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The advanced role of carbon quantum dots in nanomedical applications

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ABSTRACT

Carbon quantum dots (CQDs) have emerged as a potential material in the diverse fields of biomedical applications due to their numerous advantageous properties including fluorescence, water solubility, biocompatibility, low toxicity, small size and ease of modification, inexpensive scale-up production, and versatile conjugation with other nanoparticles. Thus, CQDs became a preferable choice in various biomedical applications such as nanocarriers for drugs, therapeutic genes, photosensitizers, and antibacterial molecules. Further, their potentials have also been verified in multifunctional diagnostic platforms, cellular and bacterial bio-imaging, development of theranostics nanomedicine, etc. This review provides a concise insight into the progress and evolution in the field of CQD research with respect to methods/materials available in bio-imaging, theranostics, cancer/gene therapy, diagnostics, etc. Further, our discussion is extended to explore the role of CQDs in nanomedicine which is considered to be the future of biomedicine. This study will thus help biomedical researchers in tapping the potential of CQDs to overcome various existing technological challenges.

1. Introduction

Carbon quantum dots (CQDs), a type of carbon-based fluorescent nanomaterial, have recently attracted great attention due to their advantages like tunable opto/chemical properties, low or non-toxicity, and environmental compatibility (Huang et al., 2014; Long et al., 2012; Sun et al., 2016; Zhu et al., 2013). The potential utility of CQDs has been recognized from a pool of advanced functional materials like graphene, carbon nanotubes, and metal-organic frameworks (Kempahanumakkagari et al., 2018; Mehta et al., 2016). Becasue of the excellent bio-compatibility and photo-stability, CQDs can be considered as an excellent substitute to replace toxic semiconductor quantum dots or unstable organic fluorophores (for biological applications) (Li et al., 2010b; Wang et al., 2011; Yang et al., 2009). CQDs were discovered accidentally during the processing of single-walled carbon nanotubes (SWCNT) (Xu et al., 2004). Since then, the fluorescence properties of CQDs were explored extensively so that they have become a completely new class of smallest viable fluorescent biocompatible nanomaterials. These small carbonaceous materials received their scientific designation as CQDs in 2006 by those who were working on their surface passivation to enhance the fluorescence (Sun et al., 2006). Thereafter, a number of simple synthesis methods for CQDs have been proposed such as laser ablation, pyrolysis, electrochemical synthesis, supported synthesis, acid oxidation, microwave-assisted synthesis, and hydrothermal synthesis (Dong et al., 2012; Ming et al., 2012; Zong et al., 2011; Li et al., 2015; Wang et al., 2013a; Liang et al., 2013). Recently, green CQDs, synthesized using organic compounds without chemical exposure, has also gained a lot of attention due to the wide availability of starting materials, high quantum yield (QY), and self-passivation (Liu et al., 2012b).

As CQDs displayed stable and tunable optical fluorescence, photostability, and compatibility, they are also capable of functioning as electron donors and acceptors (De and Karak, 2013; Liu et al., 2012c; Stengl et al., 2013; Zhang et al., 2010). The properties of CQDs have been exploited for their use as fluorescent nanoprobes for bio-imaging (Cao et al., 2007; da Silva and Gonçalves, 2011; Hola et al., 2014a, 2014b; Kong et al., 2014; Liu et al., 2015a; Luo et al., 2013; Song et al., 2014; Yang et al., 2009; Zheng et al., 2015b), gene/drug delivery agents (Gong et al., 2016; Liu et al., 2012b; Pierrat et al., 2015; Wang and Hu, 2014), and antibacterial agents (Meziani et al., 2016). Further, CQDs have been sought in many other applications ranging from light-emitting devices to catalysts (Zhang et al., 2013; Liu et al., 2015b). As such, their applications in clinical settings are expected to expand further in the near future (Huang et al., 2013).

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Table 1
List of major reviews on carbon dots and their focal points.

Order	Title	Focal points	Ref
1	Graphene quantum dots in biomedical applications: Recent advances and future challenges	• The role of graphene quantum dots in biomedical applications	(Chen et al., 2017)
2	A review of carbon dots in biological applications	• Biological applications (i.e., biosensing and bioimaging)	(Wang and Qiu 2016)
3	Shining carbon dots: synthesis and biomedical and optoelectronic applications	• Synthesis • Properties and photoluminescence mechanism • Electronic, biochemical and biomedical applications (e.g., stem cell imaging, cell nucleus imaging, in vivo imaging, fluorescence imaging, cancer therapy)	(Yuan et al., 2016)
4.	Glowing graphene quantum dots and carbon dots: properties, syntheses, and biological applications	• Brief overview on CQDs • Focused on biomedical applications of graphene quantum dots	(Zheng et al., 2015b)
5.	Synthesis, properties and biomedical applications of carbon-based quantum dots: An updated review	• Characteristics and synthesis methods of CQDs • Bio-applications (bio imaging, cellular imaging, bio sensing, drug/gene delivery)	(Namdari et al., 2017)
6.	Pharmaceutical and biomedical applications of quantum dots	• History of quantum dots • Physicochemical properties of quantum dots • Pharmacology of quantum dots	(Bajwa et al., 2016)
7.	Sustainable carbon-dots: recent advances in green carbon dots for sensing and bioimaging	• Synthesis and properties of green CQDs • Sensing and bio imaging applications	(Sharma et al., 2017)
8.	Fluorescent carbon dots for bioimaging and biosensing applications	• Overview of synthesis methods • Fluorescent properties • Biosensing and bioimaging applications • Design of a carbon dot fluorescent ratiometricbiosensing platform for the detection of enzymatic activity, substrate and inhibitor concentrations related to the production or consumption of H_2O_2	(Shi et al., 2014)
9.	CQDs: recent progress on synthesis, surface modification and applications	• Synthesis and surface modification methods • Pristine and modified CQD optical properties • Bioimaging, biosensing and drug delivery applications	(Farshbaf et al., 2018)
10.	Carbon dots: biomacromolecule interactions, bioimaging and nanomedicine	• Discusses CQD interactions with biomolecules (protein, nucleic acids, and lipids) • Bioimaging and drug delivery aspects were covered	(Peng et al., 2017)
11.	Carbon Nanomaterials for Biological Imaging and Nanomedicinal Therapy	• This review talk about all the carbon nanomaterial fullerens, carbon nanotubes, graphene, carbon dots and nanodiamonds but more specifically it discusses the application of carbon nanotubes.	(Hong et al., 2015)

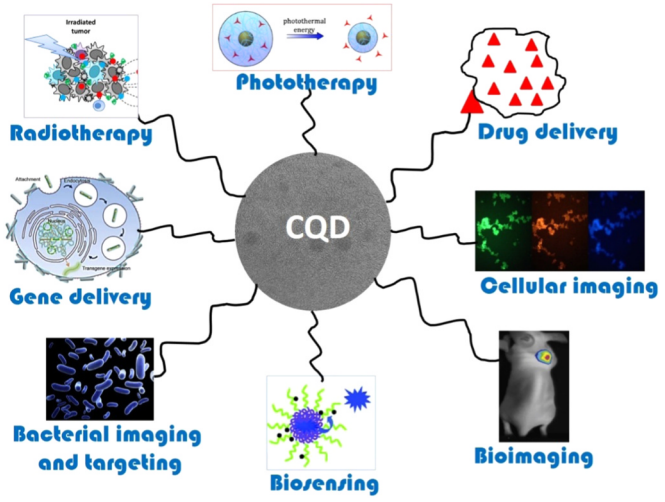

Fig. 1. Applications of CQDs in nanomedicine.

The present review was organized to help improve our understanding and awareness of the increased contribution of CQDs in the nanomedicine sector, particularly in gene therapy, drug delivery, photo thermal & radio therapy, diagnosis, bio sensing, bio imaging, and bactericidal activity. Although efforts have been made to describe the biomedical applications of CQDs, relatively little has been discussed with respect to CQD applications in nanomedicine. Table 1 summarizes a list of the related reviews on carbon dots and associated materials. In most of the previous review works, authors commonly focused on the significance of the synthesis, surface modification, and general properties of these advanced materials. Nonetheless, a detailed review on the biomedical applications is still lacking, especially with respect to nanomedical fields as depicted in Fig. 1. As such, this review is expected to offer better insights into the potential utility of CQDs in nanomedical fields along with their opportunities and challenges.

2. Synthesis and modification of CQDs for biomedical applications

2.1. Synthesis of CQDs

The selection of a synthesis method and starting material plays an important role in the properties of CQDs and associated applications. Hence, the production of CQDs should be optimized both during and after the synthesis (Lim et al., 2015). Since their accidental discovery, diverse options for CQD synthesis have been proposed including physical, chemical, or electrochemical methods (Wang and Zhou, 2014). Synthesis methods of CQD can broadly be divided into “top-down” and “bottom-up” approaches. These methods are differentiated on the basis of carbon source used for the synthesis of CQDs. The basic building block (i.e., a carbon source) is taken up for bottom-up synthesis of CQDs. Then, it undergoes carbonization, condensation, and polymerization processes resulting in fluorescent CQDs under optimized synthesis conditions (Zong et al., 2011). In the case of a top-down approach, a bulk carbon source (such as graphite rods, candle shoots, and fullerenes) is broken down into smaller units of size less than 10 nm with fluorescent characteristics (Havrdova et al., 2016; Juzenas et al., 2013; Lu et al., 2011). Notable example of top down approach includes synthesis of small size (2–3 nm) carbon quantum dots using chemical and mechanical treatment of C60 fullerenes (Chua et al., 2015; Jeong et al., 2014). “Top-down” approach mainly involves harsh chemical methods to break large molecules such as chemical ablation, electrochemical carbonization, and laser ablation, while “bottom-up” approach is based on greener method including microwave irradiation and hydrothermal/solvothermal treatment. In comparison to top-down approaches involving harsh chemical treatment and complex instrumentation, the simpler and greener bottom-up approaches for CQDs synthesis are being opted. The hydrothermal/solvothermal methods are

Table 2
Methods of synthesizing CQDs.

