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Review Article

Emerging Roles of Green-Synthesized Chalcogen and Chalcogenide Nanoparticles in Cancer Theranostics

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The last few decades have seen an overwhelming increase in the amount of research carried out on the use of inorganic nanoparticles. More fascinating is the tremendous progress made in the use of chalcogen and chalcogenide nanoparticles in cancer theranostics. These nanomaterials, which were initially synthesized through chemical methods, have now been efficiently produced using different plant materials. The paradigm shift towards the biogenic route of nanoparticle synthesis stems from its superior advantages of biosafety, eco-friendliness, and simplicity, among others. Despite a large number of reviews available on inorganic nanoparticle synthesis through green chemistry, there is currently a dearth of information on the green synthesis of chalcogens and chalcogenides for cancer research. Nanoformulations involving chalcogens such as sulfur, selenium, and tellurium and their respective chalcogenides have recently emerged as promising tools in cancer therapeutics and diagnosis. Similar to other inorganic nanoparticles, chalcogens and chalcogenides have been synthesized using plant extracts and their purified biomolecules. In this review, we provide an up-to-date discussion of the recent progress that has been made in the plant-mediated synthesis of chalcogens and chalcogenides with a special focus on their application in cancer theranostics.

1. Introduction

The complexity of successfully eradicating cancer cells without affecting normal cells has been a challenge with cancer chemotherapy. This has resulted in extensive research to develop drug delivery vehicles capable of selectively targeting cancer cells. In the past two decades, tremendous progress has been made in developing nanoparticles (NPs) as delivery agents for anticancer drugs, peptides, nucleotides, antibodies, and proteins in cancer therapy [1–3]. NPs are usually below 100 nm in size and hence possess efficient permeation ability and a large surface area to volume ratio, allowing functionalization with small molecules such as cofactors, metal ions, and polymers [4]. This is critical for their role in drug targeting, gene delivery, cancer diagnosis, and other biomedical applications [5]. NPs display outstanding physical and chemical properties, which vary according to their shape and size. The different forms of NPs synthesized thus far include nanorods, nanoshells, nanocages, nanoprisms, nanoclusters, nanowires, and nanostars. The dimension and morphology of NPs depend on their precursor materials, method, and synthesis conditions, which in turn affect the functionality of the NPs.

NPs can be made from materials such as metals, ceramics, semiconductors, organic polymers, inorganic polymers, and lipid biopolymers. Of particular interest in cancer research are metallic NPs, semimetals, and lipid biopolymers, due to their small size, ease of functionalization, and biocompatibility. While metallic NPs have long been employed in cancer therapy, semiconductors, especially chalcogens and chalcogenides (semiconductor nanocrystal with quantum confinement property), are beginning to gain significant attention [6, 7]. Chalcogens derive their name from the Greek words "chalkos" and "genes," meaning "ore" and "born," respectively [8]. They are traditionally associated with elements belonging to group sixteen of the periodic table such as sulfur, oxygen, selenium, tellurium, polonium (a radioactive metalloid), and livermorium (a

synthetic element) [8]. Sulfur, selenium, and tellurium are the most studied of these metalloids as nanocomposites with potential for cancer therapeutics. Sulfur and sulfur-containing compounds have been traditionally used as fertilizers, antimicrobial, and antifungal agents. However, at the nanoscale, sulfur possesses interesting properties such as biodegradability, nontoxicity, and biocompatibility, with significant applications in catalytic bioremediation and as antimicrobial and anticancer agents [9–12]. Selenium is a metalloid with chemopreventive properties that functions physiologically as a micronutrient. Its importance also stems from its ability to participate in the de novo synthesis of selenoproteins and enzymes. So far, selenium nanoparticles have been well studied for their biocompatibility, optical, and photoconductive properties [13]. Tellurium is derived from the Latin word "tellus," which means Earth. With chemical and structural relationships to those of selenium, tellurium also demonstrates appreciable pharmacological activities; however, unlike selenium, it is not an essential mineral and is not critical for any biological activity in humans. It exists in different oxidation states as telluride (–2), elemental tellurium (0), tellurite (+4), and tellurate (+6) [14].

Chalcogens such as sulfur, selenium, and tellurium combine chemically with other metals at the nanoscale to form alloys known as chalcogenide NPs. They can be grouped as mono-, di-, and polychalcogenides depending on the number of different chalcogens they contain. Chalcogenides have also been grouped as binary or ternary nanocrystals [15]. The former consists of two distinct elements (e.g., Cu_2Se and ZnS) combined in the same or different ratio, while the latter is an aggregation of three distinct elements (e.g., $CuInSe_2$ and $CuGaSe_2$). Chalcogenide NPs synthesized thus far include PbS, PbSe, CdSe, PbTe, PbSSe, PbSeTe, PbSTe, Ag_2S, Ag_2Se, Bi_2Se_3, ZnS, ZnSe, CuS, CdTe, and CdS.

Structurally, chalcogenide nanoassemblies exist in the form of nanoclusters, NPs, and quantum dots. Similar to other nanoassemblies, their properties depend on size and morphology. Generally, these NPs are synthesized using top-down and bottom-up approaches. The former involves reducing a bulky starting material by lithographic techniques into small particles, while the latter involves the assembly of smaller units into nanosized particles either by chemical or biological approaches (biogenic synthesis) [16]. Chemical synthesis of NP includes the dispersion of preformed polymers, polymerization of monomers, and ionic gelation method [17]. These techniques are usually swift and require capping agents to stabilize the NPs. In spite of its efficiency, the toxicity of chemical reductants and their side products generated during the process constitute a challenge for biological applications, necessitating the use of eco-friendly biological agents for NP synthesis.

While there have been a large number of reviews on NP synthesis via green chemistry, the green synthesis of chalcogens and chalcogenides remains under-reported despite its growing potential in recent years. Over the years, several biogenic agents have been explored to synthesize chalcogens and chalcogenides (Figure 1). This review explores the current knowledge on the green synthesis of chalcogens and chalcogenides with respect to their potential in cancer theranostics.

2. Optical and Electronic Properties of Chalcogenide Quantum Dots

Chalcogenide NPs have attracted significant research interest because of their optical and electronic properties. This category includes quantum dots (QDs), which are metalloids with particle size diameters of 1–20 nm, and size-dependent tunable photoemission properties [18, 19]. In a semiconductor, at the highest energy level, the electron combines with the hole by Coulomb's force to form excitons and returns to the ground state [20]. During this process, photoluminescent energy is emitted at an intensity that corresponds to the bandgap energy, confinement energy, and energy of bound excitons (equation (1)). The energy levels can be modelled using a particle in a box [21].

$$E = Ec + Eb + Ee, \tag{1}$$

where E = total energy, Ec = energy of confinement, Eb = bandgap energy, and Ee = energy of excitons. The energy of confinement within a three-dimensional box has been given as follows:

$$Ec = \frac{h^2\pi^2}{2x^2}\left(\frac{1}{m_h} + \frac{1}{m_e}\right), \tag{2}$$

where m_h, m_e, and x correspond to the mass of the hole, the mass of free electron, and radius of the quantum dot, respectively. The energy of confinement can be controlled by varying the particle size. At reduced masses, the equation becomes

$$Ec = \frac{h^2\pi^2}{2\mu x^2}, \tag{3}$$

where μ = reduced mass.

