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Sidra Sarwat, Fiona Stapleton, Mark Willcox & Maitreyee Roy

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Title: **Quantum dots in Ophthalmology: A literature review**

Authors: Sidra Sarwat, Fiona Stapleton, Mark Willcox and Maitreyee Roy

Affiliation: *School of Optometry and Vision Science, University of New South Wales (UNSW), Sydney, Australia*

Corresponding author: Dr Maitreyee Roy
School of Optometry and Vision Science, UNSW Sydney
Address: Level 3 North Wing Rupert Myers Building, Gate 14 UNSW, Barker Street, Kensington, 2033 NSW, Australia
Phone: +61 2 9385 7874
Email: maitreyee.roy@unsw.edu.au

Biography of the corresponding author

Dr Maitreyee Roy is a Senior Lecturer and Deputy Director of the Optics and Radiometry Laboratory at the School of Optometry and Vision Science. Dr Roy was awarded her PhD from the School of Physics at the University of Sydney. She is an accomplished optical physicist with broad experience in government and academic institutions with strong R&D background from conception, design to implementation particularly in optical metrology, 3D optical imaging and nanoparticle metrology. Her current research focuses on the fields of biophotonics and optical imaging directed towards the development of ultra-high-resolution ophthalmic instrumentation using novel liquid-crystal technology and nanotechnology with the aim for advances in optical imaging of the eye. Dr Roy holds numerous memberships with professional societies nationally and internationally, notably OSA, SPIE, AOS, OSI, and AMMS and serves as a reviewer for several optics journals. She is an Australian Standards Committee member for eye and face protection standards.

Abstract

Purpose: The aim of the current review was to summarize the current applications, the latest advances and importantly, highlight research gaps in the use of quantum dots in the eye. Quantum dots are nanoscale semiconductor crystals with characteristic size and tunable optical properties, which deliver bright and stable fluorescence suitable for bioimaging and labelling.

Methods: A systematic search was conducted following the PRISMA guidelines. This review systematically searched published data to summarize the characteristics and applications of quantum dots in ophthalmology. Two hundred and eighty published articles were initially selected for this review following searches using the criteria quantum dots AND nanoparticles AND ophthalmology in the databases PubMed, MEDLINE, Scopus, Embase and Web of Science.

Results: After duplicates were removed, a total of 22 eligible articles were included for the review. Quantum dots potentially provide a range of diagnostic and therapeutic applications in ophthalmology. Quantum dots offer visible and near-infrared emission, which is highly desirable for bioimaging, due to reduced light scattering and low tissue absorption. Their applications include *in vivo* bioimaging, labelling of cells and tissues, delivery of genes or drugs and as antimicrobial composites.

Conclusion: Quantum dots have been used in ophthalmology for bioimaging, electrical stimulation and tracking of gene/stems cells, and ocular lymphatics. However, there is no detailed description of their desirable characteristics for use in ophthalmology, and there is limited information about their cytotoxicity to ocular cells and tissues.

Keywords: Quantum dots, nanoparticles, ophthalmology

Introduction:

Nano-medicine involves the creation of inorganic nanoparticles (1-100 nm) that behave as self-sustained functional units comparable to the size of intracellular structures, peptides and drugs.[1] Nano-medicine has been used for the precise monitoring and delivery of therapeutic molecules to targeted tissues in a range of ocular diseases[2] and in biomedical *in vivo* imaging.[3] Quantum dots (QDs) are size-tunable (2-10 nm) semiconductor nanoparticles that emit single wavelengths of light when their electrons are excited at a specific wavelength of light.[4] On the atomic scale, the emission wavelength of light depends on the size of the QDs. Therefore, the emission wavelength can be modulated by changing the size of the QDs during synthesis.

Larger QDs (>10 nm) emit lower wavelengths (blue) of the electromagnetic spectrum compared to smaller QDs (2-10 nm) (Figure 1). (Figure 1 should come here) As the size of the QDs increases, the difference in energy between conduction and valence band also increases. When the electrons in the valence band are excited into the conduction band and then de-excited, QDs emit a specific wavelength of light depending on the difference in energy of the valence and conduction bands. Hence, by tuning the size of the QDs, the emitted wavelength can be changed. This phenomenon, referred to as quantum yield, enables QDs to be excited by broad absorption spectra and exhibit narrow emission spectra.[5] However, large sized nanoparticles (100 nm) have been extensively used as drug delivery systems,[6] as they are not suitable for bioimaging due to lack of quantum yield.[7] QDs are chemically and biologically 100 times more photostable and 20 times brighter under similar experimental conditions than traditional fluorescent dyes[8,9] which can be photobleached and fade by >90% in less than a minute.[10] QDs have the advantage of being suitable for single and multi-color bioimaging of multiple biomolecules simultaneously.[4,11] QDs with near-infrared (NIR) emission have been developed for live tissue imaging as they offer low

