	50–300	Porous silica framework	Controlled cargo release, targeted drug transportation	[184]
11	Calcium phosphate nanoparticles	50–200	Mineral-based systems	Gene vector potential, pH-responsive release	[185]
12	Carbon nanotubes	1–100	Carbon allotrope-based	Improves therapy efficiency, assists in diagnostics	[186]
13	Iron oxide nanoparticles	1–100	Magnetic metal particles	Aid in image-guided delivery and therapy intensification	[187]
14	Nanospheres	50–500	Diverse core types (polymer/metal/silica)	Deliver and discharge drugs, enhance absorption by tumor cells	[188]
15	Nanosuspensions	50–1000	Drug particles suspended in fluids	Boost solubility and bioavailability, promote targeted therapy	[189]

No.	Nanoparticle	Size (nm)	Delivery Platform	Therapeutic Mechanism in GBM	Ref
16	Hydrogels	10–1000	Hydrophilic polymer network	Support localized therapy, drug depot in tissues	[190]
17	PLGA nanoparticles	100–1000	Biodegradable polyester	Enable slow-release delivery and tumor-specific localization	[191]
18	PEG-coated nanoparticles	50–200	Polymeric with stealth PEG	Evade immune system, extend blood circulation time	[192]
19	Bioresponsive nanoparticles	50–200	Stimuli-sensitive carriers	Discharge drugs in response to tumor microenvironment	[193]
20	PLGA (co-glycolic acid) nanoparticles	100–500	Biodegradable co-polymers	Controlled drug delivery and tumor cell targeting	[194]

Clinical transition of nanoparticle-based therapies in glioblastoma

The translation rate from preclinical models to clinical cancer trials is approximately less than 8% [195]. Given below are some early-phase clinical trials that provide crucial understanding of safety, feasibility, pharmacokinetics, and preliminary efficacy. Table 2 shows current ongoing and completed clinical trials on nanoparticles in glioblastoma retrieved from clinicaltrials.gov.

EGFR (V)-EDV-Dox Nanocells (Clinical Trials.gov Identifier: NCT02766699) on 2016-10-25)

The EnGeneIC Delivery Vehicle (EDV) system which is composed of bacterially derived nanocells loaded with doxorubicin and targeted against EGFR, entered a phase I/II open-label clinical trial in recurrent GBM. This study tested a dose-escalation design with weekly infusions over seven weeks, followed by radiological evaluation. The results of phase I demonstrated that doses up to 5×10^9 nanocells were actually well tolerated and safe [196].

AGuIX Nanoparticles as Radio-sensitizers (ClinicalTrials.gov Identifier: NCT04881032)

The NANO-GBM trial identified intravenous gadolinium-based nano-particles (AGuIX) as radiosensitizers in newly diagnosed GBM patients undergoing radiotherapy and temozolomide. In phase Ib, patients tolerated up to 100 mg/kg without dose-limiting toxicities attributable to AGuIX, and MRI confirmed widespread intratumoral distribution.

Table 2: Ongoing and completed clinical trials on nanoparticles in glioblastoma. Data retrieved from ClinicalTrials.gov.

Clinical Trials. gov ID	Registered on	Phase	Status	Intervention / Nanoparticle	Indication	Reference
NCT02766699	2016-10-25	Phase I	Completed	EGFR (V)-EDV-Dox Nanocells	Recurrent GBM	[196].
NCT04881032	2022-03-07	Phase I/ II	Active, not recruiting	AGuIX Nanoparticles as Radiosensitizers	Newly diagnosed GBM	[197]
NCT03020017	2017-05-25	Early Phase I	Completed	NU-0129 (Spherical Nucleic Acids)	Recurrent GBM	[198]
NCT00734682	2008-08-01	Phase I	Completed	liposomal irinotecan	Recurrent High-Grade Gliomas	[199]
NCT06271421	2024-01-01	Not applicable	Recruiting	NanoTherm® (ANCHIALE)	Adjuvant Therapy of Glioblastoma Multiforme	ClinicalTrials.gov ID: NCT06271421

The recommended phase II dose (100 mg/kg) is now being tested in the randomized portion of the study to evaluate efficacy outcomes such as 6-month progression-free survival [197].

NU-0129 (Spherical Nucleic Acids, ClinicalTrials.gov Identifier: NCT03020017)

A first-in-human, open-label phase 0 trial studied NU-0129, a gold nanoparticle-based spherical nucleic acid (SNA) carrying siRNA against the GBM oncogene Bcl2L12. Patients with recurrent GBM received a single intravenous infusion followed by tumor resection. This study showed successful tumor penetration, uptake in glioma cells, and reduction of Bcl2L12 protein expression, with no report of grade 4–5 toxicities. This trial established SNAs as a feasible and safe precision-medicine approach for systemic RNAi delivery in GBM patients [198].

Nanoliposomal Irinotecan (Clinical Trials.gov Identifier: NCT00734682)

A phase I trial assessed liposomal irinotecan (nal-IRI, MM-398, PEP02) in patients with recurrent high-grade gliomas, stratified by UGT1A1 genotype. The formulation delays drug circulation and enhances tumor exposure compared to conventional irinotecan. Dose escalation identified maximum tolerated doses of 120 mg/m² in wild-type patients and 150 mg/m² in heterozygotes. The toxicity profile (diarrhea, dehydration, fatigue) was consistent with known irinotecan effects, supporting further evaluation, including convection-enhanced delivery approaches [199].

NanoTherm® ANCHIALE Study (Clinical Trials.gov Identifier: NCT06271421)

The ANCHIALE trial (NCT06271421) assesses NanoTherm® therapy, a nanoparticle-based magnetic hyperthermia system, in patients with recurrent glioblastoma multiforme (GBM). After surgical resection, iron oxide nanoparticles (NanoTherm ASI) are introduced into the resection cavity, followed by six hyperthermia activations using an external magnetic field (days 10–28). Patients are examined for up to two years, with endpoints including progression-free survival, overall survival, quality of life and safety. Compared to the Stupp protocol, this approach aims to improve survival outcomes and treatment tolerability.

Future directions and challenges

Clinical trials of nanoparticle therapies in glioblastoma remain preliminary but promising. NU-0129 showed intratumoral gold uptake with target knockdown, and AGuIX enabled tumor distribution through MRI. However, consistent improvements in efficacy and patient outcomes are still lacking, demonstrating the challenges of clinical translation.

Although preclinical models suggest variable nanoparticle penetration into the brain, human data required is inadequate. NU-0129 confirmed intratumoral gold uptake and AGuIX demonstrated measurable contrast enhancement, yet most clinical studies still rely on surrogate pharmacokinetic or safety endpoints instead of regulated measurements of tumor exposure, making cross-trial comparisons difficult. Most GBM nanoparticle studies remain confined to Phase 0–I, emphasizing safety and pharmacokinetics rather than efficacy. Cohorts are typically small and clinically heterogeneous, mixing newly diagnosed and recurrent patients, differing resection status and variable molecular subtypes which makes it difficult to come to strong and steady conclusions. Systematic reviews of nanomedicine translation highlight that such trial designs inherently limit the detection of clear efficacy signals.