More so, the energy of the excitons is given as "Coulomb's energy of electron-hole interaction" [22] expressed by the following equation:

$$Ee = -\frac{1}{E^2{}_x} \times \frac{\mu}{m_e} \times R_y \quad \text{or} \quad -\frac{1.8e^2}{4\pi\varepsilon\varepsilon_0 r}, \tag{4}$$

where E_x and R_y connote size-dependent dielectric constant and Rydberg's energy, respectively.

Combining the equations, the total energy of the quantum dot is given as follows:

$$E = Eb + \frac{h^2\pi^2}{2x^2}\left(\frac{1}{m_h} + \frac{1}{m_e}\right) - \frac{1.8e^2}{4\pi\varepsilon\varepsilon_0 x}. \tag{5}$$

In a three-dimensional quantum box, the band and excitons energy are infinitesimal and can be ignored [23]. The energy of the photon is given as Eigen energy expressed in 3D time-harmonic Schrodinger's equation as follows:

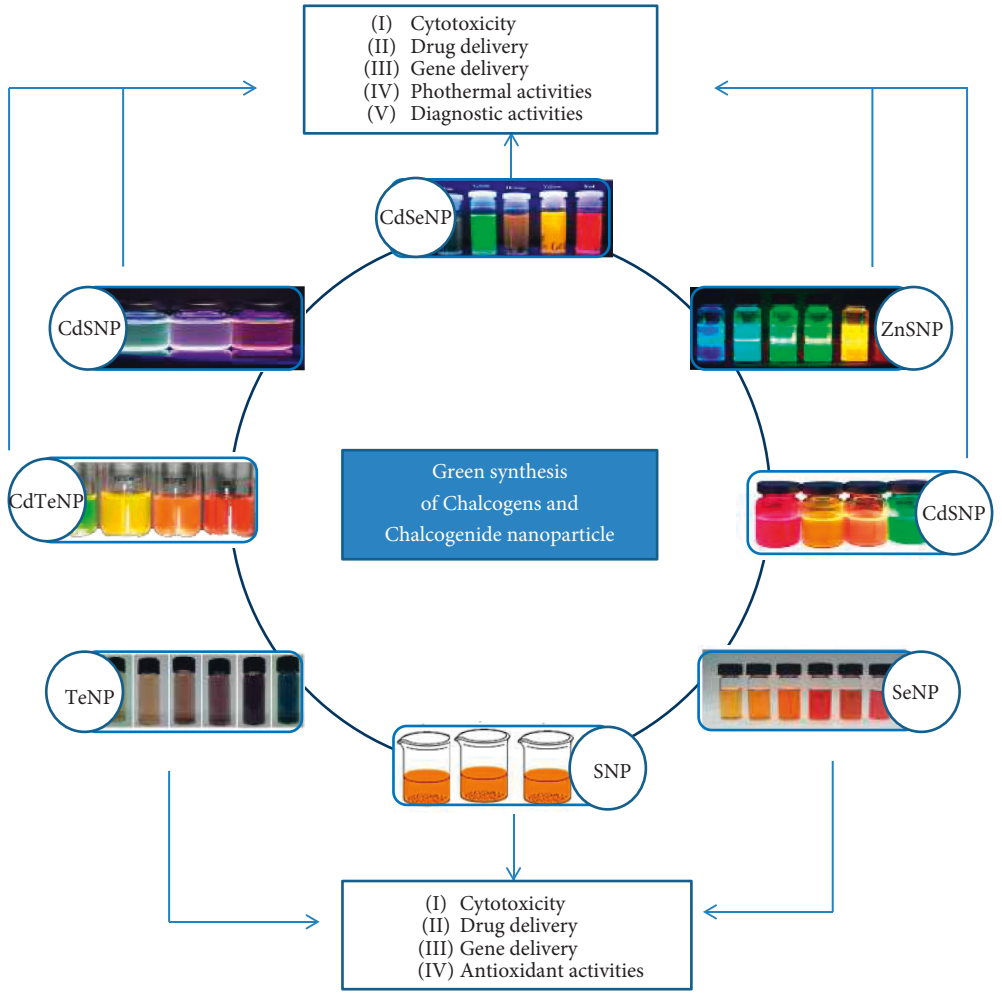

Figure 1: Green synthesized chalcogens and chalcogenide nanoparticles and their applications. NP = nanoparticle, Cd = cadmium, Se = selenium, S = sulfur, Zn = zinc, and Te = tellurium.

$$E_i = \frac{h^2\pi^2}{2m}\left(\frac{n_x^{\,2}}{l_x} + \frac{n_y^{\,2}}{l_y} + \frac{n_z^{\,2}}{l_z}\right). \quad (6)$$

The above equations are theoretical assumptions that describe the electronic transitions of semiconductor quantum dots. They highlight the role of quantum confinement in the electronic behaviour of quantum dots [22]. Quantum confinement varies inversely with the size of quantum dots; hence, larger particles do not show the quantum confinement effect [24]. The confinement of charge carriers (such as excitons) in a small region of space less than the carrier's wavelength results in a unique quantization effect [25–27]. Quantum dots with sizes smaller than the exciton Bohr radius have an increased bandgap and total emission energy. Quantum confined NPs show varying photoemission spectra, which are dependent on their size. By tuning their sizes, they can produce fluorescent emissions of different wavelengths (400–700 nm; Figure 2). QD with very small dimensions have the high surface area to volume ratio and reflect a blue photoluminescent shift, while larger QDs show a redshift [28]. It is therefore expedient to ensure a size-controlled synthesis of chalcogenide, which would show desirable optical and electronic properties.

3. Biogenic Synthesis of Chalcogen and Chalcogenide Nanoparticles Using Plant Extracts

This approach involves the use of plant materials in form of plant juice or solvent extracts from the plant material. Plants contain different secondary metabolites that give them the ability to reduce heavy metals and other metallic ions. The use of plant juice and aqueous extracts has several advantages over other conventional biogenic syntheses approaches because it does not require a tedious downstream technique for extraction and purification of the synthesized NPs. The safety and ability to serve as a reducing and a capping agent are added to the list of properties that make this approach a preferred choice [30]. There are many NPs in this category that have found applications in various fields of biotechnology [31].

Different parts of the plant, from the more common leaves, fruit, and bark to the less common buds, seeds, peels,

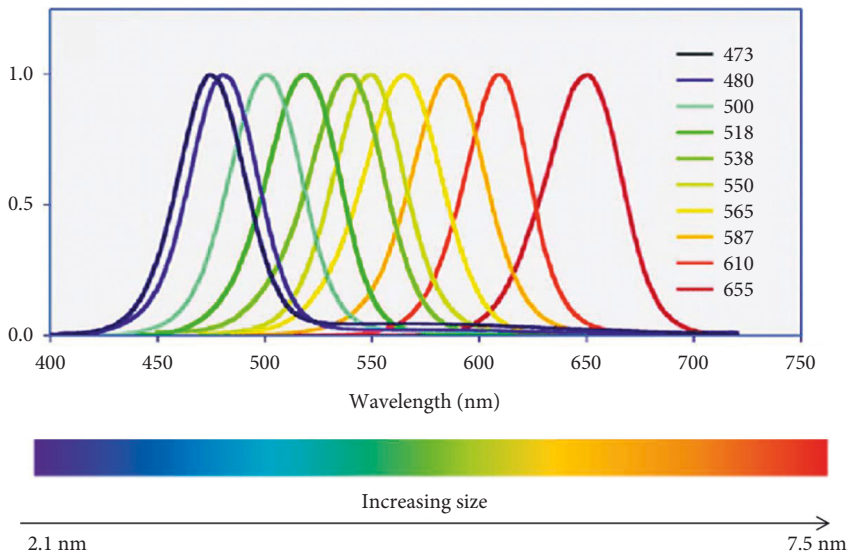

Figure 2: Size-tunable photoluminescence spectra of quantum dots (adapted from [29]).

and pulps, have been used to synthesize NPs [32]. *Capsicum annuum* extracts have been used to reduce selenite to SeNPs [33], while leaf extracts of *Azadirachta indica*, *Catharanthus roseus*, and *Mangifera indica* demonstrated efficacy in the reduction of sulfur ions in sulfur compounds to produce sulfur NPs (SNPs). The underlying reaction appears to proceed via the formation of a stable complex between sulfur ions and the plant phytoconstituents, possibly mediated by electrostatic interaction. Electrons are transferred from the organic molecules to reduce S^{2-} to SNPs [34]. Generally, the suitability of plants as reductants in the synthesis of NPs is a function of the antioxidant content of the plant parts.

