Quantum dots for bio-imaging technology: A systematic review

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ABSTRACT

Quantum dots (QDs) have a variety of applications, including use in solar cells, drug delivery, biomaterials, and the development of water resource protection technologies. Being the leading materials in the medical field, QDs are currently used in drug delivery, preparation of antibodies and vaccines, gene delivery, and bio-imaging. One of the areas of interest in recent years has been the investigation of their key properties in bio-imaging. Bio-imaging is of particular importance in identifying diseases and many types of cancer, which can increase the quality of treatment and improve patient outcomes. The results of this research showed that various materials, such as cadmium selenium QDs, zinc sulfide QDs, indium phosphide QDs, and graphene QDs, could be used in this field. Among the different materials, Graphene, carbon, zinc-based, cadmium-based, and gold QDs have been of interest. In general, promising results have been observed in bio-imaging of various cancer cells, glioma cells, and even cancer treatment, which could be an important development in medical sciences and bioengineering. The present study is organized to review the latest achievements in this field, and suggestions for future research are presented in each section. It is suggested that the development of graphene and carbon QDs should receive more attention from researchers due to their higher biocompatibility. Furthermore, simultaneous drug delivery with bio-imaging could be among the issues that will be discussed in future research.

Keywords:
Quantum dots; Bio-imaging; Cancer treatment; Medical sciences; Bioengineering

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1. Introduction

Quantum dots (QDs), as one of the prominent products resulting from scientific investigations, are currently considered in the development of new technologies and play a crucial role in expanding scientific knowledge. QDs play a role in developing and increasing the efficiency of solar cells,[1,2] creating lasers with new efficiencies,[3] purifying water resources,[4] quantum computing,[5] *etc.*

Among the technologies mentioned, QDs are also of great interest in the realm of medical and biological sciences, particularly in the aspects of cellular uptake or trafficking.[6] Furthermore, according to previous research, QDs have many applications in bio-imaging, drug delivery,[7] biosensors,[8] and the development of various implants and dentistry.[7,9] **Figure 1** shows a summary of the applications of QDs in biomedical applications.

QDs are generally divided into different categories: (i) Core-shell QDs, (ii) alloyed QDs, and (iii) carbon-based QDs. Typically, conventional QDs consist of a semiconductor core (*e.g.*, CdSe, GaAs, InP, and InAs) surrounded by a semiconductor shell with a wide band gap, such as ZnS.[10] QDs may be made of heavy metals or silicon, or of carbon and graphene. In general, there are two approaches to QDs synthesis, namely the top-down[10,11] and bottom-up approaches.[10,12] In the top-down approach, to develop QDs, a bulk semiconductor is thinned to a diameter of about 30 nm by methods such as reactive ion etching, electron beam lithography, or wet chemical etching.[13] The bottom-up methods include various methods, including sol-gel, micro-emulsion, hot solution decomposition, molecular beam epitaxy, and sputtering, all of which have their own advantages and disadvantages.[10,14]

The review focuses entirely on the latest achievements of QDs in biological imaging. The