Despite good heterogeneity of GBM, few nanoparticle trials incorporate prospective stratification by key tumor biomarkers such as MGMT methylation, EGFR amplification or IDH status. In the absence of biomarker-guided enrollment or correlative endpoints, risks overlooking responsive subgroups may allow negative aggregate results to diminish true therapeutic benefit.

Nanoparticle systems are well suited for multimodal therapies, such as combining drugs with radiosensitizers, immune modulators, or gene therapies. Yet, most GBM trials test single agents in isolation. Keeping in consideration the tumor's complex resistance mechanisms, adaptive trial designs which explore rational combinations for example, nanoparticle radiosensitizers with immune checkpoint inhibitors remain underutilized.

Clinical trials rarely provide extended follow-up on nanoparticle retention, off-target distribution, immune effects, or potential genotoxicity. Evidence from nanotoxicology studies shows variable inflammatory and genetic effects across particle types, highlighting the need for standardized, potential safety monitoring in future trials. Variability in animal models, dosing metrics, and outcome measures, such as imaging versus histology, limits reproducibility and boosts expectations for clinical success. Reviews consistently call for standardized preclinical pipelines, validated imaging biomarkers, and centralized assay platforms to enhance predictability.

In conclusion, clinical trials on nanoparticle-based therapies for glioblastoma emphasizes promising advances but their results remain limited by small sample sizes, incomplete long-term data and inconsistencies between trial phases. Addressing these gaps requires larger, multi-pivotal research with standardized endpoints and long-term monitoring. Only through such coordinated efforts can the true therapeutic importance of nanoparticles in glioblastoma therapy can be fully realized.

Conclusion

Glioblastoma (GBM) remains one of the most aggressive and therapeutically challenging brain tumors, characterized by high recurrence rates, resistance to standard therapies and poor patient outcomes. Nanotechnology offers a paradigm shift in GBM management by enabling precise, multifaceted therapeutic delivery across the BBB while minimizing systemic toxicity. This review highlights the diverse landscape of nanoparticle systems and bioinspired platforms engineered to enhance the efficacy of chemotherapeutics, radiotherapy, immunotherapy, gene therapy and photothermal treatments. Notable advances have demonstrated improved tumor specificity, favorable pharmacokinetics and synergistic therapeutic outcomes. Bioresponsive and targeted nanocarriers further address intratumoral heterogeneity and drug resistance, reinforcing their translational promise. Moreover, innovative strategies have emerged to reprogram the tumor microenvironment, target glioma stem cells and amplify immune-mediated tumor suppression. Despite these advances, the clinical translation of nanoparticle-based therapies remains limited. Key challenges include nanogenotoxicity, immunogenic responses, manufacturing reproducibility and limited long-term safety data. Additionally, regulatory hurdles and the complex biology of the GBM microenvironment hinder widespread clinical adoption. Nonetheless, the convergence of materials science, neuro-oncology and bioengineering presents an unprecedented opportunity to redefine GBM treatment. Continued interdisciplinary research, standardization of protocols and investment in clinical trials are critical to bridge the gap between

laboratory innovation and clinical application. Ultimately, nanomedicine has the potential to evolve GBM therapy from a palliative approach to a precise, personalized and more effective paradigm.

Author contribution

H.S. conceived the study; H.S. and A.K. drafted the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received to assist with the preparation of this manuscript.

Declarations

Ethical approval

Not applicable, since the work does not involve any study with human participants or animals.

Clinical Trial number: Not applicable

This article is a narrative review. Not applicable.

References

1. Wirsching HG, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol. 2016;134:381-397.
2. Berger TR, Wen PY, Lang-Orsini M, Chukwueke UN. World Health Organization 2021 Classification of Central Nervous System Tumors and Implications for Therapy for Adult-Type Gliomas: A Review. JAMA Oncol. 2022;8(10):1493-1501.
3. United Kingdom National Health Service. Brain tumours. 2023. Available from: https://www.nhs.uk/conditions/brain-tumours/.
4. Cancer Research UK. Glioblastoma. 2023 [cited 2025 March 30]. Available from:https://www.cancerresearchuk.org/about-cancer/brain tumours/types/glioblastoma.
5. Valenzuela-Fuenzalida JJ, Moyano-Valarezo L, Silva-Bravo V, Milos-Brandenberg D, Orellana-Donoso M, Nova-Baeza P, et al. Association between the Anatomical Location of Glioblastoma and Its Evaluation with Clinical Considerations: A Systematic Review and Meta-Analysis. J Clin Med. 2024;13(12):3460.
6. Rong L, Li N, Zhang Z. Emerging therapies for glioblastoma: current state and future directions. 2022;41(1):142.
7. Hochberg F, Toniolo P, Cole P, Salcman M. Nonoccupational risk indicators of glioblastoma in adults. J Neurooncol. 1990;8(1):55-60.
8. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neurooncol. 2015;17 (Suppl 4):iv1-iv62.
9. Alifieris C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. Pharmacol Ther. 2015;152: 63-82.
10. Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs. 2016;20(5 Suppl):S2-S8.
11. Posti JP, Bori M, Kauko T, Sankinen M, Nordberg J, Rahi M, et al. Presenting symptoms of glioma in adults. Acta Neurol Scand. 2015;131(2):88-93.
12. Mondal A, Kumari Singh D, Panda S, Shiras A. Extracellular Vesicles As Modulators of Tumor Micro-environment and Disease Progression in Glioma. Front Oncol. 2017;7:144.
13. Sizoo EM, Braam L, Postma TJ, Pasman HR, Heimans JJ, Klein M, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. Neurooncol. 2010;12(11): 1162-1166.
14. Kesari S, editor. Understanding glioblastoma tumor biology: the potential to improve current diagnosis

and treatments. Seminars in oncology. Elsevier; 2011.
15. Nam L, Coll C, Erthal LCS, De la Torre C, Serrano D, Martínez-Máñez R, et al. Drug Delivery Nanosystems for the Localized Treatment of Glioblastoma Multiforme. Materials. 2018;11(5):779.
16. Lima FR, Kahn SA, Soletti RC, Biasoli D, Alves T, da Fonseca ACC, et al. Glioblastoma: therapeutic challenges, what lies ahead. Biochim Biophys Acta Rev Cancer. 2012;1826(2):338-349.
17. Janjua TI, Rewatkar P, Ahmed-Cox A, Saeed I, Mansfeld FM, Kulshreshtha R, et al. Frontiers in the treatment of glioblastoma: Past, present and emerging. Adv Drug Deliv Rev. 2021;171:108-138.
18. Cohen MH, Johnson JR, Pazdur R. Food and Drug Administration Drug Approval Summary: Temozolomide Plus Radiation Therapy for the Treatment of Newly Diagnosed Glioblastoma Multiforme. Clin Cancer Res. 2005;11(19):6767-6771.
19. Mittal S, Klinger NV, Michelhaugh SK, Barger GR, Pannullo SC, Juhász C. Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies. J Neurosurg. 2018;128(2):414-421.
20. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neurooncol. 2014;16(Suppl 4):iv1-iv63.
21. Rapp M, Baernreuther J, Turowski B, Steiger H-J, Sabel M, Kamp MA. Recurrence Pattern Analysis of Primary Glioblastoma. World Neurosurg. 2017;103:733-740.
22. Arvanitis CD, Ferraro GB, Jain RK. The blood–brain barrier and blood–tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20 (1):26-41.
23. Cui J, Xu Y, Tu H, Zhao H, Wang H, Di L, et al. Gather wisdom to overcome barriers: Well-designed nano-drug delivery systems for treating gliomas. Acta Pharm Sin B. 2022;12(3):1100-1125.
24. Pardridge WM. The blood-brain barrier and neurotherapeutics. NeuroRx. 2005;2(1):1-2.
25. Narsinh KH, Perez E, Haddad AF, Young JS, Savastano L, Villanueva-Meyer JE, et al. Strategies to Improve Drug Delivery Across the Blood–Brain Barrier for Glioblastoma. Curr Neurol Neurosci Rep. 2024;24(5):123-139.
26. Iturrioz-Rodríguez N, Bertorelli R, Ciofani G. Lipid-Based Nanocarriers for The Treatment of Glioblastoma. Adv NanoBiomed Res. 2021;1(2): 2000054.
27. Meyers JD, Tennyson D, Clemens B, Basilion JP. Nanoparticles for Imaging and Treating Brain Cancer. Nano-medicine. 2013;8(1):123-143.
28. 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.
29. Farhoudi M, Sadigh-Eteghad S, Mahmoudi J, Farjami A, Mahmoudian M, Salatin S. The Therapeutic Benefits of Intravenously Administrated Nanoparticles in Stroke and Age-related Neurodegenerative Diseases. Curr Pharm Des. 2022;28(24):1985-2000.
30. Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, et al. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. Semin Cancer Biol. 2021;69:166-177.
31. Manzari-Tavakoli A, Babajani A, Tavakoli MM, Safaeinejad F, Jafari A. Integrating natural compounds and nanoparticle-based drug delivery systems: A novel strategy for enhanced efficacy and selectivity in cancer

