REVIEW

Editorial Process: Submission:11/02/2023 Acceptance:03/08/2024

Applications of Quantum Dots in Preventive Oncology

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Abstract

QDs are semiconductor nanocrystalline materials with distinct optical and electronic characteristics due to their microscopic size and quantum mechanical properties. They are often composed of materials such as cadmium selenide (CdSe), cadmium telluride (CdTe), or indium phosphide (InP) and are typically in the size range of 2 to 10 nanometers in diameter. These tiny particles are used in various scientific and technological applications. Some key characteristics and applications of quantum dots are size-dependent Optical Properties with tunable emission. The color of light emitted by quantum dots highly depends on their size. Smaller QDs emit blue or green light, while larger ones emit red or near-infrared light. This tunability makes them valuable in various applications, especially in molecular medicine and oncology research. Quantum dots can exhibit a high quantum yield, meaning they efficiently emit light when excited, making them excellent fluorescent probes for non-invasive imaging. This review discusses the applications of QDs and their role in biomedical research and patient care, focusing on non-invasive imaging and preventive oncology.

Keywords: Quantum dots- preventive oncology- fluorescent imaging- sensors- drug delivery

Asian Pac J Cancer Prev, **25 (3)**, 747-756

Introduction

Quantum dots (QDs) are being explored in next-generation solar cells because they can absorb wider wavelengths of light compared to traditional solar materials [1]. Used in display technology to improve the color and performance of LCD screens, they result in brighter, more energy-efficient screens, and enable quantum computing as possible qubits, the basic units of quantum information processing [2, 3]. Functionalized QDs can be used in drug delivery systems to deliver therapeutic agents to specific targets in the body. QDs are also used in various chemical and biological sensors because they are sensitive to environmental changes [4]. They also act as fluorescent labels in biological and medical imaging [5, 6]. Their brightness, photostability, and tunable emission make them ideal for monitoring and imaging biological molecules, cells, and tissues. Despite all these advantages, some QDs, especially those containing heavy metals such as cadmium, can cause toxicity problems [7]. Cadmium-based QDs were previously considered to be toxic to cells. CdTe QDs increased mouse hepatocytes and enhanced reactive oxygen species (ROS) [8]. QDs also induced apoptosis in HeLa cells and inhibited cell proliferation [9]. Green Cd QDs are more toxic than yellow ones, suggesting a size-dependent QD toxicity mechanism [10]. CsdTe QDs also changed mitochondrial membrane potential and increased Ca2+ levels. Scientists are developing safer alternatives and coatings to mitigate this problem. Studies have shown that quantum dots accumulate on the cell surface by binding to cell surface receptors and are then internalized by receptor (or clathrin)-mediated endocytosis [11]. QDs are usually transported into mammalian cells mainly by clathrin-mediated endocytosis [12]. However, some cell types combine these pathways to capture QDs.

Thus, QDs, with their unique optical properties, serve as versatile tools in biomedicine, enabling precise imaging of cellular structures and processes, crucial for diagnostics. Additionally, their application extends to targeted drug delivery, offering a promising avenue for localized and efficient therapeutic interventions in the treatment of various diseases (Figure 1).

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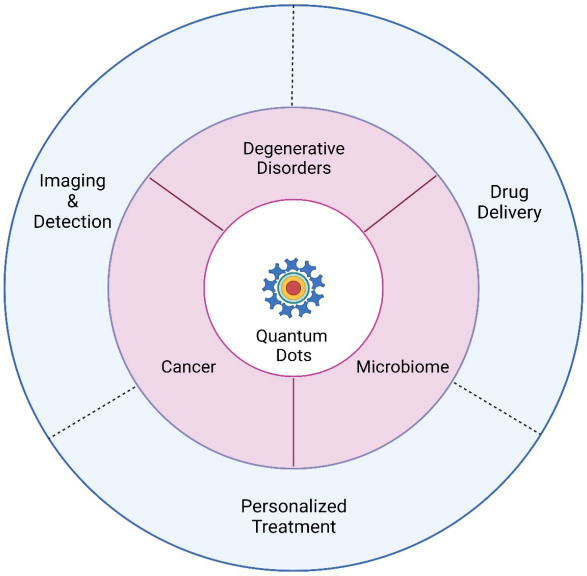