Order No.	Method of synthesis & precursors	Application	Model	Cytotoxicity	Ref
A. Bottom-Up Approach					
1.	Hydrothermal treatment of citric acid, hyaluronic acid and ethylenediamine	Targeted drug delivery to cancer cell	Bio-nanoplatform (CQD-HA-SiO4-DOX) Cancer cell line	Low cytotoxicity	(Mishra et al., 2018)
2.	Pyrolysis of konjac flour	Mitochondria targeting, long time cell imaging	Bionanoplatform (Fe_3O_4@$mSiO_2$ − TPP/CDs)	Low cytotoxicity	(Teng et al., 2014)
3.	Microwave synthesis method using acrylic acid and ethylene diamine followed by functionalization with glycidyl methacrylate	Targeted cancer drug delivery	Nanogel (copolymerized with zwitterionic amino acid ornithine methacrylamide)	Low cytotoxicity	(Li et al., 2016)
4.	Thermal combustion of rice straw	Detection and counting of bacteria	Bacterial imaging and identification	-	(Mandal and Parvin 2011)
5.	Pyrolysis of aminoethylethanolamine and glycerol followed by quaternization with BS-12	Differential bacterial recognition against gram positive bacteria	Bacterial imaging and identification	Low cytotoxicity	(Yang et al., 2016)
6.	Hydrothermal carbonization of *lactobacillus plantarum*	Anti-biofilm	Bactericidal	Low cytotoxicity	(Lin et al., 2018b)
7.	Hydrothermal treatment of bacterial DNA	Transformation of bacteria	Bacteria, human cell line	No cytotoxicity	(Ding et al., 2015)
8.	Thermolysis of d-glucose and l-aspartic acid	Targeting brain tumor, bioimaging	Glioma (brain cancer)	Low cytotoxicity	(Zheng et al., 2015a)
9.	CQD-RhB-silica CQDs synthesized by thermal decomposition of N-(aminoethyl)-g-aminopropylmethoxysilane, conjugated with rhodamine B on silica	Biosensing and diagnosis (Cu^{2+})	Mouse	Low cytotoxicity	(Liu et al., 2014a)
10.	CQD-TPP: CQD were synthesized from decomposition of o-phenylenediamine	Mitochondria targeting for diagnosis and therapeutics	Living cells	-	(Wu et al., 2017)
11.	mPEG-OAL-DOX/CQD: pyrolysis of citric acid, cross-linked with PEGylated oxidized alginate (mPEG-OAL)	Theranostic nanoparticle for targeted drug delivery to cancer cells	In-vitro cell model	Low cytotoxicity	(Jia et al., 2016)
12.	CQDs Pt(IV)@PEG-(PAH/DMMA): Thermal pyrolysis of citric acid, conjugated with drug cisplatin and electrostatically conjugated with PEG-(PAH/DMMA)	Targeted drug delivery to tumor	In-vitro and in-vivo	Low cytotoxicity	(Feng et al., 2016c)
13.	Hydrothermal treatment of chitosan, ethylenediamine and mercaptosuccinic acid	Mitochondria targeting and imaging	In-vitro	Less cytotoxic	(Hua et al., 2017)
14.	Hydrothermal treatment of citric acid monohydrate	Glioma targeting and bioimaging	Both in-vitro and in-vivo	Less toxic	(Gao et al., 2018b)
15.	MSN-SS-CD_{HA}-DOX: Thermal decomposition of citric acid and conjugated with HA, which were further conjugated with mesoporous silica nanoparticles enclosing the anti-tumor drug, doxorubicin	Multifunctional nanosystem (targeted and controlled drug delivery along with bioimaging)	In vivo mouse model	Less toxic	(Wang et al., 2017b)
16.	MSN-SS-CD_{PAA}-DOX: Hydrothermal polymerization method using poly-acrylic acid	Multifunctional nanosystem (targeted and controlled drug delivery along with bioimaging)	In vitro cancer cell line	Less toxic	(Jiao et al., 2016)
17.	CQD-PEI: Oxidation and hydrothermal reaction of polyethleneimine	Gene transfection	Cell line	-	(Hu et al., 2014a)
18.	CQD-PEI-BB: Oxidation of glucose and PEI followed by quaternized with benzyl bromide	Gene transfection and antibacterial	Cell line	-	(Dou et al., 2015)
19.	FA-Gd@CQD: Green CQD synthesized from waste crab shell doped with Gd^{+} and conjugated with folic acid	Targeted drug delivery	Cell line	Low cytotoxicity	(Yao et al., 2017)
B. Top-down Approach					
1.	CQD synthesized from ethanolamine by chemical treatment	Biosensing and diagnosis (H_2S)	CQD-organic dye conjugates human cell lines	-	(Yu et al., 2013)
2.	CQD-ssDNA: Chemical oxidation of candle soot	SNP polymorphism detection (disease diagnosis)	In vitro	-	(Li et al., 2011a, 2011b)
3.	Cl-CQD: CQD synthesized from MWCNT were functionalized with –COCl and conjugated with anti-desmin	Cancer diagnosis	Patient blood samples	-	(Li et al., 2017)
4.	Arc discharge of graphite rod yielded nanopowder, refluxed in nitric acid followed by dialysis	Phototherapy	Human prostate cancer cell lines	Cytotoxic to cancer cells	(Juzenas et al., 2013)
5.	Nitric acid oxidation of candle soot	Phototherapy	Cell line	Highly cytotoxic to cancer cells	(Havrdova et al., 2016)
6.	CQD-PEG-Ag: Acidic oxidation of carbon nanotube and graphite	Radiotherapy	Cell lines	Cytotoxic to cancer cells	(Tao et al., 2012)

more popular, as they are environment-friendly with high quantum yield. Furthermore, these methods are faster, easily scalable, and cost effective. Nonetheless, they also suffer from some demerits (e.g., poor control over the size of synthesized CQDs). Note that the size of CQDs can be managed by post treatments such as sonication, filtration, dialysis, centrifugation, column chromatography, and gel-electrophoresis (Wang and Hu, 2014). Table 2 summarizes the methods used for the synthesis of CQDs utilized in biomedical applications.

2.2. Surface modification of CQDs

Surface functionalization/passivation play an important role in absorption and photoluminescence properties of the carbon dots (Ren et al., 2019; Zheng et al., 2015b). Further functionalization of CQDs plays an important role in other properties by altering their ability to interact with other organic molecules, ions, drug and living organisms. Functionalization status of CQD also depends on starting material and method used for the synthesis, which affect their functional properties such as bio imaging and bio-sensing (Dang et al., 2018; Hou et al., 2015; Wang et al., 2015). Thus, surface passivation of CQDs is one of the most important options to consider with respect to their biological applications (e.g., in terms of cytotoxicity, internalization, and cell localization) (Liu et al., 2010; Zhao et al., 2011).

Different kinds of macromolecules are used for surface passivation of the CQD that may be neutral or charged (positively or negatively). Neutral macromolecules include polyethylene glycol (PEG). PEG is biocompatible and biodegradable and prevents the non-specific binding of proteins to avoid an immune response (Alcantar et al., 2000; Bjugstad et al., 2010; Nie et al., 2014). Cationic macromolecules such as polyethyleneimine (PEI) provide a positive charge to CQDs, which helps them to bind negatively charged proteins in cell membranes. Thus, positively charged CQDs affect cell membrane integrity, which helps in the transfection of cells (Iida et al., 2007; Moghimi et al., 2005). Also, positively charged functional groups such as PEI are useful in the binding of DNA and RNA to CQDs (Kircheis et al., 2001; Pierrat et al., 2015). Additionally, positive charges will also help in overcoming endosomal degradation through destabilization of the endosomal membrane. Further PEI-coated CQDs have thermo and pH-regulated properties that are useful in developing stimuli-based drug release (Yin et al., 2013).

The functionalization procedures leading to overall neutral or negative charges on the surfaces of the CQDs are advantageous for therapeutic applications. This is because neutral groups can escape from immune system clearance, while negatively charged surface groups can avoid adsorption on proteins due to electrostatic repulsion, which ensures their extended circulation in blood (Bae and Park, 2011; Gratton et al., 2008; Knop et al., 2010; Lee et al., 2008a). However, the overall quantities of neutral or negative charges on CQD surfaces also affect their internalization efficiency in cancerous cells. This was observed as a subsequent decrease in their therapeutic activity (Huang et al., 2013; Xiao et al., 2011). In contrast, the positive surface charge facilitates cellular internalization due to its electrostatic interactions with the negative cell membrane charge, which is advantageous (Lee et al., 2008b; Mintzer and Simanek, 2009). In addition, positively charged CQDs can also escape endosomal degradation inside the cell via a “proton sponge” effect (Fischer et al., 2003; Ge and Liu, 2013; Jin et al., 2013; Kou et al., 2013; Liu et al., 2013a). Therefore, the functionalization procedure plays a vital role in the fate of CQDs in biomedical applications.

2.3. Doping of CQDs

The doping of foreign elements such as nitrogen and sulfur atoms can facilitate the formation of new kinds of surface states in CQDs to obtain high photostability, surface passivation, and good QY. Considering these facts, N and S doped CQDs were synthesized using L-cysteine and citric acid as primary precursors (Dong et al., 2013). Thus, the obtained pristine CQDs exhibited a high QY and excellent fluorescence properties. One step synthesis approaches have been developed for nitrogen doped CQDs (N-CQDs) using different nitrogen and carbon rich chemical precursors. The doping of nitrogen during synthesis enhanced the fluorescence intensity as well as QY of the resulting N-CQDs. A facile one step hydrothermal synthesis method was introduced for N-CQDs, which were applied for live cell imaging in light of their low toxicity and high QY (22% in ethanol) (Teng et al., 2014). Further, NCQDs were excellent bio-imaging agents over CQDs due to their high resistance to photo bleaching, enhanced emission efficiency, and amphoteric properties (Qian et al., 2014). N-CQDs synthesis from chemical cleavage of graphitic phase polymeric carbon nitride (GPPCN) had very high quantum yield (46%) and excellent Fe^{3+} sensing capabilities (Zhao et al., 2015). Recently, N and S doped CQD were synthesized from organic material such as caffeine and urea by solid state synthesis to impart high quantum yield and flourscence properties along with high affinity for silver (Dang et al., 2018).