The first successful plant extract-mediated synthesis of quantum dots was reported by Borovaya et al. (2014), using the *Linaria* spp. root extract to reduce cadmium sulfate to CdS NPs (Figure 3). The CdS nanoparticles produced were stable for about 10 days [35]. Following this study, other chalcogenide quantum dots, such as CdTe, CdSe, and ZnS, were synthesized using plant extracts [36–38]. Recently, a three-step mechanism of CdSe synthesis was proposed: (1) extract-mediated reduction of metallic ion to zero-valent state nanocrystal by intermixing metal salt precursors with plant extracts, (2) spontaneous coalescence between nanocrystals known as Ostwald ripening, and (3) preferential alignment of nanocrystals along regions of phase transformation [39]. While proteins, flavonols, phenols, glycosides, and other phytochemicals are being examined for their critical role in the reduction and capping of the NPs, further studies are necessary to understand the plant-based chalcogenide synthesis process [38, 40].

4. Green Synthesized Chalcogens and Chalcogenides with Anticancer Potential

Several chalcogens and chalcogenides have shown outstanding physicochemical and pharmacological properties crucial for cancer prevention and chemotherapy. While these properties have been attributed to the role of the metalloid constituents, the morphology, and the size of the particles, it should be noted that the green syntheses of the NPs confer additional advantages, since the metabolites from the plants may sometimes also act as capping agents [41]. We will look further at some of the potential anticancer applications of these green synthesized NPs (Table 1).

4.1. Green Synthesized Chalcogens. Chalcogens, predominantly sulfur, selenium, and tellurium, have been synthesized through green chemistry. Although they have certain similarities in their electronic structure, these elements have distinctive properties that confer selective advantages in cancer chemotherapy.

4.1.1. Selenium. Green SeNPs have demonstrated antimicrobial, photocatalytic, antioxidant, and anticancer activities. Their antioxidant effects are linked to their sequestration capacity of Se at the reactive oxygen species (ROS) release site, thus preventing the release of free radicals that mediate DNA oxidative damage [13]. The significant role of NP size in free radical scavenging suggested that SeNPs with smaller sizes possess better scavenging activity compared to larger NPs [52]. The anticancer mechanism of SeNPs has been linked to their ability to bind to metal ions and intracellular proteins. For instance, SeNPs bind to Cu^{2+} and DNA forming a ternary complex leading to the reduction of Cu^{2+} to Cu^{+}, which is later reoxidized to generate reactive oxygen species and induce cell death. This cell death mechanism has been described as cancer-specific since copper (Cu) ions (which are more abundant in cancer cells) are critical for generating the free radicals responsible for oxidative damage [53]. SeNPs also interact with intracellular proteins involved in glycolysis and mitochondrial activity, as cellular oxidative stress and mitochondria dysfunction were observed prior to apoptosis induction in human melanoma (A375) cells following exposure to SeNPs [54]. SeNPs also

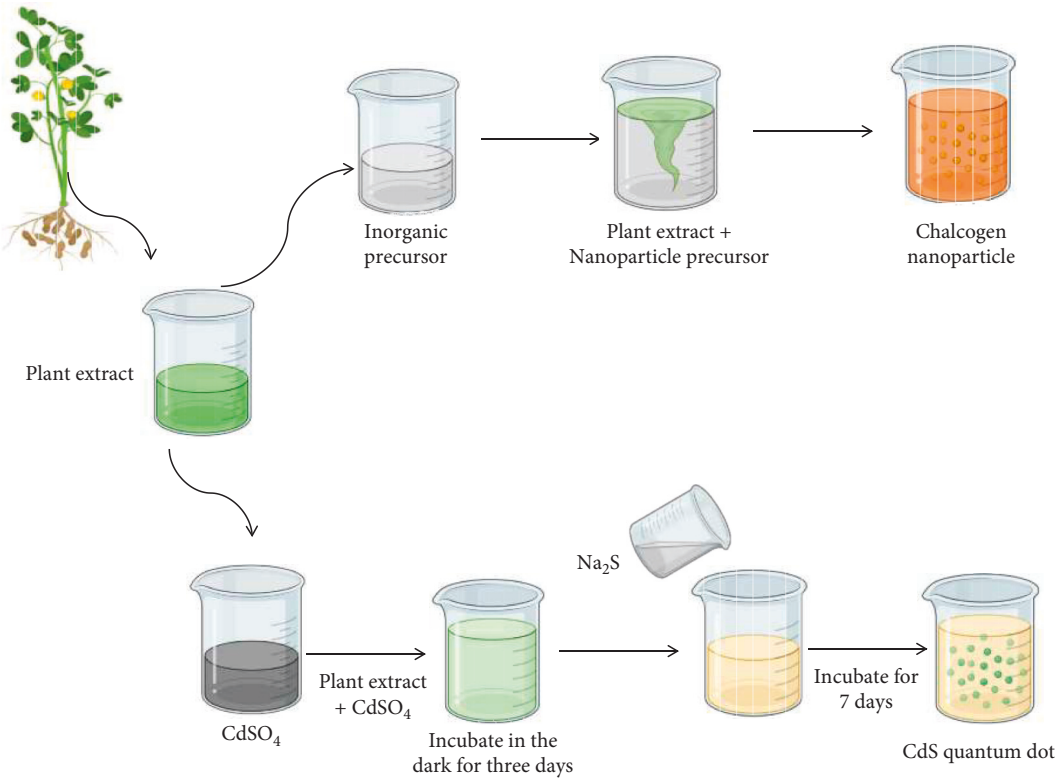

Figure 3: Illustration of the protocol involved in the synthesis of chalcogens and chalcogenide nanoparticles.

upregulated proapoptotic Bcl-2 and downregulated anti-apoptotic Bcl-2 expression in HepG2 cells [55]. These observations suggest that the anticancer role of SeNPs is via ROS-dependent mitochondrial-mediated intrinsic apoptosis [41]. SeNPs also stimulate p53 release and induce caspase-8 expression, indicating activation of extrinsic apoptosis. Furthermore, SeNPs also mediate tumor cell necrosis and autophagy [56, 57]. In addition to their cytotoxic activity, selenium nanoparticles also displayed a chemopreventive action by inducing cell cycle arrest in human umbilical vein endothelial cells [58]. Biogenic SeNPs have also been reported to possess immune-stimulatory functions [59]. The exposure to SeNPs promoted the inhibition of cancer cell migration via inhibition of annexin A2, a pleiotropic protein involved in cancer cell motility. They also inhibited the expression of matrix metalloproteinase, which is involved in tumor metastasis [60]. The anticancer activity of SeNPs is summarized in Figure 4.