therapy. Cancer Med. 2024;13(5): e7010.
32. Saleh TA. Trends in nanomaterial types, synthesis methods, properties and uses: Toxicity, environmental concerns and economic viability. Nano-Struct Nano-Objects. 2024;37:101109.
33. Sun L, Liu H, Ye Y, Lei Y, Islam R, Tan S, et al. Smart nanoparticles for cancer therapy. Signal Transduct Target Ther. 2023;8(1):418.
34. Ruiz-Garcia H, Ramirez-Loera C, Malouff TD, Seneviratne DS, Palmer JD, Trifiletti DM. Novel Strategies for Nanoparticle-Based Radiosensitization in Glioblastoma. Int J Mol Sci. 2021;22(18):9673.
35. Musielak E, Krajka-Kuźniak V. Lipidic and Inorganic Nanoparticles for Targeted Glioblastoma Multiforme Therapy: Advances and Strategies. Micro. 2025;5(1):2.
36. Trivedi MS. Role of nanostructures and immunotherapies in management of glioblastoma multiforme: Current perspectives and challenges. Asian J Pharm. 2021;15(4).
37. Ghaznavi H, Afzalipour R, Khoei S, Sargazi S, Shirvalilou S, Sheervalilou R. New insights into targeted therapy of glioblastoma using smart nanoparticles. Cancer Cell Int. 2024;24(1):160.
38. Rezaei V, Amir R, Khademi F. Glioblastoma multiforme: a glance at advanced therapies based on nanotechnology. J Chemother. 2020;32(3):107-117.
39. Wu Q, Berglund AE, Etame AB. The Impact of Epigenetic Modifications on Adaptive Resistance Evolution in Glioblastoma. Int J Mol Sci. 2021;22(15):8324.
40. Kanu OO, Hughes B, Di C, Lin N, Fu J, Bigner DD, et al. Glioblastoma Multiforme Oncogenomics and Signaling Pathways. Clin Med Oncol. 2009;3:CMO.S1008.
41. Ohgaki H, Kleihues P. The Definition of Primary and Secondary Glioblastoma. Clin Cancer Res. 2013; 19(4):764-772.
42. Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. Acta Neuropathol. 2015;129(6):829-848.
43. Bergström T, Forsberg-Nilsson K. Neural stem cells: Brain building blocks and beyond. Upsala J Med Sci. 2012;117(2):132-142.
44. Verdugo E, Puerto I, Medina MÁ. An update on the molecular biology of glioblastoma, with clinical implications and progress in its treatment. Cancer Commun. 2022;42(11):1083-1111.
45. Tang J, Karbhari N, Campian JL. Therapeutic Targets in Glioblastoma: Molecular Pathways, Emerging Strategies, and Future Directions. Cells. 2025;14(7):494.
46. Kowalski-Chauvel A, Lacore MG, Arnauduc F, Delmas C, Toulas C, Cohen-Jonathan-Moyal E, et al. The m6A RNA Demethylase ALKBH5 Promotes Radioresistance and Invasion Capability of Glioma Stem Cells. Cancers. 2021;13(1):40.
47. Loras A, Gonzalez-Bonet LG, Gutierrez-Arroyo JL, Martinez-Cadenas C, Marques-Torrejon MA. Neural Stem Cells as Potential Glioblastoma Cells of Origin. Life. 2023;13(4):905.
48. Ah-Pine F, Khettab M, Bedoui Y, Slama Y, Daniel M, Doray B, et al. On the origin and development of glioblastoma: multifaceted role of perivascular mesenchymal stromal cells. Acta Neuropathol Commun. 2023;11(1):104.
49. Appin CL, Brat DJ. Molecular Genetics of Gliomas. Cancer J. 2014;20(1):66-72.
50. Ma X, Sun C, Ding X, Xu J, Zhang Y, Deng T, et al. Mechanism analysis and targeted therapy of IDH gene mutation in glioma. Am J Cancer Res. 2025;15(1):248-270.
51. Wang H-Y, Tang K, Liang T-Y, Zhang W-Z, Li J-Y, Wang W, et al. The

