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REVIEW ARTICLE

Advancements in Gadolinium–doped Carbon Quantum Dots for Dual–Modal Bioimaging: Synthesis and Applications

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ABSTRACT: Carbon quantum dots (CQDs) represent a revolutionary class of nanoparticles with exceptional biocompatibility, photostability, and tunable optical properties, making them indispensable in biomedical applications. This review focuses on the synthesis and applications of gadolinium-doped carbon quantum dots (Gd-CQDs), particularly in dual-modal bioimaging, which combines magnetic resonance imaging (MRI) and fluorescence imaging. Among various synthesis techniques, the one-step solvent method and the one-pot synthesis method are emphasized, with the latter emerging as a more efficient approach due to its enhanced fluorescence and superior stability. The integration of gadolinium, a widely used MRI contrast agent, into CQDs addresses the challenges posed by conventional gadolinium-based agents, such as their retention in the brain and bones, by offering a safer and more versatile alternative. Gd-CQDs exhibit unique properties, including high biocompatibility, tunable fluorescence, and efficient magnetic resonance contrast, making them ideal candidates for non-invasive diagnostic imaging. Moreover, their potential extends beyond imaging to include applications in targeted drug delivery and real-time monitoring of biological processes. By leveraging advancements in genomics and proteomics, Gd-CQDs pave the way for personalized medical interventions tailored to individual molecular profiles. Future research should focus on optimizing synthesis techniques to enhance particle stability, reduce cytotoxicity, and incorporate multifunctional ligands for improved diagnostic capabilities. This review underscores the transformative potential of Gd-CQDs in advancing medical imaging technologies and bridging the gap between diagnostics and therapeutics.

Keywords: Gadolinium-doped carbon quantum dots (Gd-CQDs), Dual-modal bioimaging, Synthesis techniques, Magnetic resonance imaging (MRI), Nanoparticles in medicine, Fluorescence imaging

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1. INTRODUCTION

Quantum dots (QDs) are nano-crystalline semiconductors with physical dimensions smaller than the Bohr radius. Due to the quantum confinement effect, the electronic and optical properties of QDs exhibit distinct dependencies on nanoparticle sizes and composition, producing vibrant fluorescence colors for QDs of varying semiconductor sizes [1]. Metal gates are used to electrostatically confine electrons to a small region (or "dot") in the interface plane of a semiconductor heterostructure, creating a two-dimensional electron gas. As a result, the electronic motion is restricted in all three dimensions, making QDs a zero-dimensional system [2]. In recent years, fluorescent nanoparticles, particularly semiconductor QDs, have drawn significant interest for their applications as optical imaging tools [3]. Mesoscopic

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systems include QDs and exist between microscopic systems like atoms and macroscopic bulk matter. The term "mesoscopic" refers to systems where the electron's phase coherence length exceeds or matches the system size [4].

A new class of carbon nanomaterials, including graphene quantum dots (GQDs) and carbon quantum dots (CQDs), has emerged. First identified in 2004 during the electrophoresis of single-walled carbon nanotubes and later through laser ablation of cement and graphite powder, carbon dots refer to suspensions of small carbon nanoparticles [5]. Functionalized carbon nanotubes have shown bright fluorescence due to surface flaws, paving the way for carbon-based QDs as promising bioimaging tools [6]. These nanostructures are non-toxic, water-soluble, highly photostable, and possess a large cross-section for two-photon excitation, making them excellent candidates for bioimaging applications. Compared to CdSe-ZnS QDs, carbon QDs exhibit superior cellular uptake and fluorescence brightness [7].

Carbon-based QDs have gained popularity due to their benign, abundant, and affordable nature. Their strong luminescence and good solubility have enabled applications in fluorescence imaging of cells [8]. Their visible excitation and emission wavelengths, fluorescence brightness, and high photostability make CQDs effective tools in cellular imaging. Additionally, multimodal imaging—integrating fluorescence imaging and magnetic resonance imaging (MRI)—provides sensitive functional imaging and high-resolution histological data. The utility of MRI is enhanced by contrast agents, categorized as T1 and T2 agents. Gadolinium-doped carbon QDs (Gd-CQDs) are an emerging class of magneto-fluorescent materials with high biocompatibility, tunable fluorescence, and stability [9].

The carboxylic, amine, and hydroxyl groups on the surface of Gd-CQDs contribute to their water solubility and biocompatibility. These functionalized nanoparticles do not blink, dissolve in water, and are non-toxic, making them valuable as nano-probes for bioimaging [10]. Furthermore, the development of fluorescence imaging depends on higher-performance fluorescent probes. Traditional QDs often contain toxic heavy metals, whereas Gd-CQDs achieve multimodal imaging while maintaining good biosafety [11]. They also show promise for detecting lead (Pb^{2+}) and mercury (Hg^{2+}) ions in environmental samples. For instance, Liu et al. reported ultrasensitive C-dots capable of detecting Hg^{2+} in water at a detection limit of 1 fM [12]. Similarly, nitrogen-doped C-dots have been used as sensitive nanosensors for Hg^{2+} detection [13].

Despite their advantages, Gd-CQDs pose some risks, such as systemic fibrosis and renal retention of gadolinium [14]. Nevertheless, they have immense potential in bioimaging, metal ion detection, and biomolecule sensing. Future advancements in Gd-CQDs include developing ultrasensitive technologies for point-of-care testing (POCT). With unique properties such as tunable size, high surface-to-volume ratio, and stability, QDs are emerging as specialized tools in biomedical applications. Their photo-stability and long fluorescence lifetime make them particularly useful for single-molecule tracking [15]. The integration of QDs into biomedical and pharmaceutical technologies is expected to drive significant innovations in diagnostics and therapeutic applications.

In this review, we focus on the synthesis methods and applications of gadolinium-doped carbon quantum dots (Gd-CQDs), emphasizing their dual-modal bioimaging capabilities. We compare their advantages with other quantum dots, explore their potential for environmental sensing and diagnostics, and highlight the future directions in their development for biomedical and technological advancements.

2. CARBON AND ZnO QDS: IMPACT OF DOPING OF GADOLINIUM ON FLUORESCENT PROPERTIES

2.1. Carbon QDs

Carbon Quantum Dots (QDs) represent a novel class of fluorescent nanomaterials that are rapidly emerging as competitors to traditional semiconductor QDs. These Carbon QDs (CQDs) exhibit unique optical properties, such as excellent aqueous solubility, robust physicochemical and photochemical stabilities, high fluorescence quantum yields, and non-blinking emissions. Most importantly, their biocompatibility makes them suitable candidates for various biomedical applications, including in vitro and in vivo optical bioimaging (Figure 1). Due to their nanoscale dimensions, CQDs possess immense potential in a wide range of applications, including bioimaging, sensing, and drug delivery [11].

