Review Article

Quantum Dots as Emerging Theranostics in Cancer Treatment

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Mishra: Quantum Dots Based Cancer Theranostic

Cancer is among the main reasons of mortality worldwide. Early diagnosis offers the best chance of recovery for cancer patients. Scientists are still unable to successfully treat cancer spreading to various vital organs, despite the considerable strides in understanding the complex mechanisms leading to cancer formation and metastasis in recent years. The processes of tumor invasion, carcinogenesis and metastasis are still unclear because of the complexity of cancer cells and the microenvironment of tumors. Therefore, to understand the intricate molecular information underpinning the biological behaviours of tumors, it is imperative to develop a novel technology for cancer diagnosis and real-time observation right away. Quantum dots are luminescent semiconductor nanocrystals with a nanometer size range. Due to their unusual optical properties, including excellent brightness, simultaneous detection of many signals, long-term stability and adjustable emission spectra, they appeal as potential diagnostic and therapeutic systems in cancer. Due to their high quantum yields, low toxicity, biocompatibility and flexibility for various surface modifications, quantum dots are currently promising for bioanalytical investigations. The capacity of quantum dots for multiplexed sensing with various emission wavelengths to simultaneously detect a variety of biomarkers of illness is intriguing.

Key words: Quantum dots, cancer, nanocrystals, therapeutic system, drug delivery, diagnosis

Cancer is one of the leading causes of death worldwide[1]. According to estimates, 9.6 million fatalities in 2018 (or 1 in every 6 deaths) were attributed to cancer. World Health Organization (WHO) stated that around 70 % of cancer-related fatalities occurred in Low- to Middle-Income Nations (LMINs). Researchers have predicted that by 2030, there will be 16-18 million more instances of cancer annually, 60 % of which will occur in emerging nations. According to the WHO, only 12 nations are anticipated to achieve a reduction of one-third in early cancer death by 2030[2]. More money must be spent on treating non-communicable illnesses like cancer if sustainable development goals are to be met[3].

The increasing prevalence of cancer puts enormous physical, emotional and financial strains on people, families and ultimately, the world's health systems. Many cancer patients globally cannot obtain a timely diagnosis and treatment because health agencies in LMINs are the least prepared to handle this load. Only 1 in every 5 LMINs possesses the data required informing the cancer treatment and mitigation strategy, although the global cost of treatment for cancer in 2010 was predicted to be 1.16 trillion United States Dollars (USD). According to reports, between 30 % and 50 % of all cancer cases are preventable and may be treated with a long-term, cost-effective plan. The prognosis-quality therapy and survivorship care are increasing the survival rates of cancer patients in many different nations[4]. Due to the intricacy of cancer cells and the Tumor Microenvironment (TME), the processes of carcinogenesis, cancer invasion and metastasis are yet unknown. Therefore, it is essential to create a unique method for cancer diagnosis and real-time monitoring immediately to comprehend the complex molecular data underlying the biological behaviors of tumors[5-7].

Engineered fluorescent Quantum Dots (QDs) show distinct optical as well as chemical characteristics and have demonstrated considerable promise as prospective platforms for biological applications[8]. The clinical utility of QD-based nanotechnology

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Accepted 22 October 2024
Revised 26 June 2024
Received 22 December 2023
Indian J Pharm Sci 2024;86(5):1564-1574

in cancer diagnosis and detection including the principal difficulties in adapting QD-based detection techniques for clinical applications and encouraging future approaches are discussed in this review.

WORLDWIDE CANCER STATISTICS

Due to the aging and expanding global population, as well as the rising prevalence of cancer-causing activities, the global cancer burden continues to increase [9,10]. According to the World Cancer Report 2014, the global cancer burden rose to approximately 4 million new cases per year, with a projected increase to 22 million cases annually over the next 20 y.. Cancer deaths are expected to increase from 8.2 million to 13 million annually throughout this time frame. Despite recent advancements in early diagnosis and surgery-centered multidisciplinary treatments, the clinical outcome is still far from satisfactory. This is largely because of the complex cancer development process, which is a multifactor and multistep continuum, not just a disease of imbalance with a variety of molecular dysfunction and cell signalling disturbance, but a disease of imbalance with a variety of molecular dysfunction and cancer-favoring TME[11].