comparison of clinical and biological characteristics between IDH1 and IDH2 mutations in gliomas. J Exp Clin Cancer Res. 2016;35(1):86.
52. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739-744.
53. Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. J Exp Med. 2010;207(2):339-344.
54. Gullick WJ, Marsden JJ, Whittle N, Ward B, Bobrow L, Waterfield MD. Expression of Epidermal Growth Factor Receptors on Human Cervical, Ovarian, and Vulval Carcinomas. Cancer Res. 1986;46(1):285-292.
55. Inal C, Emrullah Y, Bilal P, Roman P-S, Cheng H. Emerging treatment for advanced lung cancer with EGFR mutation. Expert Opin Emerg Drugs. 2015;20(4):597-612.
56. Siegelin MD, Borczuk AC. Epidermal growth factor receptor mutations in lung adenocarcinoma. Lab Invest. 2014;94(2):129-137.
57. De Luca A, Normanno N. Predictive Biomarkers to Tyrosine Kinase Inhibitors for the Epidermal Growth Factor Receptor in Non-Small-Cell Lung Cancer. Curr Drug Targets. 2010;11(7):851-864.
58. Li AR, Chitale D, Riely GJ, Pao W, Miller VA, Zakowski MF, et al. EGFR Mutations in Lung Adenocarcinomas: Clinical Testing Experience and Relationship to EGFR Gene Copy Number and Immunohistochemical Expression. J Mol Diagn. 2008;10(3):242-248.
59. Jung MJ, Woo CG, Lee S, Chin S, Kim HK, Kwak JJ, et al. Gene copy number variation and protein overexpression of EGFR and HER2 in distal extrahepatic cholangiocarcinoma. Pathology. 2017;49(6):582-588.
60. Birkman E-M, Ålgars A, Lintunen M, Ristamäki R, Sundström J, Carpén O. EGFR gene amplification is relatively common and associates with outcome in intestinal adenocarcinoma of the stomach, gastro-oesophageal junction and distal oesophagus. BMC Cancer. 2016;16(1):406.
61. Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, Soreq H, et al. Amplification and overexpression of the egf receptor gene in primary human glioblastomas. J Cell Sci. 1985;1985(Suppl 3):161-172.
62. Alexandru O, Purcaru SO, Tataranu LG, Lucan L, Castro J, Folcuţi C, et al. The Influence of EGFR Inactivation on the Radiation Response in High Grade Glioma. Int J Mol Sci. 2018;19(1):229.
63. Ekstrand AJ, Sugawa N, James CD, Collins VP. Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the N- and/or C-terminal tails. Proc Natl Acad Sci U S A. 1992;89(10):4309-4313.
64. Yamazaki H, Yasuhisa F, Yoshito U, Norikazu T, Tomoyuki K, Shigehiko T, et al. Amplification of the Structurally and Functionally Altered Epidermal Growth Factor Receptor Gene (c-erbB) in Human Brain Tumors. Mol Cell Biol. 1988;8(4):1816-1820.
65. Ramnarain DB, Park S, Lee DY, Hatanpaa KJ, Scoggin SO, Otu H, et al. Differential Gene Expression Analysis Reveals Generation of an Autocrine Loop by a Mutant Epidermal Growth Factor Receptor in Glioma Cells. Cancer Res. 2006;66(2):867-874.
66. Ohgaki H, Kleihues P. Genetic alterations and signaling pathways in the evolution of gliomas. Cancer Sci. 2009;100(12):2235-2241.
67. Kita D, Yonekawa Y, Weller M, Ohgaki H. PIK3CA alterations in primary (de novo) and secondary glioblastomas. Acta Neuropathol.

2007;113(3):295-302.
68. Stiles BL. Phosphatase and tensin homologue deleted on chromosome 10: Extending its PTENtacles. Int J Biochem Cell Biol. 2009;41(4):757-761.
69. Hashemi M, Etemad S, Rezaei S, Ziaolhagh S, Rajabi R, Rahmanian P, et al. Progress in targeting PTEN/PI3K/Akt axis in glioblastoma therapy: Revisiting molecular interactions. Biomed Pharmacother. 2023;158:114204.
70. García-Montaño LA, Muñoz YL, Martinez F, Gallegos K, Kang H, Piccirillo SG. Abstract 544: Dissecting the functional impairment of wild-type Tp53 in human glioblastoma. Cancer Res. 2023;83(7 Suppl):544.
71. Zhang Y, Dube C, Gibert M, Cruickshanks N, Wang B, Coughlan M, et al. The p53 Pathway in Glioblastoma. Cancers. 2018;10(9):297.
72. Wade M, Li Y-C, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. Nat Rev Cancer. 2013;13(2):83-96.
73. Kastenhuber ER, Lowe SW. Putting p53 in Context. Cell. 2017;170 (6):1062-1078.
74. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci U S A. 2013;110(15):6021-6026.
75. Pierini T, Nardelli C, Lema Fernandez AG, Pierini V, Pellanera F, Nofrini V, et al. New somatic TERT promoter variants enhance the Telomerase activity in Glioblastoma. Acta Neuropathol Commun. 2020;8(1):145.
76. Philpott C, Tovell H, Frayling IM, Cooper DN, Upadhyaya M. The NF1 somatic mutational landscape in sporadic human cancers. Hum Genomics. 2017;11(1):13.
77. Shahcheraghi SH, Tchokonte-Nana V, Lotfi M, Lotfi M, Ghorbani A, Sadeghnia HR. Wnt/beta-catenin and PI3K/Akt/mTOR Signaling Pathways in Glioblastoma: Two Main Targets for Drug Design: A Review. Curr Pharm Des. 2020;26(15):1729-1741.
78. Barzegar Behrooz A, Talaie Z, Jusheghani F, Łos MJ, Klonisch T, Ghavami S. Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. Int J Mol Sci. 2022;23(3):1353.
79. Wang S, Gu S, Chen J, Yuan Z, Liang P, Cui H. Mechanism of Notch Signaling Pathway in Malignant Progression of Glioblastoma and Targeted Therapy. Biomolecules. 2024;14(4):480.
80. Sharma P, Aaroe A, Liang J, Puduvalli VK. Tumor microenvironment in glioblastoma: Current and emerging concepts. Neurooncol Adv. 2023;5(1).
81. Tamai S, Ichinose T, Tsutsui T, Tanaka S, Garaeva F, Sabit H, et al. Tumor Microenvironment in Glioma Invasion. Brain Sci. 2022;12(4):505.
82. Akhtar MS, Swamy MK, Umar A, Al Sahli AA. Biosynthesis and Characterization of Silver Nanoparticles from Methanol Leaf Extract of Cassia didymobotyra and Assessment of Their Antioxidant and Antibacterial Activities. J Nanosci Nanotechnol. 2015;15(12):9818-9823.
83. Thabit AK, L. CJ, Nicolau DP. Antimicrobial resistance: impact on clinical and economic outcomes and the need for new antimicrobials. Expert Opin Pharmacother. 2015;16(2):159-177.
84. Wong IY, Bhatia SN, Toner M. Nanotechnology: emerging tools for biology and medicine. Genes Dev. 2013;27(22):2397-2408.
85. Senthilnathan B. A Comprehensive Review on Disease Related Applications of Nanotechnology. EAS J Pharm Pharmacol. 2023;5:98-104.
86. Rehan F, Zhang M, Fang J, Greish K. Therapeutic Applications of Nanomedicine: Recent Developments

