Biological applications of ternary quantum dots: A review

Abstract: Semiconductor nanoparticles, also known as quantum dots (QDs), have gained significant interest due to their outstanding optical properties with potential biological and biomedical applications. However, the presence of heavy toxic metals such as Cd, Pb, and Hg in conventional QDs have been a major challenge in their applications. Therefore, it is imperative to seek a viable alternative that will be non-toxic and have similar optical properties as the conventional QDs. Ternary I–III–VI QDs have been found to be suitable alternatives. Their optical properties are tunable and have emissions in the near-infrared region. These properties make them useful in a wide range of biological applications. Hence, this review focuses on the recent progress in the use of ternary QDs in Forster resonance energy transfer (FRET), nanomedical applications such as drug and gene delivery. It also discusses the biophotonic application of ternary I–III–VI QDs in optical imaging, biosensing, and multimodal imaging. Furthermore, we looked at the pharmacokinetics and biodistribution of these QDs, and their toxicity concerns. Finally, we looked at the current status, challenges, and future directions in the application of these ternary QDs.

Keywords: quantum dots, imaging, biophotonics, FRET, biodistribution, gene delivery

1 Introduction

Luminescent semiconductor nanoparticles known as Quantum dots (QDs) has been the pivot of most research endeavour in recent times [1,2]. QDs remain one of the important emerging functional materials in biomedical research due to their excellent optical, electronic, and physical properties, which make them preferred over conventional fluorophores [3–6]. By virtue of the quantum confinement effect, they exhibit size influenced fluorescent emission. Therefore, wide emission spectra within the range of 450–1,500 nm can be achieved by adjusting their size. The change in bandgap that accompanies the size increase allows the emission of photons by the QDs from the visible to near infrared region [7–9]. The size-induced optical properties is of much interest in biological applications such as bioimaging, biosensing, drug delivery etc., because fluorescence is one of the most important phenomena in biological related research.

However, recently ternary I–III–VI QDs have been preferred to the conventional II–VI binary QD due to
the absence of toxic heavy metals such as Cd and Pb. This has made them less toxic and environmentally friendly. Besides the low toxicity, ternary QDs also possess excellent optical and electronic properties such as tunable absorption band to the near-infrared (NIR) region, wide Stokes shift, large photoluminescence lifetime, etc. [10,11]. These properties are very important for various therapeutic applications. The tunable absorption characteristic ability of ternary QDs influences their fluorescence in animal cells and tissues. Consequently, ternary QDs have been investigated for bioimaging, in vivo and in vitro applications. These sets of QDs have also been used as drug conjugates for effective and safe delivery of the drug to the target point. A lot of studies have been carried out on these ternary QD/drug conjugates, especially in relation to photodynamic therapy (PDT), a treatment for diverse forms of cancers, infections, and inflammations. It is an alternative to surgery and chemotherapy. In recent years, technology involving the use of QD-based bioimaging and biosensing have been on the increase [12]. This will definitely lead to new frontiers in nanotechnology.

Although reviews on the application of non-toxic ternary QDs in biological and biomedical fields have been reported, in this review, we discussed extensively the application of these ternary QDs in FRET, pharmacokinetics, and biodistribution. The synthesis strategies, core/shell structure, functionalisation, and bioconjugation of ternary QDs have been extensively discussed in our previous work [13]. Thus, this particular review highlights the recent development on the use of ternary QD drug conjugates for therapeutic and diagnostic purposes. We begin by discussing the tunable optical properties of ternary I–III–VI QDs, followed by their applications in FRET systems, therapeutics, biophotonics, and pharmacokinetics. Finally, their toxicity-related issues and future outlook are also discussed.

2 Tunable optical properties of ternary I–III–VI QDs

Ternary I–III–VI QDs (where I = Cu or Ag, III = Ga or In, and VI = S or Se) are made up of less toxic elements, thereby making them preferred to the conventional binary QDs. Quantum confinement experienced by these sets of QDs allows for their tunable optical properties. The distortion in size and bandgap experienced when their composition is altered causes the emission of photons from the visible to the NIR region and allows the tuning of absorption spectra [14–17]. The size-dependent optical properties and emission of photons in the NIR region are some of the reasons for their applications in biological research [18,19]. Their coefficient of absorption, photostability, high quantum yield, good luminescence decay time, and large Stokes shift also contribute to their usefulness in biological research [20,21]. The band gaps displayed by some of these QDs include 1.05 eV (CISe), 1.5 eV (CIS), 1.87 eV (AlS), and 1.2 eV (AlSe) to mention a few [22,23].

