Cancer Nanotechnology

REVIEW Open Access

Empowering rapid diagnosis and treatment of glioblastoma with biofunctionalized carbon quantum dots: a review

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Abstract

Glioblastoma (GBM), classified as a grade IV glioma, poses a significant challenge in the medical field due to the lack of efficient early detection techniques and targeted treatment options. This review addresses this critical unmet need by evaluating the transformative potential of carbon quantum dots (CQDs) and graphene quantum dots (GQDs), along with their biofunctionalized derivatives. These advanced nanomaterials offer remarkable opportunities to revolutionize the diagnosis and treatment of GBM at the cellular level. The excellent biocompatibility, stability, and adjustable surface properties of biofunctionalized GQDs (bGQDs) and biofunctionalized CQDs (bCQDs) create a strong foundation for the targeted management of GBM. Careful surface modifications enable selective toxicity toward GBM cells while preserving the health of normal cells. This approach enhances penetration through the blood–brain barrier and targets tumor cell nuclei precisely. Furthermore, the photophysical properties of bCQDs and bGQDs make them suitable for innovative anticancer treatments, including photodynamic and photothermal therapies. By incorporating anticancer agents and receptor-mediated targeting systems within bCQDs and bGQDs, therapeutic effectiveness is significantly improved through enhanced drug delivery and increased tumor specificity. Developing sensitive and selective biosensors for GBM using bCQDs and bGQDs as fluorescent and electrochemical sensing platforms enables real-time monitoring of disease progression. This review emphasizes the promising future of fluorescent CQDs and GQDs as powerful alternatives to traditional GBM management strategies, paving the way for more effective and personalized approaches in nanomedicine.

Clinical trial number Since this study is a review, it is not eligible for submission to the clinical trial registry.

Keywords: Glioblastoma, Biofunctionalized carbon quantum dots, Biofunctionalized graphene quantum dots, Biosensing, Bioimaging

Introduction

One of the most aggressive malignancies is Glioblastoma (GBM), which is the most prevalent malignant primary tumor in the brain and central nervous system. GBM causes 48.6% of malignant CNS tumors and 14.5% of all CNS tumors (Grochans et al. 2022). The median overall survival (OS) of patients with GBM is only 15 months (Grochans et al. 2022) and may increase to 21 months with a survival rate of 26% (Stupp et al. 2017a; Patel and Chavda 2024).

The incidence of GBM differs in existing reports from 3.19 cases per 100,000 person-years to 4.17 per 100,000 person-years (Batash et al. 2017; Razavi et al. 2016). The increased incidence rate of GBM is reported in older age, and the median incidence age is 64. Children and adults have the least common incidence rate, while those aged between 74 and 85 have the highest incidence rate. GBM incidence in males and females is 4.00 and 2.53 per 100,000 persons, respectively. In addition, the incidence is 40% lower in American Indians and Alaska Natives than in non-Hispanic whites. In contrast, the highest incidence is recognized in Australia, Northern and Western Europe, and North America (Ostrom et al. 2019).

Tumor localization is often in the cerebral hemispheres' subcortical white matter, more frequently in the parietal, occipital lobes, temporal, and frontal (Gupta et al. 2020). The origin of GBM is astrocytic glial cells, and it accounts for grade IV astrocytoma. This tumor appears where high-grade gliomas are detected in the midline structure, including the thalamus, cerebellum, spinal cord, and brainstem (Chen et al. 2022). The tumor localization primarily affects the clinical presentation of the disease. Seizures, behavioral changes, deficits in focal neurology, and increased intracranial pressure are the most common symptoms.

GBM seriously alters the typical structure of blood vessels, leading to chaotic and permeable vessels characterized by abnormal walls and insufficient pericyte support. This impairment affects the functionality of the blood–brain barrier (BBB) and results in edema, inflammation, and infiltration by the immune system. While there is an increase in endothelial cell numbers, hypoxia continues to be present, which restricts the efficacy of drug delivery. The tumor microenvironment encourages neovascularization through several mechanisms, including co-option, angiogenesis, vasculogenesis, vessel invasion, and disruption of BBB (Fig. 1) (Rosińska and Gavard 2021).

According to classic magnetic resonance imaging (MRI), glioblastoma morphology has an irregular shape, ring-enhancing, or rim-enhancing lesion with a central dark area of necrosis, which may not exist in some subtypes. The tumor may spread toward the corpus callosum into the opposite hemisphere, which results in a butterfly lesion (Fig. 2) (Chen et al. 2022).

GBM pathophysiology

About 40% of GBM cases experience the increment of Epidermal Growth Factor Receptors (EGFR), where their phenotypic changes upon overexpression, amplification, and mutation. RNA reverse transcription, or insertion, causes EGFR amplification (Carlsson et al. 2014).

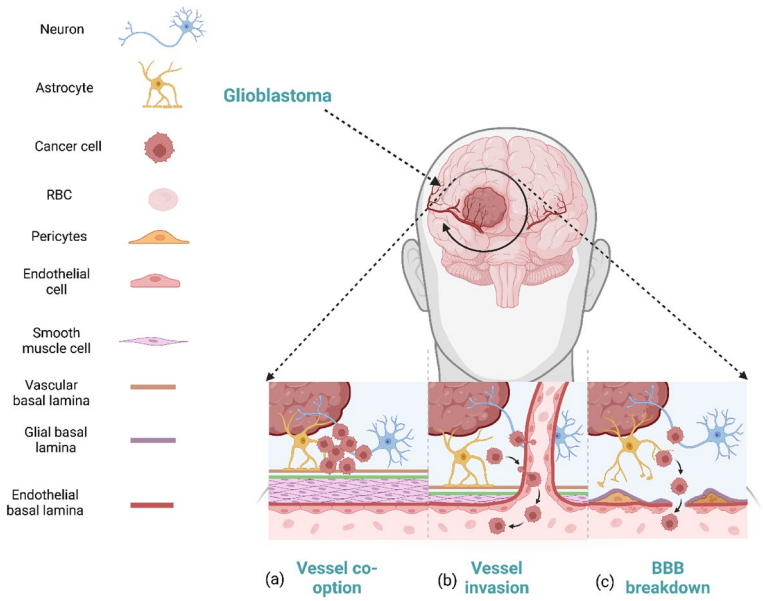

Fig. 1 Schematic overview of glioblastoma invasion and its impact on the blood–brain barrier: (**a**) vessel co-option, where tumor cells utilize existing vessels for growth and migration; (**b**) vessel invasion, with tumor cells breaching the vessel wall and interacting with perivascular cells; and (**c**) blood–brain barrier breakdown, leading to increased permeability and facilitating tumor progression, immune evasion, and drug resistance

P53, as a tumor suppressor protein, can repair DNA or induce apoptosis of irreparable DNA. The p53 mutant cells grow beyond consideration and overtake the non-p53 mutant cell population, which causes the expansion of high-grade glioma (Sidransky et al. 1992). A study showed higher levels of nuclear p53 expression in long-term survivors than in short-term survivors (Burton et al. 2002). Delivery of the p53 gene using nanoparticles in standard chemotherapy to glioblastoma and cancer stem cells resulted in apoptosis induction and survival improvement in mouse models (Kim et al. 2014).

Nearly 60% of primary tumors expressing mutant p53 can be concurrent with Phosphatase and Tensin Homolog Deleted on Chromosome 10 (PTEN) mutation. One of the tumor suppressor genes that modulate cellular homeostasis and get mutated in 5–40% of GBMs is PTEN. It can be used as an indicator in patients older than 45. The decreased level of p 53, associated with Nonsense mutation of PTEN, can lead to shorter survival in the murine xenograft model (Xu et al. 2014).

Isocitrate dehydrogenase (IDH-1) mutations are the reasons for the alteration of low-grade gliomas to secondary GBM, as it can be detected in 83% of all secondary GBM cases. This type of mutation reduces the enzyme efficiency and enzymatic function gain depending on the substrate. The mutation in which the arginine at codon site 132 is replaced with a histidine (R132H mutation) increases the converting ability of IDH-1 for the alpha-ketoglutarate to 2-hydroxyglutarate (2HG) that is an onco-metabolite (Jin et al. 2013).

A multidimensional analysis of 216 GBM patients shows genetic alterations, such as Neurofibromin 1 gene inactivation, mutations in Erythroblastic Oncogene B (ERBB2), and methylguanine–DNA methyltransferase (MGMT) methylation. When GBM occurs,

