Review Article

A review on theranostic applications of carbon quantum dots in the treatment of cancer

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Abstract

Carbon Quantum Dots (CQDs/QDs) are nano sized, light emitting spherical particles with unique structural and functional properties. Presently, QDs are highly being used as the new class of fluorescent marker due to its distinctive electronic and imaging properties, high quality signaling, photo bleaching resistance, etc. Due to the aforementioned properties QDs are one of the most researched nanoparticles which can be used for both imaging and therapeutic purpose. Furthermore high selectivity, flexibility, solidity, and capability to penetrate various cells and organelles allows QDs in imaging and targeting the delivery of cancer therapeutics. However, despite all advantages QDs suffers major roadblocks due to poor biocompatibility, toxicity and aggregation of particles.

Thus in this article we have reviewed the structural anatomy of QDs, various methods of synthesis, applications of QDs and various roadblocks of using QDs in living tissues.

Keywords: Quantum Dots (QD), photobleaching, fluorescent marker, biocompatibility and cancer therapeutics

Introduction

In the recent scenario, the development of nanoparticles having both diagnostic and target-specific therapeutic activity is gaining huge attention [1-9]. Due to unique structural and functional properties, nanoparticles are preferred over other discrete molecules in any target-specific treatment [1-3]. Moreover, when nanoparticles are conjoined with ligands like peptides, antibodies, and other such small molecules they offer a promising cancer target application [10-13]. Recently various types of theranostic nanostructures such as magnetic nanoparticles [14-15], iron oxide nanostructure [16], theranostic nanoliposomes [17], dendrimers [18-19], metallic nanoparticle (gold nanoparticles) [20-21], Carbon Quantum dots [22-23], etc. are being developed for diagnosis, drug delivery and treatment strategy in cancer therapy [24-26]. Among all aforementioned nanostructures, engineered Quantum dots (QD) possess unique characteristics like crystalline metalloid structure, Quantum captive/intermittent effects, tunable imaging, and target properties [27-28] and above all a size range around 1-5nm which is smaller than Bhor radius [29]. Although the unique properties of quantum dots offer high selectivity, flexibility, solidity, and capability to penetrate various cells and organelles [30] yet there are various challenges like poor biocompatibility, toxicity, aggregation of particles, nonspecific binding, etc. are associated with Quantum dots, thus the researchers are mainly exploring on the development, bioconjugation, imaging and targeting the delivery of cancer therapeutics [31-32].

1. Surface chemistry of Quantum dots:

Quantum dots are spherical-shaped semiconducting agents (fig 1) with 2-10nm diameter and comprise of 200-10000 atoms approximately [33]. Semiconductor Quantum dots possess electron shells in the range 1-5eV which proves its photosensitizing behavior [34-35]. Similarly, a high number of atoms and high electron densities help in incurred absorption of X rays and Gamma rays [36]. Thus the aforementioned characteristics have made Quantum dots a very promising candidate for use in biological detection, optoelectric detections, etc. [33].

1.2 Electron state:

Bulk semiconductors are identified by a composition-dependent energy bandgap, which is the least amount of energy

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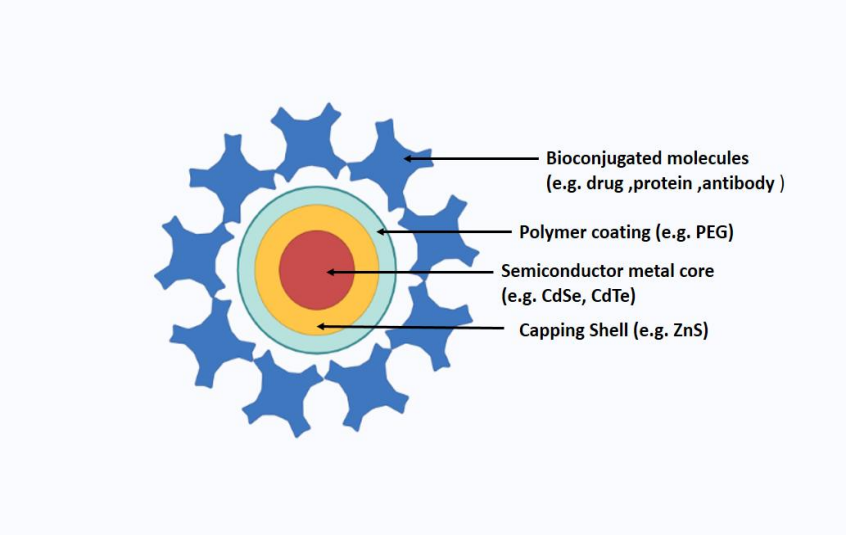

