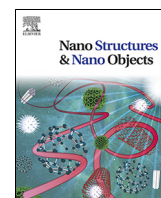


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## Synthesis strategies and application of ternary quantum dots – in cancer therapy

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### ABSTRACT

Semiconductor nanoparticles also known as quantum dots (QDs) have continued to receive more attention from researchers due to their unique optical, magnetic and photo physical properties which made them useful as biomedical materials, solar cells, catalyst etc. However, ternary I–III–VI QDs have shown to be a safer alternative to the binary II–VI or IV–VI QDs due to the absent of heavy toxic elements such as Cd and Pb. Cancer management and therapy in Africa has been bedevilled by a lot of challenges such as inaccurate diagnosis and ineffective therapeutic methods. Therefore, the need to develop an appropriate approach for cancer detection and treatment is of paramount importance. Tunable optical properties and absorption in the near infra-red region of the ternary QDs makes them useful as fluorescent probes in cancer detection and treatment. They have the ability to detect specific cancer cells including those that are not easily detected by modern imaging technique. Also, properties such as non-bleaching, stability, water solubility etc. made them a desirable fluorophore when compared to conventional dyes. Most cancer drugs suffer from inherent shortcomings such as limited absorption, insolubility and aggregation. However, these shortcomings can be overcome when these drugs are applied in form of conjugated systems. The use of QDs as conjugates has revolutionised the treatment of cancer in the 21st century. This review provides information about the synthesis strategies, optical properties, hydrophilization and bioconjugation of ternary I–III–VI QDs. Furthermore, we described the various biomedical applications in biosensors, bioimaging, drug delivery and phototherapeutic techniques. Finally, we looked at the challenges and future perspective of these QDs in cancer management.

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## 1. Introduction

Cancer management globally has been challenging. Globally, around 9.6 million cancer related cases were recorded in 2018 and new cases rose to 18.1 million [1]. The cancer burden is projected to double by 2035 [2]. This figure exceeds the death from malaria, HIV and tuberculosis combined and thus calls for serious action. Non-availability of cancer treatment facilities and little or no access to conclusive diagnoses at various hospitals in developing countries have been major setbacks in tackling this terminal ailment. Accurate diagnosis through the excellent imaging of cancer cells, drug effectiveness and ability to deliver the cancer drug to the specific site are all essential for proper cancer management. Most cancer cases are detected after the tumour have been developed which makes the treatment difficult and sometimes ineffective. On the other hand, most cancer drugs suffer from inherent shortcomings such as limited absorption, insolubility and aggregation. However, these shortcomings can be overcome when these drugs are applied in the form of conjugated systems [3,4].

Quantum dots (QDs) are semiconductor nanomaterials with inherent ability that allows them to emit fluorescence when exposed to light [5,6]. QDs have continued to receive more attention from researchers due to their unique optical, magnetic and photo-physical properties which made them useful as biomedical materials, solar cells, catalyst and so on [7].

Ternary QDs from group I-III-VI elements have received growing interest in cancer management owing to their lower toxicity and radiation stability. Due to their specificity and biosensitivity, ternary QDs conjugates has the potential of detecting specific cancer cells (such as HeLa cells and HER-2 breast cancer cells) including those which are not easily detected by modern imaging techniques such as Magnetic Resonance Imaging (MRI) and X-rays [8,9].

Furthermore, conjugated ternary QDs can also be used for targeted drug delivery i.e delivery of the cancer drug to where it will be most effective without harming the healthy tissues. This ultimately ensure effective treatment under small amount and lower cost of medication. Ternary QDs also possess photothermal properties which can heat the cancer cells when used as conjugates with cancer drugs [5,10]. Exploiting specific binding properties of QDs conjugates as a mechanism for selective delivery of cancer drugs to tumour cells would be a major solution to the menace of cell-killing agents for treating cancer. Apart from ternary QDs, certain studies have also described carbon based QD (such as carbon quantum dots, graphene quantum dots, C3N quantum dots, and g-C3N4 quantum dots) as a non-toxic QD useful for biological and biomedical applications [11-13]. However, they differ from ternary I-III-VI QD in terms of composition, structure and mostly importantly in fluorescence ability [14].

The biomedical and biological applications of ternary QDs have been reported by several authors [15,16]. In this review, most of the reference materials are related to the application of ternary QDs in biomedical applications for cancer treatment. We will be looking at the various synthetic approach, the techniques employed in improving photoluminescence, quantum yield and

optical properties of QDs as it relates to their core shell systems. Furthermore, we will also study the biological applications of ternary QDs particularly AIS, CuInS and CuInSe in drug delivery, imaging, biosensor, bioconjugation etc. The toxicity of these QDs will also be discussed.

## 2. Key concept of ternary QDs

Unlike binary QDs, ternary I-III-VI QDs (I = Cu or Ag, III = Ga or In and VI = S or Se) consist of less toxic elements (devoid of Cd, Hg etc.). They are regarded as promising candidates for developing QDs that are eco-friendly due to their favourable optical properties and low toxicity [17]. Optical properties of QDs can be tunable due to quantum confinement effect. Quantum confinement takes place when the QDs attain a size less or equal to that of the Bohr's radius [18-20].

Variances in the atomic composition of ternary QDs distorts their size, this distortion in size affects the band gap. The change in band gap and size permits them to emit photons from the visible to the near infra-red region. The emission of photons as a result of variance in atomic composition enables the tuning of the absorption spectra [21,22]. Their usefulness in bio imaging, phototherapy, drug delivery and biosensing can be attributed to their size dependent optical properties and tunable emissions to the near infrared region [23,24]. Ternary QDs showed band gaps of 1.05 eV, 1.5 eV, 1.87 eV and 1.2 eV for ClSe, CIS, AIS and AISE respectively [25,26]. In addition to this, ternary QDs are found to have a large coefficient of absorption, excellent photostability, high quantum yield, good luminescence decay time and large stoke shift [27-29]. Tunable emission spectra of ternary I-III-VI QDs makes them a good candidate for biomedical applications as fluorescence is an important parameter for majority of medical research [30,31].

