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Review Article

Quantum dots as theranostic nano delivery system in combating various diseases

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Abstract

Conventional chemotherapy lacks insolubility, selective targeting and bio-imaging of the chemotherapeutics aggravating the diseased state with developed drug resistant toxicity in the biological system. To overcome these obstacles and other biological barriers, nano-sized semiconductor quantum dots (QDs) having the unique photoluminescence and electronic physicochemical properties such as size-tunable light emission, narrow emission range, high brightness and photo-stability for making them the suitable diagnostic probe materials in bio/immune -sensing platform have attracted attention for targeted theranostic photodynamic therapy to bridge nanotechnology and cargo therapy assay. In general, QDs, linked to photoluminescence, induce generation of free radicals, disrupt cell walls/membranes and arrest gene expression as antimicrobial/anti-cancer agents in nano theranostic platform for concomitant sensing, imaging and therapy in the biological system. QDs may be conjugated with polymers, ligands, cargos and other biomolecules through covalent and non-covalent bonds for different specific targeting and controlled liberation of cargos to the diseased site/s of concern to get higher theranostic efficacy. This review focuses mainly the physicochemical characteristics of QDs, their synthesized methods, surface functionalizations, mechanism of action, biomedical applications, toxicity, biodistribution, pharmacokinetics and elimination as nano delivery system.

Keywords: Conventional chemotherapy; Diseases; Quantum dots; Theranostic efficacy; Nano delivery system.

Introduction

Many people suffer from life-threatening diseases that are aggravated more by the development of drug resistance through conventional chemotherapy throughout the world every year [1,2]. When the body is exposed by infectious agents or other toxins, body's primary and secondary defense mechanisms become evolved to kill microorganisms/parasites or counter the generation of reactive oxygen/nitrogen species (ROS/RNS) through antioxidant defense mechanism and innate and acquired immune defense mechanisms [3,4]. However, when the burdens of infectious/toxic agents overpower the body's protective defense mechanisms, free radicals generated become accumulated into the cells causing acute to chronic inflammation-related cellular injuries leading to development of diseases such as infection, oxidative damages, neurodegenerative diseases and cancer [3-6].

To overcome the obstacles acquired by the conventional chemotherapy, and biological barriers, nano theranostic based QDs have gained significant interest in monitoring, diagnosis, drug delivery and therapy against diseases owing to their elevated quantum yield, size-regulatable light emission, and well opto-chemical steadiness [7-10]. The cores of QDs are commonly comprised of several materials such as zinc, cadmium, lead, chalcogenides (ZnSe, CdSe, CdS and CdTe), arsenides (InAs and GaAs), copper salt (CuCl), semiconducting phosphides (GaP and InP), and nitrides (GaN), while the shells of ZnSe, CdSe, PbS, ZnTe, ZnS, ZnO and CdS enclose the cores [11]. Several other QDs are also composed of metals or semiconductor substances (Co., Ni, Au and Pt), and metalloid QDs like silicon [12-14]. QDs (2-10 nm in sizes), smaller than Bohr's exciton, are normally comprised of substances (such as Pb, Cd and Hg) from groups II-VI, III-V, and IV-VI in the periodic table of the Mendeleev, while ternary I-III-VI QDs denote I = Cu or Ag, III = Ga or In, and VI = Se or S [15-17]. The electrochemical positions of DNA or proteins are commonly denoted as QDs [13], while the charging energy of QDs denotes the amount of energy that a QD requires to absorb for emitting a single electron from the dot. The most commonly used QDs are composed of carbon quantum dots (CQDs), graphene quantum dots (GQDs), and cadmium-based QDs [18-20]. GQDs, the graphene blocks with two-dimensional (2D) transverse size (<100 nm), having excellent physico-chemical and biological characteristics, consist of only one atomic layer of carbon atoms, and also contain various functional groups such as hydrogen, oxygen and multiple atomic layers with sizes (<10 nm) [21]. CQDs (average size <10 nm), possessing high water solubility, tempting photoluminescence and photostability, may be loaded with drugs through π-π stacking to improve the drugs-solubility, to reduce drugs' side effects

and to extend the tumor retention period [22-23]. The cores of QD-crystals may be doped with rare earth metal ions, copper, silver, manganese or cadmium for enhancing their photoluminescence features [24,25]. The ligands frequently utilized in QDs-synthesis are thiols, alcohols and essential amines [26,27]. The bio-conjugations of QDs with natural products, viruses, carbohydrates, peptides or DNA fragments are assisted by ligands via the electrostatic, covalent coupling or hydrophobic interactions [28,29]. The surface ligands such as cysteamine, thioglycolic acid, polyethylene glycol (PEG) or water-soluble polymers with carboxyl may anchor the drug components with QDs via electrostatic or covalent bindings for forming nano-drug complex vehicles and monitoring the fluorescent traces of drug-materials in cells or animals [30]. This review elucidates mainly the recent advances of QDs in various biomedical applications against diseases to consider them as theranostic nano delivery system.

Synthesis of quantum dots

A few synthesis methods of QDs are described below:

Organic phase / organometallic method:

Utilizing this method, monodispersed QDs with the core structure and uniform surface derivatizations are prepared via the organometallic process. Bis (trimethylsilyl) selenium and Me_2Cd are used as organometallic precursors. Monodisperse CdSe is achieved via the pyrolysis of organometallic reagents under 250-300 ◦ C by the injection in a hot coordinating liquid [31-33]. The toxicity free indium phosphide (InP) QDs are also prepared following this method [34]. The various sizes of high yields of QDs formed are regulated by the variations of the reaction time or the changes in the temperature [35-37].