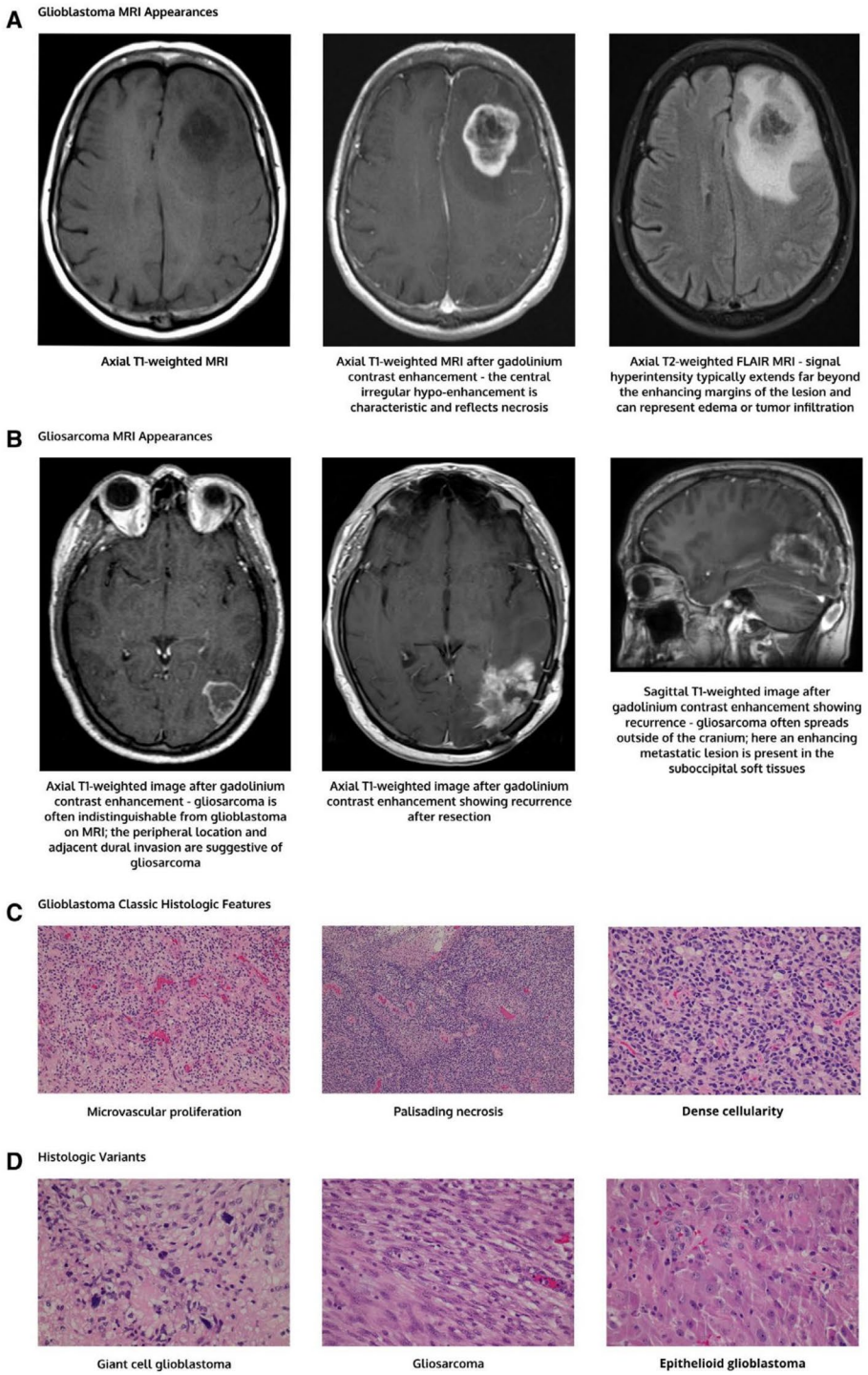

Fig. 2 Radiographic and histologic appearances of glioblastoma are shown in this figure, where part A shows Typical images obtained from magnetic resonance imaging (MRI), part B demonstrates the MRI images of gliosarcoma, part C reports the classic histologic features of glioblastoma, and the last part (part D) is about the histologic variants of glioblastoma. The fluid-attenuated inversion recovery is indicated by FLAIR (Tan et al. 2020). License Number: 5830670442125

a neurotrophic tyrosine kinase receptor type 1-neurofascin gene undergoes the fusion process that causes 3T3 proliferation, acting like an oncogene (Kim et al. 2014).

The MIR-491 gene is responsible for encoding miRNA 491-5p and miRNA 491-3p. The loss of *MIR-491,* connected to Insulin-Like Growth Factor Binding Protein 2 (IGFBP2), Cyclin-Dependent Kinase 6 (CDK6), and EGFR overexpression, affects the proliferation and invasion of GBM. *MIR-49* intervenes in the proliferative pathways of EGFR, CDK6, and IGFBP2, causing impairment of GBM cancer stem cells (Li et al. 2015).

GBM biomarkers

GBM biomarkers are used to develop potential remedies and reverse the effects of cancerous growth or decrease disease progression. There are several main biomarkers to be discussed, including Platelet-derived Growth Factor Alpha Receptor (PDGFRA), EGFRO^6-MGMT, and IDH, and several other relevant biomarkers, such as vascular endothelial growth factor (VEGF), neurofibromatosis type 1 (NF1), and p16lNK4A (Sasmita et al. 2018) (Fig. 3).

MGMT is in chromosomal position 10q26, which encodes the proteins to repair DNA and alkyl groups at the O^6 position of guanine. Several transcription factors can modulate the expression of MGMT, including specificity protein 1 and nuclear factor kappa B (NF-κB). This modulation occurs via their promoter activation to express MGMT enhancement (Cabrini et al. 2015). MGMT methylation raises the efficacy of temozolomide (TMZ) as an alkylating agent in the chemotherapy process.

Two signs of GBM, especially in the classical subtype and primary class, are the increase in genetic rearrangement of EGFR (EGFRvIII) and EGFR (Yoshimoto et al. 2012). The gene encoding EGFR is identical to the one encoding the Receptor tyrosine kinases (RTKs). Histone modifications at chromosome 7p12 on gene enhancers result

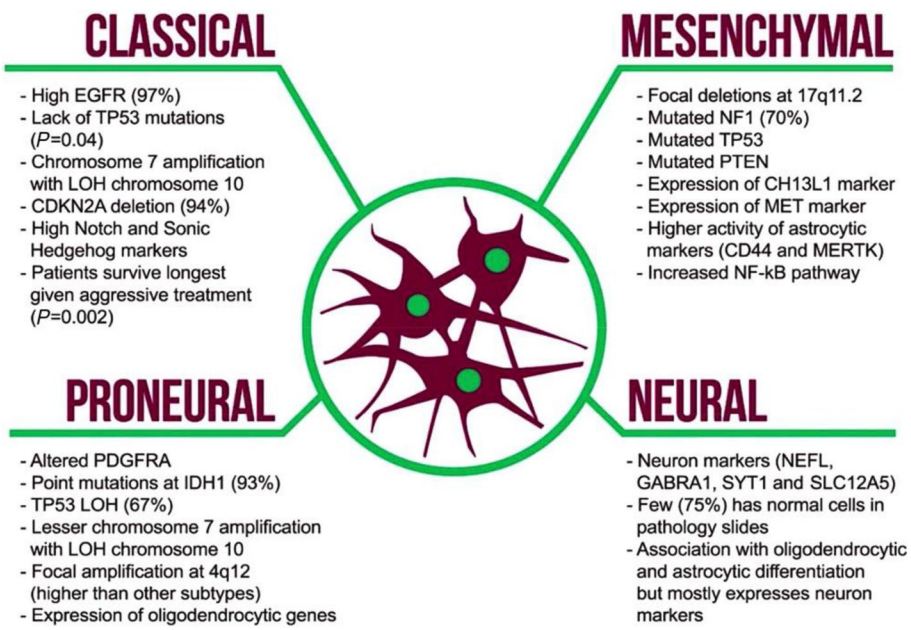

Fig. 3 Molecular biomarkers correlated with different subtypes of GBM. (Sasmita et al. 2018). License Number: 5830680668935

in EGFR mutation, leading to EGFRvIII formation. The increase and mutation of EGFR are exploited for predictive biomarkers (Shinojima et al. 2003). The RTKs/Ras/phosphoinositide 3-kinase (PI 3-kinase) pathway would activate due to the presence of EGFR; this can lower the integrity of G1 to S checkpoint in the cell cycle, leading to an upregulated proliferation. The presence of EGFR can cause problems in the prognosis of most cases of GBM.

One of the receptors of specific growth factors, overexpression, which results in abnormal and uncontrolled cellular growth, is PDGFRA. Several PGFR ligands and receptors are found in gliomas, including GBM. The first types are PDGFRA and PDGFRB. The former is a prognostic biomarker for GBM, specifically the proneural subtypes of GBM (Taylor et al. 2012; Ozawa et al. 2010). The rise in PDGFRA almost always happens alongside the presence of mutations in Isocitrate dehydrogenase (IDH), which is reported at a higher rate in secondary GBM. PDGFRA is selectively localized on the tumor cells, while PDGFRB is on the vasculature surrounding the tumor cells (Sasmita et al. 2018; Nazarenko et al. 2012). Expression of PDGFR occurs as early as low-grade diffuse astrocytoma, and it is dramatically overexpressed in high-grade secondary GBM tumors. PDGFRA-positive patients have the most prolonged overall survival, almost 10 years (Motomura et al. 2013). A study reported that RNA interference in PDGFRA tumor cells caused a significant decrease in cell proliferation so that it can be considered a potential drug target (Heldin 2013).

Extracellular vesicles (EVs) are recognized as heterogeneous groups of lipid bilayer-delimited particles, which can be divided into different subtypes, such as exosomes, apoptotic bodies, microvesicles, and ectosomes. Classifying these subtypes is based on their size, biogenesis, and molecular structure. EVs transfer several bioactive molecules, such as different RNA species, through body fluids (Stella et al. 2021). The closed covalent RNA molecules, mostly non-coding and synthesized by protein-coding genes from pre-mRNA through back-splicing, are called circular RNAs (circRNAs) (Memczak et al. 2013). The expression of circRNA in gliomas and GBM is dysregulated. In GBM tissues, CircSMARCA5, a tumor-suppressive circRNA, is suppressed compared to normal brain parenchyma. The expression of circSMARCA5 affects the overall and progression-free survival of patients with GBM. Moreover, it adjusts the pro- to anti-angiogenic VEGFA isoform ratio and microvascular density of GBM tissue (Barbagallo et al. 2019). Isocitrate dehydrogenase is one of the most significant genetic biomarkers of GBM (Han et al. 2020). Alteration of IDH produces 2-HG, tumor genesis, and causes DNA hypermethylation and tumor genesis (Jadoon et al. 2022).

Diagnostic trends for GBM

Clinical presentations of GBM

Since different functional areas are affected in GBM, several clinical manifestations are anticipated, like the symbols of smaller tumors in imaging, loss of vision, numbness, alteration of language, and persistent weakness. When the tumor is located in brain components, such as the temporal lobe, corpus callosum, or frontal lobe, the clinical presentations are mood disorder, mild memory disorder, fatigue, and executive dysfunctions. These kinds of tumors tend to grow larger. Some newly diagnosed patients may have seizures easily controlled by anticonvulsants (Chaichana et al. 2009).

Imaging features of GBM

A ring-enhancing lesion is infiltrative and heterogeneous, in which the central part accounts for necrosis, while the surrounding part is considered peritumoral edema. Commonly, deep white matter and corpus callosum are involved. Typically, a ring-enhanced necrotic lesion with peritumoral edema is created rapidly from a small non-enhancing lesion (Yan et al. 2009; Capper et al. 2010). Among all available imaging modalities, MRI can differentiate GBM from nonglial tumors and infections (Smirniotopoulos et al. 2007). Secondary GBM (IDH-mutant GBM) is a bulky, non-enhancing tumor, including necrosis and edema, and a predilection at the temporal and frontal lobe (Ohgaki and Kleihues 2013).

Pathological diagnosis

In the pathological samples, infiltration of Glial Fibrillary Acidic Protein (GFAP) immunopositive tumor with marked microvascular proliferation, necrosis, Pleomorphism, and brisk mitotic activity may be observed using microscopy and immunostains. Usually, the cellular morphology is predominantly astrocytic, but sometimes, it can be a subset of tumor cells with primitive neuroectodermal features or oligodendroglial (Louis et al. 2016).