Figure 1. Application of Quantum Dots in Medical Research

QD in Oncology Imaging

Due to their distinctive optical and physicochemical characteristics, QDs have attracted significant interest in cancer research and therapy [13]. The detection, diagnosis, imaging, and treatment of cancer have all shown promise for these nanoscale semiconductor particles [14, 15]. The use of quantum dots in oncology research and imaging, as well as their potential effects on the field, are covered in this review. In order to image cancer, quantum dots can be used as extremely effective fluorescent probes [16, 17]. They are excellent for identifying and monitoring cancer cells and tissues due to their bright and stable fluorescence properties. To specifically target cancer cells, QDs can be coupled with biomolecules that are specific to tumors, such as antibodies or peptides [18]. QDs can be used in conjunction with other imaging methods like computed tomography (CT) or magnetic resonance imaging (MRI) to provide supplementary data for a precise cancer diagnosis known as multimodal imaging [19, 20]. They can also serve as vehicles for the delivery of drugs [21]. Chemotherapeutic medications can be added to or enclosed in QDs, enabling targeted drug delivery to cancer cells [22]. As a result, systemic toxicity is decreased and therapeutic efficacy is increased. In theranostic applications, QDs can act as both drug carriers and imaging agents [23, 24]. This makes it possible to track the delivery of drugs and how they affect cancer cells in real time. To find cancer biomarkers, QD can be incorporated into biosensors. This makes it possible to track the delivery of drugs and how they affect cancer cells in real-time. To find cancer biomarkers in blood or other bodily fluids, QD can be incorporated into biosensors [25-27]. Early-stage cancer can be detected by alterations in the fluorescence characteristics of QDs when certain biomolecules are present. Near-infrared (NIR) light can reach deep inside tissues and can be absorbed by QDs [28, 29]. QDs produce heat when exposed to NIR light, enabling localized photothermal therapy to eradicate tumors or cancer cells [30]. According to Shim and Song, [31] and Yang et al. [32], QDs can label cancer cells or tumor tissues to track their response to treatment. Fluorescence distribution or intensity changes can offer information about the effectiveness of a given therapy and aid in its optimization. In surgical oncology, particularly in breast cancer and melanoma, QDs are used in Sentinel Lymph Node Mapping to quickly map sentinel lymph nodes [33, 34]. This lessens the need for extensive lymph node dissections by making it easier to locate and remove lymph nodes that might be impacted by cancer spread. Aloe vera extracts have been constructed to form amorphous carbon QDs with apoptosis effects on MCF-7 cancer cells, positioning them as a valuable fluorescent probe for live imaging [35]. In fact, cancer surface markers play a dominant role in detecting cancers. The overexpression of folate receptors in various cancers, including breast, brain, cervical, and ovarian cancer, makes folic acid an ideal ligand for targeting and imaging cancer cells. Researchers, such as Liu and colleagues, successfully synthesized luminescent carbon quantum dots with high quantum yield (95%) using folic acid as a precursor, exhibiting excellent properties like photostability and biocompatibility [36].