and Future Perspectives. Molecules. 2024;29(9):2073.
87. Chakraborty A, Mohapatra Saswati S, Barik S, Roy I, Gupta B, Biswas A. Impact of nanoparticles on amyloid β-induced Alzheimer's disease, tuberculosis, leprosy and cancer: a systematic review. Biosci Rep. 2023;43(2).
88. Lu W, Chen H, Liu T, Hu J, Zhu L, Tao X, et al. Serine-modified silver nanoparticle porous spray membrane: A novel approach to wound infection prevention and inflammation reduction. Int J Pharm. 2025;670:125120.
89. Mojtahedi F, Nasiri MR, Ali SN, Mohammadgholi A, Mohebbi S, Shahbazi Z, et al. Novel chitosan-alginate dressings with UIO-66-NH2 nanoparticles and ferula gummosa extracts for effective wound healing. Colloids Surf A Physicochem Eng Asp. 2025;719:137004.
90. Amiri F, Alishahi F, Mohammadifar G, Izadidehkordi S, Charmduzi F, Dialameh F, et al. Enhanced Anticancer Efficacy of Selenium Nanoparticles Encapsulated in Niosomes: A Novel Therapeutic Strategy. Indian J Clin Biochem. 2025.
91. Ata Te, Al-Ani I, Karameh N, Atta MR, Dayyih WA. Alectinib-Loaded Chitosan–Alginate Nanoparticles: A Novel Synthesis Method with In Vitro and In Vivo Evaluations. Pharmaceutics. 2025;17(4):492.
92. Saberian E, Jenčová J, Jenča A, Jenča A, Salehipoor F, Zare-Zardini H, et al. Bleomycin-loaded folic acid-conjugated nanoliposomes: a novel formulation for targeted treatment of oral cancer. Front Bioeng Biotechnol. 2025;13.
93. Fathalizadeh M, Homayouni Tabrizi M, Tehranipour M. A novel alpha-terpineol-loaded niosome formulation coated with hyaluronic acid and evaluation of its anticancer properties in vitro. J Mol Liq. 2025;424:127139.
94. Anwar M, Rehman M, Ur-Rehman T, Khan MI, Ahmed N, Madni A, et al. Ternary lipids-based novel thermoresponsive lipid nanoparticles for targeting doxorubicin to breast cancer cells. J Pharm Sci. 2025;114(6):103723.
95. Sabra MS, Allam EAH, El-Aal MA, Hassan NH, Mostafa A-HM, Ahmed AAN. A novel pharmacological strategy using nanoparticles with glutathione and virgin coconut oil to treat gentamicin-induced acute renal failure in rats. Naunyn Schmiedebergs Arch Pharmacol. 2025;398(1):933-950.
96. Cai Y, Qiao M, Xie X, Zhou Y, Yu R, Song F, et al. Intracellular MRSA-targeted lipid-polymer hybrid nanoparticles for macrophage reprogramming and intracellular MRSA eradication. Chem Eng J. 2025;505:159665.
97. Nematalla HA, Elharoun M, Bargash SN, Abd-Alhaseeb MM, Sharafeldin HA, Zewail M, et al. Novel Nose-to-brain delivery of carbenoxolone via mucoadhesive solid lipid nanoparticles for Parkinson's symptoms management: In vitro and in vivo evaluation in a rotenone-induced rat model. Int J Pharm. 2025;670:125197.
98. Müller EK, Białas N, Epple M, Hilger I. Nanoparticles Carrying NF-κB p65-Specific siRNA Alleviate Colitis in Mice by Attenuating NF-κB-Related Protein Expression and Pro-Inflammatory Cellular Mediator Secretion. Pharmaceutics. 2022;14(2): 419.
99. Gawel AM, Singh R, Debinski W. Metal-Based Nanostructured Therapeutic Strategies for Glioblastoma Treatment—An Update. Biomedicines. 2022;10(7):1598.
100. Hu Y. Application of nanomaterials for the treatment of glioblastoma. Trans Mater Biotechnol Life Sci. 2024;7:414-419.
101. Kerr BN, Duffy D, McInerney CE, Hutchinson A, Dabaja I, Bazzi R, et al. Evaluation of Radiosensitization and

Cytokine Modulation by Differentially PEGylated Gold Nanoparticles in Glioblastoma Cells. Int J Mol Sci. 2023;24(12):10032.
102. Kostka K, Sokolova V, El-Taibany A, Kruse B, Porada D. The Application of Ultrasmall Gold Nanoparticles (2 nm) Functionalized with Doxorubicin in Three-Dimensional Normal and Glioblastoma Organoid Models of the Blood-Brain Barrier. 2024;29(11).
103. Allen NC, Chauhan R, Bates PJ, O'Toole MG. Optimization of Tumor Targeting Gold Nanoparticles for Glioblastoma Applications. Nanomaterials. 2022;12(21):3869.
104. Durand M, Chateau A, Jubréaux J, Devy J, Paquot H, Laurent G, et al. Radiosensitization with gadolinium chelate-coated gold nanoparticles prevents aggressiveness and invasiveness in glioblastoma. Int J Nanomedicine. 2023:243-261.
105. Durand M, Lelievre E, Chateau A, Berquand A, Laurent G, Carl P, et al. The detrimental invasiveness of glioma cells controlled by gadolinium chelate-coated gold nanoparticles. Nanoscale. 2021;13(20):9236-9251.
106. He C, Ding H, Li L, Chen J, Mo X, Ding Y, et al. Gold nanoparticles enhance the ability of radiotherapy to induce immunogenic cell death in glioblastoma. Int J Nanomedicine. 2023:5701-5712.
107. Kulkarni M, Nadendla K, Pai A, Ashili S, Maibach H, Manikkath J. Lipid nanoparticles for the treatment of glioblastoma multiforme: Current status of research and clinical translation. J Drug Deliv Sci Technol. 2025;108:106891.
108. Brüßeler MMT, Zam A, Moreno-Zafra VM, Rouatbi N, Hassuneh OWM, Marrocu A, et al. Polyinosinic/ Polycytidylic Lipid Nanoparticles Enhance Immune Cell Infiltration and Improve Survival in the Glioblastoma Mouse Model. Mol Pharm. 2024;21(12):6339-6352.
109. Chang L, Zhang Y, Li M, Zhao X, Wang D, Liu J, et al. Nanostructured lipid carrier co-delivering paclitaxel and doxorubicin restrains the proliferation and promotes apoptosis of glioma stem cells via regulating PI3K/Akt/mTOR signaling. Nanotechnology. 2021;32(22):225101.
110. Pashirova TN, Nemtarev AV, Buzyurova DN, Shaihutdinova ZM, Dimukhametov MN, Babaev VM, et al. Terpenes-Modified Lipid Nanosystems for Temozolomide, Improving Cytotoxicity against Glioblastoma Human Cancer Cells In Vitro. Nanomaterials. 2024;14(1):55.
111. Shumer-Elbaz M, Ad-El N, Chulanova Y, Brier D, Goldsmith M, Bismuth M, et al. Low-frequency ultrasound-mediated blood-brain barrier opening enables non-invasive lipid nanoparticle RNA delivery to glioblastoma. J Control Release. 2025;385:114018.
112. Ruan S, Zhou Y, Jiang X, Gao H. Rethinking CRITID Procedure of Brain Targeting Drug Delivery: Circulation, Blood Brain Barrier Recognition, Intracellular Transport, Diseased Cell Targeting, Internalization, and Drug Release. 2021;8(9):2004025.
113. De Gaetano F, Cristiano MC, Venuti V, Crupi V, Majolino D, Paladini G, et al. Rutin-Loaded Solid Lipid Nanoparticles: Characterization and In Vitro Evaluation. Molecules. 2021;26(4):1039.
114. Battaglia L, Dianzani C, Muntoni E, Marini E, Bozza A, Bordano V, et al. Ultrasmall solid lipid nanoparticles as a potential innovative delivery system for a drug combination against glioma. Nanomedicine. 2025;20(1):37-52.
115. Ak G, Ünal A, Karakayalı T, Özel B, Selvi Günel N, Hamarat Şanlıer Ş. Brain-targeted, drug-loaded solid lipid nanoparticles against glioblastoma cells in culture. Colloids Surf B Biointerfaces. 2021;206:111946.
116. Baghel YS, Bhattacharya S. Lipid