One key aspect of advancing CQD research involves achieving fluorescence emissions in the red/near-infrared (NIR) spectral regions, as these wavelengths penetrate biological tissues more effectively. Studies are ongoing to enhance these properties through doping and surface functionalization, enabling specific targeting in cellular and in vivo imaging applications [12]. Additionally, significant research efforts are being directed toward understanding fluorescence mechanisms in CQDs to further improve their design and functionality. Modified graphene materials and other carbon nanostructures are expected to evolve further in this area [13].

2.2. Fluorescent Properties of Carbon QDs

Despite extensive studies, the exact mechanisms behind CQD fluorescence remain unclear. Two primary fluorescence mechanisms have been proposed: excitation-dependent and excitation-independent emissions. These mechanisms arise from two distinct origins: (1) band-gap transitions involving π-domains, and (2) surface defect-related emissions. Band-gap transitions result in strong absorption but weak emission, while surface defect-related emissions show weak absorption

but strong visible emission [14].

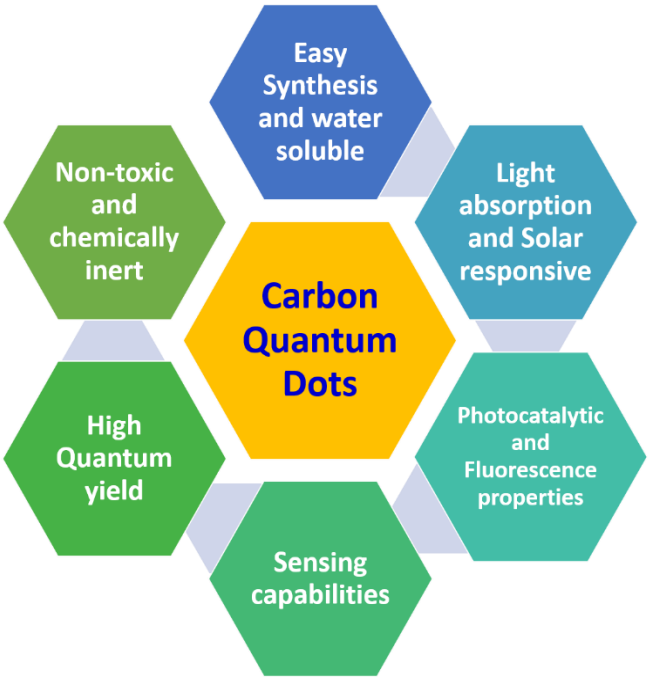

Fig. 1. Application of Carbon QDs in various fields.

Surface passivation or functionalization plays a crucial role in stabilizing these surface defects, enhancing radiative recombination, and producing brighter emissions [15, 16]. The manipulation of these defects and electronic states through doping offers a promising strategy to enhance the fluorescence properties of CQDs.

2.2.1. Enhanced Fluorescent Properties of Carbon QDs by Doping

Doping is a widely studied approach to enhance the optical and electronic properties of CQDs. The size and properties of CQDs can be influenced by factors such as reactant concentration, reaction temperature, and reaction time. Hydrothermal synthesis, using precursors like citric acid [17], orange juice [18], glucose [19], and banana juice [20], has been a popular method for producing CQDs with bright fluorescence. Most CQDs reported so far exhibit blue light emission and excitation-dependent spectra. However, doping CQDs with elements such as nitrogen (N), sulfur (S), phosphorus (P), and boron (B) can alter their emission spectra and enhance their fluorescence intensity. For instance, nitrogen-doped CQDs exhibit strong green fluorescence and are widely used in cell sensing and imaging applications [21, 22].

The UV absorption of CQDs, typically around 287 nm, arises from n-σ* and π-π* transitions associated with C=O and C=C bonds, respectively. Various interpretations have been proposed for the origin of CQD fluorescence, including surface defects, quantum size effects, and electron-hole recombination in sp2 carbon clusters embedded in a sp3 matrix [23, 24].

Recent studies using ultrafast spectroscopy have shown that fluorescence in CQDs originates from functional groups, such as carbonyl and carboxyl, located at the edges of the carbon backbone [25]. Doping CQDs introduces additional emission centers and traps, allowing for the tuning of their emission spectra from green to red wavelengths. However, the interaction between dopant atoms and surface states can create competition among emission centers, complicating the fluorescence mechanism [26, 27]. Further studies are needed to fully understand the fluorescence-shifting phenomena in doped CQDs [28].

2.3. ZnO QDs

Zinc Oxide (ZnO) QDs are another class of versatile nanomaterials with extensive applications in biomedicine, optoelectronics, and energy harvesting. Zinc, an essential trace element, plays a crucial role in various biological systems. ZnO nanoparticles are environmentally friendly and have been widely explored for in vivo bioimaging and cancer detection [29, 30].

Recent advancements have focused on tailoring the luminescence properties, bandgap energy, and crystal structures of ZnO QDs. While significant progress has been made in synthesizing ZnO nanoparticles through methods like hydrolysis of zinc salts in polyol media or mono-solvents, challenges remain in achieving high purity, narrow size distribution, and defect-free crystalline structures [31].

2.3.1. Effect of Doping on ZnO QDs

Doping ZnO QDs with specific elements is an effective strategy to modify their optical, electronic, and chemical properties. By introducing foreign ions into the ZnO lattice, researchers can adjust the bandgap, enhance photocatalytic activity, and induce weak ferromagnetic behavior. These properties have significant implications for nanomedicine, enabling multifunctional theragnostic systems capable of simultaneous diagnosis and therapy [32, 33].

For example, doping ZnO QDs with gadolinium (Gd) enhances their luminescence and biocompatibility, making them suitable for bioimaging and therapeutic applications. The dopant ions interact with the ZnO lattice, altering the electronic structure and improving the fluorescence properties. Such modifications also enable the use of ZnO QDs in advanced applications, such as photodynamic therapy and reactive oxygen species generation [34, 35].

2.4. Key Differences between ZnO and Carbon QDs

While both ZnO and Carbon QDs are nanoscale materials with unique properties, they differ significantly in

composition, optical characteristics, synthesis methods, and applications.