Breast Cancer (BC) is affecting about 2.1 million females annually. In 2018, 627 000 women died from BC, making up about 15 % of all women's cancer-related fatalities[12]. Typically, BC is classified according to how easy it can expand. Ductal carcinoma *in situ* begins in a milk duct but does not spread to the other breast tissue. Invasive or infiltrating types of BC i.e., invasive lobular carcinoma and invasive ductal carcinoma might spread to the breast tissue around them. The invasive ductal carcinoma constitutes up to 70 %-80 % of all BCs[13]. Inflammatory BC and triple-negative BC are also types of invasive BC. Inflammatory BC makes up 1 %-5 % of all BCs and is a rare kind of invasive BC. Fig. 1 shows various types as well as signs and symptoms of BC in females[14].

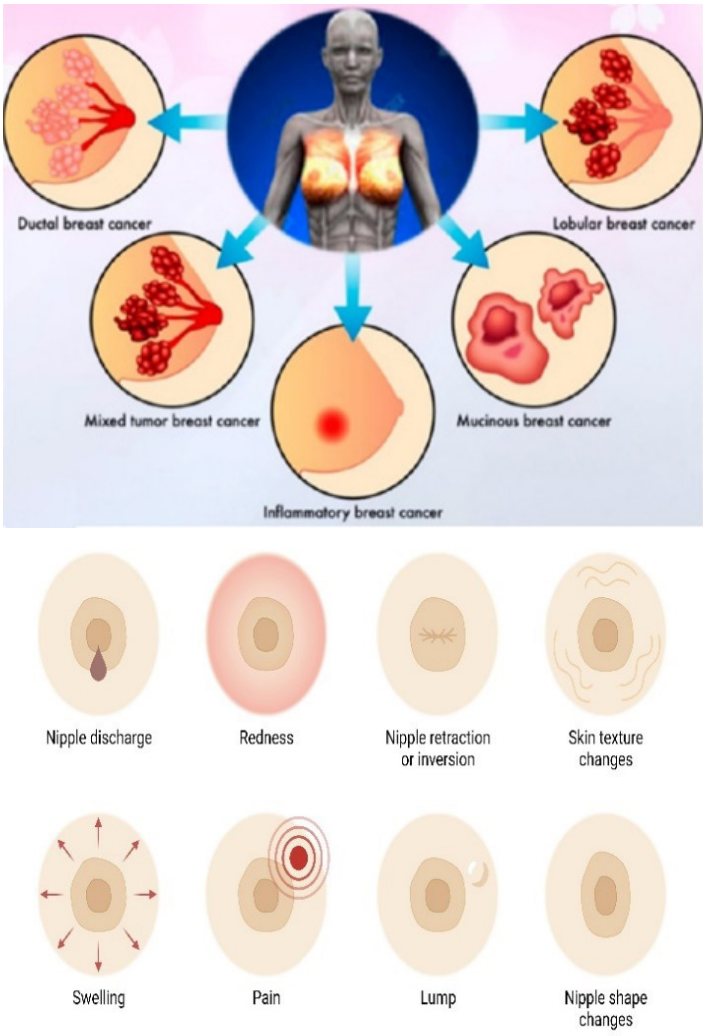

Fig. 1: Sign and symptoms and types of breast cancer

BC is becoming more serious cause of death in women. In this regard, scientists are working at the cellular level using cutting-edge nanomaterials to create early diagnostic and therapy techniques for BC[15-18]. However, the requirement for its execution in clinical practice is impeccable[14].

QDs: EMERGING THERANOSTIC AGENTS

Due to their potential applications in cancer diagnosis and treatment, QDs are gaining attention[19]. Fluorescent probes made from semiconductor QDs have proven effective in the detection and treatment of cancer. They were a unique fluorophore that, due to their size, exceptional stability, lack of photobleaching and water solubility, may replace conventional organic dyes[20]. Successful advancements in the nanotechnology fields[21] and cancer nanomedicine have been developed as a result of formulation development, molecular biology and bioimaging[22,23].

