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REVIEW PAPER

Recent advances of carbon quantum dots in tumor imaging

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ABSTRACT

Currently, there is a significant interest among individuals in the field of bioimaging and detection. Nanostructure-based biosensors have emerged as a superior method for detecting substances due to their unique properties, which enable them to efficiently locate minute quantities of substances. Carbon quantum dots (CQDs) outperform conventional quantum dots due to their solubility, reduced toxicity, and simplified production process. These attributes make CQDs highly valuable and hold immense potential for medical applications. CQDs are extremely small structures, measuring less than 10 nm in all dimensions. These materials possess exceptional characteristics, such as compatibility with living tissues and the ability to emit light, making them ideal for medical imaging purposes. This review explores the recent advancements in bioimaging utilizing CQDs, delving into their properties, challenges, and future possibilities for further study. As a result, CQDs have gained popularity as a viable option for various medical applications, including drug delivery, gene therapy, light-responsive substances, and antibacterial agents. The review also discusses ongoing efforts to enhance these nanomaterials for improved imaging within the body, efficient drug delivery, and cancer treatment. In summary, this article investigates the latest progress in bioimaging using CQDs and presents insights into surface modification, characteristics, obstacles, and future prospects. Consequently, CQDs have garnered significant attention in diverse bio applications, ranging from nanosystems to brain tumor treatment and bioimaging.

Keywords: *Bioimaging, Brain tumor, Carbon quantum dots, Drug delivery systems, Surface modification*

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INTRODUCTION

As of late, individuals have been getting modern and troublesome maladies like different sorts of cancer that are truly difficult to treat. One critical portion of diagnosing and treating cancer is being able to tell the contrast between cancer cells and solid cells. Unused medications for cancer are accessible that are less hurtful than conventional chemotherapy. These medications target the cancer straightforwardly, so they have less side impacts and can be utilized more viably than chemotherapy for numerous sorts of cancers [1-5].

Inside the 21st century, nanotechnology has moved forward how find and treat sicknesses. Nanotechnology has been exceptionally vital in making superior sensors, solutions, ways of giving solutions, and ways of putting qualities into cells [6-8]. This innovation makes exceptionally exact ways to discover and treat distinctive illnesses. Researchers have used little innovation to create restorative medications superior. This has made a difference move forward healthcare a part [9].

Nanomaterials are divided into different types, and one type is called quantum dots. Quantum dots are tiny crystals made of semiconductor materials that are smaller than the Bohr radius. These tiny crystals have unique qualities related to light and electricity that are clearly influenced by their size and what they are made of. Different sizes of quantum particles have different colors. In any situation, it is very important to understand that quantum dots made of metal, like cadmium, can be very harmful. Despite extensive research and development, the utilization of cadmium-based carbon QDs in biological utilizations is restricted due to their potential to disrupt the skeletal system within the body [10-13].

Nanomaterials have greatly improved medical uses, including imaging, delivery of medicine,

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treating genetic diseases, detecting diseases, and using heat to treat diseases [14]. The utilization of gold nanoparticles has experienced a substantial surge in various fields, specifically in the domains of photothermal therapy and imaging. These small particles, known as nanoparticles, possess attractive properties that make them suitable for imaging and detection purposes.

Polymeric nanoparticles and liposomes have been used for delivering medication [15]. Additionally, small particles called semiconductor quantum dots are showing potential as useful materials for both identifying and healing purposes. QDs were made in 1980 for the first time. They have characteristics that can be changed by altering their size and arrangement. Indeed, gold nanoparticles are incredibly useful in various medical applications [16]. Additionally QDs offer numerous advantages over traditional materials such as organic dyes, making them highly promising for biomedical applications. QDs exhibit a high quantum yield (QY), remarkable resistance to photodegradation, and consistent photoluminescence (PL). The exceptional attributes of QDs make them highly sought-after for a diverse array of biomedical uses [17].

However, it is important to acknowledge that semiconductor QDs also have certain drawbacks. The presence of toxic elements like cadmium, arsenic, selenium, and mercury in certain QDs has raised concerns regarding their potential toxicity. As a result, these QDs are not considered biodegradable or environmentally friendly materials [18].

It is crucial to address these toxicity issues and explore alternative materials for safer biomedical applications. [19]. CQDs have hydrophilic groups on their surface, making them highly soluble in water and able to bind to various groups. In terms of energy gap transitions, they display fluorescence characteristics that are comparable to semiconductor QDs.

CQDs, also known as CDs, offer the advantages of metal quantum dots, such as fluorescent emission and bio-bonding, without the drawbacks of toxicity and complex preparation methods [20].

The utilization of fluorescent materials in optical bioimaging has garnered attention as a promising approach for cancer diagnosis. QDs, specifically fluorescent semiconductor nanostructures, are recognized as a promising method for optical bioimaging due to their diminutive size, high photostability, non-blinking fluorescence, and customizable color options [21].

Carbon nanotubes possess unique optical properties and biocompatibility, making them well-suited for bioimaging applications. In particular, the application of carbon nanotubes in photoacoustic bioimaging, utilizing their optical properties, has yielded significant advancements in cancer detection and diagnosis [22].

CQDs, have arisen as an inventive classification of fluorescent probes for cancer diagnosis. CQDs exhibit excellent properties like, photostability, surface flexibility, biocompatibility, water dispersibility, low toxicity, and favorable optical characteristics. Moreover, they can be created at a reduced expense in comparison to QDs [23].

Existing literature provides a comprehensive review of synthetic methods, classification, sources, and other properties of CQDs [24]. However, despite their promising properties, CQDs face limitations in *in vivo* imaging as they only absorb wavelengths in the ultraviolet region. To overcome this challenge, numerous engineering strategies have been explored, particularly for specific purposes, which have transformed CQDs into potential candidates for successful *in vivo* imaging. There have been numerous articles exploring the production and application of CQDs in the field of nanomedicine [25].

This paper intends to examine the development of CQDs as fluorescent probes used for live bioimaging, emphasizing recent advancements in target-specific bioimaging [26].

QDs are tiny inorganic structures, ranging from 4 to 10 nanometers, with high quantum yield and resistance to light fading. They can absorb a wide range of light and emit focused light, making them ideal for biological applications. The center can be made of different types of tiny materials like MoS2 CdS, PbS/Ag2S ,CdTe/CdSe, or PbSe [27-30].

To solve the problems of organic core limitations like low aqueous dissolution in water, easily breaking down, and being harmful to living cells, a protective layer that is safe for living systems is often added to the surface of QDs [31]. But, this coating can make them bigger, which might affect how specific they are. Due to these difficulties, CQDs have become a hopeful option for biosensors in different diagnostic methods. Metal QDs like cadmium-containing QDs (CdQDs) have benefits in biomedical detection. However, the toxicity of these metal-based QDs prevents their use. Biocompatible CQDs are a safer choice

for disease diagnosis sensors. They also cost less to produce than similar options [32].

Besides being compatible with living organisms, CQDs have amazing qualities that make them very valuable in biosensors. These materials have many good qualities that make them great for creating biosensors. They have a large surface area, are good at conducting electricity, are stable, and have good optical properties. For example, the strong glow that CQDs have is an important feature in biosensors that use light to detect things [33].

In this study, we undertake the task of categorizing various methods used to modify the surface of CQDs. Additionally, we analyze recent research findings to gain insights into the limitations and challenges that are associated with each of these techniques. The final section of the article focuses on the significant advancements of CQDs in the biomedical field. In particular, we highlight their development and application in three distinct disciplines: bioimaging, drug delivery systems, and bioanalytical detection.

Synthesis methods

Bottom-up synthesis approaches

Bottom-up synthesis techniques, including pyrolysis, thermolysis, thermal combustion, hydrothermal/solvothermal treatment, and microwave irradiation, are considered environmentally friendly and sustainable compared to top-down synthesis approaches. One example is the solvothermal method, which enables the synthesis of CQDs using eco-friendly waste biomass sources such as vegetable and fruit peels, coffee grounds, and paper waste. This approach promotes the use of renewable resources and minimizes waste production [34].

Carbonization is another bottom-up method in which precursors like biomass undergo hydrolysis and subsequent chemical reactions. This process results in the formation of nucleation clusters, followed by the generation of micrometer-sized carbon particles [35].

Gosh et al. conducted a study in which they used hydrothermal method to produce CQDs from sweet lemon peel. After cooling, brown CQDs were successfully obtained. These methods are highly preferred due to their advantageous features such as high fluorescence quantum yield, and environmentally friendly features [36].

In this approach, CQDs are synthesized through a chemical reaction of precursors that takes place in a solvent medium within a closed vessel under high pressure and temperature conditions (Fig. 1) [37].