Polymeric Hybrid Nanoparticles: Formulation Techniques and Effects on Glioblastoma. Pharm Sci. 2022;28(2):174-193.
117. Rehman M, Madni A, Shi D, Ihsan A, Tahir N, Chang KR, et al. Enhanced blood brain barrier permeability and glioblastoma cell targeting via thermoresponsive lipid nanoparticles. Nanoscale. 2017;9(40):15434-15440.
118. Tan B, Liu S, Wang F, Yu Y, Sun T. Applications of polymeric nanoparticles in drug delivery for glioblastoma. Front Pharmacol. 2025;15.
119. Xiao X, Teng F, Shi C, Chen J, Wu S, Wang B, et al. Polymeric nanoparticles—Promising carriers for cancer therapy. Front Bioeng Biotechnol. 2022;10.
120. Ghasempour E, Hesami S, Movahed E, Keshel SH, Doroudian M. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy in the brain tumors. 2022;13(1):527.
121. Dhar D, Ghosh S. A review of recent advances in magnetic nanoparticle-based theranostics of glioblastoma. 2022;17(2):107-132.
122. Lin J, Lin Z, Liu L, Lin W, Xie X, Zhang X. Enhancing glioma-specific drug delivery through self-assembly of macrophage membrane and targeted polymer assisted by low-frequency ultrasound irradiation. Mater Today Bio. 2024;26:101067.
123. Paranthaman S, Goravinahalli Shivananjegowda M, Mahadev M, Moin A, Hagalavadi Nanjappa S. Nanodelivery Systems Targeting Epidermal Growth Factor Receptors for Glioma Management. 2020;12(12).
124. Zhang H, Jiang W, Song T, Song M, Liu S, Zhou J, et al. Lipid-Polymer Nanoparticles Mediate Compartmentalized Delivery of Cas9 and sgRNA for Glioblastoma Vasculature and Immune Reprogramming. 2024;11(32): e2309314.
125. Ding M, Zhu A, Zhang Y, Liu J, Lin L, Wang X, et al. Neutrophil-based Trojan horse containing polymer nanotherapeutics for sono-activatable ferroptosis-immunotherapy of orthotopic glioma. Nano Today. 2024;57:102398.
126. López Ruiz A, Bartomeu Garcia C, Navarro Gallón S, Webster TJ. Novel Silver-Platinum Nanoparticles for Anticancer and Antimicrobial Applications. 2020;15:169-179.
127. Skóra B, Masicz M, Nowak P, Lachowska J, Sołtysek P, Biskup J, et al. Suppression of sonic hedgehog pathway-based proliferation in glioblastoma cells by small-size silver nanoparticles in vitro. 2023;97(9):2385-2398.
128. Soroushnasab H, Gharbavi M, Eskandari M, Rezaeejam H, Ghorbani R, Johari B. Methotrexate-conjugated silver nanoparticles enhance chemoradiotherapy effects on U87 human glioblastoma multiforme cells: As a radiosensitizer agent to improve X-irradiation efficacy. J Drug Deliv Sci Technol. 2025;107:106791.
129. Goswami S, Verma Y, Rana SVS. Nanoparticles of silver and titanium can increase temozolomide sensitivity against human glioblastoma: an in vitro study on apoptosis and inflammation. Naunyn Schmiedebergs Arch Pharmacol. 2025.
130. Plotnikov EV, Drozd AG, Artamonov AA, Larkina MS, Belousov MV, Lomov IV, et al. Silver nanoparticles enhance neutron radiation sensitivity in cancer cells: An in vitro study. Nanomedicine. 2025;65:102813.
131. Eugenio M, Campanati L, Müller N, Romão LF, de Souza J, Alves-Leon S, et al. Silver/silver chloride nanoparticles inhibit the proliferation of human glioblastoma cells. Cytotechnology. 2018;70(6):1607-1618.
132. Cen J, Dai X, Zhao H, Li X, Hu X, Wu J, et al. Doxorubicin-Loaded Liposome with the Function of "Killing Two Birds with One Stone" against

Glioma. ACS Appl Mater Interfaces. 2023;15.
133. Chen H, Huang J, Wang H, Xu Y, Chen J, Deng T, et al. Multifunctional liposome boosts glioma ferroptosis and immunotherapy through reinforcement of chemo-dynamic therapy strategy. Mater Today Bio. 2025;31:101521.
134. Cheng Y, Zhu K, Yang L, Mao M, Wu Y, Xuan M, et al. A Self-Homing Liposomal Nanobot for Active Therapy of Glioblastoma. Angew Chem Int Ed. 2025;64:e202512948.
135. Zhang H-Q, Wang Y, Geng X, Dong M, Liu Z, Sun C, et al. ANG-Modified Liposomes Coloaded With α-Melittin and Resveratrol Induce Apoptosis and Pyroptosis in Glioblastoma Cells by Impeding Wnt/β-Catenin Signaling. CNS Neurosci Ther. 2025;31(5):e70437.
136. Knežević NŽ, Kaluđerović GN. Silicon-based nanotheranostics. Nanoscale. 2017;9(35):12821-12829.
137. Nik A, Zare H, Razavi S, Mohammadi H, Torab-Ahmadi P, Yazdani N, et al. Smart Drug Delivery: Capping Strategies for Mesoporous Silica Nanoparticles. Microporous Mesoporous Mater. 2020;299:110115.
138. Mundžić M, Ultimo A, Mladenović M, Pavlović A, Gobbo OL, Ruiz-Hernandez E, et al. Chlorotoxin-functionalized mesoporous silica nanoparticles for pH-responsive paclitaxel delivery to Glioblastoma multiforme. Heliyon. 2025;11(1).
139. Zhu H, Ni X, Su J, Qin Y, He X, Liu B, et al. Multifunctional Mesoporous Silicon Nanoparticles for MRI-Based Diagnostic Imaging and Glioma Therapy. ACS Appl Mater Interfaces. 2025.
140. Nozhat Z, Wahab A, Mushtaq A, Iqbal MZ, Kong X. Metformin loaded Mn3O4@SiO2 core–shell nanoparticles for glioblastoma multiforme targeted therapy. Colloids Surf B Biointerfaces. 2025;254: 114789.
141. Hsu T-I, Chen Y-P, Zhang R-L, Chen Z-A, Wu C-H, Chang W-C, et al. Overcoming the Blood–Brain Tumor Barrier with Docetaxel-Loaded Mesoporous Silica Nanoparticles for Treatment of Temozolomide-Resistant Glioblastoma. ACS Appl Mater Interfaces. 2024;16(17):21722-21735.
142. Qiao R, Fu C, Forgham H, Javed I, Huang X, Zhu J, et al. Magnetic iron oxide nanoparticles for brain imaging and drug delivery. Adv Drug Deliv Rev. 2023;197:114822.
143. Caro C, Paez-Muñoz JM, Pernía Leal M, Carayol M, Feijoo-Cuaresma M, García-Martín ML. Metabolically-Driven Active Targeting of Magnetic Nanoparticles Functionalized with Glucuronic Acid to Glioblastoma: Application to MRI-Tracked Magnetic Hyperthermia Therapy. Adv Healthc Mater. 2025;14(3):2404391.
144. Ghadiri M, Vasheghani-Farahani E, Atyabi F, Kobarfard F, Mohamadyar-Toupkanlou F, Hosseinkhani H. Transferrin-conjugated magnetic dextran-spermine nanoparticles for targeted drug transport across blood-brain barrier. J Biomed Mater Res A. 2017;105(10):2851-2864.
145. Beola L, Iturrioz-Rodríguez N, Pucci C, Bertorelli R, Ciofani G. Drug-Loaded Lipid Magnetic Nanoparticles for Combined Local Hyperthermia and Chemotherapy against Glioblastoma Multiforme. ACS Nano. 2023;17(18):18441-18455.
146. Aslan TN. Cationic Micelle-like Nanoparticles as the Carrier of Methotrexate for Glioblastoma Treatment. Molecules. 2024;29(24): 5977.
147. Maliyakkal N, Appadath Beeran A, Udupa N. Nanoparticles of cisplatin augment drug accumulations and inhibit multidrug resistance transporters in human glioblastoma cells. Saudi Pharm J. 2021;29(8):857-873.
148. Lajous H, Riva R, Lelièvre B, Tétaud C, Avril S, Hindré F, et al.