2.4. Combinations/composites of CQDs with other nanoparticles

CQDs have been conjugated with other nanoparticles such as silica nanoparticles to increase the selectivity and specificity for imaging during drug delivery. Conjugation of different nanoparticles will facilitate the build-up of a biocompatible multifunctional nanosystem that can help integrate different functions of cancer treatment (such as imaging and drug delivery) into a single system, referred to as a bio-nanoplatform (Kateb et al., 2011; Topete et al., 2014). A similar platform (Fe_3O_4@$mSiO_2$ − TPP/CQDs) was also built based upon konjac flour derived CQDs conjugated with triphenylphosphonium (TPP) modified mesosilica magnetite (Fe_3O_4@$mSiO_2$) nanoparticles (Zhang et al., 2015). The developed novel platform was then studied for mitochondrial targeting, cell imaging, and magnetic field enhanced cellular uptake. This platform had lower toxicity and apoptosis rates in human cell lines (A549, CHO, HeLa, SH SY5Y, HFF, and HMEC-1). This has been further explained by the supporting role of TPP, which included: (a) cellular uptake of conjugate (Fe_3O_4@$mSiO_2$ − TPP/CQDs), (b) endosomal/lysosomal escape of the conjugate to prevent its degradation, (c) its targeted localization in mitochondria, and (d) its magnetic field induced cellular uptake in human cell lines (A549 and HFF). In contrast, CQDs imparted bright fluorescence to the platform for intracellular bio-imaging. Likewise, similar hybrid bio-nanoplatforms were reported for efficient cellular uptake, mitochondrial targeting, and bioimaging (Zhang et al., 2015). In another study, the CQD-HA (CQD-hyaluronic acid) was conjugated with mesoporous silica nanoparticles to facilitate targeted delivery of the drug doxorubicin. The potential of the developed platform was demonstrated for receptor-targeted and response stimulated controlled drug release in tumor cells and for real-time bio-imaging applications (Wang et al., 2017a).

Biological material has also been interfaced with CQDs to build a multifunctional drug delivery nanosystem. In such an attempt, a newly developed zwitterionic amino acid ornithine methacrylamide (OrnAA) was co-polymerized with CQD (derived from acrylic acid and ethylene diamine precursor based on a microwave synthesis method followed by functionalization with glycidyl methacrylate) to form a nanogel with enhanced stability and fluorescence properties (Li et al., 2016). Thus, the resulting nanogel was conjugated with folic acid. The FA-CQD-nanogel was then demonstrated for its capacity in targeted delivery to folate receptors expressing cancerous cells. The targeted delivery both helped lower the cytotoxicity to normal cells and enabled targeted imaging during therapy (Li et al., 2016).

3. Cytotoxicity of CQDs

Cytotoxicity is the major issue in the development of drugs and therapeutics. If the drug affects normal tissue in addition to diseased

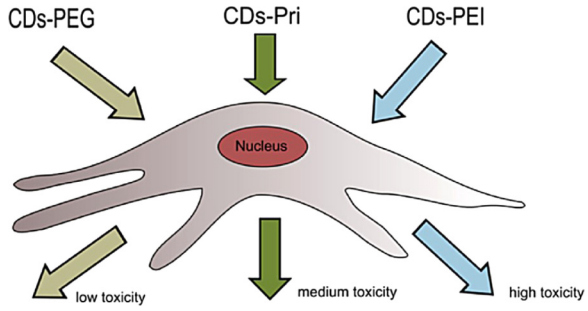

Fig. 2. Cytotoxicity of CQDs with different surface functionalities.

tissue, it can cause severe side effects. Thus, many attempts have been made for targeted therapy using vehicles for drugs such as nanoparticles. Quantum dots are one of these alternatives, and they also have photoluminescence, which is also advantageous for intracellular imaging. However, quantum dots may have serious cytotoxic issues. CQDs have advantages over the conventional quantum dots in that the former is less toxic and more biocompatible. CQDs thus have been widely studied for cytotoxicity in different cell lines and across different concentration levels with or without surface passivation. They have shown very low cytotoxicity and easy penetration into cells (Hola et al., 2014a, 2014b; Li et al., 2012; Ray et al., 2009). To learn more about CQD cytotoxicity, some studies have been conducted in mice to evaluate in *vivo* toxicity and immune response (Gao et al., 2013; Wang et al., 2013b). For example, an increase in Th1 and Tc lymphocytes was observed following an injection with a high dose of CQDs (Gao et al., 2013).

The carbon cores of CQDs are not toxic. Nonetheless, their cytotoxicity depends on the nature and charge of the functional groups (Wang et al., 2011). Neutral functional groups (e.g., polyethylene glycol, CQD-PEG) have shown the best results and are the least toxic (Havrdova et al., 2016; Ju et al., 2013; Wang et al., 2013b), as shown in Fig. 2. Negatively charged functional groups, i.e., Pristine, CD-Pri, are reported to cause cell cycle arrest, stimulated proliferation, and can induce oxidative stress. In contrast, positively charged functional groups (polyethylene imine, CQD-PEI) are reported to cause cell cycle arrest at the G0 phase (Havrdova et al., 2016). However, these toxic effects of CQDs were observed at high concentrations ($\geq$ 50 μg/ml), but toxicity to cells was not observed at lower concentrations ($\leq$ 25 μg/ml). Earlier reports have shown that nanoparticles affect cellular morphology in a reactive oxygen species (ROS) dependent manner (Buyukhatipoglu and Clyne, 2011; Magrez et al., 2006; Soenen et al., 2014). Higher ROS can be harmful because it can cause cell death, unlimited proliferation, and cancer (or many other diseases) (Buyukhatipoglu and Clyne, 2011; Ju et al., 2013; Liu et al., 2013b; Verbon et al., 2012; Wells et al., 2009). In addition, animal studies have shown that there were no toxic effects of PEGylated CQD in vivo on mice at a dose of 8–40 mg CQD/kg mass of the mouse supplied intravenously (up to 28 days). CQDs concentrated in the liver and spleen, although they did not affect the functions of these organs. Also, studies of all physiological parameters were similar between the control and different doses of CQDs at time points higher than that for most in-vivo imaging studies (Yang et al., 2009). Promising results have been observed both in vitro and in vivo regarding cytotoxicity (Hola et al., 2014a, 2014b; Yang et al., 2009). Even so, there is still a strong need to characterize the optimal passivating agent and concentration of CQDs in cell cultures and animal models, especially regarding the long-term effects, before going to human studies.

4. Biomedical applications of CQDs: imaging and sensing

4.1. CQDs in bacterial imaging and bactericidal applications

The rapid diagnosis of bacterial infection is vital for its clinical treatment due to their devastating health effects (Gao et al., 2014; Levy and Marshall, 2004). Additionally, the quest for effective bactericidal agents has been a clinical requirement to curb bacterial infection and existing drug/antibiotic resistance (Bao et al., 2011; Fernandes 2006; Fischbach and Walsh, 2009; Wang et al., 2016b). Therefore, the coupling of existing efficient bactericidal molecules (such as quaternary ammonium compounds (QAC) onto nanoparticles (NPs)) are of primary interest in the quest for drug delivery systems for antibacterial related applications (Liu et al., 2014a; Tang et al., 2013; Thamphiwatana et al., 2014; Tian et al., 2014; Wang et al., 2015; Wang and Qiu, 2016; Zhang et al., 2016; Zhu et al., 2011).

Nanoparticles were demonstrated to have great potential in combating bacterial infection. For example, nanoparticles conjugated with a drug by covalent (Gu et al., 2003) or non-covalent interactions exhibited enhanced antibacterial activity (Ahangari et al., 2013). Further, such conjugation helped in reducing the minimum inhibitory concentration (MIC) relative to un-conjugated (free) drug counterparts (Gu et al., 2003; Li et al., 2010a). However, as these nanoparticles do not have fluorescent properties, they are not capable of providing detection and inhibition at the same time. On the other hand, CQDs have a unique excitation-dependent fluorescence emission property, mainly in the blue or green region. Some functional CQDs have also been synthesized with a multicolor fluorescence emission property (Bao et al., 2015; Nie et al., 2014). CQDs prepared from rice straw (thermal combustion), showed specific and selective interactions with receptors on bacterial cells. As such, these CQDs were used for rapid detection and counting of bacterial cells in sewage water using fluorescence microscopy (Mandal and Parvin, 2011).

Over the last few years, extensive research efforts have been put towards the design of multifunctional CQDs for simultaneous imaging, classification, and killing of bacterial cells. Along these lines, Yang and co-workers (Yang et al., 2016) have developed quaternized CQDs (CQDs- lauryl betaine (BS-12, a quaternary ammonium compound) conjugate; it is also abbreviated as CQDs-C12). The obtained conjugates demonstrated enhanced clinical applications toward imaging and cellular differentiation due to their lower cytotoxicity (Yang et al., 2016) (Fig. 3). Cell imaging was done using Confocal laser scanning microscope. This approach, when used for bacterial differentiation, was further demonstrated for selective gram positive bacterial staining in a much faster, simpler, and sensitive manner using flow cytometer compared to the traditional Gram staining method (Yang et al., 2016). The Gram positive bacterial cells showed more sensitivity towards lipophilic molecules over Gram negative bacteria due to the difference in their cell wall architecture and composition (Lien et al., 1968). However, the CQDs synthesized by hydrothermal treatment (autoclaving at 150 °C for 12 h of glucose and PEI followed by passivation with benzyl bromide) showed potent antibacterial activity against both gram positive and gram negative bacteria (Dou et al., 2015). CQDs (formed via pyrolysis of Spermidin powder) had shown potent antibacterial activity against *S. aureus* (*in vivo*) and other pathogenic bacteria *in* vitro (Jian et al., 2017).