Due to their unique physicochemical properties, QDs have attracted a lot of attention from researchers for use in optical imaging [37, 38]. They can be made to emit visible fluorescence in a range of wavelengths because of their adjustable size, which makes them useful for in multilayered and multicolor tissue and cell imaging as compared to other fluorescent materials [39, 40]. In brain cancer, known for its challenges due to the blood-brain barrier, Zheng et al. [41] developed carbon QDs (CD-Asp) from D-glucose and L-aspartic acid, capable of crossing the blood-brain barrier and serving as a fluorescent imaging probe for glioma cells [41]. Qiao et al. [42] highlighted the highest selectivity of carbon QDs towards glioma cells when synthesized in a specific molar ratio [42]. Betel leaves, renowned for their use as a mouth freshener due to their rich content of antioxidants, vitamins, and minerals [43], have been utilized by Atchudan et al. [44] to derive nitrogen-doped carbon quantum dots (B-NCD). These carbon QDs exhibit multicolor fluorescence and have been demonstrated for multicolor imaging on HCT 116 colon cancer cells by the authors [45]. InP QDs also emerge as a promising, eco-friendly substitute for Cd-based QDs in diagnostics and bioimaging. Zhang et al. excelled in specific labeling of liver cancer cells and in vivo tumor-targeted imaging in live mice, highlighting their potential for advanced cancer diagnosis and image-guided surgery [11]. To enhance the technique, Cao et al. [46] integrated high-quality dual-color quantum dots particle probes into a multilabel lateral flow immunoassay system, creating an immunodetection platform for instant and quantitative detection of gastric cancer markers (pepsinogen I & II) in serum samples [46].

Furthermore, this technology allows for real-time, in-situ observation of a variety of biomarkers, enabling quantification of expression levels of biomarkers and providing a more comprehensive understanding of biomolecular interactions and their relationship to disease onset, progression, and prognosis, which has the

potential to facilitate clinical diagnostics and treatment decisions [47, 48]. Recent research has revolutionized this technology and driven it towards nucleic acid-functionalized quantum dots, which show promise as imaging probes for cancer cell bioimaging, combining QDs' optical properties with bioconjugation facilitated by nucleic acid functionalization. In a study Zn-doped CdTe QDs were synthesized and DNA-functionalized through a one-pot hydrothermal method. These DNA-functionalized QDs were successfully tested for detecting MUC1 in lung adenocarcinoma A549 cells in vitro and in tumor-bearing nude mice in vivo [49]. In 2014, Ma et al. addressed challenges in using QDs for living imaging of intracellular tumor-related markers, proposing a new type of DNA-functionalized QD for extracellular and intracellular targeting and imaging of cancer markers. They designed a heterobivalent QD using a DNA template with a central phosphorothioate domain for QD growth and two phosphate domains at each end for extracellular nucleolin and intracellular mRNA targeting. The QDs were facilitated into cells via micropinocytosis, bypassing lysosomal sequestration, allowing for effective sensing and imaging of intracellular targets [50]. Extending their work, the same group introduced a novel approach for single-cell imaging using QDs through DNA-programmed polymerization of QDs with aptamers, forming linear QD-aptamer polymers. This bottom-up assembly approach, utilizing hybridization chain reaction, enhanced cell-sensing sensitivity through multivalent binding and multiple QD signal amplification. The study focused on optimizing signal amplification for sensing specific cancer cell markers, particularly the cell surface receptor PTK7 in human acute lymphoblastic leukemia cells (CCRF-CEM) [51] (Figure 2).