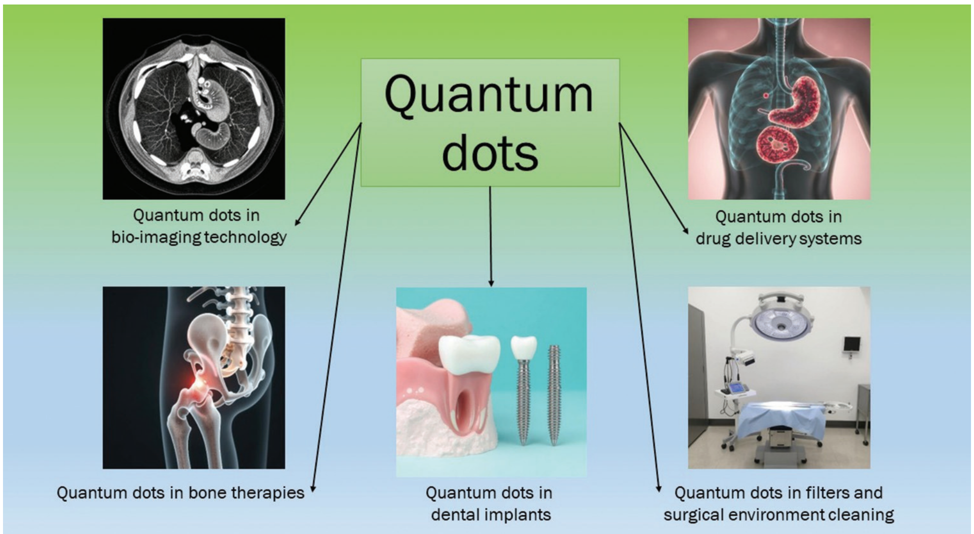

Figure 1. A schematic of the main biomedical applications of quantum dots

current section provides a general background knowledge regarding QDs, which is followed by a comprehensive review of the approach of various materials that can be used in imaging, and a list of suggestions for future research.

2. Graphene QDs (GQDs)

GQDs are nanoscale graphene fragments that exhibit unique optical and electronic properties due to their quantum confinement effects. Typically measuring <100 nm in size, GQDs are characterized by their high surface area, excellent conductivity, and strong photoluminescence, which make them attractive for various applications.[15-17] GQDs are of great interest in biomedical applications, and it has recently been reported that these materials may be useful in the treatment of Parkinson's and Alzheimer's diseases.[18] GQDs also have serious applications in biological imaging.

Kang *et al.*[19] proposed a facile and green approach to develop GQDs from coal that could be used in bio-imaging. In this study, researchers demonstrated that GQDs can be grown using a pulsed laser in liquid and coal, which leads to increased fabrication efficiency. The results of this study showed that GQDs fabricated by this method exhibited excellent optoelectronic properties and could be exploited in bio-imaging.

It is worth noting that in the field of bio-imaging, near-infrared (NIR) fluorescence imaging is of interest due to its high tissue penetration depth and low autofluorescence backgrounds.[20,21] In this regard, Valimukhametova *et al.*[21] demonstrated that five types of biocompatible GQDs can be used for this purpose. Their results showed that at biocompatible concentrations of 0.5–2 mg, GQDs enter HEK293 cells and enable *in vitro* imaging in visible and NIR light. The QDs types used also showed promising biocompatibility. In addition to these results, it is suggested that in the future, drug delivery of these five groups should be investigated simultaneously, which could be a suitable research area.

Another recent achievement in the field of GQDs is the simultaneous use of GQDs attached with L-cysteine. According to the results of Moeini *et al.*,[22] GQDs-L-cysteine shows a red shift in photoluminescence results compared to GQDs, which can be useful in bio-imaging. However, it is suggested that this issue should be further investigated in drug delivery, as it may also be used in this field.

It is noteworthy that QDs generally have low degradation and high biocompatibility. **Table 1** summarizes the cytotoxic effects of GQDs. This is a great advantage for this class of QDs in imaging applications.

The results of Schroeder *et al.*'s research[30] have also confirmed the usefulness of GQDs and their low toxicity in biological imaging. This was also confirmed by Chen,[31] with an emphasis on catalytic applications of GQDs, who showed that GQDs have excellent dispersion in aqueous solutions due to their molecular size and that sulfonated GQDs are quasi-homogeneous catalysts for catalytic chemo-catalytic biomass conversion. Finally, Wang *et al.*[32] also emphasized the bio-imaging applications of GQDs.

Therefore, it is suggested that more focus should be placed on drug delivery applications of GQDs, in conjunction with their bio-imaging applications. Furthermore, given the unique properties of GQDs, these materials may be useful in dental implants and represent a suitable research area for the future. It is important to note the relevance of specific ISO standards in the field of dentistry, particularly concerning dental implants. ISO 14801:2016 outlines the mechanical testing methods for endosseous dental implants, providing guidelines for fatigue testing under simulated conditions. In addition, ISO 17327:2018 addresses safety and performance aspects of

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dental implants, making both standards essential references in implant dentistry.