4.1.2. Tellurium. Te and its compounds (including inorganic tellurides, organo-Te, and Te complex) have shown significant antimicrobial and anticancer activities [61]. Te has been synthesized as nanorods, nanodots, nanowires, and nanocubes [62–64]. These NPs have demonstrated antioxidant, antimicrobial, and anticancer activities similar to those of the element. The use of biological materials such as microorganisms and plants in the synthesis of Te nanoparticles is gaining attention. Besides these favorable biological activities, evidence has suggested that the NPs synthesized through biogenic routes offer the additional advantage of selective toxicity compared to their chemically synthesized counterparts [42, 65, 66]. Similar to Se, Te also serves as a free radical scavenger [67]. However, tellurides have shown more antioxidant activities than Se [68]. Their low electronegative potential, ability to donate electrons, radical trapping tendencies, and glutathione peroxidase-mimicry nature are some of the likely reasons for its antioxidant function [69, 70].

The mechanism of TeNP cytotoxicity has not been fully unravelled, but studies indicate that it might be related to its ability to bind cellular protein and DNA, causing oxidative and DNA damage leading to cell death via mitochondrial-dependent pathways [71, 72] (Figure 5). Also, it is suggested that the biocompatibility of biogenic TeNPs might be dependent on the nature of capping biomolecules. This was elaborated in a comparative study involving TeNPs synthesized with lemon (LEM-TeNPs), lime (LIM-TeNPs), and orange extract (OR-TeNPs) [42]. Although the available research on the anticancer potential of biogenic TeNPs is still very limited to draw any conclusions, they show promising prospects worthy of exploration.

In spite of these pharmacological activities, the use of Te and its compounds has not been fully explored in drug design due to their toxicity [73, 74]. They can interact strongly with mitochondrial enzymes and proteins through the sulfhydryl group of cysteine, causing neurodegeneration [75]. Te, due to its similarity to Se, also interacts with

Table 1: Green synthesized chalcogen and chalcogenide nanoparticles with anticancer properties.

Plant and extract	Nanoparticle	Size (nm)	Shape	Activity	Ref
Orange – Citric juice	TeNPs	2–15	Rods	Anticancer effect in human melanoma cells (≤50 μg/ml)	[42]
Lemon – citric juice	TeNPs	100–200	Cubic	Anticancer effect in human melanoma cells (≤50 μg/ml)	[42]
Lime – citric juice	TeNPs	100–200	Cubic	Anticancer effect in human melanoma cells (≤50 μg/ml)	[42]
Fenugreek – seed extract	SeNPs	50–150	Oval	Dose-dependent (25–100 μg/ml) cytotoxicity in human breast-cancer cells (MCF-7)	[43]
Allium sativum – garlic clove extract	SeNPs	40–100	Spherical	Better biocompatibility in Vero cells than chemically synthesized SeNPs	[44]
Hawthorn – fruit extract	SeNPs	113	Spherical	Antitumor activity in HepG2 cells Induced intracellular oxidative stress and mitochondrial dysfunction to initiate apoptosis via the mitochondrial pathway	[41]
Ceropegia bulbosa – tuber extract	SeNPs	52.5 ± 3	Spherical	Higher cytotoxicity in MDA-MB-231 cells compared to normal breast cells	[45]
Arabinogalactan from *Larix principis-rupprechtii*	SeNPs	94–156	Spherical	Significant dose-dependent inhibitory activity (10–100 μg/ml) in A549, HepG-2, and MCF-7 cells via apoptosis	[46]
Drumstick – leaf extracts	SeNPs	23–35	Spherical	Highest cell inhibition in A549 cells Effective against Caco-2, HepG2, and MCF-7 cells	[47]
Urtica dioica – leaf extract	SeNPs	21.7–83.6	Spherical	Significant anticancer activity against HepG2 cells Nontoxic to Vero cells	[48]
Aloe vera – leaf extract	TeNPs	20–60	Spherical	Cytotoxicity in HDF and melanoma cells	[49]
Ocimum tenuiflorum – inflorescence extract	Ag@SeNPs	33.1 ± 2.7	Near spherical	Dose-dependent cytotoxicity in HEK293 and MCF7 cells	[50]
Stevia rebaudiana – leaf extract	ZnS NPs	8.35	Spherical	Cytotoxic to MCF-7 cells	[37]
Camellia sinensis – leaf extract	CdS	2–5	Spherical	Arrested A549 cell growth at the S phase of the cell cycle	[51]

selenoenzymes such as glutathione peroxidase, thus lowering cellular redox modulatory activities and causing conditions of oxidative stress that mediate cellular damage [76]. Te intake in patients has also been associated with nausea, vomiting, and bad breath [77]. However, their synthesis via green chemistry offers NPs with lower toxicity and interesting anticancer properties that should be explored in future studies.

4.1.3. Sulfur. Sulfur (S) has long been employed as an antimicrobial for treating different bacterial and fungal infections and in agriculture to produce fertilizers, pesticides, and fungicides. The emergence of SNPs has led to the discovery of additional properties apart from that inherent in sulfur. SNPs possess exceptional reactivity and properties such as antibacterial, antifungal, antioxidant, anticancer, and wound healing. Most reports of SNPs synthesis have however focused on the use of chemical methods such as membrane assisted precipitation, sodium polysulfide hydrolysis, ultrasonication, supersaturated solvent methods, electrochemical methods, eggshell membrane template methods, liquid-phase chemical precipitation, surfactant-assisted method, microemulsion method, solvent-free method, organic and inorganic polysulfide decomposition method, PEG-600, ethanolamine-assisted method, and PEG-200 in the sublimed sulfur technique [78–80]. These methods have achieved excellent SNP yield, controlled size and shape, and high NP purity in recent years [78–80].

Despite these advantages of chemically synthesized SNPs, the challenge of environmental compatibility of reactant and side products, reaction time, and stringent reaction conditions have raised serious concerns resulting in a recent paradigm shift toward biologically synthesized SNPs. Plants and fungi have been reported to efficiently synthesize highly stable SNPs. Most studies on the synthesis of SNP have however focused on the antimicrobial action of SNPs rather than their anticancer activity [81, 82].

Sulfur has been shown to possess onco-protective activity in many bioactive compounds in plants by modulating redox imbalances (Figure 6) [83, 84]. Furthermore, its cytoprotective antioxidant potential in *in vivo* mouse models has been reported [85]. This could be linked to its presence in amino acids such as methionine and cysteine and in the formation of disulfide bridges in tertiary protein structures [85]. These amino acids have also been shown to scavenge free radicals [86]. Methionine has been reported to be an antioxidative gatekeeper in many proteins, where it is readily oxidized and pivotal to the repair mechanism for the prevention of oxidative damage. Hence, they act intracellularly as endogenous antioxidants [87]. Lee and coworkers (2016) were the first to report the anticancer activity of SNPs in oral cancer cells by apoptosis induction [88]. Although the mechanism of SNP cytotoxicity in cancer cells has not been fully elucidated, three mechanisms of cytotoxic action have been implicated in the anticancer activity of SNP (Figure 6), namely ion-dependent oxidative damage, cell cycle arrest, and cell permeation leading to cell death [88].