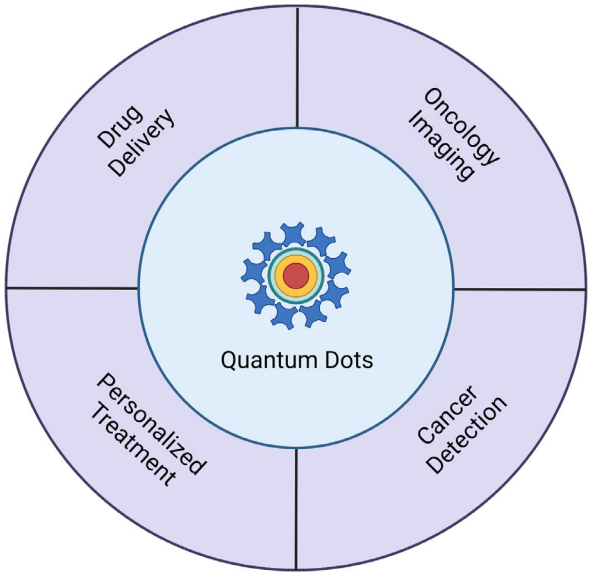

Figure 2. Applications of Quantum Dots in Cancer

Applications of QDs in Cancer

According to Kashyap et al. [52] Wilkinson et al. [53] Houghton et al. [54] and Fahad, [55] breast cancer is one of the most prevalent cancers in the world and has the highest incidence rate among women [52-55]. For cancer staging, sentinel lymph node biopsy (SLN) is a common practice [56, 57]. When patients are exposed to ionizing radiation during surgery, organic dyes or radiocolloids used in SLN mapping result in local tissue damage [58]. Without a biopsy, QD can map the SLN [34, 59]. The best course of action is surgical resection of the primary tumor. However, because it can be challenging to define the tumor margin, cancer cells frequently survive and recur. Functionalized QDs can be used for image-guided tumor resection to visualize cancer cells [60, 61]. Photostable near-infrared QDs are available. These QDs are appropriate for deep-seated tumors because of their improved deep-tissue penetration [62, 63]. Although quantum dots have many benefits for cancer research and treatment, there are some issues with their toxicity and long-term safety that need to be resolved before they are widely used in clinical settings