scattering and absorption of the incident light, yielding good tissue penetration and optical signals.[12] The large Stokes shift (the difference between the peak absorption and emission wavelengths) enables fluorescent signals from QDs to be easily separated from the excited light[7] and provide QDs more photostability than organic fluorophores against light scattering.[13] In ophthalmology, commonly used visible light may cause autofluorescence from ocular structures, therefore reducing the contrast of ocular fluorophores.[14] However, QDs can offer both visible and NIR emission of the electromagnetic spectrum without interfering with autofluorescence.[15] Based on these characteristics, QDs can offer a range of bioimaging and labelling applications in ophthalmology, which may give better insight into pathophysiological mechanisms occurring in ocular structures and diseases than conventional organic dyes. The labelling properties of QDs can be enhanced by attaching functional groups on their surface,[16] therefore enabling a wide variety of applications in biology.[17-20] Functional groups such as polyethylene glycol (PEG) and amino acids adsorbed on the surface of a hydrophilic cadmium selenium core covered by a zinc sulfide shell (CdSe/ZnS)[21] have been used to target and image tumor associated vasculature.[16]

Methods

A systematic search was conducted following PRISMA guidelines.[22] PubMed, MEDLINE, Scopus, Embase and Web of Science were searched using keywords: quantum dots AND nanoparticles AND ophthalmology, to August 2018 with no back-date restriction. The following data were extracted: type, size, concentration and volume of QDs being used, experimental model, target tissue/cells, emission/excitation wavelength of light being used, toxicity data and major application in ophthalmology. All data were collected regardless of the synthesis procedure or source of QDs. Formal statistical meta-analysis was not performed because of the heterogeneity of the study designs, various outcome measures, variety of QDs and different experimental models.

Inclusion criteria

- Original research articles published in English
- Studies involving QDs with size of 20 nm or less
- Studies based on cell lines or animal models and human subjects
- Significant applications of QDs for ocular applications

Exclusion criteria

- Case reports, case series, systematic reviews and conference proceedings
- Studies based on the secondary applications of QDs in the eye.

The literature search produced 280 research articles (Figure 2). After duplicates were removed, 31 articles were selected for further evaluation. 8 studies were excluded based on eligibility criteria, and 1 full article was removed based on the least contribution of quantum dots to ocular application. 22 full articles were eligible for the review. Table 1 summarizes the characteristics of QDs used in the selected research articles and their applications in ophthalmology. (Figure 2 should come here)

This review will describe the current applications of QDs used in eyes for diagnostic and therapeutic purposes.[23] The general principles of QDs applied in ophthalmology are reviewed, including topical and systemic drug delivery, gene delivery, stem cell transplantation, as antibacterial eye drops and as an imaging agent for diagnostic and surgical purposes. Characteristics of individual QDs and toxicity concerns are also summarized to describe possible future applications in ophthalmology.

Characteristics of QDs used in ophthalmology

i. Size & composition of QDs

The size-dependent optical properties of QDs enable a high Stokes shift, which is essential for bioimaging.[24,11] The size of QDs facilitates the fluorescence emission of visible or NIR light which has been used to visualize corneal and retinal cells,[25-28] and lymphatic flow.[29-31]

Smaller QDs can be more effective than larger ones[32] under certain circumstances as they improve cellular uptake and elimination by phagocytes in targeted cells.[33] QDs (20 nm) can cross the blood retinal barrier after intravenous administration in mice[32] and bind retinal vasculature.[34] The smallest and largest size QDs which have been used in ophthalmology is 3.28 nm[26] and 25 nm.[35]

Cadmium selenium QDs with zinc sulfide core (CdSe/ZnS-QDs) are the most common QDs that are biocompatible and commercially available in a wide range of sizes.[4] As shown in figure 3, in CdSe-QDs the core of CdSe is surrounded by a zinc sulfide shell which protects the cadmium and selenium from leaching out from the core.[36] (Figure 3 should come here)

QDs with such a core and protective shell are able to cross biological barriers such as the blood retinal barrier[26,32] without disruption of their constituent elements. The shell, commonly zinc sulfide, increases the inertness[37] and decreases detrimental interactions between QDs and living tissues.[38] The size-dependent characteristics, along with the protective shell enable suitable QDs to be made for ocular and systematic administration with reduced likelihood of photobleaching within living tissues.

