Available online at www.jourcc.com

Journal homepage: www.JOURCC.com

Journal of Composites and Compounds

A review of clinical applications of graphene quantum dot-based composites

Ebadollah Asadi [a], Arash Fassadi Chimeh [b], Amir Hossein Vakili Tahmorsati [c], Sahar Hosseini [d], Seyedhamidreza Rahimi [e], Bijan Sarkhosh [f], Leila Bazli [g], Rozhin Bashiri [h]*

[a] *Department of Chemistry, Amirkabir University of Technology, Tehran, Iran*
[b] *Department of Chemical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[c] *Department of Biomedical Engineering, Islamic Azad University, Central Tehran Branch, Tehran, Iran*
[d] *Visveswarapura institue of health sciences, Rajiv gandhi university .560041.bangalore.karnataka.India*
[e] *Department of Biomedical Engineering, Islamic Azad University, Tehran Science Research Branch, Tehran, Iran*
[f] *Department of chemistry, university of Isfehan, Isfahan, Iran*
[g] *School of Metallurgy and Materials Engineering, Iran University of Science and Technology, Tehran, Iran*
[h] *Department of Applied Chemistry, Faculty of Pharmaceutical Chemistry, Pharmaceutical Science branch, Islamic Azad University, Tehran, Iran*

A B S T R A C T

This review represents an overview of the graphene quantum dots (GQDs) synthesis and their applications as carriers or probes for the sensor, imaging, drug delivery, and diagnosing of diseases. Furthermore, recent developments in the GQDs for therapy and their potential toxicity for both in vitro and in vivo are reviewed. The recent findings and issues for GQDs and their composites with respect to stability and optimal size and toxicity at various applications are presented.

Peer review under responsibility of JCC Research Group.

A R T I C L E I N F O R M A T I O N

Article history:
Received 29 July 2019
Received in revised form 18 October 2019
Accepted 27 November 2019

Keywords:
Quantum dots
Graphene
Drug delivery
Theranostics

Table of contents

* *Corresponding author: Leila Bazli; E-mail: leilabazli64@gmail.com*
DOR: 20.1001.1.26765837.2019.1.1.6.5
https://doi.org/10.29252/jcc.1.1.6

1. Introduction

Quantum dots (QDs) are semiconductor fluorescent inorganic nanocrystals. Their size ranges from 1 to 10 nm. Their small size has made them unique in comparison with macrocrystalline materials. GDs with unique properties have been used in many branches of science; for example, their use in pharmaceutical and medical technology is evolving [4, 5]. The notable features of quantum dots are their rich surface area and optical properties that have led to their applications as probes for targeted drug delivery as well as treatment fields. In fact, by combining with ligands, QDs can target intended cells or tissues. Recently, with advances in the production of biocompatible quantum dots, their use for in vivo applications has become more prominent [7].

QDs can be also in the form of a semiconductor core, with a coating (as a shell), and a cap that results in good solubility in various solvents such as aqueous buffers. The unique optical and semiconducting characteristics of QDs are derived from the inorganic core [9]. The QDs are luminescent nanocrystals that are used for carriers or probes in medical applications such as drug delivery [10-13], imaging, and therapy due to their rich surface chemistry [15]. Ligands are used as functionalizing groups in QDs for specific target applications in cells or tissues [7]. In addition, ligands have the main role in the stability of colloids, distribution of particle size, solubility, the morphology of particles, and limiting the agglomeration and excessive particle growth [19]. Indeed, ligands result in electrostatic or hydrophobic interactions and covalent coupling of QDs to carbohydrates, DNA fragments, peptides, viruses, and other products [21]. The structure of QDs coupled with ligands is illustrated in Fig. 1. During the synthesis of QDs, organic materials such as carboxylic acids, primary amines, alcohols, long-chain carbon, and thiols, can be used as ligands [9]. Recently, the preparation of biocompatible QD has resulted in providing suitable nanocrystals with potential applications for in vivo utilization [2].

2. Physicochemical properties of quantum dots

Due to the nanocrystals grain boundary and electron hole pairs (excitons) of QDs, they have unique optical properties. In addition, photophysical properties of QDs include photochemical robustness, broad absorption and size-tunable spectra, high yields of fluorescent quantum, significant coefficients of absorption extinction, resistance to the effect of photobleach and fluorescence intermittency reduction. The above-mentioned photo-physical features make QDs suitable to be applied in different biomedical fields such as diagnosis, drug delivery, gene therapy, etc. [9, 22].

2.1. Size-tunable absorption and emission

Another feature of QDs is the size-tunable light emission properties (Fig. 2). As mentioned above, the QDs diameter ranges from 2 to 10 nm. The size adjusting of QDs results in the tuned fluorescence at an extensive wavelength (WL) from 400 to 4000 nm that enables the determination along with the visible light, ultraviolet (UV), and infrared spectra. The confinement degree increases by the decrease in QDs diameter, results in an increase in the energy of bandgap, and finally generates a higher energy exciton. This causes a change in the emission to the low WL of blue spectra due to the high energy of bandgap. Energy has an inverse relationship with the light WL. In semiconductor material having bulk form, the electrons are in continuous levels of energy but in the form of nanomaterials, the electrons exist in discrete energy levels because of the quantum confinement [23, 24].

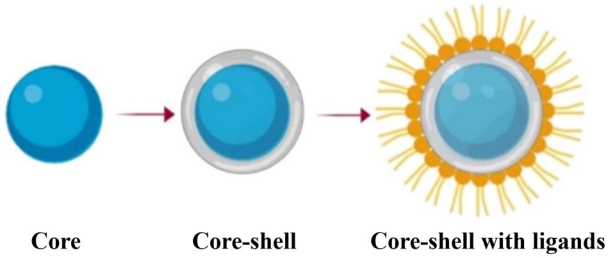

Fig. 1. Schematic illustration ligand-linked Quantum dots (QDs).

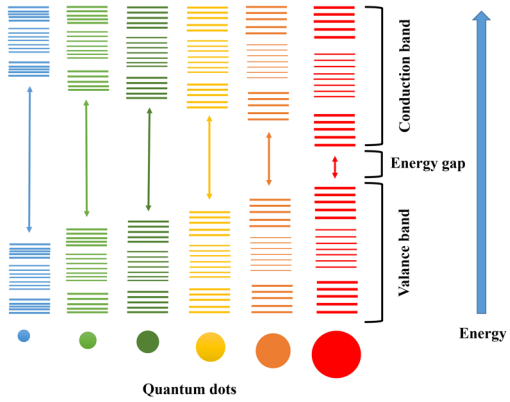

Fig. 2. The size-tunable optical characterization of QDs.

2.2. Composition tunable light emission

The core chemical composition has an effect on light emission. In other words, different emissions are formed based on the quantum dots associated elements. For example, wavelength emission of the cadmium sulfide (CdS), the cadmium tellurium (CdTe), and the cadmium selenium (CdSe) are near UV blue region, infrared region (NIR) and under visible region, respectively [25].

2.3. Spectra of absorption and emission

The spectra of absorption refer to the spectra that are generated by the photon energy absorption (hυ) resulting in the atom transition from the lower to higher energy levels. On the other hand, the emission spectra refer to the spectra generated by a molecule or atom transition from higher to lower energy levels by a photon energy emission (hυ). The multiple quantum dots can be excited from a single light source with WL lower than emission WL because of its wide absorption band. The mentioned feature causes simplified designing of high speed and inexpensive sets. The emission spectra width of QDs can be decreased to 20 nm in the range of visible spectra, which provides separate signals detection without cross talk [26, 27].

2.4. Coefficients of absorption extinction

The absorption extinction coefficient is defined as the amount of light being absorbed in a specific wavelength by a chemical material that makes materials brighter probes in in-vivo conditions. In this condition, light intensities are significantly decreased due to absorption and scattering [28].

2.5. High quantum fluorescent yields

Fluorophores are known by high fluorescent quantum yield as the intrinsic properties. This feature is the ratio of absorbed photons to emit-

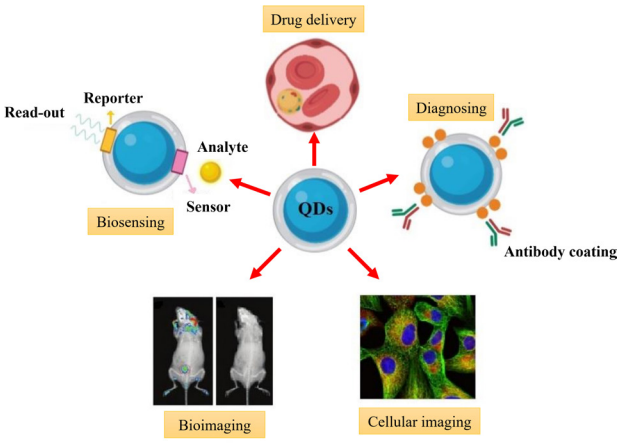

Fig. 3. Application of GQDs in nanomedicine.

ted photons during fluorescence and it is determined by Lumina fluorescence spectrometry [29].

2.6. Photo chemically robust

The high photo and chemical degradation resistance of QDs are due to their inorganic nature. Due to these properties, QDs have become an effective and excellent imaging instrument in the long term [30].