Biofilms are the layers of the microorganisms (mainly bacteria) formed within an extracellular matrix on both living and nonliving surfaces through secretion. Biofilms are very harmful to humans, as they can cause chronic infections. As biofilms can be resistant to treatment, they can lead to cell death (Anderson and Pedersen, 2003). Additionally, biofilms are among the major challenges in industrial facilities, since they can corrode surfaces, slowly leading to gradual infection and degradation (Vertes et al., 2012). A variety of nanomaterials, including metal/metal oxides, polymeric nanoparticles, liposomes, hydrogels, and nano-enzymes, have been extensively

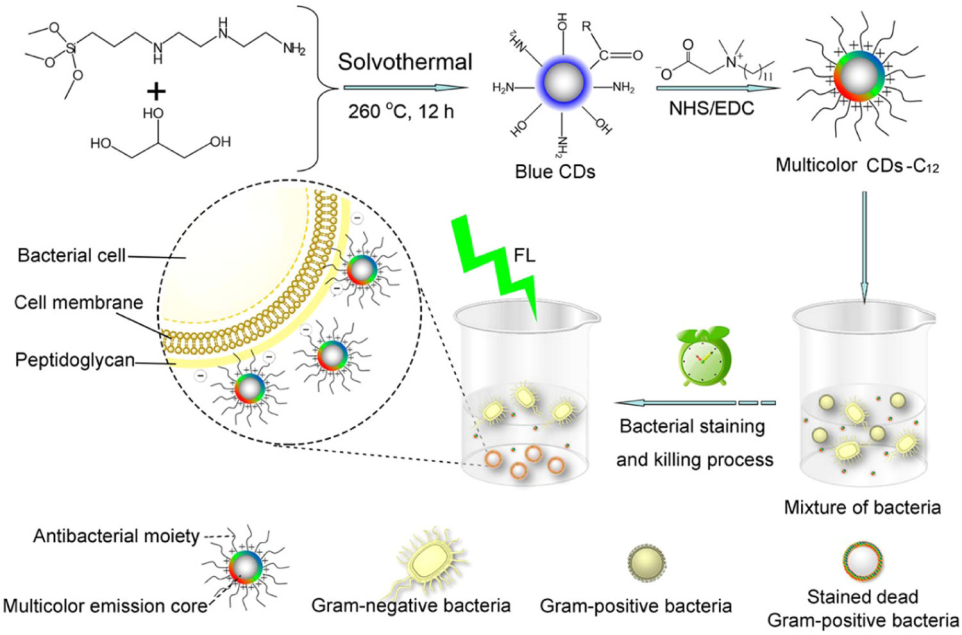

Fig. 3. Schematic showing the preparation of quaternized CQDs-C12 and their application in imaging and killing selective gram-positive bacterial(Ge and Liu 2013).

investigated to target these biofilms due to their inherent bactericidal activities (Boda et al., 2015; Duong et al., 2014; Geilich et al., 2017; Khan et al., 2014; Nguyen et al., 2015; Song et al., 2018). However, their toxic effects on other beneficial microorganisms and human cells (cytotoxicity) limit their potential utilization in controlling biofilms (Hu et al., 2009; Wang et al., 2017b). CQDs synthesized from *lactobacillus plantarun* by a hydrothermal carbonization process prevented the formation of a biofilm of *E. Coli.* They were bactericidal and were biocompatible with low toxicity towards cells (Lin et al., 2018a). DNA-based CQDs (DNA-CQD) were also found to have no or little cytotoxicity against an *E.coli* in culture for up to 6 h. The growth of bacteria was unaltered by the presence of DNA-CQD in the culture media (Ding et al., 2015). These DNA-CQDs can be used for transformation into bacteria.

4.2. CQDs in bioimaging and biosensing

The most important application of CQDs can be realized in the field of bio-imaging due to their biocompatibility, low toxicity, and fluorescent properties in living systems. Simple CQDs synthesized from the decomposition of citric acid monohydrate and diethylene glycol bis (3-aminopropyl) showed excellent fluorescence emission with very low cytotoxicity during imaging (fluorescence microscopy)of CQD-treated human cell lines and in the livers and kidneys of CQD-fed mice (Wang et al., 2017a). DNA-CQD synthesized from bacterial DNA were internalized by human kidney cell lines HEK 293. Also, they were taken up by both gram-positive (*S. cerevisiae*) and gram-negative bacteria (*E. Coli.*). They could be easily visualized under a confocal microscope (Ding et al., 2015). CQD-Asp synthesized by simple thermolysis of d-glucose and l-aspartic acid were able to penetrate the blood-brain barrier and to precisely target glioma compared to a normal brain. Thus, as CQD-Asp had higher selectivity for glioma cells than a normal brain, indicating that they could act as fluorescent imaging agents for non-invasive brain glioma diagnosis (Zheng et al., 2015a) (Fig. 4).

Biosensing is another important application of CQDs that exploit their photoluminescence. CQDs conjugated with organic dyes were effectively used for analysis of H_2S. The blue emission of CQD-organic dye was converted to green in the presence of H_2S (Yu et al., 2013). CQD-organic dye conjugates were able to detect the changes in physiological levels of H_2S inside the human cell lines HeLa and L929 under a fluorescence microscope, where a color change from blue to green

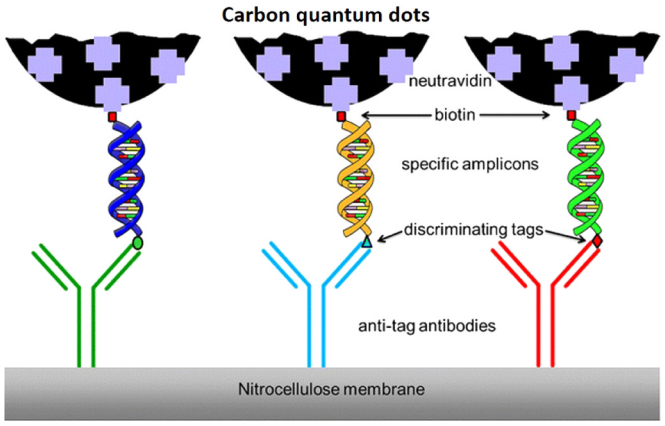

Fig. 4. Schematics for CQD-based nucleic acid microarray immunoassay (NAMIA). Neutravidin adsorbed onto CQD detects biotin-labeled amplicons. The discriminating tag was recognized by its respective antibody, which was immobilized onto nitrocellulose membranes (Cao et al., 2013).

was observed upon exposure of cells to H_2S. This CQD-based H_2S sensor was highly sensitive with a very low detection limit of 10 nM (Fig. 5). This study showed the potential of CQD to develop a potent diagnostic probe for quantification of H2S in patient samples for human health diagnosis (Yu et al., 2013).

CQDs have shown excellent metal sensing capabilities with enhanced selectivity and sensitivity. CQD synthesized from N-(aminoethyl)-g-aminopropylmethoxysilane had ethylenediamine groups that selectively interacted with Cu^{2+}, which quenched the fluorescence of CQD without having any effect on rhodamine B. Thus, CQD-RhB-silica nanoparticles were made for in-vivo imaging of Cu^{2+} inside the live cells (Liu et al., 2014a). N-CQD (synthesized from graphite-based material) had also been used for synthesis of highly stable photoconductor based photoluminescence probe for the detection of Fe^{3+} with low detection limit (2 μM) over a highly dynamic range (2–200 μM) (Zhou et al., 2015). Recently, CQDs synthesized from paper by hydrothermal methods were also used for the detection of organophosphorus pesticides based on turn-off fluorescence principle by Fe^{2+} produced by pesticide (LOD of 3ng/ml in biological samples) (Lin et al.,

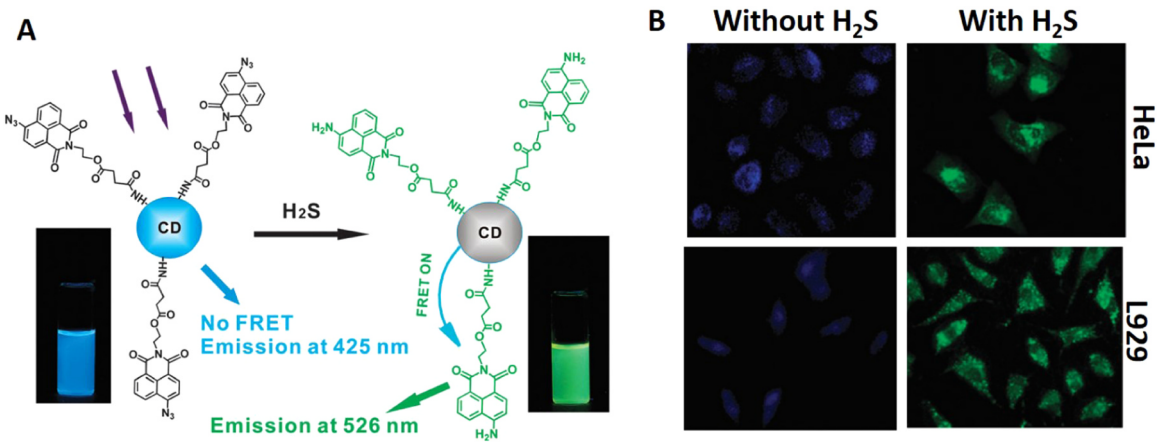

Fig. 5. A. Schematic of CQD-based sensor for ratiometric detection of H_2S. B. Fluorescence images of human cell lines HeLa and L929 incubated with CQD sensors in the absence and presence of H_2S (Hu et al., 2009).

2018a). N-P-CQDs synthesized by hydrothermal treatment of alendronate sodium was applied for highly sensitive and selective detection of uranyl ion with a detection of 4.5 nM (Shamsipur et al., 2018b). Recently, N-CQDs were synthesized from hydrothermal treatment of phyllanthusacidus fruit juice, which has multifunctional properties viz. selective and sensitive detection of Fe^{3+} ions (detection limit 0.9 μM); fluorescence ink and cell imaging without any functionalization or labeling (Atchudan et al., 2018). Many similar studies have proven that CQDs synthesized by simple methods can showcase selective and sensitive detection of different ions and molecules in real life samples (Iqbala et al., 2018; Liao et al., 2018; Niu et al., 2018; Shamsipur et al., 2018a; Wang et al., 2017b).

CQDs have also been used as a fluorescent label in immunoassays, e.g., microarray immunoassays (Posthuma Trumpie et al., 2012) (Fig. 6) and lateral flow assays (LFAs) (Gordon and Michel, 2008). CQDs are preferred over other fluorescent labels in immunoassays due to their merits of low cost, stability, and higher sensitivity. Thus, CQDs have the potential for developing sensitive immunoassays for diagnosis; for instance, CQD-based immunoassays could detect antigens in the picomolar range (e.g., 50 pg/ml; 2 pM) (Gordon and Michel 2008; Parpia et al., 2010). CQD-based nanoprobe has been devised to detect ascorbic acid in living cells as well as tissues in mouse models with a detection limit of as low as 270 nM (Feng et al., 2017). These studies indicated that CQD can play an important role in sensing organic molecules important for diagnosis of many diseases inside the living body in a non-invasive manner without causing toxic effects on the organisms. Further, CQD can be devised into effective nanoprobes for circulating molecules and cells inside urine and blood for early detection of cancer and other such diseases.