The hydrothermal treatment method has been employed with various precursors, including citric acid, hyaluronic acid, ethylenediamine, D-galactose, bacterial DNA, chitosan, mercaptosuccinic acid, and polyacrylic acid [38-42]. For example, Campos et al. utilized D-galactose as a precursor in the hydrothermal process to fabricate CQDs [43]. The properties of CQDs can vary based on the synthesis process, precursor, and conditions employed. For example, Jiang et al. synthesized N-CQDs using a hydrothermal purification method by carbonizing chitin in the presence of ammonia in the reaction medium. The addition of ammonia had a positive effect on the synthesis process, increasing decomposition and carbonation and improving the fluorescence quantum yield compared to the sample prepared without ammonia [44].

The hydrothermal treatment method has been utilized with various precursors, such as citric acid, hyaluronic acid, ethylenediamine, D-galactose, bacterial DNA, chitosan, mercaptosuccinic acid, and polyacrylic acid [45]. For example, in a study by Campos et al., D-galactose was used as a precursor in the hydrothermal process to create CQDs [46]. The properties of CQDs can vary depending on the synthesis process, precursor, and conditions employed. In another study, Jiang et al. synthesized N-CQDs using the hydrothermal treatment method by carbonizing chitin at a temperature of 240 °C for 10 hr in the presence of ammonia in the reaction media. The addition of ammonia had a positive effect on the synthesis process, leading to enhanced degradation, carbonization, and an improved fluorescence QY of 25.8% compared to 17.6% without ammonia [47].

Top-down synthesis approaches

Chemical ablation method involves the use of oxidation processes to control the fragmentation of reactants and produce CQDs. These include a

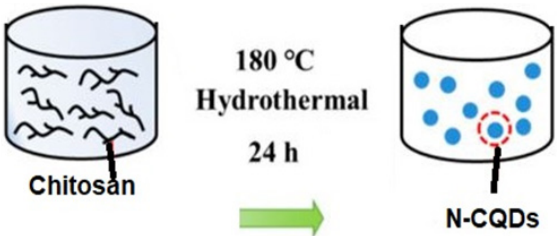

Fig. 1. Schematic representation of hydrothermal method of nitrogen doped CQDs

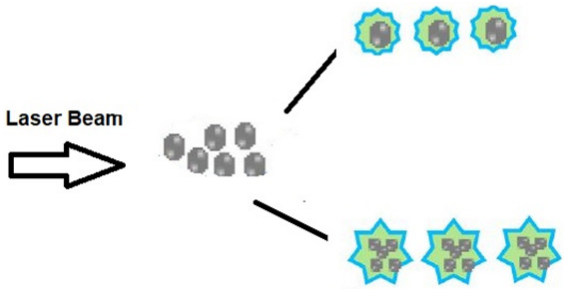

Fig. 2. Schematic representation of the mechanism for the size control of CQDs

multi-step process, harsh chemical conditions, and limited control over the size of the resulting CQDs [48]. The laser ablation method involves the use of laser pulses at specific time intervals to synthesize CQDs. When the laser interacts with a graphite flake, it generates a localized region of high pressure and high temperature, forming a vapor/plasma plume around the edge of the graphite flake and the surrounding liquid medium. By controlling the laser pulse width, bubbles of different densities can be created, enabling the production of CQDs with varying sizes (Fig. 2) [49-52].

In this way, the characteristics of a few engineered approaches for the manufacture of CQDs are summarized within the following subsection (Table 1).

Toxicity

Researchers have conducted a study on the toxicity of carbon or graphene QDs (C/G QDs) on animals, discovering that the toxicity increases with the size of the QDs [53]. Furthermore, the way C/G quantum dots interact with surfaces affects their ability to cause harm, such as producing harmful reactive oxygen molecules inside cells that can potentially result in death. However, we cannot make sure that C/G QDs will not have any harmful effects like ROS. However, the harmful effects of C/G QDs can be controlled and handled. Right now, PEG has been used to decrease ROS generation [54]. However, there is a lack of further research on other ways to do this. This makes PEG a risky factor for using C/G QDs in medicine. So, it is very important to do more studies in the future to make sure that C/G QDs can be used safely in medicine. It's important for synthesized QDs used in biomedicine to be compatible with the body's tissue system. Right now, there are more option to do tests outside the body (*in vitro*) than inside the body (*in vivo*) to check for harmful effects. To better understand if C/GQDs are harmful, it is important to do more experiments outside of living organisms [55].

Engineering of CQDs for Bioimaging

The enhancement of CQDs for chemical

Table 1. A comparison of synthetic approaches reveals the diversity in fabricating carbon quantum dots (CQDs)

Synthesis Type	Advantages	Disadvantages	Ref.
Solvothermal / Hydrothermal Microwave irradiation	1. Quick and scalable: Nanostructures can be produced rapidly and in large quantities, allowing for efficient and scalable manufacturing processes. 2. Cost-effective: The production of nanostructures is cost-efficient, making them an affordable option for various applications. 3. Environmentally friendly and non-toxic: Nanostructures are manufactured using environmentally friendly methods and materials, ensuring minimal harm to the environment and human health. 4. Uniform particle size: Nanostructures can be produced with a consistent and uniform particle size distribution, ensuring reliable and predictable performance	1. Poor control over sizes: There may be limitations in controlling the exact size of nanostructures, resulting in variations and inconsistencies. 2. High energy consumption: The production of nanostructures often requires high energy inputs, which can contribute to increased environmental impact and costs.	[11]
Laser ablation	1. Rapid and effective: Tunable surface states allow for rapid and effective adjustments to meet specific needs. 2. Tunable surface states for rapid and effective customization.	Low quantity yield and poor control of size necessitate modification when using small molecule precursors for nanostructure synthesis.	[12]
Chemical ablation	1. Most accessible: Nanostructures can be obtained from various sources, making them easily accessible to researchers and industries. 2. Nanostructures from various sources for maximum accessibility.	Drastic processes and multiple steps can lead to poor control over sizes when using small molecule precursors for nanostructure synthesis.	[13]
Electrochemical Carbonization	1. This approach enables precise control of nanostructure size, allowing for tailored material properties. 2. Single-step synthesis method improves efficiency and saves time in producing these nanostructures. 3. The steady and consistent production of nanostructures is ensured by this approach, leading to reliable and reproducible results.	Small molecule precursors are utilized to synthesize nanostructures, enabling control over size and properties.	[13]

applications is achieved through the modification of their properties. Various techniques are employed to overcome limitations associated with CQDs, such as the use of chemicals and antibiotics, while also improving their biological characteristics, including cell cycle and photoluminescence (PL) properties. Several methods are utilized to modify CQDs [56]. This section provides a comprehensive explanation of these techniques and their significance in optimizing CQDs for biological applications.

Doping

Altering the appearance of CDs can be achieved through chemical doping. Because the sp2 clusters in (nitrogen- graphene QDs)N-GQDs are estimated and positioned together, they exhibit consistent and predictable properties when excited [57]. Hu and colleagues discovered a straightforward method for making N-GQDs by treating GO with water in the presence of alkali without any additional surface changes [58].

The N-GQDs synthesized using plasma beat laser removal exhibited a remarkably intense blue light emission with a high brightness level of 24. The addition of nitrogen (N) to the GQDs structure through plasma resulted in the generation of strong blue light [59].

Ju and his colleagues studied how the concentration of nitrogen affects the characteristics of photoluminescence. It was found that when N molecules were added to GQDs, the wavelength of light emitted turned blue (16. 7 M), the brightness of the light increased by 25 times compared to GQDs. Recently, Ren and their team made carbon particles called N-doped micropore carbon quantum dots (NM-CQDs) by adding nitrogen to them. These particles are very small and have a high fluorescence when exposed to light [60].

They achieved this by using materials derived from living organisms. Encouraging studies show that the light emitted by NMCQDs can function independently in different situations, including varying levels of acidity, duration of exposure to light, type of light used for excitation, and temperature [61]. The S and N-CQDs, which were made using a water-based method, may be able to kill bacteria. The abnormal amount of hydrogen sulfide (H_2S) in tissue can easily affect how cells work and may cause dangerous conditions like Alzheimer's disease. In a study, scientists added copper to CQDs (Cu-CQDs) to help see living cells and detect H_2S. To evaluate the feasibility, it was decided to use H3122 lung cancer cells as a test case [62]. A significant decrease in the level of a certain substance inside cells was observed when a combination of 100 µM NaHS and Cu-CQDs was studied. As NaHS increased, the amount of PL inside the cells decreased a lot. The results showed that the Cu-CQDs had great potential in monitoring the levels of H_2S in cells [63]. Scientists conducted a study where they used a material called copper to improve their ability to observe living cells and identify a gas called H_2S [64]. To see if it works, the researchers chose H3122 lung cancer cells as an example. Jin and their colleagues found that S-doped GQDs (S-GQDs) worked well for imaging cells without causing hurt to the cell layer. A little diminish in cell work was watched when the concentration of S-GQDs expanded by 100 times, from 10 to 1000 µg/ml. Moreover, it was illustrated that the appearance of HeLa cells remained unaltered when refined with S-GQDs [65]. In addition, the S-GQDs easily entered the internal portion of the cell. Moreover, no clear modifications were watched within the morphology of the cells when developed with S-GQDs, Zhang and their team found that by adding nitrogen and sulfur to GQDs (referred to as NS-GQDs) with K2S2O8, the resulting reaction had an ECL that was 5.8 times higher compared to regular GQDs [66]. Nafiujjaman and his team made a substance called chlorine (Cl) and N-doped GQDs (Cl-GQDs-N) using a simple method called hydrothermal procedure. The researchers observed that the concentration of photoluminescence (PL) increased when they added Cl (Chlorine) and N (Nitrogen) to GQDs (graphene quantum dots) [67].