Similar to Se, sulfur can bind to copper ions (abundant in cancer cells) with high affinity resulting in Cu accumulation and Cu-induced oxidative damage [9].

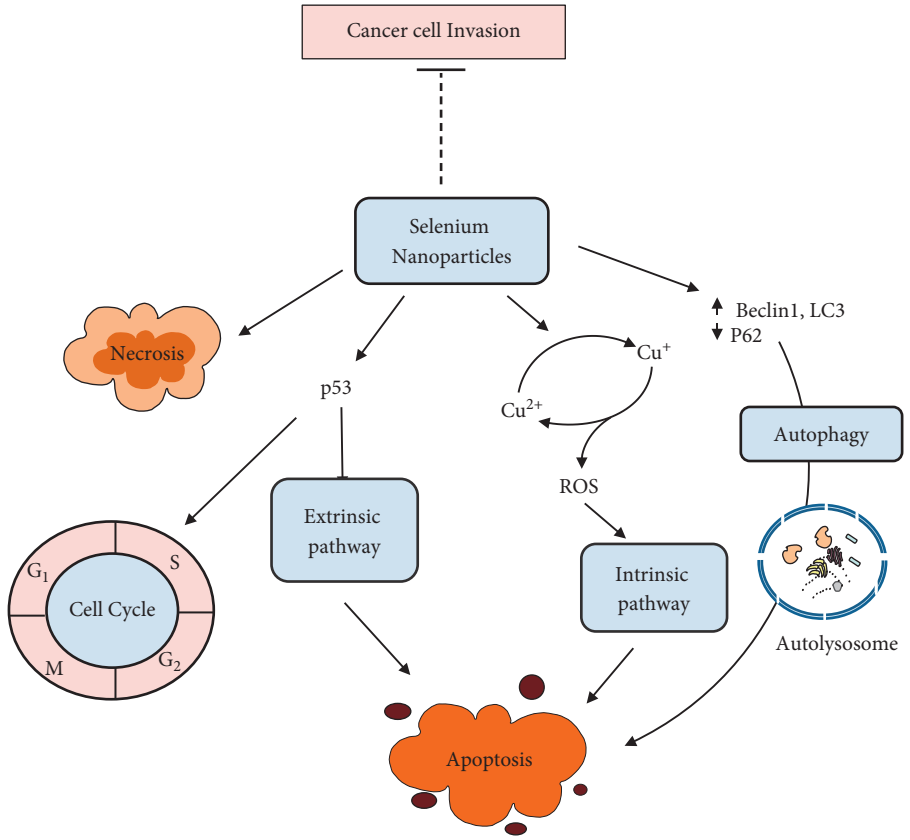

Figure 4: Anticancer mechanisms of selenium nanoparticles.

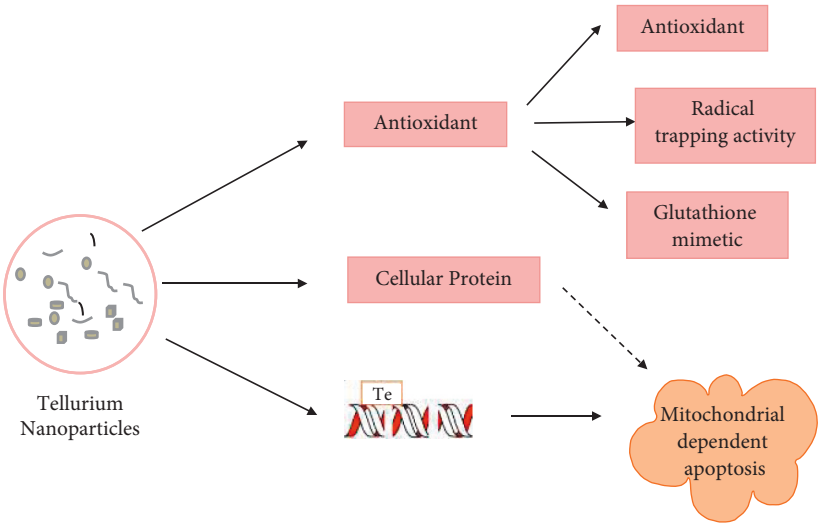

Figure 5: Anticancer mechanism of tellurium nanoparticles.

Furthermore, Cu acts as a cofactor for mitogen-activated protein kinases (MAPK) and facilitates the phosphorylation of the extracellular-signal-regulated kinases (ERK) in the MEK/ERK signalling pathway, leading to the activation of downstream effector proteins such as CREB, JNK, fos, myc, C-Jun, and Ets, which are mediators of cell proliferation. The binding and sequestration of Cu by SNPs impact Cu availability, essentially inhibiting cancer cell proliferation via the MEK/ERK signalling pathway [12, 89].

SNPs also inhibit cell proliferation by mediating cell cycle arrest by inhibiting cyclin-dependent kinases. Although further research is required to understand the underlying mechanism, a link between the CDK inhibitory activity of SNP and the inhibitory effects of p53 and p21 on cyclin E/CDK2, and the resulting replicative senescence has

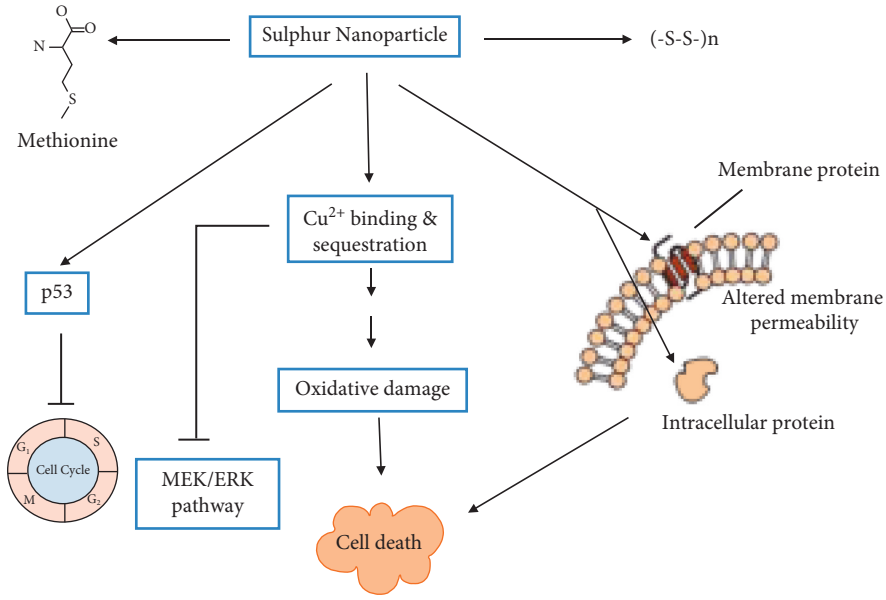

Figure 6: Anticancer mechanism of sulfur nanoparticles.

been reported. This pathway has also been linked to the apoptotic mechanism of SNPs [88]. Another possible cytotoxic mode of SNP may through its interaction with intracellular and membrane proteins that results in altered membrane permeability leading to cell death [12, 62]. This protein binding can be achieved either by direct interaction of SNPs with the sulfhydryl group of proteins that form hydrogen sulfide [63] or by complexation of SNPs to form polysulfides that bind to the sulfhydryl groups of proteins and modulate their structure and activity [12].