CQDs have been used for the detection of single nucleotide polymorphism (SNP), which has a very important role in the diagnosis of many genetic diseases and (more importantly) cancers. The detection of SNP was based on fluorescence quenching, which was sensitive enough to detect even a single base mismatch (Li et al., 2011a, 2011b) (Fig. 7). The sensing mechanism is based upon fluorescence recovery of a dye (6-carboxyfluorescein (FAM)), labelled onto ssDNA (selective bio

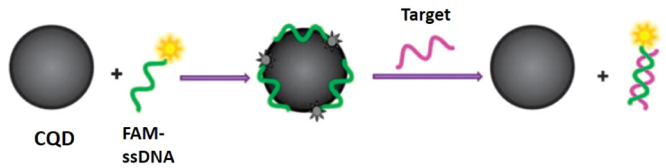

Fig. 7. Schematic illustrating CQD-based fluorescent nucleic acid detection (Hu et al., 2014a).

recognition element) in the presence of target DNA. The fluorescence of the ssDNA/dye sensor system is quenched on adsorption onto the CQD surface due to electron transfer between CQDs and the fluorescent dye. In the presence of target DNA, a dsDNA hybrid is formed to induce the desorption of ssDNA/dye systems from CQDs and to subsequently recover the fluorescence of the dye. The fluorescence intensity in turn was dependent upon the concentration levels of target DNA (Li et al., 2011a, 2011b). Thus, CQDs can be exploited to develop a cost-effective test for the detection of single nucleotide polymorphism (SNP) in diseases. CQDs have also been used for staining proteins after SDS PAGE electrophoresis. CQD had better sensitivity than the traditional staining agents such as Commissie Brilliant blue and silver (Na et al., 2013).All these studies indicate that CQD ought to play an important role in the future of development of cheap and sensitive sensors for non-invasive detection of ions, molecules, and metals for use in food, environmental, and biomedical diagnostics which will help improve the human health.

5. Biomedical applications of CQDs: diagnosis, therapy, and drug delivery

5.1. CQDs in diagnosis

Another important application of CQDs in the field of biomedicine is in diagnostics. Semi-conductive quantum dots have been used for in vivo diagnosis of disease (Larson et al., 2003; Schroedter et al., 2002; Zheng et al., 2007). Quantum dot-based nanoprobes are fast and cost-

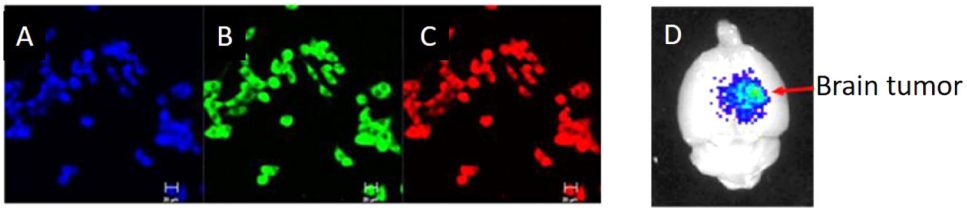

Fig. 6. CQD-Asp showing excellent cell and bioimaging properties. Laser confocal microscopy images of C6 cell lines (rat brain glioma cells) (A–C) treated with CD-Asp, under excitation of 405, 488, and 555 nm (scale bar - 20 μm). D. Ex vivo imaging of the mouse brain 90 min after the injection of CD-Asp into the mouse's tail (Hsu et al., 2012).

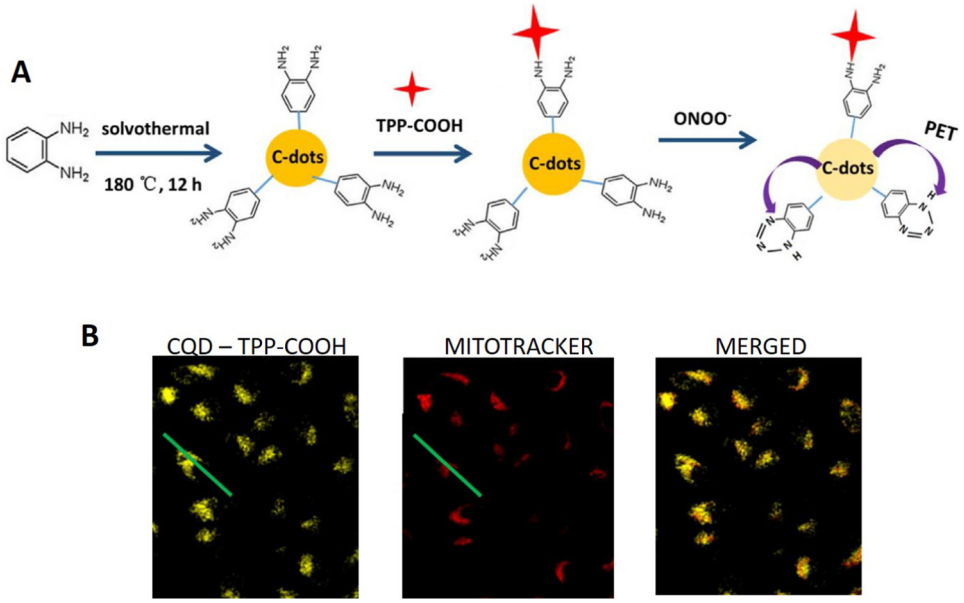

Fig. 8. (A) Schematic of the synthesis of the mitochondria targeting nanoprobe and possible mechanism of fluorescence quenching of the nanoprobe in the presence of peroxynitrite ($ONOO^-$). (B) Confocal fluorescence images for MCF-7 cells co-stained with nanoprobe and Mito-tracker (Wu et al., 2017).

effective methods compared to the other available methods. As CQDs have the advantage of low toxicity over traditional semi-conductive quantum dots, they are preferably used in *in vivo* labeling (Tao et al., 2012).

CQDs synthesized from MWCNTs (multi-walled carbon nanotubes) were functionalized with –COCl (by treatment with acids and $SOCl_2$), thus forming Cl-CQDs (Li et al., 2017). Cl-CQDs were later conjugated with anti-desmin to detect the protein desmin. Desmin is found in high concentrations in the serum of colorectal cancer patients (Li et al., 2017; Ma et al., 2009). This nanoprobe based on CQDs could be used to detect desmin in samples of patient serum with high specificity and sensitivity (Li et al., 2017). This discovery should help open a new research area for the development of a cheap, sensitive, and specific diagnostic platform using CQDs.

Recently, CQD-based nanoprobes have been utilized in the detection of peroxynitrite ($ONOO^-$), a reactive oxygen species produced in mitochondria (Wu et al., 2017). Mitochondria are the powerhouses of cells and are known for the production of ATP through respiration (Ernster and Schatz, 1981). Reactive oxygen/nitrogen species (ROS/RNS), which play an important role in cell signaling, are produced during the process of ATP production. However, the enhanced production of peroxynitrites is suspected to cause some diseases as they are abundantly observed in many diseases (Kawanishi and Inoue, 1997). High ROS/RNS have also been correlated with mitochondria induced programmed cell death. Thus, intracellular detection of peroxynitrite is very important for the proper diagnosis of these disease conditions. Mitochondria targeting TPP (triphenylphosphonium) modified CQDs (CQD-TPP) were also synthesized using o-phenylenediamine, which was also able to detect peroxynitrite with high sensitivity (detection limit of 13.5 nM) and selectivity in living cells (Wu et al., 2017) (Fig. 8). These CQD-based on-off fluorescence nanoprobes have shown enormous potential for the development of mitochondria targeting in live cells for diagnosis and therapeutics.

Recently, CQDs were reported to differentiate between cancerous and normal cells based on the redox potential (Zheng et al., 2015a). Silicon and N-doped CQD, prepared by solvothermal treatment of glycerol and N-(3-(trimethoxysilyl)propyl) ethylenediamine, exhibited sensitivity for Fe^{3+} ions with a detection limit of 16nM with an on-off fluorescence mechanism. These CQD with Fe^{3+} ions ($CQDs/Fe^{3+}$) could detect cancer cells with an on-off-on mechanism as reductive environment of cancerous cells reduced Fe^{3+} ions and led to revival of fluorescence of CQDs (Gao et al., 2018a). Further FA-CQDs and carbon quantum dots-apatamer conjugates were able to detect selectively cancer cells (Liu et al., 2018; Motaghi et al., 2017).

As such, these authors showed enormous potential of CQD for the development of cheap, effective, and sensitive diagnostic nanoprobes and point of care (POC) devices. CQDs have recently been used for the development of microfluidic paper analytics devices for diagnosis in biological samples (Anjana et al., 2018; Kurdekar et al., 2016; Motaghi et al., 2017; Yuan et al., 2014). POC diagnostic devices will not only help reduce the cost of diagnostics but can help reach the heathcare to poor inaccessible rural population in developing countries.

5.2. CQDs in dual role-phototherapy and radiotherapy

CQDs have also been used extensively in phototherapy and clinical treatment for superficial tumors such as skin cancer. This method involves the concentration of photosensitizers in the tumor tissue followed by irradiation to trigger the formation of ROS, which induces apoptosis (programmed cell death) (Hsu et al., 2013). CQDs functionalized with positively charged molecules can induce the production of ROS in cell lines (Havrdova et al., 2016). As such, CQDs can be exploited in phototherapy. Radiotherapy is another important therapy for tumors. Also, PEI-functionalized CQDs (CQD-PEI) were used as photosensitizers in DU145 and PC3 cells (Tao et al., 2012). These CQDs had potent photodynamic effects and produced reactive oxygen species (type I mechanism) and singlet oxygen (Type II mechanism) (Juzenas et al., 2013).