ii. **Surface modification and use of surface modified QDs**

Polyethylene glycol (PEG),[34,39,40] amine ($-NH_2$)[40,41] and carboxylic acid (-COOH)[26,31] are common functional groups used for surface modification of QDs, depending on the target tissue and biological requirements. QDs modified with functional groups can be further conjugated with genes (DNA),[40] stem cells[42] and receptor antagonists[43] to specifically target,[27,44] trace[25,30] and image[25,30] ocular cells and ocular lymphatics.[31] Conjugates of chitin and cadmium tellurium QDs (CdTe-QDs) have enhanced antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared to chitin alone.[45] Carbon QDs (6 nm) synthesized from spermidine with a high surface positive charge show high antibacterial activity compared to spermidine alone.[41] These might be important in ocular

therapeutic applications as *S.aureus* and *P.aeroginosa* are common ocular pathogens.[46] QDs linked to the tracer dioctadecyl tetramethylindocarbo cyanine perchorate-labeled acetylated LDL (DiI-acLDL) via polyethylene glycol (PEG) have improved fluorescent imaging, compared to DiI-acLDL, in endothelial progenitor cell sub-populations (bone-marrow-derived circulating stem cells) for long term monitoring of neovascularisation of laser-induced choroidal neovascularization (CNV) in a rat model.[27] The surface charge of QDs can also be optimized to improve the biodistribution and elimination of the QDs across cell membranes of the kidneys.[47] QDs with such surface modifications may expand the range of ocular applications such as targeted imaging of ocular tissues and effective administration of ophthalmic drugs.

iii. Dose/Concentration of QDs

Delivering an optimal concentration of localized diagnostic and therapeutic agents is essential for an effective application.[48] In general, QDs have been administered to the eye topically,[35] via intravitreal[29] and intravenous injections.[32] Whilst an average of 10 µL of fluorescein is commonly used for the diagnosis of ocular diseases,[49] a study used 0.5 µL of InPGa/ZnS QDs to successfully visualize the tear film layers with excellent contrast.[35] Similarly, 10 µM CdSe/ZnS have been used to trace the differentiation pattern of transplanted ocular fat stem cells (OFSC) into corneal epithelial cells.[42] In addition, 10 nM CdSe/ZnS was used to monitor and facilitate lymphatic drainage in the anterior chamber.[50] Aqueous QDs in 200 µL have been used to visualize the vitreous during vitrectomy with excellent contrast.[29] Also, 1g/kg of gold nanoparticles, administered intravenously, were able to cross the blood retinal barrier (BRB) and become distributed in all retinal cells.[32] However, the optimal concentration range of QDs for safe ocular administration in humans has not yet been clearly defined and may change with the type of QDs used, their surface modification and desired application.

iv. Optimal excitation wavelengths of QDs

Fluorescent QDs have been used as contrast agents for bioimaging[9] as they offer tunable optical characteristics[51] compared to organic dyes, which usually offer only a single excitation or emission wavelength.[10] They can emit intense and stable fluorescence for an extended time compared to other stains both *in vitro* and *in vivo*.[9] Table 1 summarizes the emission characteristics of QDs in the visible and NIR regions of the electromagnetic spectrum. This spectrum range is likely to be well tolerated by ocular tissues and allows good tissue penetration.[7] The availability of QDs offering visible or NIR emission facilitates their possible use with existing imaging systems such as the commercially available confocal,[39,52] hyperspectral,[31] and transmission electron microscopy[32]. (Table 1 should come here)

Use of QDs in ocular disease diagnosis

i. QDs as bio labels

QDs can be used as bioimaging labelling tools as they can be designed with specific affinity to biomolecules in living cells.[53] QDs-assisted multicolor bioimaging has enabled visualization of blood vasculature, antigen receptors and lymph nodes in single tissue.[54] CdSe/ZnS-QDs with a large Stokes shift (to avoid auto-fluorescence) have been used to label immunoglobulin G in the retinal pigment epithelium in rats.[27] QDs have enabled long term multispectral imaging of longitudinal endothelial progenitor cell sub-populations that contribute to ocular neovascularization in a rat model of laser-induced CNV.[27] CdSe/ZnS-QDs linked with human immunodeficient virus (HIV)-1 encoded transactivator of transcription (TAT) peptides have been used to study human limbal epithelial cells and their survival behavior in an *in vitro* system.[25] Although neural cells are difficult to image with conventional biomicroscopes due to their structural complexity,[55] QDs can specifically label the intact retinal architecture and produce images with reduced photobleaching.[56] Antibody functionalized QDs conjugated with glial fibrillary acidic protein have been used to target

and label the astrocytes and Muller cells in laser-induced gliosis, a proliferation of glial cells, in the retina of rats.[44]

The C-C chemokine receptor 3 (CCR-3) gene is highly expressed in CNV,[57] and *in vivo* imaging of CCR-3 with QDs has enabled early detection of spontaneous CNV that was undetectable with fluorescein angiography in mice.[52] Lineage-negative bone marrow cells were labelled with CdSe/ZnS-QDs via with -PEG and -COOH to monitor their survival, integration and differentiation in vitreous of mice.[58] Similarly, OFSC were labelled with QDs to explore their differentiation in replacement of damaged corneal epithelial cells.[42] The high affinity of surface modified QDs for specific cells, receptors and genes have been used for early diagnosis of retinal diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa in rats.[59]