### 2.1. Ternary QDs core/shell system

Ternary I-III-VI QDs synthesised as core QDs show low quantum yield and surface defects [32,33]. This occurs due to their high surface to volume ratio as a result of their small size. Therefore, adequate surface passivation is important to ensure increase in quantum yield, fluorescence and stability. In other to improve quantum yield, ensure stability and minimise or reduced surface defect, the core surface is usually coated with shell materials possessing a larger band. The choice of shell materials is dependent on the desired application of the QDs. The use of Zn<sup>2+</sup> and ZnS as shell materials for ternary QDs with focus on biological applications are widely discussed in this review. Core/shell QDs systems allows for the modification of properties for suitability in various biomedical and industrial applications. Thermal stability, dispersibility and functionality of the core can be modified when coated with appropriate shell material.

Taking into consideration, band alignment between the conduction and valence band of the core materials, core/shell QD systems can be classified into type I, type II and quasi type II [17, 34]. In type I core/shell systems, the energy of the conduction band of the core is lower than that of the shell while reverse is the case for the valence band [34]. The holes and electrons

are enclosed within the core. In type II core/shell systems, the electrons and holes are present in two different compartments, causing the rate of recombination of the charged carriers to be slow. The slow rate of recombination of the charge carriers is the reason for the increased luminescence lifetime exhibited by type II core/shell systems [35]. In Quasi type II core/shell systems, one carrier is localised in the core or shell while the other is delocalised as a whole particle.

ZnS is much preferred as a shell material due to the following reasons; (i) wider band gap (3.7 eV) and a small ionic size of zinc, this enables proper band alignment with the ternary QDs (ii) the structure of ZnS ensures the removal of trap states and prevents leakage caused by the charge carriers in the ternary QDs [36,37]. In another study, Speranskaya et al. [38] reported a 52% improvement in photoluminescence quantum yield (PLQY) after shelling CIS core with ZnS. The schematic representation for the synthesis of CIS/Zn core/shell system is shown in Fig. 1. The emission range of these core/Zn shells make them suitable for biological application. Studies have confirmed the suitability of ZnS as shell materials with ternary QDs. With CuInS<sub>2</sub> core, Chen et al. [39] reported a QY of 48% and PL of 500–800 nm; Huang et al. [40] reported a QY of 88% and PL of 400–800 nm to mention a few.

## 2.2. Synthesis of ternary I-III-VI QDs

The synthesis of ternary QDs can be challenging and their chemistry can be complex owing to the chemical properties of the precursor cations. In<sup>3+</sup> is a hard Lewis acid while Cu<sup>+</sup> and Ag<sup>+</sup> are soft Lewis acids. Due to this, their reaction with sulphur compounds leads to the formation of unbalanced cationic precursors. Consequently, the product formed contains more of copper, silver and indium sulphides than the ternary QDs. To achieve good reaction yield, the reactivity of Cu and In has to be regulated. This can be achieved through; (i) the use of a suitable capping ligand e.g. carboxylic acid, thiols (ii) the use of stabilising agents (iii) using a single precursor which can produce both cations (Cu and In) precursors [42,43].

Several methods for the synthesis of ternary I-III-VI QD core shell systems have been reported (see Fig. 2, Tables 1 and 2). They include; hot injection method [44,45], solvothermal method [46, 47], microwave assisted method [48], hydrothermal [26,49] and heating up method [33,50]. During synthesis, factors such as temperature and time, temperature of injection (particular to hot injection method), pH, nature of solvent utilised, reactivity and stoichiometry of precursors are vital to ensure the desired size and composition of the QDs.

### 2.2.1. Hot injection method

This method involves the reaction of precursors and surfactants at very high temperature in the presence of stabilisers. Coordinating solvent and surfactants are heated in a reacting chamber in the presence of an inert gas (nitrogen or argon). After which precursors are rapidly injected into the hot solution leading to supersaturation. Consequently, the precursors become aggregated therefore inducing nucleation and growth of the nuclei. The size distribution of the QDs is dependent on the speed of injection. Narrow size distribution is enhanced through fast injection. This method of synthesis is associated with monodispersed QDs. It is said to be a technique that gives high quality and pure QDs [34]. Researchers have employed this method in the synthesis of ternary QDs. Zhong et al. [20] synthesised CuInSe with photoluminescence quantum yield (PLQY) of 50% for *in vivo* bio-imaging applications; Liu et al. [51] synthesised AgInS<sub>2</sub>, with PLQY of 30% and emission peak in the range of 480–900 nm. In another development, Deng et al. [52] synthesised AlSe<sub>2</sub> with PLQY of 40%, and emission peak also in the range of 600–1000 nm. ZnS was used as shell materials to improve the optical properties of the QDs in all of the highlighted cases.

### 2.2.2. Heating up method

This method can also be referred to as the non-injection method. Reaction solutions are prepared at low temperature and heated up for crystallisation to take place at a high temperature. The heating up process is achieved via decomposition of metal salt in the presence of surfactant and solvent with high boiling point. The size distribution of the QDs is determined by nature of crystallisation and the reactivity of the precursors determines the reaction temperature. In this method, supersaturation is instantaneous and accompanied by a fast crystallisation. This method is effective for size, morphology and elemental control of the QDs. CuInS<sub>2</sub>/ZnS [36], AgInTe<sub>2</sub>/ZnS [53] and AgInSe<sub>2</sub> [54] have been produced using heating up approach with emission peak in the range of biomedical applications. This synthetic approach is suitable for large scale synthesis as large amount of precursors can be used in a large volume reactor.

### 2.2.3. Solvothermal method

This approach offers several advantages when compared to the other synthetic methods. The synthesis environment enhances the formation of crystals with little lattice defects leading to the effective control of the shape and size distribution of the QDs. Secondly, the use of low boiling point organic solvent permits a higher reaction pressure when reaction occurs at a higher temperature. This behaviour largely affects the crystallinity of the QDs. Thirdly, certain structural properties of the precursors can be transferred to the product for the effective control of the morphology of the products. Finally, this process consumes less energy and does not involve the use of costly solvents. CuInSe<sub>2</sub>/ZnS [55], CuInSe<sub>2</sub> [56] and CuInS<sub>2</sub> [57] have been synthesised via the solvothermal approach with emission peaks in the range of biomedical applications. Solvothermal synthesis reduces the release of harmful vapour during reaction making the process environmentally friendly.