Further, CQDs have been exploited in radiotherapy. PEG-coated CQDs functionalized with silver (CQD-PEG-Ag) were used as a radio sensitizer in Du145 and PC3 cells in vitro (Tao et al., 2012). These CQDs selectively entered cancer cells and avoided the cytotoxicity to normal cells observed in conventional radiotherapy. Upon application of X-rays, the CQD produced reactive species and damaged cancer cells, causing cellular apoptosis. In another work, CQD–chlorine e6–hyaluronate (CQD-Ce6-HA) conjugate was also demonstrated for the photodynamic therapy of melanoma in mice (Beack et al., 2015). CQDs were synthesized from thermal decomposition of glycerin and were then conjugated with Ce6, a nontoxic photosensitizer with a high yield of singlet oxygen. CQD-Ce6 conjugate was further conjugated with

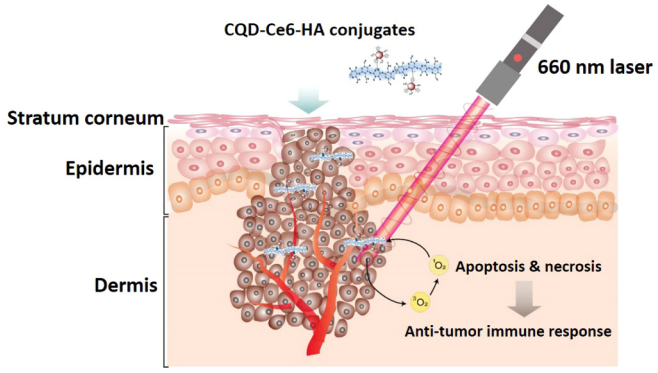

Fig. 9. Schematic of phototherapy of melanoma skin cancers after transdermal delivery of carbon quantum dot – chlorin e6 – hyaluronate (Cdot-Ce6-HA) (Schroedter et al., 2002).

hyaluronic acid for targeted delivery into cancer cells. Thus, the obtained CQD-Ce6-HA conjugate induced apoptosis to completely suppress melanoma skin cancer in a mouse model (Fig. 9) (Beack et al., 2015).

5.3. CQDs in drug delivery

Although cancer and other localized diseases have been treated conventionally by chemotherapy, such an approach generally lacks specificity and causes toxicity and multidrug resistance problems (Li et al., 2014a). Therefore, methods based on targeted drug delivery have been sought as alternatives to improve drug efficacy while reducing the side effects (Liu et al., 2012a; Rosenholm et al., 2010; Sharma et al., 2006). However, in such alternative methods, targeting agents are also affected by premature leaking of the drug before it reaches the target site (Roy et al., 2010; Zhou et al., 2014). Therefore, there is a strong need for the development of effective targeting agents such as CQDs with many distinguishable advantages. Over the last few years, the development of multifunctional nanosystems has been a vibrant area of research. CQDs have been reported for the development of dual nanocarrier systems involving bioimaging and therapeutic agents. They have emerged as a substitute to semiconductor QDs that suffer from a number of shortcomings like poor solubility, high toxicity, and insufficient loading capacity for drugs (Acharya, 2013; Li et al., 2014b). In this respect, CQDs are fascinating nanoparticles that can serve a dual function of bio-imaging and drug delivery with minimal concerns about cytotoxicity. This was not possible in the earlier stages of development as cytotoxicity was encountered for most other nanoparticles. Table 3 summarizes the active contribution made by CQDs towards drug delivery.

Drug leakage and non-specific delivery to normal cells can indeed cause cytotoxicity problems. Hence, to overcome such problems, CQDs were modified through functionalization. Some brilliant attempts have been made using PEG for functionalization of CQDs to facilitate the transmission of targeted therapy to the tumor microenvironment (Jia et al., 2016). CQD-based theranostic nanoparticles (mPEG-OAL-DOX/CQD) were synthesized using CQDs (prepared by pyrolysis of citric acid) cross-linked with PEGylated oxidized alginate (mPEG-OAL) that were conjugated with doxorubicin (DOX) via an acid-labile Schiff base linkage. These theranostic materials were capable of releasing the drug in an acidic tumor microenvironment in a pH-dependent manner (Jia et al., 2016). This pioneering work led to the development of imaging guided drug delivery and pH-responsive site-specific release of drugs in acidic tumor conditions. As such, intensive efforts were made to increase the antitumor activity of doxorubicin (DOX) with fewer side effects by reducing drug leakage in physiological media. This study group further exploited receptors expressed by cancer cells, i.e., hyaluronic acid (HA), (targeting CD44 surface receptors highly expressed by tumor cells (Kim et al., 2010) and folic acid (targeting folate receptors highly expressed by tumor cells (Parker et al., 2005). They conjugated these receptors to CQD along with PEG (for pH responsive drug release in a tumor microenvironment) to obtain theranostic nanogels (FA-PEG-HA-CD). Thus, the efficiency of the obtained theranostic gels was demonstrated for dual receptor mediated targeted controlled delivery of doxorubicin (DOX) (Jiao et al., 2016). Although CQD-based theranostic materials have shown lower cytotoxicity and higher tumor targeting efficacy in *in vitro* systems (Jia et al., 2016; Jiao et al., 2016), more investigations are needed to practically confirm the efficacy of such systems in animal models.

In another work, amine functionalities present on CQD surfaces were utilized to obtain a positively charged CQD-Pt (IV) conjugate (Feng et al., 2016b). The pH responsive CQD Pt(IV)@PEG-(PAH/DMMA) material was generated by functionalizing a conjugate with negatively charged PEG-(PAH/DMMA) (an anionic polymer of dimethyl-maleic acid) using electrostatic interactions. Under an acidic tumor environment, the material underwent disintegration due to the breakage of pH-induced electrostatic interactions, resulting in the release of CQD-Pt(IV) into the tumor extracellular microenvironment. However, the material is not responsive to neutral physiological conditions (Feng et al., 2016b). Additionally, the developed CQD-based drug nanocarrier exhibited increased circulation time due to several factors including: negative charge/PEGylation (Dou et al., 2015; Feng et al., 2016c; Sun et al., 2016), their high abundance at the tumor due to the pH responsive effect (Alexis et al., 2008; Feng et al., 2016c; Sun et al., 2016; Xu et al., 2013), easy internalization, decreased side effects in normal cells, endosomal escape, and the regulated release of the drug cisplatin from cisplatin(IV) prodrug in the reductive environment inside cancer cells (Feng et al., 2016c). These CQD-based nanocarriers were demonstrated to have higher tumor efficacy along with low cytotoxicity for both in vitro and in vivo conditions (Fig. 10) (Feng et al., 2016b; Gao et al., 2018b).

Further advances in CQD research have also been achieved in targeted delivery to organelles such as the nucleus and mitochondria inside cells. Mitochondria are very important organelles in light of their roles in many cancers and metabolic/neurodegenerative disorders. Recently, CQDs synthesized in a simple one step hydrothermal procedure using diverse media (e.g., chitosan, ethylenediamine, and mercaptosuccinic acid), were found to possess mitochondrial targeting properties (Hua et al., 2017; Wu et al., 2017). Such CQDs can be used for mitochondrial imaging as well as targeted drug delivery to mitochondria. They have many advantages (e.g., simple cost-effective synthesis, photostability, low toxicity, and live cell mitochondrial imaging) relative to commercial mitochondrial probes (Hua et al., 2017; Wu et al., 2017).

The treatment of brain tumors and other brain diseases (i.e., neurodegenerative disorders) has always been challenging due to the decreased permeability of the brain, short retention of the drug inside the brain (Soroceanu et al., 1998), and the presence of the blood brain barrier (Spano et al., 2005). Brain tumors have been cited as a leading cause of morbidity and mortality across the world (Agarwal et al., 2011). Consequently, there is an urgent need for accurate imaging of tumor cells for proper diagnosis and prognosis of brain tumors. CQDs might play an important role in the treatment of brain tumors. CQDs have been exploited for targeting brain tumors through combination with tumor penetrating peptides, i.e., RGERPPR; these combinations have been shown to penetrate tumor vascular walls and target brain tumor (Yang et al., 2013). CQDs synthesized by the hydrothermal treatment of citric acid monohydrate with diethylene glycol bis (3-aminopropyl) ether, were functionalized with maleimide-polyethylene glycol-aminosuccinimide succinate (Mal-PEG-NHS) and the tumor-penetrating peptide RGERPPR; the resulting nanoplatform was then employed to target glioma and provide bio-imaging *in vivo* (Gao et al., 2018b). However, it was reported in another study that CQD-Asp synthesized from d-glucose and l-aspartic acid had highly selective

Table 3
A summary of CQD use in drug delivery.

Order	Source of CQD	Drug / Method	Disease / Model System	Efficiency	References
1.	MSN-SS-CD_{PAA}-DOX CQD synthesized by hydrothermal polymerization method using poly-acrylic acid	Multifunctional nanosystem (targeted and controlled delivery of drug doxorubicin along with bioimaging)	In vitro (human prostate cancer cell line)	High therapeutic effect against cancers and good biocompatibility and stability compared to naked mesoporous silica particles containing the drug doxorubicin	(Jiao et al., 2016)
2.	FA-Gd@CQD green CQDs synthesized from waste crab shell doped with Gd^{+} and conjugated with folic acid	Targeted drug delivery of doxorubicin	HeLa cell line	Significantly higher toxicity towards HeLa cells and less cytotoxicity in in vivo (zebrafish embryos and other cell lines)	(Yao et al., 2017)
3.	MSN-SS-CD_{HA}-DOX CQD synthesized by decomposition of citric acid and conjugated with HA, which were further conjugated with mesoporous silica nanoparticles enclosing the anti-tumor drug, doxorubicin	Multifunctional nanosystem (targeted and controlled drug delivery of doxorubicin along with bioimaging)	In vivo mouse model	High therapeutic efficiency towards cancer cells	(Wang et al., 2017b)
4.	CQD-Asp (thermolysis of d-glucose and l-aspartic Acid)	-	In-vivo mouse model of brain tumor	High biocompatibility and less toxicity	(Zheng et al., 2015a)
5.	CQD (hydrothermal treatment of citric acid monohydrate, with diethylene glycol bis ether)	-	Both in-vitro and in-vivo model of glioma (brain cancer)	Successful targeting of glioma	(Gao et al., 2018b)
6.	CQDs Pt(IV)@PEG-(PAH/DMMA) CQD, prepared by thermal pyrolysis of citric acid, conjugated with drug cisplatin and electrostatically conjugated with PEG-(PAH/DMMA)	Cisplatin	In-vitro and in-vivo model of cancer	High tumor inhibition efficiency and low side effects	(Feng et al., 2016b)
7.	CQD Nitric acid oxidation of candle soot	Phototherapy	Cell line	Highly cytotoxic to cancer cells	(Havrdova et al., 2016)
8.	CQD-PEG-Ag acid oxidation of carbon nanotubes and graphite	Radiotherapy	Cell lines	Cytotoxic to cancer cells	(Tao et al., 2012)
9.	mPEG-OAL-DOX/CQD CQD, prepared by pyrolysis of citric acid, cross-linked with PEGylated oxidized alginate (mPEG-OAL)	doxorubicin	In-vitro cell model	Cytotoxic specifically to cancer cells	(Jia et al., 2016)
10.	CQDs hydrothermal treatment of citric acid, hyaluronic acid and ethylenediamine	Bio-nanoplatform (CQD-HA-SiO4-DOX)	Cancer cell line	Low cytotoxicity	(Wang et al., 2017b)
11.	CQDs Microwave synthesis method using acrylic acid and ethylene diamine followed by functionalization with glycidyl methacrylate	Targeted cancer drug delivery	Nanogel (copolymerized with zwitterionic amino acid ornithine methacrylamide)	Low cytotoxicity	(Li et al., 2016)