Current treatment approaches for GBM

Chemotherapy

TMZ is considered the first-line therapy used significantly. It is a prodrug converted to monomethyl triazene 5-(3-methyl-1-triazeno) imidazole-4-carboxamide (Bei et al. 2010). The signaling cascade of cell cycle checkpoint activation is promoted by methylation of O6 of guanine, which causes mutations to escape from the Mismatch Repair system (MMR). The promoted signaling cascade induced by MMR results in the activation of checkpoints in the cell cycle, followed by the arrest of the G2–M cell cycle, and single- and double-strand breaks in DNA lead to apoptosis (Khabibov et al. 2022).

Carmustin (BCNU) is an alkylating agent and nitrogen mustard compound used for GBM chemotherapy. It causes inter-strand crosslinks in guanine and cytosine bases of DNA (Baer et al. 1993). Lomustine is another alkylating agent that can be used in treating GBM due to its high lipophilicity and small size; these properties let the drug easily pass the blood–brain barrier (Wu et al. 2021).

Anti-angiogenic therapies

Anti-angiogenic therapy can normalize the function and structure of blood vessels that belong to the tumor. One example of anti-angiogenic drugs is bevacizumab, a recombinant humanized IgG1 monoclonal antibody, which inhibits the connection of VEGFA to its receptors and decreases the downstream signaling pathways (García-Romero et al. 2020). Tyrosine Kinase Inhibitors (TKIs) are the group of molecules that connect the intracellular ATP-binding catalytic site of activated tyrosine kinase domain and block the biomarkers, such as EGFR, PDGFR, and VEGFR; in the case of GBM, they play an anti-angiogenic role (Wang et al. 2023). Cediranib is a multi-kinase inhibitor whose target is VEGFR and can be used alone or in combination with lomustine (Batchelor et al. 2010).

Tumor treating field (TTF)

The EF-14 trial, a significant study in the field of GBM, demonstrated that adding TTFs to maintenance therapy with TMZ chemotherapy raised the OS by 4.9 months for patients with newly diagnosed GBM (Stupp et al. 2017b; Stupp et al. 2015). This addition did not significantly increase systemic adverse reactions and was associated with sustained or improved quality of life. This trial's data led to the FDA approval of TTFs for newly diagnosed GBM in 2015 (Zhu et al. 2017; Mrugala et al. 2014).

The most commonly used TTF delivery system is Optune, which consists of a field generator, a power source, and four transducer arrays. These are attached orthogonally to the patient's scalp and produce alternating electric fields across the brain and tumor site. This treatment has shown promise as an effective therapeutic option for GBM patients (Rominiyi et al. 2021).

Surgery

Maximal resection can effectively improve the survival of patients with a central focus on the patient's age or tumor's molecular status (Noorbakhsh et al. 2014). In contraindicated situations, the best method to verify the histology or evaluate the molecular status of the tumor is a stereotactic biopsy (Eigenbrod et al. 2014).

Other alternative therapies include reoperation, systemic treatment, re-irradiation, supportive care, and combined modality therapy. To choose the best treatment option for GBM, several valuable factors must be considered, including size and location of the tumor, age, Karnofsky performance score (KPS), prognostic factors, previous treatment(s), and patterns of relapse (Weller et al. 2013).

GBM treatment difficulties

Several clinical trials have been conducted to evaluate the effectiveness of possible treatments for GBM. However, the clinical outcome of using TKIs in adult patients was not favorable. This was because of the broad inclusion criteria, poor pharmacokinetics, and resistance to TKIs. One of the reasons that limited the efficacy of current treatments was their poor BBB permeability (Brar et al. 2022). Furthermore, TKIs were cytochrome P450's substrates, making their metabolites more hydrophilic and less selective than the leading drug (Salmaso et al. 2021; Gandin et al. 2015). The infiltrative nature of the brain, tissue sensitivity, and the danger of losing its function direct the surgical procedure for treatment (Fernandes et al. 2017). As the brain can become resistant to chemotherapeutic agents, the response of GBM to chemotherapy is poor. This is while radiotherapy may cause necrosis in brain tissue with the risk of losing function (Fernandes et al. 2017; Urbańska et al. 2014). TTF is safe, but several side effects have been observed with its performance, including mild to moderate skin reaction in 44% of patients and grade 3 skin reaction in 1–2% of patients (Louis et al. 2016).

Carbon nanoparticles for the diagnostic ailment of various pathologies

Carbon-based nanoparticles (CNP) provide three significant carbon groups of nanoparticles: (1) amorphous carbon nanoparticles (carbon dots, ultrafine carbon particles, and carbon nanoparticles); (2) sp^2 carbon nanomaterials (carbon nanotubes,

graphene, carbon nanohorns, fullerene, and graphene quantum dots); and (3) nanodiamonds (Holmannova et al. 2022; Gholami et al. 2020; Emadi et al. 2020) (Fig. 4). CNPs of pure carbon have extraordinary features, such as outstanding electrical and heat conductivity mechanical properties, including strength, toughness, extreme stiffness, low toxicity with high biocompatibility, and high stability (Holmannova et al. 2022; Hashemi et al. 2022).

Since accurate and early disease diagnosis is vital, imaging quality can be improved using CNPs (Mousavi et al. 2021). The natural ability of some classes of CNPs is their fluorescence emission upon photoexcitation. Graphene quantum dots, carbon nanotubes, and carbon dots have significantly large surfaces, which is beneficial for carrying multiple molecules. They also have fast excretion from the kidney or hepatobiliary systems (Liu et al. 2020; Mousavi et al. 2024a). Combining the fluorescent effect of CNPs with medical imaging techniques such as positron emission tomography (PET), MRI, and computed tomography (CT) improves details display, quality, and imaging sensitivity.

Using CNPs with near-infrared optical imaging has more profound penetration properties, which benefits deep tissue exploration without autofluorescence. This system embraces benefits like easier angiography of the whole body and brain, visualizing the organs, and conducting imaging-guided therapy for cancer and surgery (Wan et al. 2018; Li et al. 2016). CNPs have practical intraoperative, preoperative, and perioperative applications. For example, a study reported CNP therapy in patients with gastric cancer without severe adverse reactions, while the method could be used for detecting smaller lymph nodes. For thyroid cancer, CNPs differentiate parathyroid glands and lymph nodes. In endoscopic tattooing of colorectal cancer, they can detect and localize tumors and precancerous lesions before and after operation; this reduces surgery trauma (Li et al. 2016).

There are two types of graphene-based nanomaterials (GBNM): graphene oxide (GO) and reduced graphene oxide (rGO). Since GBNMs have exceptional properties and high

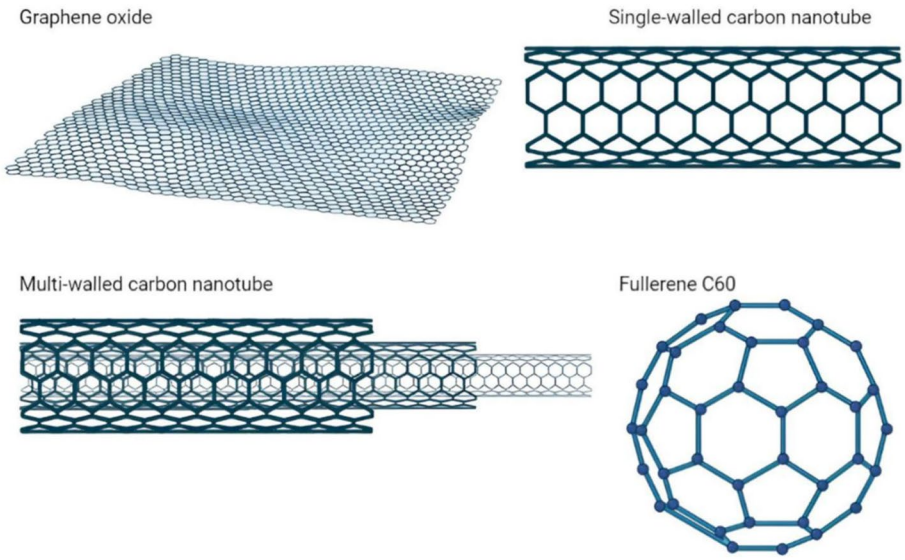

Fig. 4 Main types of carbon nanoparticles (Holmannova et al. 2022)

biocompatibility, they can be used in various biomedical applications. Compared with GO, rGO has higher electrical conductivity, which is advantageous for electrochemical biosensors. Unfortunately, rGO represents high hydrophobic and poor dispersion in aqueous solutions, which leads to drug delivery in non-target areas. However, GO is more hydrophilic and has better water dispersion, making it an excellent drug carrier (Báez 2023; Golkar et al. 2023).

There are special CNPs, called Carbon nanotubes (CNTs), which are highly effective molecules for drug delivery compared to other nanocarriers. Their inherent capacity and large surface area make them suitable for chemical interactions with ligands and linkers via interactions, such as π–π stacking, hydrogen bonds, and hydrophobic interactions. There are two types of CNTs: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) (Thakur et al. 2023). MWCNTs are more advantageous than the former because of their excellent stability, lower probability of drug leakage, multiple functionalization sites, and greater rigidity, which causes high drug loading capacity (Thakur et al. 2023; Mousavi et al. 2024b). Graphene and MWCNTs have short-term and long-term applications for hospital monitoring through electroencephalogram (ECG).

Since CNPs, especially carbon nanodots, nanotubes, graphene, or graphene oxide, can be linked to metallic NPs, organic polymers, or dyes, they could act as contrasting agents in tomography (Holmannova et al. 2022).

Carbon quantum dots (CQD)

There is a novel group of the smallest carbon-based fluorescent nanomaterials that attained significant attention due to their unique features, such as stable and tunable optical fluorescence, biocompatibility, photostability, water solubility, non-toxicity, easy functionalization, and their functions as donors and acceptors of electrons (Devi et al. 2019). CQDs are quasi-spherical nanoparticles that have carbon cores and functional groups as shells, including amino and carboxyl groups. There are three major types of CQDs: carbon nanodots (CNDs), polymer dots (PDs), and graphene quantum dots (GQDs). These categories have different structures; some have sp^2 hybridized amorphous structures, some are nanocrystalline carbon atoms clusters, some have sp^3 hybridized diamond-like structures, and others have graphene monolayer or multilayer crystalline structures (Zhu et al. 2020). CQDs can be pivotal in numerous applications, such as bioimaging, drug delivery, sensing, photocatalysis, and energy storage.