Composition: Carbon QDs are primarily composed of carbon atoms, typically derived from carbon-rich precursors like organic compounds or biomass. Zinc oxide QDs, in contrast, are made of zinc and oxygen atoms [36]. The optical properties of carbon QDs are strong and controllable fluorescence. They have a huge range of wavelengths from which they can emit light. Depending on their size, surface functionalization, and doping, they can emit anything from ultraviolet (UV) to near-infrared (NIR).

Optical Properties: The optical properties of ZnO QDs, on the other hand, are primarily controlled by their size and crystal structure despite having a wide bandgap. They emit UV light and have the potential to be used in UV lasers and optoelectronic devices [37]. Carbon QDs are suitable for a variety of biomedical applications, including bioimaging, drug delivery, and sensing, because they are generally regarded as being biocompatible. They are not toxic and are simple to functionalize for specific uses. On the other hand, zinc oxide QDs might show some cytotoxicity, depending on their size, surface coating, and exposure circumstances. This prevents them from being used directly in some biological and medical applications, though surface modification can increase their biocompatibility [38].

Biocompatibility: Carbon QDs are highly biocompatible, making them ideal for biomedical applications such as bioimaging and drug delivery. ZnO QDs, however, may exhibit cytotoxicity depending on their size, surface coatings, and exposure conditions. Surface modifications can improve their biocompatibility for medical use [38].

Synthesis: The processes used to create Carbon QDs and ZnO QDs are different. Several methods, such as hydrothermal/solvothermal processes, microwave-assisted synthesis, or laser ablation, can be used to create carbon quantum dots. Typically, sol-gel processes, thermal decomposition, or precipitation techniques are used in the synthesis of ZnO QDs [39].

Applications: Both varieties of QDs have applications in various industries. Solar cells, optoelectronics, drug delivery, bio imaging, and sensing all make extensive use of carbon quantum dots. For biomedical and optical applications, they are appealing due to their tunable fluorescence properties, biocompatibility, and functionalization potential. ZnO QDs are used in electronics, optoelectronics, photo catalysis, and UV photo detection because of their distinctive electronic and optical characteristics [40].

While both Zinc oxide and Carbon quantum dots have unique properties and uses, carbon QDs are more frequently used in the biomedical and optical fields, whereas zinc oxide QDs are used in electronics and photo detection. Doped Carbon Dots for Bio imaging and sensing [41]. The scientific community has paid a lot of attention to carbon dots (C-dots, CDs) or (CQDs) over the past ten years as an affordable and biocompatible substitute for semiconductor quantum dots. Doped C-dots in particular have excellent fluorescent properties and have been used to great effect in a variety of applications. This mini review provides an overview of recent developments in the synthesis of doped C-dots derived from carbon-rich sources and their potential use in biomedical and sensing applications [42]. Additionally, we'll go over a few difficulties and sketch out some potential directions for this fascinating subject.

2.5. Doped Carbon Dots for Bioimaging and Sensing

Doped Carbon Dots (C-dots or CQDs) have garnered significant attention as affordable and biocompatible alternatives to traditional semiconductor QDs. The incorporation of dopants such as nitrogen, sulfur, or phosphorus enhances their fluorescence properties, making them highly effective in various applications [43-47]. Recent advancements have focused on synthesizing doped C-dots from carbon-rich sources for biomedical and sensing applications. For instance, nitrogen-doped C-dots exhibit bright fluorescence and are used in detecting biological molecules, such as glucose, hydrogen peroxide, and dopamine. Similarly, boron-doped C-dots have been employed for sensing glucose and hydrogen peroxide through charge transfer mechanisms [45-50]. Despite their promising potential, challenges remain in understanding the precise mechanisms of fluorescence in doped C-dots. Future research should address these gaps and explore novel doping strategies to further enhance their performance in bioimaging and sensing applications. The ongoing exploration of Carbon and ZnO QDs is poised to unlock new possibilities in nanotechnology and materials science. For Carbon QDs, the focus will likely remain on understanding fluorescence mechanisms, optimizing synthesis methods, and expanding applications in bioimaging, sensing, and energy harvesting. For ZnO QDs, future efforts will aim to overcome challenges in synthesis, improve biocompatibility, and enhance multifunctional properties through innovative doping strategies. As the scientific community continues to delve into the properties and applications of these quantum dots, their impact on fields ranging from medicine to optoelectronics is expected to grow significantly. The development of doped QDs, in particular, holds promise for creating next-generation nanomaterials with tailored functionalities for diverse applications.

3. SYNTHESIS AND BIOCOMPATIBILITY OF GADOLINIUM-DOPED CARBON QUANTUM DOTS (GD-QCDS)

3.1. Synthesis of Gd-QCDs

Quantum dots (QDs) have become an essential focus in materials science due to their potential in imaging and sensing. While traditional semiconductor QDs pose toxicity concerns, carbon-based QDs (C-dots) offer eco-friendly and biocompatible alternatives, particularly in biomedical applications like fluorescence imaging and MRI [41, 42].

This review explores the synthesis, characterization, and biomedical potential of gadolinium (Gd)-doped carbon quantum dots (Gd-QCDs), which combine strong fluorescence, low cytotoxicity, and excellent MRI contrast [42].

The synthesis of Gd-QCDs is a one-pot process involving pyrolysis of gadopentetic acid, tris(hydroxymethyl) aminomethane (Tris base), and betaine hydrochloride. The gadopentetic acid acts as the gadolinium source, while Tris base serves as the carbon precursor. During pyrolysis at 250°C, gadolinium ions are uniformly integrated into the carbon matrix through interactions between the negatively charged carboxylic groups in gadopentetic acid and Tris base, enabling molecular-level mixing (Figure 2) [36]. The resulting Gd-QCDs are highly water-dispersible with a zeta potential of +17 mV, ensuring stability over extended periods. Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) revealed an average particle size of 3–4 nm, consistent with dynamic light scattering (DLS) measurements. The synthesis strategy bypasses post-synthesis doping steps, streamlining the production process while achieving precise doping [48]. Gd-QCDs exhibit unique structural and optical properties. Energy Dispersive X-Ray (EDX) mapping confirmed the uniform distribution of gadolinium, while X-ray Photoelectron Spectroscopy (XPS) identified two Gd 4d peaks at 142 eV and 147 eV, indicating consistent Gd coordination post-pyrolysis [36]. Fourier Transform Infrared (FTIR) spectroscopy further demonstrated minimal changes in functional groups after thermal treatment, emphasizing structural stability. Optical analysis revealed excitation-dependent fluorescence with a maximum emission at 445 nm, characteristic of C-dots. These properties make Gd-QCDs suitable for fluorescence imaging. Under UV light, Gd-QCDs display bright green and yellow emissions, supporting their potential for bioimaging applications. Gadolinium-based contrast agents enhance MRI signals through proton relaxation. T1-weighted imaging of Gd-QCDs demonstrated signal intensities comparable to commercial Gadovist at equivalent Gd concentrations (0.364 mmol/L). This highlights their potential as dual-functional agents for fluorescence and MRI imaging. Notably, Gd-QCDs outperform conventional gadolinium oxide nanoparticles in terms of biocompatibility and signal enhancement [46].