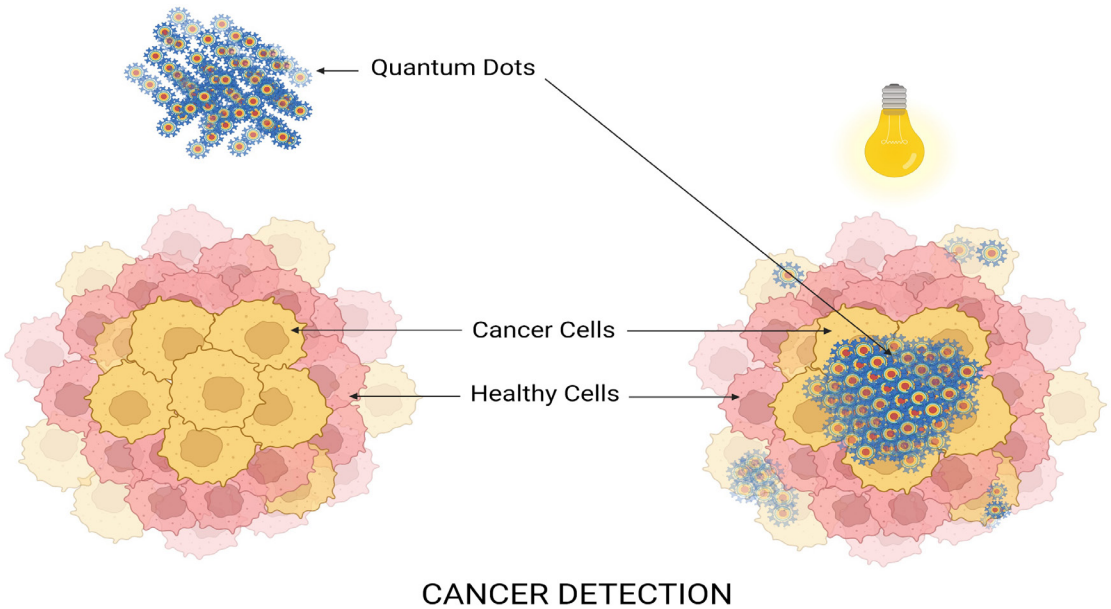

Figure 3. Cancer Detection Using Quantum Dots

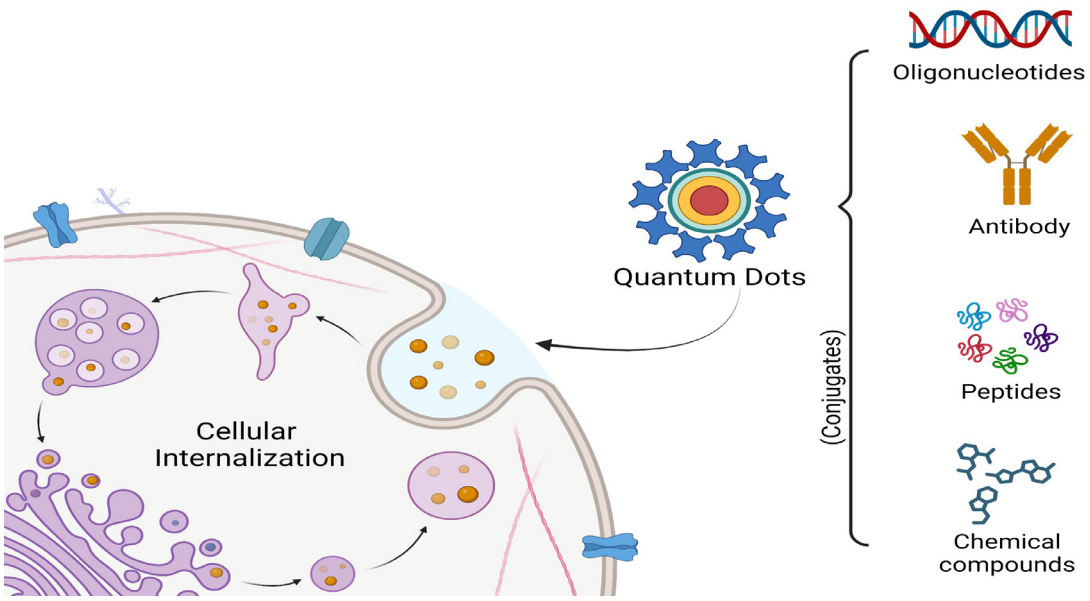

Figure 4. Cancer Therapy Using Quantum Dots

[64]. To ensure the security of their application in cancer diagnosis and treatment, researchers are still looking into the biocompatibility and potential risks of QDs. However, the adaptability and distinctive qualities of QDs offer hope for enhancing our comprehension of cancer and cancer management approaches [65]. A significant role for QDs in preventive oncology emphasizes early detection and risk assessment to reduce the incidence and impact of cancer [66]. Here are some ways in which QDs can be applied in drug deliveries

QDs in Drug deliveries

Due to their special qualities, such as tunable optical characteristics, biocompatibility, and adaptable surface functionalization, QDs have become promising tools in drug delivery systems [67, 68]. Targeted drug delivery, controlled release, and real-time monitoring are just a few benefits associated with their use in drug delivery [69-71]. Targeting ligands like antibodies, peptides, or aptamers can be used to functionalize QDs [72, 73]. These ligands allow for precise binding to cancer cells or other target tissues, guaranteeing that the drug payload is delivered exactly where it is needed. Targeted drug delivery minimizes harm to healthy tissues and reduces off-target effects. This method lessens side effects while increasing the therapeutic index of medications. In addition to

Table 1. Applications of Quantum Dots in Biology. Table shows different types of Qdots and their application with relevant references.

	Quantum Dots	Applications	References
1	B and Co-doped C-QD	Bio-imaging (Lysosomes)	(Deng et al., 2023)
2	Boron-doped Graphene QD	Bio-imaging (Stem Cell line)	(Fan et al., 2014)
3	Cadmium based QD	Anti-Autophagy	(Fan et al., 2016)
4	Cadmium-based QD	Autophagy Formation for Cell Survival	(Luo et al., 2013)
5	CdSe	FRET	(Peng et al., 2016)
6	CdSe/ZnS	FRET	(Hikmet et al., 2003)
7	CdSe/ZnS	DNA Hybridization	(Fu et al., 2004)
8	CdSe/ZnS/antibody	DNA Hybridization	(Goldman et al., 2002)
9	CdSe/ZnSe/ZnS	Intra-cellular pH sensors	(Liu et al., 2007)
10	CpG doped QD	Immunotherapy	(Golshadi and Schrlau, 2017)
11	C-QD	Bio-imaging and Bio-labelling	(Atchudan et al., 2021; Murugan et al., 2019)
12	C-QD	Antiviral	(Ting et al., 2018; Dong et al., 2017)
13	Graphene QD	Photostability and Phototoxicity	(Kulahava et al., 2023)
14	PEG/BSA coated QD	Anticancer	(Chen et al., 2017)
15	QD	Antibiotic	(Huh et al., 2011)
16	QD	High Thoroughput Experimentation	(Ali et al., 2023)
17	ZnO QD	Anti-Apoptosis	(Wahab et al., 2016)
18	ZnSe/ZnS	FRET	(Kim et al., 2003)