The GQDs with Cl and N emitted a blue light when exposed to UV light, and had a photoluminescence quantum yield of 20. They also studied how Cl-GQDs-N's brightness changes when the light wavelength increases from 350 nm to 380 nm. When the wavelength increases from 390 nm to 450 nm, the concentrated outflow seems to decrease[68]. The experiments showed that the tiny particles called Cl-GQDs-N were able to easily enter the cells in a lab setting. The scientists tested the harmful effects of Cl-GQDs-N at a high concentration (1 mg/mL) on kidney cells and cancer cells. It has been confirmed that Cl-GQDs-N are safe to use in the body and have great potential for medical imaging [69].

Surface functionalization

Other types of living things can be used to

change GQDs and CQDs because they have places on their surfaces where reactions can happen. People are paying a lot of attention to making changes to amino things [153]. Certain types of species have the ability to change the distance between energy levels and modify how light interacts with them [70].

The optical properties of GQDs were found to be upgraded through functionalization, as illustrated by Wang et al [71]. They watched that the QY of GQDs expanded from 4.7% to 13.8%. GQDs regularly show two major crests at 450 nm and 510 nm, comparing to the π-π* move of sp2 spaces and the n-π* move of surface utilitarian bunches, individually [72].

Be that as it may, the moment crest of GQDs moved from 510 nm to 520 nm, showing alterations within the surface utilitarian bunches.

Fu et al, conducted a consider where they altered CQDs utilizing thiosemicarbazide (TSC), [73]. TSC was conjugated to the surface of CQDs through amide bonds between the carboxyl bunch of CQDs and the amine gather of TSC, coming about in NPs with an estimate of roughly 2.38 nm. UV-Vis examination of the NPs uncovered the appearance of a unused top at 289 nm after conjugation [74]. Another advantage of functionalization was the solidness of the PL of CQDs over a wide extend of pH values (from 3 to 10) due to the tall pKa esteem of TSC and its intaglio shape. Besides, the TSC-CQDs remained steady in arrangements with changing concentrations of NaCl. The essential strategy utilized by the functionalized NPs for identifying copper particles was through PL extinguishing, which happened as a result of the arrangement of a complex between Cu particles and the altered NPs [75].

Moreover, Li et al, examined the functionalization of graphene oxide (GO) to improve its properties for different applications. They utilized a one-step strategy to covalently connect polyethyleneimine (PEI) onto the surface of GO sheets [76]. The introduction of functionalization techniques has led to improved dispersibility of graphene oxide (GO) in water and enhanced stability of the GO-PEI composite. The presentation of PEI moreover driven to upgraded electrical conductivity of the GO sheets [77]. Besides, the functionalized GO showed upgraded adsorption capacity for overwhelming metal particles such as lead (Pb) and mercury (Hg). The presence of amino groups from PEI facilitated strong interactions with the metal particles, resulting in effective removal from aqueous solutions [78]. The functionalized GO also showed great solidness and recyclability, making it a promising fabric for natural remediation applications. In expansion, Li et al. illustrated that the functionalized GO had progressed mechanical properties compared to perfect GO. The PEI functionalization brought about malleable quality and Young's modulus, making the fabric more reasonable for applications requiring mechanical vigor. In general, the functionalization of GO with PEI demonstrated to be a flexible approach for upgrading its properties, counting dispersibility, solidness, electrical conductivity, adsorption capacity, and mechanical quality[79]. Undoubtedly, aptamers play a vital part in altering nanoparticles (NPs) for focused applications. Within the ponder conducted by Liu et al. [80], they utilized an anti-VEGF aptamer to functionalize CDs for tumor focusing on. The method included coating the surface of CDs with NH2-PEGNH2 through the interaction between the amine gather of PEG and the carboxyl gather of CDs[81]. Hence, the aptamers were joined to the CDs' surface by responding the carboxyl gather with the amine gather of the PEG-coated CDs. The expansion of aptamers essentially improved the capacity of the CDs to target tumor cells, as proved by the higher PL watched in cells treated with aptamer-conjugated CDs compared to CDs without aptamers. Moreover, the emphatically charged CDs focused on mitochondria due to their propensity to tie to the adversely charged mitochondrial layer[82]. CDs without aptamers showed no particular focusing on, as the PL concentrated of both human fibroblast cells (HFFF) and cancer cells (4 T1) shown comparable extinguishing. Alternately, the aptamer-conjugated CDs displayed distinctive PL power due to the variety in nucleolin expression on the cancer cells. The utilization of aptamers for NP functionalization empowers focused on conveyance, moved forward specificity, and improved demonstrative capabilities in different biomedical applications [83].

Zhao et al, utilized ethanediamine-derived CDs to covalently bind folic acid (FA) through amino groups, demonstrating the potential of functionalized CDs for targeted drug delivery and imaging [84].

Hai et al, illustrated the imaging capability of folic corrosive typified graphene quantum dabs (FA-GQDs) for cancer cells. They effectively created

pH detecting tests and cell imaging frameworks utilizing FA-GQDs, which were connected for discovery in cell culture[85]. The analysts utilized HeLa cells stacked with FA-GQDs to examine cell fluorescence imaging beneath diverse pH conditions (5, 6, 7, 8). The results showed that the green channel of photoluminescence concentrated in HeLa cells got to be brighter as the pH expanded to 8, whereas the blue channel remained nearly indistinguishable. This affirms past discoveries that GQDs show a pH-independent excitation wavelength and as it were the emanation concentrated changes [86].

Polymer capping

CDs often possess defects that can reduce their photoluminescence quantum yield (PL QY) by impeding electron recycling [49]. To address this issue, surface functionalization techniques have been employed, including coating CDs with polymer chains (Fig. 3). These coatings not only decrease the surface conductivity of the CDs but also improve their optical performance [87]. For example, Gonçalves et al. [52] functionalized laser-excised CDs with PEG (polyethylene glycol) and mercaptosuccinic acid, and observed that longer reaction times resulted in increased defects and decreased PL density. Another study [53] demonstrated that encapsulating GQDs with a PEG matrix reduced their toxicity compared to unencapsulated GQDs. PEGylated GQDs were also obtained by forming a composite with multi-walled carbon nanotubes, which resulted in reduced toxicity at high doses. Similarly, Chong et al. [55] compared the use of PEI and PEG as passivation agents for CDs and found that CD-PEI exhibited superior properties, such as high QY, longevity, and high PL density, compared to CD-PEG. Additionally, another study [56] demonstrated that PEI-modified GQDs with different molecular weights exhibited a wide range of PL emissions. In terms of surface toxicity, a study [57] investigated the effects of PEI, intact (unmodified), and PEG coatings and found that highly charged PEI was the most toxic, while neutral PEG had the least effect and did not compromise the intact color of the cells [88].

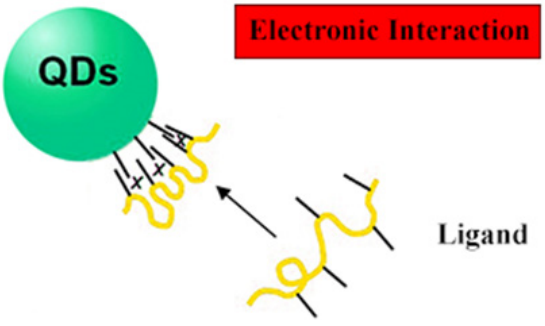

Fig.3. Polymer capping of QDs

Tackled the issue of PL quenching in acidic conditions by employing a surface passivation technique using PEG on GQDs. Thus, the use of polymer capping was found to be advantageous in preserving the PL intensity of GQDs in different pH environments [89]. Diamine-terminated oligomeric PEG1500N was utilized for surface passivation of acid-treated particles [90]. CQDs were fabricated using laser ablation and then functionalized with PEG200 and mercaptosuccinic acid. The researchers found that increasing the reaction time led to a decrease in surface defects and an increase in PL intensity compared to the influence of different capping chemicals, including PEG, polyvinylpyrrolidone (PVP), and bovine serum albumin protein (BSA), on the PL intensity of CQDs [91]. They concluded that CQDs capped with BSA exhibited the highest PL intensity addressed the issue of toxicity associated with GQDs by embedding them in a PEG matrix [92]. The researchers found that PEGylation significantly reduced the toxicity of GQDs at high concentrations. Additionally, PEGylation improved the drug delivery capability of GQDs and reduced the production of reactive oxygen species (ROS) as side effects [93]. It was detailed that PEGylated graphene quantum dots (PEG-GQDs) appeared negligible poisonous quality on Hela cells. This finding suggests that PEG-GQDs have a low level of cytotoxicity, making them suitable for various biomedical applications [94]. The utilized CQDs were adjusted with cresyl violet, a natural color, and coated with PEG for *in vivo* tumor imaging in mice [95]. The non-toxic behavior of these CQDs advance highlights their potential for bio-imaging applications, demonstrating their security for utilization in natural frameworks. In a study conducted by Havrdova et al, the analysts examined the effect of surface charge on the poisonous quality of coatings [96]. They compared the impacts of PEI, perfect coatings, and PEG coatings. The results showed that the emphatically charged PEI coating displayed the most elevated poisonous quality, with the capacity to indeed enter the cell core. On the other hand,

the negatively charged perfect coating caused some anomalies due to interaction with cells. In comparison, the unbiased PEG coating had nearly no dangerous impacts on cells. This proposes that the surface charge of coatings plays a vital part in deciding their harmfulness, with emphatically charged coatings being more poisonous and contrarily charged or unbiased coatings being less damaging to cells [97].