### 2.2.4. Hydrothermal method

In the field of nanochemistry, green chemistry approach for the synthesis of nanoparticles is highly desirable. Cost effectiveness and environmental friendliness of the process is the aim of most researchers. One of the advantages of this method is the use of non-toxic solvent and reagents. This process does not necessarily require synthesis in an inert atmosphere thus making the synthesis cost effective. The synthesis is achieved by the reaction between a metal precursor and surface ligands. The precursor used are mostly water-soluble metallic nitrates and halide while the sulphur sources are usually Na<sub>2</sub>S [58] and thiourea (CS(NH<sub>2</sub>)<sub>2</sub> [59]. The advantage offered by this approach include; (i) good product yield (ii) use of non-toxic solvent and reagents (iii) low cost of synthesis (iv) reproducibility [60,61]. The first attempt of synthesising AIS by Luo et al. [62] using this method resulted into a low QY. However, for effectiveness in bio-medical applications it is necessary for QDs to have a high QY, to be water dispersible and to be biocompatible. Several studies have shown that the use of hydrophilic ligands as sulphur sources such as dodecanethiol [27], L-Cysteine [63] and diethyldithiocarbamate [64] have produced water soluble ternary QDs with good QY suitable for biomedical applications.

### 2.2.5. Microwave irradiation method

Synthesis of ternary QDs using microwave irradiation technique is gaining much attention due to the numerous advantages it offers. In this method, the synthesis is carried out at the boiling point of the solvent, therefore enabling the production of small particle size QDs at normal pressure. The product formed is of high purity with a fast reaction time. Reproducibility and product yield are also enhanced. AIS QDs was synthesised using

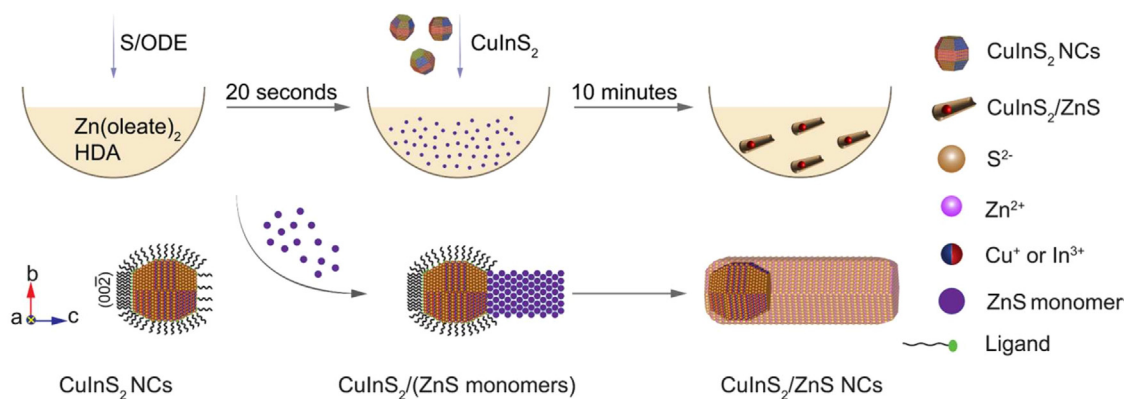


Fig. 1. Schematic representation of ternary CIS/Zn core/shell system [41].

the microwave assisted approach by Xiong et al.<sup>a</sup> [65] via a two-step approach and using ZnS as shell material. The product obtained showed low toxicity, good fluorescence and emission range suitable for *in vivo* bio-imaging application. QDs have been synthesised by various researchers using this synthetic approach. AgInS<sub>2</sub> [66], CuGaSe<sub>2</sub> [67] CuInS<sub>2</sub> [68]. The small size, biocompatibility and thermal stability of these QDs makes them useful for biological applications [17].

### 3. Hydrophilization of ternary QDs

Fluorescent QDs of high quality are usually synthesised using non-polar solvent at a high temperature, as a result they have hydrophobic surfaces. This can be attributed to the presence of aliphatic amines, carboxylic acids, alkyl phosphines etc. Meanwhile for effective applications of these QDs in cancer management they require water dispersibility, biocompatibility and presence of active sites for subsequent functional conjugation. Therefore, functionalisation of their surface is mandatory to ensure solubility in aqueous solutions. Strategies need to be employed for the conversion of the hydrophobic phase to hydrophilic. There are three strategies to this as shown in Fig. 3. These are; ligand exchange, Salinisation and encapsulation [79–81].

Ligand exchange is achieved by substituting the hydrophobic surface of the QDs with hydrophilic molecules that can easily bind with the QDs surface. The surface ligand ensures the QDs are dispersed in aqueous media and also protects the core from leaching into the biological environment. These conditions are essential for successful *in vitro* and *in vivo* biological applications [82]. Widely used ligands are thiol groups (due to their affinity for metals), amines and carboxylic acids [83]. In this approach, the hydrodynamic size of the QDs is retained and allows for monodispersity of the QDs in aqueous media. This improves their ability for FRET based sensing and makes them good candidates for biological applications [84]. When choosing the appropriate ligand, utmost consideration should be given to the affinity that exist between the ligand and the QDs. However, some limitations are associated with this method, conditions such as concentration, pH and temperature affect the stability of the attached ligand. In order to overcome this limitation and to create opportunities for wider biological applications, thiol containing molecules such as L-cysteine [85] and polyethylene glycol-dihydrolipoic acid (PEG-DHLA) [86] have been used for the functionalisation and solubilisation of QDs with a major improvement in *in vivo* and *in vitro* stability. Kim et al. [87] in their work on the synthesis of CuInS<sub>2</sub>/Zn core/shell quantum dots replaced the initially aliphatic capped surface ligand with a hydroxyl-terminated thiol ligand. The functionalised QDs displayed improved dispersibility in polar solvents. The synthesis of 1-dodecanethiol (DDT) capped

CuInS<sub>2</sub>/ZnS QDs was reported by Li et al. [88]. The QDs was transferred to the aqueous phase by functionalising the surface with DHLA. The functionalised QDs was successfully used as labels for *in vivo* imaging. The main difficulty encountered in this method is the susceptibility to oxidation of the thiol group and the attached ligand. This can further degenerate to the reduction in fluorescence QYs and formation of aggregates.

