Micro Nano Bio Aspects

https://www.mnba-journal.com

Online ISSN: 2980-8081

Theranostic safe quantum dots for anticancer and bioimaging applications

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ARTICLE INFO

Review paper

Article history:
Received: 04 Jul 2022
Revised: 10 Aug 2022
Accepted: 13 Aug 2022
ePublished: 15 Aug 2022

Keywords:
Chemotherapeutic drugs, Adverse side effects, Quantum dots, Photoluminescence, electroluminescent, Bioimaging, Nanocarriers, Theranostic agent

ABSTRACT

The main hindrance for administrating conventional chemotherapeutic drugs includes adverse non-specific side effects, which can be debilitating and life-threatening. The recent emergence of multidrug-resistant cancer cells to a wide range of chemotherapeutic drugs is another complicating issue, particularly in cancer metastasis. Passive and active targeting of cancer cells by effective drug delivery systems (specifically, nanocarriers) may attenuate these side effects and bypass drug resistance. In addition, *in vivo* imaging of cancerous tumors can help in the timely diagnosis and real-time treatment of cancer in the first stages of cancer growth by detecting drug distribution in cancer cells and other body parts. Among the numerous organic and inorganic nanomaterials available to researchers and clinicians, quantum dots have exhibited promising results owing to their significant photoluminescence and electroluminescent properties and simple functionalization with anticancer agents. However, the safety of quantum dots has been a significant drawback limiting their wide-spread use in medicine. This review highlights that new quantum dots can be applied as theranostic agents safely for improved diagnosis and therapy for various types of cancers. In this review, both diagnostic and therapeutic properties of some novel quantum dot nanocarriers in combination with other nanomaterials and anticancer agents are discussed according to recent investigations. Moreover, the disadvantages of these new safe quantum dots are discussed with poignant thoughts on what is needed for their future clinical use.

DOI: https://doi.org/10.22034/mnba.2022.154865

Introduction

The anticancer activity of current chemotherapy drugs can result in severe side effects encompassing cardiotoxicity (doxorubicin) [1], renal toxicity (cisplatin) [2], hypersensitivity reactions (L-asparaginase) [3], diarrhea and constipation (vincristine) [4], severe hyponatremia (cyclophosphamide) [5], and hepatotoxicity (docetaxel) [6] to just name a few (Table 1). In addition, the inability of chemotherapeutic drugs to act against multidrug-resistant cancer cells can result from various mechanisms including epigenetic changes, altering drug metabolism and inactivating drugs, changes in the drug targets, increases in DNA-repair, overexpression of efflux pumps, as well as anti-apoptotic and epithelial-to-mesenchymal transition-inducing pathways (Figure 1) [7].

As described in the next section, to reduce these side effects, various micro and nano formulations composed of safe organic and inorganic materials have been introduced in recent years [8-15]. For instance, as presented in Table 2, glutathione, starch (main carbohydrate in crops such as maize, wheat, and potatoes), polyvinyl pyrrolidone (PVP), and poly-L-lactic acid (PLA) have been applied to attenuate the cytotoxicity of red-allotrope selenium nanoparticles (NPs), tellurium (Te) nanowires, Te nanorods, titanium nanocolumns and Te nanorods, and selenium NPs, respectively [16-20]. The following sections present the reasons that each of these nanomaterials increases the safety of quantum dots. For example, as an antioxidant in archaea, bacteria, fungi, animals, and plants, glutathione can protect cells from reactive oxygen species (ROS) and heavy metals [21, 22]. PVP as a water-soluble

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stabilizer polymer synthesized from the monomer *N*-vinylpyrrolidone, is approved by the Food and Drug Administration (FDA) due to its safety [23]. Biocompatible and biodegradable polymers composed of PLA have been approved by the FDA since 2004 for the safety development of injectable medical devices [24]. Moreover, selenium is part of our natural diet and has been approved by the FDA for specific medical applications due to its safety.

Table 1. Adverse side effects of some significant chemotherapeutic drugs.