After synthesizing quantum-sized CQD from graphite via laser ablation, Sun and his colleagues tried numerous mechanisms (bottom-up and top-down methods) to prepare CQDs (Dong et al. 2012). The top-down method is exfoliation and cutting large sp^2 carbon domains into small pieces using ultrasonic treatment, laser ablation, electronic scissoring, arc discharge, chemical oxidation, and hydrothermal/solvothermal treatment, using molecular oxidation (HNO_3, $KMnO_4$, H_2SO_4, $KClO_3$ oxidation) and free radical oxidation approaches (Pan et al. 2010; Qiao et al. 2010) (Fig. 5). Introducing an oxygen-containing group, resulting from the reaction between precursors and chemical oxidizing reagents, may cause structural defects. The production of CQDs occurs when the activated edges make larger sp^2 carbon domains break into smaller pieces under high temperature or pressure. The rapid disconnection and scissoring of large carbon

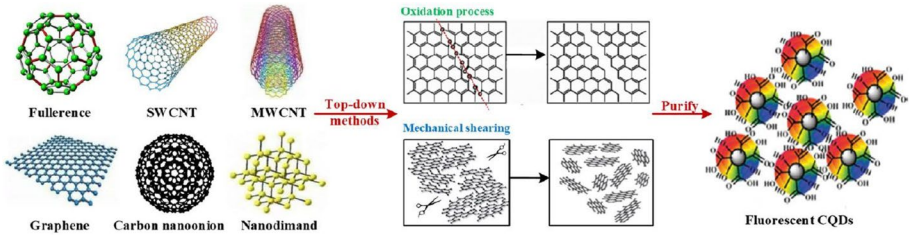

Fig. 5 Schematic diagram of the top-down pathway for the fabrication of CQDs. Adapted with permission from (Zhu et al. 2020) Copyright (Abootalebi et al. 2020) American Chemical Society

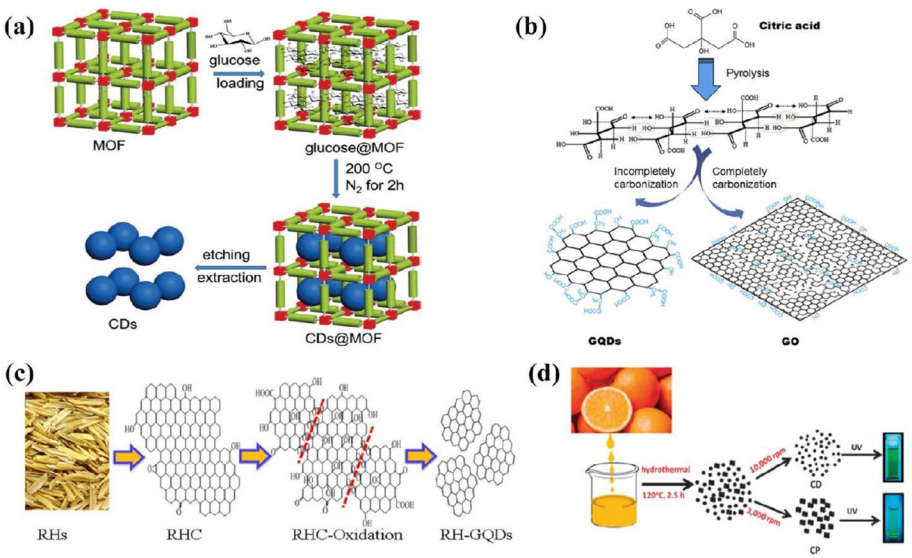

Fig. 6 Preparation of biomass-derived CQDs using Bottom-up approaches. (**a**) Schematic representation using a porous MOF as the template through, (**b**) pyrolysis method, (**c**) acidic oxidation, and (**d**) hydrothermal treatment (Zhu et al. 2020). It was adapted with permission from (Zhu et al. 2020) Copyright (Abootalebi et al. 2020) American Chemical Society

domains occur when the electrolytic oxidation of a water anode releases reactive free radicals (Zhu et al. 2020).

Controlled interaction of organic molecules with sp^2 carbon domains results in CQDs synthesis by bottom-up methods, such as microwave irradiation, hydrothermal/solvothermal treatment, pyrolysis, and template (Abbas et al. 2018). Several resources are used in bottom-up approaches, such as biomass waste, organic acids, and saccharides (Fig. 6). Intermolecular coupling or carbonation process is the primary reaction. When the small organic molecules undergo a series of chemical reactions after heating above their melting point, they are ready to form CQDs (Li et al. 2013).

Biomolecule-derived carbon quantum dots

The fabrication of CQDs can be conducted using a wide range of biomolecules and biopolymers, such as amino acids (Pei et al. 2015), carbohydrates (Niino et al. 2016), proteins (Lapshina et al. 2019), nucleic acids (Tian et al. 2021), and vitamins (Carneiro et al. 2019), which are selected based on their applications, as they can have effects on

heteroatoms and functional groups of CQDs, as well as their electrical and optical features (Naik et al. 2022).

The functional groups of amino acids, amine and carboxylic acid, make them critical precursors for the synthesis of CQDs. In addition, low prices, biocompatibility, good solubility, and abundance are the main reasons for the wide usage of amino acids. Among all amino acid-derived CQDs, cysteine-derived CQDs have demonstrated various optimistic features, including photocatalytic activity, antibacterial activity, and cytocompatibility. Therefore, they can be used for cell imaging, treatment of bacterial infections, and biosensing (Pei et al. 2015).

Proteins are prominent substances that produce CQDs because of their amide groups (Otzen 2002). Albumin has significant properties, such as water solubility, biodegradability, and biocompatibility, making it a great candidate for CQDs synthesis. The highly fluorescent CQDs can be synthesized using bovine serum albumin (BSA), human serum albumin (HSA), gelatin, and hemoglobin (Liang et al. 2013).

Carbohydrates, or saccharides, have hydrogen, oxygen, and carbon atoms in their structure and are considered hydrophilic biomolecules. Sugar or monosaccharide is the smallest carbohydrate with low molecular weight. Carbohydrates function and regulate various processes in living organisms, such as preventing blood coagulation, energy storage, fertilization, and the immune system. Carbohydrates have strong multicolor fluorescence (Peng and Travas-Sejdic 2009) and sustainability (Demir-Cakan et al. 2009), which is helpful for carbon-based nanomaterial synthesis (Naik et al. 2022). Biomass is a rich source of lipids and carbohydrates, leading to a potential source of efficient production of CQDs (Gusain et al. 2021). High-water solubility, non-toxicity, low cost, and excellent penetration from the blood–brain barrier (BBB) are the leading causes of selecting glucose as a precursor for CQD synthesis (Ma et al. 2012). In addition, polysaccharides, such as chitosan, chitin, and cellulose, are the main substances for synthesizing carbohydrate-derived CQDs (Liu et al. 2016a).

Nitrogenous nucleobases, pentose sugar, and phosphate group of nucleic acids are the rich source of carbons for the synthesis of CQDs. The covalent bonds in DNA molecules remain intact through CQD synthesis. The interaction between one DNA's phosphate group and another DNA's amino group causes the crosslinking of DNA strands for polymerization, condensation, dehydration, and carbonization (Guo et al. 2013; Zheng et al. 2019).

Other biomolecules, such as vitamins, folic acid, and glutathione, may be used in CQD synthesis and are studied for imaging human breast cancer cells (Naik et al. 2022).

The inherent medicinal properties of plants, for example, anti-inflammatory, antvenom, antibacterial, self-healing, anti-aging, induction of apoptosis, tumor inhibition, and cell cytotoxicity induction, are beneficial for treating and diagnosing cancer. Such features are used in the production of medicinal plant-based CQDs. The advantages of using plants are their simple synthesis routes and easy availability. The synthesized CQDs have water solubility, non-toxicity, high PL, and photostability (Naik et al. 2022).

Bioconjugation strategies for CQD-based agents

There are several strategies to strengthen the bonding between the target recognition molecules and the surface of CQDs. Several main factors should be controlled in the

bioconjugation process (Díaz-González et al. 2020): (1) BM (biomolecule)/QD ratio; (2) maintenance of optimal activity of CQD and BM, the orientation of BM on CQDs; (3) complete separation of CQDs and BM (if the forster resonance energy transfer (FRET) experiment is required); and (4) the strength of the CQD–BM bond (Fig. 7).

The bioconjugation strategies are described as follows:

A. Direct connection between BMs and CQDs: in this strategy, the direct joining of BMs to the surface of semiconductor CQDs can be performed through a covalent bond since the nucleic acids, peptides, and proteins would connect to CQD's surface via their thiol and imidazole groups (Sapsford et al. 2013).
B. Connection of BMs through ligands: this is based on the covalent bonds between the BMs and ligands that are first attached to the surface of CQDs. The attached ligands can be monodentate-like 3-mercaptopropionic acid (MPA) or bidentate-like dihydrolipoic acid (DHLA), which can bind to the surface of CQDs using their thiol groups (Sperling and Parak 1915).
C. Connection of BMs via encapsulating shell: QDs can be encapsulated using a layer of amorphous silica or a copolymer. The outer sphere of silica increases the stability and solubility of QDs, where the emission properties do not change. The encapsulation using an amphiphilic copolymer can be performed through the interaction of the latter's long hydrophobic tails and pristine QD ligands and the interaction of hydrophilic and functionalized segments with water molecules of the solvent (Zhou et al. 2017).
D. Connection of BMs through Biotin/Streptavidin: the protein found in albumen is called Avidin, which comprises four identical subunits with biotin-binding sites. Using two deglycosylated derivatives of Avidin, including streptavidin and neutravidin, is advantageous, making the biotinylation of QDs and BMs straightforward (Sapsford et al. 2013; Foubert et al. 2016).