Hybrid Gd3+/cisplatin cross-linked polymer nanoparticles enhance platinum accumulation and formation of DNA adducts in glioblastoma cell lines. Biomater Sci. 2018;6(9):2386-2409.
149. Ren Y, Yang H, Xu D, Zhang Z, Gao S, Yu R. Application of Multifunctional Metal Nanoparticles in the Treatment of Glioma. Int J Nanomedicine. 2025;20:625-638.
150. Suwannasing C, Suwannasom N, Iamcharoen P, Dokkham R, Maun P, Srisai P, et al. Albumin-Coated Copper Oxide Nanoparticles for Radiosensitization of Human Glioblastoma Cells Under Clinically Relevant X-Ray Irradiation. Nanomaterials. 2025;15(17):1376.
151. Parsaei S, Yaghoobi H, Beshkar P, Khonakdar Sangdehi HA, Khosravi Farsani MR, Safari O. Zingerone based green synthesized sodium doped zinc oxide nanoparticles eliminate U87 glioblastoma cells by inducing apoptosis. Sci Rep. 2025;15(1):13516.
152. Minaei SE, Khoei S, Khoee S, Mahdavi SR. Sensitization of glioblastoma cancer cells to radiotherapy and magnetic hyperthermia by targeted temozolomide-loaded magnetite tri-block copolymer nanoparticles as a nanotheranostic agent. Life Sci. 2022;306:120729.
153. Minchenko DO, Rudnytska OV, Khita OO, Kulish YV, Viletska YM, Halkin OV, et al. Expression of DNAJB9 and some other genes is more sensitive to SWCNTs in normal human astrocytes than glioblastoma cells. Endocr Regul. 2023;57(1):162-172.
154. Das S, Roy S, Dinda SC, Bose A, Mahapatra C, Basu B, et al. Carbon nanotubes in brain targeted drug delivery: A comprehensive review. Results Chem. 2025;15:102206.
155. Karadag B, Zeybekler SE, Gelen SS, Sabour-Takanlou L, Sabour-Takanlou M, Biray Avci C, et al. Electrodeposition of carbon nanotubes and conjugation of arginyl-glycyl-aspartic acid for the following of glioblastoma cells on bionanocomposites.Bioelectro-chemistry. 2025;164:108937.
156. Groualle FE, Onion D, Watts JA, Rance GA, Noy A, Coyle B, et al. Bioelectronic Modulation of Glioblastoma via Wireless Carbon Nanotube Porin Interfaces. bioRxiv. 2025:2025.07.04.663176.
157. Pareek A, Kumar D, Pareek A, Gupta MM. Advancing Cancer Therapy with Quantum Dots and Other Nanostructures: A Review of Drug Delivery Innovations, Applications, and Challenges. Cancers. 2025;17(5):878.
158. Pandey SN, Afzal M, Goyal A, Padma Priya G, Mohanty B, Goyal K, et al. Quantum dot biosensors for Glioblastoma: Merging nanotechnology with precision oncology. Inorg Chem Commun. 2025;179:114671.
159. Fuster E, Candela H. A Transcriptomic Analysis of T98G Human Glioblastoma Cells after Exposure to Cadmium-Selenium Quantum Dots Mainly Reveals Alterations in Neuroinflammation Processes and Hypothalamus Regulation. Int J Mol Sci. 2022;23(4).
160. Cabral Filho PE, Cardoso AL, Pereira MI, Ramos AP, Hallwass F, Castro MM, et al. CdTe quantum dots as fluorescent probes to study transferrin receptors in glioblastoma cells. Biochim Biophys Acta. 2016;1860(1 Pt A):28-35.
161. Kregielewski K, Fraczek W. Graphene Quantum Dots for Glioblastoma Treatment and Detection-Systematic Review. Int J Mol Sci. 2025;30(12).
162. Bhogale D, Mazahir F, Yadav AK. Recent Synergy of Nanodiamonds: Role in Brain-Targeted Drug Delivery for the Management of Neurological

Disorders. J Clust Sci. 2022;59(8): 4806-4824.
163. Chen Z, Yuan SJ, Li K, Zhang Q, Li TF, An HC, et al. Doxorubicin-polyglycerol-nanodiamond conjugates disrupt STAT3/IL-6-mediated reciprocal activation loop between glioblastoma cells and astrocytes. J Control Release. 2020;320:469-483.
164. Elsayyad NME, Elkady OA, Swidan MM, Rashed HM, Sakr TM, Abdelhamid AM, et al. Zonisamide nanodiamonds for brain targeting: A comprehensive study utilising in silico, in vitro, in vivo, and molecular investigation for successful nose-to-brain delivery for epilepsy management. Drug Deliv Transl Res. 2025.
165. Nikfar B, Musavi M, Chaichian S, Guo G, Momtazi-Borojeni AA. Nanomotor-mediated drug delivery with efficient blood–brain barrier crossing for active targeting and therapy of glioblastomas: a systematic review. Nanoscale. 2025;17(28):16592-16608.
166. Ye J, Fan Y, Kang Y, Ding M, Niu G, Yang J, et al. Biomimetic Dual-Driven Heterojunction Nanomotors for Targeted Catalytic Immunotherapy of Glioblastoma. Adv Funct Mater. 2025;35(9):2416265.
167. Wang H, Lan D, Cao H, Zhao W, Gui H, Han Z, et al. Self-Propulsion of Biomimetic Nanomotors Promotes Diffusion and Convection Transport for Enhanced Radiotherapy in Solid Glioblastoma. J Am Chem Soc. 2025;147(28):25072-25087.
168. Escudero A, Hicke FJ, Lucena-Sánchez E, Pradana-López S, Esteve-Moreno JJ, Sanz-Álvarez V, et al. Glucose-Fueled Gated Nanomotors: Enhancing In Vivo Anticancer Efficacy via Deep Drug Penetration into Tumors. ACS Nano. 2025;19(22):20932-20955.
169. Gowda BHJ, Ahmed MG, Almoyad MAA, Wahab S, Almalki WH, Kesharwani P. Nanosponges as an Emerging Platform for Cancer Treatment and Diagnosis. Adv Funct Mater. 2024;34(7):2307074.
170. Yin Y, Tian N, Deng Z, Wang J, Kuang L, Tang Y, et al. Targeted Microglial Membrane-Coated MicroRNA Nanosponge Mediates Inhibition of Glioblastoma. ACS Nano. 2024;18(42):29089-29105.
171. Fan N, Bian X. Hierarchical self-uncloaking CRISPR-Cas13a-customized RNA nanococoons for spatial-controlled genome editing and precise cancer therapy. Sci Adv. 2022;8(20):eabn7382.
172. Bruns J, Egan T, Mercier P, Zustiak SP. Glioblastoma spheroid growth and chemotherapeutic responses in single and dual-stiffness hydrogels. Acta Biomater. 2023;163:400-414.
173. Adiguzel S, Karamese M, Kugu S, Kacar EA, Esen MF, Erdogan H, et al. Doxorubicin-loaded liposome-like particles embedded in chitosan/hyaluronic acid-based hydrogels as a controlled drug release model for local treatment of glioblastoma. Int J Biol Macromol. 2024;278(Pt 4):135054.
174. Isik S, Yucel D, Hasirci V. Development of a Hydrogel Platform with GBM and Microglia: A Potential Glioblastoma Tumor Model. ACS Appl Bio Mater. 2025;8(9):7757-7770.
175. Ponomareva N, Brezgin S, Karandashov I, Kostyusheva A, Demina P, Slatinskaya O, et al. Swelling, Rupture and Endosomal Escape of Biological Nanoparticles Per Se and Those Fused with Liposomes in Acidic Environment. Pharmaceutics. 2024;16(5):667.
176. Cai X, Drummond CJ, Zhai J, Tran N. Lipid Nanoparticles: Versatile Drug Delivery Vehicles for Traversing the Blood Brain Barrier to Treat Brain Cancer. Adv Funct Mater. 2024;34 (41):2404234.
177. Marrocco F, Falvo E, Mosca L, Tisci G, Arcovito A, Reccagni A, et al.