4.2. Green Synthesized Chalcogenides. Chalcogenides synthesized via the green approach have demonstrated significant anticancer activity in *in vitro* and *in vivo* experimental models. Silver-selenium bimetallic NPs (Ag-Se) synthesized by green chemistry using gallic acid and quercetin showed significant antioxidant and anticancer potential [90]. The mechanism of cancer cell death although not fully studied has been related to the antioxidant and anticancer potential of the respective biological reductants, since chemically synthesized Ag-selenide NPs showed no cytotoxicity [64, 91]. Similarly, green synthesized ZnSNPs were cytotoxic to MCF-7 cells, with no toxicity in normal cells, but with significant antioxidant activities [92].

Nanocrystals of the semiconductor chalcogenides known as QDs or quantum rods are distinguished for their quantum confinement properties, which confer characteristic optical attributes. Although QDs are mostly synthesized for drug delivery and biosensing, there have been several reports on the anticancer activity of green synthesized chalcogenide QDs. The bioreduction of cadmium sulfate and sodium sulfide by tea leaf extracts (*Camellia sinensis*) produced cadmium sulfide QDs (CdS QDs) that demonstrated significant cytotoxicity in lung cancer (A549) cells (Figure 3). This cytotoxicity involved induction of apoptosis that leads to arrest in the S phase of the cell cycle, with good biocompatibility in normal cells [51]. The QDs of CdS synthesized using the hairy roots of *Rhaphanus sativus* showed greater cytotoxicity in the human breast cancer cells (MCF-7) than in the gastric adenocarcinoma cells (AGS), with apoptosis identified as the mechanism of cell death [93].

The effect of CdS QDs has been mainly linked to cellular oxidative stress [94, 95], with different mechanisms being suggested (Figure 7). Subsequent to photodynamic therapy in CdS-QDs-treated cancer cells, Cd^{2+} is released from the core of the nanoshell [96, 97] and combines with molecular oxygen generating superoxide anion radicals and unpaired QDs [96, 98]. The high concentration of oxidizing species results in oxidative stress that causes damage to DNA and other intracellular proteins and eventually leads to mitochondrial-dependent apoptosis [96, 99–101].

Similarly, other Cd-based chalcogenides, such as CdSe and CdTe, have also demonstrated significant anticancer activity with mechanisms similar to those of CdS. In an investigation of the cytotoxicity of CdTe QDs in HEK293 and HeLa cells, it was observed that the QDs bound to serum proteins and crossed the cellular membrane via clathrin-mediated endocytosis. Upon incorporation into the cells, they were degraded in the lysosomes, and the Cd^{2+} was released leading to ROS causing mitochondria swelling and cell necrosis [102]. Similarly, CdTe QDs also mediate cell death in cancer cells via intrinsic and extrinsic apoptosis [103]. It was further reported that ROS-induced DNA damage leading to cell cycle arrest and cell necrosis were the mechanisms behind the cytotoxic effect of CdSe QD in A549 cells [104].

QDs have also been used in photodynamic therapy (PDT) in cancers. QDs absorb photons of light energy of a specific wavelength to produce electron holes known as excitons. This energy is then transferred from excitons to surrounding species or directly to molecular oxygen to form singlet oxygen radicals that mediated cellular damage [105].

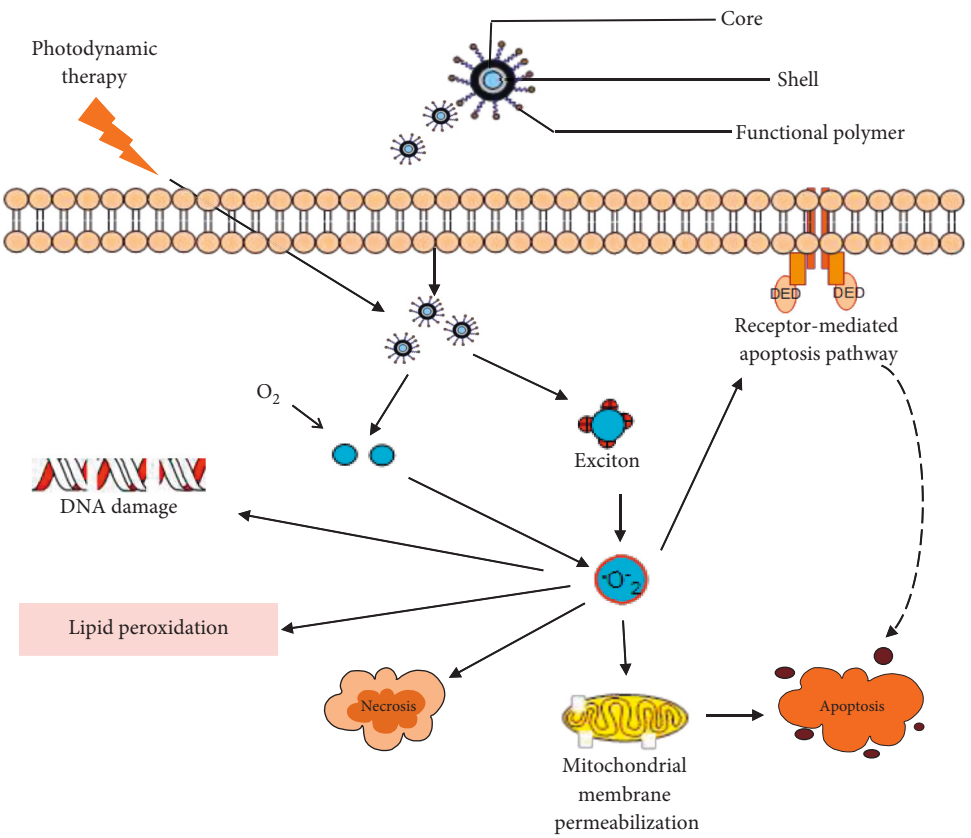

Figure 7: Anticancer mechanisms of semiconductor quantum dots.

However, the success of this therapeutic approach depends on the efficiency of the QD internalization by tumor cells. It should be noted that not all QDs are capable of demonstrating anticancer activity. Some chalcogenide quantum dots, such as zinc oxysufhide QDs, are biocompatible; do not pose a risk of cytotoxicity; and are synthesized primarily for use as biosensors [106]. Biocompatible QDs conjugated via carboxymethylcellulose ($Zn_xCd_{1-x}SQD$) were reported to demonstrate tremendous fluorescence activity [107]. Biocompatible nanochalcopyrites, including $CuInS_2$, $AgInS_2$, and ZnInS, have also been synthesized and have been applied as biosensors in cancer therapy [108–110].

5. Chalcogen and Chalcogenide Nanoparticles: Potential in Biomedicine

The advances made over the years in nanomedicine have seen the development of a variety of nanodelivery platforms such as lipid-based NPs (liposomes and micelles), organic and inorganic polymers (chitosan, polyethyleneimine, poly (lactic-coglycolic acid), and polyethylene glycol), synthesized as single-unit NPs or as copolymers. Others include metalloids, metal oxides, and metallic NPs such as selenium, ferrite, silver, and gold NPs, which in several designs have had their versatility enhanced through surface functionalization with polymers. Hence, they have been vigorously studied because of their higher cargo capacity and optical properties.