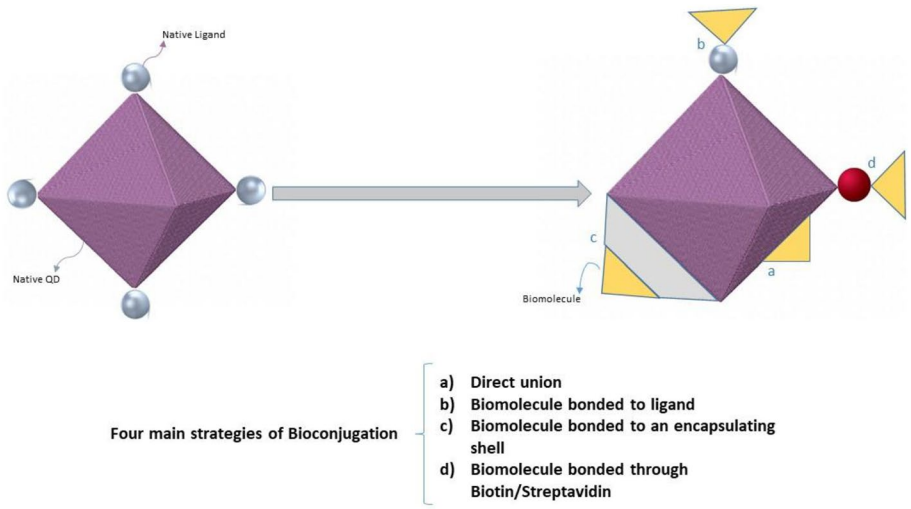

Fig. 7 Four main Bioconjugation Strategies of QDs

E. Covalent coupling: this strategy is based on the covalent bonding of the attached ligands on the surface of QDs and the incoming BMs. Using EDC (1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride) Moreover, sulfur–NHS (*N*-Hydroxysulfosuccinimide sodium salt) is one of the easy-to-perform bioconjugation reactions. The other bioconjugation route is amine and carbonyl group reactions to attain an imine group (Foubert et al. 2016; Karakoti et al. 2015).
F. Bioorhogonality: this kind of chemical reaction does not affect the unrelated functional groups of BMs and QDs or the surrounding biological environments. They only influence the target functions. Some examples of this kind of reaction include the cycloaddition between strained double bonds and tetrazine (tetrazine ligation), copper-catalyzed alkyne-azide cycloaddition (click chemistry), and hydrazine formation by reacting with the hydrazine and carbonyl groups (hydrazine ligation). Notably, any functional group can be attached to peptides and nucleotides to initiate the synthesis process and subsequent modifications (Sapsford et al. 2013; Massey and Algar 2017).

Biofunctionalized CQD for diagnostic GBM biosensing and imaging

Due to their distinctive optical and electrochemical properties, CQDs and GQDs emerge as significant tools in diagnosing and managing GBM. However, possessing these attributes alone does not suffice for practical application. The full potential of CQDs and GQDs in GBM diagnostics is realized through biofunctionalization. This targeted modification of their surfaces with specific biomolecules is essential for achieving the sensitivity, specificity, and versatility required for accurate GBM detection and monitoring.

Biofunctionalization facilitates the precise targeting of CQDs and GQDs toward specific GBM biomarkers, enhances their interactions with target cells, and allows their integration into a wide range of diagnostic platforms, from high-sensitivity laboratory assays to rapid point-of-care devices. The following categorization outlines the various biofunctionalization strategies utilized to convert biofunctionalized CQDs (bCQDs) and biofunctionalized GQDs (bGQDs) into highly effective agents for GBM sensing and diagnosis, underscoring how these modifications transform our capacity to detect and manage this challenging disease.

bCQDs/bGQDs as fluorescent labels for GBM detection

- **Fluorescence enhancement/quenching:** bCQDs/bGQDs can be used as fluorescent labels in "turn-on" or "turn-off" assays to detect biomolecules related to GBM. In most of these processes, QDs are fluorescent labels for fluorescent enhancement-based methods (turn on) and fluorescent quenching-based methods (turn off).
- **FRET technology:** bCQDs/bGQDs can also be employed in Förster resonance energy transfer (FRET)-based assays to study interactions between biomolecules in GBM. A study used sensitive FRET technology to evaluate energy transformation from exited state donor to proximal ground-state acceptor in interactions among BMs (Chen et al. 2017). Using bQDs for fluorescent labeling has several advantages,

such as broad absorption spectra, stability against photobleaching, long fluorescence lifetime, narrow emission spectra, and size-controlled luminescence.

- **Multiplexing capability:** Different-sized bCQDs/bGQDs with varying emission spectra allow multiplexed detection of multiple GBM biomarkers. To achieve QDs' excellent multiplexing capability, different-sized QDs with varying intensity levels should be attached to polymeric particles at controlled ratios.

Despite many advantages of using QDs as fluorescent labeling, they have a few drawbacks, including intrinsic blinking, low long-term stability, and complex and expensive production (Wu et al. 2016; Zhang et al. 2013).

Biofunctionalization for targeted GBM detection

•**IL13-conjugated QDs:** Conjugating QDs with interleukin-13 (IL13) allows for targeting glioma stem cells or exosomes in CSF or serum, potentially enabling early diagnosis and recurrence detection. A study has reported that exosomes in cerebrospinal fluid (CSF) may indicate the presence of glioma tumor cells or even cancer-initiating cells (Madhankumar et al. 2017). This is a key example of biofunctionalization for targeting. Locating interleukin-13 (IL13) on the surface of polyethylene glycol-modified cadmium selenide (CdSe) QDs is beneficial in detecting the presence of glioma stem cells or exosomes in serum or CSF. It can bring an opportunity to develop a simple diagnostic tool to detect early stage tumor recurrence, distinguish pseudoprogression and recurrent tumors, and perhaps diagnose high-risk patients (Madhankumar et al. 2017).

Angiopep-2 conjugated GQDs: Attaching angiopep-2 to sulfur-doped GQDs enhances their selective detection of glioma cells. This is another example of biofunctionalization for targeting. Sulfur-doped GQDs (S-GQDs)@Au–CNS nanocomposites were created through the Au–thiol connection of S-GQDs and gold–carbon nanospheres (Au–CNS) and used in glioma cell detection. The synthesized nanocomposites enhanced the electrochemical activity and can selectively detect the glioma cells as they were conjugated to angiopep-2 (Ang-2) (Ganganboina et al. 2021).

bCQDs/bGQDs in electrochemical biosensors

- **Electroactive labels:** bCQDs/bGQDs can act as electroactive labels in electrochemical devices for GBM detection, offering an alternative to fluorescence-based methods. Electrochemical devices, emerging as an alternative to fluorescence assays, have advantages, including their inexpensive, sensitive, and simple instrumentation. bQDs are elemental and are used as electroactive labels in electrochemical bQD-based bioassays and biosensors (Campuzano et al. 2019). However, limitations such as blinking, low long-term stability, and complex/expensive production may affect the applications of this method. The detection methods mentioned above are time-consuming and need well-educated personnel with centralized laboratories for the detection and biosensing assays. Since these methods are unsuitable for point-of-care (POC) diag-

nosis, several POC diagnostic systems are required to obtain appropriate information from sampling sites (Christodouleas et al. 2018).

bCQDs/bGQDs in point-of-care (POC) diagnostics

Microfluidic systems are high-throughput and automated approaches compared to centralized laboratory assays. They are inexpensive, portable methods with a low consumption of reagents and analyze quickly. However, microfluidic systems need bulky, energy-consuming, off-chip fluidic handling components and massive detectors. Therefore, they are replaced with paper-based devices, which do not need an off-chip fluidic handling element, capillary force the liquid instead of external forces (Gong and Sinton 2017). The other advantages of paper-based devices are their low cost, availability, biodegradability, simple modifications, and flexibility.

- **Paper-based devices:** bCQDs/bGQDs are used as signal reporters in paper-based devices for rapid, low-cost POC diagnosis of GBM. Paper-based devices are divided into dipstick assays, microfluidic paper analytical devices (μPADs), and lateral flow assays (LFAs) (Bahadır and Sezgintürk 2016). These devices use bQDs as signal reporters to detect nucleic acids, single nucleotide polymorphism, and protein biomarkers.
- **Smartphone-based diagnostics:** Combining bCQDs/bGQDs with smartphone technology offers a promising approach for accessible and portable GBM diagnostics. In addition to paper-based devices, smartphones for POC applications have a promising perspective as they are inexpensive, accessible, and functional. In addition, they can easily share the data through cloud engineering (Roda et al. 2016).
- **Barcode assays:** Attaching bCQDs/bGQDs to polymeric particles enables their use in barcode assays for multiplexed GBM target detection in POC settings. In modern healthcare systems, barcode assays are beneficial for POC applications due to their capability to detect multiple targets from the samples, fast analysis, and precise diagnosis (Liu and Jiang 2019). Attaching QDs on polymeric particles can be used as signal probes. The detection of human immunodeficiency virus, syphilis, and hepatitis B was performed through an on-chip sandwich hybridization assay (Han et al. 2001).

bQDs could improve the capability of molecular imaging techniques. Fluorescence imaging is beneficial for detecting real-time molecular interactions with significant sensitivity. However, conventional fluorescent dyes cannot optimally function because of their low stability, reduced signal penetration, photobleaching problems, and poor tissue specificity. As QDs are highly stable with tunable optical properties and high ability, they can play an alternative role in photoluminescence imaging.

Biofunctionalization for enhanced molecular imaging of GBM

Typical fluorescent imaging reagents in biological specimens are endogenous, where an enzyme-mediated process is needed to produce visible light inside the organism. This is opposite to other exogenous reagents, and the exogenous method is more appropriate for fluorescent imaging. The bQD–BM hybrids are significantly used in fluorescent imaging due to the outstanding production of nanoplatforms for evaluating the

single-molecule dynamics of living cells, deep disease detection, protein–protein interactions inside the cells, and identify tumor cells as tailored-bioconjugated QDs can significantly attach to cancer biomarkers. When QDs are utilized as luminescence tags, the interaction between existing chemical species and the surface of QDs changes the fluorescent emission. Accordingly, a study was performed in which mercaptoacetic acid (MAA)-capped CdSe/ZnSe/ZnS QDs were produced to track pH changes in SKOV-3 human ovarian cancer cells (Liu et al. 2007). In these methods, the severe restriction was the poor selectivity and limited applicability in real settings (Díaz-González et al. 2020).