The salinisation method is based on the well-known silica chemistry developed for the coating of metallic nanoparticles. This method has advantages due to the non-toxicity, inertness and optical transparency of the coated silica surface. In this approach, a formation of highly linked protective shell takes place around the QDs. This is due to the reaction between polymerised methoxysilane groups and the thiol group of the precursor molecule used for hydrophilisation of the QDs surface. Mercaptopropyltrimethoxysilane (MPTMOS) is a typical example of a precursor used for this purpose [89]. The major advantage of this method is that silica exhibits a high level of biocompatibility and can be easily functionalised thereby making them suitable for conjugation. Consequently, QDs emanating from this approach are good candidates for bioanalytical applications [90].

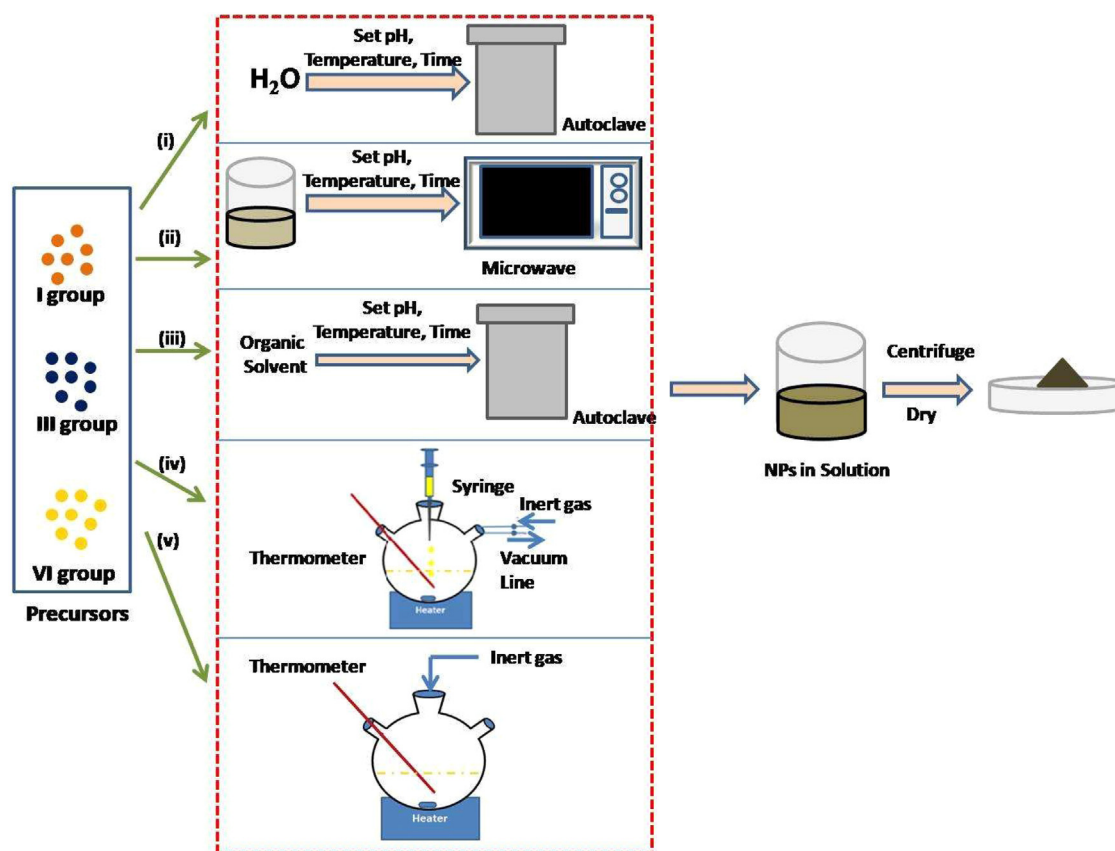
In the third approach, the surfaces of QDs are encapsulated with amphiphiles with the use of non-polar molecules as reaction intermediates. The hydrophobic shell of QDs interacts with that of the amphiphilic polymeric material through electronic or hydrophobic interaction while the hydrophilic portion ensures solubility thereby providing aqueous stability. Several amphiphilic polymers have been used in this approach, such as Polymaleic anhydride [91], Polyacrylamide [92] or biopolymers such as DNA/RNA [93]. Polyethylene glycols (PEG)-based coating are applied to the QDs to ensure stability and biocompatibility. However, for effective application of these QDs in bioanalytical processes, it is important for the PEG molecules to be activated with the suitable thiol, amine or carboxylic groups in order to enable the formation of hydrophilic cross links between the QDs surface and the PEG layer [94,95]. This method is an improvement on the ligand exchange method as it addresses the shortcomings of aggregation and poor luminescence quantum yield. In this approach, the optical properties and size of this QDs remain unchanged.

Surface modification and functionalisation of QDs is important to ensure stability, solubility in various solvents and for the development of a QD-biomolecule conjugate that will be useful in specific biomedical applications such as detection, bioimaging and therapeutics.

### 4. Bioconjugation to biomolecules

For water soluble QDs to be relevant in biomedical applications such as bioimaging, drug delivery and other biological





**Fig. 2.** Mechanism of various synthetic methods: Illustration of various synthetic strategies (i) Hydrothermal (ii) microwave irradiated (iii) solvothermal (iv) hot injection and (v) heating up method for synthesis of I–III–VI core and core/shell QDs [34].

**Table 1**

Characteristics of different synthetic methods of tertiary QDs.

Synthetic method	Advantage	Disadvantage
Solvothermal	Size control, minimal release of toxic vapours, control of morphology and crystallinity of the QDs	Requires the use of organic solvent
Hot Injection	Size control and good QY	An inert atmosphere is required, use of organic solvent not suitable for large scale synthesis
Heating up method	Effective for large scale synthesis and reproducibility	Carried out at high temperature and organic is solvent required
Hydrothermal	Cheap, environmentally friendly and water soluble	Low photoluminescence QY and poor size control
Microwave irradiated	Environmentally friendly, energy consumption is low, pressure and temperature can be controlled, rapid nuclear growth, reduced time of crystal formation and narrow size distribution	Low PLQY

**Table 2**

Overview of synthetic methods and applications of tertiary QDs.