QDs, luminous nanocrystals are utilized for both imaging and delivery of various bioactive in a controlled pattern. These fluorescent entities with integrated carrier and imaging functionalities enable the administration of diagnostic and therapeutic agents. QDs are a very hopeful technique for personalized medicine because of their high sensitivity, unique optical features and flexible surface chemistry[24]. Given the persistent nature of cancer, researchers face the major challenge of combining detection and therapy (theranostics) using Graphene Quantum Dots (GQDs). GQDs have rapidly gained prominence in the fields of materials science and biomedicine.[14]. It is mentioned that different surface alterations on QDs have a direct impact on their attributes, such as their toxicity and optical capabilities. These materials are employed in clinically targeted molecular treatment and imaging due to the positive outcomes[25].

Fabrication techniques of QDs:

The QDs can be prepared by bottom-up and top-down methods. The use of cheap, non-toxic raw materials, simple post-processing steps, straightforward operations, rapid reactions and renewable resources are only a few advantages of the environmentally friendly synthesis of QDs. Prospective uses for these nanomaterials in biomedical and clinical sciences include bioimaging, diagnostics, bioanalytical testing and biosensors[26].

All of the top-down and bottom-up approaches proposed for the synthesis of QDs may be divided into three categories i.e., physical, chemical and biological methods[27-29]. Depending on the production process, the size of QDs can range from a few nm to a few μm and *via* careful growth processes, the particle size distribution can be regulated within 2 %[30]. The methods used to create QDs vary depending on whether they are cadmium-based or cadmium-free and they range from conventional methods to cutting-edge methods.

Features of QDs:

Nanoscale semiconductor crystals known as QDs are intriguing materials in a variety of scientific fields, including biology[31,32]. QDs were initially identified by a Russian scientist named Alexei Ekimov in the 1980s. These substances are made up of elements from groups II-VI or group III-V of the periodic table having physical dimensions less than the exciton's Bohr radius[33,34]. Their utility is getting better more than 20 y after they were first introduced.

QDs are exceptional prospects for *in vitro* and *in vivo* imaging because of their irreplaceable optical features. The inorganic core of the QDs is responsible for the optical and semiconductor capabilities. Before ligands are applied to the active core surface of a QD, it is frequently passivated by another inorganic shell. This enhances the optical characteristics of QDs because the shell's material has a wider band gap than the core, preventing electrons and holes from entering the shell[35]. Due to the confinement of electron-hole pairs (excitons) inside the nanocrystal grain boundaries, QDs exhibit distinctive visual features. QDs are ideal for a wide range of biomedical applications due to their unique photo-physical characteristics, which include broad absorption spectra and size-tunable narrow emission spectra, size- and composition-tunable light emission, high fluorescence quantum yields, enormous absorption extinction coefficients, photo-chemical robustness, barrier properties to the photo bleach effect, large stokes shift and decreased fluorescence intermittency[36]. QDs, which are luminous semiconductor nanocrystals just a few nanometers in size, require further research to address several critical issues and better understand the risks associated with their development and use in cancer treatment[37-39]. [39]. Due to their low toxicity, biocompatibility, high quantum yields and versatility for various surface modifications, silicon QDs, non-blinking QDs and QDs with decreased size and regulated valence are currently particularly tempting for use in bioanalytical applications. The potential for multiplexed sensing

employing QDs with different emission wavelengths to simultaneously detect a variety of biomarkers of illness is intriguing[40]. QDs have gotten a lot of interest since Ekimov and Efros classified them as a class of nanomaterials in the early 1980s. Although the earliest research focused on Cadmium Selenide (CdSe)-based nanocrystals, the field has subsequently expanded to encompass a variety of classes of nanoparticles with different chemical compositions for their core, shell and passivation[41].