Drugs	Formula	Major side effects	Mechanism of action	Ref.
Doxorubicin	$C_{27}H_{29}NO_{11}$	Cardiotoxicity	Induction of apoptosis in cardiomyocytes caused by upregulation of death receptors	[1]
Cisplatin	$[Pt(NH_3)_2C_{l2}]$	Nephrotoxicity	The uptake of platinum related to cisplatin in the proximal tubule cells of the kidney	[2]
L-asparaginase	$C_{1377}H_{2208}N_{382}O_{442}S_{17}$	Hypersensitivity reaction	Induction of anti-asparaginase IgE and IgG as well as the immunoglobulin receptors FcεRI and FcγRIII	[3]
Vincristine	$C_{46}H_{56}N_4O_{10}$	Diarrhea and constipation	A combination of mechanisms involving secretory dysfunctions, changes in gastrointestinal innervation, inflammation, and gastrointestinal dysmotility	[4]
Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$	Severe hyponatremia	Stimulation of arginine vasopressin release and increase in renal effects	[5]
Docetaxel	$C_{43}H_{53}NO_{14}$	Hepatotoxicity	Enhanced serum enzyme levels such as alanine aminotransferase specifically at higher doses	[6]
5-Fluorouracil	$C_4H_3FN_2O_2$	Gastrointestinal disorders	5-Fluorouracil can change the tertiary structure of trypsin, pepsin, and α-amylase	[25]

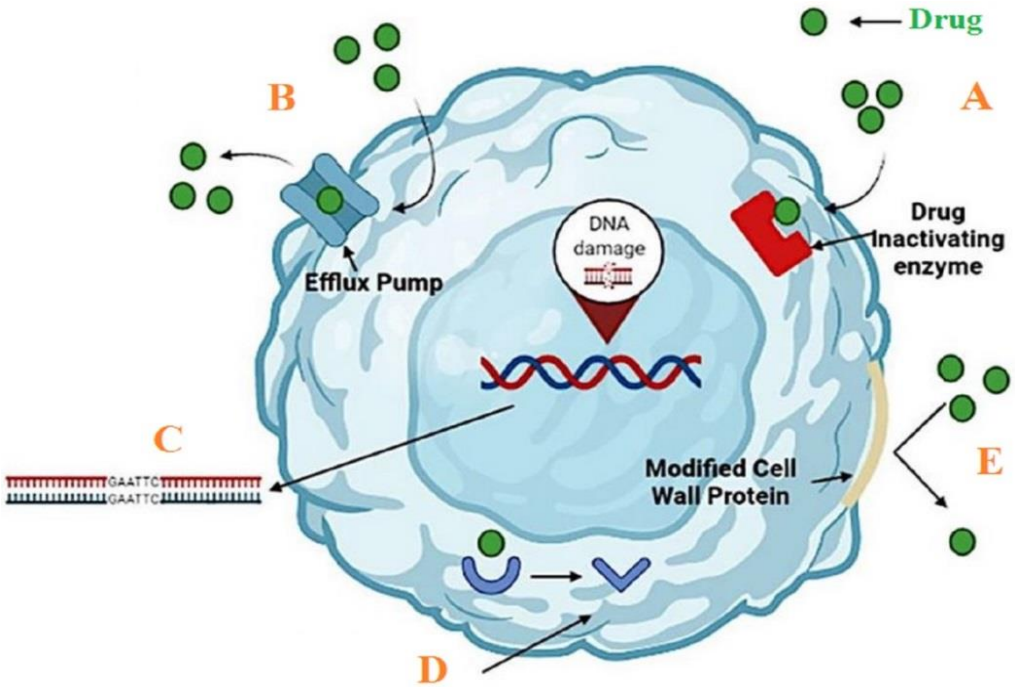

Fig. 1. Drug resistance mechanisms: A) inactivation of drugs, B) overexpression of the efflux pump, C) increased nucleic acid damage repair, D) changing drug target, and E) inhibition of drug influx or uptake (Copyright permission under the terms and conditions of the Creative Commons Attribution (CC BY) license) [26].

Table 2. Some nanomaterials used to produce safe QD chemistries.