Liu et al, arranged nanocomposites PEI -modified GQDs and zinc oxide nanoparticles (ZnO NPs) employing a sol-gel strategy. They compared the antibacterial properties of these nanocomposites with PEI-free ZnO/GQD nanocomposites [98].

The analysts found that the ZnO/GQD-PEI nanocomposites shown fabulous antibacterial characteristics against E. coli compared to the ZnO/GQD nanocomposites. This advancement in antibacterial action was credited to the nearness of PEI, which improved the scattering and adsorption of the nanocomposite on bacterial cells. coli treated with ZnO/GQD-PEI nanocomposites was lower than that of E. coli treated with ZnO/GQD nanocomposites, demonstrating the improved antibacterial viability of the previous [99].

CDs composite materials

Combining carbon monoxide with different nanomaterials has the potential to modify or enhance their inherent properties [58]. One example of this is the creation of nanocomposites called CDs@ZIF-8, where CDs are incorporated into a zeolitic imidazolate framework-8 (ZIF-8) structure. These nanocomposites possess a unique dodecahedral diamond shape and exhibit strong orange-red PL emission [62]. The development of CDs@ZIF-8 coatings highlights their capabilities in diverse applications. In the field of cancer cell detection, an electrochemiluminescence (ECL) detection system has been developed using porous silica nanoparticles (MSNs) coated with CQDs. These hybrid nanoparticles, known as CQDs@MSNs, are utilized as nanoprobe agents. By optimizing the ratio between CQDs@MSNs and MUC1 aptamer, a specific biomolecule used for cancer cell targeting, an ideal ratio of 4:1 has been determined based on incubation time [64]. Notably, the detection of breast cancer cells (MCF-7) has proven to be more straightforward compared to SKBr-3 and K562 cells using this system [64].

The morphology of the nanocomposites was watched to be a customary precious stone dodecahedral unit with porosity. The nanocomposites shown a solid orange-red photoluminescence outflow, showing the fruitful coating of CQDs on the surface of ZIF-8. The PL emission serves as evidence of the successful formation of the CQDs@ZIF-8 nanocomposites and their potential for various applications.This composite material served as a catalytic surface, inducing the oxidation of 3,3`,5,5'-tetramethylbenzidine (TMB) in the presence of hydrogen peroxide (H_2O_2) and causing a noticeable change in color[100].

The GSH present in the sample led to the reduction of the oxidized form of TMB (oxTMB), thereby inducing a concentration-dependent alteration in the UV-visible spectra. Fluorescence (FL) imaging of the MCF-7 cancer cells was watched after an 8-hr hatching with CQDs@MSNs within the cell culture and on the altered indium tin oxide cathode. One such calculate is the brooding time, which straightforwardly influences the ECL reaction. It was watched that the longer the brooding time, the higher the ECL concentrated [101].

By and large, this ECL discovery strategy utilizing CQDs-coated MSNs gives a promising approach for recognizing MCF-7 cancer cells and offers experiences into the variables influencing the ECL escalated, such as brooding time [102].

Nozaki et al. [186] illustrated that nitrogen-doped carbon quantum dots (N-doped CQDs) can serve as successful photosensitizers for creating oxygen (O_2) beneath obvious light. They utilized 9,10-anthracendipropionic corrosive (ADBA) as a catching specialist and watched a diminish in white driven light illumination within the nearness of N-doped CQDs inside the primary 30 minutes [103].

The researchers found that the amount of oxygen generated is highly dependent on the ratio of the capturing agent (TA) to polyethyleneimine. The most effective ratio was determined to be TA:PEI = 1, resulting in the highest oxygen generation. To further enhance oxygen generation and improve photostability, the researchers synthesized a nanocomposite by incorporating gold nanoparticles (Au NPs) with N- CQDs [104]. Chloroauric acid (HAuCl4) was reduced by the N-doped CQDs to produce Au NPs. The nanocomposite exhibited 2.3 times higher

oxygen generation compared to N-doped CQDs alone, indicating that the incorporation of Au NPs enhanced the production of oxygen [105].

Also, the researchers studied how the nanocomposite and N-doped CQDs emit light when exposed to certain wavelengths of light. They specifically looked at how the light emission decreases over time at a wavelength of 485 nm, when the materials are excited with light at a wavelength of 365 nm [106]. The time it takes for the light emitted from the N-CQDs-Au NPs nanocomposite to fade away (approximately 2. 3 nanoseconds) was discovered to be longer than the time for the light emitted from N-doped CQDs to fade away (approximately 1. 5 nanoseconds). This indicates that the presence of Au NPs improves the ability of the nanocomposite to emit light [107]. Overall, this study highlights the potential of N-doped CQDs as photosensitizers for oxygen generation and demonstrates the beneficial effects of incorporating Au NPs to enhance oxygen production and photostability [108].

Distinct layers or shells surrounding a central core (Core-shell structures)

The modification of cyclodextrin nanoparticles through core-shell formation is an important technique for enhancing their biomedical applications(Fig. 4) [65,67]. One effective approach is to use metal nanoparticles (NPs), such as silver (Ag), in combination with cyclodextrin (CD) to form the shell structure. For example, waste lint carbon can be utilized in a microwave-assisted hydrothermal process to produce water-dispersed CDs. This method offers a rapid, efficient, cost-effective, and straightforward synthesis route for cancer diagnostic applications [68]. The interaction between metal ions and carbon dots in the core-shell structure leads to the quenching of photoluminescence energy by trapping electrons and holes, thus reducing radiative recombination. In one study, Kong et al. developed a core-shell

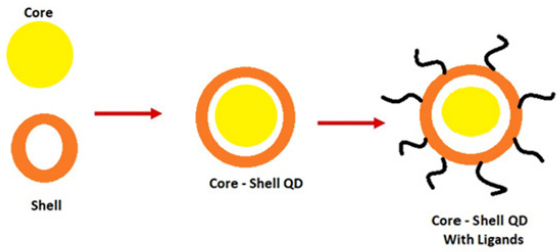

Fig. 4. shells surrounding a central core (Core-shell structures)

structure of GQDs coated with silver for the detection of uric acid [69]. Similarly, in another study, GQDs were coated with core-shell silver nanoparticles for the detection of prostate-specific antigen (PSA). The interaction between the adsorbed Ag $(NH_3)^{2+}$ cations and the carboxyl and OH groups of GQDs is involved in the formation of these devices. Subsequently, the Ag $(NH_3)^{2+}$ ions aggregate and transform into Ag nanoparticles. The presence of Ag NPs causes a decrease in the PL of GQDs, which can be restored by etching the Ag NPs with hydrogen peroxide (HO), resulting in a strong PL intensity that correlates with increasing PSA concentration [70].

In their investigate, Bhogal et al. [188] created a core-shell structure comprising of CDs as the center and a molecularly engraved polymer (MIP) as the shell, utilizing the sol-gel strategy. This structure was utilized for the discovery of ketoprofen. The MIP displayed particular location capabilities, whereas the CDs illustrated appropriate photoluminescence properties. In this way, the core-shell structure demonstrated to be valuable for precise detecting [71].

The CDs were gotten through the pyrolysis of citric corrosive. The carboxyl gather of the CDs and the amine gather of N-β-(aminoethyl)-γ-aminopropyltrimethoxysilane (AEAP) experienced a response, coming about within the holding of CDs to AEAP. AEAP served as both a functionalizing specialist and a monomer for polymerization [84].

The key to detecting ketoprofen was the extinguishing of the PL of CDs within the nearness of the medicate. The degree of extinguishing was unequivocally subordinate on the concentration of the medicate [109].