Synthetic method	QD NP	Application	Reference no
Solvothermal	AISe <sub>2</sub>	Biological detection and labelling	[69]
	CIS/ZnS	<i>in-vivo</i> imaging	[70]
Hot injection	CISE/ZnS	<i>in-vivo</i> imaging	[71]
	CISE/ZnSe	Biolabelling, bioimaging	[72]
	AIS/ZnS	Bioimaging	[73]
Heating up method	CIS/Zn	bio detection	[74]
	AIS/Zns	<i>in-vivo</i> imaging	[36]
Hydrothermal	CIS	<i>in-vivo</i> imaging	[75]
	AIS/Zn	fluorescence imaging	[76]
Microwave irradiated	AIS	High contrast cell imaging	[77]
	CIS/ZnS	Biodetection and bio-imaging	[78]

applications they must be bonded to functional biomolecules such as proteins, enzymes, antibodies and nucleic acids [97].

Irrespective of the final use, the application of QDs in biological systems is dependent on their ability to undergo bioconjugation in a well-controlled and desired manner. An assembly that pairs a

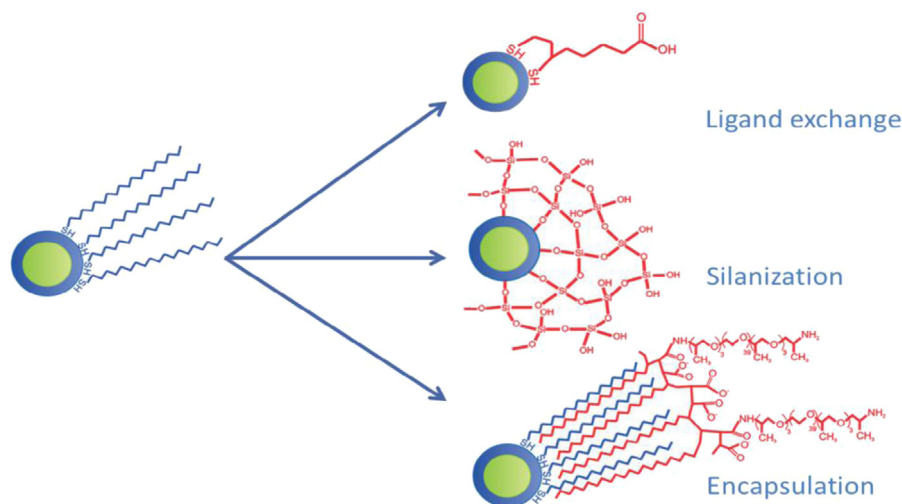


Fig. 3. Approaches to hydrophilization of QDs [96].

QDs to a biological molecule regardless of the chemistry of bonding is known as a QDs conjugate [98]. In biological applications of QDs, the biomolecule should be attached in such a manner that the inherent properties of the QDs will not be distorted. Bio-conjugation of biomolecules to QDs surfaces involves two main approaches: Covalent linking and non-covalent binding [96]. In covalent conjugation, molecules are coupled to the QDs surface or the ligand attached to the QDs with the help of cross-linking molecules with reactive functional groups. For conjugation of functional biomolecules to take place there must be different binding affinities. This include the use of bifunctional ligand such as mercaptopropionic acid (MPA) and DHLA which can join the QDs surface to the biomolecule including proteins (albumen, antibodies) and nucleic acids [99]. An appreciable number of possible reactions by which biomolecules can be bonded covalently with surface ligands of QDs have been described in literature [96, 98, 100]. They include bonding through biotin/streptavidin [101], 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-Hydroxysuccinimide (NHS) coupling [102].

Non-covalent conjugation strategy involves the electrostatic attachment between the biomolecule and QDs surface, and encapsulation or adsorption on the surface using engineered protein molecules. This approach involves the non-specific adsorption of molecules such as polymers, protein, enzymes and so on. Adsorption is made possible due to the large surface area of the QDs which enables the non-selective binding of the molecules independent of any functional attachment [80]. The mechanism of adsorption is based on electrostatic interaction with the QDs surface and oppositely charged biomolecules [101]. The choice of the method to use is based on certain properties of the QDs such as chemical composition, the presence or absence of ligands and active sites, size of the QDs and the chemical nature of the QDs [89]. Due to the large area to volume ratio, series of different biomolecule can be attached to a single QDs for multifunctioning. Several studies have shown that surfaces of ternary QDs conjugated with biomolecule in a well-controlled manner has the ability of binding, adsorbing and transporting drugs and protein. This, makes them good candidates for cancer management in relation to detection, drug delivery to mention a few. Tsolekile et al. [5] carried out the synthesis of TPPS4-CuInS/ZnS conjugates, results from the study showed an improved singlet oxygen quantum yield from 0.19 before conjugation to 0.69 upon conjugation (Fig. 4). In another study, Michalska et al. [103] synthesised ZCIS-peptide conjugate as nanoprobe for cancer imaging. The result from the study reveals that the conjugates was effective as fluorescence nanoprobes for selective labelling of HER2-positive cancer cells (Fig. 5)

## 5. Biomedical applications of ternary QDs

Core and core/shell QDs have found several applications in the field of biomedicine. A lot of studies have been carried out with regards to this [104–106]. Ternary QDs have been used for *in vivo* and *in vitro* imaging, detection/localisation, and treatment of cancer cells due to their unique properties such as broad absorption range in the NIR region, narrow emission, phototherapeutic abilities, large stoke shift etc. Precisely, they find applications in biosensing, targeted drug delivery system, bio-imaging and tissue engineering.

In this section we provided a general overview on certain biomedical applications of ternary QDs.