Angiotensin receptor type 1 is upregulated in retinal blood vessels during diabetic retinopathy (DR), and AMD.[60,61] Photocoagulation and intravitreal injections of anti-VEGF are common treatment methods for these diseases.[62] Amino PEG functionalized CdSe/ZnS-QDs conjugated with angiotensin receptor blockers (ARB) delivered intravenously can target high expressing Angiotensin II receptor type 1 (AT1R) in retinal endothelial cells in mice and inhibited their signaling.[34] QDs with multiple ARB on their surface block the AT1R, in both *in vitro* and *in vivo* models, to reduce the pathogenesis of diabetic retinopathy and age-related macular degeneration.[34] These QDs accumulated in mice specifically in the targeted retinal and choroidal blood vessels and were eventually eliminated via kidneys.[34]

Gamma-aminobutyric acid (GABA) receptors are neurotransmitter receptors which are well characterized in retinal neurons[63] and muscimol (5-aminomethyl-3-hydroxyisoxazole) is a well-known agonist of GABA receptors.[64] CdSe/ZnS-QDs conjugated to muscimol linked via PEG specifically bind to surface membrane GABA-receptors and block their expression in the retina of Xenopus.[43] CdSe/ZnS-QDs with increased number of muscimol linked via PEG

chains also increased the binding of the QDs to the target tissues in Xenopus.[39] Both studies indicate the specific binding of QDs to the surface proteins and effect on increased multi-valency on binding efficacy of conjugate.[39,43]

ii. QDs as imaging agents

The transparent fluids of the eyes, including the tear film, aqueous and vitreous, maintain the optical clarity of retinal images[65,66] but require excellent contrast agents for their examination. QDs-TOPO (try octyl phosphine oxide) with aqueous dipeptide (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline) have been used to detect the Weiss ring in posterior vitreous detachment (aqueous environment) and their use during vitrectomy resulted in better visualization than conventional dyes in porcine eyes due to their excellent contrast.[29] Hydrophilic and hydrophobic indium gallium phosphide (INGAP/ZnS) QDs have been used to monitor the spreading of the aqueous and lipid layers of the tear film on the human ocular surface.[35] These QDs enabled visualization tear film layers over the human cornea with excellent contrast.[35]

The cornea and retina maintain their homeostasis by protecting their physiological environment through specific ocular barriers respectively,[67] such as intact adjacent cells of the corneal epithelium and blood retinal barrier.[68] QDs penetrated deeper after disrupted barrier function, thus enabling qualitative investigation of transplanted human cultured epithelial cell sheets.[26] CdSe/ZnS-QDs derivatized with a variant of the human immunodeficient virus (HIV)-1 encoded transactivator of transcription (TAT) peptide have been used to study the integrity of cultured stratified human epithelial cells under the force and speed of normal blink in *in vitro* model.[69]

QDs can be excited by traditional sources of visible light employed in ophthalmic devices,[70] which facilitates their use in diagnosis.[29,35] Impaired aqueous humor flow results in increased intraocular pressure (IOP) and glaucoma, which can cause irreversible vision loss.[71] Drainage

of the aqueous humor from the eye occurs through the trabecular meshwork and also via the uveoscleral pathway in the ciliary body.[72] The presence of lymphatic channels in the ciliary body can aid in reducing IOP associated with glaucoma.[73] CdSe/ZnS-QDs enabled *in vivo* hyperspectral fluorescence imaging of this lymphatic drainage in mouse eyes.[31] The small hydrodynamic size of CdSe/ZnS-QDs enabled their penetration in latanoprost, therefore have been used to trace latanoprost via fluorescence emission and demonstrate the role of latanoprost in enhancing lymphatic drainage from the ciliary body in mice.[30] CdSe/ZnS-QDs labelled microspheres have also been used to trace and image segmental flow routes of trabecular meshwork within the aqueous outflow pathway in mice and humans.[40,50] HIV-TAT derivatized QDs have been used to label versican (a proteoglycan) and trace its potential effect in regulating IOP, where QDs were retained in the trabecular meshwork with no toxic effects in *ex vivo* porcine and human eyes.[50] These studies suggest that QDs can help monitor long term aqueous outflow pathways in the future for glaucoma treatment.

Therapeutic uses of QDs

i. ***QDs as antibacterial agents***

Bacterial keratitis is an infection of the cornea, which may have vision-threatening consequences.[74] *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common causes of keratitis.[46] CdTe-QDs QDs in conjugation with chitin have also shown increased antibacterial activity against *S. aureus* and *P. aeruginosa in vitro* than chitin alone and have been suggested as an antibacterial agent for the treatment of corneal infections.[41,45] Carbon QDs in conjunction with spermidine showed enhanced antibacterial activity against *Escherichia coli*, *S. aureus*, *P. aeruginosa*, and *Salmonella enterica* than spermidine alone.[41] When used as antibacterial eye drops in a rabbit model of bacterial keratitis, these carbon QDs reduced the growth of *S. aureus*.[41] Furthermore, QDs showed no signs of corneal inflammation in normal eyes.[41]