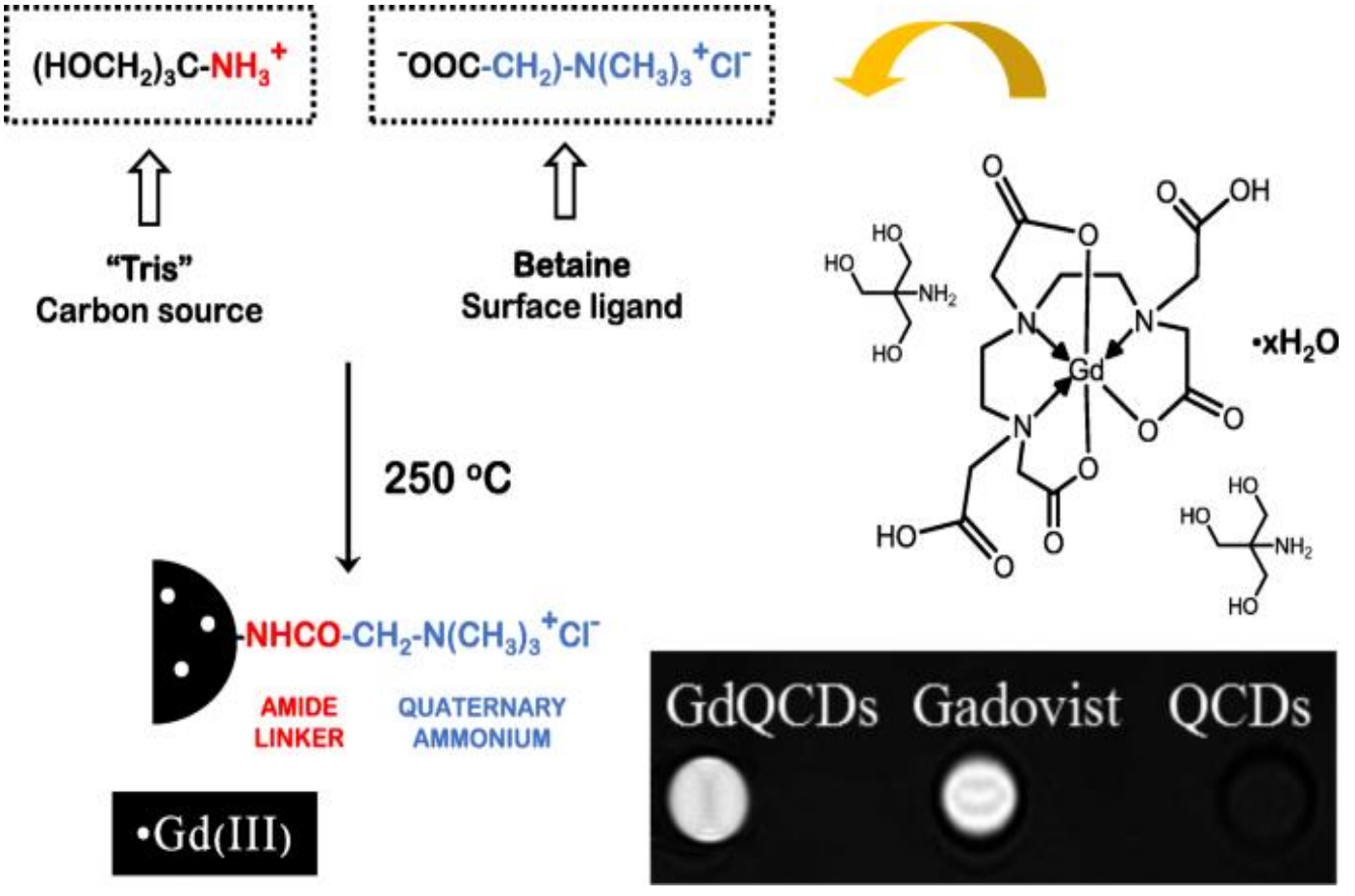

Fig. 4. Gd-QCDs syntheses via a scheme. The coordination of remaining O and N heteroatoms causes the Gd (III) centers to become immobilized in the carbonaceous matrix. Reprinted with permission from ref. [36], Yoo, D., Park, Y., Cheon, B. and Park, M.H., 2019. Carbon dots as an effective fluorescent sensing platform for metal ion detection. *Nanoscale Research Letters*, *14*, pp.1-13. Copyright © Springer Nature.

The cytotoxicity of Gd-QCDs was evaluated using the MTT assay on HeLa cells and compared to undoped C-dots. Gd-QCDs exhibited high cell viability, with an IC50 value of 121 mg/mL—only slightly lower than the undoped C-dots (190 mg/mL). These values are significantly less toxic than Cd-based QDs, which are known for severe cytotoxicity [48]. To ensure safe biomedical application, free Gd^{3+} ion leakage was assessed using a xylenol orange assay. Results confirmed minimal Gd^{3+} release over 24 hours, further validating their biocompatibility. Hemolysis assays also demonstrated negligible red blood cell disruption, confirming excellent blood compatibility [50-56].