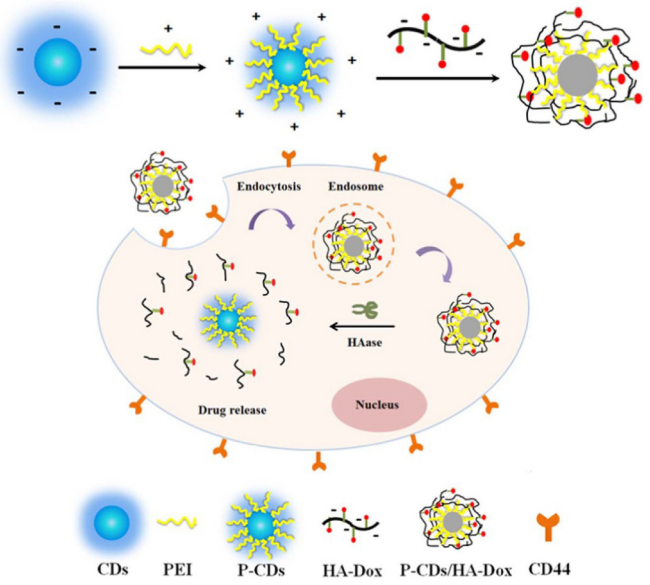

Fig. 10. Schematic depicting the formation of nanoprobes used for targeted cancer cell imaging and drug delivery (Gratton et al., 2008).

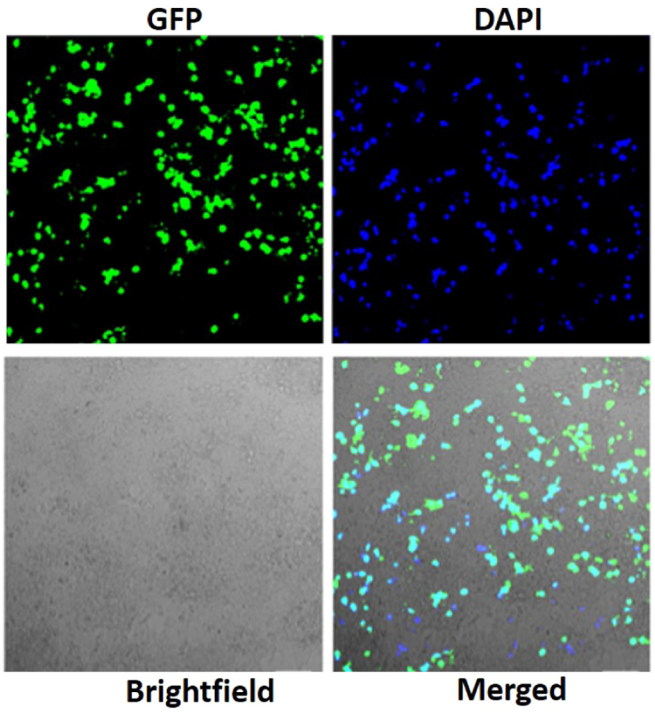

Fig. 11. Fluorescent images of GFP expression obtained by confocal laser scanning microscope in 293T cells transfected with DNA/PCD complexes (Hola et al., 2014a).

targeting ability towards glioma cells both in vitro and in vivo. The high affinity of CQD-Asp for tumor brain cells over normal ones makes them a promising fluorescent imaging agent of brain glioma. Additionally, CQD-Asp could be used in the development of a single nanoplatform for simultaneous diagnostic, targeting, and therapeutic mechanisms (Zheng et al., 2015a).

CQD-HA (synthesized from citric acid and hyaluronic acid) were conjugated with mesoporous silica nanoparticles (MSN-SS) for use with the anti-tumor drug doxorubicin (Wang et al., 2017b). The MSN-SS covered with CQD-HA was then employed for targeted delivery of DOX in cancerous cells using CD44 surface receptors. Further responsive drug release was mediated in response to GSH and HAase in tumor cells only. These MSN-SS-CD_{HA}-DOX complexes exhibited lower cytotoxicity toward normal cells while exhibiting higher anti-tumor activity towards cancer cells in a targeted manner (Wang et al., 2017b). The bio imaging studies of this material, when tested against mice (*in-vivo*), revealed that CQDs did not accumulate in the liver; this result indicates their non-toxic behavior. In a similar approach, CD_{PAA} synthesized from poly-acrylic acid (PAA) was used for the formation of an MSN-SS-CD_{PAA}-DOX drug carrier, which also exhibited properties comparable to the MSN-SS-CD_{HA}-DOX complex (Jiao et al., 2016). Further, HA-based CQDs were used as a core for the development of mesoporous silica nanoparticles, C-hMOS, which had both the capacity to carry the anticancer drug doxorubicin (DOX) and optical imaging ability (Kang et al., 2017). These nanocarriers showed improved loading efficiency and sustained release of DOX in a pH dependent manner. They also successfully induced apoptosis suppression of tumor growth in mice and simultaneous imaging during treatment (Kang et al., 2017).

5.4. CQDs in gene/protein delivery

An efficient method of delivering genes to animal cells can find immediate applications in gene therapy. Also, the transfection of exogenous proteins inside the cells is an important tool to study the role of the protein in cellular environments, which is highly dependent upon localization inside the cell. Conventionally, genes are cloned inside a vector with a tag (e.g., GFP), which is then transfected inside the cells. Nonetheless, that system has limitations in terms of signal loss and lower transfection efficiency due to challenges associated with transfection (Kim et al., 2010). The lower transfection efficiency makes dye labeling of proteins/genes necessary. Most of the current non-viral gene vectors such as calcium phosphate nanoparticles (Cao et al., 2013) and cationic polymers (Deng et al., 2013; Yu et al., 2015) do not possess the property of self-imaging. Therefore, the fabrication of a fluorescent molecule that can allow drug/gene delivery along with imaging is imperative.

CQDs seem to have the potential to resolve the problem of gene delivery along with imaging to visually indicate the delivery of genes into cells. Recently, sodium alginate derived CQDs were effectively used for delivering genes into human cell lines while serving as a fluorescent marker for gene delivery at the same time. The transfection efficiency of CQDs was as high as that of lipofectamine, although it exhibited the added advantages of cell imaging along with very low cytotoxicity and high biocompatibility (Zhou et al., 2016). Further, functionalization with positively charged groups helped CQDs in gene/DNA delivery applications. It was found that PEI functionalized CQD (CQD-PEI) had positively charged amino groups on the surfaces, which helped condense DNA onto CQD through electrostatic interactions. The obtained functionalized CQDs transferred genes inside the cells with high transfection efficiency compared to the conventional method (Hu et al., 2014a) (Fig. 11). Further, these PEI-CQDs showed higher fluorescence than the GFP label. Apart from condensing DNA onto the surface, PEI can have a proton-sponge effect so that CQD-PEI can be effectively internalized inside the cells by the t effect via endocytosis. Unprotonated amine groups also helped in gene release inside the cytoplasm by buffering endolysosomal pH (Godbey et al., 1999). Recently, CQDs developed with glucose and PEI quaternized with benzyl bromide had a very high transfection rate (10^4 times higher than the conventional method) in human embryonic kidney cells, HEK 293T (Dou et al., 2015). CQDs were thus coupled with gold nanoparticles for assembly, followed by conjugation with PEI–pDNA for delivering of DNA to cells (Kim et al., 2013).

6. Green CQDs and their applications in nanomedicine

Green CQD (GQCDs) were first synthesized in smaller sizes (5 ± 2 nm) and with low QY (3.8%) from coffee grounds using hydrothermal

Table 4
Synthesis methods and biological applications of GCQDs.

Order	Category	Organic Precursor	Synthesis method	QY (%)	Biological application	References
1.	Fruit Source	Orange Juice	Hydrothermal	26	Bioimaging	(Sahu et al., 2012)
		Watermelon peel	Carbonization	76	Bioimaging	(Zhou et al., 2012)
		Banana juice	Heating	8.95	-	(De and Karak 2013)
		Apple juice	Hydrothermal	4.27	Bioimaging	(Mehta et al., 2015)
		Papaya	Hydrothermal	18.5	Bioimaging and Biosensing (Fe^{3+})	(Liao et al., 2016)
		Lemon peel	Hydrothermal	14	Biosensing (Cr^{6+})	(Tyagi et al., 2016)
		Lemon Juice	Hydrothermal	28	Bioimaging	(Ding et al., 2017)
		Mango pulp	Carbonization	0.48-3.92	Bioimaging	(Sharma et al., 2017)
2.	Food and Beverages	Whey	Hydrothermal	11.4	Biosensing (Se^{6+})	(Devi et al., 2017)
		Nescafe coffee powder	Heating	5.5	Bioimaging	(Jiang et al., 2014)
		Milk	Hydrothermal	12	Bioimaging	(Wang and Zhou 2014)
		Bread	Acid oxidation	4.5	Bioimaging	(Saxena and Sarkar 2013)
3.	Animal Derivatives	Egg	Combustion/ microwave	14	Biosensing (glutathione)	(Wang et al., 2012)
		Bombyxmori silk	Hydrothermal	13.9	Bioimaging	(Wu et al., 2013)
		Honey	Hydrothermal	19.8	Biosensing (Fe^{3+})	(Yang et al., 2014)
		Dried shrimp	Hydrothermal	54	Bioimaging	(D'souza et al., 2016)
		Pig skin	Hydrothermal	24	Bioimaging and biosensing (Co^{2+})	(Wen et al., 2016)
		Flour	Microwave	5.4	Biosensing (Hg^{2+})	(Qin et al., 2013b)
4.	Human Derivatives	Hair fibers	Acid treatment	11.1	Bioimaging	(Guo et al., 2016; Sun et al.,
		Hair	Thermal treatment	10.75	Biosensing (Hg^{2+})	2013)
		Human urine	Thermal treatment	14	Biosensing heavy metal (Hg^{2+} Cu^{2+}), Bioimaging	(Essner et al., 2016)
5.	Vegetables	Cabbage	Hydrothermal	16.5	Bioimaging	(Alam et al., 2015)
		Garlic	Hydrothermal	17.5	Bioimaging	(Zhao et al., 2015)
		Onion waste	Hydrothermal	28	Bioimaging and Biosensing (Fe^{2+})	(Bandi et al., 2016)
		Carrot juice	Hydrothermal	5.5	Biosensing (S^{2-})	(Liu et al., 2017)
6.	Waste materials	Paper waste	Thermal	9.3	Bioimaging	(Wei et al., 2014)
		Paper ash	Thermal	10.8	Bioimaging	(Wei et al., 2013)
		Waste frying oil	Heating with acid	3.66	pH Sensing	(Hu et al., 2014b)
7.	Leaves and more	Bamboo	Hydrothermal	7.1	Biosensing (Cu^{2+})	(Liu et al., 2014b)
		Willow leaves	Hydrothermal	-	-	(Qin et al., 2013a)
		Sugarcane bagasse Pulp	Hydrothermal	12.3	Bioimaging	(Thambiraj and Shankaran 2016)
		Shiitake Mushroom	Hydrothermal	5.5	pH sensing and lysosome imaging	(Wang et al., 2016a)