2.7. Photobleaching resistance

The decrease in intensity of fluorescence occurs due to light responding reactions or optical excitation that is the result of irreversibly luminescent material decomposition and is known as photobleaching [29].

Generally, QDs show a blinking behavior that is an attractive phenomenon because it is observed during continuous excitation of the molecule. This occurs due to photo-excited carriers trapping and detraining that leads to the QDs fluctuation between non-emissive and emissive states. In a short time, the fluctuation intensities known as 'quantum jumps' usually remain for small periods in comparison with fluorophores. However, the quantum dots containing thick crystalline shells would not blink [7].

3. Graphene quantum dots

In the past, carbon quantum dots (CQDs) were found by accident during working on single-walled carbon nanotubes (SWCNT) [31]. Then, the CQDs fluorescence features were reported so CQDs have become a new group of the smallest viable fluorescent nanomaterials with high biocompatibility. Recently, graphene quantum dots (GQDs) have attracted significant attention because of their advantages such as environmental compatibility, biocompatibility, photo-stability, and low toxicity [32-36]. Thus, carbon quantum dots can be used as good substitutes and applied in biological fields instead of unstable organic fluorophores or semiconductor quantum dots that are toxic [37]. Various simple fabrication routes for GQDs have been reported viz. laser ablation, hydrothermal method, acid oxidation, pyrolysis, electrochemical method, acid oxidation, and microwave-assisted methods [38-43]. Also, green GQDs prepared by organic compounds without chemical exposure, which has good availability, self-passivation, and high quantum yield (QY) [44]. As GQDs showed tunable and stable optical fluorescence, compatibility, and photostability, they are able to function as electron acceptors and donors [42, 45-47]. The GQDs have been investigated in bio-imaging as fluorescent nanoprobes [41, 42, 48-53], drug/gene delivery agents [38, 54-56], and antibacterial agents [57]. Furthermore, GQDs have been used in various applications ranging from catalysts to light-emitting devices [58-60]. In addition, their usages in clinical applications are expected to be expanded in the future [59, 61].

There are various methods to produce nanomaterials such as sol-gel [62-66], electrospinning method [67-69], coprecipitation [70], metallurgy powders [71, 72], SHS methods [73], and mechanical alloys [74, 75]. Moreover, there are several nanomaterials as nanoparticles [76, 77], nanolayers [78], nanosheets [79], and quantum dots [80]. Among the mentioned materials, GQDs have attracted more attention due to their unique applications.

3.1. Graphene quantum dot synthesis

The synthesis method has a major role in the properties of GQDs as well as their applications. Thus, the GQDs production should be tuned during and after their production [81]. Since the emergence of GQDs, different methods have been used to produce GQDs such as chemical, physical, and electrochemical techniques [56]. These methods of GQDs

Table 1.
Various methods for the fabrication of GQDs used in biomedical applications

Method of synthesis & precursors	Application	Ref.
Top-down Approach		
GQD synthesized through the chemical treatment from ethanolamine	diagnosis	[1]
GQD-ssDNA: chemical oxidation of candle soot	diagnosis	[2]
CL-GQD:GQD fabricated by MWCNT conjugated with anti-desman and functionalized with-COCL	Cancer diagnosis	[3]
GQD-PEG-AG; Acidic oxidation of CNT and graphite	Radiotherapy	[6]
Bottom-up Approach		
GQD-PEI; hydrothermal and oxidation reaction of polyethyleneimine	Gene transfection	[8]
MSN-SS-CD-DOX: Hydrothermal polymerization route using poly-acrylic acid	Targeted and controlled drug delivery along with booming	[14]
Microwave synthesis route using ethylene diamine and acrylic acid as well as functionalization with glicidyl methacrylate.	Targeted cancer drug delivery	[16]
Thermal combustion of rice straw	Detection and counting of bacteria	[17]
GQD-RhB-silka	Diagnosis	[18]
Hydrothermal treatment of citric acid monohydrate	Glsoma targeting and bio imaging	[20]

synthesis can be categorized into the “top-down” and “bottom-up” procedures. These routes are based on the source of carbon that is utilized for the GQDs fabrication. In the bottom-up approach, the basic building units are collected to produce the desired material. Hence, to produce fluorescent GQDs by the bottom-up method, the block is operated in carbonization, condensation, and polymerization processes at optimized conditions of synthesis [82]. In the top-down approach, a bulk source of carbon (e.g. fullerenes, candle shoots, and graphite rods) is broken down into a diameter of less than 10 nm with fluorescent properties [83-85]. General examples of the last method are the mechanical and chemical treatment of C60 fullerenes that produce carbon quantum dots with small sizes (2–3 nm) [86, 87]. The top-down method requires chemical routes such as electrochemical carbonization, chemical ablation, and laser ablation to break down the molecules with large size. In the case of the bottom-up method, greener methods are used such as hydrothermal/solvothermal treatment and microwave irradiation. Indeed, the top-down procedures require complex instrumentation and severe chemical treatments but the bottom-up processes are greener and need simple procedures for the synthesis of GQDs. Among bottom-up routes, the hydrothermal/solvothermal techniques are more common due to the high quantum production efficiency and environment-friendly nature. In addition, these routes are cost-effective, easily scalable, and fast. It has been reported that the GQDs size controllability is hard through this method, but some post-treatments can be used in this case like dialysis, filtration, sonication, column chromatography, centrifugation, gel-electrophoresis and column chromatography [56]. Table 1 lists the routes used for the fabrication of GQDs used in biomedical applications.

4. Applications

As common organic label dyes cannot have emission around 650 nm, which belongs to near-infrared emission, QDs have attracted attention because of their tunable optical characteristics. QDs exhibit some characteristics including size-tunable light emission, high quantum yield, and improved chemical and photo-stability. A specific light wavelength is able to excite different types of QDs, and the simultaneous detection of their narrow emission bands for multiple assays is possible. The simultaneous imaging, sensing, and therapy is widely studied by developing nano-theranostics platforms such as QDs (Fig. 3) [88, 89]. In this paper, the latest progress in QDs utilization and biomedical applications has been reviewed.

4.1. Sensors

Due to electronic and optical properties, luminescent graphene quantum dots (GQDs) have lately been of great interest. GQDs are composed of single, double, and multiple layers of graphene sheets having the diameters between 3 to 20 nanometers and lateral size less than 100 nanometers [90, 91]. Excellent photostability, robust chemical inertness, high fluorescent activity, high biocompatibility, and low toxicity are among the properties of GQD [92], which are the result of quantum confinement effect and edge effect (zigzag or armchair).

Table 2.
Summary of works performed on GQDs as sensors

Electrode	Linear range (µM)	LOD (µM)	Conditions	Real sample	Ref.
MWCNT. COOH/SPCEs	14.5.100	4.6	Nacl(PH=7.0)	Blood serum	[93]
MT/HMDE	25-375	0.5	BR buffer (PH= 7.2)	Blood serum	[94]
GO.MWNTs/ GCE	1.3-26	0.192	KCL(PH= 7.4)	Blood serum	[95]
GQDs-thio/ npGCE	0.2-110	0.09	PBS,K-CL(PH= 7.0)	Blood serum, urine	[96]

Owing to these characteristics, GQDs can be employed for a wide range of applications including sensors, biosensors, bioimaging, and photovoltaic devices [97]. Gholivand et al. [96], used the grapheme quantum dots-thionine and nanocarbon electrode (porous glassy structure) to detect an anticancer drug (cisplatin). Their results showed that the combination of dyes with nanomaterials would lead to tuned electroanalytical applications of the modified electrodes in chemistry. Also, it was shown that the glassy nanoporous QDs, which are produced with thionine, could interact with drugs (cisplatin) and increase the accumulated target at the electrode. Their as-prepared electrode had good sensitivity, selectivity, and reproducibility compared to other cisplatin sensors reported in other works. Table 2 summarizes the studies conducted on the application of QDs as sensors.

4.2. Biomedicine

Kaur et al. [98] doped nitrogen (heteroatom) to graphene and produced GQDs with promising properties based on carbon nanomaterials. Their doping approach resulted in an improvement in the properties of QDs in environmental and energy fields. This caused the residual reagents elimination such as acids. Their as-synthesized materials showed excellent properties for the use in different fields like fuel cells, sensors, photocatalytic processes, batteries, solar cells, and photocatalytic processes. Lah et al. [99] used quantum dots for fluorescence sensing application by a tapered optical fiber (TMMF). The quantum dots were introduced with the aim of increasing the sensing process. In their study, nano-sized GQDs particles were produced by organic biochar. Subsequently, they coated the GQDs with the purple solution of gold nanoparticles that were functionalized by cysteamine. The GQDs with the coating layer of Au nanoparticles were obtained by carbon-nitrogen bonding reaction from carboxyls and nitrogen-hydrogen from amine groups. In their investigation, various annealing treatments were analyzed to determine the optimum sensitivity for the sensor. Fastening between the sensing element and TMMF occurs through the annealing process that changes the GQDs coating layer thickness. They reported that TMMF, which was coated by GQDs and annealed at 70 °C had a higher peak of fluorescence emission at 652 nm. In addition, the best linearity and the detecting sensitivity were achieved by the samples annealed at 70 °C. They reported that the linearity was 81% and the sensitivity was equal to 0.047 au. %. Meanwhile, TMMF coated with Au-GQDs showed higher intensity of fluorescence emission in comparison with others.