### 5.1. Biosensors

Fluorescent biosensors have been used for the effective diagnosis of diseases at the cellular level. In comparison with conventional organic dyes and fluorophores, QDs displays better photo-chemical and photophysical properties therefore, making it them a better candidate for fluorescence probes in biosensing applications. Ternary QDs are however considered more ideal due to their stability, low toxicity and affordability as against Cd based QDs. Fluorescence resonance energy transfer (FRET) QD-based biosensors have been widely used for the detection of biomolecules such as sugars, DNA, RNA, cancerous cells, cancer biomarkers etc. [107, 108]. Renuga et al. [109] synthesised CuInS<sub>2</sub>-based core multishell nanocrystals with low cytotoxicity and described their usefulness as an effective bioimaging probe and, as an attractive candidate as biological contrasting agent.

Immunoassay is important in regard to clinical diagnosis, testing and biomedical applications. QD-based sensing immunoassay showed detection of toxins, drug residues, chemical residues, and biomarkers. Xiong et al.<sup>b</sup> [110] used CuInS<sub>2</sub>/ZnS NPs as signal labels for a fluoroimmunoassay of the biomarker IL-6, and they were found useful in applications for biomarkers of cancer. Zhu et al. [111] used QD based immunoassay for the detection of water pathogens. Biotinylated antibody was coupled to the coated QDs and the result showed an improvement over the conventional staining kits due to better photostability of the QDs. They also observed a much-improved signal to noise ratio for the QDs. Anti-body conjugated QDs was used for multicolour cellular staining by Wu et al. [112] The study revealed that the QDs showed more resistance to photobleaching (oxidation process that makes them lose their fluorescence) relative to the

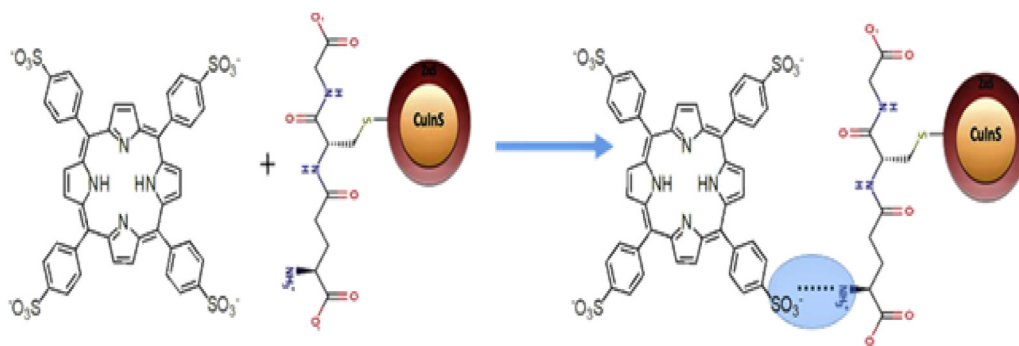


Fig. 4. Schematic illustration of the conjugation of CIS/ZnS and meso-tetra-(4-sulfonatophenyl) porphyrin (TPPS4) [5].

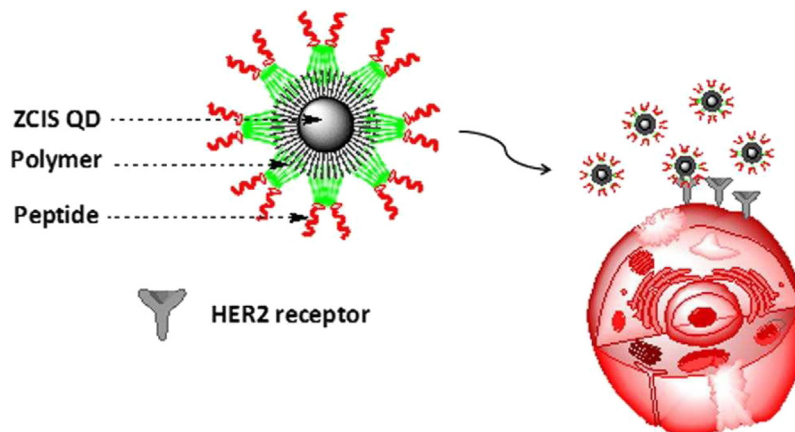


Fig. 5. Schematic illustration of  $\text{CuInZn}_x\text{S}_{2+x}$  QDs conjugated with peptide [103].

conventionally used organic dyes under constant illumination. Antibodies conjugated QDs can be applied for the detection of cancer biomarkers in immunoassays. More research work is still required to be carried out on the copper and silver ternary QDs to explore their potential towards biomedical applications.

## 5.2. Bioimaging applications

Imaging is an essential modality used in deciding an efficient cancer therapy. Imaging tools are important for diagnostics and therapeutic monitoring processes, and they have been used extensively in cancer therapy [113]. However, modern imaging techniques has some limitations. They are not very sensitive to small number of malignant cells and the inability to locate specific cancer cell surface markers. In a lot of cases, these cell surface markers assist in the diagnosis of cancerous growth. Therefore, it is important to improve on imaging techniques or develop very sensitive and biospecific imaging probes. Ternary QDs due to their excellent properties such as narrow tunable emission spectra, non-toxicity, photo-physical properties have been used in bio-imaging applications such as magnetic resonance imaging (MRI) and optical imaging [5,114].

### 5.2.1. Magnetic resonance imaging (MRI)

Unique features such as non-invasiveness and strong contrast in soft tissues makes MRI a valuable imaging tool for cancer diagnosis. MRI produces the 3D image of the human body without using an ionisation radiation. MRI images consist of two imaging modes; longitudinal weighed ( $T_1$ ) and transverse ( $T_2$ ) weighed images [17]. In order to achieve molecular imaging in MRI, targeted contrast agents are necessary. These contrast agents have the ability of speeding up the  $T_1$  and  $T_2$  relaxation rate in cancer

cells which in turn increase the contrast between normal and cancer cells. Metallic doped magnetic ternary I–III–VI QDs are widely used as contrast agents in MRI measurements due to their absorption in biological window and fluorescent transitions. In their work Yu et al. [115] prepared Gd doped CIS/ZnS QD using the hot injection method and used it as a biomodal bioimaging nanoprobe. The results showed the doped CIS/Zn QDs produced an enhanced MRI contrast while still exhibiting strong PL emission. Furthermore, Yang et al. [116] in their study ascertained that Gd (III) chelate conjugating CIS QDs can enhance NIR fluorescence and MRI imaging.