In biomedical applications of ternary QDs, tuning of emission spectra is paramount, as fluorescence is a vital parameter in biomedical research. The tuning of these optical properties is largely achieved through the variation in atomic compositions of the QDs and the introduction of other elements into their composition [24–26]. Kang et al. [27] reported a 12 and 34.7% increase in the tuning of emission wavelength for CISe/ZnS QDs and AgInSe/ZS QDs, respectively. This was observed when the composition of In was increased for both Cu/In ratio and Ag/In ratio in both QDs (Figure 1a and b). Also, appropriate shelling, doping, and functionalization have been found to increase the photoluminescence (PL) intensity, enhance stability, remove surface defects, and facilitate emission in the NIR of ternary QDs [28–30]. This is beneficial to biological applications. For effective charge carriers, shelling or coating material should possess a wider bandgap than the core. Also, the crystal and lattice parameters must be similar to ensure unhindered epitaxial-like growth of the shell [31]. In addition to the safety advantage, ternary QDs display longer fluorescence lifetimes and long excited state lifetimes when compared to other forms of QD, making them good fluorophores favourable in biological applications.

3 FRET of ternary I–III–VI QDs

Energy transfer through a non-radiative process from a fluorescent donor to a lower energy acceptor through dipole-dipole interaction is referred as FRET [32]. Consequently, the fluorescence intensities of the donor are reduced, while that of the acceptor molecule are increased. This energy transfer occurs within a critical radius known as Forster radius. This analytical method is sensitive, reliable, and widely used in biological experiments [20,33]. FRET technique has also been found to be more sensitive to nanoscale changes in distance between acceptor and donor moieties [34]. Recently, ternary QDs have been employed as energy donors and acceptors in FRET systems in order to improve efficiency and analytical effectiveness [35]. Figure 2a describes the mechanism of the FRET process.
It involves the absorption of photon by a parent QD leading to an energy transfer from its excited state to the ground state of the nearest accepting chromophore through non-radiative means \[36\].

QDs FRET-based probes have been applied in biological systems such as bioimaging [37], photodynamic therapy [38], diagnostic, and biosensing [39,40]. Their unique properties such as size-dependent optical properties, photostability, tunable emission NIR, and resistance to photobleaching makes them a preferred candidate for nanosensors when compared to conventional organic FRET pairs [18,19]. These sets of QDs permit the excitation of different emission wavelengths by a single excitation source. This is possible as a result of their large range of absorption wavelengths and their relatively wide extinction coefficient. These properties make them suitable as bio-sensors in detecting multiplex analysis [41,42]. QDs have been widely utilised as FRET donors for a variety of acceptors. Until now, the widely used QD for FRET-based probes and sensors are either CdSe or CdTe, which hinders biological

![Figure 1](a) PL spectra of CISe/Zns, (b) AlSe/Zns core shell/QD at various Cu/In and Ag/In precursor ratios; with permission from ref. [27]; Green Chemistry.

![Figure 2](a) Schematic diagram of energy transfer between a donor and an accepting chromophore; with permission from ref. [36]; Elsevier. (b) Schematic illustration of FRET process between functionalized CIS/ZnS QDs and IR Dye QC-1; with permission from ref. [45]; ACS.
applications due to the toxic nature of Cd ions [43]. Therefore, the use of Cd-free QDs such as ternary I–III–VI QD is vital. Their broad absorption and narrow emission spectra allow single-wavelength excitation of multiple donors and can avoid crosstalk with acceptor fluorophores [20]. Xing et al. [44] developed a FRET biosensing system using MnCuInS/ZnS (MCIZ) and urchin-like Au-NPs as a donor–acceptor pair. The FRET pair was developed for the purpose of detecting HER2 protein. In the study, MnCuInS/ZnS QDs were encapsulated in BSA for easy conversion of MnCuInS/ZnS QDs from the organic phase into an aqueous solution. The resulting nanoparticles were applied as the energy donor, and the fluorescence intensity was enhanced to a large extent. As for the energy acceptor, urchin-like Au nanoparticles (Au-NPs) were selected mainly due to its stability and quenching ability for NIR fluorescence. Thus, the NIR MnCuInS/ZnS@BSA and urchin-like Au-NPs were designed as a novel donor–acceptor pair for FRET assay. The proposed FRET-based biosensor produced an enhanced FRET effect for highly sensitive detection of HER2 in human serum samples with a detection range of 2–100 ng mL\(^{-1}\) and a low detection limit of 1 ng mL\(^{-1}\). This sensing system reduces the interference of other biomolecules in the NIR region. It also showed the potential of application in in vitro and in vivo diagnosis.