In order to detect the full RH range, Qi et al. [100] produced a quartz crystal microbalance (QCM) humidity sensor which was coated by a film of GQDs-chitosan (CS). They used the oscillating circuit technique for the investigation of the dynamic response and used impedance analysis to determine the recovery behaviors and performance of static humidity sensing. The results showed that GQDs as fillers in nanometer size can lead to good dispensability in the CS matrix, which causes enhanced mechanical properties. Moreover, more adsorption sites are achieved due to the hydrophilicity nature of CS and GQDs. They reported that the highest humidity sensitivity, and also high recovery time and rapid response, long-term reversibility, tiny humidity hysteresis (approximately 1.6% RH), long-term stability, and ideal reproducibility were achieved for the optimized QCM sensor, which makes these sensors capable of sensing a wide range of water vapor content.

Safardoust et al. [101] doped nitrogen and sulfur in graphene quantum dots (S, N-GQDs) by the hydrothermal method. Their sources of carbon and nitrogen sulfur were citric acid and thiourea, respectively.

Their results indicated that the fluorescence emission of S, N-GQDs was depended on the excitation. In order to detect ascorbic acid (AA), they applied the produced S, N-GQDs as photoluminescence probe. They used the "off-on" mode for detection. Addition of Cu^{2+} to S, N-GQDs solution, caused the fluorescence quenching and addition of ascorbic acid to Cu^{2+}/S, NGQDs solution resulted in the improvement in the solution fluorescence intensity. At AA concentration from 10 to 500 μm, a linear response was observed with a 1.2 μM-detecting limit.

Tang et al. [102] produced a modified carbon electrode with a glassy structure by electrodeposition of gold nanoparticles and graphene quantum dots (GQDs/GNPs/GCE). Their prepared electrode showed good electrocatalytic activity, stability, and large surface area that is electrochemically active. They reported that the GQDs/GNPs/GCE produced in optimized conditions had good performance related to, linear calibration range, reproducibility, detection limit, and stability for luteolin determination. In addition, they proposed that the prepared sensor was able to detect luteolin content in real samples such as *peanut hulls*.

Zhao et al. [103], synthesized a new carbon nanocomposite MoS2-carbon nanotube - @ graphene oxide nanoribbons (CNTs@ GONRs) for the production of an ultra-sensitive quercetin sensor, which showed good detection performance for a wide linear range of quercetin (Que) and an ultra-low limit of detection (LOD). Also, their sensor showed accurate, stable, and good detection for Que in real specimens. Thus, their sensor was promising for applying in electrochemical detection fields. The summary of the above-mentioned work is presented in Table 3.

4.3. Imaging

One of the major recent advances in QDs applications is their application in multicolor and sensitive cellular imaging, because of noticeable enhancement in their synthesis, surface conjugation, and chemistry [104].

Sheng et al. [105] doped quantum dots with nitrogen (N-GQDs) using a hydrothermal process. In this study, PVP K90, glutamate, and citric acid were used as raw materials and the prepared sensor showed a 64.2 % quantum yield. They reported that the new fluorescence probe of nitrogen-doped GQDs can be used both for marking MCF-7 cells and the detection of Cr(VI).

Fan et al. [2] prepared GQDs with specific properties for imaging of the mitochondria or cell nucleus by a facile method suitable for large-scale production. Their aim was to solve the weak points of GQDs such as low-targeted specificity and selectivity, unachievable large-scale synthesis by green methods, and unreported imaging of mitochondria. The synthesized GQDs- tetraphenylporphyrin (TPP) and GQDs- polyethyleneimine (PEI) had low cytotoxicity, a high yield of about 60%, and good optical properties. They reported that both GQDs have high target selectivity for the cell nucleus and can be used for mitochondria imaging. They claimed that the synthesized GQDs did not exhibit the photobleaching and cytotoxicity compared to common fluorescent dyes.

Table 3.
Summary of the QDs used in biomedicine

Researcher	Composite	Application	Ref.
Gholivand	GQD-thno/ npGCE	Voltammetric sensor	[96]
Lah	Au-GQD		[99]
Qi	CS-GQD	Optical sensors	[100]
Safardoust	S,N- GQD	Humidity Sensor	[101]
Tang	GQD/GNP/GCE		[102]
Zhao	CD/GQD/GCE	Ascorbic acid concentration sensitive sensors	[103]

In addition, the synthesized GQDs can be used as new materials for monitoring and locating mitochondria and the cell nucleus in the field of biomedical. In other work, Gvozdev et al. [106] synthesized semiconductor nanocrystal composed of polycationic aluminum phthalocyanines (Pc) complex and the human transferrin in hollow form. Due to the hydrophobic and electrostatic interactions, Pc molecules diffuse into the shell of QD while protein formed covalent bonding onto the organic shell of QD. The results showed high Pc delivery efficiency to the A431 cells. Moreover, HC was stable in cells. They reported the successful transfer of energy from the QD to Pc and the HC photodynamic influence in the cells, which offers QDs as light-harvesting antennas to enhance the effective absorption photosensitizer molecules cross-section in the blue-green spectral region and the increase of the photodynamic action of Pc.

Hai et al. [107] prepared an imaging system and pH sensing by encapsulating graphene quantum dots in folic acid (FA-GQDs) as a probe. Their tests showed that encapsulated FA-GQDs are stable and homogenous and the FA was bound to the GQDs surface. The synthesized FA-GQDs showed pH-sensitive properties and multicolor emission characteristics. In addition, they proposed a pH sensor with ratio-metric fluorescence based on the response of pH at low excitations (280 nm). It has been used for the pH determination of cell suspensions and aqueous specimens. The pH-sensitive, broad emission properties of FA-GQDs offer a great potential for application related to particular living cells multicolor imaging and pH sensing.

Huang et al. [32] introduced a new and effective method for GQDs preparation from graphene oxide (GO) by the one-step thiolene click reaction which is efficient and cheap compared to conventional routes. In addition, the results showed good biocompatibility, strong green fluorescence, uniform nanoscale size, and stable photostability. They purposed the impartment of carboxyl groups with GQDs having great suitability and water solubility to be modified with different polymers for drug delivery applications. Overall, the suggested that the one-step thiolene click reaction is a high-efficiency method for designing the characteristics of GQDs for applications in various biomedical fields.

Jin et al. [108] selected a nontoxic and cost-effective source of sulfur to prepare S-GQDs with high luminescence by a simple hydrothermal approach in one-step. Their objective of doping sulfur was the improvement of the fluorescent intensity of QDs. The synthesized S-GQDs showed low cytotoxicity that would simply diffuse into the membranes of the HeLa cell. Also, they reported that incubated S-GQDs with the common bacteria medium had low antiseptic qualities. They suggested that sulfur doping enhances the optical properties and indicates the potential of these GQDs for bioimaging applications.

In the Mahmood Kashan et al. [109] study, a simple, low-cost, green, bottom-up synthesis approach was suggested for the production of a biocompatible probe of His-GQDs using histidine and citric acid. The luminescent probe had excellent solubility in water, low cytotoxicity, and optimal fluorescence efficiency. The size distribution was near to 2 nm. They reported that the synthesized His-GQD were able to enter the cytoplasm of human ACHN cells and showed low cytotoxicity and high viability, hence, they are promising candidates for in-vitro cellular imaging.

Mondla et al. [110] prepared smart graphene quantum dot (NSGQD) with S and N donor having good fluorescence properties. The radiative recombination of trapped holes and electron on the surface of NS-GQD was the reason for the smart fluorescence properties. They reported that the unique fluorescence characterization of NS-GQD is due to heteroatoms (N and S) existence. The term "smartness" is due to its performance

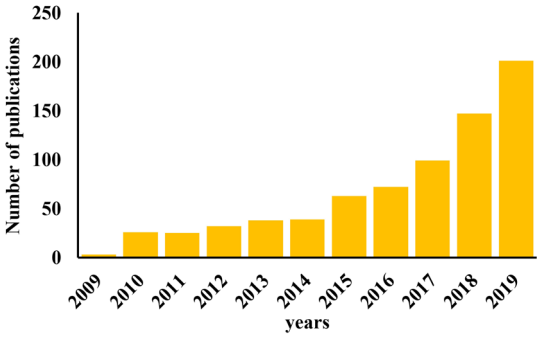

Fig. 4. Number of publications reporting GQDs for cancer therapy.

as a promising fluorescent probe in the field of intracellular imaging, which is comparable to the available commercial dye. In addition, DCQ was formed due to interaction between the functional group in NS-GQD and drug streptomycin, in which Stm and NS-QGD are mixed with each other in a simple approach to form a carbogenic structure. On the other hand, the antibacterial efficacy was improved by DCQ due to the free radicals generation in bacteria and it is safe in terms of synthesis processes.

Rajender et al. [111] synthesized edge controlled GQDs with few layers and high fluorescence yield through a solvent dependent process. To investigate the cancer cells' bioimaging, the high photoluminescence (PL) production of GQDs was used. Their study proposed that the functional groups and edge sites of graphene quantum dots can be controlled by the addition of various solvents in the GQDs top-down processing. Different analyses demonstrated the oxygenated functional groups on the edge of GQDs. A high 32% PL quantum yields (QY) (32%) was obtained by the GQDs synthesis using dimethylformamide (DMF) solvent. This high amount is resulted from defects of oxygen functional groups and the enriched edge sites. They reported that the PL emission efficiency in the solvent medium is related to GQDs dielectric constant. The cancer cell lines bio-imaging results showed blue PL emission inside the cells, which demonstrated their good ability for bio-imaging applications. Also, good biocompatibility of synthesized graphene quantum dots with A-375 cells was observed in comparison with that of HeLa cells.