QDs AS CANCER DIAGNOSTIC AGENTS

Due to the rising rates of cancer, cardiovascular disease, neurodegenerative disorders, autoimmune diseases and numerous infections worldwide, it is essential to develop strategies that can quickly and accurately detect the ultralow concentrations of relevant biomarkers, pathogens, toxins and pharmaceuticals in biological matrices. Many research efforts are now required to construct biosensors for their early identification and treatment using nanomaterials like QDs (fig. 2). These nanomaterials successfully enhance the repeatability, selection and sensitivities of the sensing performance[42].

BC:

The preferred diagnostic techniques for BC continue to be pathological laboratory tests like blood tests and biopsies, as well as biomedical diagnostic tests like computed tomography scans, positron emission tomography scans, ultrasound imaging, Magnetic Resonance Imaging (MRI) and mammography. Gene expression profiling is frequently employed as a diagnostic tool for the index of BC cell lines in place of immunohistochemical techniques[43,44].

In BC, QDs-based imaging investigations were carried out, including tissue imaging for assessing prognostic biomarkers and researching relationships between biomarkers, *in vivo* imaging for showing BC xenograft tumor, recognizing BC metastases and mapping the axillary lymphatic system[15,6]. Future applications of QDs-based imaging on clinical BC will mostly be focused on tissue investigation, particularly in BC molecular pathology and will include a variety of biomarkers[45].