In general, Bhogal et al. thought about illustrating the potential of the core-shell structure comprising CDs as the center and MIP as the shell for exact detecting of ketoprofen. The particular discovery capabilities of the MIP and the PL properties of the CDs combined to make a profitable detecting stage [110]. In this regard, Kong et al. created a core-shell structure comprising of GQDs as the center and a silver shell for detecting uric corrosive. The Ag shell protected the GQDs and resulted in the quenching of their PL. The detecting instrument depended on the carving of the Ag shell by hydrogen peroxide (H_2O_2) within the nearness of uric corrosive. Upon evacuation of the shell, the PL of the GQDs was reestablished. The PL concentration was upgraded

with expanding sums of uric corrosive due to the rise in H_2O_2 concentration [111].

Basically, someone came up with an idea to use a structure made up of silver nanoparticles and GQDs to detect prostate-specific antigen. The combination of this structure involved the electric attraction between the carboxyl and hydroxyl groups of GQDs and the $Ag(NH_3)^{2+}$ cation attached to their surface [112]. Agglomeration of $Ag(NH_3)^{2+}$ leads to the formation of Ag nanoparticles. The small silver particles stopped the emission of light from the graphite quantum dots. However, the light emission can start again if the silver particles are removed using hydrogen peroxide. The researchers observed an increase in the rate of improvement, which was measured by looking at the levels of PSA [113].

Ma and his colleagues, used a structure with CDs in the center and silver nanoparticles to find glucose. The silver nanoparticles stopped the glow of the CDs. The water and hydrogen peroxide made during the process of converting glucose to gluconic acid removed the silver shell, releasing the CDs and restoring the glow. This structure made with CD@AgNPs showed that it can be useful as a sensor for glucose [114]. So that the results illustrated the possibility of core-shell structures including GQDs or CDs and Ag NPs for detecting different analytes such as uric corrosive, PSA, and glucose. The extinguishing and rebuilding of PL serve as key pointers for the discovery prepare [115].

Crossing the blood–brain barrier

The main problem in treating brain tumors is that most treatments cannot get through the blood-brain barrier (BBB) in high enough amounts to be effective. The BBB is made up of small blood vessels, brain cells, and a protective layer. It acts like a wall, controlling what substances can get into the brain and spinal cord [116]. The tight junctions between cells in blood vessels stop most agents from going through, but some substances like oxygen and carbon dioxide can still pass through (Fig. 5).

Researchers discovered that CDs created from carbon powder using only the top-down approach could not pass through the blood-brain barrier. Transferrin receptors (TfRs) are found a lot on cells in the brain blood vessels. This is good because these receptors can be used to carry transferrin-conjugated CDs and other small particles across the blood-brain barrier using a process called receptor-mediated transcytosis [117]. This research showed that tiny, fluorescent particles called CDs, which were coated with angiopep-2, were able to enter the brain through the blood-brain barrier in rats and gather in tumor cells in a mouse model of brain cancer [118].

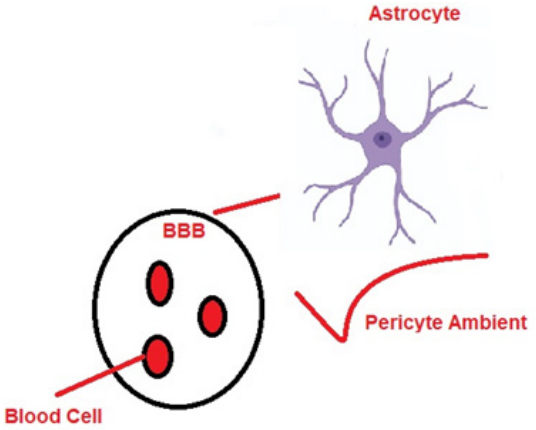

Fig. 5. The blood-brain barrier restricts entry into the brain

Utilization of carbon dots for tumor bioimaging

Bioimaging includes different methods like fluorescent imaging, magnetic resonance imaging (MRI), multimodal imaging, and imaging. CDs, or carbon dots, glow brightly and do not easily fade when exposed to light. The objective is to develop specialized particles that emit red light and have tumor-targeting capabilities [119]. These particles are ideal for medical imaging and surgeries that use fluorescent light. They make it easier to see the difference between tumor and non-tumor tissue, even when there are issues with autofluorescence. They made a red light by using o-Phenylenediamine (o-PDA) and combining it with transferrin ligand. Other research teams have also been able to get similar results, which means they can take pictures in really acidic places that are similar to the insides of tumors [120]. CDs that emit light in the near-infrared range, which is between 700 to 1400 nm, are good for imaging inside living organisms. NIR light can go deep into tissues, so it's good for imaging without cutting the body. Gadolinium-doped CDs are commonly used for MRI scans because they improve the visibility of images and are quickly removed from the body after the scan. Iodine-doped CDs are very safe for the body and are better than regular contrast agents for improving computed tomography scan images [121].

The use of live cell imaging has become an important method for studying how living things work and how cells function in the present moment. It lets us see and take pictures of these processes without touching the specimen. Quantum dots made of carbon have really good properties for being used in bioimaging [122]. They give off strong light, do not harm cells, and work well in the body, which makes them great for seeing inside the body. CQDs and GQDs are commonly used in bioimaging, especially for imaging cells. To find out more detailed information about how they are used, you can look at Table 2.

Using CQDs for medical purposes such as imaging in clinics and biology, as well as for diagnostic and therapeutic treatments like cancer imaging and phototherapies, has been acknowledged. For example, in a research study, a small amount of CQDs combined with wheat straw (at a certain concentration) was injected into mice through a vein in their tail [123]. This allowed researchers to take pictures using special equipment. Researchers have studied the use of CQDs as fluorescent markers for imaging different types of cells. CQDs have special qualities that make them good for bioimaging. They are not harmful, good for the environment, don't have many negative effects, can be dissolved in water, and can emit light in the visible to near infrared range. coli) cells, and human embryonic stem cells, are used in scientific research to study various aspects of cell biology and disease [124]. These cell lines have different characteristics and functions. For example, Ehrlich ascites carcinoma cells are used to study cancer, HepG2 cells are used to study liver diseases, E. coli cells are used to study bacterial infections, and human embryonic stem cells are used to study development and potential treatments for diseases. Coli, HeLa cells, human lung cancer cells (A549), and NIH-3T3 fibroblast cells have been effectively seen using CQDs. Specifically, very small particles known as CQDs measuring 4. 4 nanometers were produced from Nescafe instant coffee. These particles have the ability to emit light and have a brightness of around 5. 5% [125].

Coffee-based nanoparticles called carbon quantum dots have been used to take pictures of cancer cells and small fish without needing any special modifications. In a research study, scientists found and observed human breast cancer cells called MCF-7 cells [126]. They used a type of carbon particles called carbon dots that were coated with a substance called PPEI-EI for a special type of microscope called two-photon luminescence microscopy. CQDs glowed brightly in the inside of the cell and on the cell's outer layer after being kept at a temperature of 37 °C for 2 hr. Carbon dots could enter the cells only when the temperature was higher, and no uptake of carbon

Table 2. Recent advancements in bioimaging have seen the application of CQDs and GQDs in various studies

Imaging Position	Cell Line	Concentration of QDs	Ref.
MCF-7	Cell membrane, cytoplasm, nucleus	100 µg/mL	[118]
H2452, HUVEC	ND	50µL/mL, 100 µL/mL	[110]
L929 fibroblasts	Membrane, cytoplasm	0.30 mg/mL	[45]
A549 MCF-7	Cell cytoplasm	25 µg/mL	[47]
MC3T3	Cell cytoplasm	2.5 mg/mL	[85]
HeLa	Cell nucleus	0.01 mg/mL	[97]
MDA-MB231	Cell	0.1 mg/mL	[24]
Nematodes	ND	100 µg/mL	[22]
HEK-293 cells	Cell membrane	40 µg/mL	[120]
HeLa	Membrane, cytoplasm	0.01 mg/mL	[121]
HT-129	ND	ND	[122]

dots was seen when the temperature was 4 °C. Moreover, a type of microscope called two-photon luminescence microscopy was used to detect hydrogen sulfide (H_2S) in tissues and cells. This was done by using a substance called CQDs, which can emit fluorescent light when activated [127].

In addition to CQDs, scientists have also studied changing CQDs by adding a Cu(II) complex. This change made the quantum dots lose their fluorescence, and the formation of copper sulfide made the fluorescence come back[128]. A different study focused on making green graphene quantum dots (GQDs) that dissolve easily and have a high efficiency of 11. 4% These tiny graphene quantum dots had really good light emission and they stayed the same in water and different types of liquid substances. Additionally, small-sized yellow-green light-emitting particles called GQDs were created by treating graphite with a powerful oxidizing agent. The GQDs measure to be around 10 nanometers in size. These tiny particles are safe, stable under light, and were easily dissolved in liquid. Their ability to emit light when excited was found to be about 7% and they have been effectively used in observing cells [122-127].