Xia et al. [45] reported a study of FRET between colloidal CIS/ZnS QDs and a dye molecule (IRDye QC-1). The increasing quenching of CIS/ZnS emission and reduction in its photoluminescence decay time following the increasing amount of conjugated dye molecules show that the CIS QDs acted as the energy donor while the dye molecule was the energy acceptor in a donor–acceptor FRET system. Dynamics of the QD-dye FRET pair was simulated using two experimental models, which were based on the multieponential PL decay of the QDs (Figure 2b). The result showed a donor–acceptor distance (6.5 nm), which is in agreement with the hydrodynamic radius of the amine-functionalised QDs. The study described the potential of using non-toxic ternary QDs-based FRET nanoprobes in wide range biological applications such as biosensing, biomedical imaging, photodynamic therapy etc.

### 4 Therapeutic applications of ternary QD

Conjugated ternary QDs can act as a vehicle for the transmission of a substance of interest to the specific site inside the body or specific organ where it is needed. In addition to the non-toxic nature of these QDs, other properties such as their water solubility, excellent biocompatibility, and controlled release profile of drugs at target sites make them preferred nano-carriers compared to other carriers such as liposomes, chitosan, and polymer nanoparticles [46]. Selected therapeutic applications of drug and gene delivery are discussed here.

#### 4.1 Drug delivery system

Recently, QDs interaction with biological systems has received much interest in pharmacy, pharmacology, and medicine [47]. Ternary QDs permit attachment of various ligands with different functionalities and have been considered as good candidates for drug delivery systems. This is due to their excellent loading capacity of both hydrophobic and hydrophilic therapeutic drugs, regulated release profile, and increased therapeutic ability of the drugs [48]. QDs-loaded drug formulation is beneficial in pharmacokinetics for achieving targeted delivery, improved uptake by cells, and long circulation lifetime [49]. The technology involved in the application of these QDs in drug delivery is evolving by the day. These QDs can be cross-linked to peptides, antibodies, and other biomolecules to target biological systems, making them applicable in diagnosis and drug delivery. For effective QDs drug delivery, factors such as in vivo stability, solubility, and biodistribution should be carefully considered. The drug to be administered is usually entrapped in the QDs with the aim of attaching it to a particular surface of the cell. On reaching the target site, the QDs dissociate in order to release the drug. The release of the drug can be triggered by certain parameters such as light or heat [50]. It may also require certain biological reactions, temperature, and pH control of the target sites. Drug entrapped QDs can distort the mechanism of membrane transport and improve to a large extent the absorption of the drug in the affected cells. QDs also enhance properties such as water-solubility and release function, consequently increasing the drug efficacy and reducing the side effect [51,52]. Wu et al. showed that AIS/ZnS-methotrexate (anticancer drug) conjugate displayed effective drug delivery and imaging functionalities with minimal toxicity [53]. In another study, Ruzycka-Ayoush et al. [54] used AIS/ZnS modified with MUA, 1-cysteine, and lipoic as a carrier for doxorubicin (DOX) in treating lung cancer cells. Inhibition of migratory potential of A549 cells was observed for the DOX-QD conjugates at tolerable toxicity levels. The study further revealed the therapeutic efficiency of DOX-loaded AIS/ZnS indicating...
their promising role as a novel drug delivery agent to lung cancer cells. DOX loaded with MUCI aptamer – (CGA) functionalised CIS QDs was reported to effectively deliver the drug to the targeted prostate cancer cells [55]. The authors also reported a connection between the PL intensity of the CIS QDs and doxorubicin, thereby making it possible to keep track of the cancer drug concentration.

4.2 Gene delivery

Recently, gene therapy has been of much interest as a major therapeutic option in the treatment of various forms of genetic diseases. Several diseases occur as a result of either malfunctioning or the absence of endogenous genes within the body system. The effectiveness of the body’s defence system can also be determined and controlled by the activities of specific genes. Vast knowledge and understanding of certain genetic pathways will impact to a large extent on healthcare matters, especially genetically acquired or inherited diseases [56,57]. In addition, genetic therapy can either regulate or reverse certain social disorders such as drug addiction behavioural or mental disorders [58].

One of the ways of achieving gene therapy is through gene augmentation therapy. It involves enhancing or boosting the function of a deficient or malfunctioning gene through the introduction of an appropriate plasmid DNA (pDNA) within which an active genetic component can be incorporated. A lot of pre-clinical studies have shown the use of engineered viruses (viral vectors) to be effective in gene delivery; however, their translation on the human application have been discouraged due to the high risk of mutagenicity and immunogenicity associated with the application [59,60]. Consequently, the emergence of “non-viral” genes are being explored as a viable alternative. These non-viral genes offer several advantages some of which include: ease of preparation, less immunogenicity, lack of recombination potential etc.