Figure 1: figure showing anatomy of Quantum dot [37]

1.2 Electron state:

Bulk semiconductors are identified by a composition-dependent energy bandgap, which is the least amount of energy required to rouse an electron from its ground state to a higher energy level. However, due to the relaxation of energy when the excited electrons again return to their ground state, it emits photons that are fluorescent [38]. It has been noted that the energy band gap of Quantum dots is inversely proportional to the size of the Quantum dots i.e. with the decrease in size of Quantum dots there is an increase in energy bond gap and vice versa [39]. This abovementioned phenomenon helps in the identification of Quantum dots as an increase or decrease in energy gap causes a change in their absorption spectrum which in turn changes the emission wavelength from one spectral region to another [39].

Furthermore, it has been noted that a lone light fount can be used to excite Quantum dots having different wavelengths, not only from the ultraviolet region but also throughout the near-infrared, mid-infrared, and visible portions [40-42].In addition, when the emission so emitted by Quantum dots are compared with that of fluorescent proteins and organic dye, it is seen that Quantum dot emissions are 10-100 times brighter than others. Hence Quantum dots are highly used for molecular and cellular imaging purposes [38].

2 Synthesis of QDs:

For the invention and discovery of the Carbon Quantum Dots (CQDs) or Carbon Nano Dots (CNDs), various methods or techniques of preparation are responsible for developing the QDs. The top-down and bottom-up method clarify the CQDs, in top-down method, the macromolecule is destroyed or dispersed into small size of CQDs by chemical and physical technique and in another hand, bottom-up method mainly refer to the carbonization and polymerization of a series of small molecules into CQDs through the chemical reaction process

2.1 Arc Discharge

The preparation of CNDs by arc discharge method is invented in 2004 [43]. The three types of carbon nanoparticles with different relative molecular mass and fluorescence properties when preparing Single-walled carbon nanotube by arc discharge method. It can emit blue, yellow, green, and orange fluorescence at 365nm. The surface of CNDs was attached by the hydrophilic carboxylic group and good water solubility was obtained by this arc discharge method. However, it possesses a large particle size distribution in the view of different size numbers of carbon nanoparticles from the discharge process. Large particle size carbon particles would decrease the specific surface area of the CNDs, which may limit the active reaction site during the electrocatalytic technique.

2.2 Laser Ablation

Laser Ablation is a very common method for the preparation of carbon nanodots. Sum et al,2006 and Li et al, 2011 reported this method is more convenient for the preparation of CNDs, The laser ablation method uses a high energy laser pulse to iridate the surface of the target to a thermodynamic state, in which high temperature and high pressure are generated, heat up and evaporate into a plasma state, then the vapor crystalized to form nanoparticles. Narrow size distribution, good water solubility, and fluorescence characteristics of CNDs provided by the Laser ablation method.[44-45]

2.3 Acidic Oxidation:

Acidic oxidation is another type of method for the synthesis of CNDs. The acidic oxidation method significantly improved the water solubility and fluorescence characteristics. This technique or method has been widely used to exfolic and decomposes bulk carbon into nanoparticles. Simultaneously, introduced hydrophilic group like hydroxyl group on the surface thereof to obtain CNDs [46]. In 2014 Yang et al reported that large-scale synthesis of heteroatomdroped CNDs via acidic oxidation followed by the hydrothermal reduction process. CNDs or carbon nanoparticles derived from Chinese ink were oxidized by a mixture solution of H_2SO_4, $NaClO_3$, and HNO_3. This type of CNDs having good electrolytic activity.

2.4 Combustion/Thermal Route:

The thermal route method is another type of method or technique or bottom-up approach of synthesis of CNDs.