Although bioimaging applications of GQDs have potential, there are still issues that need more research. Earlier research has worked on making tiny dots called GQDs that can emit different colors of light, from very bright blue to invisible red. However, the amount of light emitted by these GQDs was found to be less than that of regular semiconductor quantum dots [130]. This shows that more work needs to be done to improve this aspect. GQDs that produce a strong red-near infrared light are good for bioimaging purposes. Tiny tools with many uses may offer solutions for problems in industries and the environment when it comes to taking pictures and studying living things. GQDs can be used in therapy and imaging for different reasons because they have special properties related to light and radioactivity [131]. But, there are not many reports about using GQDs to take images of targeted tumors inside the body. We need to study more about using antibodies or peptides combined with GQDs to diagnose cancer. We need to solve some problems with GQDs [91]. These include things like using multiple photons, treating brain genes, using them for brain activities, and getting them to pass through the blood-brain barrier. More research is needed to assess how GQDs can harm cells. This should take into account things like their shape, size, and outer layers [71]. Affordable and environmentally friendly techniques have been used to create a large quantity of high-quality GQDs by adding polyethyleneimine or (3-carboxyl) phenyl bromide phosphine. GQDs-polyethyleneimine was made by a basic method with water, and then combined with (3-carboxyl) phenyl bromide phosphine using an amide bond. These two materials showed low harm to cells, had useful properties for light and were able to target and visualize either mitochondria or the cell nucleus. This shows that GQDs are very important in bioimaging, especially in taking pictures of the cell nucleus and mitochondria for diagnosis and treatment, both inside and outside the body [132].

CDs for in vitro tumor cell bioimaging

The advancement of technology is crucial in the early detection and prevention of cancer, a disease that claims millions of lives each year. CDs, which have been functionalized for fluorescence imaging, show great promise in differentiating tumors [77-80]. The interaction between active CDs and cancer cell sites is of particular interest. Researchers have successfully targeted glioma cells by developing pegylated CDs from glutamate and glucose precursors, resulting in enhanced sensitivity for glioma imaging compared to normal brain tissue [81]. CDs have also been used effectively to label breast cancer cells through endocytosis [82]. Additionally, the use of environmentally friendly CDs derived from natural biomass has led to cost reduction and simplified synthesis processes. Recent studies have introduced a novel carbon-based nanomaterial for photodynamic therapy (PDT) of tumors in mice, utilizing fluorescence imaging in the near-infrared range [83]. CDs derived from eutrophic algae flowers have been employed as biomarkers to visualize specific cancer cell lines [84]. These findings expand the application of fluorescent CDs in tumor identification within the field of biomedical research. Furthermore, CDs hold great promise as nanocarriers for drug delivery, therapeutics, stem cell delivery, and stem cell differentiation [85-87]. To enhance the cancer detection capabilities of CDs, the incorporation of sensitive aptamers has been explored. For example, a fluorescent immunosensor has been developed by combining highly sensitive antibody-ssDNA aptamers with CDs, enabling selective

imaging of cancer cells [88]. N-doped CDs with anti-tumor properties have also been developed for the detection of tumor biomarkers [89]. However, the recognition of cancer cells with CDs remains a challenge, as not all cancer cells can recognize these molecules and ligands. Therefore, increasing the focus and specificity of fluorescent CDs is crucial for effective monitoring of cancer cells.

CDs for in vivo tumor imaging

Fluorescent CDs have gained significant attention in recent years for their potential in diagnosis and therapy *in vivo*. A major breakthrough was achieved by Yang et al., who successfully demonstrated the first imaging of CDs in mice using three different injection methods. Subsequent studies have extensively investigated the biodistribution, clearance, and uptake of CDs in animal models. Furthermore, CDs have been explored as probes for tumor and brain cells, as well as for cancer treatment with red fluorescence. These advancements highlight the promising prospects of fluorescent CDs for diagnostic and therapeutic purposes.

Theranostic application of CDs

Impressive progress has been made in the field of cancer treatment through the innovative development of CDs that emit red fluorescence. These CDs have demonstrated remarkable efficacy in both photoacoustic (PA) and photothermal therapy (PTT) conversions. By utilizing polythiophene benzoic acid, researchers have successfully engineered red-emitting CDs that not only emit fluorescence in the red spectrum but also exhibit the combined effects of photodynamic therapy (PDT) and PTT. When exposed to laser irradiation, these carbon dots generate singlet oxygen (1O2) and exhibit exceptional PTT conversion efficiency. As a result, they serve as a versatile theranostic platform for the simultaneous implementation of PDT-PTT therapy, enabling precise treatment within the therapeutic window [5]. These breakthrough advancements have stimulated further exploration in this field. To enhance water absorption in the red region and support the body's water-splitting mechanisms, multilayer CDs have been designed. These CDs have shown promising inhibitory effects on the growth of cancer cells, effectively combating PDT resistance induced by hypoxia. Interestingly, *in vivo* experiments have validated their ability to reduce tumor hypoxia, highlighting their potential in cancer therapy [113]. Another noteworthy development is the creation of chitosan-CD hybrid nanogels (CCHN) for NIR imaging-guided cancer therapy. These nanogels exhibit exceptional colloidal stability, bright and enduring fluorescence, efficient near-infrared photothermal conversion, and intelligent drug release characteristics [115]. Furthermore, the combination of N-doped carbon dots with transition metal ions, such as copper (Cu), has emerged as a promising nanoplatform for cancer treatment. These red-emitting CDs act as effective thermal agents for monitoring temperature during the course of PTT/PDT for cancer. Their ability to emit fluoresence in the near-infrared range enables accurate cancer diagnosis, while facilitating *in vivo* imaging of the PTT/PDT combination [116]. Overall, the development of red-emitting CDs represents a significant leap forward in cancer treatment, offering immense potential for therapeutic imaging and diagnosis, particularly in the context of eye cancer.

Diagnostic application

Pei and his team have created hybrid nanosponges called CD-CQD that are fluorescent and glow bright blue when exposed to 365 nm light. These nanosponges are also safe for use in the body. These new particles, called hybrid QDs, were made by mixing CQDs and cyclodextrin (CD) together. The mixture had five times more CD than CQDs. These new hybrid QDs are used for both diagnosis and treatment (theranostic) of diseases, specifically cancer [125-126]. In another study, Fateh et al. made a new structure by blending tiny pieces of graphene with small magnetic particles. This happened by using the repellent force between the carbon chains on the surface of GQDs and the magnetic nanoparticles in the middle [132]. Scientists created a hybrid nanostructure known as GO-PEI-GQDs by using electrostatic layer-by-layer assembly with a polyethylene imine bridge [86]. The researchers looked at different ways to use the GO-PEI-GQDs complex, such as for imaging cells, treating cancer with heat, and studying how cells response to stress [133].

Surprisingly, when exposed to a certain laser for 5 minutes at specific concentrations, GO-PEI-GQDs showed a very good response by increasing the temperature by 44-49 °C. The research showed that GO-PEI-GQDs had positive effects on cancer cells. They were able to create stable

images, had better heat effects, and were toxic to the cells. Using a mix of GO and GQDs in materials helps improve certain medical treatments like cancer theranostics [132]. Recent research related to hybrid QDs was utilized for their diagnostic/ imaging applicability in different types of cancers is summarized in Table 3.

Drug delivery

New studies have looked at how hybrid QDs can be used to help diagnose and take pictures of different kinds of cancer. Scientists are studying hybrid QDs as a way to deliver drugs to specific parts of the body in a controlled way. This allows the drugs to work properly and for the right amount of time [134]. Using small materials called nanomaterials with drugs has shown potential in delivering drugs directly to tumors. This can be helpful in decreasing the negative effects of drugs. Also, very small size of nanomaterials improved the dissolution of slightly aqueous soluble agents. Nanotechnology in drug delivery systems (DDSs) allows the delivery of multiple drugs at the same time, transferring large drug molecules, and tracking the biodistribution of drugs using imaging agents on carriers [135]. CQDs have shown great potential in delivering drugs and can be used as powerful nano-antibiotics for infections inside cells. Also, drugs called CQDs can be made to work with microbial B to create nanofluorescent probes that can be used for diagnostic imaging and treating tumors [136]. Scientists have recently become interested in using CQDs for delivering drugs. Table 4, in the paper shows a brief description of the use of various CQDs in delivering medications.