Biocompatible materials	Type of nanomaterial	Characterization	Treated healthy cells with related non-cytotoxic doses	Ref.
Glutathione	Red-allotrope selenium NPs	Spherical shape with a mean size of 123.5 nm and zeta potential of -22.05 mV	Human dermal fibroblast cells, 55 µg/mL	[16]
Starch	Te nanowires	A mean diameter of 20 nm and several microns in length	Human dermal fibroblast cells, 70.05 µg/mL	[17]
PVP	Te nanorods	A diameter of 22 nm and length of 86.3 nm	Human dermal fibroblast cells, 100 µg/mL	[18]
PVP	Coatings composed of titanium nanocolumns and Te nanorods	300 nm long columns tilted 40° and 150 nm long columns tilted 20°	Human osteoblast cells, 100 µg/mL	[19]
PLA	Se NPs	A size range of 90-110 nm	Human osteoblast cells, about 120% cell availability after 60 s incubation time in 0.025 M sodium selenite (Na_2SeO_3) and 0.1M glutathione	[20]

Nanomaterials can be classified based on their nano-dimensions and their chemistry. Nanoparticles, nanospheres, quantum dots (QDs), fullerenes, and liposomes are zero-dimensional nanomaterials compared to nanotubes, nanorods, and nanowires are one-dimensional as well as nanoplates and nanofilms which are two-dimensional nanomaterials [9, 27]. While there are general promising properties for the use of all nanomaterials in medicine, such as their incredibly high surface-to-volume ratios, ability to avoid or minimize immune system clearance, ability to enter tumors and tumor cells, ease of functionalization, etc., some nanomaterial properties depend on the material they are composed of. Organic (natural polymeric nanoparticles), inorganic (metal/metal oxide nanoparticles), and organic/inorganic nanomaterials (core-shell protein/metal nanoparticles) can be formed from different sources enabling them with even more promising properties for anti-cancer applications [10, 28-31]. In terms of novel properties for cancer diagnosis and therapies, nanomaterial size ranges of 2-10 nm cause specific photoluminescence and electroluminescence abilities due to their more considerable band gap energy compared to bulk materials [32].

Core-type safe QDs

Uniform compositions of materials including one chalcogen, in particular, selenium (Se), sulfur (S), and tellurium (Te) with metals can form core-type QDs with unique electroluminescence, magnetoelectronic, and photoluminescence properties for safe cancer detection and therapy [33]. To reduce cytotoxicity and enhance drug delivery, detecting the amounts of anticancer drugs in biological samples (including urine and human plasma) is critical. Table 2 shows Se and Te nanomaterials have emerged as safe nanomaterials explored for QD applications. For example, it is essential to detect the specific amount of gemcitabine hydrochloride ($C_9H_{12}ClF_2N_3O_4$), an anticancer drug against breast, ovarian, bladder, pancreatic, and lung cancer, which can cause side effects of fatigue, chills, headache, fever, and muscle pain in patients after taking the first dose [34].

Doping CdTe QD with metal ions (such Au^{3+}) can increase its biocompatibility and stability. Au-doped CdTe QDs with a size of 3 nm and cubic structure establish van der Waals forces and hydrogen bonding with gemcitabine and have drug recoveries of 98% and 95% from urine and plasma samples, respectively [35]. The modification of QD surfaces with natural compounds, specifically plant metabolites, can increase the biocompatibility of QD in physiological conditions. In this regard, the methanolic leaf extract of *Camellia sinensis*, $QdSO_4$, and Na_2S synthesized green CdS QDs at a size range of 2–5 nm. These QDs inhibited the growth of A549 cancer cells during the S phase of their cell cycle (specifically, 20% of cell viability after 24 h was observed at a concentration of 50 ppm of QDs) with a low hemolysis rate of 1.83% at a concentration of 60 ppm [36].