3. Carbon QDs (CQDs)

CQDs are nanosized carbon-based materials that exhibit unique optical properties, including strong photoluminescence and size-tunable emission. Often synthesized from carbon-containing precursors through various methods such as hydrothermal or solvothermal processes, CQDs are valued for their biocompatibility, low toxicity, and environmental friendliness compared to traditional QDs made from heavy metals.[33-35]

In a study by Salvi *et al.*,[36] the importance of CQDs and their applications in biomedical and medical engineering was examined. Their results indicated the potential capabilities of CQDs in bio-imaging and bio-sensing. Furthermore, the results of Daby *et al.*'s research[37] indicate that CQDs are suitable candidates for bio-imaging, *in vivo* drug delivery, and cell tracking due to their high fluorescence, tunable emission, and light stability, as well as their simultaneous drug delivery capability in the treatment of cancer, eye diseases, and cardiovascular diseases.

It is worth mentioning that lignin-hybridized CQDs (L-CQDs) have also been studied.[38] This type of QDs has a diameter of <10 nm and exhibits excitation-dependent photoluminescence behavior with emission maximum ranging from 454 to 535 nm under excitation at 375–460 nm, with a great potential in bio-imaging applications due to its low toxicity and high biocompatibility. It is suggested that in the future, in addition to imaging, drug delivery applications by means of L-CQDs should also be investigated. Applications of L-CQDs in drug delivery were proposed based on research by Jana and Dev,[39] which found that CQDs, in addition to bio-imaging, can also be used in simultaneous drug delivery.

It is worth noting, as mentioned in **Figure 2**, that CQDs have also been considered in the development of biosensors.[40,41] Lin *et al.* have confirmed the development of probes using CDS/Boh for the determination of doxorubicin.[42] Huang *et al.* also reported the use of nitrogen-doped GQDs probes in glucose sensing and tracking.[43] Rezaei *et al.*[44] also emphasized the use of Cu_2O–CDs/NF probe for the detection and tracking of dopamine. These are indications of the biosensing potential of CQDs. Given this potential, researchers are recommended to simultaneously explore the drug delivery, bio-imaging, and biosensor properties of CQDs. These potentials are important in facilitating the treatment and diagnosis processes of some diseases.

4. Zinc-based QDs (Zn-QDs)

Zn-QDs are semiconductor nanocrystals that typically consist of zinc oxide (ZnO) or zinc sulfide (ZnS) and are known for their tunable optical properties, high photostability, and potential for various applications. These QDs exhibit efficient photoluminescence, making them valuable in fields such as optoelectronics,[45] solar cells,[46] and biomedical imaging.[47] Compared to cadmium-based QDs, Zn-QDs are considered more environmentally friendly due to their reduced toxicity.

Table 1. Cytotoxic effects of GQDs

Type of GQD	Media/Cell/Animal model	Cytotoxicity	References
GQDs	*In vivo* toxicity in rats	Effects in the liver or lung at doses above 10 mg/kg	23
GQDs	MDA-MB231	Low toxicity	24
GQDs	HeLa	About an 80% cell survival rate	25,26
GQDs	Zebrafish	No toxic effect observed	27
Carboxylated-GQD	Liver, spleen, kidney, and tumor	Accumulation observed in the mentioned organs after 24 hours of intravenous injection	28
GQDs	*C. elegans*	Nerve damage if in contact for a long time.	29
GQDs	SKH1 female nude mice	No histopathological damage observed	28

Abbreviation: GQD: Graphene quantum dot.

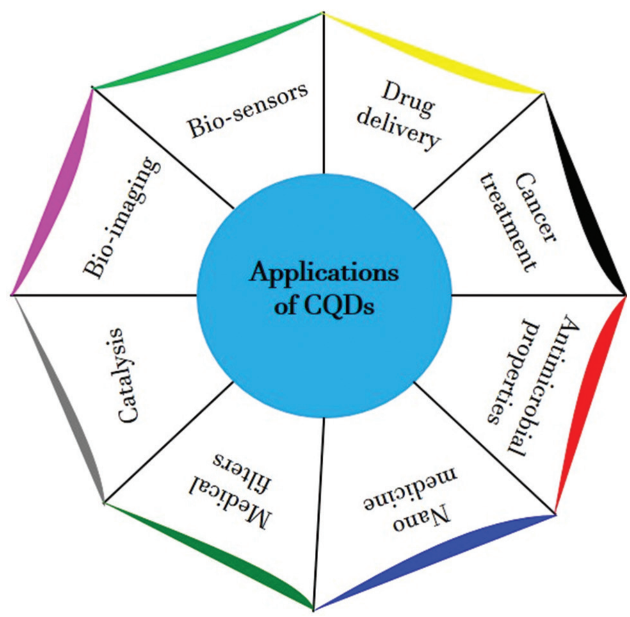

Figure 2. Biomedical and medical applications of CQDs
Abbreviation: CQD: Carbon quantum dot.