Water phase / aqueous solution method:

Ionic perchlorates as precursors are used in this eco-friendly and economical method for biological application. CdTe QDs are prepared in an aqueous medium utilizing ligands such as hydrosulfyl-containing materials, 3-mercaptopropionic acid (3-MPA) and glutathione (GSH) [38-40].

Hydrothermal / green synthesis method:

QDs with high quantum yields and narrow sizes are prepared to reduce the surface defects created during the synthesis process utilizing this method. In general, the reagents are adjoined to the hermetic container and the temperature (lukewarm) is increased to 80-240 ◦ C (supercritical) for 3-12 h to get a high pressure leading to a resultant reduction in the surface defects and reaction time of developed QDs [41-49].

High-temperature synthesis method:

In this method, dimethyl cadmium ($Cd(CH_3)_2$) or cadmium oxide (CdO) as precursors together with tetrahydro-phosphoric acid (TDPA) and trioctylphosphine oxide (TOPO) are used at high temperature (250-300 ◦ C) to produce colorless chalcogenide nanocrystal QDs [50,51]. In addition, selenium (Se), tellurium (Te) and sulfur (S) stocks may also arrange high quality monodispersed QDs [52].

Polyol method:

Polyol denotes a compound containing multiple hydroxyl functional groups. In this method, diethylene glycol and acetic acid derivation of the metals such as Cd and Zn are mixed with thiourea in 10% excess. The acetic acid mixture is prepared separately for synthesizing the applicable nanoparticles at 180 ◦ C for 2h [53].

Chemical oxidation method:

This method utilizes the strong oxidants such as sulfuric acid (H_2SO_4), nitric acid (HNO_3) and hydrogen peroxide (H_2O_2) for treating carbon precursors at high temperature for the synthesis of CQDs [41]. The carbon sources may be the macromolecular materials such as graphene, the small molecule substances such as sucrose, or the bleached eucalyptus kraft pulp as the raw material to synthesize CQDs utilizing easy operation, short reaction time, high reproducibility and excellent fluorescence characteristics [54-58]. In this method, after the dehydration and carbonization of organic precursors, the carbonaceous materials are oxidized by the concentrated acid to break into small carbons, while the various oxygenated functional groups such as hydroxyl, carboxylic and carbonyl groups may be introduced into the resulting CQDs.

Following the chemical oxidation method for the synthesis of photoluminescent GQDs, the precursors such as graphene oxide, carbon bonds of graphene, carbon nanotubes, Vulcan XC-72 carbon black or black carbon are utilized for their destruction by HNO_3, H_2SO_4, or H_2O_2 [56,59-65].

Surface functionalizations of quantum dots

As the basic structures of the metallic QDs contain metal cores and hydrophobic shells with high surface-to-volume ratio having very potent unspecific reactive interactions with macromolecules, prone to aggregations and variations in fluorescences, their surfaces are functionalized with a large number of carboxylic acid groups by utilizing various hydrophilic agents, while the dendrons, peptides with cysteine residues, oligomeric phosphines or thiol-containing molecules may replace the hydrophobic surface ligand biomolecules (such as tri-n-octylphosphine oxide (TOPO)) with different sulfhydryl or protein groups [66-75]. The cores of QDs may act as the structural scaffold, and the small molecule hydrophobic drugs and the imaging contrast agents may be embedded between the inorganic cores and the amphiphilic polymer coating layers (Figure1). Hydrophilic therapeutic agents such as small interfering RNAs (siRNAs), antisense oligodeoxynucleotides (ODNs) and targeting biomolecules such as proteins, peptides, tumor markers, polysaccharides, antibodies, aptamers and small molecule ligands may be immobilized onto the hydrophilic portion of the amphiphilic polymers through the covalent or non-covalent bonds (Figure1). Generally, the bioconjugation strategies depend on the size and surface charge of QDs as well as functional groups existed on the biomolecules, and their modifications are achieved by several processes such as passive adsorptions, multivalent chelations, electrostatic interactions, covalent crosslinked reactions (sulfhydryl couplings, active ester maleimide mediated amines and carbodiimide mediated amides formations) [76,77]. The coatings of QDs with mercapto acid or polymers like thiolated PEG may produce stable covalent bondings, while QDs may be encapsulated in silica shells utilizing silane chemistry as their organic functionalities [75,78,79].