Graphene safe QDs

Another major QD with excellent quantum confinement, biocompatibility, photostability, edge effects, and cell membrane permeability include graphene QDs composed of a few layers of graphene fragments with a size lower than 10 nm and absorption in the UV region (230–320 nm) [37, 38]. Graphene QDs and doxorubicin were loaded into a carboxymethyl cellulose hydrogel film to achieve the prolonged delivery of doxorubicin sensitive to pH with anticancer activity toward blood cancer cells (K562) by increasing the number of apoptotic cells. The main role of graphene QDs in this formulation was to increase tissue and cell permeability in a concentration-dependent manner. In this way, at graphene QD concentrations of 0%, 10%, 20%, and 30%, water vapor permeability values were approximately 8.25×10^{-8}, 9.5×10^{-8}, 1×10^{-7}, and 1.02×10^{-7} g/mhPa, respectively [39].

White graphene safe QDs

White graphene or boron nitride nanosheets with a hexagonal atomic structure can serve as an excellent electrical insulator with enormous band gap energy of 5.9-6 eV. They can be prepared using borazine's chemical vapor depiction method [40, 41]. A plethora of desirable properties, including ultraviolet photoluminescence, a high level of oxidation resistance, elastic modulus equal to ~36.5 GPa, and thermal conductivity ~600 W/m.K, have been indicative of white graphene [42]. One of the leading causes of death among women is breast cancer owing to metastasis and disease recurrence by breast cancer stem cells in which white graphene may help [43]. Reduced side effects with reduced DNA damage can be expected for a conjugate of doxorubicin, graphene QDs and white graphene owing to their high cellular uptake and specific effective delivery of doxorubicin to the cell nucleus. According to the results from measuring DNA amount by Hoechst 33258 (a nucleic acid stain that emits a blue color after being bound to dsDNA under observation by fluorescence microscopy or flow cytometry) and ROS indication via H_2DCFDA, boron nitride QDs with a size range of 10–15 nm (10 µg/mL) in combination with doxorubicin (20 µM) showed significant nuclear cleavage of MCF-7 cancer cells compared to control cells after 24 h (Figure 2a-c) [44].

Carbon safe QDs

Excellent biocompatibility and optical properties are the main advantages of carbon QDs [45]. A conjugate of a carbon QDs-doxorubicin complex was incorporated into lipid-coated calcium phosphate with pH sensitivity employed to target tumor cells. Reduced systematic toxicity was found for this formulation because of the enhanced permeability and retention effect (EPR) of tumor tissue compared to healthy tissue. Doxorubicin-carbon QDs@lipid-coated calcium phosphate and carbon QDs-doxorubicin exhibited prominent tumor inhibition rates at 53.6% and 46.1%, respectively [46]. Polyaziridine or polyethylenimine (PEI) with highly positive charges have been used to modify nanocarriers for augmented cell nucleus drug delivery. Therefore, for increasing doxorubicin delivery to the nucleus, carbon QDs-doxorubicin was modified by PEI. In this way, a mixture of PEI-25k and glycerol was treated via a microwave hydrothermal method. Intracellular uptake of these nanoformulations was approximately 4.7-times higher than doxorubicin alone [47]. Active targeting of cancer cells is vital for effective anticancer activity of drug delivery systems. Modifying carbon QDs by transferrin glycoproteins can increase the carrier's hydrophilic properties and interactions with

cancer cell receptors. Doxorubicin-transferrin-carbon QDs significantly inhibited MCF-7 cell lines with multidrug resistance compared to doxorubicin and transferrin-carbon QDs alone [48].