- **Target-guided fluorescent imaging:** Conjugating CQDs/GQDs with antibodies or other targeting molecules (peptides, proteins, DNA) enables selective imaging of GBM biomarkers and tumor cells. This is a crucial aspect of biofunctionalization. Further advances in this field resulted in target-guided fluorescent imaging, used to monitor molecular surface dynamics of membrane-associated molecules, selectively detect multiple tumor biomarkers, and quantify molecular interactions at the cellular and subcellular levels. QDs label these cells with antibodies attached to their surface to trigger the location and distribution of tumors and tumor cells. For example, a study encapsulated QDs in carboxylated triblock polymeric micelles and created anti-mesothelin antibodies on their surface for detecting cancerous areas. This combination reached the pancreatic tumor site after only 15 min of intravenous injection. It is possible to use such a platform at the early detection stages of human pancreatic cancer (Ding et al. 2011). The significant challenge in this method is that the cells greatly uptake the nanoscale bQDs. There are various mechanisms for cell delivery of the modified combination based on active and passive transportation. The cellular uptake pathway of bQDs is widely dependent on the cell type and differentiation. Endocytosis is a significant way for uptaking non-conjugated water-stabilized bQDs (Díaz-González et al. 2020).
- **Active vs. passive targeting:** Let's discuss both active (ligand–receptor-mediated) and passive (enhanced permeability and retention effect) targeting strategies for delivering bCQDs/bGQDs to GBM. For active transportation of bQDs, they should be ligand–receptor-mediated with antibodies, proteins, or peptides to minimize unwanted cellular uptake. Water-stable nanoprobes can be produced using the functionalization of QDs with uncharged hydrophilic moieties or zwitterion molecules to eliminate the undesired bindings. The most usual way for molecular imaging is the conjugation of QDs with antibodies. Although targeted delivery can occur using peptides, proteins, and DNA. Conjugation of QDs with peptides can be used in target cellular BMs, such as G-protein-coupled receptors, ion channels, growth-factor receptors, and integrin (Rosenthal et al. 2011; Medintz et al. 2005).
- **PEGylation:** PEGylation of CQDs/GQDs is used to improve their stability, reduce unwanted cellular uptake, and enhance their circulation time. In a study, PEG was attached to the surface of ZnS/CdSe fluorescent QDs and streptavidin, labeled with biotinylated aptamer via streptavidin/biotin. This complex was used in fluorescence-guided surgery to resect glioma safely (Tang et al. 2017). In another study, PEGylated QD-Aptamer was used to image glioma cell lines, which overexpress growth factor receptor variant III. It was concluded that QD-Apt could be

a fluorescent agent suitable for molecular diagnosis, postoperative examination of gliomas, and image-guided surgery (Burton et al. 2002).

- **Near-infrared (NIR) imaging:** NIR-emitting bCQDs/bGQDs are preferred for in-vivo imaging due to reduced autofluorescence and deeper tissue penetration. Examples include InAs(ZnCdS) QDs and CuInSe2/ZnS QDs conjugated with tumor-targeting peptides. Fluorescent-emitted bQDs in the visible zone can only be used for in-vitro bioimaging applications. Endogenous auto fluorescent emitted from biological components is in the visible light spectra that interfere with the signals from QD-labeled BMs. Developing bQDs with near-infrared (NIR) emission spectra can resolve this limitation. The absorbance of this spectrum and the biological autofluorescence are much lower, and they can efficiently pass through biological tissues. For in vivo applications and imaging, NIR bQDs are beneficial since they can increase the contrast, penetration depth, and sensitivity, while the optical damage to the body decreases (Wang et al. 2018; Aswathy et al. 2010). A study demonstrated that NIR InAs (ZnCdS) bQDs with polymeric imidazole ligands could image the tumor vasculature in vivo (Allen et al. 2010). The most resilient NIR-emitting bQDs are the core–shell systems of $CuInS_2$ and $CuInSe_2$. To target the tumor, $CuInSe_2$/ZnS bQDs with a NIR emission and conjugated tumor were created by synthesizing them with a PEG linker to target the peptide Cys–Gly–Lys–Arg–Lys (CGKRK). The tumor absorbed These bQDs more than those with only PEG (Liu et al. 2016b). In a separate investigation, plerixafor was utilized to functionalize Ag_2S NPs, creating a CXC chemokine receptor 4 (CXCR4) inhibitor. This synthesized complex demonstrated the ability to conduct in vivo imaging of metastatic breast cancer cells by selectivity binding to highly metastatic breast cancer cells via CXCR4 receptors (Wang et al. 2018).
- **Multimodal imaging:** Combining CQDs/GQDs with other imaging modalities, such as MRI (using SPIONs), allows for more comprehensive GBM diagnosis and image-guided surgery. Recently, much attention has been paid to multimodal fluorescent-magnetic-based nanomaterials as they benefit the diagnosis and treatment of many diseases. For example, the conjugated superparamagnetic iron oxide NPs (SPIONs) with theranostic liposome (QSC-Lip), cilengitide (CGT), and QDs on a platform can be guided to glioma for surgical resection of glioma (Xu et al. 2018). In a study, nitrogen-doped polymer-coated CQDs (N-CQDs) were synthesized using N-Methyl-2-pyrrolidone (NMP). CQDs-based NCDDG as a dual-modal imaging system was synthesized using gadolinium (Gd) and diethylenetriamine penta-acetic acid (DTPA). To prove the bioimaging capabilities of the CQDs-based NCDDG system, an ex vivo bioimaging study was performed on the U87 GBM cell line incorporating NCDDG (300 μg/mL) at different times (Du et al. 2018).

Biofunctionalization for improved cellular uptake and tumor targeting

Nanoplatforms can enhance the existing resolution and detect small-sized tumors to treat GBM at early stages (Jain 2011). The capability of BBB penetration in CDs effectively helps the management of GBM and other brain diseases (Zheng et al. 2015).

- **Tumor-penetrating peptides:** Conjugating CQDs/GQDs with tumor-penetrating peptides (e.g., RGERPPR) enhances their specific targeting of GBM cells while minimizing uptake by normal brain tissue (Gao et al. 2018).
- **L-aspartic acid CQDs:** CQDs functionalized with L-aspartic acid (CQD-Asp) demonstrate high cellular uptake and selective localization in gliomas. L-aspartic acid CQD (CQD-Asp) has high cellular uptake and is easily removed from the tumor site. They are selectively localized in glioma with minimal effects on other tissues. Compared to CQD-G (glucose), CQD-Asp more selectively targets GBM (Zheng et al. 2015).
- **Hydrophilic polymer coating:** Coating CQDs/GQDs with hydrophilic polymers improves their water solubility, biocompatibility, blood circulation time, and targeting of leaky tumor vasculature. Coating the Gd^{3+} ion–CQDs with a hydrophilic polymer increased the uptake of Gd^{3+}-loaded CQDs by U87 cells. Applying synthesized N-isopropyl acrylamide (NIPAAM)@C-Dots in GBM bioimaging showed notable stability. Moreover, the synthesized bCQDs revealed good biocompatibility and long-term cellular imaging for various dosing (Kim et al. 2018). The developed nanosized polymer-coated N-doped carbon nanodots (pN-CNDs) using 1-methyl-2-pyrrolidinone (NMP) had appropriate water solubility, biocompatibility and stable high fluorescence. The good permeability of pN-CNDs led to increased accumulation in glioma cells. Using hydrophilic polymer as a coating agent improved the blood circulation time and targeted the sites with leaky endothelium. These features introduced pN-CNDs as a suitable candidate for GBM treatment (Wang et al. 2015).
- **Gd3 + -loaded bCQDs:** These are used as dual-modal imaging systems for GBM, combining fluorescence from bCQDs with MRI contrast from gadolinium. In addition, the synthesized bCQDs could easily penetrate across the vascular walls to reach the tumor sites. As Gd^{3+}–polymer-loaded CQDs have large sizes, the obtained image was darker in the central part of the glioma, and the margin parts were brighter. In addition, a considerable reduction in the cell viability of the U87 cell line treated with bCQDs was detected by MTT experiments. Overall, it was proved that Gd^{3+}-loaded carbon dots could be used as effective probes for brain tumor imaging (Liu et al. 2018).

In summary, key Takeaways for Biofunctionalization in GBM sensing and diagnosis include: (a) targeting: biofunctionalization is essential for targeting CQDs/GQDs to specific GBM biomarkers, cells, or tumor microenvironments; (b) sensitivity: biofunctionalization enhances the sensitivity of CQD/GQD-based detection methods; (c) specificity: biofunctionalization improves the specificity of GBM diagnosis by reducing off-target effects; (d) multimodal imaging: combining CQDs/GQDs with other imaging modalities offers more comprehensive diagnostic information; and (e) POC applications: bCQDs/bGQDs are crucial for developing rapid and accessible POC diagnostic tools for GBM. Table 1 summarizes the applications of bCQDs, bGQDs, and CDs in glioma biosensing and imaging.

Table 1 Biofunctionalized CQDs, GQDs, and CDs for glioma biosensing and imaging

Type of biofunctionalization	Targeted cells/tissues	Size	Mechanism	Beneficial effect	References
Localization of interleukin-13 on the surface of polyethylene glycol-modified cadmium selenide (CdSe)	Human glioma cells U251, human glioma stem cells T3691 and T387	24 nm	Binding firmly to glioma cells and Glioma initiating cells expressing the oncogenic IL13Rα2	Early tumor recurrence detection distinguishes recurrent tumors from pseudoprogression	(Sperling and Parak 1915)
Decoration of AuNP carbon nanospheres on Sulfur CQDs	Glioma cells in human serum samples	250–300 nm	Immobilization of the Angiotensin 2, increase in impedimetric sensing via pulse-induced mechanism	Ultrasensitive detection of glioma cells	(Zhou et al. 2017)
Decoration of biotinylated Aptamer 32 on the streptavidin–PEG–CdSe/ZnS QDs (SA-QDs)	U87 cell line, HUVEC cell line, U87-EGFRvIII cell line	20 nm	Penetrating BBB and binding to EGFRvIII	Detect EGFRvIII in tumor tissues, in vivo glioma imaging	(Bahadır and Sezgintürk 2016)
Decoration of CGKRK (Cys–Gly–Lys–Arg–Lys) on cadmium-free $CuInSe_2$/ZnS core/shell QDs	NG2-positive mouse glioma cells expressing green fluorescent protein (GFP–CT2A)	36 nm	Targeting the vasculature and tumor cells in glioblastoma	Deep tissue penetration of light for NIR imaging	(Liu et al. 2007)
Decoration of superparamagnetic iron oxide nanoparticles (SPIONs) and cilengitide (CGT) on QDs	Rat glioma model	100 nm	Producing an obvious negative-contrast enhancement effect On Glioma by magnetic resonance imaging, making tumor emitting fluorescence under MT	Guiding surgical resection of Glioma	(Ding et al. 2011)
Decoration of clinical Gd-DTPA on the surface of polymer-coated nitrogen-doped carbon nanodots	U87 cell line	30 nm	Transportation across the BBB	Dual-modal targeted MR/Fluorescence imaging of Glioma with high sensitivity and resolution	(Tang et al. 2017)
Decoration of N-isopropyl acrylamide (NIPAAM) on the surface of CDs	C6 cell line	2–3 nm	Enhancing quantum yield, improving the stability	Acting as a multicolored label for long-term cellular Imaging with a wide dosing window	(Aswathy et al. 2010)
Decoration of 1-methyl-2-pyrrolidinone (NMP) on the surface of polymer-coated nitrogen-doped CNDs	U251 glioma cell line	5–15 nm	Entering glioma cells in vitro via enhanced passive targeting	Mediating Glioma fluorescence imaging	(Allen et al. 2010)
CDs derived from D-glucose and L-aspartic acid as starting materials	C6 glioma cell line	2.28 nm	Freely penetrating BBB and precisely targeting glioma tissue	Bioimaging function toward glioma cells	(Medintz et al. 2005)
Decoration of Mal–PEG–NHS and a tumor penetrating peptide (RGERPPR) on CQDs	U87 cell line	9 nm	Penetrating the tumor tissue vascular wall and targeting Glioma	Tissue imaging and targeting of brain gliomas	(Liu et al. 2016b)