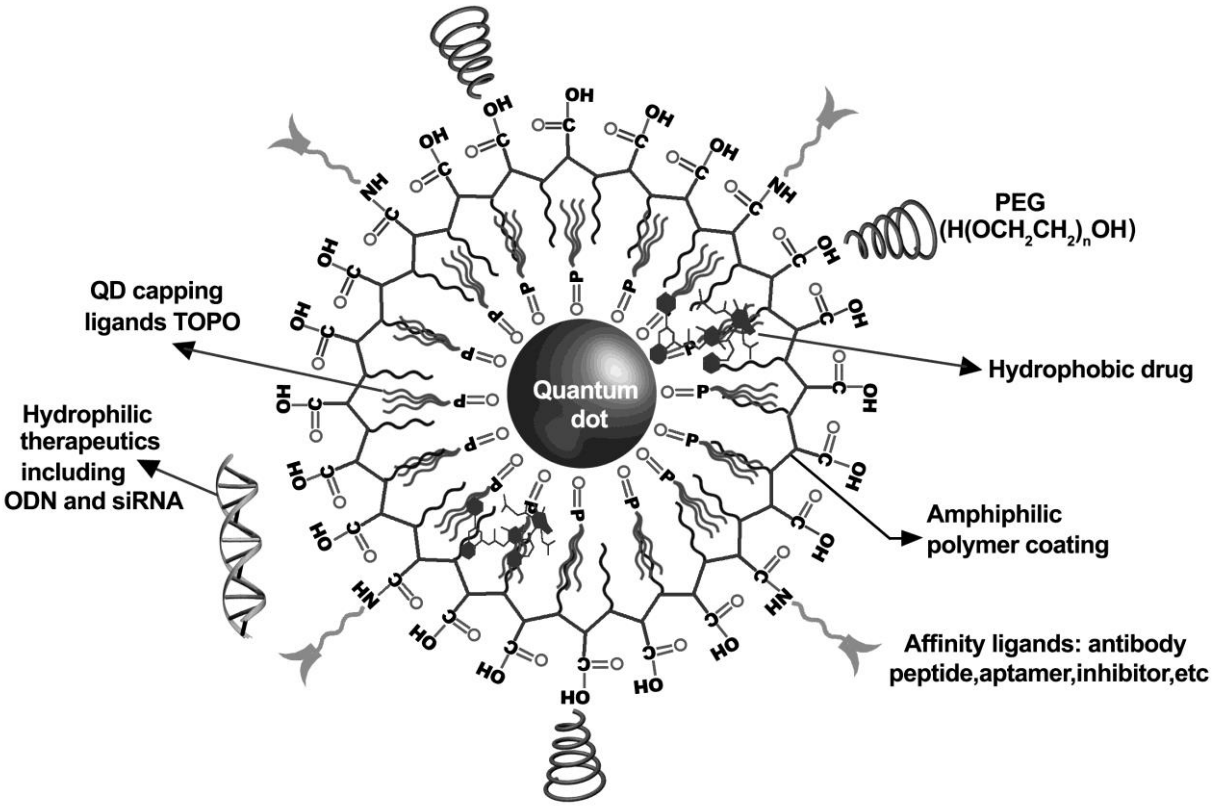

Figure 1. Schematic demonstration of a multifunctional quantum dot anchored with amphiphilic polymer.

Characterizations of quantum dots

Important information regarding the structure, morphology, and physicochemical changes owing to the conjugation reactions are evaluated by QDs' optical characterizations [80,81]. The optical characterizations of QDs are done by UV-Visible and photoluminescence spectroscopy [82]. The sizes and structures of QDs are determined by scanning transmission electron microscopy (STEM), X-ray fluorescence and X-ray diffraction [83]. The sizes of QDs are determined by transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), and atomic force microscopy (AFM) [84,85]. The composition and size of optically active QDs are evaluated by photoluminescence, photoluminescence excitation, and Raman scattering spectroscopy [86]. To monitor the sizes of epitaxially arranged QDs, the methods like AFM, TEM, scanning tunneling and magneto-tunneling experiments are performed [87-89,80]. The other technique to characterize QDs is applied by nuclear magnetic resonance spectroscopy [87].

Mechanism of actions of quantum dots

The general inhibitory actions of QDs on microbial organisms/diseased cells take place mainly through three molecular mechanisms: (1) damages of cell membranes/walls, (2) generation of reactive oxygen species (ROS) for destroying the cells, and (3) anchoring to nucleic substances (RNAs/DNAs) for inhibition of cell proliferation.

The QDs interact with the phospholipid bi-layers to roughen and shrink the cell membranes. The ruptured cells owing to the direct attachments of the QDs cause the discharge of cellular contents [90]. The electrostatic interactions between the positive charge of QDs and the negative charge of cellular contents create membrane stresses in the cell walls, while the release of metal / ions into the cells enhances the toxicity inside the cells, leading to cell death.

Owing to the high electron transfer, QDs may produce huge number of free electrons to create pits. The photo-activated QDs may generate excessive free radicals such as superoxide singlet oxygen (O^{2-}), triplet oxygen, hydroxide anions (OH^{-}), and per-hydroxyl anions. The ROS, accumulated inside the cells, inhibit replication and respiration, causing death of microbes / diseased cells.

A few QDs may intrude and accumulate inside the cellular nucleus. The interactions between the nuclear contents and QDs enable the inhibition of cellular respiration, division, replication, and production of adenosine triphosphate (ATP). The damage of nucleus causes the apoptotic death of cells.

Biomedical applications of quantum dots

The inhibitory activities of QDs on microorganisms or diseased cells chiefly take place through the destruction of cell membranes/walls, production of ROS for destroying the cells, and binding with nuclear DNA/RNA materials for arresting cellular proliferation. QDs are generally functionalized with polymers, ligands, biomolecules, and photosensitizers, and loaded with cargos for cellular targeting, bioimaging and delivery, and inducting more ROS and improving their attachments to microbial components or diseased cells for their destruction or prevention from neurodegeneration as the enhancement of their microbicidal, anti-carcinogenic, anti-degenerative or other theranostic efficacies (Tables 1-3).