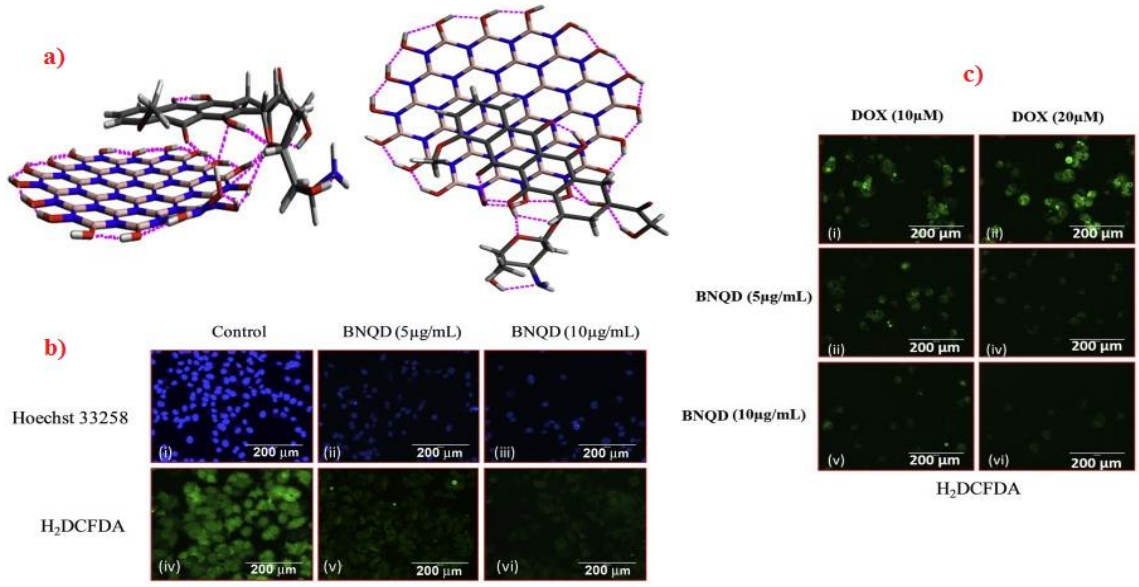

Fig. 2. a) Complex of boron nitride QD (BNQD) and doxorubicin (DOX), b) anticancer activity of BNQD, and c) anticancer activity of the BNQD/DOX complex; Hoechst 33258 (a fluorescent blue dye employed for measuring DNA amount) and H_2DCFDA (a cell-permeant indicator for ROS). Reproduced under the Creative Commons license [44].

As demonstrated in Table 1, gastrointestinal disease (such as diarrhea) can be caused by the consumption of 5-Fluorouracil via a mechanism of the conformational change of trypsin, α-amylase, and pepsin enzymes [25]. 5-fluorouracil-chitosan‑carbon QD-aptamer with a zeta potential and mean size of + 31.2 mV and 122.7 nm demonstrated down-regulation of Bcl-2 and up-regulation of Bax mRNA level expression in MCF-7 cells compared to a control (not treated samples) [49]. Suitable *in vivo* imaging and eradication of cancer cells (via autophagy and apoptosis effects) can be possible by loading carbon QDs and doxorubicin hydrochloride by mitochondria as a novel delivery system. This negative microformulation (mitochondria-carbon QD-Dy680 with a size of 1µm and zeta potential of -18.6 mV) slowed urine clearance (after 60 min of intravenous injection) compared to carbon QD-Dy680 (after 10 min) [50].

Core-shell and alloyed safe QDs

Core-shell QDs are composed of a core semiconductor coated by a second material as the shell semiconductor with a higher band gap [51].

Theranostic applications were indicated for these new QD formulations such as [^{109}Cd]CdSe/ZnS QDs bio-conjugated to the monoclonal antibody of rituximab as the tumor-targeting ligand [52]. Core-shell QDs of CdTe/CdS were formulated by using the anticancer drugs tamoxifen (P-gp inhibitor) and 5-fluorouracil (activator of p53) which were effectively employed for fluorescent imaging of human breast cancer cells MDA-MB-231/MDR [53]. As illustrated in Figure 4a, ZnCuInSe/ZnS core/shell QDs were functionalized by the αvβ6-targeting peptide (A20FMDV2) for targeting head and neck squamous cell carcinoma which have a high level of αvβ6 integrins and were employed for NIR imaging-guided surgery and bioimaging [54] (Figure 3a). Lipophilic core-shell QDs of CdSe/ZnS were incorporated into cationic lipid nanocarriers, followed by surface functionalization by anti-EGFR aptamer and loading Bcl-2 (apoptosis-inhibiting protein) and protein kinase C-iota (PKC-ι) siRNA as a potential oncogene (Figure 3 b). In addition to using this nanoformulation for *in vivo* fluorescence imaging properties (Figure 3 c), MDA-MB-231 tumor xenografts were treated for breast cancer using

this nanoformulation showing tumor growth inhibition at 42.37% at a concentration of 10 mg/kg, every 3 days of injection for a period of 31 days (Figure 3d) [55].