In drug delivery systems that aim for specific targets, folic acid (FA) and hyaluronic acid (HA) are often used substances that can attach to specific receptors on tumor cells. Folic acid attaches to receptors that have higher amounts of folic acid, while hyaluronic acid attaches to CD44 receptors [137]. These systems are used in different types of tumor cells. These special molecules help to specifically target cancer cells. For instance, scientists made FA-modified carbon dots (FA-Gd @ CQDs) by cooking waste crab shells and Gd3+ metals together in a microwave. These FA-Gd @ CQDs were discovered to attack HeLa cells that have the folate receptor. When the FA-Gd @ CQDs were given the anti-tumor drug doxorubicin (DOX), they showed that they could fight cancer in HeLa cells. This means they might be useful in targeting cancer treatment [138]. In a different research, Zheng used special substances called d-glucose and l-aspartic acid to create new particles called carbon quantum dots (CQD-Asp). These particles were designed to treat a specific type of brain cancer called gliomas. The images of CQD-Asp were injected through the tail vein

Table 3. Summary of recent studies using hybrid quantum dots for cancer diagnostics/imaging purposes

Sample	Cancer Type	Imaging Technique	Ref.
QDs/DNA/CdTe	Non-specific cells	Fluorescence Diagnosis	[122]
CQDs	Tumor cells	Photoluminescence and photoacoustic imaging	[124]
QDs/Gelatin (chondroitin)	Breast tumor	Fluorescence imaging	[125]
CQDs Doped with N and F	Squamous cell carcinoma	Near-infrared fluorescence (NIRF) and PET imaging	[127]
QDs/ streptavidin	Breast tumor	Diagnosis	[108]
NGQDs	Skin	Imaging and diagnosis	[88]
QDs conjugated with cDNA aptamer/ Magneton-fluorescence carbon	Cervical	Fluorescence and magnetic resonance (MR) imaging	[64]
CQDs / polyethyleneimine	Hepatocellular carcinoma	Bioimaging	[22]
Carboxyl/ CdTe-QDs	HeLa and MCF-7 cells	Bioimaging	[34]
QDs /Iron selenide	Skin	Bioimaging	[22]
QDs/Au/SiO_2	Breast tumor	Imaging	[129]
CQDs	Cervical	Fluorescence imaging	[130]
Magneton-fluorescence carbon-QDs / cDNA/ aptamer	Cervical	Fluorescence and magnetic resonance (MR) imaging	[112]
Lactoferrin QDs	Breast tumor	Fluorescence imaging	[131]
Magnetic GQDs	Cancer cells	Electrochemical detection imaging	[132]
GQDs	Cancer cells	MRI and fluorescence imaging	[133]

Table 4. Short explanation of how different types of small particles can be used to deliver medicines

Sample	Drug	Cell Type	Size(nm)	Ref.
PCDs	Doxorubicinon	HeLa cells	3-6	[12]
Lis-CDs(lisinopril -loaded carbon dots)	Lisinopril	HeLa cells	2.5 ± 1.0	[127]
5-FU-CQD	5-FU	MCF-7	4.82 ± 0.75	[108]
Lycorine-CDs	Lycorine		2-4	[88]
		HepG2		
boldine-CDs	Boldine		6	[68]
		MCF-7		
CD-Oxa	Oxaliplatin	HeLa cells	2.71 ± 0.43	[112]
CDS-DOX	Doxorubicin	MCF-7	3.9 ± 0.7	[34]
IL-HCDs	Curcumin	HeLa cells	5.8	[122]
IL-OCDs	Curcumin	HeLa cells	7.2	[130]
		7.2		
CQDS-DOX	Doxorubicin	A549 cells	6.8 ± 1.3	[131]
		6.8 ± 1.3		
CD-DOX	Doxorubicin	ACC-2 cells	20	[133]
CDS-DOX	Doxorubicin	MCF-7	3.9 ± 0.7	[136]

showed a much brighter signal at the glioma site compared to healthy brains [139]. The researchers estimated that CQD-Asp might work by forming a group similar to RGD in the CQD edges. This group is known for targeting glioma, a type of brain tumor. This means that CQD-Asp is very good at targeting glioma cells. The special features of the area around a tumor, like low acidity, ability to change in response to stimuli, different enzyme levels, high reactive oxygen, and sensitivity to sound, light, and heat can be used to create diagnostic and treatment tools. Researchers have studied different types of drug delivery systems that can respond to specific conditions in the body, such as light, pH levels, or reduction, to treat tumors more effectively [140]. For instance, Yuan created a drug-loading system that is safe for the environment. He did this by heating milk and using an electrical effect to mix it with a cancer-fighting drug called doxorubicin (DOX). Lab tests showed that CQDs-DOX was easily uptaken by cells and released based on the levels of acidity [141]. In another study, researchers put a type of drug called cisplatin onto tiny particles called CQDs. They also added a special material on the outside of these particles. This system released positively charged CQD-Pt (IV) in a tumor microenvironment that has a lot of glutathione to treat the tumor [142].

Uptake and biodistribution of CDs in guided drug delivery

Thoroughly assessing the risks and long-term safety of fluorescent carbon dots in biomedical research is of utmost importance. The biodistribution and uptake of CDs *in vivo* should be evaluated comprehensively to understand their role in various applications. To study the biodistribution, radiolabeling techniques have been utilized [94]. Initial studies in mice using near-infrared (NIR) CDs indicated the accumulation of CDs in the kidneys. Researchers have also developed CDs coated with 3-aminopropyltrimethoxysilane (APTMS) for targeted cellular imaging of mitochondria and differentiation of malignant cells from normal cells. These APTMS CDs are cost-effective, easy to prepare, and demonstrate rapid cellular entry and specific targeting of mitochondria for at least 24 hr, making them suitable for mitochondrial imaging. Expanding the potential applications, the ability of APTMS CDs to target mitochondria enables the differentiation of healthy and tumor cells. Investigations into the metabolic processes, tumor uptake mechanisms, and *in vivo* biodistribution of CDs have also been conducted [95]. For instance, nitrogen-doped CDs coated with polymers have shown accumulation in gliomas, making them valuable for imaging analysis of such tumors. In mice, tumor cells primarily take up CDs and excrete them through the

kidneys, with minimal uptake by hepatocytes. The biodistribution and pharmacokinetic properties of CDs are influenced by their surface charge and hydrophilicity. Optimizing these properties is crucial to minimize protein adsorption and ensure the safety and efficacy of CDs. While these studies offer valuable insights into the diverse applications of fluorescent CDs, further research is necessary to fully understand their toxicity, absorption, biodistribution, and broader potential *in vivo*. Enhancing the specificity and reducing potential adverse effects can be achieved by optimizing the surface properties of CDs [96]. Researchers have exploited CDs with excellent optical properties, biocompatibility, and fluorescence imaging sensitivity to develop cancer-specific drug delivery systems. These CDs act as nanocarriers for targeted drug delivery, monitoring drug release, and recording drug delivery [105]. Charge-switchable CDs have been designed to inhibit tumor growth with minimal side effects. Additionally, hollow CDs doped with phosphorus and nitrogen have been developed as nanocarriers for pH-dependent drug release, demonstrating high drug-loading capacity, small particle size, rapid cellular uptake, and a hollow structure. These CDs enable nuclear drug delivery and photodynamic therapy for cancer treatment [107]. By combining luminescent CDs with DOX, an innovative drug delivery system has been created that allows real-time visualization of drug release and photodynamic therapy [107]. This cutting-edge approach efficiently transports DOX to target cells and releases it upon exposure to near-infrared radiation. Furthermore, the incorporation of HA with DOX and the utilization of CDs for bioimaging have enabled precise drug delivery to tumors expressing the CD44 receptor [108]. This targeted delivery system enhances the uptake of CD-based drugs by cancer cells and increases their therapeutic efficacy. Additionally, researchers have explored the reversible release of DOX from CDs as a potential strategy for cancer treatment [108]. However, thoroughly evaluating the biotoxicity of these drugs and ensuring their long-term compatibility with tissues are crucial as the use of CDs in cancer therapy expands. Ongoing research in this field is essential to guarantee the safety and effectiveness of CDs in clinical applications.

Utilization of carbon dots for tumor bioimaging

The treatment landscape for malignant gliomas, a challenging type of brain tumor, has witnessed a significant advancement with the recent discovery that 45 nm small CDs possess the ability to effectively penetrate the blood-brain barrier and accumulate in the brain [112]. This breakthrough holds great promise for the development of improved therapies and diagnostic approaches. Epifluorescence imaging studies have revealed that these CDs reach their peak concentration in the brain within a mere 5 minutes post-injection through the tail vein [113]. Researchers have successfully employed glucose and aspartic acid (Asp) to functionalize CDs, specifically targeting glioma activity Notably, when aspartate-functionalized CDs were administered, distinct fluorescence signals were observed in glioma tissue blocks as early as 20 minutes after injection, demonstrating the CDs' ability to selectively target glioma sites by crossing the blood-brain barrier [114]. This groundbreaking discovery holds immense potential for the diagnosis and treatment of malignant gliomas, a significant intracranial disease [114]. Additionally, a compelling study conducted by Lu et al. has shown that nitrogen-doped CDs (N-CDs), which are biocompatible, can also traverse the blood-brain barrier. This finding was corroborated by *in vitro* imaging of a BBB model, suggesting that CDs modified with polyethyleneimine can efficiently deliver drugs to the brain [115]. Extensive research efforts have been dedicated to exploring the concept of modified CDs for targeted drug delivery across the blood-brain barrier [116]. In summary, the remarkable ability of small carbon dots (CDs) to traverse the blood-brain barrier and selectively target malignant glioma sites represents a significant advancement in the field of glioma treatment and diagnosis [12]. This breakthrough discovery opens up new avenues for innovative approaches in drug delivery and therapy, instilling hope for improved outcomes in managing this complex condition [117].