Different groups of investigators have utilized zinc oxide (ZnO) QDs and surface-modified silver indium sulfide-zinc sulfide (ZnS) (Ag/In/S-ZnS) hybrid QDs as their antifungal activities against *Microsporum gypseum/canis*, *Trichophyton mentagrophytes*, *Candida albicans/tropicalis*, and *Candida albicans,* respectively through the phagocytic uptakes into the cells and the attachments to the nuclear materials followed by ROS-generated cellular damages, death and growth inhibition (Table 1) [91,92]. A few other groups of investigators have used acetate/nitrate, polyvinylpyrrolidone (PVP) or poly ethylene

glycol surface-modified ZnO QDs against Gram positive / negative bacteria to get antibacterial efficacy through membrane penetration, ROS-generation, DNA/cell damages, cell death and growth inhibition (Table 1) [92-96].

Table 1. The chief activities of a few quantum dots against microbial organisms.

Quantum dots (QDs)	Sizes (nm)	Microorganisms	Main activities	Ref.
ZnO	2-7	*Microsporum gypseum/canis, Trichophyton mentagrophytes, Candida albicans/tropicalis*	The QDs enter into the fungal cell walls through phagocytosis, and are attached to nuclear materials, leading to cellular damages, death and growth inhibition.	91
Ag/In/S-ZnS	9.5-10	*Candida albicans*	Produce ROS to damage fungal cells.	92
Acetate/nitrate-ZnO	3-7	*Escherichia coli*	The photoexcitation generates the electron-hole pairs, while the electrons trapped by the O_2, induct excessive ROS, and Zn^{2+}causes membrane and DNA damages leading to cell death.	92-94
PVP-ZnO	2-10	*Listeria monocytogenes, Salmonella enteritis, Escherichia coli*	The QDs penetrate via the cell membranes causing damages of cell organelles.	95
PEG-ZnO	~10	*S. aureus, E. coli*	The QDs show antimicrobial activities generating ROS and H_2O_2 to inhibit microbial growth.	96
Zn/rifampicin/Tf/Ag	~10	*Mycobacterium smegmatis/bovis* BCG	Cellular toxicity leading to apoptotic death	97
CdS/Ag_2S	2-19	*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*	The QDs penetrate via the cell walls and attach to DNAs resulting damages of DNA structures.	98
CdSe	7	*Pseudomonas aeruginosa*	Internalization of Cd^{2+} causes cellular and genomic toxicities.	99
TGA/TGH/Lysine-CdSe	8	*Staphylococcus aureus*	Enhanced toxicity of Cd^{2+} causes cellular death.	100
Streptavidin-CdSe/ZnS	~2	*E. coli* O157:H7	To detect pathogen by the labeled biotinylated anti-*E. coli* O157:H7 antibody through avidin-biotin binding.	101
CdSe/TiO_2/Na-nographene sheets	10	*Escherichia coli*	The photogenerated delocalized π electrons generate ROS causing cell death.	102
CdTe	5-10	*Escherichia coli*	The QDs enter into the cell membranes causing membrane stress, while the heavy metal ions, inserted into the cells, decline the gene expression of SOD.	40
Rocephin-CdTe	3	*Escherichia coli*	Rocephin damages the cell membrane, and CdTe QDs enter into the cell and are attached to the nuclear materials to prevent the gene expression of anti-oxidase.	103
MPA-CdTe	1-10	*Salmonella typhimurium, Acinetobacter baumanni, Pseudomonas aeruginosa*	The QDs anchore to the phospholipid layers of bacteria, while Cd^{2+} disrupts the cellular pathways and retards the cellular respiration.	104
Graphene	3-8	*Escherichia coli, Staphylococcus aureus, B. subtilis, P. aeruginosa*	Generation of ROS for damaging the cell walls/membranes	105,106
Nitrogen-doped graphene	~8	*Escherichia coli*	Photodynamic antimicrobial therapy through the production of ROS, and bio-imaging	107
PEG-Ag-Graphene	5-8	*Pseudomonas aeruginosa, Staphylococcus aureus*	The QDS anchore to the thiols of the proteins (enzymes) of the cell membranes /walls resulting in the leakage of cellular metabolites.	108
Antibody (Ab) anti-F protein conjugated CdTe	~3-5	respiratory syncytial virus (RSV)	Detection of RSV	109

Table 1. Contd.1.

Quantum dots (QDs)	Sizes (nm)	Microorganisms	Main activities	Ref.
Streptavidin-F/G protein conjugated Ab- anti-F/G	605 / 525	RSV	Detection of RSV	110
QD-Antibody (ZnS-CdSe barcodes)		*Hepatitis B, C,* and HIV	Detection of virus	111
CQD/Gd^{3+}-CQD-Ab	<10	Microorganisms and SARS-CoV-2	Microbial prevention/inhibition and virus detection	112-114
Boronic acid modified CQD	2-5	HSV1/HIV1/HCoV-229E	Prevention/inactivation of virus infection	115-117
Benzoxazine monomer-derived CQD	<10	*Japanese encephalitis, Zika and Dengue* viruses*, Porcine parvo* virus*, Adeno-associated* viruses	Blocking of viral infection through inhibition of virus-cell interactions	118
CQD-DNA-Au/GO		HIV DNA virus	Detection of viral target DNA	119
Sulfur-doped CQD	1-7	Influenza, Dengue, Zika, Hepatitis E and Chikungunya	Fluorescence detection and analysis of virus	120
Antigen-CQD-adjuvant-chitosan/ polyethyleneimine/ovalbumin vaccine	~36 / 125	Intranasal / Avian leukosis virus	Intranasal / Anti-viral immune efficacy	121,122