Wang et al. [112] prepared theranostic nanoparticles by doping boron and nitrogen in GQDs. The nanoparticles had a PL emission spectrum from 950 nm to 1100 nm. They presented the first results of near-Infrared-II (NIR-II) imaging (>1000 nm) in-vivo for blood vessels and internal organs in a mouse model using a metal-free QD. They reported that the NIR light was absorbed and transferred into heat by the nanoparticle, so the nanoparticles can be used as photothermal therapy (PTT) agents in cancer treatment applications. Their study results revealed that the irradiation of NIR for 5 minutes, while the nanoparticle was injected systemically, led to complete suppression of the growth of tumor cells [113]. Furthermore, they reported its potential for imaging-guided therapy for cancers due to its desirable therapeutic and fluorescent characterizations. Table 4 summarizes the above-mentioned research.

4.4. Drug delivery

The use of GQDs for in-vivo drug delivery is broadly investigated. QDs have high delivery efficiency because of their intermediate size that decreases the uptake by the reticuloendothelial system and the renal clearance leading to the increase in the blood circulation time [80].

Senel et al. [114] synthesized N-doped GQD and reported its properties such as cost-effective production, DNA interaction, potential cell growth, and antioxidant and antimicrobial activities. They observed that GQDs doped with nitrogen could be linked to DNA through electrostatic and intercalation route. According to their report, the formulations

Table 4.
Application of GQDs in tumor treatment field

Researcher	Composite	Application	Ref.
Fan	GQD	Mitochondria vector illustration	[2]
Hai	PH sensitive FA-GQD	Cellular Imaging	[107]
Huang	GQD	Cellular Imaging	[32]
Ragender	GQD	Biological imaging of cancer cells	[111]
Wang	-	Biological imaging of cancer cells	[112]

Table 5.
GQDs applied in the field of drug delivery

Researcher	Composite	Application	Ref.
Senel	SiRNA/GQD/ DOX	Therapy of A549 cancer cells	[114]
Akbarzadeh	Hybrid silica / GQD/PEGylated	Therapy cancer	[115]
Innazzoa			[116]
Javanbakht	CMC/GQDDOX	Therapy of K562Leukemia cells	[117]
Nasrollahi	GQD/CDDP	Breast Cancer Cells	[118]

containing short interfering RNA (siRNA) synthesized by GQDs can decrease and minimize the side effects and anticancer drug toxicities resulting from common chemotherapy methods. They reported that due to the QDs luminescence characteristics, the GQD-containing formulations led to the penetration into cells and the reduction in cancer cell numbers based on ephrin-A (EpHA2) reduction, which showed high efficiency in A549 cells. They reported that this is the result of the GQDs shearing effect on DNA and siRNA. Based on their research, the QDs effect can be maximized in higher doses and cause lower cell viability by breaking the cancer cells DNA. Also, they showed the bioimaging capability of QDs in low doses. In addition, a complex of siRNA-GQDs is effective at low dose for A549 cells.

Akbarzadeha et al. [115] studied the silica-coated dipole quantum dots. They reported the synthesis of smart nano aptamer-targeted by mesoporous silica-coated QDs having bimodal imaging capacity. In addition, their in-vivo experiment results indicated that the prepared targeted hybrid system showed the capability of MR and fluorescent imaging.

Iannazzoa et al. [116], studied the graphene QDs for drug delivery as well as a cancer treatment. They indicated that the prepared GQDs have a great ability of drug delivery into cancer cells and biocompatibility. Also, the multimodal conjugation provides the possibility of incorporating both targeting ligands and drugs in nanomaterials. This led to minimizing the toxicity and side effects of conventional chemotherapy.

Javanbakhta et al. [117] reported that a hydrogel film of nano-carboxymethyl cellulose/graphene quantum dots (CMC/GQDs) could be applied for drug delivery applications. They synthesized the film using the casting route to introduce GQDs as in the CMC hydrogel as a polymeric matrix. The hydrogel film of CMC/GQDs exhibited an excellent degradation, mechanical properties, swelling, and permeability. The presence of GQD in CMC film led to the prolonged doxorubicin (DOX) release and pH-sensitivity. According to cytotoxicity results, the DOX/CMC/GQD nanocomposite had a great capability to act as an anticancer agent with high efficiency. They also reported that the prepared nanocomposite did not have noticeable toxicity against K562 blood cancer cells.

Nasrollahi et al. [118] studied GQD nanoparticles, which were bond-

ed to an antibody (scFvB10) for targeted cellular imaging and Cisplatin (CDDP) delivery.

Using strong GQDs fluorescence as bioimaging agents, the mechanism of targeting and efficient uptake of antibody-linked GQDs through the EGFR-mediated endocytosis were conformed. Using 50% loading of CDDP, targeted delivery of the drug was achieved by the antibody-linked GQDs.

In a study conducted by Li Ruiyia et al. [119], core-shell drug delivery agents consisting of, MGC-803 cell membrane shell and gold nanoparticle as the core, were synthesized. In comparison with free DOX, the prepared sample showed both light and pH-stimulated DOX release, homotypic cancer cells targeting, and chemo/photothermal therapy having a higher activity against cancerous cells. Their excellent biocompatibility and high anticancer activity were confirmed by in-vivo and in-vitro investigations. A new approach to design and synthesize nanocarriers for the diagnosis of cancer in the early stages and in-situ treatment has been suggested in this research.

In a study carried out by Xiaoqian Su et al. [120], nanoparticle uptake in cells and secretion of drug molecules into cells by altering FRTE signal in cancer cells were checked out. They also observed an increase in the therapeutic effect of doxorubicin in combination with Fe_3O_4@SiO_2@GQD-FA nanoparticles. In general, the reported nanoparticles can be considered as a suitable basis for the effective diagnosis and treatment of cancer. Table 5 lists the above-mentioned research

4.5. Diagnosis

One of the applications of GQDs in the field of biomedicine is in diagnosis. The advantages of having low toxicity of GQDs over traditional semi-conductive QDs has made them suitable for in-vivo labeling [6, 121].

In the fields of diagnosis and cancer therapy, quantum dots show great potential to be applied as fluorescence labels. The quantum dotes are suitable for distinguishing and specific applications due to their physicochemical properties. The mode of QDs implementation has a specific effect on their applications. The GQDs are ideal candidates due to the size-dependent and symmetric photoluminescence band combined with very wide absorption bands. On the other hand, GQDs are good reactive oxygen species (ROS) producers and have excellent potential for applications in photodynamic therapy fields. Despite the QDs potentials, various unsolved problems have remained. One of the major issues is that QDs can be used for real-life applications if all interdependencies between their chemical and physical properties have been determined. This becomes the main concern for GQDs application due to the insufficient information about different aspects of their key optical properties such as extinction coefficients, lifetimes, PLQYs, photo brightening mechanisms, and photobleaching. It is promising that GQDs are relatively new-materials and the publications rate in cancer therapy applications and diagnosis is increasing rapidly (Fig. 4). Furthermore, there is a big gap in knowledge about the toxicity of both types of quantum dots and semiconductor QDs. This is the main factor that needs to be studied immediately because the main application of QDs is in biomedical fields specially and the important factors are their biocompatibility and cytotoxicity. Unfortunately, there is no standardized methodology for such assessment and it is, therefore, impossible to compare results obtained from different biomedical applications found in the literature [122].

Suleiman et al. [123] evaluated cancer cells using nitrogen-doped graphene quantum dots. To detect colon, breast, and stomach cancer cells, a novel silo sensor based on Rayleigh scattering was used. There are also groups of NH or NH_2 in the GQDs that provide more active sites for bonding between cells and matter. The biocompatibility of quantum dot nanomaterials was evaluated by the MTT method. Cellular uptake evaluation revealed that FA-N-GQD uptake increased in HT29, MKN45, and MCT7 target cells, and the uptake of FA-N-GQD in non-target cells also decreased. The prominent features of the introduced cytosensor include its functional system based on the interaction between antigens, sensitivity to cancer cells, and low toxicity. He et al. [124] worked on quantum dots to detect cancer. In their studies, quantum dot performance in targeted drug delivery and imaging were checked out. Actually, these QDs are improved to reduce toxicity and increase the shelf life of blood with other nanoparticle dots.

Fan et al. [125] showed that pH-responsive fluorescent (pRF-GQDs) could detect cancer in the early stages of tumor formation. The reasons for the application of PRF-GQDs as a prospector are their high sensitivity against cancerous cells, high safety, and fluorescence switching between healthy weaves and tumors. Considering these properties, pRF-GQDs are good options to diagnose or treat cancer. In addition, electrochemical reaction, as an effective approach to dope carbon materials with heteroatoms make it possible to finely alter their intrinsic properties and introduce new characteristics. Tuning the properties through the atoms doping approach allows the synthesis of GQDs responding to pH deviates from 7.4.