Among the limitations of successful gene therapy is the inability to deliver sufficient genes to the target tissues and cells and the inability to monitor gene delivery and therapeutic response from the affected tissues and cells [61,62]. Over time, commonly used non-viral vectors such as liposomes and certain polymeric NPs have displayed shortcomings in the area of visualizing and monitoring the DNA delivery process [63]. Recently, the use of QDs as non-viral vectors have been shown to accomplish effective monitoring of gene therapy through fluorescence imaging [64,65]. The use of QDs with appropriate surface modification has been employed as a vehicle for integrating genetic materials such as plasmid DNA and RNA for targeted gene delivery to the required cells and tissues, and this is gaining much attention in pharmacotherapy [58,66]. Ternary QDs show greater potential in gene therapy applications when compared to other highly luminescent QDs due to the absence of toxic elements and its inherent optical properties. CuInS2 ternary QDs functionalised with polyethylenimine (PEI) followed by adsorption into microbubbles (MBs) were used for modal imaging and gene delivery by Yang et al. [67]. The functionalised ternary QDs were conjugated with plasmid DNA and were delivered to the targeted tumour site (Figure 3). The result from the study showed that the derived composite MBs@QDS@PEI/pDNA enhances both ultrasound and fluorescent imaging. In vitro experiment also confirmed that pDNA could be released from the derived composite and it is a promising material for targeted gene delivery. In another study, Subramaniam et al. [68] carried out the removal of oncogene genes in brain tumour cell line (U87) using SiRNA. For effective delivery of the SiRNA, they are conjugated to AgInS2-ZnS (ZAIS) QDs using PEI. The result indicated that the QDs-siRNA were appreciably taken up by the cells and the oncogene genes were knocked off. Also, a green fluorescence decline of 80% was observed, indicating effective translocation of SiRNA into the cells.

5 Biophotonic applications of ternary QDs

Biophotonics is the science of utilizing generated photons/light for imaging and identifying biological matter [69]. It is an exciting frontier that involves a fusion of photonics and biology. The knowledge and application of biophotonics allow for early detection of diseases and offer possibilities for diagnostic, imaging, and light-assisted and light-guided therapy, to mention a few. Over time, QDs have found usefulness in biophotonic sensing and imaging, and they have been widely used for this purpose [70,71]. Ternary I–III–VI QDs, in particular, are of high stability, low cost, and low toxicity than the conventional cadmium-based QDs, thereby making them an ideal candidate for biophotonic applications. The tuning of optical properties of ternary I–III–VI QDs enables them to be useful for successful imaging and monitoring biological sites and also to understand their molecular interactions. Multimodal imaging of biological species can be achieved
when these QDs are combined with contrast agents. This information allows for the early detection of certain diseases as the molecular interaction that occurs prior to these diseases can be monitored\([71,72]\). Detailed molecular imaging can be achieved when these QDs are integrated into various types of imaging techniques. QD nanoprobes that are sensitive to pH, temperature, or even the activities of biomolecules within a cell or tissue can be employed for detailed molecular imaging\([73,74]\).

In this section, we will discuss briefly the selected biophotonic applications of these QDs. These include; optical imaging, biosensing, photo-therapeutic, and multimodal imaging.

### 5.1 Optical imaging

In biological and biomedical research, optical image is a very important tool due to its capacity to give in-vivo and in-vitro information of high resolution\([25,48]\). This technique has numerous advantages, including high sensitivity, low cost, portability, and potential for multiplex images. Optical imaging is a useful technique in surgery endoscopic procedures. It is applied in early tumour detection and image-guided cancer resection. For surgery to be successful in cancer treatment, the tumour removal has to be maximised, the duration of surgery shortened, and the damage experienced by the neighbouring tissues has to be minimal\([75]\). Optical imaging permits real-time visualisation of the tumours, therefore, allowing image-guided surgery. The use of QDs in tumour imaging and detection for image-guided surgery is gaining attention by the day\([76,77]\). The use of QDs is convenient, non-invasive, offers excellent resistance to photo-bleaching and allows for long term visualisation for intra-operative image-guided surgery\([75,78]\). Their inherent properties such as tunable emission spectra, large Stokes shift, high photostability etc., make them preferred to the conventional traditional organic dyes in many imaging applications\([79]\). Furthermore, unlike the traditional organic dye, they can be easily bioconjugated with biomolecules for targeted imaging due to their large surface area and rich surface chemistry.