To develop Zn-QDs, Caires *et al.*[48] investigated the optical properties and bio-imaging characteristics of ZnS QD/biopolymer photoluminescent nanoprobes (ZnS@CMC nanoconjugates). Their results showed that the ZnS@CMC did not show any cytotoxicity, and the material can be used in bio-imaging of malignant glioma cells. These results were confirmed by Manzoor *et al.*'s research.[49] They prepared a suitable biocompatible QDs system using a simple aqueous method at room temperature. One of the important results obtained is that the QDs system was non-toxic when it was in contact with cells such as the normal lung fibroblast cell line (L929). Furthermore, the bright and stable luminescence of these QDs indicates their crucial role in the imaging of single cancer cells and cancer cell colonies. Other results, such as those by Manaia,[50] emphasize the capabilities of ZnO and Zn0.8Mg0.2O QDs in bio-imaging.

Other research on Zn-based QDs have also confirmed the applications of ZnS-AgInS2,[51] CuInSe/ZnS core/shell NIR QDs,[52] and Zn-Cu-In-S/ZnS core/shell QDs[53] in biological imaging. Researchers are recommended to further explore applications of Zn-QDs in drug delivery, in addition to bio-imaging.

5. Cadmium-based QDs (Cd-QDs)

Cd-QDs are among the materials that have garnered increasing attention in the development of medical systems due to their properties. Among the items of interest are cadmium-selenium QDs (CdSe-QDs)[54] and cadmium-tellurium QDs (CdTe-QDs).[55]

In this context, the synthesis of CdTe-QDs by two marine bacteria (*Bacillus pumilus* and *Serratia marcescens*) has been reported by Pawar *et al.*[56] Their results showed that the estimated dimensions of the nanostructures were approximately 10 nm—a size suitable for bio-imaging of yeast and animal cells.

One of the main problems of Cd-QDs is the high cytotoxicity of cadmium.[57-59] In this regard, Ghormade *et al.*[60] demonstrated that using a green synthesis strategy to embed CdTe-QDs in biocompatible CNPs can reduce cytotoxicity to some extent compared to using CdTe-QDs in the normal state. In other words, the toxicity of capped CdTe-QDs can be reduced, indicating that capping is a new research area worthy of investigation and that new capping methods should be explored with the aim of reducing cell toxicity attributed to Cd-QDs. In addition, the successful biosynthesis of CdTe-QDs using yeast cells has also been reported.[61]

Despite concerns about cadmium toxicity, Cd-QDs continue to be a frontrunner in treatment and imaging. It has been reported that CdSe-QDs nanomaterials in the solution phase at molar concentrations, due to their size and surface properties, can damage cancer cells and ultimately lead to their death without damaging the tissue, corroborating their efficacy in the treatment of hepatocellular carcinoma.[62] Research has also shown the stability of CdSe-QDs capping with mercaptopropionic acid. This compound can be used in the imaging of HeLa cancer cells and HEK-293 normal cells.[63] **Table 2** provides a summary of the types of Cd-QDs and their applications in cellular imaging.

6. Gold QDs (Au-QDs)

Au-QDs represent an emerging class of quantum materials that have applications in various fields, including solar cells,[2] electronics,[67] and biomedicine.[68] It should be noted that research in these areas has been extremely new and innovative, and their potential in medical applications deserves more focused research in the future.