ii. QDs a drug delivery system

QDs may be a promising alternative for drug delivery owing to their ability to bypass ocular barriers and a reduction in the need for repeated administration. Intravenously administered gold nanoparticles (20 nm) can pass through retinal blood barrier to become distributed in all layers of the retina. These nanoparticles did not affect the structure or cell viability of retinal endothelial cells, astrocytes and retinoblastoma cells in mice.[32] This study suggests the use of gold nanoparticles as an alternative for drug delivery across the BRB, which may be applied *in vivo* to treat retinal diseases. Amino PEG functionalized CdSe/ZnS-QDs coated with angiotensin receptor blockers (ARB) have been delivered intravenously in mice and shown to target and inhibit high expressing angiotensin II receptor type 1 (AT1R) expressing retinal endothelial cells.[34] These QDs accumulated specifically in the targeted retinal and choroidal blood vessels and were eventually eliminated via kidneys in mice.[34] Such AT1R targeting QDs might be used to reduce the pathogenesis of diabetic retinopathy and age-related macular degeneration as this receptor has been shown to degradation and neuronal dysfunction in diabetic retinas[75] and the choroidal neovascularization that occurs during macular degeneration.[76] QDs of 20 nm can be distributed in high and low outflow regions of the trabecular meshwork in the anterior segment, and used to characterize the extracellular collagen proteins and genes expressed in outflow regions of the trabecular meshwork.[40] This biodistribution of QDs in the trabecular meshwork suggests the possible use of QDs as gene/protein delivery system for the glaucoma. In addition, carbon QDs were suggested as antibacterial eye drops against ocular pathogens for their topical administration on ocular surface to combat keratitis.[41]

iii. QDs as electrical stimulators

Retinal diseases cause irreversible loss of vision due to damage of neural cells (photoreceptors and retinal ganglion cells) and/or the retinal pigment epithelium.[77] Electrical

stimulation has been used as a neuroprotective therapy for CNS (central nervous system) diseases,[78] and there is some evidence of beneficial effects of QDs in retinal cells in the eye. Silicon QDs are biocompatible with retinal cell lines,[79] and can be used for electrical stimulation of retinal neural cells to increase their survival rate in a rat model of retinal degeneration.[59] Intravitreal injection of silicon QDs in rats increased electroretinogram signals over time in retinal rod cells compared to gold QDs.[59] Histological examination also indicated higher nuclei counts in the silicon QDs treated group, thus demonstrating their beneficial effects on cell survival rate in retinal degeneration.[59]

Cytotoxicity of QDs

At present, there is limited knowledge on possible cytotoxicity of QDs towards different ocular cells.[37] Cytotoxicity depends on multiple factors derived from both the physicochemical properties such as size, charge, functional groups, and oxidative, photolytic, and mechanical stability.[80] Studies specifically examining the effect of dose, duration, frequency of exposure, mechanism of action are very few.[80] Similarly, only 7 out of 22 studies examined in the current literature review reported possible cytotoxicity of QDs towards ocular cells. There are only two studies which investigated the cytotoxicity of QDs on corneal epithelial cells.[41,81] Other studies reported only observation of localized acute responses towards ocular cells such as in the vitreous,[29] retina,[32,52] lymphatics,[31] and in cultured limbal epithelial cells.[25] Different functional groups on CdSe/ZnS-QDs, their concentration and exposure time in a mouse model can affect cell viability of bovine corneal stromal cells.[81] In contract, carbon QDs have generally good biocompatibility and low in vitro cytotoxicity, hemolysis, hemagglutination, and genotoxicity towards corneal epithelial cells.[41] CdTe-QDs show no toxic effects on cells or cell membranes at low concentrations (<7 μg/mL) in murine L929 fibroblast cells.[82] Intravenously administered gold nanoparticles (10 nm) that passed through retinal blood barrier caused no cytotoxicity to retinal neurons,

endothelial cells or peri-endothelial cells.[32] Similarly, no acute signs of cytotoxicity were observed for CCR3-targeted QDs when imaging CNV regenerated retinal and choroidal cells in mice,[52] vitreous during vitrectomy in porcine eyes,[29] trabecular meshwork in mice [31] and limbal stem cells *in vitro*.[25]

Discussion

QDs are promising bioimaging tools for improved diagnosis, and effective delivery of therapeutic drugs in ocular diseases.[83,23] The ocular structures that have been targeted by QDs include the tear film,[35] cornea,[26,81] vitreous,[29] retina,[27] choroid[52] and lymphatics.[31] QDs have been surface modified with different functional groups to help target receptors,[39,43] transfer genes[52] and stem cells in the eyes.[42] Intravenously administered small QDs (≤20nm) can be delivered to ocular tissues as they can cross the blood retinal barrier and can be eliminated via kidneys.[32] Gold nanoparticles (20 nm) can be distributed in all the layers of the retina, including cultured retinoblastoma cells with minimum side effects on normal retinal endothelial cells, and astrocytes.[32] In contrast, large nanoparticles (100 nm) are not able to cross the blood retinal barrier,[32] and may have less applications as an antimicrobial agent against common ocular pathogens such as *P. aeruginosa* and *S. aureus*.[41] QDs can also increase electrical stimulation of rods in rats[59] suggesting their possible use to treat certain retinal diseases such as retinitis pigmentosa and retinal dystrophy. QDs have been used so far for targeted delivery and labelling,[15] but their applications are likely to be substantial and wide ranging.[83]