In their study, Liu et al.\([80]\) synthesised water-soluble luminescent AgInS\(_2\) QDs as NIR probes for in vivo and in vitro targeting and imaging of tumours. The water solubility was achieved by their encapsulation with F127 triblock micelle polymers. The bioconjugated QDs displayed sharp PL spectra and quantum yield (QY) of 35%. With the use of a whole-body animal optical imaging set-up, the conjugated AgInS\(_2\) nanocrystals formulation was employed for passive targeted delivery to the

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**Figure 3**: Schematic diagram of: (a) MBs@QDs@PEI/pDNA formation, (b) NIR fluorescence and target delivery by ultrasound-targeted microbubble destruction; with permission from ref. [67]; Royal Society of Chemistry.
tumour site. The result from the study indicates that the tumour tissue accumulation occurred due to the passive process as a result of the enhanced permeability and retention effect. The small size, high luminescence, and high QY of AgInS₂ make it a viable candidate as a biological contrasting agent for sensing and imaging purposes. CuInS₂ and AgInS₂ QDs are the most commonly used ternary I–III–VI QDs [80]. Among other reasons, the ability to achieve their synthesis under mild conditions (moderate temperature) and the use of non-toxic precursors is a major reason for this [81]. Various reports have described the application of CuInS₂ and AgInS₂ in optical imaging [82,83]. CuInS₂/ZnS QDs encapsulated with chitosan micelle was used for tumour targeting of micelles in cells by Deng et al. [84]. The study showed the application of biocompatible CuInS₂ QDs in multicentre bioimaging applications. In another development, AgInS₂ QDs encapsulated with multidentate polymer was used for in vivo imaging by Tan et al. [85]. The results showed that these QDs were suitable for deep tissue imaging as shown by the excellent contrast images observed.

### 5.2 Ternary QDs-based biosensing

Biosensing is crucial in medical diagnostics. Body fluids such as urine, saliva, sweat etc., when collected from humans, are powerful indicators of any malfunctioning part of the body and can play an important role in disease diagnostics. Recently, the unique properties of QDs have been harnessed in the detection of various chemical and biological interactions [52,85]. The high stability, low cost, and minimal toxicity of ternary QDs make them attractive for biosensing applications. Utilizing poly-(dimethyl diallyl ammonium chloride) (PDAD) conjugated 3-Mercaptopropionic acid capped CuInS₂ ternary QD as a probe, Liu et al. [86] developed an effective fluorescence detection system for lysozyme. The concentration of lysozyme in the body fluids such as serum and urine suggests the presence of diseases such as leukaemia, meningitis etc. Lysozyme is an essential biomarker, and its selective sensing is vital. The study reveals that the CuInS₂ QDs show good selectivity for lysozyme over other proteins, suggesting the application of CuInS₂ as NIR fluorescence probe for lysozyme assay. As shown in the schematic diagram in Figure 4, the fluorescence of the conjugated CuInS₂ was quenched by adding lysozyme aptamer. This was attributed to the electrostatic attraction between the PDAD and the aptamer as confirmed by the previous studies [87]. The authors also envisaged the potential application of this ternary QDs for lysozyme selective detection and quantification in relation to biomedical and biological research. In another study, 3-aminophenyl boronic acid functionalised CuInS₂ QDs were applied as PL probes for the detection of dopamine, a very important catecholamine neurotransmitter.

![Figure 4: Strategy for lysozyme sensing. (a) Coexistence of the MPA-capped CuInS₂ QDs and cationic polyelectrolyte PDAD. (b) Electrostatic bonding of the lysozyme aptamer and PDAD. (c) Bonding of the lysozyme aptamer and lysozyme; with permission from ref. [86]; Royal Society of Chemistry.](image-url)
that controls a wide variety of human behaviours, such as learning, motor control, arousal enforcement to mention a few [88]. The acid-functionalised QDs were reactive toward vicinal diols to produce cyclic esters in alkaline solutions. This reaction generated quenched fluorescence signal, which was applied as probes for dopamine detection. Based on the fluorescence quenching of the functionalised CuInS2 other diols such as catechol, pyrogallol, and gallate can also be successfully detected.

With the use of a similar approach, the same research group reported the use of CuInS2 QDs fluorescent probe for the determination of dicyandiamide. This approach was used in differentiating dicyandiamide from other amino acid and nitrogen pollutants such as melamine in milk samples. Highly luminescent AgInS2/ZnS QDs with a long PL lifetime of 424.5 ns and QY of 40% have been used as fluorescent probes for detecting intracellular Cu2+ ions in HeLa cells [89].