A few researchers have utilized transferrin-modified silver (Ag) QDs anchored with zinc and rifampicin as composite materials to treat and kill bacterial cells (Table 1) [97]. A few other researchers have used CdS/Ag_2S composite QDs against bacterial treatment to get higher cell wall/DNA -damage-oriented antibacterial efficacy (Table 1) [98]. A few scientists have utilized CdSe QDs to attain higher microbicidal efficiency through Cd^{2+} cellular internalization followed by cellular and genomic toxicity (Table 1) [99]. A few other scientists have applied thioglycolic acid (TGA) and mercapto-acetohydrazide (TGH)-lysine-capped CdSe QDs against *Staphylococcus aureus* to get higher microbicidal efficiency through Cd^{2+} toxicity-induced cellular death (Table 1) [100]. A few investigators have utilized streptavidin-functionalized CdSe/ZnS QDs to detect and kill *E.coli* O157:H7 pathogen through avidin-biotin binding (Table 1) [101]. A study of the composite CdSe/TiO_2/nanographene QDs has shown their anti-bacterial activity through photo-induced ROS-generated cellular killing (Table 1.) [102]. Another study with CdTe QDs against *Escherichia coli* has exhibited membrane stress and metal-induced decline of SOD-gene expression (Table 1.) [40]. The investigation with rocephin-functionalized CdTe QDs has revealed the cell membrane damages with nuclear attachment for preventing the gene expression of anti-oxidase (Table 1.) [103]. Another investigation with 3-mercaptopropionic acid (MPA)-anchored CdTe QDs has elucidated the disruption of the bacterial cellular pathways with the retardation of their respiration (Table 1.) [104]. A lot of investigators have utilized graphene, nitrogen-doped graphene and PEG-Ag-graphene QDs against various bacterial treatments to get higher microbicidal efficacies through ROS-generated cellular damages, photo-induced ROS-produced cellular killing, bioimaging, and the damage-related leakage of cellular metabolites (Table 1.) [105-108]. Another group of investigators have used antibody-anti-F protein conjugated CdTe QDs to detect respiratory syncytial virus (RSV) (Table 1.) [109]. A few researchers have utilized streptavidin-F/G protein conjugated antibody-anti-F/G for the detection of RSV (Table 1. Contd.1.) [110]. A few other researchers have applied antibody-ZnS-CdSe barcodes QDs to detect hepatitis B and C virus, and HIV (Table 1. Contd.1.) [111]. A few scientists have utilized CQD/Gd^{3+}-CQD-antibody to detect SARS-CoV-2 virus and their killing [Table 1. Contd.1.) [112-114]. A few other scientists have applied boronic acid-modified CQDs for the prevention / inactivation of HSV1/HIV1/HCoV-229E virus infection (Table 1. Contd.1.) [115-117]. The investigation utilizing benzoxazine monomer derived CQDs has been performed against Japanese encephalitis, zika and dengue viruses, porcine parvo virus and adeno-associated viruses to block their infection via inhibition of virus-cell interactions (Table 1. Contd.1.) [118]. Another investigation on CQDs-DNA-Au-GO has been done to detect HIV DNA virus through viral target-DNA (Table 1. Contd.1.) [119]. One study on sulfur-doped CQDs has been applied for the fluorescence detection and the analysis of influenza, dengue, zika, hepatitis E and chikungunya (Table 1. Contd.1.) [120]. Another study for using antigen-CQDs-adjuvant-chitosan/polyethyleneimine/ ovalbumin vaccine has been performed to get intranasal/anti-viral immune efficiency against intranasal/avian leukosis virus (Table 1. Contd.1.) [121,122].

A few researchers have used quinic acid carbon QDs to deliver gemcitabine into breast cancer cells for getting increased cytotoxicity with the inhibition of cancer, whereas quinic acid conjugated N-CQDs have shown their theranostic luminescent tumoral accumulation and inhibition of cancer (Table 2) [123]. A few other researchers have utilized FA-DOX-GdNS-CQDs to treat HeLa and HepG2 cancer cells for getting folate receptor mediated image-guided targeted delivery with anti-cancer efficacy (Table 2) [124]. A few investigators have applied Ag-Cu-doped CQDs to deliver doxorubicin to tumor cells for availing synergistic anti-tumor efficacy (Table 2) [125]. A few other investigators have used T-SCQDs against Gram positive bacteria to target, identify and track bacterial peptidoglycan with their colonies (Table 2) [126]. A few scientists have utilized HA/DOX/PEG-ZnO QDs for hyaluronic acid receptor mediated delivery of doxorubicin to A549 tumor cells to get therapeutic efficacy in tumor cells-killing and their inhibition of growth (Table 2) [127]. A few different groups of scientists have used black phosphorus QDs / pH-responsive black phosphorus QDs (BO QDs@PEI+RGD-EG-DMMA) to treat cancer / tumor for availing image-based anti-cancer efficacy with PDT effect / anti-tumor efficiency (Table 2) [128,129].

Table 2: A few quantum dots utilized to target and inhibit cancer.