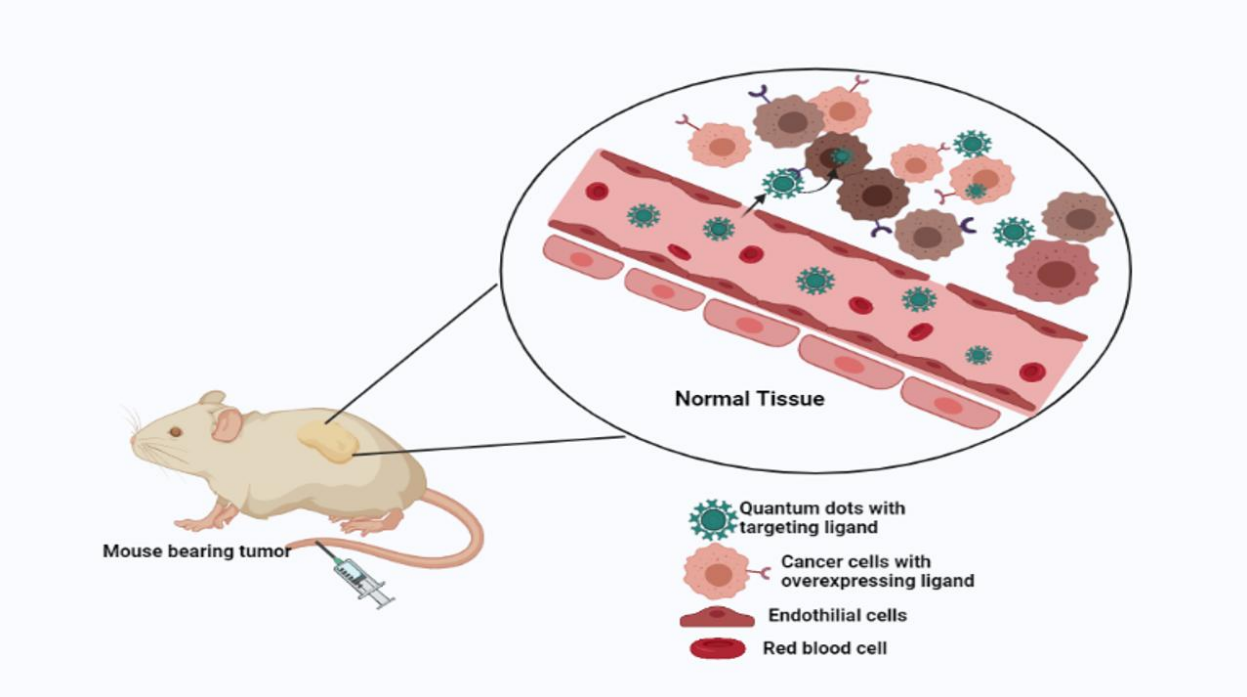

Figure2: Schematic diagram of active targeting of Quantum dots to cancer cells by enhanced permeation retention (EPR) effects. [38]

The combustion /thermal oxidation method for the preparation of CNDs is first proposed by Xu et al and followed by many researchers [47]. Lu et al (2017) prepared fluorescence CNDs by combustion of citric acid followed by functionalization of carboxyl group through conjugation of acetic acid moiety under high temperature. They obtain carbon nanodots having uniform size 8.5 nm and a rich carboxyl group on the surface of QDs [48].

2.5 Microwave pyrolysis

Microwave pyrolysis is the bottom-up approach of QDs preparation. This method has been well established due to its rapid synthesis and commercialization [49]. The combination of PEG 200 and saccharide(glucose) in water form a transparent solution, followed by heating in a microwave oven [50]. The prepared CNDs exhibit and excitation-dependent PL properties. This method is first reported by Zhu et al. This method is a simple fast and environment-friendly preparation method for CNDs.

2.6 Hydrothermal/Solvothermal Synthesis:

Hydrothermal/Solvothermal Synthesis is another type of method for manufacturing of QDs it is a widely used synthesis procedure of QDs because the setup is simple and the outcome particle is almost uniform in size with high QY. Shen et al (2019) reported that, In a typical approach, small organic molecules and/or polymers are dissolve in water or organic solvent to form the reaction precursor, which was then transferred to a Teflon-lined stainless steel autoclave. The organic molecules and/or polymers merged at relatively high temperatures to form carbon seeding cores and then grow into CNDs with a particle size of less than 10 nm [51].

2.7 Electrochemistry Method:

The electrochemical method is a simple and convenient preparation technique, which can be carried out under normal temperature and pressure conditions. Synthesis of QDs by electrochemistry method has been widely reported for the sake that it is facile to tune the particle size and PL performance of the synthesized QDs [52]. Anwar et al prepared blue-emission CNDs with an averaged particle size of 2.4 nimbies electrochemical carbonization of sodium citrate and urea in deionized (DI) water, which can be utilized as a highly sensitive detector for Hg2+ in wastewater. Electrochemistry method is also effective and widely used to fabricate efficient electrocatalyst, but for the CNDs synthesized by this method applied for electrocatalyst is rarely reported. Therefore, the integration of CNDs synthesis and electrocatalyst construction through one-pot electrochemical production is intriguing.