An optimized synthesis route for gadolinium-doped carbon dots (GCDs) involved the pyrolysis of citric acid (CA), branched polyethyleneimine (BPEI), and Gd-DTPA at 180°C. This method produced uniform nanoparticles with consistent fluorescence and MRI performance. Characterization via High-Resolution TEM and X-ray Diffraction confirmed the crystalline structure, while Inductively Coupled Plasma Mass Spectrometry (ICP-MS) quantified gadolinium content, ensuring precise doping levels [48]. Dual-modal imaging combines fluorescence and MRI, leveraging the strengths of both techniques. HeLa cells treated with Gd-QCDs exhibited bright fluorescence under confocal microscopy, enabling detailed cellular visualization. Simultaneously, T1-weighted MRI scans showed strong contrast enhancement, further demonstrating their dual imaging capability. In vitro studies showed no significant cytotoxic effects on NIH_3T3 fibroblasts at various Gd-QCD concentrations. Additionally, fluorescence imaging revealed effective cellular uptake, confirming their suitability for bioimaging. Hemolysis and leakage assays verified their safety in blood-contact applications. In vivo studies on small animal models are needed to confirm these findings [48]. Gadolinium-doped carbon quantum dots represent a promising class of nanomaterials for biomedical imaging. Their unique combination of fluorescence and MRI contrast, coupled with low cytotoxicity and water dispersibility, positions them as effective dual-modal imaging agents. The streamlined synthesis process further enhances their appeal for scalable production. Future work should focus on in vivo evaluations and functionalization strategies to expand their applications in theranostics and targeted drug delivery [54-60].

3.2. Animal Models and In Vivo MR Imaging

C57BL mice (n=6, male, gray-haired, approximately 25g) were obtained from Sun Yat-sen University's Laboratory Animal Center for the in vivo MR imaging study. Ethical approval was granted by the Animal Experimentation Ethics Committee of Sun Yat-sen University, adhering to animal treatment guidelines. Mice were anesthetized using 0.075 mL chloral hydrate via intraperitoneal injection, followed by intravenous administration of 0.25 mL Gd-DTPA (Magnevist) or GCDs at a Gd concentration of 0.01 M [61].

TEM images (Figure 3(A)) revealed sub-round particles with a 15 ± 5 nm diameter, consistent with DLS measurements (10-20 nm). HRTEM (Figure 3(B)) indicated a lattice spacing of 0.279 nm, corresponding to the (100) facet of graphite, suggesting the graphite structure was preserved during synthesis [62-66].

XPS and FTIR analyses showed that GCDs consisted of 58.52% C, 25.34% O, and 15.3% N. Elemental mapping confirmed uniform Gd distribution, while Gd 4d XPS spectra showed peaks at 141 eV and 147 eV, indicative of Gd3+ oxidation state [63]. C 1s spectra highlighted the graphitic sp2 carbon structure with a dominant CC peak at 284.5 eV. FTIR spectra showed bands at 1398.3 cm^{-1} (C-H bending) and 2981.8 cm^{-1} (C-H stretching), while Kaiser tests confirmed 2.6% (w/w) free amines. Functional groups such as O-H, C=O, and C-O were also identified [64-72].

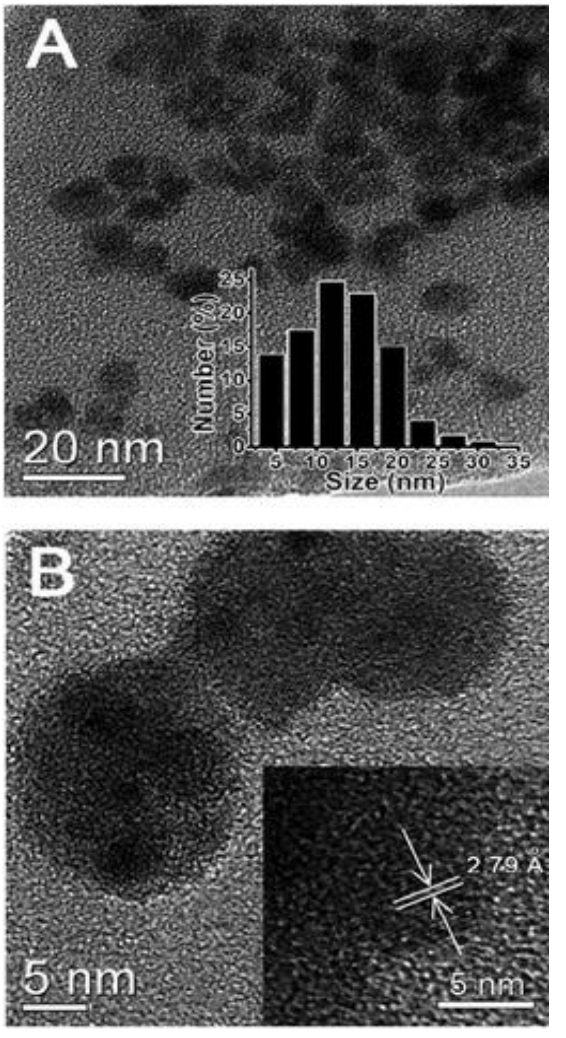

Fig. 3. (A) TEM image of GCDs, Inset: the histogram of GCD size distribution obtained from DLS measurements. (B) HRTEM image of GCDs. Inset: the HRTEM image of GCDs with lattice spacing. Reprinted with permission from ref. [66], Pan, Y., Yang, J., Fang, Y., Zheng, J., Song, R. and Yi, C., 2017. One-pot synthesis of gadolinium-doped carbon quantum dots for high-performance multimodal bioimaging. *Journal of Materials Chemistry B*, *5*(1), pp.92-101.Copyright © Royal Society of Chemistry.

Gd-CDs were synthesized via a one-step solvent-free method. A solution of Gd-DTPA (100 mL) and 0.1 mmol L-arginine was heated at 200°C for 10.5 hours and freeze-dried. Quantum yield (QY) was determined using quinine sulfate in H_2SO_4, with photoluminescence spectra recorded at 360 nm excitation [66, 73-78]. TEM and DLS confirmed spherical Gd-CDs with an average diameter of 5.38 nm. FTIR spectra identified characteristic absorption bands such as O-H/N-H stretching (3363 cm^{-1}), C=O stretching (1601 cm^{-1}), and C-N stretching (1317 cm^{-1}). XPS spectra revealed major contributions from C, N, and O, with Gd^{3+} peaks at 1187 and 1219 eV [67].

Human ovarian cancer cells (HO-8910), renal cancer cells (786-O), and tubular epithelial cells (HK-2) were cultured in RPMI 1640 or DMEM media supplemented with 10% FBS and 1% penicillin-streptomycin at 37°C in a 5% CO_2 atmosphere [68]. The MTT assay evaluated the cytotoxicity of Gd-CDs. Both 786-O and HK-2 cells were exposed to various concentrations of Gd-CDs, and cell viability was measured using a microplate reader [69]. Bio-TEM revealed intracellular localization of Gd-CDs in 786-O cells at 2 and 4 hours of exposure. Samples were fixed, dehydrated, and sectioned for imaging [70]. Fluorescence labeling was performed on 786-O and HO-8910 cells. Cells were incubated with Gd-CDs, fixed with paraformaldehyde, and imaged using a confocal laser scanning microscope (CLSM) [71].