5.3 Multimodal molecular imaging

Molecular imaging is one of the fastest growing areas of science. It is the ability to view the inner body system of humans to better understand the biological complexities and achieve the treatment of diseases. It entails the non-invasive study of the in vivo biological process both at a cellular and molecular level. Multimodal imaging using nanoparticles in synergy with integrated functional entities have attracted a lot of interest, leading to a wide range of imaging tools for biomedical applications [90–92]. Multimodal imaging technique can be described as the combination of two or more imaging techniques. This can be achieved through the use of multi-modal probes and contrast agents that permit improved visualisation of biological materials and much-improved reliability of accumulated data [93]. As no molecular imaging technique is perfect, no one imaging modality can provide all the necessary information; therefore, it is important to come up with a synergistic approach of combining the advantage of one technique with another and also minimizing the disadvantage of such technique over the other. For example, MRI technique have been widely used as an imaging tool in cancer diagnosis due to certain exemplary features such as non-invasiveness and strong contrast in soft tissues. However, the technique still has shortcomings, such as inadequate imaging speed and low sensitivity, whereas Positron Emission Tomography is highly sensitive but has weak resolution. Recently, multimodal imaging approach has received widespread attention from researchers [94]. Guo et al. [95], in their work, successfully synthesised Gd-doped Zn-CIS ternary QDs for the purpose of magnetic resonance and fluorescence dual imaging purposes. The incorporation of Gd into the ZCIS QD is to ensure greater MRI enhancement without interfering with the fluorescence properties of the ZCIS/QDs. MRI and fluorescence imaging studies were successfully carried out for both in vivo and in vitro studies. The result from the study revealed that the Gd-doped ternary QDs have the ability to function as a dual-modal contrasting agent and can simultaneously produce MRI contrast enhancement and fluorescence emission for in vivo imaging. In addition, the synthesis of NIR emitting Zn-Cu-In-Se/Zn1−xMnxS core/shell QDs was carried out by Sitbon et al. [96]. Under optimised conditions, synthesised Mn-doped ternary QDs were found to be suitable as multimodal in vivo probes when used as MR/NIR fluorescence imaging of regional lymph nodes in mice. Cheng et al. [97] reported the synthesis of MR/Fluorescence nanoprobe using covalently conjugated Gd-diethylenetriaminepentaacetic acid (DTPA) and CuInS2/ZnS. The as-synthesised dual modal probe was functionalised with folic acid to achieve active tumour targeting. Results from the study indicate that the dual nanoprobe is an effective T1 contrast agent with longitudinal relaxivity value of 3.72 mM−1s−1 and selectivity towards HeLa, HepG2, and MCF-7 cells. The use of ternary QDs base probes in various multimodal imaging applications has also been reported in various studies. They include silica nanohybrids embedded CuInS2/ZnS as tri-modality MR/fluorescence imaging probes [98], CuInS2/ZnS Mn as bi-modal nanoprobes for MRI and PL in in vivo imaging applications [99], and AgInS2–ZnS combined with MnFe2O4 for PL/MR dual-modal imaging [100]. Jiang et al. [101] used CuFeSe2 as a nanotheranostic image for the multimodal imaging photothermal therapy of cancer (Figure 5), Yang et al. [102] used DTPA-Gd modified CuInS2/ZnS for bimodal MR/NIR imaging,

![Figure 5: Illustration on the use of CuFeSe2 ternary quantum dot (TQD) for multimodal imaging photothermal therapy of cancer; with permission from ref. [101]; ACS.](image-url)
while Zhang et al. [103] used CuInS$_2$/ZnS and DTPA coupled imaging for MR/fluorescent imaging.

6 Pharmacokinetics and biodistribution of ternary I–III–VI QDs

The study of the absorption, distribution, metabolism, and excretion of drugs from the body is known as pharmacokinetics [104,105]. Pharmacokinetics addresses the biodistribution of drugs from the vascular space into organs and tissues of the body system and their removal from the body through metabolism and excretion over a period of time. The mode of distribution in the cells, tissues, and organs of the body system is an important characteristic of any drug formulation. Bio-distribution measurement provides key information about the presence or absence of a drug at a particular targeted site where the accumulation is desirable. In pharmacokinetic studies, the drug concentration in the plasma and all other connecting tissues is being analysed over time. This is to ascertain the extent of metabolism and excretion of the drug. This is achieved by serial collection and analysis of the blood samples. Additional labelling has to be employed for non-fluorescent drugs so that they can be detected in the blood. Radioactive labelling is the most widely used for this purpose [106]. However, PL-based detection of non-fluorescent drugs can be achieved by labelling with non-toxic QDs [107]. The use of QDs for drug labelling can, to a large extent, influence drug fate and ensure favourable pharmacokinetics. The size and surface characteristics of these QDs influence their performance as drug carriers; therefore, encapsulation of the hydrophobic drug in the QD-drug formulation may be necessary to improve the absorption and availability [108,109]. In addition, the rate of liver metabolism is reduced with the use of QDs thereby leading to prolonged retention, increased half-life, and reduced opsonisation [110].