targeted deliveries, QDs also aid in the encapsulation of drugs to allow for a controlled release [74, 75]. Drug molecules can either be attached to the surface of QDs or encapsulated within their core. The drug is shielded from deterioration by this encapsulation, enabling a controlled and prolonged release [76]. In response to particular stimuli like changes in pH, temperature, or enzyme activity, researchers have created QD-based drug delivery systems [77-79]. These stimuli cause the drug payload to be released at the intended site, increasing drug efficacy. Strong and stable fluorescence characteristics are present in QDs [80, 81]. When loaded with drugs, they allow for real-time in vivo drug release and distribution monitoring. This monitoring offers insightful information on the pharmacokinetics and pharmacodynamics of drugs. Multiple drugs or therapeutic agents can be transported simultaneously using QD. Combination therapy, in which various medications are administered together to improve treatment outcomes using complementary mechanisms of action, is made possible by this capability [82]. The type and stage of the patient's cancer, genetic makeup, and drug sensitivity can all be taken into account when designing quantum dot-based drug delivery systems [60, 83]. The efficacy of treatment is maximized by this personalized approach. Quantum dots can be used as imaging tools as well as drug delivery systems. Clinicians can see drug distribution in real-time by incorporating imaging agents into the QD-based delivery system, guiding the clinicians to visualize drug distribution in real-time, by the delivery process [82, 84]. Jha et al. [85] synthesized biodots, carbon dots derived from DNA, for treating non-small lung cancer. They developed liposomes loaded with ETP and conjugated with cetuximab, effectively targeting tumor cells [85]. Later, Yadav et al. [86] reported the synthesis of protein CDs (PND) from lysozyme, loaded with melatonin, a potent antioxidant with anti-tumor properties. The resulting melatonin-loaded PNDs (MPND) demonstrated significant cellular uptake when treated with breast cancer cells [86]. To enhance the efficacy of Gemcitabine, a chemotherapy drug, Yunus et al. [87] conjugated it with CQDs derived from sucrose via ultrasonication. In vitro and in vivo studies revealed that the CDs-GEM conjugate selectively targeted cancerous cells and efficiently penetrated cell membranes [87]. To improve targeted drug delivery in gastric cancer treatment, Lei et al. [88] developed GIC@HM NPs, a nanomedicine using Graphene Oxide based QDs to co-load ICG and CS-6, wrapped with a hybrid membrane (erythrocyte and gastric cancer cell membranes). This nanomedicine offered both photothermal therapy and chemotherapy, enhancing treatment efficacy [88]. DNA aptamer-conjugated QDs target growth factor receptors, crossing the BBB to accumulate in tumor cells for fluorescent visualization. QDs, as both probes and drug carriers, can deliver chemotherapeutic agents, enhancing drug permeability. For instance, carboxymethylcellulose-based QDs conjugated with doxorubicin serve as photoluminescent probes targeting glioblastoma cells [3]. Similarly, carbon QDs conjugated with transcriptional factors and doxorubicin exhibit enhanced cytotoxicity against pediatric brain tumors in vitro, reducing viability compared to free doxorubicin. Carbon QDs with specific functional groups selectively interact with receptors upregulated in cancer cells, enabling targeted delivery of topotecan in a glioma mouse model, demonstrating effective tumor cell killing with reduced toxicity to normal tissues [89]. Extending this scope of literature to other neurodegenerative disorders, the optical characteristics of QDs have also been exploited in treating several neurodegenerative disorders. In a recent study, Lin et al. [90] introduced an innovative brain-targeted platform using ZnO QDs for delivering a gene aimed at interfering with SNCA expression in Parkinson's disease treatment. Their findings revealed that ZnO QDs successfully traverse the blood-brain barrier, releasing the gene through lysosomal escape. Additionally, they demonstrated the neuroprotective effects of this nanoplatform, highlighting its ability to reverse neurodegenerative processes in Parkinson's disease models [90]. In a separate investigation, Kim et al. [91] reported that graphene QDs (GQDs) effectively permeate the blood-brain barrier, providing protection against dopamine neuron loss induced by α-syn preformed fibrils and mitigating associated behavioral deficits [92]. This particular technique has also been implemented to inhibit Aβ peptide aggregation, underscoring its clinical application to treat Alzheimer's disease.