3 Application of Quantum dots

3.1 In-vitro Bioassay:

Due to unique spectral characteristics and resistance to photobleaching [53], QDs acts as a good candidate as reporters in a large number of in vitro bioassays like biosensors and immune assays [54,55].

Immunoassay as suggests involves specific antigen-antibody reactions to ascertain and measure target molecules in the biological system. Mattousi et al in their US Naval research Laboratory conjugated QDs with antibodies in order to detect and quantify proteins and small molecules [56-57]. The result so obtained proved that QDs due to their tapered and uniform emission patterns and unique spectral properties acts as "generalized" agents in immunoassay.

Table1: table showing various observations of cadmium accumulation in the body

Researchers	Observations	Reference
Yang et al.	▪ Prepared Cd-QD750 and injected intravenously to mice and Inductive coupled plasma mass spectrometry (ICP-MS) was used to measure and quantify cadmium disposition in various tissues. ▪ From the result, it was noted that there was a continuous increase in the amount of QD750 in various organs like the kidney, spleen, and liver. ▪ Hence the researchers concluded that QDs had a very long half-life and accumulation of QDs also means accumulation of cadmium which in turn may cause toxic effects.	[80]
Kincher et al.	▪ Performed cytotoxicity study of various QD conjugates (Cd and Zn). Furthermore, various surface coating and surface modifications were carried out. ▪ The resulting data suggested that the release of Cd^{2+} ions from the nanoparticles were not only toxic in nature but also tends to accumulate in various tissues which in turn plays a vital role in cell cytotoxicity.	[81]
Cho et al.	▪ Carried out a study to check cytotoxic effects of Cadmium telluride QDs and aimed to find out the intercellular accumulation of Cd^{+2} ions in human breast cancer cells. ▪ The result showed Cadmium telluride QDs are capable of inducing cell death by the formation of ROS.	[82]

Similarly, other characteristics like photobleaching resistance and Fluorescence Resonance Energy Transfer (FRET) donat [58-59] make QDs ideal for biosensor applications. Meditiz et al [60] prepared an in-situ biosensor by conjugating QDs with maltose-binding proteins for the detection of carbohydrates. The results prove that the QD biosensor can be used as an ideal tool for studying bioassay in near future.

3.2 Labeling specific cell and tissue specimens:

QDs- based probes are nowadays being effectively used in labeling fixed cells and other tissue specimens [61].

Xing Yong Wu et al in their study conjugated IgG molecules and streptavidin with QDs and formed an IgG-QD- streptavidin complex and investigated its ability to label a distinct cellular target i.e., Her2 (cancer marker highly exposed on the surface of breast cancer cells). The result so obtained from the experiment proved that the labeling signals so obtained were bright, distinct, and photostable for the intended target. Moreover detection of two cellular targets with one excitation. Wavelength was found out in the case of IgG-QD- streptavidin complex proving the fact that QDs-based probes are successful in cellular imaging and show a considerable advantage in multiple target detection [62].

In another study, Thimas J fountaine et al. successfully stained sections of tonsil tissues which was previously fixed in formalin and embedded in paraffin with five different Streptavidin-QDs conjugates. This multispectral staining showed low background, high specificity, and high emission intensity. Furthermore, the signals so obtained were stable in nature and resistant to photobleaching proving its relevant clinical application in near future.[63]

3.3 Imaging and tracing membrane receptor:

QDs are highly being used as imaging and tracking agent for specific membrane receptors so present in the surface of the living cells [64].

Maxime Dahan et al in their research work used QDs to study the lateral movement of glycerin receptors in living neurons. In the beginning, single QD tracking was used to study the mobility of glycerin receptors. Continuous images of QD-glycerin receptors were obtained from the extrasynaptic region of neurons. Results proved the capability of QDs to track the mobility of individual receptor neuronal surfaces [65].