5. Conclusions and future insights

QDs are nanoparticles with high photo-luminescence having the potential to be used for targeted drug delivery and imaging. Although GQDs perform well in areas such as sensors, drug delivery, and bio-imaging, they have limitations such as overall toxicity and body clearance in biomedical applications. This has led to the synthesis of quantum dot-based composites. Indeed, by combining GQDs with biologically active molecules and/or nanoparticles, theranostic platforms are constantly being developed. This review on GQDs reported their potential properties and their applications as carriers for sensor and drug delivery applications. Additionally, research on synthesizing routes according to their application was investigated. There may be a need for future investigations focusing on other heteroatoms doping. Controlled doping of GQDs and graphene would be possible by performing more studies with theoretical analysis, which may lead to an increase in their efficiency for environmental and energy source applications. There might be an increasing interest in the utilization of N-doped carbon materials for the applications related to photocatalysis for the remediation of water pollutants. Moreover, there are few reports addressing nitrogen-doped graphene and nitrogen-doped GQDs to inactivate the microorganisms in water and air. The disinfecting effect of these materials on water and air may be environmental studies. In order to produce GQDs with various functional groups and characteristics, other components may be also investigated. Hence, certainly, all these promising properties of NS-GQD would introduce them as good candidates for biomedical applications in the recent future. According to recent studies, further research on doping nitrogen into GQDs for drug development is appealing. It is thus expected that many of the knowledge gaps mentioned above will be addressed.

Acknowledgments

The authors received no financial support for the research, authorship and/or publication of this article.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

REFERENCES

[1] C. Yu, X. Li, F. Zeng, F. Zheng, S. Wu, Carbon-dot-based ratiometric fluores-cent sensor for detecting hydrogen sulfide in aqueous media and inside live cells, Chemical Communications 49(4) (2013) 403-405.

[2] H. Li, Y. Zhang, L. Wang, J. Tian, X. Sun, Nucleic acid detection using carbon nanoparticles as a fluorescent sensing platform, Chemical Communications 47(3) (2011) 961-963.
[3] C.-f. Li, Z.-k. Yan, L.-b. Chen, J.-p. Jin, D.-d. Li, Desmin detection by facile prepared carbon quantum dots for early screening of colorectal cancer, Medicine 96(5) (2017).
[4] M. Geszke-Moritz, M. Moritz, Quantum dots as versatile probes in medical sci-ences: Synthesis, modification and properties, Materials Science and Engineering: C 33(3) (2013) 1008-1021.
[5] T. Rahimi-Aghdam, Z. Shariatinia, M. Hakkarainen, V. Haddadi-Asl, Nitrogen and phosphorous doped graphene quantum dots: Excellent flame retardants and smoke suppressants for polyacrylonitrile nanocomposites, Journal of hazardous materials 381 (2020) 121013.
[6] H. Tao, K. Yang, Z. Ma, J. Wan, Y. Zhang, Z. Kang, Z. Liu, In vivo NIR fluo-rescence imaging, biodistribution, and toxicology of photoluminescent carbon dots produced from carbon nanotubes and graphite, Small 8(2) (2012) 281-290.
[7] K.-T. Yong, Y. Wang, I. Roy, H. Rui, M.T. Swihart, W.-C. Law, S.K. Kwak, L. Ye, J. Liu, S.D. Mahajan, Preparation of quantum dot/drug nanoparticle formu-lations for traceable targeted delivery and therapy, Theranostics 2(7) (2012) 681.
[8] L. Hu, Y. Sun, S. Li, X. Wang, K. Hu, L. Wang, X.-j. Liang, Y. Wu, Multi-func-tional carbon dots with high quantum yield for imaging and gene delivery, Carbon 67 (2014) 508-513.
[9] V. Reshma, P. Mohanan, Quantum dots: Applications and safety consequences, Journal of Luminescence 205 (2019) 287-298.
[10] L. Liu, H. Jiang, J. Dong, W. Zhang, G. Dang, M. Yang, Y. Li, H. Chen, H. Ji, L. Dong, PEGylated MoS_2 quantum dots for traceable and pH-responsive che-motherapeutic drug delivery, Colloids and Surfaces B: Biointerfaces 185 (2020) 110590.
[11] X. Zhao, W. Gao, H. Zhang, X. Qiu, Y. Luo, 20 - Graphene quantum dots in biomedical applications: recent advances and future challenges, in: C. Mustansar Hussain (Ed.), Handbook of Nanomaterials in Analytical Chemistry, Elsevier2020, pp. 493-505.
[12] E. Asadi, M. Abdouss, R.M. Leblanc, N. Ezzati, J.N. Wilson, S. Azodi-Deil-ami, In vitro/in vivo study of novel anti-cancer, biodegradable cross-linked tannic acid for fabrication of 5-fluorouracil-targeting drug delivery nano-device based on a molecular imprinted polymer, RSC Advances 6(43) (2016) 37308-37318.
[13] E. Asadi, M. Abdouss, R.M. Leblanc, N. Ezzati, J.N. Wilson, D. Kordestani, Synthesis, characterization and in vivo drug delivery study of a biodegradable na-no-structured molecularly imprinted polymer based on cross-linker of fructose, Polymer 97 (2016) 226-237.
[14] J. Jiao, C. Liu, X. Li, J. Liu, D. Di, Y. Zhang, Q. Zhao, S. Wang, Fluorescent carbon dot modified mesoporous silica nanocarriers for redox-responsive con-trolled drug delivery and bioimaging, Journal of colloid and interface science 483 (2016) 343-352.
[15] M. Abdouss, E. Asadi, S. Azodi-Deilami, N. Beik-mohammadi, S.A. Aslan-zadeh, Development and characterization of molecularly imprinted poly-mers for controlled release of citalopram, Journal of Materials Science: Materials in Medi-cine 22(10) (2011) 2273.
[16] W. Li, Q. Liu, P. Zhang, L. Liu, Zwitterionic nanogels crosslinked by fluo-res-cent carbon dots for targeted drug delivery and simultaneous bioimaging, Acta biomaterialia 40 (2016) 254-262.
[17] T.K. Mandal, N. Parvin, Rapid detection of bacteria by carbon quantum dots, Journal of biomedical nanotechnology 7(6) (2011) 846-848.