Quantum dots (QDs)	Cancer/tumor/organisms	Chief activities	Ref.
Quinic acid-gemcitabine-CQDs/N-CQDs	Breast cancer cells / tumor cells	Enhanced cytotoxicity and inhibition of cancer	123
FA-DOX-GdNS-CQDs	HeLa and HepG2 cancer cells	Imaging, targeting and anticancer efficacy	124
DOX-Ag-Cu-CQDs	Tumor	Synergistic anti-tumor efficacy	125
T-SCQDs	Gram positive bacteria	Targeting, identifying and tracking of bacterial peptidoglycan with their colonies	126
HA/DOX/PEG-ZnO QDS	A549 tumor cells	Tumor cells killing and growth inhibition	127
Black phosphorus QDs	Cancer	The dual modality imaging-based anti-cancer efficacy with PDT effect	128
pH-responsive black phosphorus QDs (BPQDs@PEI+RGD-EG+DMMA)	Tumor	Anti-tumor efficiency	129
FA-Graphitic carbon nitride QDs	Tumor	FR-specific targeting and ROS producing ability to suppress cancer cell development	130
GQDs	A549 lung cancer cells	Cytotoxic efficacy	131
Nitrogen-doped GQDS	Cancer cells	Chemotherapeutic efficacy against cancer cells	132
CIS-GQDS	Cancer	Increased cellular uptake with anti-cancer efficacy	133
Peptide (iRGD)-GQDs/Iron oxide	Cancer cells	Fluorescent bioimaging and cancer cell targeting	134
FA-PEG-TNGs-amine GQDS	Cancer cells	Cancer cells targeting, nuclear uptake and damaging of DNA	135
GO QDs-anti-GPC3-antibody	HepG2 tumor cells	Detection of glypican-3-expressed HepG2 liver tumor cells	136
Cysteine-MnO_2 QDs/polydopamine (PDA) NPs	Neuronal cells	Detection of dopamine (DA) through the FRET mechanism	137
CdTe QDs	Pancreatic cancer Panc1 Raw 264.7 cells	Anti-cancer efficacy	138
PEI-MWCNT-ASODNs-MAA-CdTe QDs	Human cervical cancer HeLa cells	Imaging and anti-cancer efficacy	139
CdTe@CdS@ZnS QDs-PTX	Tumor	Theranostic cancer therapy with tumor growth inhibition	140
FA-oligomeric NPs-CdTe/CdS QDS	Tumor	Tumor targeted imaging and anti-tumor efficacy	141
FA-HSV-TK/GCV-CdSe Te/ZnS QDS	Liver cancer / tumor	Folate receptor targeted tumor imaging and cancer inhibition	142
Quercetin-CdSe@ZnS QDS	Drug resistant *E. coli* / *B. subtilis*; BGC-823 cancer cells	Anti-bacterial and anti-cancer efficacy	143
GEM-cRGD-PEG-MMP9-CdSe/ZnS QDS	Pancreatic cancer / tumor	Targeted accumulation in tumor to kill cancer cells	144
PSA A10 RNA aptamer-DOX-CdSe/ZnS QDs	Prostate cancer LNCaP and PC3 cells	FRET-based fluorescent imaging, drug release, and anti-cancer efficacy	145
ADM-PEG-MPA-CdSe/ZnS QDS	HeLa cervical cancer cells	FRET-based real time monitoring of drug release and apoptotic cellular death efficacy	146
siRNA-lipofectamine/MAA-PEG-CdSe/ZnSQDS	Fibroblast 3T3-J2 cells	Fluorescent imaging with gene silencing efficacy	147
Chitosan-HER2 siRNACdSe/ZnS QDs-HER2antibody	MCF-7 and SKBR3 breast cancer cells	Imaging and gene silencing efficacy	148
PTX-SiO_2-ZnSe:Mn@ZnS QDs	Cancer	Fluorescent imaging with chemotherapeutic anti-cancer efficacy	149
5FU-FA-CS-Mn:ZnS QDs	Breast cancer MDA-MB-231 cells	Tumor inhibition through apoptotic cellular death	150
Mn:ZnSe QDs-siRNA nanoplexes	Pancreatic cancer cells	Gene silencing in tumor cells	151
PEI-$AgInS_2$-ZnS-siRNA QDs	Brain tumor U87 cells	Fluorescent imaging and siRNA translocation with anti-cancer efficacy	152
PEI-$CuInS_2$-pDNA-ternary QDs-MBs	Tumor	Imaging and targeted gene delivery with anti-cancer efficacy	153
Peptide F3/siRNA-PEG-Amino QDs	HeLa cervical cancer cells	Tumor targeting and gene silencing anti-cancer efficacy	154