Amyloidosis is a well-known pathological condition characterized by the aggregation and deposition of amyloid proteins in the form of cross-beta sheets or fibrils around cells. These deposits often lead to the formation of plaques, contributing to organ and tissue failures, and has been implicated in degenerative disorders such as Alzheimer's disease and Parkinson's disease, and has been associated with bacterial biofilms [93]. GQDs have been identified as remarkable inhibitors of amyloid aggregation [94], demonstrating the ability to counteract the toxicity associated with pathogenic proteins. Additionally, GQDs exhibit functional surface properties that make them effective in targeting and delivering anti-amyloid treatments. The small size of GQDs and their capacity to produce high levels of reactive oxygen species positions them as potential therapeutic agents for disassembling biofilms associated with amyloidosis. Through mechanisms such as ROS production and membrane breakage, GQDs offer promise in addressing the challenges posed by amyloidosis in various biomedical applications. In a 2018 study, adenine-modified GQDs exhibited antibacterial activity under white light [95]. The GQDs demonstrated significant antibacterial effects against gram-positive *S. aureus* and gram-negative *E. coli*. While *E. coli* showed nearly no proliferation or vital activity, *S. aureus* did not show much effect. They were also found to alleviate colitis in mice induced by dextran sulfate sodium. Oral administration of GQDs resulted in amelioration of disease severity, with histological improvements and decreased pro-inflammatory cytokine levels. Intraperitoneal injection of GQDs also demonstrated protective effects against body weight loss, modulating immune cells and polarizing macrophages from M1 to M2 in colitis mice [96]. These findings suggest GQDs as a microbiota-friendly and

anti-inflammatory treatment option for colitis without observed toxicity or adverse effects on gut microbiota. Further, to explore the impact of nanoparticles on the gut and microbiota, BALB/c mice received intravenous cadmium telluride quantum dots (CdTe QDs). The study revealed that changes in gut microbiota were associated with the effects of CdTe QDs on the gut, liver immune systems, and lipid metabolism [19]. This suggests a potential interplay between nanomaterials and gut microbiota, highlighting the need for further investigation.

Quantum dots are also useful tools for developing and testing pharmaceuticals. They can be used to study drug behavior, efficacy, and safety in in vitro cell culture and in vivo animal models [97, 98]. Despite the fact that targeted and controlled release are just two benefits that QDs have to offer in terms of drug delivery, toxicity, and biodegradability, body clearance issues still need to be addressed [99, 100]. Drug delivery research focuses on creating safer and more biocompatible quantum dot materials and surface modifications [101, 102]. Quantum dots have the potential to significantly improve therapeutic outcomes, enhance drug delivery methods, and advance personalized medicine (Figure 3).