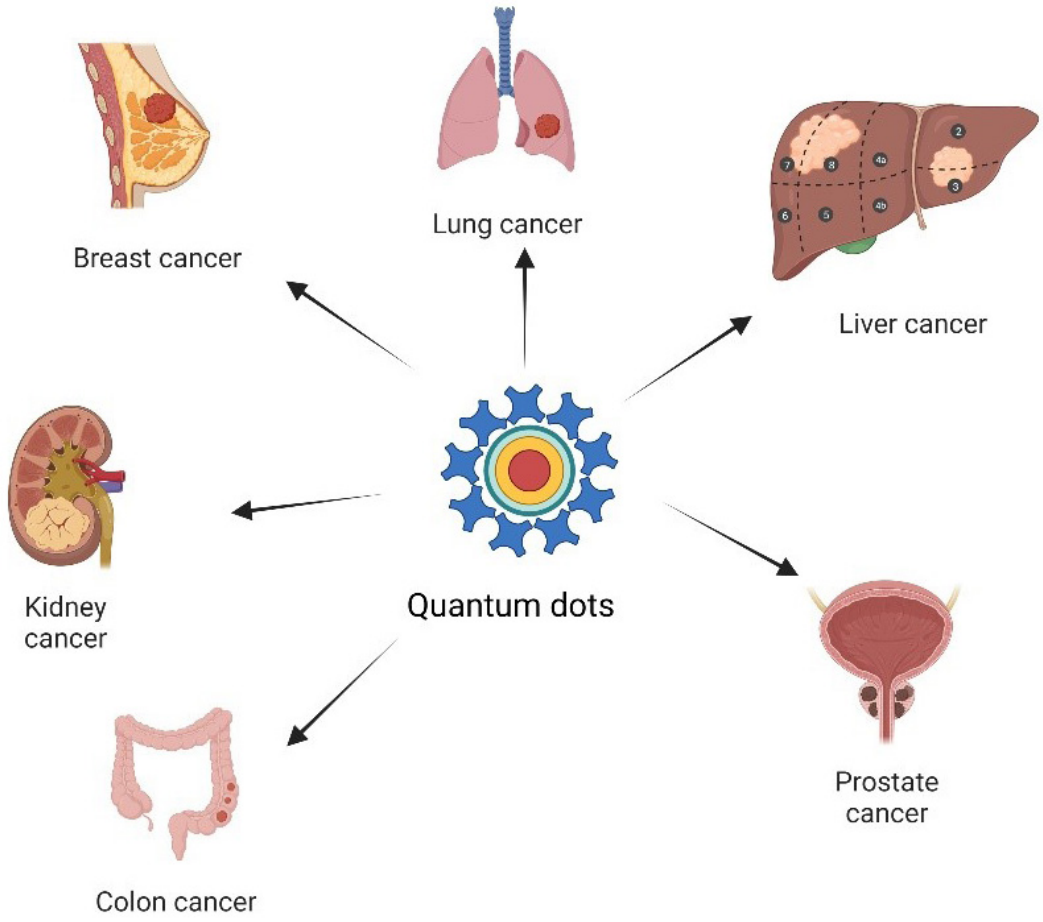

Fig. 2: QDs as cancer diagnostic agents

The limitations of the many genomic expression approaches, including Oncotype Dx test, MammaPrint® and BC Index (BCI), often include the requirement that BC has not yet spread to the lymph nodes for them to be effective. The inherited mutation of the BC gene is the genetic cause of BC (BRCA1 or BRCA2). About 25 %-30 % of invasive BC patients have elevated levels of HER2, a 185 kDa protein also known as c-erbB-2 or HER2/neu, which is strongly associated with more aggressive tumor biological characteristics[46]. The first to create QDs-based strategies for HER2 targeting in mice mammary tumor sections and human BC cells (SK-BR-3). Additionally, they created a technique to concurrently detect HER2 and human anti-nuclear antigens in a single BC cell using several QD colors. The usefulness of HER2 detection using QDs for BC has been supported by a couple of researches. HER2 over-expressing BC alive mice model was tracked using a single particle QD coupled with an anti-HER2 antibody, which effectively detected five delivery processes as follows. HER2 binding to the cell membrane, traveling from the cell membrane to the perinuclear region, occurring during extravasation, first inside the circulation within a blood vessel and in the perinuclear region[47].

25 distinct subtypes have been identified using information from QD-based quantitative spectral analysis of HER2, ER, and PR, including High Hormone Receptor (HHR), Low Hormone Receptor (LHR)-low HER2 total load (LTH2), LHR-high HER2 total load (HTH2), negative hormone receptor (NHR)-low HER2 total load (LTH2), and Negative Hormone Receptor (NHR)-HTH2[48,49].

Thomas Ashworth, an Austrian scientist, first identified Circulating Tumor Cells (CTCs) in patient cadavers in 1869[50]. Since they are released from primary tumors into circulation to relocate to distant organs, CTCs play a crucial role in metastases and their number is highly correlated with clinical prognosis[51]. CTCs have not entered common clinical practice despite being discovered more than a century ago, mostly due to a lack of technology to isolate these incredibly uncommon cells. QDs have been created as a brand-new class of fluorescent probes with several distinctive features for therapeutic use. Numerous initiatives have been taken to increase target sensitivity and specificity[52-55]. It has been suggested that particular cancer cells can be captured and separated using built-in bifunctional nanospheres and further trifunctional nanospheres using both QDs and magnetic nanoparticles. Then, wheat germ agglutinin changed the trifunctional nanospheres to readily collect Prostate Cancer (PC) cells without harm. Later, these monoclonal antibody-based probes were used to target a variety of cancer cells, including leukemia cells and PC cells. For these two types of cancer cells, the capture efficiencies were 96 % and 97 % respectively, after 25 min and using this approach, it was possible to quickly identify a small percentage of cancer cells (approximately 0.01 %) intermingled with a vast population of normal cells in culture[56].

Fluorescent labeling of aptamers is a useful technique for cell imaging and aptamer tracking. The aptamer SL2-B, which is targeted towards the Heparin-Binding Domain (HBD) of the VEGF165 protein, was coupled to QDs to produce the QD-SL2-B aptamer conjugate. The photobleaching impact of the QDs and the QD-aptamer combination was evaluated before incubating the cells[57].

QDs are intravenously injected into orthotopic breast and pancreatic tumors in mice using the tumor-penetrating iRGD peptide. The extravascular cancer cells and fibroblast still hold intact QDs after quenching the excess QDs, producing a tumor-specific signal[58].