A few other scientists have applied FA-graphitic carbon nitride QDs for bioimaging, medication delivery and photodynamic therapy to treat tumor through folate receptor targeting and ROS-generated suppression of cancer cell development (Table 2) [130]. A lot of researchers have utilized GQDs, nitrogen-doped GQDs, cisplatin-GQDs, iRGD peptide-GQDs/Iron oxide, folic acid-PEG-TNGs-amine GQDs, and graphene oxide-anti-GPC3-antibody to treat cancer cells / cancer for getting higher cytotoxic, chemotherapeutic, anti-cancer, fluorescent bioimaging and cancer cell targeting, cancer cell targeting, nuclear uptake and damaging of DNA, and detection of glypican-3-expressed HepG2 liver tumor cells -efficiencies, respectively (Table 2) [131-136]. A few researchers have used cysteine-MnO_2 QDs/polydopamine (PDA) NPs to treat neuronal cells for the detection of dopamine (DA) through the FRET mechanism (Table 2) [137]. A study on CdTe QDs has been investigated against pancreatic cancer Pans 1 Raw 264.7 cells to get their anti-cancer efficacy (Table 2.) [138]. Another study on PEI-MWCNT-ASODNs-MAA-CdTe QDs has been elucidated to treat human cervical HeLa cancer cells to obtain image-based anti-cancer efficiency (Table 2.) [139]. Different groups of investigators have utilized CdTe@CdS@ZnS QDs-PTX, FA-oligomeric NPs-CdTe/CdS QDs and FA-HSV-TK/GCV-CdSe Te/ZnS QDs to treat tumor / liver cancer for getting enhanced theranostic tumor growth inhibition and folate receptor mediated targeted tumor imaging and cancer inhibition efficacy (Table 2.) [140-142]. A few other investigators have used CdSe@ZnS QDs to deliver quercetin against drug resistant bacteria and BGC-823 cancer cells for availing bactericidal and anti-cancer efficacy (Table 2.) [143]. A lot of investigators have used GEM-cRGD-PEG-MMP9-CdSe/ZnS QDs, PSA A10 RNA aptamer-DOX-CdSe/ZnS QDs, ADM-PEG-MPA-CdSe/ZnS QDs, siRNA-lipofectamine/MAA-PEG-CdSe/ZnS QDs, and chitosan-HER-2-siRNA CdSe/ZnS QDs-HER-2 antibody to treat pancreatic cancer / tumor, prostate cancer LNCaP and PC3 cells, HeLa cervical cancer cells, fibroblast 3T3-J2 cells, and MCF-7 and SKBR3 breast cancer cells for getting targeted drug-delivered tumor cells-accumulation and their killing, FRET-based fluorescent imaging, drug release and anti-cancer efficacy, FRET-based real time monitoring of drug release and apoptotic cellular death efficacy, fluorescent imaging with gene silencing efficiency, and imaging and gene silencing efficacy, respectively (Table 2.) [144-148]. A few other groups of investigators have utilized PTX-SiO_2-ZnSe:Mn@ZnS QDs and 5FU-FA-CS-Mn:ZnS QDs to treat cancer / MDA-MB-231 breast cancer cells for getting fluorescent image-based chemotherapeutic anti-cancer efficacy or tumor inhibition through apoptotic cell death (Table 2.) [149,150]. A lot of other researchers have utilized Mn:ZnSe QDs-siRNA nanoplexes, PEI-$AgInS_2$-ZnS-siRNA QDs, PEI-$CuInS_2$-pDNA-ternary QDs-MBs, and peptide F3/siRNA-PEG-amino QDs for the treatment of pancreatic cancer cells, brain tumor U87 cells, tumor, or HeLa cervical cancer cells to get fluorescent-based gene silencing and delivery with anti -tumor/cancer efficacy (Table 2.) [151-154].

A few investigators related on glycine-proline-glutamate-GQDs, siRNAs-amino-PEG-CdSe/ZnS QDs, Aβ-antibody QDs, and CdSe/ZnS QDs against Alzheimer's disease (AD) and SK-N-SH cells have revealed the inhibitory aggregation of β-amyloid fibrils, imaging, targeting and silencing of β-secretase genes to inhibit Aβ-synthesis, tracking of Aβ-accumulation to diagnose AD, and to detect apolipoprotein E as biomarker for AD, respectively (Table 3) [155-158]. A few other investigations related on GQDs/GO QDs and ZnS:Mn QDs against Parkinson's disease (PD) have elucidated the prevention from the loss of dopamine, α-syn-accumulation, fibrillation and brain death, and the detection of dopamine, respectively (Table 3) [159-161]. A study with mBt BDNF-QD655 to treat AD/Huntington's disease has focused on the mechanism of axonal injury (Table 3) [162]. Other studies with PrPSc-magnetic particles-QDs / PrP-nitrilotriacetic acid-PEG-QDs against Prion disease have been used to detect Prion-proteins (Table 3) [163,164]. A lot of investigations related on Se-CQDs, gly-QDs, antibody-QDs, βNGF-QDs, anti-TrkA-NGF-QDs, Bt-proteins-peptides QDs, and TGA-CdTe QDs to treat astrocytes, PC12 and N2a, neurons, glia cells and neuritis have exhibited the inhibition of ROS-generated cytotoxicity and cell death, neuronal tracking, assessment of neurite-outgrowth, neuronal differentiation, tracking of AMPA, and imaging of cells (Table 3) [72,165-170].

Table 3. A few quantum dots used to target against neurodegenerative disorders.

Quantum dots (QDs)	Neurodegenerative diseases/neuron/glia cells	Chief activities	Ref.
Glycine-proline-glutamate-GQDs	Alzheimer's disease (AD)	Inhibitory activities on the aggregation of β-amyloid fibrils, newly produced precursor cells and neurons enhanced.	155
siRNAs-amino-PEG-CdSe/ZnS QDs	AD/SK-N-SH cells	Utilized to transfect siRNAs for imaging, targeting and silencing β-secretase (BACE1) genes to arrest Aβ-synthesis.	156
Aβ-Ab-QDs	AD	Tracking of Aβ-accumulation and early molecular diagnostic imaging of AD.	157
CdSe/ZnS QDs	AD	Detection of apolipoprotein E (ApoE) for recognizing the biomarker of AD.	158
GQDs/GOQDs	Parkinson's disease (PD)	Prevent the loss of dopamine neurons, α-syn-accumulation and fibrillation to reduce mitochondrial disorders, cause loss of synapses, and prevent brain death.	159,160
ZnS:MnQDs	PD	Detection of dopamine.	161
mBt BDNF-QD655	AD/Huntington's disease	Investigation of the mechanism of axonal injury.	162
PrPSc-magnetic particles-QDs / PrP-nitrilotriacetic acid-PEG-QDS	Prion disease (Protein infectious particle)	Detection of prion proteins.	163,164
Se-CQDs	Astrocytes, PC12 and N2a	Inhibition of cytotoxicity, ROS production and cell death.	165