Gd-CDs and Gd-DTPA were diluted to Gd concentrations of 0.46-3.18 mM. T1-weighted images were acquired using Spin-Echo sequences with specific parameters [72]. Cells incubated with Gd-CDs or Gd-DTPA were re-suspended in agarose gel for MR imaging, where Gd-CDs demonstrated superior imaging contrast [73]. Kunming mice received PBS, Gd-DTPA, or Gd-CDs (14.5 mg/kg Gd concentration) via intravenous injection. T1-weighted MR images were obtained at different time points post-injection, using optimized parameters [75]. Serum biochemistry tests were conducted on mice treated with PBS, Gd-DTPA, or Gd-CDs. Blood samples were collected on days 1, 7, and 21 to evaluate toxicity markers [76]. Gd-CDs exhibited high monodispersity and a narrow size distribution. ICP-MS analysis confirmed a 12% (wt%) Gd content, suitable for MR imaging. FTIR and XPS analyses verified the presence of functional groups critical for stability and imaging efficiency. Gd-CDs outperformed Gd-DTPA in in vitro and in vivo imaging, delivering enhanced contrast in MR images [77]. The structural features and imaging performance highlight the potential of Gd-CDs for biomedical applications (Figure 4) [78].

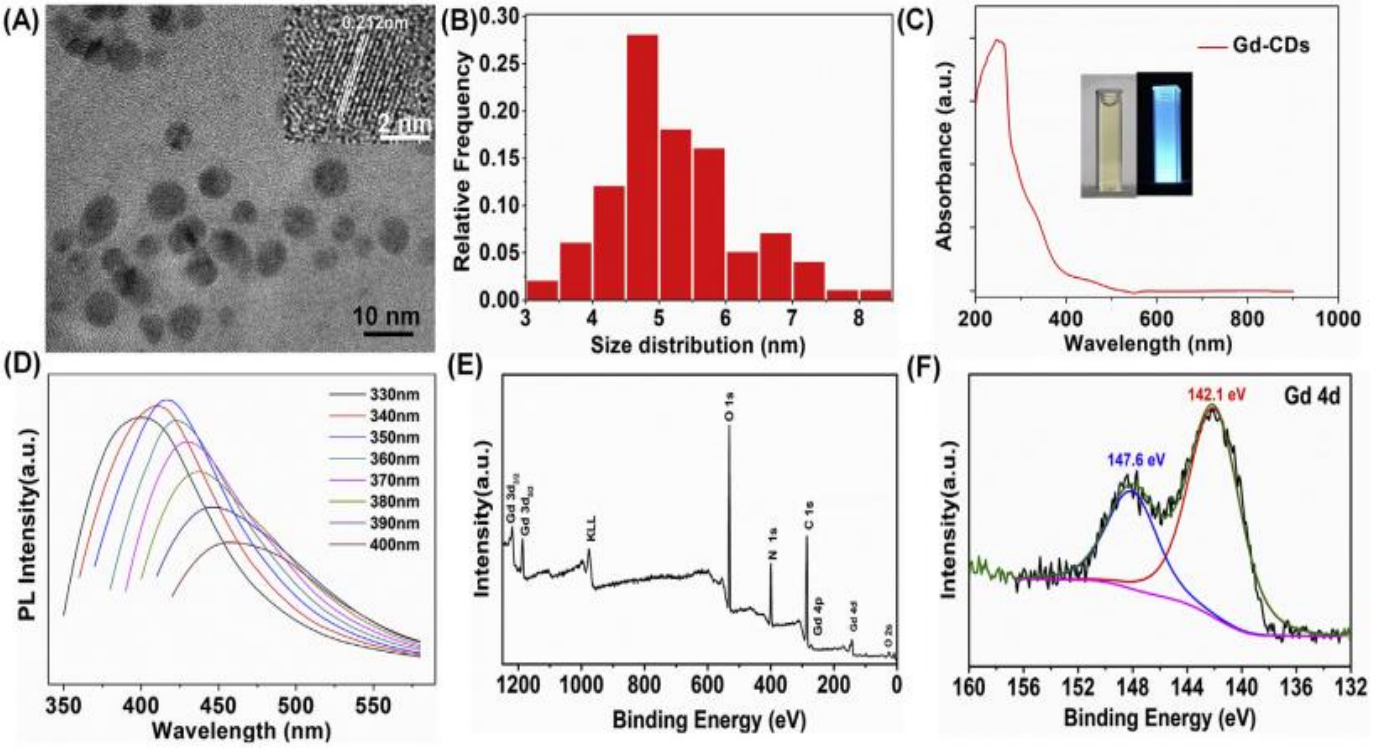

Fig. 4. Characterizations of Gd-CDs: (A) TEM images of Gd-CDs, (inset, high resolution TEM images), (B) Size distributions of Gd-CDs; (B) UVevisible absorption of the Gd-CDs, inset pictures show the Gd-CDs under natural light and UV light, (D) The PL emission of the Gd-CDs with excitation wavelengths from 330 nm to 400 nm in 10 nm increments. XPS spectrum of Gd-CDs: (E) Full-scan spectrum, (F) Gd4d spectrum. Reprinted with permission from ref. [78], Wang, L., Zhou, W., Yang, D., Zhe, H., Mei, S., Yuan, J., Zhang, W., Li, H., Fan, H., Xie, F. and Guo, R., 2021. Gadolinium-doped carbon dots with high-performance in dual-modal molecular imaging. *Analytical Methods*, *13*(21), pp.2442-2449. Copyright © Royal Society of Chemistry.