treatment (Hsu et al., 2012). In contrast, hydrothermal treatment of grass resulted in the formation of nitrogen doped CQDs with higher QY and lower size (Liu et al., 2012b). Later on, GCQDs have also been synthesized from numerous organic materials as a carbon sources, including fruit, fruit juices, fruit peels, food, beverages, animal derivatives, human derivatives, vegetables, waste material, leaves, and other materials (Das et al., 2018), as summarized in Table 4. Although the QY varied with different source materials, the highest QY (76%) was obtained with the carbonization of watermelon peel (Zhou et al., 2016).

GCQDs contain several surface functionalities due to the presence of protein and other macromolecules in the precursor organic material. Hence, they generally do not require surface passivation (Sharma et al., 2017).They are therefore usually co-doped with N or S during synthesis. The resulting GCQDs exhibited high fluorescence QY and good biological activity. They are known to have an amorphous nature due to their disordered carbon architecture, which has been reported by several researchers based on XRD and SAED investigations. They have interesting optical and fluorescence behavior due to optical confinement, surface defects, surface states, and degree of oxidation (Feng et al., 2016a; Sharma et al., 2017; Wei et al., 2014). The excellent optical properties of GCQDs make them promising substitutes in biomedical applications over synthetic CQDs due to their ease of synthesis, no requirement of expensive chemicals, no need for post-surface modification, etc. In light of these advantages, they have been used extensively in bioimaging (e.g., mammalian cells, bacteria, and fungi for both in vivo/ex vivo imaging) (Sharma et al., 2017). Their surface functionalities play a significant role in their interna lization by cells, nuclei, and macrophages (D'Angelis do E. S. Barbosa et al., 2015; Shi et al., 2015; Wei et al., 2013; Wu et al., 2013). It was reported that the internalization efficiency was lower in non-functionalized CQDs than in target specific functionalized CQDs (D'Angelis do E. S. Barbosa et al., 2015; Ramanan et al., 2016; Thoo et al., 2017). In a recent work, GCQDs synthesized from waste crab shells were doped with Gd^{3+} and conjugated with folic acid (FA-Gd@CQD); these materials showed promising results in targeting folate receptor positive HeLa cells relative to receptor deficient HePG2 cells (Yao et al., 2017) (Fig. 12). An in-vivo bio-distribution study of multicolored CQDs (FCP-B, FCP-G, and FCP-Y) synthesized by controlled carbonization of mango fruit showed size dependent bio-distribution. In particular, large CQDs (FCP-Y) were found to accumulate in the liver, while smaller ones (FCP-B and FCP-G) were distributed mainly in the urinary bladder; hence, they were easily cleared (Jeong et al., 2014). The typical fluorescent properties of GCQDs are utilized to develop various biosensors. For example, Hu et al. (2017a, 2017b) developed an “on-off-on” sensor for coenzyme (CoA) detection (Hu et al., 2017a, 2017b). The researchers synthesized a highly fluorescent N, S-co-doped GCQD (diameter ~3.5 nm) sensor material using water chestnuts and onions as the only precursor materials. Thus, the obtained GCQDs showed a decrease in intensity with respect to Cu^{2+} ion concentration (“on-off” sensing), which was recovered in the presence of CoA (“off-on” sensing). Hence, the same material could detect both Cu^{2+} ions and CoA sequentially. The authors reported a 0.01 μM detection limit for CoA, which is a biologically important diagnostic marker for understanding the pathogenesis of diseases (Hu et al., 2017a, 2017b).

GCQDs provide a sustainable option over chemically synthesized CQD. Nonetheless, extensive characterization of the synthesis mechanisms is still necessary to ensure the reproducibility of the process. As mentioned above, GCQDs are generally synthesized from natural organic precursors, which may have enormous variations in their composition. The initial precursor, synthesis method, and method reproducibility play a significant role in determining the optical properties of synthesized GCQDs. This might change the behavior of the different lots of synthesized GCQDs. Hence, there is a need to define the composition of the organic materials used for the synthesis of GCQDs.

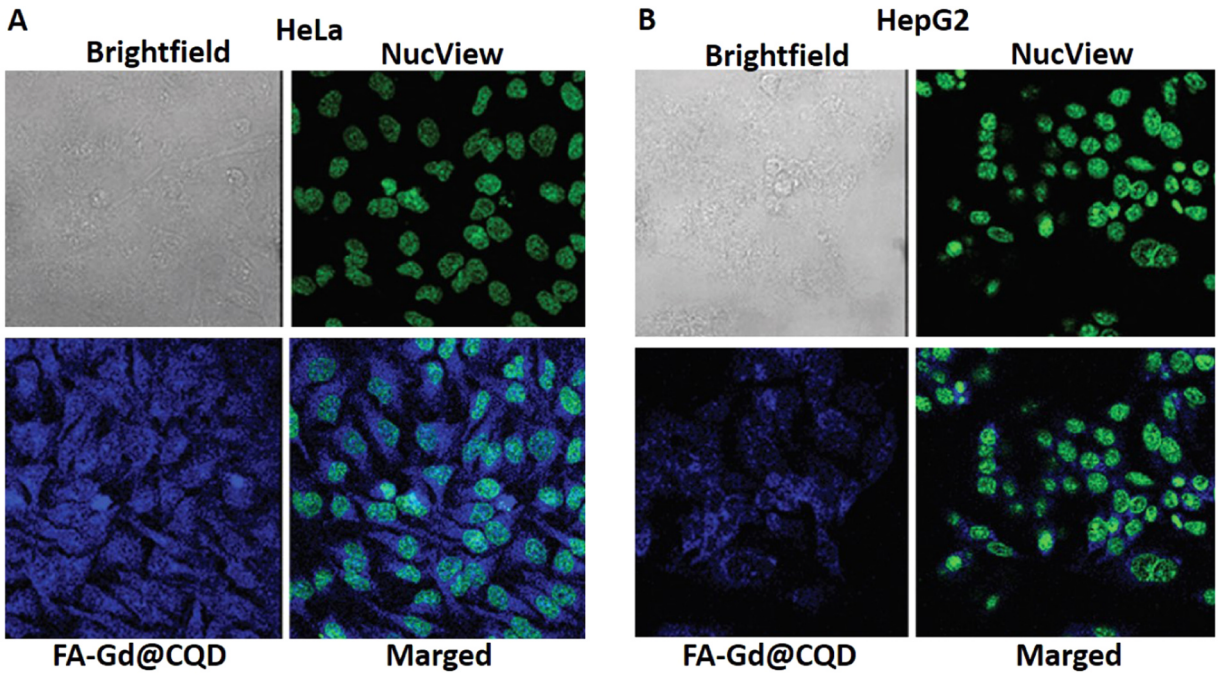

Fig. 12. Fluorescence images of HeLa (A) and HepG2 (B) cells incubated with FA-Gd@CQDs, fixed and stained with NucView agent (Yao et al., 2017).

Further, different methods have been employed for the synthesis of GCQDs from organic materials. Consequently, a comparative analysis is necessary to find the most suitable methods for their synthesis and scaling up the process to ensure successful commercial applications in the biomedical domain.

7. Conclusions

In the last decade, CQDs have been explored intensively for applications in diverse fields. Synthesis of CQDs has seen a complete transition from complex methods of electro-oxidation to simple green synthesis using common organic materials. CQDs have replaced other metal nanoparticles and/or semiconductor quantum dots due to their merits of biocompatibility and photoluminescence. Despite the many attractive properties of CQDs, there is still need for improvement. There is a particular need for a standard method for CQD synthesis with defined composition, structure, and high QY.

CQD-based biosensing and bioimaging applications should be improved to make them more sensitive and selective to avoid background and auto-fluorescence. Further, CQDs should revolutionize the field of biomedicine (e.g., nanomedicine). The photochemical stability and non-toxic chemical composition of CQDs have given them advantages in *in vivo* biomedical applications in comparison to conventional semiconductor quantum dots. Intensive efforts have been made by researchers to utilize CQDs for targeted drug/gene delivery in tumor cells using targeted receptors. Due to their biocompatibility, CQDs for “theranostics” applications are finding their position among futuristic materials for cancer treatment. Yet more research is required to realize their practical use in theranostic applications toward cancers. There is a need to extensively study the pharmacokinetics and bio distribution of CQDs under different factors and processes such as passivation, doping, and conjugation. Further, the synthesis techniques for CQD-based nanocomposites and related approaches (e.g., CQD doping) have also shown promising results in vitro under lab conditions. Hence, there is a need to expand their utility in therapeutics and many other biomedical applications including bioimaging, diagnosis, bio sensing, gene therapy, and drug therapy. Additionally, the vast amount of data presently available on their biomedical applications need to be evaluated statistically to move from lab studies to real-world applications.

Author credit statement

P. Devi and K. Kim conducted conceptualization, investigation, and formal analysis of this article. P. Devi and S. Saini took care of data curation, validation, visualization, and writing of the original draft. K. Kim did validation and organized the review and editing of the paper.

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Declaration of interests

None.

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