PC:

Sensitive and multicolor imaging of cancer cells under *in vivo* settings using QDs probes coated with Prostate-Specific Membrane Antigen (PSMA), a significant marker of PC, has been described[59]. Additionally, the same group investigated E-cadherin, high-molecular-weight cytokeratin, p63 and -methyl acyl CoA racemase *in situ* detection to perform QD-based high-throughput digital mapping of molecular, cellular and glandular changes on surgical PC specimens[60] which, particularly at complicated and dubious illness loci, is not accessible by Hematoxylin and Eosin (H&E) staining and Immunohistochemistry (IHC) techniques. Shi *et al*.[59] demonstrated the higher quality of multiplexed QDs for the detecting of prostate-specific membrane antigen in grown PC cells[61].

Ovarian cancer:

The epithelial antigen CA125, a helpful tumor marker for ovarian cancer, may also be found using QDs in various specimen types, including fixed cells, tissue slices and xenograft pieces. The signals from the QDs probes have been more distinct and brighter than those from the traditional organic dye. The simultaneous detection of BRAF and BRCA Deoxyribonucleic

Acid (DNA) using a nano-on-micro technology-based multiplexed DNA sensor was also reported by Ai *et al*.[60]. This method has significant promise for the early identification of diseases such as BC, ovarian cancer and papillary thyroid carcinoma[62-64].

Pancreatic cancer:

Bombesin (BN) receptors in the healthy pancreas, which are absent in pancreatic cancer, have been designed as a target by Montet *et al*.[63] instead of targeting upregulated or overexpressed molecules in cancer cells[65]. The BN-Cy5.5 nanoparticle offers a potential method for imaging pancreatic cancer by reducing the T2 signal of a healthy pancreas and improving the capacity to see the tumor in a model of pancreatic cancer using MRI. Multifunctional QDs have become efficient materials for simultaneous cancer diagnostics, targeting and therapy. The main barrier to clinical translation for QDs is still toxicology[37].

Liver cancer:

To target liver tumors, Yu *et al*.[64] created customized QDs-anti-Alpha-Fetoprotein (AFP) probes. As these probes gathered inside the tumor, they fluoresced, allowing for active tumor-targeted and spectroscopic hepatoma imaging[66]. Additionally, the QDs-based pictures could demonstrate lung metastasis, recurrence and subcutaneous tumor progression.

Lung cancer:

A method for quantifying protein expression, including Epidermal Growth Factor Receptor (EGFR), pan-cytokeratin and E-cadherin, of lung cancer tissues from xenograft models, was developed and validated by Ghazani *et al*.[65]. This method provided an automated mathematical tool to remove auto-fluorescence, normalize tumor protein normalized to cellular content and produce a thorough profile of tumor-derived antigen on a tissue microarray[67]. When compared to conventional IHC, QDs-IHC had a greater sensitivity for detecting caveolin-1 and Proliferating Cell Nuclear Antigen (PCNA) in lung cancer[37,68-70].

Other solid tumors:

Recent developments in the conjugation of QDs and the extracellular domain of EGFR proteins[71] allow for the rapid identification of tumor type, grade and chemoresistance by biological markers characteristics and enable nanoparticle-based, mechanistic studies of the role of activated EGFR in the growth and invasiveness of brain tumors as extracellular domain of EGFR proteins could induce receptor activation to enable the precise detection of intracellular[72]. Multicolor QDs can also be utilized to diagnose Hodgkin's lymphoma[73]. Four protein indicators (Cluster of Differentiation (CD)15, CD30, CD45 and CD Pax5) that were imaged multiplexed enabled the quick identification and discrimination of the uncommon Hodgkin's and Reed-Sternberg cells from encroaching immune cells[38,74,75].

QDs IN TREATMENT OF CANCERS

With QDs-based probes, *in vitro* and *in vivo* molecular imaging has seen significant developments. However, the intriguing physical and chemical properties of well-known QDs may also be related to their potentially harmful effects on living cells and tissues. Further research on some crucial issues is necessary to appropriately quantify the risks associated with the manufacturing and use of QDs in treating cancer[76]. The literature has examined the use of QDs for anticancer therapy using drug administration, gene delivery, and the recently established Photodynamic Therapy (PDT)[10,24,77,78].