In another study, Maria M et al. used QDs to track biotin-NGF (Nerve growth factor) receptor bound on the surface of PC12 cells. The results proved the capability of tracking NGF-receptor within neuritis and the photostability and brightness of QDs permit an extended real-time analysis. [66]. Similarly, S.S. Rajan et al detected the presence of TrkA receptor mobility in the internal neural PC12 cells with help of QDs.[67]

This tracking capability of QDs has highly inspired scientists to supervise the mobility and presence of various other receptors like tyrosine kinase [66-67], integrin [68-69], various membrane lipids [70,71], etc.

3.4 In vivo tumor imaging:

Tumors or abnormal growth of tissues in the body require urgent diagnosis and treatment. Tumor imaging is one of the most explored areas in bioimaging because it facilitates nit not imaging but also management and post-operative planning. However, imaging of tumors provides a huge challenge because of its distinctive structural anatomy. Moreover, tumor-induced angiogenesis leads to the formation of blood vessels that are unpredictable and inconsistent in nature [72-75]. Thus the development of nanotherapeutic agents for imaging and treatment of tumors. Along with other nanoparticles, QDs also give an assurance in tumor imaging because of their capability to produce acute fluorescent signals and incorporate into multiples signal or system [38]. Thus aforementioned characteristics of QDs allow a high sensitivity and high specificity in tumor imaging (figure 2).

Gao et al [10] prepared semiconductor QDs and aimed to target and image human prostate cancer inoculated and growing in mice. Luminescent QDs so prepared were encapsulated with ABC triblock copolymer and injected systemically and subcutaneously in tumor-bearing mice. Results showed that QDs were successful in fluorescent imaging of cancer cells. Furthermore, it was observed that ABC triblock copolymer conjugated QDs showed greater in vivo tumor targeting than non-conjugated ones.

Similarly in another study, Xuefeg Yu et al [76] prepared bioconjugated QDs by conjugating QDs with alpha-fetoprotein (AFP) antibodies. For detection of hepatocellular carcinoma. The evaluation studies showed that AFP antibody-conjugated QDs enable good spectroscopic imaging and targeting of hepatocellular carcinoma cells. Weiba Cai et al [77] prepared Arginine-glycine-aspartic acid (RGD) peptide labeled QDs for imaging U87MG human glioblastoma tumors in mice. The results so obtained proved that QDs can be effectively used in cancer detection and image lead surgery. Furthermore, various studies are being carried out to demonstrate the capability of QDs to detect the complex structure of pathogenesis of tumor cells. Stroh et al prepared QDs and used the QDs as a fluorescent marker to spectrally differentiate various types of cells within the tumor microenvironment. They used the multiphoton microscopic technique to capture images of tumor microenvironments. The images successfully showed that QDs can effectively use to study the pathophysiology and anatomy of the tumor microenvironment.

4 Roadblocks of Quantum dots:

Although QDs are widely being studied in imaging and targeting cancer, yet the use of QDs in living cells encounters major roadblocks due to their chemical composition. QDs as mentioned earlier are chemically composed of heavy metals like mercury (Hg), lead (Pb), cadmium (Cd), etc which are toxic in nature. Due to the presence of these heavy metals, it has been observed that QDs binds and forms clusters in the cell membrane which in turn causes a toxic effect in the body. In the maximum of cases, Cadmium toxicity is observed. Cadmium being a nephrotoxic agent [78] are capable of causing a major roadblock in various applications of QDs in living cells (table 1). Researchers are working to modify and coat the surface of QDs to present penetration and aggregation of heavy metals in cells and hence causing minimal cytotoxicity to healthy living cells [79].

Conclusion:

Theranostic application of nanotechnology-based biomedicines has shown a cutting edge over conventional drug delivery systems. Quantum dots (QDs) are one such nanomedicine. Due to unique structural and functional properties, QDs are widely being explored in the development, bioconjugation, imaging, and targeting, and delivery of different types of drugs. Furthermore, currently, QDs are widely being used studied in various applications like in vitro bioassay, labeling specific cell and tissue specimens, imaging and tracing membrane receptors, in vivo tumor imaging, etc. Various research studies have shown that QDs can effectively use in invivo imaging, diagnostic, and treatment of cancer. Despite several applications, the primary concern with QDs is their potential toxicity. Thus, various safety measures are being taken into account during the preparation and application of QDs as the use of QDs in living cells encounters major roadblocks due to their chemical composition.

Thus from this review, we can conclude that QDs based nanomedicines can widely be used in imaging, diagnostic, and therapy of cancer.

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