4. DOPED C-DOTS FOR SENSING APPLICATIONS

Environmental pollution caused by heavy metals like lead (Pb^{2+}) and mercury (Hg^{2+}) has severe implications for human health and the ecosystem. Addressing this challenge, doped carbon dots (C-dots) have emerged as promising materials for detecting these hazardous ions in water [38]. Doped C-dots exhibit unique fluorescent properties, making them highly sensitive sensors for environmental monitoring. Researcher have developed ultrasensitive C-dots specifically designed for Hg^{2+} detection [80]. These C-dots demonstrated remarkable sensitivity, identifying Hg^{2+} in tap, lake, and river water with a detection limit as low as 1 femtomolar (fM). In another study, researchers reported a sensitive nanosensor using fluorescent nitrogen-doped C-dots with a detection limit of 0.23 μM. The extraordinary fluorescent properties of these C-dots arise from their unique optical characteristics, which facilitate the detection of trace amounts of Hg^{2+} ions in diverse water sources. C-dots have also shown efficacy in detecting Pb^{2+} ions. For instance, chocolate-based C-dots achieved a detection threshold of 12.7 nanomolar (nM). Researchers also synthesized nitrogen-doped C-dots using a microwave method, achieving a similar detection limit of 15 nM [81]. These sensors rely on fluorescence quenching mechanisms, which may involve nonradiative electron transfer from excited states to the electronic orbitals of Pb^{2+}. Additionally, the hydroxyl groups on the C-dot surfaces and chelation of Pb^{2+} contribute to fluorescence quenching, enhancing detection specificity. Beyond Hg^{2+} and Pb^{2+}, the fluorescent characteristics of C-dots enable the detection of various other metal ions, including Ag^{+}, Cu^{2+}, Zn^{2+}, and Cr^{6+} [79]. However, the broad sensitivity of C-dots to multiple metal ions can reduce selectivity for specific hazardous ions. Surface modification of C-dots with tailored receptors can address this challenge, improving selectivity for target ions [80].

The fluorescent properties of C-dots have been exploited to detect organic molecules. For example, C-dots dispersed in dimethyl sulfoxide (DMSO) exhibited fluorescence quenching upon acetone addition, with a detection limit of up to $1:10^{-7}$ molar ratio (DMSO:acetone). Boron-doped C-dots have also demonstrated great potential in detecting glucose and hydrogen peroxide (H_2O_2) molecules. Shan and colleagues showed that charge transfer between boron and H_2O_2 enabled quantitative detection of H_2O_2 in the concentration range of 0.1 to 1.0 mM. Furthermore, cyclic voltammetry was employed to detect glucose over a range of 1–12 mM using nitrogen-doped C-dots [81].

Nitrogen-doped C-dots have been successfully used to detect a wide array of substances, including pyridine, dopamine, amoxicillin, micro-RNA, and catechol. They have also been applied in pH and temperature measurements. The shifting fluorescence properties of doped C-dots provide versatile sensing capabilities, but further research is required to fully understand the underlying mechanisms, including the precise localization of doped elements and their role in fluorescence sensing [82, 83].

Gadolinium contrast media are commonly used in magnetic resonance imaging (MRI) to enhance image clarity and quality. These contrast agents, often referred to as "dyes," play a critical role in improving diagnostic accuracy by highlighting specific tissues, abnormalities, or diseases. Gadolinium contrast media consist of gadolinium ions bound to chelating agents, which safeguard against gadolinium toxicity while preserving its contrast-enhancing properties [84, 85]. These substances enhance MRI images, making it easier for radiologists to detect tumors, blood vessel abnormalities, and inflammation. Approximately one in three MRI scans involves the use of gadolinium contrast medium to improve image clarity [84].

The decision to use gadolinium is based on the radiologist's assessment of the potential benefits. Before the scan, patients are thoroughly evaluated for medical history and potential contraindications, such as severe kidney disease, allergies, or pregnancy [86]. If deemed necessary, gadolinium is administered during the scan to improve diagnostic precision. In some cases, omitting gadolinium might necessitate a repeat scan, underscoring its importance in certain scenarios [88].

Gadolinium contrast media are generally safe, with over 90% of the injected dose excreted within 24 hours in individuals with healthy kidneys [89]. Temporary reactions, such as headaches, nausea, and localized lightheadedness, are the most common minor side effects. In rare cases, patients may experience mild skin rashes indicative of allergic reactions, which usually resolve within an hour [90]. Severe allergic reactions, such as anaphylaxis, occur in approximately 1 in 10,000 patients. These reactions are effectively managed with standard emergency treatments [91]. A rare but serious condition associated with gadolinium-based contrast agents is nephrogenic systemic fibrosis (NSF). This disease is characterized by skin thickening and internal organ damage, primarily in patients with severe kidney dysfunction. The risk of NSF has been minimized by using low-risk gadolinium preparations and carefully assessing patient suitability [92]. Recent findings indicate that approximately 1% of the injected gadolinium dose may be retained in tissues, particularly in bones and the brain. While no adverse effects have been conclusively linked to these small amounts, radiologists now carefully weigh the benefits and risks before recommending gadolinium contrast [93- 95].

Gadolinium-doped carbon quantum dots (Gd-doped CQDs) offer immense potential in bioimaging. By incorporating gadolinium ions, these CQDs gain enhanced magnetic properties, making them suitable for use as MRI contrast agents. This allows for improved visualization of tissues, cells, and biomarkers. Additionally, the strong fluorescence properties of Gd-doped CQDs enable their use as fluorescent probes for labeling and tracking biomolecules or pathogens in biological samples. Functionalizing their surfaces with targeted ligands enhances their specificity, facilitating precise imaging and detection [96].

Gd-doped CQDs are also effective in detecting metal ions in biological and environmental samples. The presence

of gadolinium ions enhances the fluorescence sensitivity, enabling accurate detection through fluorescence quenching or enhancement mechanisms. This makes them valuable for monitoring metal ion concentrations in biological fluids and tissues, as well as in environmental applications [97]. Functionalized Gd-doped CQDs serve as excellent platforms for detecting biomolecules such as proteins, enzymes, nucleic acids, and metabolites. When specific receptors or aptamers are attached to their surfaces, these CQDs can selectively bind target biomolecules, inducing changes in fluorescence properties that allow for sensitive detection [98].

The small size, biocompatibility, and surface functionalization capabilities of Gd-doped CQDs make them ideal vehicles for targeted drug delivery. They can encapsulate therapeutic agents and deliver them to specific tissues or cells, with real-time monitoring possible via MRI imaging due to their gadolinium content. This dual functionality enhances their utility in therapeutic applications [99]. Gd-doped CQDs exhibit exceptional optical and magnetic properties, making them versatile tools in biomedical applications. They are used in fluorescent labeling, bioimaging, targeted drug delivery, metal ion detection, and biosensing. Their biocompatibility and functionalization potential position them as promising candidates for future advancements in nanomedicine and environmental monitoring [100].