Gly-QDs	Neurons	Neuronal targeting for tracking glycine receptors and analyzing lateral dynamics in the cell membranes.	166
Antibody-QDs	Neurons and glia cells	Specific labeling of neurons and glia cells.	167
βNGF-QDS	Neurites	Assessment of neurite-outgrowth.	168
Anti-TrkA-NGF-QDs	Neuronal PC12 cells	Receptors targeted initiation of neuronal differentiation.	169
Bt-proteins-peptides QDS	Hippocampal neurons	Labeling and tracking of AMPA receptors on cultured neurons.	72
TGA-CdTe QDs	PC12 cells	Imaging of cells	170

Toxicity of quantum dots

The cytotoxicity of QDs is chiefly dependent on the nature of the core materials, color, size, presence or absence of protective shells, capping materials used, surface chemistry, dose, coating bioactivity, and exposure route [171,172]. The QDs, having toxic core composition such as Cd, Pb or Hg, release their heavy metal ions to produce cellular toxicity with additional enhancement of residual organic molecules [173-176]. CdSe/ZnS QDs have shown their cytotoxicity through Cd^{2+} released apoptotic cell death with inflammation [177,178]. CdTe/CdS/ZnS QDs have also exhibited their cytotoxicity through the release of Cd^{2+} ions and intracellular distribution of QDs [179]. Heavy metal ions-free QDs / ternary (I-III-VI) QDs such as Ag_2Se, $CuInS_2$-ZnS and $AgInS_2$-ZnS have shown their suitability as non-toxic materials [180-182].

It is reported that nontoxic quaternate cationic CQDs may act as an adjuvant for promoting antigen presentation and inducing robust immune response [183]. Ovalbumin (OVA)-CQDs treated mice have shown more secretion of OVA-specific IgG and proliferation of CD4+ and CD8+ T cells stimulating both the humoral and cellular immune responses [22]. CQDs-RTB (ricin toxin binding subunit B) NPs have shown nitric oxide production of macrophages with more secretion of cytokines, TNF-α and IL-6 to modulate the immune activity [22].

Biodistribution, pharmacokinetics and elimination

The biodistribution patterns of QDs depend mainly on their sizes, surface modifications, routes of administrations, and the status of diseases. The biodistributions of CIS/ZnS QDs/folic acid through intravenous injection into nude A549 tumor cells-bearing mice have been monitored over a period of time or after 4 h / 30 min post-injection, while their accumulations have been observed mostly at the liver and tumor sites, or the liver and the spleen, respectively [184,185]. The biodistributions of CIS/ZnS QDs in healthy mice injected intravenously has shown the most of the accumulation of the QDs in the lungs [186]. The *in vivo* murine biodistribution patterns of bare CIS QDs, Zn-doped CIS(ZCIS) QDs and CIS/ZnS QDs over a span of 1,7, and 28 days have exhibited the rapid excretion with about 25% of CIS-QDs and residual accumulation in the vital organs such as liver, kidney and lung after 28 days [187]. The analysis of organ index has shown the appreciable increase of both bare CIS QDs and ZCIS QDS mostly in the liver and spleen, while no significant increase for CIS/ZnS QDs. It has been revealed that the organ index for the kidneys has not been persistent, however an substantial difference in mass accumulation has been monitored at only one-time point each for CIS QDs (day 28) and CIS/ZnS QDs (day 7). The biodistribution pattern of PEG-Ag_2Se QDs in mice after intravenous injection has exhibited their preferred accumulation in the spleen and liver, but the transformation and / or clearance within one day after administration [188]. The liberated Ag from the QDs has been excreted via both the feces and urine, and the Se component has been barely eliminated [188]. Generally, non-decomposed larger NPs (>6 nm) are sequestered in the spleen and liver for few months, while smaller NPs (<5 nm) are eliminated through glomerular bed [189].

Conclusions and future perspectives

The intrinsic physico-chemical properties of QDs (optical, electronic, chemical, mechanical and photo-thermal) such as electron charge transfer characteristics with easy availability of π electron conjugate system, high spatial and temporal resolution, tunable and uniform sizes, flexible cargo-linking and coating/doping mechanisms, large surface-to-volume ratios and wide spectrum of surface reactive groups have enabled them as attractive theranostic delivery system for various biomedical applications such as biosensing, bioimaging, disease diagnosis/detection, cargos-delivery and release, photothermal therapy, and treatment and inhibition/prevention of infections/diseases with higher targeted therapeutic efficiencies. However, a thorough investigation regarding the synthesis protocol scalability of specific QDs with appropriate functionalizations with ligands/cargos/other biomolecules for their optimizations, and biological interactions regarding their toxicities, immune responses, biodistribution and fates, and scaled-up low-cost ecofriendly productions with batch-to-batch uniformity, and route of administrations especially oral and intravenous, is required to get maximum biological effectiveness of QDs to consider them as suitable theranostic nano-delivery system before going to translational applications.

Conflict of interests

The author declares no conflicts of interest.

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