The level of success or failure of any targeted therapy procedure can be ascertained if the biodistribution of the drug-QDs formulations is fully understood [111]. QDs-based labelling is preferred to radioactive labelling due to the following: (i) it provides a more reliable biodistribution profile, (ii) it permits monitoring of biodistribution in live animals, thereby reducing the number of animals required for analysis and also provide a more reliable data because the issue of animal to animal variation between time point would not arise, and (iii) side effect is minimised significantly [112–114]. In separate studies, the biodistribution of CIS/ZnS QDs/folic acid conjugated systems in major body organs over a period of time was carried out by Deng et al. [115] and Yong et al. (2010) [116]. The QDs-drug conjugate in both cases was intravenously injected into nude tumour-bearing mice. Deng et al. [115] observed a 4 h post-injection clearance at the liver and tumour sites for the nude mice bearing A549 tumours. Yong et al. [116] observed a 30 min clearance of the QDs conjugate at the liver and the spleen. In another work, Li et al. [117] studied the biodistribution of CIS/ZnS QDs in healthy mice after intravenous injection. The results (Figure 6) showed that most of the QDs are accumulated in the lung.

![Figure 6](image-url)
7 Toxicity concerns of ternary QDs

The toxicity of QDs remains a major obstacle for these set of nanoparticles to be used in clinical research. The toxic or non-toxic nature of QDs goes a long way in determining their intrinsic behaviour and characteristics. The main source of QDs toxicity has been ascribed to the release of heavy metal ions such as Cd\textsuperscript{2+}, Pb\textsuperscript{2+}, and Hg\textsuperscript{2+} which are present in their composition [56,118]. Other factors determining the toxicity or non-toxicity of QDs include size, colour, absence or presence of protective shells, behaviour of capping agents, chirality of capping agents, nature of the core, to mention a few [119,120]. This is of great concern to biomedical and biological researchers and has prompted the development of heavy metal ion-free QDs such as ternary I–III–VI QDs. Several studies have described ternary QDs as “non-toxic” [121–125]. Using histological imaging, Chen et al. [126] carried out the in vitro and in vivo immunotoxicity studies of CulnS\textsubscript{2} (PEGylated) using Dc 2.4 cell line and BALB/c mice, respectively. Their findings showed that PEGylated CulnS\textsubscript{2} QDs altered the function of Dc 2.4 in vitro but showed little or no toxicity to the immune system in vivo. This indicates that this set of PEGylated ternary QDs is biocompatible and has the potentials for bioapplications. In another recent development, our group evaluated the cytotoxicity of bare CIS/ZnS QDs and mTHPP porphyrin conjugated CIS/ZnS QDs on BHK 21 (normal fibroblast cell line) and THP-1 (leukaemia cancer cell line) [127]. The study showed that both the bare and mTHPP porphyrin conjugated QDs have excellent biocompatibility towards BHK 21, while dosage-dependent toxicity was observed for the cancer cell lines (Figure 7).

The increase in toxicity for the QDs-porphyrin conjugate against the THP-1 cancer cell lines at higher dosage concentrations was attributed to the synergistic effect of the QDs and porphyrin.

Adequate surface passivation is required to improve quantum yield, ensure stability, and avoid surface defects when synthesizing QDs. The use of ZnS as shelling/passivation material has been widely accepted among diverse QD systems due to its large bandgap and ease of synthesis. Furthermore, studies have shown that ZnS shells reduce the core QDs toxicity in in vitro and in vivo application through the following mechanism; prevention of particle degradation, trapping of toxic ions and avoiding the formation of reactive oxygen stress (ROS) [128,129].