Biofunctionalized CQD for enhancing GBM treatment efficacy

bCQDs and bGQDs offer promising avenues for improving the treatment of GBM. Realizing their full potential is contingent upon biofunctionalization, a critical process that entails modifying the surfaces of CQDs and GQDs with specific molecular entities. This strategic alteration customizes their properties to tackle the formidable challenges associated with GBM effectively. Biofunctionalization transcends mere enhancement; it serves as a fundamental mechanism for enabling targeted delivery across the blood–brain barrier. This process facilitates superior drug loading and controlled release within the tumor microenvironment, thereby significantly improving therapeutic efficacy. The following categorization delineates various biofunctionalization strategies to achieve these objectives, illustrating how these modifications advance the battle against GBM.

Biofunctionalization strategies for enhanced BBB penetration and targeting

- **Glucose and amino acid modification:** Conjugating CQDs with D-glucose and L-aspartic acid enables them to cross the BBB and selectively target glioma cells. This is a biofunctionalization strategy for improved delivery. BBB is one of the most significant obstacles in detecting and treating brain cancer. A study demonstrated the benefit of using synthesized D-glucose and L-aspartic acid in crossing BBB to image c6 glioma cells with the highest selectivity toward glioma cells (Zheng et al. 2015; Qiao et al. 2018).
- **Zwitterionic modification:** Using citric acid and β-alanine to create zwitterionic CQDs enhances their penetration into cells due to positively charged moieties. This is a biofunctionalization strategy for better cellular uptake. In a study on zwitterionic CQDs, the combination of citric acid and β-analine facilitated the penetration of bCQDs into the cytoplasm of Hela cells because of their positively charged moieties (Jung et al. 2015).
- **TAT peptide conjugation:** Linking CQDs to TAT peptides allows for nuclear targeting in melanoma cells. This is a biofunctionalization strategy for targeted delivery to the nucleus. Tryphtophan-derived CQDs conjugated with transactivator of transcription (TAT) peptides are designed for nucleus imaging of mouse melanoma B16–F10 cells (Song et al. 2019). bCQDs from Betel leaves were used for multicolor imaging of HCT 166 colon cancer cells (Atchudan et al. 2018). bCQDs synthesized from Aloe Vera induced apoptosis in MCF-7 cancer cells for live imaging (Malavika et al. 2021).

Figure 8 presents a schematic representation of various biofunctionalizations of carbon quantum dots (bCQDs) designed to penetrate the BBB and target glioblastoma.

Biofunctionalization for improved drug delivery

- **Drug conjugation (covalent and non-covalent):** Attaching anti-cancer drugs to CQDs via covalent or non-covalent bonds is another biofunctionalization strategy to improve drug solubility, targeting, and delivery. Anti-cancer drugs have disadvan-

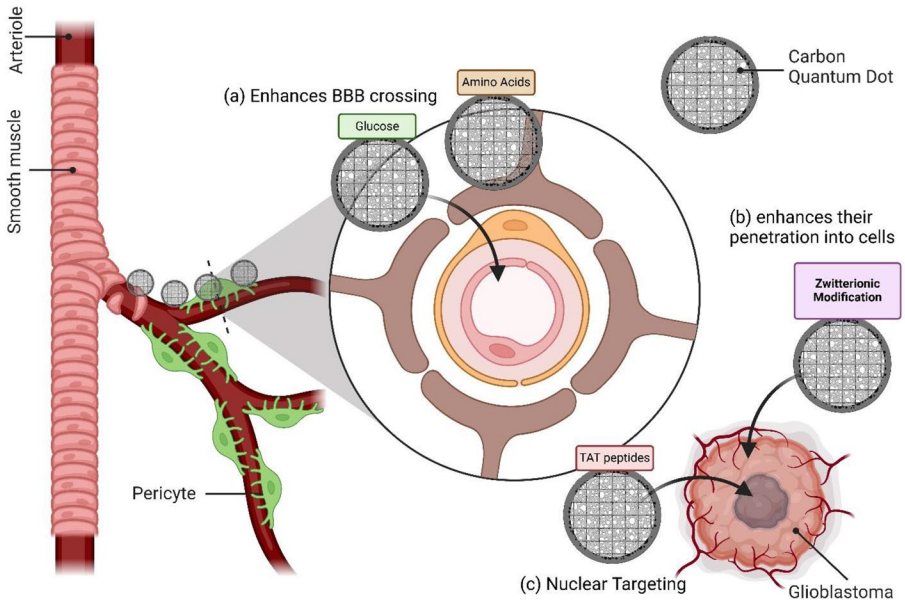

Fig. 8 Different biofunctionalized CQD for BBB penetration and glioblastoma targeting

tages, such as poor solubility, side effects, and imprecise targeting. Incorporating CQDs with anti-cancer nano-drug carriers benefits drug delivery systems because they are water soluble and biodegradable. They can facilitate fluorescence imaging to monitor the subsequent drug response, delivery, and activity. Anti-cancer drugs could be bonded to the CQDs covalently or non-covalently through their different functional groups, such as hydroxyl, carboxyl, and amine. The CQDs' fluorescence property is recovered after the drug is released.

- **pH-sensitive linkages:** Creating pH-sensitive linkages between drugs and CQDs is a biofunctionalization strategy for targeted drug release in the tumor microenvironment, which often has a different pH than healthy tissues. The microwave-synthesized CD-DOX conjugate, utilizing the carboxyl group of CDs and the amine group of DOX, is a specific example of a biofunctionalized system for pH-sensitive drug delivery. The carboxyl group of CDs and the amine group of doxorubicin (DOX) synthesize CD-DOX drug conjugates via microwave (Wang et al. 2016). This combination uses pH differences between cancerous and normal cells to kill cancer cells.

Biofunctionalization to modulate CQD/GQD properties

- **Surface charge modification:** Altering the surface charge of CQDs/GQDs through functionalization influences their interaction with cell membranes, affecting permeability and uptake. This is a biofunctionalization strategy to control cellular interactions. Perini et al. conducted a study illustrating that the biological impact of GQDs on neural cells altered following various chemical modifications to the GQDs' surface. After treating U87 GBM cells with tested GQDs, the production of ROS, secretion of neuroinflammatory molecules, and DNA fragmentation did not increase. Only the Green–GQDs had minor effects on the cell viability of the U87 cell line. The

treatment of U87 cells by Dox after treatment with GQDs had no significant impact on cell viability changes of cortical neurons. Conversely, treating U87 cells after treatment with Green–GQDs and COOH–GQDs significantly reduced cell viability; this observation indicated the synergistic effect between Dox and GQDs (Perini et al. 2020a). The study by Perini et al. emphasizes the importance of the biofunctionalization of GQDs (COOH vs. NH2) for their impact on GBM cell viability, neurosphere formation, and membrane fluidity. They proved the effects of surface functionalization of GQDs on GBM. The growth of nanospheres was monitored for two weeks, after which NH_2–GQDs did not influence the GBM sphere's growth. After being treated with 200 μg/mL of COOH–GQDs and GQDs, a considerable reduction occurred in developing novel spheres in the number and size of neurospheres. The relative membrane stability affects the proliferation and clustering of neural precursor cells, which is influenced by cell-to-cell interactions. After COOH–GQDs and GQDs administration, the membrane fluidity of GBM increased. While the surface charge of GQDs is negative, the cell membrane becomes unstable, and the formation of neurospheres is reduced; these phenomena result in tumor malignancy modulation. In conclusion, the study showed the reduction of GBM's malignancy and modulation of tumorigenesis after treatment with bGQDs both in vitro and in vivo conditions (Perini et al. 2021).

- **Functionalization for reduced toxicity:** bCQDs can increase intracellular drug concentration in cancer cells while reducing toxicity. While the mechanism is not always specified, this often involves biofunctionalization to improve biocompatibility. For example, the bCQDs derived from Nerium Oleander had several interactions with genes after penetrating cell nuclei, causing DNA damage (Şimşek et al. 2020). DNA-derived CQDs loaded with ETP and cetuximab-conjugated liposomes were synthesized to treat non-small lung cancer (Jha et al. 2020). This system also demonstrates biofunctionalization for targeted therapy in non-small cell lung cancer. Loading protein-derived QDs with melatonin is another example of biofunctionalization for improved drug delivery and therapeutic effects in breast cancer cells. The protein-derived QDs with melatonin loading were remarkably uptaken by cells and treated breast cancer cells (Yadav et al. 2021). A study conducted in 2020 showed that non-functionalized GQDs (NF-GQDs) did not lose their biocompatibility at all tested concentrations. Although dimethylformamide GQDs (DMF–GQDs) showed toxicity at high concentrations, specifically for GBM cells, but at lower concentrations, the biocompatibility of DMF–GQDs remained the same in both U87 GBM cells and primary mouse cortical neurons. The combination of Dox with GQDs considerably affected the cell viability of GBM cells. The effect of the antitumor drug and its effectiveness were elevated using DMF–GQDs. At the concentration of 100 μg/mL of DMF–GQDs, the combination of Dox with DMF–GQDs reduced the cell viability more than IC_{50} of the antitumor drug alone. This was due to increased Dox uptake from the U87 cell membrane permeability changes. The changes in cell membrane permeability are linked to the surface charge of the synthesized bCQDs (Perini et al. 2020b).
- In 2019, Shamsipour and his colleagues tried to find an effective way to deliver TMZ imaging with decreased initial burst and neurotoxicity. In that study, chitosan (CS)–

polyethylene oxide (PEO)/carboxymethyl cellulose (CMC)–polyvinyl alcohol (PVA) was used to produce coaxial nanofibers in which the core was made of CS and PEO and the shell layer was made of CMC and PVA. The conjugation of this chemotherapeutic agent with CQDs was performed to detect cellular uptake of CQDS–TMZ and morphological changes in treated cells. The U-251 MG glioblastoma cell line was used to assess appropriate drug concentration, cytotoxicity, and cell viability. The drug and its nanoconjugated form had anti-cancer activity against the U-251 MG cell line, while the drug carrier did not have any cytotoxic effect on cell viability. The trend of cellular death was similar to the equivalent amount of TMZ in its nanoconjugated form. The drug concentration of 200 μM in both formulations was set at the minimum concentration until 50% of U251 MG cells were dead (Shamsipour et al. 2019). This system used chitosan and other polymers to create nanofibers for TMZ delivery, with CQDs added for imaging. This is a form of biofunctionalization (or at least a combined biomaterial strategy) to improve drug delivery and imaging.