Quantum dots in Preventive Oncology

In preventive oncology, emphasis is made on early detection, risk assessment, and intervention strategies to lessen the incidence and effects of cancer. QDs have the potential to significantly contribute in this regard. QDs can be used in preventive oncology in the following ways:

1. Biosensors for early cancer detection

To identify specific cancer biomarkers or genetic mutations linked to cancer predisposition, QDs can be incorporated into biosensors [65, 103, 104]. These biosensors are capable of offering sensitive and focused tests for early cancer detection, enabling prompt intervention. Due to their adjustable emission wavelengths, QDs can identify several cancer biomarkers at once [105]. This capability improves cancer diagnosis precision and offers a comprehensive disease profiling.

2. Genetic markers used in risk assessment and genetic screening

To find genetic mutations or variations linked to a higher risk of getting a particular type of cancer, QDs can be used in genetic screening assays [106, 107]. These screenings can aid the risk assessment and early intervention processes. To determine a person's genetic propensity for cancer, QDs can be used in SNP genotyping assays [108]. For high-risk individuals, this information can direct preventive measures and screening procedures.

3. Environmental Monitoring

To monitor exposure to carcinogens or other environmental factors that may aid in the development of cancer, QDs can be used as components in nanoparticle-based environmental sensors [109, 110]. This is crucial for preventive oncology because it enables people and communities to take proactive measures to lower exposure.

4. QDs

QDs can be incorporated into wearable technology or sensors that monitor lifestyle and health metrics [111, 112]. This data can be used to evaluate a person's general health and cancer risk factors, enabling early intervention and prevention strategies.

5. Vaccination Strategies

By utilizing QDs, vaccines based on nanoparticles that target antigens linked to cancer can be developed [113-115]. By boosting the immune system's ability to identify and eradicate Personalized Preventive Strategies: According to an individual's genetic and molecular profile, QDs can make it easier to develop personalized preventive strategies [116]. This could involve individualized screening plans, alterations to one's lifestyle, or chemopreventive measures [117]. The removal of precancerous lesions or the start of preventive treatments may be possible as a result of earlier detection using QD-based biosensors.

6. Cancer cells

Cancer cells at an early stage, these vaccinations may be able to prevent cancer.

7. Early-Stage Treatment

For highly treatable cancers in their early stages, QD-based early detection methods can significantly increase the chances of a successful course of treatment and long-term survival (Table 1 Figure 4).

In conclusion, safety, biocompatibility, and regulatory problems are only a few of the challenges that need to be considered in the burgeoning field of QD application in preventive oncology. Furthermore, an interdisciplinary approach incorporating the understanding of molecular biology, genetics, oncology, and nanotechnology is required to fully exploit the promise of QDs in preventive oncology [118-120]. Deep tissue penetration can be achieved by engineering QDs to absorb near-infrared light. QDs produce heat in response to this light, which enables targeted photothermal treatment to eliminate cancer cells or tumors while preserving healthy tissue [121]. By activating photosensitizing chemicals to produce ROS, which in turn destroy cancer cells, photodynamic treatment can be improved using quantum dots [122]. The efficiency of ROS production and light absorption can both be enhanced by QDs. In radiation treatment, QDs can be used as radiosensitizers. QDs can maximize the beneficial effects of radiotherapy while reducing side effects by increasing the susceptibility of cancer cells to radiation.

Author Contribution Statement

SS, TPS, OSS, and RD drafted the manuscript. OSS assisted in tabulation and making images. AR, KP assisted in clinical correlation. AS provided valuable insight into preventive oncology. RD and SK conceptualized and oversaw the work.

Acknowledgements

NCDIR (National Center for Disease Informatics and Research), ICMR for funding, BioRender.com for figure preparation

Conflict of Interest

The authors declare no potential conflict of interest

Funding Statement

NCDIR for funding the project.

Abbreviations

QD= Quantum dots
NPs = NanoParticles
LED= Light emitting diodes
Cds= Cadmium sulphide
Cd2+ = Cadmium ions
CDs= Carbon dots
GQDs = Graphene Quantum Dots
ROS = Reactive Oxygen Species
CdCl2= Cadmium chloride

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