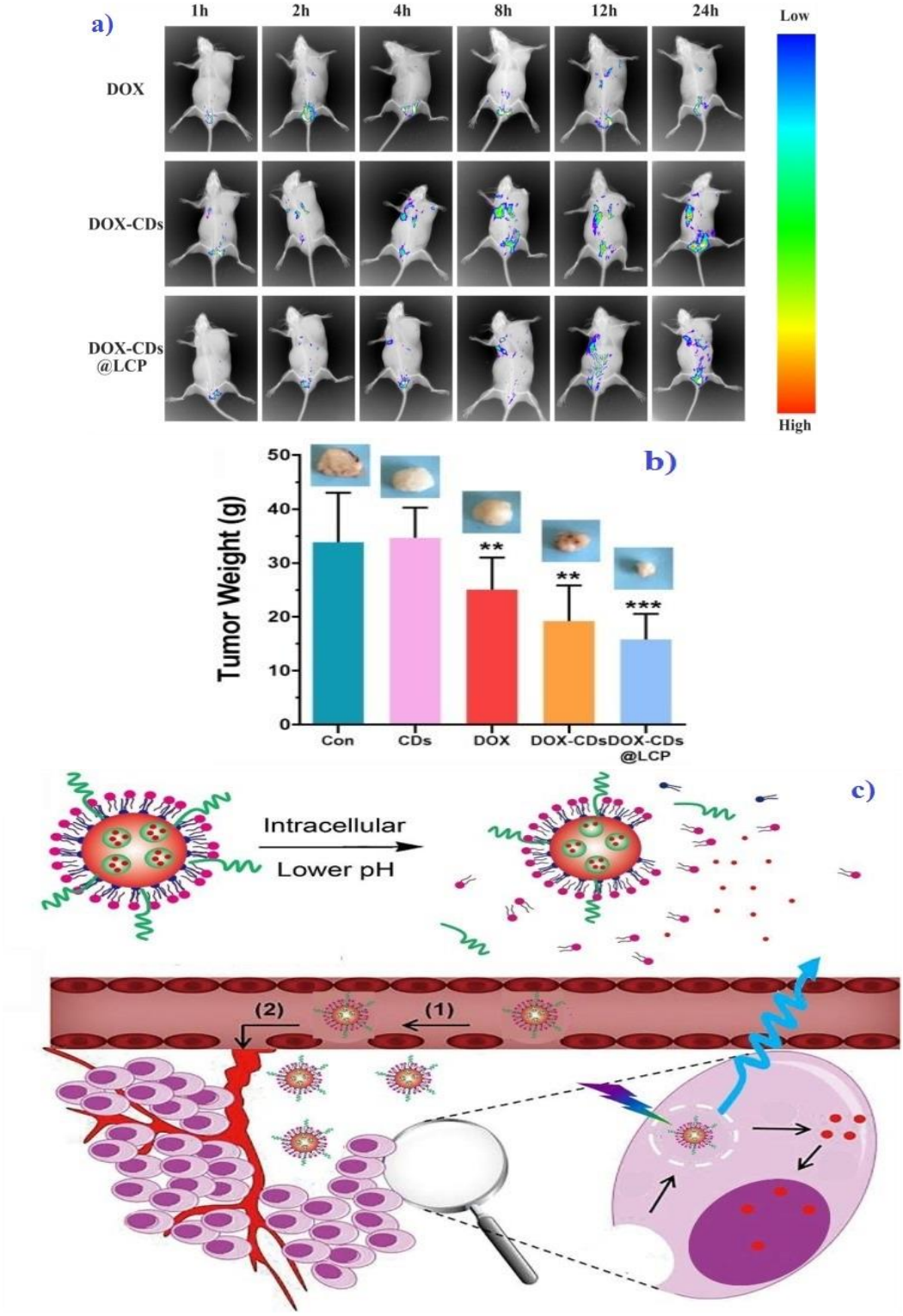

Fig. 3. a) Real-time fluorescence imaging of tumor-bearing mice after injection of doxorubicin (DOX), doxorubicin-carbon QDs (DOX-CDs), and doxorubicin-carbon QDs@lipid-coated calcium phosphate (DOX-CDs@LCP). b) The tumor weight at different treatments compared to the control ($P<0.01$ (**), and $P<0.001$(***)). c) Increased anticancer function because of the accumulation of DOX-CDs@LCP formulations at the cancer site by the EPR effect followed by the release of DOX-CDs at the low pH of tumor cells [46].