[18] Y. Liu, Y. Zhao, Y. Zhang, One-step green synthesized fluorescent carbon nan-odots from bamboo leaves for copper (II) ion detection, Sensors and Actuators B: Chemical 196 (2014) 647-652.
[19] M.F. Frasco, N. Chaniotakis, Bioconjugated quantum dots as fluorescent probes for bioanalytical applications, Analytical and Bioanalytical Chemistry 396(1) (2010) 229-240.
[20] L. Gao, X. Zhao, J. Wang, Y. Wang, L. Yu, H. Peng, J. Zhu, Multiple func-tion-alized carbon quantum dots for targeting glioma and tissue imaging, Optical Ma-terials 75 (2018) 764-769.
[21] M. Green, The nature of quantum dot capping ligands, Journal of Materials Chemistry 20(28) (2010) 5797-5809.
[22] A. Kundu, B. Park, J. Oh, K.V. Sankar, C. Ray, W.S. Kim, S.C. Jun, Multicolor emissive carbon dot with solvatochromic behavior across the entire visible spec-trum, Carbon 156 (2020) 110-118.
[23] C. Wang, X. Gao, X. Su, In vitro and in vivo imaging with quantum dots, Analytical and bioanalytical chemistry 397(4) (2010) 1397-1415.
[24] D.I. Son, B.W. Kwon, D.H. Park, W.-S. Seo, Y. Yi, B. Angadi, C.-L. Lee, W.K. Choi, Emissive ZnO–graphene quantum dots for white-light-emitting diodes, Nature Nanotechnology 7(7) (2012) 465-471.
[25] B.L. Wehrenberg, C. Wang, P. Guyot-Sionnest, Interband and intraband op-tical studies of PbSe colloidal quantum dots, Journal of Physical Chemistry B 106(41) (2002) 10634-10640.
[26] E.B. Voura, J.K. Jaiswal, H. Mattoussi, S.M. Simon, Tracking metastatic tu-mor cell extravasation with quantum dot nanocrystals and fluorescence emis-sion-scanning microscopy, Nature Medicine 10(9) (2004) 993-998.
[27] G. Bharathi, D. Nataraj, S. Premkumar, M. Sowmiya, K. Senthilkumar, T.D. Thangadurai, O.Y. Khyzhun, M. Gupta, D. Phase, N. Patra, S.N. Jha, D. Bhat-tacharyya, Graphene Quantum Dot Solid Sheets: Strong blue-light-emitting & photocurrent-producing band-gap-opened nanostructures, Scientific Reports 7(1) (2017) 10850.
[28] W.W. Yu, L. Qu, W. Guo, X. Peng, Experimental Determination of the Ex-tinction Coefficient of CdTe, CdSe, and CdS Nanocrystals, Chemistry of Mate-rials 15(14) (2003) 2854-2860.
[29] E. Yaghini, A. Seifalian, A. MacRobert, In vivo applications of quantum dot nanoparticles for optical diagnostics and therapy, 2011.
[30] K.-i. Hanaki, A. Momo, T. Oku, A. Komoto, S. Maenosono, Y. Yamaguchi, K. Yamamoto, Semiconductor quantum dot/albumin complex is a long-life and highly photostable endosome marker, Biochemical and biophysical research communi-ca-tions 302(3) (2003) 496-501.
[31] X. Xu, R. Ray, Y. Gu, H.J. Ploehn, L. Gearheart, K. Raker, W.A. Scrivens, Electrophoretic Analysis and Purification of Fluorescent Single-Walled Carbon Nanotube Fragments, Journal of the American Chemical Society 126(40) (2004) 12736-12737.
[32] H. Huang, M. Liu, X. Tuo, J. Chen, L. Mao, Y. Wen, J. Tian, N. Zhou, X. Zhang, Y. Wei, A novel thiol-ene click reaction for preparation of graphene quan-tum dots and their potential for fluorescence imaging, Materials Science and En-gi-neering: C 91 (2018) 631-637.
[33] Y.-M. Long, C.-H. Zhou, Z.-L. Zhang, Z.-Q. Tian, L. Bao, Y. Lin, D.-W. Pang, Shifting and non-shifting fluorescence emitted by carbon nanodots, Journal of Ma-terials Chemistry 22(13) (2012) 5917-5920.
[34] C.-Y. Sun, Y. Liu, J.-Z. Du, Z.-T. Cao, C.-F. Xu, J. Wang, Facile Generation of Tumor-pH-Labile Linkage-Bridged Block Copolymers for Chemotherapeutic Delivery, Angewandte Chemie 128(3) (2016) 1022-1026.
[35] J. Zhou, Z. Sheng, H. Han, M. Zou, C. Li, Facile synthesis of fluorescent carbon dots using watermelon peel as a carbon source, Materials Letters 66(1) (2012) 222-224.
[36] G. Konstantatos, M. Badioli, L. Gaudreau, J. Osmond, M. Bernechea, F.P.G. de Arquer, F. Gatti, F.H.L. Koppens, Hybrid graphene–quantum dot phototrans-is-tors with ultrahigh gain, Nature Nanotechnology 7(6) (2012) 363-368.
[37] Q. Li, T.Y. Ohulchanskyy, R. Liu, K. Koynov, D. Wu, A. Best, R. Kumar, A. Bonoiu, P.N. Prasad, Photoluminescent Carbon Dots as Biocompatible Na-no-probes for Targeting Cancer Cells in Vitro, The Journal of Physical Chemistry C 114(28) (2010) 12062-12068.
[38] P. Pierrat, R. Wang, D. Kereselidze, M. Lux, P. Didier, A. Kichler, F. Pons, L. Lebeau, Efficient in vitro and in vivo pulmonary delivery of nucleic acid by carbon dot-based nanocarriers, Biomaterials 51 (2015) 290-302.
[39] Y. Dong, R. Wang, H. Li, J. Shao, Y. Chi, X. Lin, G. Chen, Polyam-ine-func-tionalized carbon quantum dots for chemical sensing, Carbon 50(8) (2012) 2810-2815.
[40] H. Ming, Z. Ma, Y. Liu, K. Pan, H. Yu, F. Wang, Z. Kang, Large scale elec-tro-chemical synthesis of high quality carbon nanodots and their photocatalytic prop-erty, Dalton Transactions 41(31) (2012) 9526-9531.
[41] P.G. Luo, S. Sahu, S.-T. Yang, S.K. Sonkar, J. Wang, H. Wang, G.E. LeC-roy, L. Cao, Y.-P. Sun, Carbon “quantum” dots for optical bioimaging, Journal of Ma-terials Chemistry B 1(16) (2013) 2116-2127.
[42] X.T. Zheng, A. Ananthanarayanan, K.Q. Luo, P. Chen, Glowing Graphene Quantum Dots and Carbon Dots: Properties, Syntheses, and Biological Appli-ca-tions, Small 11(14) (2015) 1620-1636.
[43] Q. Liang, W. Ma, Y. Shi, Z. Li, X. Yang, Easy synthesis of highly fluores-cent carbon quantum dots from gelatin and their luminescent properties and appli-ca-tions, Carbon 60 (2013) 421-428.
[44] S. Liu, J. Tian, L. Wang, Y. Zhang, X. Qin, Y. Luo, A.M. Asiri, A.O. Al-Youbi, X. Sun, Hydrothermal Treatment of Grass: A Low-Cost, Green Route to Nitro-gen-Doped, Carbon-Rich, Photoluminescent Polymer Nanodots as an Effective Fluorescent Sensing Platform for Label-Free Detection of Cu(II) Ions, Advanced Materials 24(15) (2012) 2037-2041.
[45] B. De, N. Karak, A green and facile approach for the synthesis of water solu-ble fluorescent carbon dots from banana juice, RSC Advances 3(22) (2013) 8286-8290.
[46] Y. Liu, C.-y. Liu, Z.-y. Zhang, Synthesis of highly luminescent graphitized carbon dots and the application in the Hg^{2+} detection, Applied Surface Science