Although nascent in ophthalmology, QDs based approaches for ocular diseases may improve the understanding of the molecular physiology and pathology of ocular structures,[84,85] for example *in vivo* imaging using QDs has been used as a single diagnostic method for early stage ocular melanomas.[84] Targeted cancer cell detection using automated fluorescence microscopy may lead to an effective early cancer diagnosis and drug screening in the

future.[59,86] QDs may address irreversible vision loss in degenerated and inherited retinal diseases by stimulating the retina and promoting the production of growth factors at the cellular level.[59] Based on promising imaging and tracking characteristics, QDs have been extensively studied in *in vitro* and *in vivo* models,[54,87] however further preclinical investigations on human ocular cell lines are needed. There is also a need to investigate the effect of composition, surface modification, concentration, and volume of QDs on their bioimaging characteristics. QDs with core and shell may prevent atoms from leached out into the surrounding environment, but their long term stability and metabolic elimination are still areas of research.[37]

Due to limited literature and studies conducted on QDs, they have limitations for their use in ophthalmology. For example, QDs have been synthesized in a wide variety of procedures according to the desired biological application, but there are no standard cytotoxicity protocols for QDs.[88] Limited studies have been conducted to evaluate the cytotoxicity of QDs and optimize their concentration and duration of exposure for ocular application.[37,81] Cytotoxicity protocols should be developed for individual QDs depending upon their composition and synthesis procedures. It is important to investigate the cytotoxicity of QDs and address concerns about their systemic elimination before widespread administration in ocular tissues. Understanding the mechanisms behind cytotoxicity may lead to a better understanding of their metabolic activities in the ocular system.[89] QDs may suffer instability and agglutination in solution, affecting their emission characteristics; however these issues are usually addressed by dispersion in a suitable matrix/surfactant or surface modification.[36] An appropriate matrix provides stability and uniform dispersion,[90] thus may prevent aggregation in fluid tissues such as tear film, aqueous, and vitreous humors. Encapsulation is the most common method used to increase stability and inertness of QDs.[91] Understanding the distribution and migration pattern of QDs in human eyes is critical for understanding their

long term stability and mechanism of action.[19,92] However, there is a significant gap regarding biodegradation, elimination, and excretion of QDs.[11] The size of the QDs is increased with surface modifications[33] and may retard the elimination of QDs from the eye.

In summary, the optical characteristics of QDs, such as high contrast fluorescence, size-dependent broad emission spectra, and reduced photobleaching can provide a wide variety of applications in ophthalmology. The ability to tune the size and modify the surface of QDs can be used to target cells. However, there is limited research on the metabolism and excretion of QDs, which is important to speed their use in human. Similarly, unintended accumulation of QDs in ocular tissues has not been studied. Their synthesis from non-toxic elements such as carbon and silicon may increase their clinical application in imaging, diagnostic and therapeutic approaches in ophthalmic diseases. More research is required to explore the biological consequences, efficacy and safety of QDs for ocular applications.