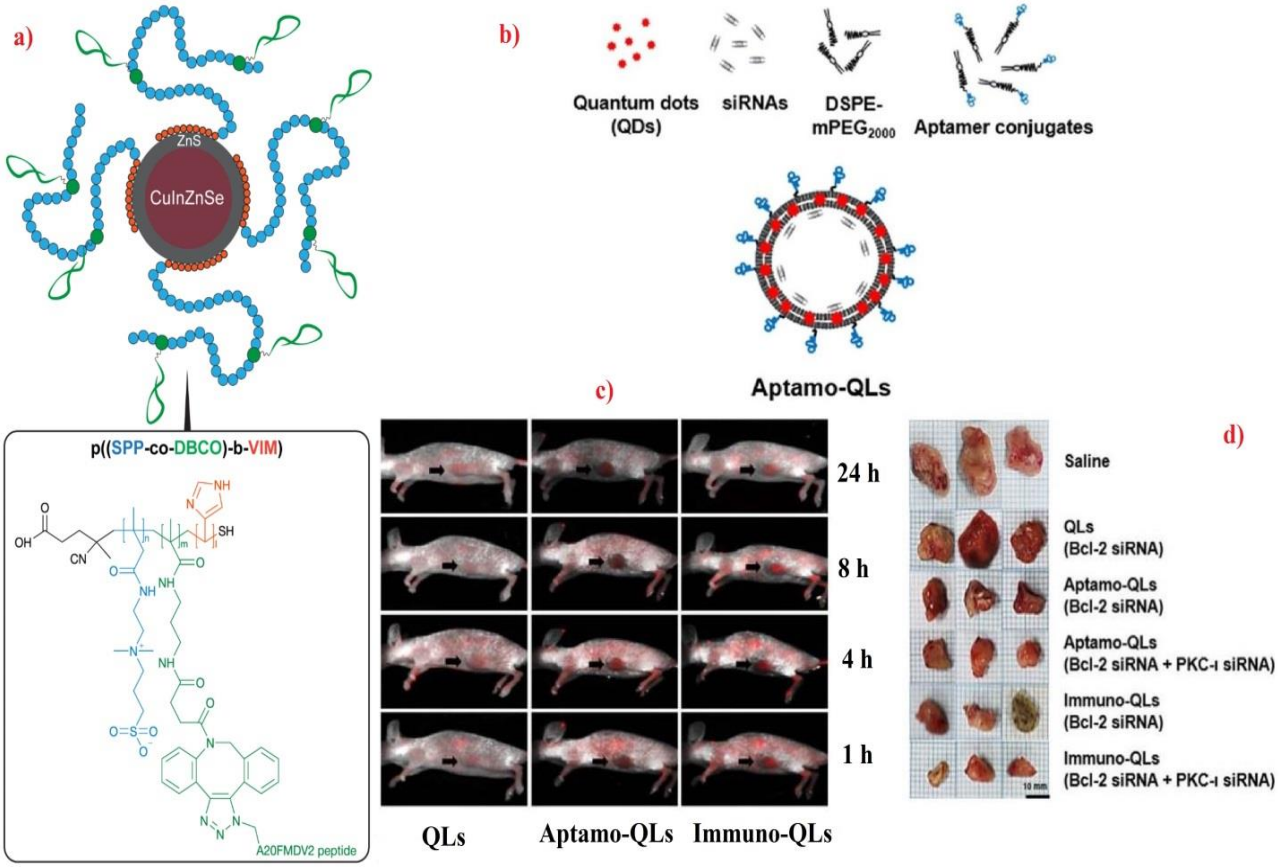

Fig. 4. a) Schematic image of a ZnCuInSe/ZnS core/shell QDs functionalized by the αvβ6-targeting peptide (A20FMDV2) [54], b) nanoformulation of aptamo-QLs (anti-EGFR aptamer-lipid nanocarriers) encapsulating anti-cancer siRNAs, c) *In vivo* fluorescence imaging by immune-QLs and aptamo-QLs, and d) Growth inhibition of tumors under treatment by aptamo-QLs and QDs and immuno-QLs (nti-EGFR antibody (Cetuximab)-coupled cationic nanocarriers) (Copyright permission under the terms and conditions of the CC BY license) [55].

At least two semiconductors with different band gap energy are needed to form alloyed QDs. These QDs should exhibit unique properties relative to parent semiconductors and bulk materials [56]. For example, biocompatible Zn-Cu-In-Se QDs with a mean size of 2.6 nm showed an absolute photoluminescence quantum yield of 14.2% and stable photoluminescence with a decay lifetime of 211 ns under near-infrared (NIR) irradiation [57].

Conclusions

In summary, to optimize the delivery of cancer drugs by QDs, one must consider the properties of the target cancer tissue as a critical factor, such as surface modification of carbon QDs by transferrin glycoproteins or the αvβ6-targeting peptide (A20FMDV2). For instance, doxorubicin should be effectively intercalated with the DNA in the cell nucleus. Modifying QDs with PEI with a high positive charge may be an appropriate strategy. To reduce the side effects of conventional anticancer drugs, active targeting of cancer cells may be possible by targeting specific ligands. Cancer cell transferrin receptors are one the main targets for the micro and nano formulation of QDs (such as carbon QDs) to improve cellular uptake the endocytosis. In addition, both bioimaging and anticancer activities can result from these formulations. Based on this review, QDs should be smartly combined with other safe micro or nanomaterials composed of Se, Te, and other chemistries for obtaining acceptable results in physiological conditions, which is more dependent on the type of cancer and stage of tumor growth. To