Nanoarchitectonics can help create really small CDs that can specifically find and destroy certain things on tumor cells, like the glycolytic or amino acid transporters. In addition to fighting cancer cells, these unique carbon dots can also get into the brain by crossing the protective barrier known as the blood-brain barrier [143]. This is able to happen because the dots have proteins called glucose transporter GLUT-1 and amino acid transporter LAT1, which assist them

in crossing the barrier. Scientists created CDs that specifically target brain tumors by using heat and water to break down equal amounts of D-glucose and L-aspartic acid. The writers thought that CDs have specific parts on their surface that help them go into cells through glucose and amino acid transporters. They made these glioma-cell-targeting CDs better by adjusting the levels of glucose and aspartic acid [144]. A special method was used to make something called CNDs. Tumor cells can absorb CNDs more easily because they look similar to amino acids, which are important for cell functions. Tumor cells actively take in amino acids, so they also take in CNDs easily. When the drug gemcitabine was connected to CNDs, it caused more cell death in cancer cells found in pediatric high-grade glioma and embryonic kidney cells compared to healthy cells. CNDs were made using a microwave by mixing citric acid and metformin [145]. These CDs can help transport medicines that target specific areas inside cells. Another method for treating brain tumors in children is by using substances that stick to certain proteins found on the surface of the tumor cells that are more active in these types of tumors. Hettiarachchi and others researchers showed that CDs were better at carrying two drugs when they were connected to a protein called transferrin. The specific CDs were much better at killing brain tumor cells compared to regular CDs alone [144]. Furthermore, when transferrin receptor-targeted doxorubicin-conjugated CDs were added to plain doxorubicin, it resulted in increased cell death in pediatric brain tumors [71]. Table 5, presents an extensive compilation of potential antigens and targeted ligands that are specifically designed for CD-mediated drug delivery, with a focus on pediatric brain tumors.

Indeed, successful delivery of drugs to B7H3 using CDs has been achieved. Additionally, nanoparticles can be employed for drug delivery to B7H3 by utilizing the same targeting approach with anti-B7H3 antibodies. This method offers potential for targeted therapy against B7H3-expressing cells [146]. Another way to use carbon dot therapy in treating brain tumors in children is to focus on the environment surrounding the tumor. The TME is made up of parts that help cancer cells grow and spread, hide from the immune system, and resist treatment. These parts include things like low acidity and low oxygen levels. Using a medicine called bevacizumab, which stops the growth of blood vessels, has been proved to help glioblastoma (GBM) patients live longer [135]. Recently, Shoval et al. showed that modified CD, with an anti-VEGF aptamer, can stop the growth of new blood vessels in the eyes of mice with a certain disease. A new strategy for treating brain tumors is being tested in clinical trials. It involves targeting specific parts of the immune system, like activating certain cells or stopping others from helping the tumor grow. This approach shows promise for future treatments. In

Table 5. A comprehensive list of potential antigens and targeted ligands for CD-mediated drug delivery specifically designed for pediatric brain tumors

Targeted Ligands	Ligand-Binding Receptor	Brain Tumor Targeting	Ref.
EphA2	Receptor	Researchers are testing YTPL peptide and anti-EphA2 antibody fragments as substances that can attach to nanoparticles and help deliver them to tumor cells	[25]
EGFR	Receptor	GE11 peptide and anti-EGFR antibodies, like Cetuximab, have been studied as substances that can help deliver nanoparticles to tumor cells	[44]
B7H3	Checkpoint inhibitor	Scientists are studying anti-B7H3 antibodies as substances that can be used to carry small particles to cancer cells	[62]
IL13Rα2	Receptor	Pep-1 is a special type of peptide that can enter cells. It has been used to help deliver nanoparticles into cells, which helps increase the amount of substances that can enter and be delivered inside the cell	[99]
GD2	Ganglioside	Anti-GD2 antibodies are used to attack cancer cells and deliver drugs directly to them.	[106]
HER2 (ErbB-2)	Receptor	KCCYSL and LTVSPWY peptides have been studied because they could possibly be used to deliver drugs to cells and target specific cells	[144]

this regard, recently, Su and colleagues conducted a study [137].

A novel treatment has been developed that specifically targets colon cancer cells by focusing on the protein PD-L1, resulting in their selective elimination. This innovative approach holds promise for combating colon cancer and potentially improving patient outcomes [71]. The integrin family is a group of proteins found on the surface of cells. They can be a good choice for delivering drugs specifically to tumors because they are often more active in cancer cells and can be found on the cells of blood vessels and tumors, including those in children's brains. RGD peptide, also known as arginine-glycine-aspartic acid, is often used to focus on integrins. Feng et al, A pH-responsive drug has been created, capable of releasing cisplatin specifically in low pH conditions. The cytotoxicity assay on breast cancer cells of this drug exhibited significant cytotoxicity, leading to cell death. Importantly, this drug has the potential to target various components of the tumor microenvironment, offering a promising avenue for the treatment of breast cancer [125].

Future points of view for carbon quantum dots (challenges and opportunities)

CQDs have been getting a lot of attention from scientists because they can stick to different types of semiconductors to convert solar energy. They have shown to be very important in fields like saving energy and studying life. This review talks about the various types of carbon sources used in CQD making [139]. It includes both regular chemicals and eco-friendly materials. It is difficult to achieve high efficiency and quality in assembling CQDs, even though they have a lot of potential. So, this review looks at how CQDs-based semiconductors are made and how they are used to clean water and break down pollutants in the environment [140]. This paper is saying that researchers should start focusing more on environmentally friendly options. Green synthetic routes for something called CQDs are still relatively new compared to methods using chemicals. The review also gives a detailed summary of how CQDs are used in photocatalysis. It also talks about the need to make sensors and bio-imaging systems more sensitive, selective, and strong. This focuses on the importance of decreasing the disruption caused by natural fluorescence in biological imaging and sensing activities that use CQDs, using delayed fluorescence methods. CQDs need to stay stable for future uses. Even though CQDs-based photocatalysts have great potential and can be designed to perform exceptionally well, there are still problems that need to be solved in a stable way [141]. To improve the technology of CQD-based composites for photocatalytic degradation, this review points out two important things: (i) finding a better way to make a lot of CQDs efficiently, since the current methods take a long time and use a lot of energy, and (ii) understanding how CQDs are made and how their light-emitting properties work, including the effects of the excellent up-converted photoluminescence. Also, the review emphasizes the need for using the same methods to create CQDs consistently in order to have precise control over their properties[142]. It also mentions that CQDs have the potential to be used as photocatalysts on their own, but this area of research has not been fully explored yet. In the future, scientists should study how to create very powerful and environmentally friendly photocatalysts. Although there are challenges, CQDs have a lot of potential to quickly advance technology in different areas, especially in bio-imaging and bio-sensing. They will keep growing alongside related research areas[142-146].

CONCLUSION

In the past few years, more and more people have become interested in biosensors that use really tiny structures. These biosensors can make it easier to diagnose and treat diseases sooner, helping patients live better lives. By measuring different indicators in one device, biosensors can be created to be able to distinguish between things and choose some of them. Nanomaterials are great for making biosensors because they have a lot of surface area, they can reflect light well, they can conduct electricity, and they are stable in their chemical and physical properties. CQDs are very small materials that are good for biosensing systems. They can quickly and accurately detect and diagnose different things, like cancer and heavy metals, in a range of fields. CQDs are very stable and safe to use. They produce a lot of light and have a high quality of light emission. They also have a lot of surface area and can conduct electricity. They are not harmful to living things and can be dissolved in water. Because of all these characteristics, they are good for making biosensors. This review is about how CQDs are

made. They can be made by either building them from small parts or by breaking down bigger things. While using top-down approaches may seem easy, they can also come with difficult or challenging situations. Hydrothermal and solvothermal methods are often used because they are simple and inexpensive. Chemical ablation is a basic method, but it needs additional steps afterward to make the CQD size consistent. Also, it is important to think about how good it is for the environment, how easy it is to grow, and how much it costs to make. Due to their high quantum yield, photochemical steadiness, and fabulous electro-catalytic action, CDs have been utilized to create profoundly delicate biosensors and appear potential for future clinical use. Scientists are using special receptors to improve the delivery of genes and drugs to specific cells. However, more research is needed. In short, we need a good plan for CDs and surface modification, which can help deliver drugs and particles to cells. This leaves ample space for research and development of better CDs for future medical uses.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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