Table 1 Description of studies included in the literature review

References	Composition of QDs	Size of QDs (nm)	Ligand	Emission wavelength (nm)	Experimental model	Target cell/tissue	Application of QDs
Khanal et al. 2010[35]	InPGa/ZnS	20-25	Lipids	600	Human	Tear film	To study the dynamics of the tear film layers
Ho et al. 2011[42]	CdSe/ZnS	15-20	OFSC	(N/A)	*In vitro*	Corneal epithelial cells	Tracking the differentiation of OFSC into corneal epithelial cells
Duncan et al. 2015[26]	CdSe/ZnS	15 & 3.28	COOH	525 & 655	*In vitro*	Corneal epithelial cells	To study the barrier function of cultured epithelial cell sheets
Jian et al. 2017[41]	Carbon QDs	6	Polyamine	N/A	*In vitro* & rabbit	Corneal epithelial cells	To enhance antibacterial activity of spermidine
Qin et al. 2018[69]	CdSe/ZnS	3.5, 6 & 13	Un-modified	525 & 655	*In vitro*	Corneal epithelial cells	To study the integrity of cultured stratified human epithelial cells
Genicio et al. 2015[25]	CdSe/ZnS	15-20	Peptide	655	*In vitro*	limbal stem cells	Tracking the survival behavior of cultured limbal epithelial cells
Keller et al. 2011[50]	CdSe/ZnS	20-25	HIV-TAT peptide	655	Human & porcine eye	Lymphatic drainage	To facilitate cellular uptake in ocular lymphatics
Tam et al. 2011[31]	CdSe/ZnS	12x6	COOH	655	Mice	Lymphatic drainage	To track the lymphatic pathway in the eye
Tam et al. 2013[30]	CdSe/ZnS	20	COOH	655	Mice	Lymphatic drainage	Labelling latanoprost to study its role in lymphatic drainage
Yamamoto et al 2007[29]	ACQDs	N/A	Dipeptide	640	Porcine	Vitreous	To visualize the vitreous during vitrectomy
Takeda et al. 2009[52]	CdSe/ZnS	15-20	Unmodified	800	*In-vitro* & *in vivo* mice	Choroidal endothelial cells	Pre-clinical detection of choroidal neovascularization
Hennig et al. 2015[34]	CdSe/ZnS	15-20	Amino PEG	655	Mice	Retinal & choroidal vessels	Multivalent binding of ARB conjugated QDs to GABA receptors
Vranka et al. 2015[40]	CdSe/ZnS	20	Amino PEG	585 & 655	*Ex vivo* organ culture model	Retinal & choroidal capillaries	Mapping the segmental lymphatic outflow in the trabecular meshwork
Kim et al. 2009[32]	Gold-QDs	20	Unmodified	N/A	Mice	Blood retinal barrier	The efficacy of QDs to cross BRB
Pathak et al. 2009[44]	QDs (invitrogen)	15-20	Streptavidin	605	Rat	Retinal Muller & astrocytes	Imaging of retinal astrocytes and Müller cells in gliosis
Pollinger et al. 2013[28]	CdSe/ZnS	15-20	Amino PEG	655	*In vitro* & Mice	Retinal Muller & astrocytes	Therapeutic efficacy of QDs to replace laser photocoagulation and intro-ocular injections
Olson et al. 2012[59]	Si and Ag QDs	5 & 8	Un-modified	750 & 520	Rat	Retinal nuclear & ganglion cells	QDs as electrical stimulator to retinal cells.
Barnett et al. 2013[27]	CdSe/ZnS	15-20	Streptavidin	655	Rat	Retinal endothelial progenitor cells	Imaging of endothelial ocular vascularization

Wang et al. 2009[93]	CdSe/ZnS	20	PEG	655	Mice	Retina	Tracking transplantation of bone marrow stem cells in CNV
Petty et al. 2010[94]	CdSe/ZnS	15-20	Streptavidin	800	Human	Retina	Immunofluorescence imaging of human retinal antigens
Gussin et al. 2006[43]	CdSe/ZnS	15-21	Muscimol-PEG	605	Xenopus	GABA receptor	To enhance binding activity of muscimol on GABA receptors
Gussin et al. 2010[39]	CdSe/ZnS	15-21	PEG	605	Xenopus	GABA receptor	To enhance binding activity of musicol on GABA receptors.

InPGa/ZnS=Indium Phosphide Gallium/Zinc sulfide, CdSe/ZnS=Cadmium Selenium/Zinc sulfide, COOH=Carboxylic acid, ACQDs=Aqueous QDs, Si and Ag-QDs=Silicon and Silver QDs, HIV-TAT=Human immunodeficiency virus-trans-activator of transcription PEG=Polyethylene glycol, OFSC=Orbital fat stem cells, BRB=Blood retinal barrier, ARB=Angiotensin receptor blockers, GABA=gamma-Aminobutyric acid, CNV=Choroidal neovascularization

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Declaration of interest statement

There are no financial disclosure or conflict of interest associated with this study.

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List of figures

Figure 1. The effect of decreasing size of QDs on the wavelength of emitted light