meet these demands, comprehensive studies focusing on biocompatibility and active targeting of cancer cells are indispensable.

Study Highlights

- Modifying QDs with PEI with a high positive charge may be an appropriate strategy.
- To reduce the side effects of conventional anticancer drugs, active targeting of cancer cells may be possible by targeting specific ligands.
- Cancer cell transferrin receptors are one the main targets for the micro and nano formulation of QDs.
- QDs should be smartly combined with other safe micro or nanomaterials composed of Se, Te, and other chemistries.
- Comprehensive studies focusing on biocompatibility and active targeting of cancer cells are indispensable.

Abbreviations

A20FMDV2: αvβ6-targeting peptide
DOX: Doxorubicin
DOX-CDs@LCP: Doxorubicin-carbon QDs@lipid-coated calcium phosphate
EPR: Enhanced permeability and retention
FDA: Food and Drug Administration
NIR: Near-infrared
NPs: Nanoparticles
PEI: Polyethylenimine
PKC-ι: Protein kinase C-iota
PLA: Poly-L-lactic acid
PVP: Polyvinyl pyrrolidone
QD: Quantum dot
ROS: Reactive oxygen species

Funding

This work was not supported by any institutes.

Conflict of interest

The authors declare that they have no conflict of interest for this study.

Ethical approval

This article does not contain any studies with animals or human participants.

Authors' contribution

MA: conceptualization, preparing the first draft, and revising; TW and LL: revising of the manuscript.

Acknowledgment

None.

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HOW TO CITE THIS ARTICLE:
Alavi M, Webster TJ, Li L. Theranostic safe quantum dots for anticancer and bioimaging applications. Micro Nano Bio Aspects. 2022;1(2):1-11. doi: https://doi.org/10.22034/mnba.2022.154865