263 (2012) 481-485.
[47] V. Štengl, S. Bakardjieva, J. Henych, K. Lang, M. Kormunda, Blue and green luminescence of reduced graphene oxide quantum dots, Carbon 63 (2013) 537-546.
[48] L. Cao, X. Wang, M.J. Meziani, F. Lu, H. Wang, P.G. Luo, Y. Lin, B.A. Harruff, L.M. Veca, D. Murray, Carbon dots for multiphoton bioimaging, Journal of the American Chemical Society 129(37) (2007) 11318-11319.
[49] J.C.E. da Silva, H.M. Gonçalves, Analytical and bioanalytical applications of carbon dots, TrAC Trends in Analytical Chemistry 30(8) (2011) 1327-1336.
[50] K. Hola, Y. Zhang, Y. Wang, E.P. Giannelis, R. Zboril, A.L. Rogach, Carbon dots—Emerging light emitters for bioimaging, cancer therapy and optoelectronics, Nano Today 9(5) (2014) 590-603.
[51] W. Kong, R. Liu, H. Li, J. Liu, H. Huang, Y. Liu, Z. Kang, High-bright fluo-rescent carbon dots and their application in selective nucleoli staining, Journal of Materials Chemistry B 2(31) (2014) 5077-5082.
[52] Y. Song, S. Zhu, B. Yang, Bioimaging based on fluorescent carbon dots, RSC Advances 4(52) (2014) 27184-27200.
[53] S.-T. Yang, X. Wang, H. Wang, F. Lu, P.G. Luo, L. Cao, M.J. Meziani, J.-H. Liu, Y. Liu, M. Chen, Carbon dots as nontoxic and high-performance fluorescence imaging agents, The Journal of Physical Chemistry C 113(42) (2009) 18110-18114.
[54] X. Gong, Q. Zhang, Y. Gao, S. Shuang, M.M. Choi, C. Dong, Phosphorus and nitrogen dual-doped hollow carbon dot as a nanocarrier for doxorubicin delivery and biological imaging, ACS applied materials & interfaces 8(18) (2016) 11288-11297.
[55] C. Liu, P. Zhang, X. Zhai, F. Tian, W. Li, J. Yang, Y. Liu, H. Wang, W. Wang, W. Liu, Nano-carrier for gene delivery and bioimaging based on carbon dots with PEI-passivation enhanced fluorescence, Biomaterials 33(13) (2012) 3604-3613.
[56] L. Wang, H.S. Zhou, Green synthesis of luminescent nitrogen-doped carbon dots from milk and its imaging application, Analytical chemistry 86(18) (2014) 8902-8905.
[57] M.J. Meziani, X. Dong, L. Zhu, L.P. Jones, G.E. LeCroy, F. Yang, S. Wang, P. Wang, Y. Zhao, L. Yang, Visible-light-activated bactericidal functions of carbon "Quantum" dots, ACS applied materials & interfaces 8(17) (2016) 10761-10766.
[58] X. Zhang, Y. Zhang, Y. Wang, S. Kalytchuk, S.V. Kershaw, Y. Wang, P. Wang, T. Zhang, Y. Zhao, H. Zhang, Color-switchable electroluminescence of carbon dot light-emitting diodes, ACS nano 7(12) (2013) 11234-11241.
[59] X. Huang, F. Zhang, L. Zhu, K.Y. Choi, N. Guo, J. Guo, K. Tackett, P. Anilku-mar, G. Liu, Q. Quan, Effect of injection routes on the biodistribution, clearance, and tumor uptake of carbon dots, ACS nano 7(7) (2013) 5684-5693.
[60] J.-H. Liu, L. Cao, G.E. LeCroy, P. Wang, M.J. Meziani, Y. Dong, Y. Liu, P.G. Luo, Y.-P. Sun, Carbon "quantum" dots for fluorescence labeling of cells, ACS applied materials & interfaces 7(34) (2015) 19439-19445.
[61] P. Devi, S. Saini, K.-H. Kim, The advanced role of carbon quantum dots in nanomedical applications, Biosensors and Bioelectronics 141 (2019) 111158.
[62] F.S. Jazi, N. Parvin, M. Tahriri, M. Alizadeh, S. Abedini, M. Alizadeh, The relationship between the synthesis and morphology of SnO_2-Ag_2O nanocomposite, Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 44(5) (2014) 759-764.
[63] F. Sharifianjazi, N. Parvin, M. Tahriri, Formation of apatite nano-needles on novel gel derived SiO_2-P_2O_5-CaO-SrO-Ag_2O bioactive glasses, Ceramics Interna-tional 43(17) (2017) 15214-15220.
[64] Z. Goudarzi, N. Parvin, F. Sharifianjazi, Formation of hydroxyapatite on surface of SiO_2– P_2O_5–CaO–SrO–ZnO bioactive glass synthesized through sol-gel route, Ceramics International 45(15) (2019) 19323-19330.
[65] M.S.N. Shahrbabak, F. Sharifianjazi, D. Rahban, A. Salimi, A Comparative Investigation on Bioactivity and Antibacterial Properties of Sol-Gel Derived 58S Bioactive Glass Substituted by Ag and Zn, Silicon (2019) 1-11.
[66] V.S. Rizi, F. Sharifianjazi, H. Jafarikhorami, N. Parvin, L.S. Fard, M. Irani, A. Esmaeilkhanian, Sol–gel derived SnO_2/Ag_2O ceramic nanocomposite for H_2 gas sensing applications, Materials Research Express 6(11) (2019) 1150g2.
[67] H. Bahrami, S.H. Keshel, A.J. Chari, E. Biazar, Human unrestricted somatic stem cells loaded in nanofibrous PCL scaffold and their healing effect on skin defects, Artificial cells, nanomedicine, and biotechnology 44(6) (2016) 1556-1560.
[68] M. Radmansouri, E. Bahmani, E. Sarikhani, K. Rahmani, F. Sharifianjazi, M. Irani, Doxorubicin hydrochloride-Loaded electrospun chitosan/cobalt ferrite/tita-nium oxide nanofibers for hyperthermic tumor cell treatment and controlled drug release, International journal of biological macromolecules 116 (2018) 378-384.
[69] P. Abasian, M. Radmansouri, M.H. Jouybari, M.V. Ghasemi, A. Mohammadi, M. Irani, F.S. Jazi, Incorporation of magnetic NaX zeolite/DOX into the PLA/chitosan nanofibers for sustained release of doxorubicin against carcinoma cells death in vitro, International journal of biological macromolecules 121 (2019) 398-406.
[70] F.S. Jazi, N. Parvin, M. Rabiei, M. Tahriri, Z.M. Shabestari, A.R. Azadmehr, Effect of the synthesis route on the grain size and morphology of ZnO/Ag nano-composite, Journal of Ceramic Processing Research 13(5) (2012) 523-526.
[71] E.H. Jazi, R. Esalmi-Farsani, G. Borhani, F.S. Jazi, Synthesis and Character-ization of In Situ Al-$Al_{13}Fe_4$-Al_2O_3-TiB_2 Nanocomposite Powder by Mechanical Alloying and Subsequent Heat Treatment, Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 44(2) (2014) 177-184.
[72] A. Esmaeilkhanian, F. Sharifianjazi, A. Abouchenari, A. Rouhani, N. Parvin, M. Irani, Synthesis and Characterization of Natural Nano-hydroxyapatite Derived from Turkey Femur-Bone Waste, Applied Biochemistry and Biotechnology 189(3) (2019) 919-932.
[73] V. Balouchi, F.S. Jazi, A. Saidi, Developing (W, Ti) C-(Ni, Co) nanocomposite by SHS method, Journal of Ceramic Processing Research 16(5) (2015) 605-608.
[74] A. Masoudian, M. Karbasi, F. SharifianJazi, A. Saidi, Developing Al_2O_3-TiC in-situ nanocomposite by SHS and analyzingtheeffects of Al content and mechanical activation on microstructure, Journal of Ceramic Processing Research 14(4) (2013) 486-491.
[75] E. Sharifi Sedeh, S. Mirdamadi, F. Sharifianjazi, M. Tahriri, Synthesis and evaluation of mechanical and biological properties of scaffold prepared from Ti and Mg with different volume percent, Synthesis and Reactivity in Inorganic, Met-al-Organic, and Nano-Metal Chemistry 45(7) (2015) 1087-1091.
[76] N. Bruna, B. Collao, A. Tello, P. Caravantes, N. Díaz-Silva, J. Monrás, N. Órdenes-Aenishanslins, M. Flores, R. Espinoza-Gonzalez, D. Bravo, Synthesis of salt-stable fluorescent nanoparticles (quantum dots) by polyextremophile halophil-ic bacteria, Scientific reports 9(1) (2019) 1953.
[77] H. Kooshki, A. Sobhani-Nasab, M. Eghbali-Arani, F. Ahmadi, V. Ameri, M. Rahimi-Nasrabadi, Eco-friendly synthesis of $PbTiO_3$ nanoparticles and Pb-TiO_3/carbon quantum dots binary nano-hybrids for enhanced photocatalytic perfor-mance under visible light, Separation and Purification Technology 211 (2019) 873-881.
[78] L. Lee, J. Hwang, J.W. Jung, J. Kim, H.-I. Lee, S. Heo, M. Yoon, S. Choi, N. Van Long, J. Park, ZnO composite nanolayer with mobility edge quantization for multi-value logic transistors, Nature communications 10(1) (2019) 1998.
[79] C. Peng, H. Xing, X. Fan, Y. Xue, J. Li, E. Wang, Glutathione Regulated Inner Filter Effect of MnO_2 Nanosheets on Boron Nitride Quantum Dots for Sensitive Assay, Analytical chemistry 91(9) (2019) 5762-5767.
[80] D.A. Hanifi, N.D. Bronstein, B.A. Koscher, Z. Nett, J.K. Swabeck, K. Takano, A.M. Schwartzberg, L. Maserati, K. Vandewal, Y. van de Burgt, Redefining near-unity luminescence in quantum dots with photothermal threshold quantum yield, Science 363(6432) (2019) 1199-1202.
[81] S.Y. Lim, W. Shen, Z. Gao, Carbon quantum dots and their applications, Chemical Society Reviews 44(1) (2015) 362-381.
[82] J. Zong, Y. Zhu, X. Yang, J. Shen, C. Li, Synthesis of photoluminescent car-bogenic dots using mesoporous silica spheres as nanoreactors, Chemical commu-nications 47(2) (2011) 764-766.
[83] M. Havrdova, K. Hola, J. Skopalik, K. Tomankova, M. Petr, K. Cepe, K. Polakova, J. Tucek, A.B. Bourlinos, R. Zboril, Toxicity of carbon dots – Effect of surface functionalization on the cell viability, reactive oxygen species generation and cell cycle, Carbon 99 (2016) 238-248.
[84] P. Juzenas, A. Kleinauskas, P. George Luo, Y.-P. Sun, Photoactivatable carbon nanodots for cancer therapy, Applied Physics Letters 103(6) (2013) 063701.
[85] J. Lu, P.S.E. Yeo, C.K. Gan, P. Wu, K.P. Loh, Transforming C 60 molecules into graphene quantum dots, Nature nanotechnology 6(4) (2011) 247.
[86] C.K. Chua, Z. Sofer, P. Simek, O. Jankovsky, K. Klimova, S. Bakardjie-va, S.t.p.n. Hrdličková Kučková, M. Pumera, Synthesis of strongly fluorescent graphene quantum dots by cage-opening buckminsterfullerene, Acs Nano 9(3) (2015) 2548-2555.
[87] C.J. Jeong, A.K. Roy, S.H. Kim, J.-E. Lee, J.H. Jeong, I. In, S.Y. Park, Flu-orescent carbon nanoparticles derived from natural materials of mango fruit for bio-imaging probes, Nanoscale 6(24) (2014) 15196-15202.
[88] C.T. Matea, T. Mocan, F. Tabaran, T. Pop, O. Mosteanu, C. Puia, C. Iancu, L. Mocan, Quantum dots in imaging, drug delivery and sensor applications, Int J Nanomedicine 12 (2017) 5421-5431.
[89] S. Tachi, H. Morita, M. Takahashi, Y. Okabayashi, T. Hosokai, T. Sugai, S. Kuwahara, Quantum Yield Enhancement in Graphene Quantum Dots via Esterifi-cation with Benzyl Alcohol, Scientific Reports 9(1) (2019) 14115.
[90] Y. Dong, C. Chen, X. Zheng, L. Gao, Z. Cui, H. Yang, C. Guo, Y. Chi, C.M. Li, One-step and high yield simultaneous preparation of single-and multi-layer graphene quantum dots from CX-72 carbon black, Journal of Materials Chemistry 22(18) (2012) 8764-8766.
[91] S. Ahmadian-Fard-Fini, D. Ghanbari, O. Amiri, M. Salavati-Niasari, Elec-trospinning of cellulose acetate nanofibers/Fe/carbon dot as photoluminescence sen-