Among the limited research in this area, Hutter and Maysinger[68] investigated the application of Au-QDs in bio-imaging. Their research showed that Au-QDs can be used in biological imaging. Au-QDs are also useful in drug delivery. Thus, in addition to bio-imaging, researchers are recommended to explore their utilization in gene delivery. Au-QDs may be suitable materials for encapsulating nucleic acids and facilitating cellular uptake. Development of vaccines with Au-QDs and gold nanoparticles has also been regarded as a desirable research area.[69]

Table 2. Summary of the types of Cd-QDs and their applications in bio-imaging

Type of Cd-QDs	Applications	References
CdSe-QDs capping with mercaptopropionic acid	Imaging of HeLa cancer cells and HEK-293 normal cells	63
Iron-doped CdTe/CdS magnetic QDs	Tracking live cells	64
Green-synthesis-derived CdS-QDs	Bio-imaging and treatment of lung cancer cells	65
CdS-QDs and the use of tea leaf waste as a bio-surfactant	Effect on breast cancer cells	65
Carboxymethylcellulose/ZnCdS	Cancer cell bio-imaging	66

Abbreviation: Cd-QD: Cadmium-based quantum dot.

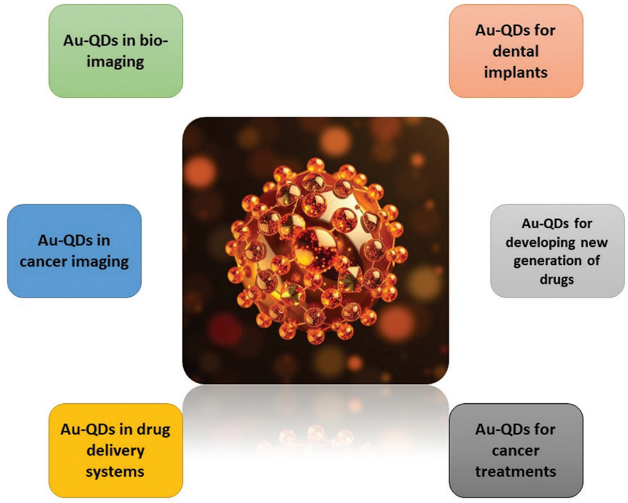

Figure 3. Key biomedical applications of Au-QDs
Abbreviation: Au-QD: Gold quantum dot.

Figure 3 depicts several key biomedical applications of Au-QDs.

7. Conclusions

Advances in quantum science are crucial factors for enhancing medical research and, therefore, the physical health of individuals. In general, QDs, due to their unique properties, can be useful in medical applications and play an important role in the prevention, diagnosis, and even treatment of various diseases. Major key points of the present review are outlined in the following:

(i) GQDs are of great interest in bio-imaging. The high biocompatibility of GQDs, like that of CQDs, is an important feature in this regard. Its non-toxicity has been widely demonstrated
(ii) In addition to bio-imaging, CQDs have potential for simultaneous drug delivery. This could lead to reduced treatment duration and increased performance

(iii) In terms of applications and usefulness, Zn-QDs are leading QDs, after the aforementioned materials, because of their good biocompatibility despite the fact that they are cadmium-free. ZnS and ZnO compounds have shown the highest efficiency and biocompatibility. In addition, applications of InP/ZnS compounds also warrant further investigations

(iv) Despite the toxicity of cadmium, Cd-QDs can be capped to make them suitable for bio-imaging. Furthermore, Cd-QDs can be used in cancer treatment by virtue of their enhanced capability in attacking cancer cells

(v) Despite being more expensive than other QDs, Au-QDs offer promising applications in bio-imaging—a nascent field that deserves more attention.

8. Future suggestions

To strengthen future progress in this field, several research recommendations are made, as follows.

(i) Because our understanding of their usefulness remains very limited at the current stage, more research efforts should be devoted to exploring applications of perovskite-based QDs, although several studies about these QDs are underway[70,71]

(ii) One of the key properties of quantum materials is entanglement, a unique phenomenon that holds significant potential for applications in medical engineering, drug delivery, and bioimaging. Leveraging this property, it may be possible to develop quantum particles specifically designed for the treatment of diseases, including cancer

(iii) Another notable property of quantum materials is known as quantum tunneling,[72] a phenomenon that plays a role in processes, such as DNA mutations, enzymatic reactions, and cellular respiration. However, its potential applications in bio-imaging and drug delivery warrant further investigation

(iv) Silicon QDs (Si-QDs[73-75]) are expected to have useful applications in multiple aspects, which warrant further research.

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Conceptualization: All authors; *Writing—original draft*: All authors; *Writing—review & editing:* All authors. All authors have read and agreed to the published version of the manuscript.
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