### 5.2.2. Optical imaging

In biomedical research, optical imaging is important in providing *in vivo* and *in vitro* information with high resolution. This imaging tool can provide multiple images thereby giving it usefulness for surgery and endoscopic processes. It is also employed for image guided surgical operation of tumours and detection of cancer cells. Due to their unique properties such as high QY, high resistance to photobleaching and long photoluminescent lifetime, ternary QDs can be used for targeted fluorescence imaging where tissues or cells are labelled with ternary QDs. This is applicable to both *in vivo* and *in vitro* processes. Regulacio et al. [117] in their study synthesised luminescent  $\text{AgInS}_2$ -Zn QDs (ZAIS), the synthesised QDs exhibited long fluorescence lifetimes, optical and colloidal stability in physiologically relevant pH values with a relatively low cytotoxicity and has high potential for use in biological labelling. The authors demonstrated that

the synthesised QDs when attached to baculoviral vectors can effectively enter and label the cells. This is an indication of its possible application in monitoring the transduction efficiency in baculovirus-mediated gene therapy. Fahmi and Chang [118] synthesised a double layer (alkyl-capping AgInS<sub>2</sub>-Zn) QDs, the alkyl layer consists of terminal groups (carboxyl and thiols) which served as reactive sites for other materials. The resultant DL-alkyl ZAIS QD was conjugated with folate for staining Human liver (HEPG<sub>2</sub>) and human breast (MCF-7) cancer cells. Confocal imaging revealed the folate conjugated ZAIS QDs were successfully docked at the tumour site. PEG conjugated Zn-doped AgInS<sub>2</sub> QDs displayed good water stability in water and PBS. When coated with silica, the cell imaging demonstration of the resultant material was successful [119]. Liu et al. [120] in their study found peptide conjugated CISe/ZnS QDs to be good tumour targeting imaging probes.

More research work is still required in the *in vivo* and *in vitro* applications of CIS/ZnS, CISe/ZnS, AIS/ZnS, AISE/ZnS QDs [34]. Improvement in technology and instrumentation reveals the limitations of each of this imaging techniques. However, solutions to these limitations are being provided from time to time as more researches have been carried out.

### 5.3. Drug delivery

In cancer therapy, the effectiveness of a drug is measured by its ability to deliver the appropriate quantity of the drug at a controlled rate and time to the desired site. Toxicity, poor targeting and non-selectiveness are the side effects accompanying the use of anti-cancer drugs [121]. Ternary QDs base drug delivery system ensures the release of a drug at the particular site or organ at a controlled rate which is far more preferable over the conventional uncontrolled release throughout the body. Increased capacity for drug loading, controlled release profile and improved therapeutic index of the drugs makes QDs a good candidate for drug delivery systems [122]. Using certain coupling strategies, the QDs can be functionalised by a range of cancer-targeting moieties such as anti-cancer drugs, folic acid and aptamer. QDs drug delivery system have unique ways of releasing drugs for effective target drug delivery. At the beginning it comes as an outbreak release and then shows a constant release over a stretch of time. This means the efficiency of the drugs can be maintained over a long stretch of time, at limited concentration, fewer intervals, and lower doses thereby reducing the side effects of these drugs on the patient [123]. For effective and concise target delivery, monitoring of pH, temperature and biological reactions is very important.

For a QDs to be efficient in drug delivery systems it should have the following properties [124]: (i) It must not interact with the drug (ii) the drug loading ability and encapsulation efficiency should be high (iii) long residence time *in vivo* (iv) excellent biocompatibility and should be non-toxic (v) good mechanical strength, stability and shape. Several works have been reported on drug delivery systems using QDs; Wu et al. [125] reported the covalent coupling of anticancer drug, methotrexate (MTX) to the surface of AgInS<sub>2</sub>/ZnS QDs. Result from the study reveals that the QD-MTX conjugate displayed good biocompatibility in MTT assays and showed negligible cytotoxicity in HeLa cells. CIS QDs bonded with doxorubicin (DOX), an anti-cancer drug was reported to effectively deliver DOX to the targeted cancer cells [59]. In another study, Girma et al. [126] described the conjugation of synthesised CuFeS<sub>2</sub> NPs with anti-cancer drug cisplatin (IV). The study revealed that the CuFeS<sub>2</sub> NPs drug conjugate reduced the side effect of the drug on normal tissues.

### 5.4. Photo-therapeutic applications

The aim of biomedical researchers is to develop alternative methods for cancer treatment that are safe, efficient and cost effective. Photo-therapeutic methods such as photodynamic therapy (PDT) and photo-thermal therapy (PTT) are preferred due to the following reasons; (i) surgery is not required (ii) non-invasiveness (iii) it is cost effective and (iv) little or no side effect [127]. Photodynamic therapy is a treatment procedure that uses a photosensitiser selectively localised to a target tissue followed by light irradiation. The photosensitiser has the ability to change molecular oxygen from the triplet oxygen to the singlet state (<sup>1</sup>O<sub>2</sub>) when exposed to single wavelength light. The energy released for the transition from the triplet ground state to the singlet excited state leads to the formation of by-products (peroxide, radicals) and results in the destruction of surrounding tumours and cancer cells via the singlet oxygen. Optical properties of QDs have been improved by the introduction of ternary QDs. Due to this improvement, these QDs penetrates more into the tissues as they do not experience much barrier from blood, pigments and melanin [128]. PTT photo-therapeutic technique involves the generation of hyperthermia from near infra-red (NIR) photoabsorbers for the destruction of surrounding cancer cells. This technique destroys cancerous cells in primary tumour or when combined with other therapeutic technique. The use of QDs as a therapeutic agent in PTT offers advantages such as spatiotemporal selectivity, rapid treatment, affordability and minimal side effect [17,129]. Fig. 5 shows a schematic illustration of the use of ZCIS for imaging and therapy applications. Other PTT agents have been employed including; gold nanoparticles [130,131] due to its ability to enhance the effect of radiotherapy on tumours, carbon nanorods [132] due to their excellent light to heat energy conversion and nano scale metal organic particles (NMOPs) [133] (see Fig. 6).