sor for mercury (II) and lead (II) ions, Carbohydrate Polymers 229 (2020) 115428.
[92] J. Shen, Y. Zhu, X. Yang, J. Zong, J. Zhang, C. Li, One-pot hydrothermal synthesis of graphene quantum dots surface-passivated by polyethylene glycol and their photoelectric conversion under near-infrared light, New Journal of Chemistry 36(1) (2012) 97-101.
[93] M. Pérez-Mendoza, C. Schumacher, F. Suárez-García, M. Almazán-Almazán, M. Domingo-García, F. López-Garzón, N. Seaton, Analysis of the microporous texture of a glassy carbon by adsorption measurements and Monte Carlo simu-la-tion. Evolution with chemical and physical activation, Carbon 44(4) (2006) 638-645.
[94] S. Berto, L. Carena, F. Valmacco, C. Barolo, E. Conca, D. Vione, R. Buscaino, M. Fiorito, C. Bussi, O. Abollino, Application of an electro-activated glassy-carbon electrode to the determination of acetaminophen (paracetamol) in surface waters, Electrochimica Acta 284 (2018) 279-286.
[95] H. Zhang, S. Li, F. Zhang, M. Wang, X. Lin, H. Li, Simultaneous detection of hydroquinone and catechol on electrochemical-activated glassy carbon electrode by simple anodic and cathodic polarization, Journal of Solid State Electrochem-is-try 21(3) (2017) 735-745.
[96] M.B. Gholivand, E. Ahmadi, M. Mavaei, A novel voltammetric sensor based on graphene quantum dots-thionine/nano-porous glassy carbon electrode for de-tection of cisplatin as an anti-cancer drug, Sensors and Actuators B: Chemical 299 (2019) 126975.
[97] S. Zhuo, M. Shao, S.-T. Lee, Upconversion and downconversion fluorescent graphene quantum dots: ultrasonic preparation and photocatalysis, ACS nano 6(2) (2012) 1059-1064.
[98] M. Kaur, M. Kaur, V.K. Sharma, Nitrogen-doped graphene and graphene quantum dots: A review onsynthesis and applications in energy, sensors and en-vi-ronment, Advances in colloid and interface science 259 (2018) 44-64.
[99] C. Lah, N. Jamaludin, F. Rokhani, S. Rashid, A. Noor, Lard detection using a tapered optical fiber sensor integrated with gold-graphene quantum dots, Sensing and Bio-Sensing Research 26 (2019) 100306.
[100] P. Qi, T. Zhang, J. Shao, B. Yang, T. Fei, R. Wang, A QCM humidity sensor constructed by graphene quantum dots and chitosan composites, Sensors and Ac-tuators A: Physical 287 (2019) 93-101.
[101] H. Safardoust-Hojaghan, O. Amiri, M. Hassanpour, M. Panahi-Kalamuei, H. Moayedi, M. Salavati-Niasari, S, N co-doped graphene quantum dots-induced ascorbic acid fluorescent sensor: Design, characterization and performance, Food chemistry 295 (2019) 530-536.
[102] J. Tang, R. Huang, S. Zheng, S. Jiang, H. Yu, Z. Li, J. Wang, A sensitive and selective electrochemical sensor based on graphene quantum dots/gold nanoparti-cles nanocomposite modified electrode for the determination of luteolin in peanut hulls, Microchemical Journal 145 (2019) 899-907.
[103] P. Zhao, M. Ni, Y. Xu, C. Wang, C. Chen, X. Zhang, C. Li, Y. Xie, J. Fei, A novel ultrasensitive electrochemical quercetin sensor based on MoS_2-carbon nanotube@ graphene oxide nanoribbons/HS-cyclodextrin/graphene quantum dots composite film, Sensors and Actuators B: Chemical 299 (2019) 126997.
[104] X. Gao, L. Yang, J.A. Petros, F.F. Marshall, J.W. Simons, S. Nie, In vivo mo-lecular and cellular imaging with quantum dots, Current opinion in biotechnology 16(1) (2005) 63-72.
[105] L. Sheng, B. Huangfu, Q. Xu, W. Tian, Z. Li, A. Meng, S. Tan, A highly selective and sensitive fluorescent probe for detecting Cr(VI) and cell imaging based on nitrogen-doped graphene quantum dots, Journal of Alloys and Compounds 820 (2020) 153191.
[106] D.A. Gvozdev, A.A. Ramonova, Y.B. Slonimskiy, E.G. Maksimov, M.M. Moisenovich, V.Z. Paschenko, Modification by transferrin increases the efficiency of delivery and the photodynamic effect of the quantum dot–phthalocyanine complex on A431 cells, Archives of Biochemistry and Biophysics 678 (2019) 108192.
[107] X. Hai, Y. Wang, X. Hao, X. Chen, J. Wang, Folic acid encapsulated graphene quantum dots for ratiometric pH sensing and specific multicolor imaging in living cells, Sensors and Actuators B: Chemical 268 (2018) 61-69.
[108] K. Jin, H. Gao, L. Lai, Y. Pang, S. Zheng, Y. Niu, X. Li, Preparation of highly fluorescent sulfur doped graphene quantum dots for live cell imaging, Journal of Luminescence 197 (2018) 147-152.
[109] H.M. Kashani, T. Madrakian, A. Afkhami, F. Mahjoubi, M.A. Moosavi, Bottom-up and green-synthesis route of amino functionalized graphene quantum dot as a novel biocompatible and label-free fluorescence probe for in vitro cellular imaging of human ACHN cell lines, Materials Science and Engineering: B 251 (2019) 114452.
[110] M.K. Mondal, S. Mukherjee, N. Joardar, D. Roy, P. Chowdhury, S.P.S. Babu, Synthesis of smart graphene quantum dots: A benign biomaterial for prominent intracellular imaging and improvement of drug efficacy, Applied Surface Science 495 (2019) 143562.
[111] G. Rajender, U. Goswami, P. Giri, Solvent dependent synthesis of edge-controlled graphene quantum dots with high photoluminescence quantum yield and their application in confocal imaging of cancer cells, Journal of colloid and inter-face science 541 (2019) 387-398.
[112] H. Wang, Q. Mu, K. Wang, R.A. Revia, C. Yen, X. Gu, B. Tian, J. Liu, M. Zhang, Nitrogen and boron dual-doped graphene quantum dots for near-infrared second window imaging and photothermal therapy, Applied Materials Today 14 (2019) 108-117.
[113] H. Bahrami, R. Roozafzoon, Z. Ghanbari, N. Jegargooshe, P. Jafari, M. Nazari, S. Heidari-Keshel, Evaluation of ELAM-1 expression alteration in endo-metriosis, Minerva ginecologica 69(2) (2017) 150-159.
[114] B. Şenel, N. Demir, G. Büyükköroğlu, M. Yıldız, Graphene quantum dots: Synthesis, characterization, cell viability, genotoxicity for biomedical applications, Saudi Pharmaceutical Journal 27(6) (2019) 846-858.
[115] M. Akbarzadeh, M. Babaei, K. Abnous, S.M. Taghdisi, M.T. Peivandi, M. Ramezani, M. Alibolandi, Hybrid silica-coated Gd-Zn-Cu-In-S/ZnS bimodal quantum dots as an epithelial cell adhesion molecule targeted drug delivery and imaging system, International journal of pharmaceutics 570 (2019) 118645.
[116] D. Iannazzo, A. Pistone, M. Salamò, S. Galvagno, R. Romeo, S.V. Giofré, C. Branca, G. Visalli, A. Di Pietro, Graphene quantum dots for cancer targeted drug delivery, International journal of pharmaceutics 518(1-2) (2017) 185-192.
[117] S. Javanbakht, H. Namazi, Doxorubicin loaded carboxymethyl cellulose/graphene quantum dot nanocomposite hydrogel films as a potential anticancer drug delivery system, Materials Science and Engineering: C 87 (2018) 50-59.
[118] F. Nasrollahi, Y.R. Koh, P. Chen, J. Varshosaz, A.A. Khodadadi, S. Lim, Targeting graphene quantum dots to epidermal growth factor receptor for delivery of cisplatin and cellular imaging, Materials Science and Engineering: C 94 (2019) 247-257.
[119] L. Ruiyi, L. Zaijun, S. Xiulan, J. Jan, L. Lin, G. Zhiguo, W. Guangli, Graphene quantum dot-rare earth upconversion nanocages with extremely high efficiency of upconversion luminescence, stability and drug loading towards controlled delivery and cancer theranostics, Chemical Engineering Journal 382 (2020) 122992.
[120] X. Su, C. Chan, J. Shi, M.-K. Tsang, Y. Pan, C. Cheng, O. Gerile, M. Yang, A graphene quantum dot@ Fe_3O_4@SiO_2 based nanoprobe for drug delivery sensing and dual-modal fluorescence and MRI imaging in cancer cells, Biosensors and Bioelectronics 92 (2017) 489-495.
[121] B.D. Mansuriya, Z. Altintas, Graphene Quantum Dot-Based Electrochemical Immunosensors for Biomedical Applications, Materials 13(1) (2020) 96.
[122] A. Rakovich, T. Rakovich, Semiconductor versus graphene quantum dots as fluorescent probes for cancer diagnosis and therapy applications, Journal of Mate-rials Chemistry B 6(18) (2018) 2690-2712.
[123] J. Soleymani, M. Hasanzadeh, M.H. Somi, S.A. Ozkan, A. Jouyban, Tar-geting and sensing of some cancer cells using folate bioreceptor functionalized nitrogen-doped graphene quantum dots, International journal of biological macro-molecules 118 (2018) 1021-1034.
[124] D. He, D. Wang, W. Quan, C.-y. Yu, Functional quantum dots for promising cancer diagnosis and therapy, J. Nanomed. Nanosurg 1(10.16966) (2015) 2470-3206.
[125] Z. Fan, S. Zhou, C. Garcia, L. Fan, J. Zhou, pH-Responsive fluorescent graphene quantum dots for fluorescence-guided cancer surgery and diagnosis, Nanoscale 9(15) (2017) 4928-4933.