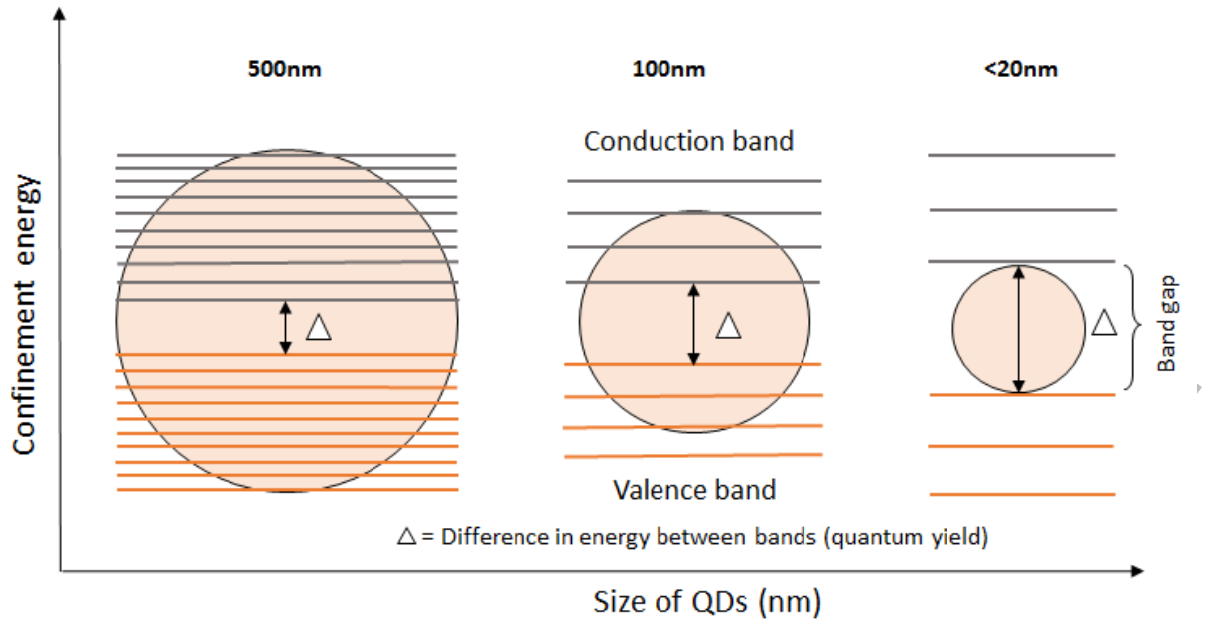

Figure 2. Flowchart of search, identification and selection method

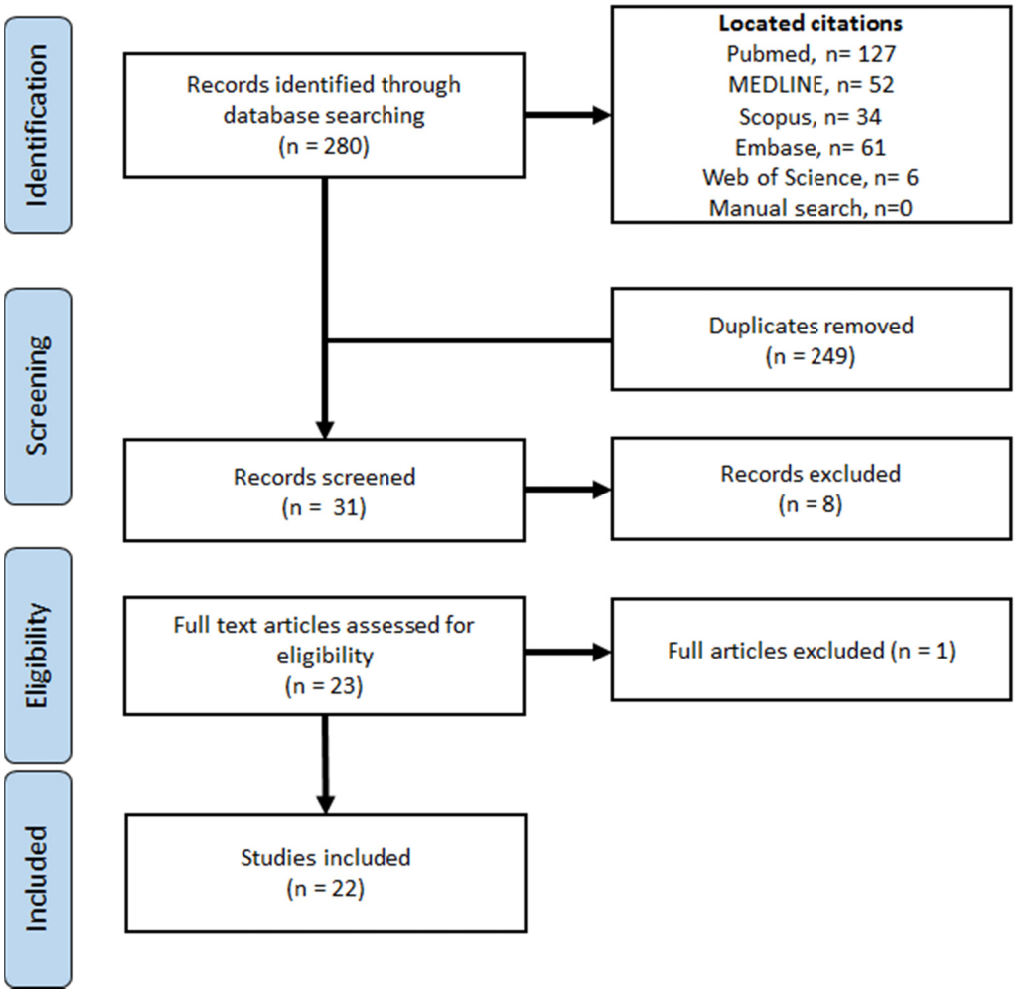

Figure 3. Prominent properties and applications of QDs (PEG=Polyethylene glycol, ZnS=Zinc sulfide, -NH2=Amine and -COOH=Carboxylic acid)