## 6. Toxicity of ternary I-III-VI QDs

Toxicity of QDs has been a major challenge over the years (Zhu et al. 2020). The level of toxicity would determine the intrinsic toxic behaviour of the QDs. The surface modification, the stability of the ligands, pharmacokinetics, method of administration etc. are to be cautiously considered [135]. Furthermore, it is important that the QDs should be eradicated from the body as soon as possible after administration.

In spite of all the progress and achievement in the study of QDs, their toxicity is not yet clearly understood. *in vitro* and *in vivo* studied has been carried out at various concentrations, size and structure, exposure time etc. thereby making it difficult to predict the toxic nature of newly synthesised QDs. Toxicity of QDs depends on certain properties such as size, charge, concentration, outer functional group, and oxidative and photolytic activity [136, 137]. The ability to eliminate QDs as fast as possible from the body is a major factor in determining the clinical application of any *in vivo* treatment. Studies have shown that QDs with a size < 5 nm can be removed through renal pathways, while those within the range of 10–20 nm can be consumed by the liver and those with sizes > 200 nm can be filtered through the reticulo-endothelial system [138–140]. On introduction to the cancer cell, the QDs spread around the cell, they get consumed by the cancer cell, and localised intracellularly so that therapeutic action can occur [17].

However ternary I-III-VI QDs have exhibited lower toxicity over time as several studies have attested to it. Shinchi et al. [141] observed low toxicity of AIS/ZnS NPs when attached to sugar-chain-fluorescent NPs for imaging NPs and biosensing applications. The study further reveals the suitability of this QDs for bioimaging



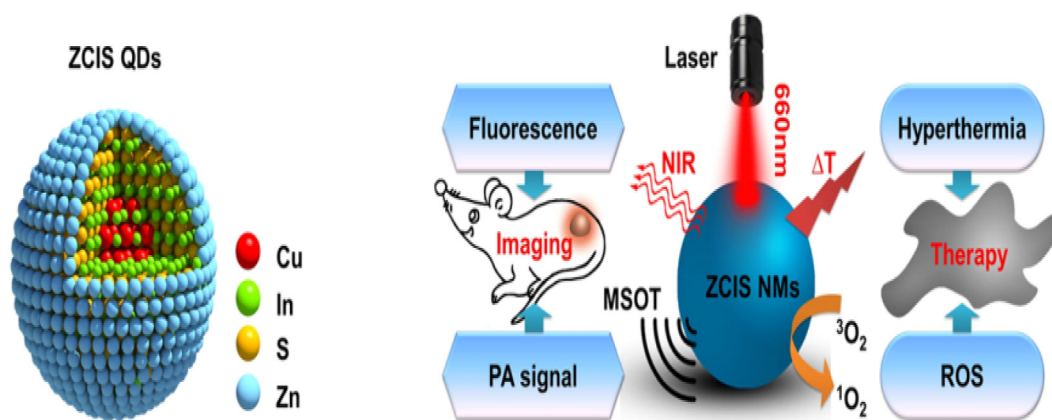


Fig. 6. Scheme illustration of ZCIS QDs used as theranostic nanomedicines with intrinsic fluorescence/MSOT imaging and PTT/PDT therapy abilities [134].

applications. CIS/Zns QDs have been found to exhibit minimal *in vivo* local toxicity when adult zebra fish were exposed to the freshly prepared QDs. Girmal et al. [142] in their study also observed reduced local toxicity when  $\text{CuFeS}_2$  was injected into an adult zebra fish. Their desirable properties such as tunable photoluminescence, high PLQY, high chemical and photo stability might have contributed to this [17,143].

Ternary QDs-drug conjugate can be easily taken up and absorbed by the body cells when applied due to their optical and structural properties such as excellent luminescence, direct band gap, non/low toxicity, large stokes shift [28,144]. Also, conjugate system has the ability of delivering the cancer drug to where it will be most effective and quick elimination without harming the healthy cells [9].

Conclusively, more work studies are still required to fully comprehend the toxicity of ternary I–III–VI QDs. Study on experimental conditions, dosages, experimental cell lines for *in vitro* studies, and animal models for *in vivo* studies should shed more light on the toxicity of these QDs as they are not totally benign to living systems.

## 7. Conclusion and future perspective

In this review, we discussed the synthesis, properties and applications of ternary QDs with major focus on the recent development of ternary I–III–VI core/shell QDs for cancer management. The synthetic methods, surface modification, bioconjugation and applications relating to cancer treatment such as biosensing, bioimaging, drug delivery, diagnosis and therapy have been described. Ternary QDs has gained much attention among researchers due to their low toxicity (devoid of Cd and Pb atoms), tunable emission and broad absorption spectra from the range of UV to near IR, higher QY and large stoke shift. These excellent properties enable their application in cancer phototheranostic procedure such as PDT, PTT, bioimaging and biosensors. The use of these non-toxic ternary QDs as photosensitisers in PDT has overcome the problem of poor tissue penetration during cancer treatment due to their ability to act as a good electron acceptor and donor to produce ROS and  $^1\text{O}_2$  for PDT [145,146]. The excitation wavelength in the NIR range exhibited by I–III–VI QDs enables deeper penetration into tissues when applied in PDT.

QD nanoprobes have also been considered suitable for biosensors, MRI and drug delivery systems in the therapy and management of cancers. Furthermore, in addition to careful material composition, bioconjugation of ternary QDs with engineered surface material such as protein, peptides etc. can lead to new biomedical applications. As the biological application of QDs is expanding as the days go by, effort should be intensified towards

the design of multifunctional QDs for multipurpose therapeutic applications. For example, developing a QD that can both serve as a contrasting agent together with photodynamic therapy would be of immense benefit. The mechanism involved in the synthesis procedure still needs to be understood better so that properties such as morphology, quantum yield and photoluminescence could be effectively controlled. Even though ternary QDs shows low toxicity when compared to binary QDs, toxicity can further be reduced using surface modification materials such as engineered protein, biocompatible polymers etc. Research should also focus on the design of QDs for the effective therapeutic control and monitoring of malignant cells. The development of novel non-toxic ternary QDs will definitely create the possibility of challenging the frontier of present cancer research and contribute to the success of clinical trials. Existing synthetic strategies and routes can be employed to achieve the synthesis of other groups of ternary I–II–VI QD NPs in the nearest future.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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