In combination with fluorescence imaging, modified QDs may effectively infiltrate cells and be employed as therapeutic agents to treat various cancers[79]. In the pharmaceutical business, QDs can be employed as tools for cell labeling, immunolabeling, medicine delivery and diagnostics[80]. Applications for silicon QD-based *in vitro* and *in vivo* imaging and drug delivery techniques are also discussed[81].

A QD aptamer-Doxorubicin (Dox) conjugate has been described by Bagalkot *et al*.[80] as a targeted cancer imaging, treatment and sensing system. This straightforward multipurpose nanoparticle technology can both give Dox to the desired PC cells and detect Dox delivery by turning on the fluorescence of QD[82].

Moving nano-diagnostic technologies from the lab to society scales will require further work. Due to their smaller size (10-150 nm), GQDs exhibit selective extravasation capacity from the circulation into tumor tissue in the event of passive targeting of tumors. They may be able to positively accumulate in tumor tissue due to Nanoparticles' (NPs') increased permeability and retention effective response[83]. Many researchers are working to make further progress in the areas of reducing the potential toxicity, improving biocompatibility and improving the capacity of GQDs to load drugs. Recent studies have shown the effectiveness of combining

GQDs with rare-earth up-converting NPs for synergistic PDT/Photothermal (PTT) and bioimaging applications in cancer therapy to solve the aforementioned issues[84]. It is reasonable to assume that GQDs-based nanoplatforms can enhance theranostic techniques in practical and biocompatible ways given the wealth of research reports on GQDs. However, there is always a silver line that must be crossed before an innovation is accepted and that is the point at which the newly developed materials become well-known or are used in common biomedical applications.

CHALLENGES IN QDs-BASED DETECTION TECHNIQUES

Nanotechnology holds enormous promise for both fundamental and therapeutic cancer research. Particularly with conjugated QDs in targeting metastasis and in quantitative detection of molecular targets, unique surface and size features of QDs offer significant potential in enhancing the clinical application and excite enthusiasm for breaking past, present technical limits. Due to the lack of clinical experience with their use, innovative QDs-based technologies have prompted concerns about biosafety, repeatability and dependability when compared to current conventional technologies. In the case of QDs, several surface modifications are said to affect properties including toxicity and optical properties directly. Due to the promising outcomes, these materials are employed in clinics for specialized molecular therapy and imaging. Several issues must be resolved before the widespread use of QDs in a therapeutic setting. Proposals are suggested and investigated with respect to the existing obstacle facing QDs to propose an appropriate approach for the therapeutic application of these materials[25].

BIOSAFETY ISSUES OF QDs

Before incorporating QDs into clinical use, we must first overcome the obstacle of reducing the QDs' cytotoxicity. QDs include potentially harmful metal atoms and because of colloidal effects and photon-induced free radical production, they may unexpectedly cause cytotoxicity[85]. There aren't many papers or sources of information on the cytotoxicity or biosafety of QDs, which is partially related to the novelty of nanotechnology[86]. These issues might not have a significant impact on the advancement of *in vitro* applications, but they pose significant obstacles to *in vivo* cancer imaging in humans. Although more attention has been paid to how QDs affect human health and the environment[87].

Cytotoxicity:

Numerous QDs have some level of cytotoxicity. The size, capping material, dosage, surface chemistry, coating bioactivity and QD exposure pathway are the key determinants of QD cytotoxicity. Target cells and tissues may experience a harmful effect from the remaining organic compounds[88]. As an illustration, Wistar rats were exposed to 0.52 mg cd/m^3 for 5 d (6 h/d) by nasal delivery. After 3 d of exposure, Cd-based QDs were discovered upon a histological investigation of the clinical variables in blood, Bronchoalveolar Lavage (BAL) fluid and lung tissue. Without harming the central nervous system, the Cd-based QDs were able to trigger local neutrophil inflammation in the lungs[89]. Due to the protective effect of the Zinc Sulfide shell preventing the escape of Cd ions from the inner side, a significant buildup of QDs was seen in the spleen. In *Drosophila melanogaster*, the long-term toxicity of CdSe-ZnS QDs with surface coating and the genotoxic effects of QDs *in vivo* were investigated. Additionally, the toxicity of QDs is examined, along with modifications for toxicity reduction. Real publications and patents are used to analyze how QDs are used in biomedicine[90].