NPs have been used to deliver drugs due to their enhanced permeability effect and tumor site-directed drug bioaccumulation. Furthermore, they have been shown to improve drug solubility and facilitate drug transport across membrane barriers. Earlier studies on the use of NPs in the delivery of chemotherapeutic agents focused on the use of organic polymers; however, the last two decades have seen a significant rise in the use of inorganic NPs for drug delivery. Like NPs generated via chemical synthesis, biogenic NPs are engineered to counter the challenges of systemic toxicity, stability, intracellular distribution, and the ability to navigate biological barriers for efficient delivery. We will focus on the current progress made in the use of chalcogens and chalcogenide NPs in drug delivery.

5.1. Chalcogens as Delivery Tools. The sulfur-based chalcogen NPs nano-S has been studied for the efficient delivery of cisplatin in cancer cells. In addition to this primary role, an interesting observation was the ability of nano-S to also sequester Cu ions in cancer cells, blocking the MEK/ERK pathway [89]. It has also been observed that functionalizing the surface of organic polymer with sulfur can increase the selectivity of the transmembrane protein, p-selectin, and cell adhesion molecule involved in tumor metastasis [111].

SeNPs have also been employed to deliver anticancer drugs due to their biocompatibility, intrinsic anticancer activity, excellent pharmacokinetics, and efficient drug loading capacity due to their tunable and polyvalent surface

morphology. Four forms of SeNPs have generally been employed in targeted drug delivery, including nude SeNPs, surface-functionalized SeNPs (using polymer, ligand, and peptide), mesoporous SeNPs, and block polymer encapsulated SeNPs. Most studies on drug loading using Se involved conjugation of the drug to the surface of the SeNPs. The ease of drug loading in SeNPs is due to unreacted molecular ions and stabilizing agents from biogenic sources that form a stable interaction with a pharmaceutical agent through their amino, carboxyl, and amide groups [112]. Recently, an eco-friendly synthesis of a noisome-Se nanohybrid drug delivery vehicle with anticancer activity and good biocompatibility has been reported [113]. The intriguing feature of this nonviral drug delivery vehicle was its potential inhibition of multidrug-resistant protein. Furthermore, mesoporous SeNPs have also been synthesized to facilitate doxorubicin delivery [114]. The NPs showed a significant high drug-loading capacity and redox responsive drug release and were nontoxic to critical organs in an *in vivo* nude mouse model. SeNPs synthesized by fenugreek seed extract were also shown to work synergistically with doxorubicin to increase cytotoxicity in MCF-7 cells [43]. SeNPs synthesized using *Spermacoce hispida* aqueous leaf extract was shown to efficiently deliver S-allyl glutathione into HepG2 cells. They initiated cell death through cell cycle arrest, DNA fragmentation, and mitochondrial-dependent apoptosis [115].

Targeted bioaccumulation of NPs such as Se has proven to be highly effective in cancer therapy over the years. Hence, SeNPs have been surface modified to facilitate targeted delivery to the required site of action. This was achieved either through a ligand receptor-targeted release or stimuli-responsive mechanism, which mostly involved the attachment of ligands or stimuli-responsive components to side chains via covalent or noncovalent interactions [116]. An interesting example of this surface modification includes the functionalization with epidermal growth factor receptor peptide to facilitate targeted delivery to the tumor microenvironment [117]. SeNPs functionalized with polyethylene glycol (PEG) and polyethyleneimine (PEI) have been used to selectively codeliver epirubicin (an anticancer drug) and NAS-24 aptamer (apoptosis induction agent) to MCF-7 cells [118]. This PEG-PEI functionalization improved drug circulation, increased NP stability, improved drug loading, and increased selectivity via toll-like receptor targeting of PEI [119]. It was also noted that conjugating galactose to the surface of SeNPs increased *in vitro* cellular uptake by hepatocellular carcinoma cells via clathrin-mediated endocytosis [120]. A concurrent *in vivo* study showed hyperaccumulation of the NPs in tumors without damage to the heart, liver, spleen, lung, and kidney. Apart from galactose, glucose is another aldohexose employed in the surface functionalization of SeNPs. These NPs also showed good biocompatibility and induced apoptosis through intrinsic and extrinsic pathways [121]. These aldose-hexoses' cell target activity can be linked to carbohydrate metabolism aberration in cancer cells as described by Otto Warburg [122]. This results in increased selective uptake of the drug-loaded NPs by cancer cells. It was also reported that folate functionalized mesoporous silica-SeNPs were able to bind to the folate receptor of cancer cells upon acid cleavage to facilitate the targeted release of doxorubicin [123]. In a study involving chemo- and photothermal therapy, SeNPs were covalently attached to RC-12 and PG-6 peptides to deliver indocyanine green and doxorubicin [124]. The peptides stimulated drug uptake via lipid raft endocytosis and clathrin-mediated endocytosis in cancer cells, which were then released after irradiation by a NIR laser to mediate ROS-induced cell death and apoptosis. The incorporation of SeNPs into a block polymer was the final approach described for drug-loaded SeNPs. Although this is still in its early stages, it has shown promising potential to deliver anticancer drugs efficiently with good biocompatibility [116, 125].

TeNPs have been incorporated into polymers and biofilms to selectively deliver chemotherapeutic agents. Te was first reported as a drug delivery vehicle in 2014 when Wei Cao and colleagues demonstrated the successful use of Te to deliver cisplatin [126]. The authors later demonstrated the efficient synthesis of a biofilm containing Te, which showed a significant potential for cisplatin drug loading and an ion-responsive drug release [127]. The use of Te to deliver cisplatin is linked to the coordination chemistry of Te and platinum [126]. The attractive property of this nanoassembly was the possibility of controlled drug release kinetics. When competitive ligand biomolecules such as mercapto ligands and spermine were introduced, they could control the release kinetics of a cisplatin conjugated Te-containing polymer. In this way, TeNPs have been used to deliver and control the release of platinum-containing drugs successfully.

Although TeNPs could scavenge ROS, due to their low electronegativity, they are also easily oxidized by ROS [128]. The oxidized Te can in turn be liberated from its coordination complex with platinum-based drugs leading to drug release at a specific target site. This approach was recently used to selectively target tumors using Te-conjugated cantharidin in combination therapy [129]. Radiations within near-infrared regions, gamma radiations, and light radiations have been used to generate this ROS for the stimuli-responsive drug release in Te-drug conjugates [130–132]. This mechanism, in turn, provides a synergistic cell-killing effect in cancer cells.

5.2. Chalcogenides in Theranostics and Bioimaging. Chalcogenides, because of their optical properties, near-infrared (NIR) absorption properties, and proficient photothermal conversion efficiency, are mostly studied for their application in photothermal ablation, bioimaging, and diagnostics in cancer therapy. The options they provide in theranostics have encouraged studies in targeted systems for drug and gene delivery. In this section, we highlight the contributions of chalcogenide NPs in biomedicine, especially as delivery tools.

The immense potential of chalcogenides as drug delivery platforms in cancer is evident in the impressive number of research publications in this area. The recent surge in the study of chalcogenides for NP design for drug delivery lies in

the options they offer in combination therapy, specifically, through photothermal ablation [133]. A recent report described a dual responsive system involving the dichalcogenide MoS_2 NPs optimized for folate targeting and loaded with the anthracycline doxorubicin [134]. Functionalized with lipoic acid-polyethyleneimine (LA-PEI) and lipoic acid-polyethylene glycol (LA-PEG) copolymers, the FA-BSA-PEI-LA-MoS_2-LA-PEG (FBPMP) nanocomposite showed sensitivity to changes in pH and NIR irradiation in the release of its doxorubicin payload in folate-positive MDA-MB-231 breast cancer cells. Furthermore, exposure of the nanocomposite to NIR irradiation at 808 nm and 0.5 $W{\cdot}cm^{-2}$ for 5 minutes induced heat and affected ablation in cancer cells, acting in synergy with doxorubicin for a marked impact on cell viability [134].