A summary of applications of bCQDs and bGQDs for treating glioblastoma is reviewed in Table 2.

Biocompatible nucleus-targeting CQD

Nucleus-targeting drug delivery systems can improve the efficacy of tumor therapy and facilitate the blocking of genes that contribute to the proliferation of cancer cells (Jung et al. 2015). This is a form of functionalization of CQD for ROS, Inflammation, and DNA Fragmentation. Studies investigating the effects of different functional groups on ROS production, inflammation, and DNA fragmentation highlight how biofunctionalization can be used to control the biological impact of CQDs/GQDs. In a study, gambogic acid (GA)-loaded CDs (CDs/GA) showed more efficient drug loading capacity, circulation, and retention. Since CDs enter the nucleus and inhibit drug pomp recognition, they can reduce cell proliferation. After releasing GA, ROS production is increased, which induces apoptosis in hepatoma and cervical cancer cells (Liu et al. 2023). In another study, the excitation-independent green-emitting fluorescent CQDs–PEI–PEG with an ultra-small size and positive surface charge was synthesized by loading polyethylenimine (PEI) and polyethylene glycol (PEG) on the surface of CQDs. Binding CQDs–PEI–PEG with CRISPR/Cas9 plasmid via electrostatic attraction could provide a nanocomplex that entered the lysozyme and increased the transfection efficiency. The synthesized nanocomplex could deliver the CRISPR/Cas9 to the HeLa cells and mutate the targeted EFHD1 gene (Zhai et al. 2022).

Current challenges and future perspectives

GBM presents a substantial therapeutic challenge characterized by poor prognosis, limited overall survival rates, and a deficiency of genuinely effective treatment options. However, bCQDs and bGQDs offer a promising opportunity to address these critical unmet needs. Their capacity to traverse the BBB and selectively target tumor tissue can potentially advance GBM therapy significantly.

A crucial area of research involves identifying and incorporating GBM-specific biomarkers within bCQD and bGQD frameworks. This targeted methodology can enhance

Table 2 biofunctionalized CQDs and GQDs in treating gliomas

Type of biofunctionalization	Targeted cell/tissue	Size	The beneficial effects	Mechanism	References
Decorating carboxymethylcellulose (CMC) with mitochondria-targeting pro-apoptotic peptide (KLA) and cell-penetrating moiety (cysteine, CYS)	U87 cell line	2.7 nm	Passive and active targeting of cancer tumors	Killing activity toward GBM cells of cysteine-bearing CMC conjugates coupled with pro-apoptotic KLA peptide	(Wang et al. 2016)
ZnS-QDs were produced using carboxymethylcellulose (CMC), then conjugated with Dox	HEK 293 T cell line, and U87 cell line	3.6 nm	Behaving as active fluorescent nanoprobes and nanocarriers with modulated drug release for killing malignant glioma cells	Internalizing by brain cancer cells	(Perini et al. 2020a)
Stabilization of Ag–In–S/ZnS QDs with chitosan, decoration of VEGF antibody on the surface of QDs	U87 and HEK 293 T cell lines	–	Behaving as bifunctional immunoconjugates	Internalization of the cells and killing them	(Perini et al. 2021)
CDs derived from D-glucose and L-aspartic acid as starting materials	C6 glioma cell line	2.28 nm	Construction of an intelligent nanomedicine	Freely penetrating BBB and precisely targeting glioma tissue	(Medintz et al. 2005; Xu et al. 2018)
Decoration of a photosensitizer (chlorine e6, Ce6) on a surface of CDs mediated by Gd^{3+} as a glue	A549 tumor-bearing mice, MGC803 cell line	–	Photodynamic therapy (PDT)	Enhancing cellular uptake and accumulation of Ce6 in the tumor	Wang et al. 2018)
Decoration of epsilon–poly-$_L$-lysine (3PL) and antimicrobial peptide agent (AMP) on a surface of ZnS QDs	U87 MG cell line	3.1 nm	Fighting against opportunistic pathogenic infection	Enhancing cellular uptake and presenting mid-antibacterial activity	Şimşek et al. 2020)
Curcumin loaded on the chitosan (CS)/gelatin (GE)/CQDs	U87 MG cell line	–	Control-released behavior with 22-h half-life	Enhanced cytotoxicity compared to pure curcumin	Jha et al. 2020)
Decoration of Dimethylformamide on the surface of GQDs (DMF–GQDs) combined with Dox	U87 MG cell line	10 nm	Toxicity, especially for GBM cells at higher concentrations	Increasing the efficacy of reduction of cell viability more than IC_{50} of antitumor drug alone Increase in the Dox uptake that originated from the U87 cell membrane permeability changes, reducing dose requirement	(Jung et al. 2015)
Green–GQDs and COOH–GQDs conjugated with Dox	U87 Glioblastoma cells and mouse cortical neurons	10 nm	Drug delivery system	Significant reduction in cell viability, changing membrane permeability	(Song et al. 2019)

personalized medicine by optimizing therapeutic efficacy while reducing the severe off-target toxicities associated with current treatment regimens. The inherent biocompatibility and modifiable surface properties of bCQDs render them suitable candidates for in vitro bioassays and biosensors, facilitating the detection of clinically relevant GBM biomarkers. This capability is vital for developing theranostic platforms that effectively integrate diagnostics and therapeutic strategies, ultimately improving patient management. Furthermore, functionalizing CQDs with specific biomarkers can bolster their selectivity, specificity, and tumor penetration, advancing the potential for more precise, image-guided surgical interventions.

Despite the benefits associated with bCQDs and bGQDs, certain challenges persist. While their robust fluorescence enables GBM detection at low concentrations, the conjugation of bCQDs and bGQDs with organic and inorganic components intended to enhance their optical and electrical characteristics may inadvertently increase particle size, thereby compromising their ability to penetrate malignant GBM cells. Therefore, optimizing both the size and concentration of these nanomaterials is essential for realizing their therapeutic potential. In addition, the lack of specificity exhibited by pristine CQDs and GQDs necessitates the formulation of advanced surface modification strategies. Future research efforts should focus on the development of receptor-targeted, surface-decorated CQDs and GQDs that exhibit enhanced affinity for GBM cells, including the exploration of novel targeting ligands, such as peptides or aptamers, beyond traditional antibodies, to improve selectivity and tumor penetration.

Despite the increasing interest in bCQDs and bGQDs for GBM treatment, current research remains limited. A comprehensive evaluation of their theranostic potential in GBM management is urgently required. The clinical translation of bGQDs and bCQDs must rigorously address safety and biodistribution concerns. Detailed investigations are crucial to assessing their capability to cross the BBB in vivo, elucidate their metabolic pathways, characterize cellular internalization mechanisms, and comprehend their potential long-term effects on glial and other brain cells. Preclinical studies, followed by meticulously designed clinical trials, are imperative for evaluating their physicochemical properties in complex biological matrices and confirming their potential for targeted delivery. A primary focus should be on a thorough understanding of the pharmacokinetics, pharmacodynamics, distribution, metabolism, and elimination of bQDs to ensure their safe and effective clinical application, including considering potential long-term toxicity and immunogenicity.

The unique attributes of quantum dots, particularly their nanoscale size, facilitate deep tissue penetration, thereby enabling high-quality imaging and histological staining. This capability affords exceptional insights into GBM pathophysiology, particularly relevant for advancing clinical investigations. The small size and low weight of bQDs render them powerful instruments in flow cytometry, allowing for bioattachment to various biomolecules (DNA, RNA, miRNA, siRNA, proteins, etc.) for fundamental research and diagnostic applications. Addressing the critical issue of selectivity remains paramount. Although the attachment of biomolecules to bQDs has enhanced target specificity, further innovation is essential to achieve genuinely personalized diagnostics and therapies. Future research should prioritize the development of highly selective bQDs capable of simultaneously targeting multiple GBM-associated biomarkers, such as specific cancer

stem cell markers or driver mutations, thereby paving the way for individualized treatment strategies. This may involve the creation of multiplexed bQDs capable of concurrently detecting a panel of biomarkers.

This review distinctly addresses the application of bCQDs and blue bGQDs in targeted therapies for GBM. It offers a comprehensive overview of the current landscape by systematically evaluating existing studies and categorizing them according to their size, shape, and function. Looking to the future, collaboration among medicinal chemists, biomaterial scientists, pharmaceutical experts, neuro-oncologists, and other relevant specialists is crucial for translating the promising potential of bCQDs and bGQDs into clinically relevant solutions for GBM patients. It is envisioned that these advanced nanomaterials will play a central role in the personalized management of GBM, resulting in earlier and more accurate diagnoses, significantly enhanced therapeutic efficacy, and, ultimately, improved patient survival and quality of life. This vision involves exploring combination therapies incorporating bQDs alongside other treatment modalities, such as immunotherapy or targeted drug delivery, to achieve synergistic effects. Developing scalable and cost-effective manufacturing methods for bQDs is essential for their widespread clinical adoption.

Author contributions
K.K, A.G, and N.O developed the idea and structure of the review article. K.K wrote the manuscript, collecting the materials from databases. A.A, M.J.R and S.A revised and improved the manuscript. A.G supervised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding
This research received no specific grant or funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 5 August 2024 Accepted: 24 February 2025
Published online: 14 March 2025

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