The cytotoxicity of QDs has been attributed to several different causes. These mechanisms, which have been previously described, can be summed up as free Cd desorption (degradation of the core of QDs); production of free radicals and interaction of QDs with intracellular components. Since the inner metal core of some types of QDs is made of hazardous metal, (such as Cadmium (Cd), Arsenic (As), Selenium (Se), Tellurium (Te) and Lead (Pb)) the stability of the outer surface layers of QDs directly affects their biocompatibility[91].

In vivo toxicity:

The toxicity caused by the leaking of heavy metal ions like Cd, Pb or As from contained QDs (II-IV, IV-VI, or III-V groups) into biological systems is one of the key obstacles to the widespread use of QDs for *in vivo* investigations. If the QD surfaces are not adequately shielded by ligands or covered by shells, the issue becomes more challenging. Until recently, several *in vitro* and *in vivo* research have been conducted to examine the cell- and tissue-toxicity of QDs[92,93], as was already established, research has revealed that QDs are not necessarily safe[94-98] and when utilized as imaging and therapeutic agents, they have various impacts on biological systems at the cellular, subcellular, and molecular levels[99]. QDs may negatively impact cell viability, growth and proliferation in addition to causing

various DNA damages[100].

SURFACE MODIFICATIONS OF QDs

The use of QDs for biological applications has certain significant limitations, as has already been addressed in the literature. One of their drawbacks is typically associated with the release of Cd, Pb or As from their structural components into the biological environment. Their poor solubility is a further constraint. Today, surface alterations have been suggested to solve the QD problems outlined above. Several strategies have been put forth in this area, including surface ligand exchange and covering QDs with biocompatible compounds (e.g., polymer layer)[101,102].

CONCLUSION

To improve the properties of QDs for particular applications, several synthesis methods and tactics have been developed during the past 10 y. Recently, this family of materials has demonstrated considerable promise in various biological applications, including tissue engineering, regenerative medicine and cancer treatment. Additionally, QDs have lately been recognized as helpful tools in several scientific fields, including real-time dual-targeted medication administration and molecular imaging of adipose regions in obese patients. QDs may successfully interact with many biomolecules because of their relatively high surface area and distinctive molecular structure. Both developed and stem cells' ultimate fates in the human body may be significantly influenced by these interactions. Due to a notable improvement in the creation of chemotherapeutic and protein-based medications, applications of QDs in cancer medicine have drawn a lot of interest among other developments.

Nanotechnology-based on QDs is a huge field. Despite the difficulties in clinical translation, QDs represent scientific advances that might transform cancer diagnostics. Although it is clear that QDs-based *in vivo* molecular imaging has benefits, their biosafety still has to be thoroughly investigated and assessed. QDs are currently used often *in vitro* for the detection of cancer-associated proteins, the capture of CTCs, and molecular pathology. These applications highlight the dynamic process of cancer formation and enable the creation of a new platform for a better understanding of tumor heterogeneity.

Despite this, the biggest obstacle for researchers will be the *in vivo* or clinical usage of QDs. Even though cell-based investigations of QDs offer some important advantages over conventional diagnostic approaches, there are still major obstacles to overcome before these approaches can be effectively applied in clinical settings. The majority of QD research relies on *in vitro* testing. To realize their potential and determine their safety and effectiveness profile, these investigations should be continued in animal models and clinical trials. To speed up the application of QDs in cancer detection and diagnosis in clinically relevant contexts, interdisciplinary partnerships combining oncologists, bioinformatics scientists, chemists, physicists, biomedical engineers, biologists, and pathologists are urgently needed.

Conflict of interest:

The authors declared no conflict of interests.

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