Nose-to-brain selective drug delivery to glioma via ferritin-based nanovectors reduces tumor growth and improves survival rate. Cell Death Dis. 2024;15(4):262.
178. Cai Y, Li W, Li M, Yao C, Zhao Y. The "All-in-One" Colorimetric System for In Situ Synthesis of Gold Nanoparticles and Mercury Detection Assisted by Nonthermal Microplasma. IEEE Trans Instrum Meas. 2024;73:1-6.
179. Khotimah H, Rahmaniar FZ, Zahra FA, Anaqah R, Nandar S. Unveiling the effects of nanoparticles-based antiepileptic drugs: Systematic review of in vivo studies. Heliyon. 2024.
180. Karami MH, Abdouss M, Rahdar A, Pandey S. Graphene quantum dots: Background, synthesis methods, and applications as nanocarrier in drug delivery and cancer treatment: An updated review. Inorg Chem Commun. 2024;161:112032.
181. Ali BH, Khoee S, Mafakheri F, Sadri E, Mahabadi VP, Karimi MR, et al. Active targeted delivery of theranostic thermo/pH dual-responsive magnetic Janus nanoparticles functionalized with folic acid/fluorescein ligands for enhanced DOX combination therapy of rat glioblastoma. J Mater Chem B. 2024;12(24):5957-5973.
182. Mineart KP, Kelley EG. Size reduction, purification, sterilization and storage/packaging of liposomes. In: Antimisiaris SG, editor. Liposomes in Drug Delivery. Academic Press; 2024. p. 489-515.
183. Littrell CA, Takacs GP, Sankara CS, Sherman A, Rubach KA, Garcia JS, et al. Systemically targeting monocytic myeloid-derived suppressor cells using dendrimers and their cell-level biodistribution kinetics. J Control Release. 2024;374:181-193.
184. Heidari R, Assadollahi V, Khosravian P, Mirzaei SA, Elahian F. Engineered mesoporous silica nanoparticles, new insight nanoplatforms into effective cancer gene therapy. Int J Biol Macromol. 2023;253:127060.
185. Ye M, Gong J, Chen W, Liu X, Zhu D. Effect of the size of nucleic acid delivery systems on their fate in cancer treatment. Explor Drug Sci. 2024;2(1):38-49.
186. Amanat MA, Farrukh A, Ishaq MUBM, Bin Shafqat B, Haidri SH, Amin R, et al. The Potential of Nanotechnology to Replace Cancer Stem Cells. Curr Stem Cell Res Ther. 2024;19(6):820-831.
187. Nozhat Z, Wang S, Mushtaq A, Deng T, Iqbal MZ, Kong X. Temozolomide loaded Fe3O4@SiO2 nanoparticles for MR-imaging directed synergistic therapy of glioblastoma multiforme in vitro. Mater Today Commun. 2024;38:108289.
188. Kumar M, Kumar D, Mahmood S, Singh V, Chopra S, Hilles AR, et al. Nanotechnology-driven wound healing potential of asiaticoside: A comprehensive review. RSC Pharm. 2024.
189. Priyadarshini S, Bora S, Kulhari H. Lipid-Based Nanocarriers for the Delivery of Phytoconstituents. In: Pooja D, Kulhari H, editors. Nanotechnology Based Delivery of Phytoconstituents and Cosmeceuticals. Singapore: Springer Nature Singapore; 2024. p. 125-167.
190. Yasir M, Mishra R, Tripathi AS, Maurya RK, Shahi A, Zaki MEA, et al. Theranostics: a multifaceted approach utilizing nano-biomaterials. Discov Nano. 2024;19(1):35.
191. Nozhat Z, Heydarzadeh S, Shahriari-Khalaji M, Wang S, Iqbal MZ, Kong X. Advanced biomaterials for human glioblastoma multiforme (GBM) drug delivery. Biomater Sci. 2023;11(12):4094-4131.
192. Askarizadeh A, Mashreghi M, Mirhadi E, Mirzavi F, Shargh VH, Badiee A, et al. Doxorubicin-loaded

liposomes surface engineered with the matrix metalloproteinase-2 cleavable polyethylene glycol conjugate for cancer therapy. Cancer Nanotechnol. 2023;14(1):18.
193. Quinn JF, Whittaker MR, Davis TP. Glutathione responsive polymers and their application in drug delivery systems. Polym Chem. 2017;8(1):97-126.
194. Silvarrey C, Alvite G, Esteves A. Nanoparticle formulation for the development of a dog nanovaccine against Cystic Echinococcosis. Biologicals. 2024;85:101737.
195. Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. Am J Transl Res. 2014;6(2):114-118.
196. Kwan K, Schneider JR, Kobets A, Boockvar JA. Targeting Epidermal Growth Factor Receptors in Recurrent Glioblastoma Via a Novel Epithelial Growth Factor Receptor-Conjugated Nanocell Doxorubicin Delivery System. Neurosurgery. 2018;82(3): N23-N4.
197. Biau J, Durando X, Boux F, Molnar I, Moreau J, Leyrat B, et al. NANO-GBM trial of AGuIX nanoparticles with radiotherapy and temozolomide in the treatment of newly diagnosed Glioblastoma: Phase 1b outcomes and MRI-based biodistribution. Clin Transl Radiat Oncol. 2024;48:100833.
198. Kumthekar P, Ko CH, Paunesku T, Dixit K, Sonabend AM, Bloch O, et al. A first-in-human phase 0 clinical study of RNA interference–based spherical nucleic acids in patients with recurrent glioblastoma. Sci Transl Med. 2021;13(584):eabb3945.
199. Clarke JL, Molinaro AM, DeSilva AA, Rabbitt JE, Drummond DC, Chang SM, et al. A phase I trial of intravenous liposomal irinotecan in patients with recurrent high-grade gliomas. J Clin Oncol. 2015;33(15_suppl):2029.