Despite their wide-ranging applications, several challenges remain in the field of doped C-dots. The mechanisms underlying fluorescence shifting, the precise localization of doped elements, and their specific roles in sensing applications are not fully understood. Further research should focus on the understanding the fluorescence mechanisms and quenching processes to optimize the sensitivity and specificity of doped C-dots. Developing tailored surface modifications to enhance selectivity for specific ions or biomolecules. Conducting comprehensive studies on the long-term safety and biocompatibility of doped C-dots, particularly in therapeutic applications. Exploring the potential of doped C-dots for large-scale environmental monitoring

5. FUTURE PERSPECTIVE

Gadolinium-doped carbon quantum dots (Gd-CQDs) hold tremendous potential for advancing bioimaging and biomedical applications. The continuous development of synthesis techniques and surface engineering will be instrumental in unlocking their full capabilities. Future research is expected to focus on the following key areas:

Optimization of Synthesis Techniques: To enhance the performance of Gd-CQDs, researchers will likely prioritize refining synthesis methods to achieve precise control over particle size, shape, and surface functionalization. Such control is crucial to improving the stability, fluorescence properties, and magnetic resonance imaging (MRI) contrast capabilities of Gd-CQDs. Additionally, efforts will be directed toward scalable, cost-effective, and environmentally friendly synthesis approaches to ensure sustainable production while minimizing cytotoxicity. Green synthesis methods, involving the use of natural or biodegradable precursors, could play a pivotal role in achieving these goals.

Improvement in Biocompatibility and Safety: As Gd-CQDs transition toward clinical applications, ensuring biocompatibility and minimizing potential toxicity will remain critical challenges. Future studies may investigate innovative surface modifications, such as functionalizing Gd-CQDs with biocompatible polymers or targeting ligands, to enhance their bioavailability and reduce adverse effects. Understanding the long-term biodistribution, degradation, and clearance pathways of Gd-CQDs in vivo will also be essential for ensuring patient safety.

Advances in Multi-Modal Imaging: The development of dual- and multi-modal imaging platforms represents a significant frontier for Gd-CQDs. While the combination of fluorescence imaging and MRI has demonstrated great promise, further integration with other imaging modalities, such as computed tomography (CT), positron emission tomography (PET), or photoacoustic imaging, could provide more comprehensive diagnostic tools. Such advancements would enable deep tissue imaging, high spatial resolution, and real-time monitoring of biological processes, paving the way for more precise and personalized medical diagnostics.

Targeted Imaging and Theranostics: Future research will likely explore the incorporation of specific targeting ligands, such as antibodies, peptides, or aptamers, onto Gd-CQDs. This functionalization will enable selective binding to disease biomarkers, facilitating targeted imaging of specific tissues or pathological conditions. Furthermore, the combination of imaging and therapeutic functions (theranostics) is an exciting area of development. Gd-CQDs could serve as platforms for delivering drugs, genes, or other therapeutic agents while simultaneously providing real-time imaging feedback on the treatment's efficacy.

Integration with Artificial Intelligence (AI) and Data Analysis: The adoption of AI and advanced data analysis tools in medical imaging could further enhance the utility of Gd-CQDs. Machine learning algorithms could process large datasets generated by multi-modal imaging systems, enabling automated image interpretation, improved diagnostic accuracy, and early detection of diseases.

Exploration of Novel Applications: Beyond bioimaging, Gd-CQDs could find applications in other fields, such as environmental monitoring, catalysis, and energy storage. For instance, their ability to detect metal ions and biomolecules could be extended to environmental sensing, while their unique optical and magnetic properties might be leveraged for developing next-generation materials for energy applications.

Regulatory Approval and Commercialization: Bridging the gap between laboratory research and clinical implementation will require meeting stringent regulatory standards. Future efforts will need to focus on conducting comprehensive preclinical and clinical studies to evaluate the safety, efficacy, and reproducibility of Gd-CQDs. Collaborations between academia, industry, and regulatory bodies will be essential to accelerate the translation of Gd-CQDs into commercially viable products.

Addressing Long-Term Concerns: Recent findings about the retention of gadolinium in tissues, such as the brain and bones, underscore the need for long-term studies to assess the potential health impacts of Gd-CQDs. Developing novel gadolinium chelates or exploring alternative doping strategies with reduced retention risks will be key areas of future research. By addressing these directions, Gd-CQDs could revolutionize the field of bioimaging and open new avenues in diagnostics and therapeutics. Their versatility, biocompatibility, and potential for multi-functional applications position them as a promising candidate for next-generation biomedical tools.

6. CONCLUSION

The development of gadolinium-doped carbon quantum dots (Gd-CQDs) marks a pivotal advancement in the field of dual-modal bioimaging, combining the strengths of magnetic resonance imaging (MRI) and fluorescence imaging. Gd-CQDs offer a range of advantages, including high biocompatibility, tunable optical properties, and exceptional photostability, making them ideal candidates for non-invasive imaging techniques. Unlike conventional gadolinium-based MRI contrast agents, which pose risks of retention in vital organs, Gd-CQDs provide a safer and more effective alternative through their unique structural and functional properties. The synthesis of Gd-CQDs has evolved significantly, with the one-pot synthesis method emerging as a reliable and scalable approach. This method ensures better control over particle size, surface chemistry, and functionalization, resulting in enhanced fluorescence and magnetic properties. Future advancements in synthesis will likely focus on incorporating environmentally friendly precursors, minimizing cytotoxicity, and improving scalability for clinical applications. Moreover, the integration of Gd-CQDs into dual-modal imaging systems presents exciting opportunities for real-time biological monitoring, deep tissue penetration, and high-resolution imaging. Further exploration of Gd-CQDs could expand their utility beyond imaging to include targeted drug delivery and precision therapeutics. The incorporation of additional imaging modalities, such as computed tomography (CT) or positron emission tomography (PET), could pave the way for multi-modal imaging platforms capable of providing comprehensive diagnostic insights. However, challenges remain, including optimizing particle stability, understanding long-term biocompatibility, and addressing regulatory hurdles for clinical translation. Gd-CQDs represent a promising frontier in medical diagnostics and therapeutics, offering unparalleled versatility and functionality. Continued innovation in synthesis techniques, combined with advancements in nanotechnology and molecular biology, will drive their adoption in clinical settings, ultimately transforming the landscape of modern medicine.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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