Using the Murine model, Kays et al. [130] carried out the in vivo biodistribution and cytotoxicity evaluation of bare CIS QDs, Zn-doped CIS (ZCIS) QDs, and ZnS passivated CIS (CIS/ZnS) QDs over a period of 1, 7, and 28 days. The result showed a quick clearance with about 25% of the CIS QDs remaining in the major organs (liver, kidney, and lungs) after 28 days. Organ index (organ weight divided by total body weight), a very sensitive method of determining toxicity, was used in measuring the organ-based toxicity of these QDs. The analysis showed an appreciable increase in the organ index of the liver and spleen for both bare CIS QDs and ZCIS QDs, while no significant increase was observed for CIS/ZnS QDs. The organ index for the kidney was not consistent: however, an appreciable difference in mass was observed at only one-time point each for CIS/ZnS (day 7) and CIS (day 28) QDs.

To have a clearer understanding of the organ-based toxicity of these QDs, the histopathology of the mouse was carried out. The organs’ micrograph compared to the control is shown in Figure 8. Geographic necrosis was observed in the liver of the CIS-QDs-dosed mice, mild inflammation was noted in the liver of the ZCIS-

\[ \text{Figure 7: Cytotoxicity effect of: (a) CIS/ZnS QD and (b) CIS/ZnS–mTHPP conjugate against THP-1 cancer cells; with permission from ref. [127]; Springer Nature.} \]
QDs-dosed mice, whereas no inflammation was seen in the micrographs of the CIS/ZnSQDs-dosed mice and that of the control. In the CIS QDs and ZCIS QDs spleen, multinucleated giant cells were observed. This is an indication of an inflammatory response. Disruption of the tissue architecture was also noted in the CIS QDS spleens together with shrinkage of the pulps. No notable histological changes were observed in the kidneys for all the tested QDs. These results suggest that the non-toxic nature of ternary QDs is not only due to the absence of heavy toxic metals such as Cd and Pb but passivating with ZnS minimizes the level of degradation, and subsequently the toxicity of the QDs.

A solid conclusion cannot be made regarding the toxicity of these TQDs because the toxicity is associated with many factors such as surface charge and modifications of the capping agents, as mentioned earlier. Therefore, more investigations are still required concerning the toxicity of these materials.

8 Conclusion and future outlook

The use of ternary QDs as an alternative to the Cd, Hg, and Pb-based QD due to their non-toxic nature have gained much attention. The ease of tuning their PL toward the NIR by altering their compositions has given it much attention among researchers. These desirable properties encourage their use in diverse biological and

Figure 8: Micrograph of the organs (liver, spleen, and kidney) in the histopathological studies of QDs-dosed mice. The yellow arrow shows the inflammatory cells, while the blue arrow shows the multinucleated cells; with permission from ref. [129]; ACS.
biomedical applications such as biosensing, bioimaging, and cancer treatment procedures such as PDT and PTT. In this study, we discussed the recent progress in the use of ternary QDs in various biological and biomedical applications. Recent development relating to ternary QDs therapeutic and diagnostic applications is described. The use of these sets of QDs in energy transfer systems such as FRET, biophotonic applications such as biosensing and bioimaging, and their nanomedical applications is also discussed in this review.

The combination of ternary QDs with contrast agents such as radioactive labels for multi-imaging and multimodal purposes will be helpful in understanding the complex nature of tumours and other diseases, therefore, enhancing their treatment and management. The possibility of developing new multi-modal probes through the integration of ternary QDs with suitable contrasting agents is a research area that can be fully exploited in the near future. The biodistribution and toxicity should be fully understood with respect to the size, shape, surface properties, and manner of administration in the respective animal models. The retention time of these QDs in relation to the presence and absence of targeting ligands should also be fully understood. Even though the ternary QDs are devoid of toxic metals such as Cd, Pb, Hg etc., their other constituents i.e. In and Se are not totally benign in living systems [112]. Critical assessment of their genotoxicity, immunotoxicity, and pharmacokinetics still need to be carried out before they can be employed in humans. Furthermore, comparative studies of their toxicity with other forms of toxic metals-free QDs such as graphene and silicon need to be extensively carried out. Their toxicological effect in various biological model is very important and need to be urgently developed. Also, the multiple methods used in evaluating the toxicity profiles of QDs make the comparison of the results challenging. The existence of a uniform and standard method of determining the toxicity of these QDs will be appreciated in biological and biomedical research. However, surface modifiers such as peptides, biocompatible polymers, DNA/RNA can be employed to further reduce their toxicity. Researchers also need to have a full understanding of the mechanism of these QDs in living systems so that their clinical applications will be achieved soon. In addition, the proper understanding of the mechanism will ensure the control of their optical and electronic properties such as PL, QY etc., which will give rise to more biological applications. For emission dependent applications such as bioimaging and sensing, a reduction in photoluminescence line width will be advantageous. In the near future, attention should be given to developing ternary QDs-based therapeutic and imaging methods for the treatment of malignant cancer cells.

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