The investigation of cobalt-selenide (Co_9Se_8) nanoplates, for photoacoustic imaging, photothermal ablation, and drug delivery, emphasizes the versatility of chalcogenide nanoconstructs. Biocompatible Co_9Se_8 nanoplates functionalized with polyacrylic acid responded to changes in pH and NIR in doxorubicin release, with amplitude cytotoxic effects observed in *in vitro* and *in vivo* models of liver cancer, especially in the induction of hypothermia by exposure to NIR [135]. Besides their anticipated photoacoustic property, Co_9Se_8 nanoplates markedly enhanced MRI contrast of the tumor area in hepatic (HepG2) tumor bearing mice. Negative enhancements observed in the T_2-weight images revealed the potential of Co_9Se_8 nanoplates as contrasting agents in clinical diagnostics, which in combination with its photoacoustic properties produces a multimodal imaging tool with higher sensitivity and precision [135, 136].

A similar multimodal imaging-guided delivery of doxorubicin by pegylated bismuth sulfide nanourchins was reported. The chalcogenide NPs had a loading capacity of 37.9% and displayed pH and thermal sensitive drug release, while the photothermal property of the construct acted in concert with the chemotherapeutic to significantly inhibit cervical tumor growth in a Balb/c mouse model [167]. Moreover, the study described the strong X-ray attenuation feature of Bi_2S_3-PEG nanourchins and suggested their potential application as a computed tomography (CT) contrast agent, which, with their innate photoacoustic and infrared thermal imaging properties, offer an invaluable possibility for monitoring the therapeutic impact of treatments in real time [137, 138]. In a recent study, a ternary Cu-Fe-Se chalcogenide nanosheet demonstrated a significant chemothermal effect in mouse mammary tumors, similar to the examples already described. Furthermore, with its inherent multimodal imaging properties, the pharmacokinetics of the anticancer drug and nanosheets were elucidated, thus highlighting another application of chalcogenide NPs in nanomedicine [139].

In a related study describing the mitigation of hydrophobicity and toxicity in Cu_9S_5 nanocrystals by coating with mesoporous silica ($mSiO_2$) to yield Cu_9S_5@$mSiO_2$, following PEG functionalization, Cu_9S_5@$mSiO_2$-PEG nanocomposite showed efficient doxorubicin encapsulation efficiency (63.8%), and a large amplitude drug release at pH 4.8, suggesting pH sensitivity. Upon exposure to NIR at 980 nm and 0.78 $W{\cdot}cm^{-2}$ for 10 minutes, Cu_9S_5@$mSiO_2$-PEG-DOX had a marked impact on the viability of human colorectal cancer cells *in vitro*, while the mean tumor weight was reduced by a significant 83% [140]. A different design, but of similar composition, drug-loaded Cu_9S_5@mSiO2 nanofibers were studied for their efficacy in mouse hepatoma [141]. In another system involving a combination of silica and copper sulfide, silica nanorods were decorated with CuS NPs and then functionalized with lactobionic acid—an agonist of asialoglycoprotein receptors for targeted delivery of doxorubicin to HepG2 cells. As expected, in conjunction with the pH-dependent release of doxorubicin from the SNT-LA-CuS-PEG nanocomposite, exposure to NIR radiation enhanced the drug release profile, with the thermal energy generated improving tumor inhibition *in vivo* [142, 143]. In a similar report, Zhang and coworkers described a novel nanocomposite consisting of a mesoporous silica scaffold, to which CuS nanospheres were conjugated via two complementary DNA sequences (MSN-DNA-CuS) [144]. This unique design employing the oligonucleotides and CuS nanospheres as gatekeepers was a thermally regulated drug delivery system allowing for a reversible opening and closing of the drug release portals of the drug-loaded MSN. On exposure to NIR and the consequent hypothermia brought about by the CuS, the oligonucleotides dehybridized, permitting the outward movement of the drug. At the same time, detached CuS nanospheres contributed to cancer cell death through thermal ablation, acting in synergy with the released drug [144].

Most studies involving nucleic acid-based functionalization of chalcogenides are generally on the development of molecular probes for diagnostics and imaging; however, chalcogenides have also been applied in nucleic acid delivery [145, 146]. In an interesting study, Guo and coworkers described a dual photothermal-immunotherapy strategy that involved the chalcogenide CuS NPs as a delivery platform and photo-absorber, with oligodeoxynucleotides rich in cytosine-guanine (CpG) motifs as an immunologic adjuvant [147, 148]. The idea was to target primary tumors with photothermal ablation and to initiate antitumor immunity against metastasized tumor cells. The study, conducted in a mouse model of breast cancer, involved the intratumoral injection of hollow chitosan-functionalized CuS NPs (Chi-HCuSNPs) loaded with a CpG-rich oligonucleotide and elicited a significant inhibition of tumor growth by 68% and 86% in primary and distant tumors over 12 days and 24 days, respectively. Mechanistically, upon treatment with NIR laser, primary tumor cells were disrupted by photothermal ablation, and hollow CuS NPs disintegrated into nanocrystals, releasing their oligonucleotide cargo, which was taken up by the plasmacytoid dendritic cells in the tumor microenvironment. Plasmacytoid dendritic cells then secreted the cytokine IFγ, which on the one hand activates innate immunity by activation of natural killer cells (NK) and on the other hand initiates the activity of antigen-specific $CD8^+$ T cells by orchestrating the conversion of activated myeloid dendritic cells to antigen-presenting professional dendritic cells [148]. The synergistic

impact of the chalcogenide CuS NPs and their cargo underlines the immense clinical potential of this class of NPs.

In another report, CdTe/CdS core/shell QDs were employed as a scaffold and tracker for the thymidine kinase (HSV-TK) gene of the suicide herpes simplex virus. The HSV-TK gene belongs to the class of therapeutic genes whose gene products convert prodrugs to their cytotoxic metabolite and has been used extensively in chemotherapy [149, 150]. The HSV-TK gene conjugated to the QD via an EDC/NHS (ethyl (dimethylaminopropyl) carbodiimide/N-hydroxy succinimide) coupling was efficiently trafficked to the nucleus of treated cervical cancer cells, with the QD providing the option of tracking the nanocomplex. As expected, the addition of the prodrug ganciclovir significantly reduced viability in treated cells due to the conversion to active ganciclovir triphosphate, a DNA polymerase inhibitor [146].

QDs have evolved as one of the most sought-after nanomaterial in drug delivery. Similar to NPs, their small size allows for an increase in permeation retention capacity and provides a large surface area for drug conjugation. Their superinfinitesimal dimension confers additional properties including ease of shape and size adjustment and the facility of doping and pliability associated with drug functionalization [151]. QDs can be conjugated with drugs via electrostatic interaction, covalent bonding, or surface adsorption. Extensive studies on the use of QDs as a drug delivery vehicle have been carried out. This is because of the deep interest in their amenability to stimuli-responsive drug release. QDs have been applied in photothermal therapy to facilitate subcutaneous drug uptake after irradiation. NIR irradiation has also been used to stimulate drug and thermal energy release in camptothecin-loaded CuS QD, causing cancer cell death [152].

6. Limitations and Future Perspective

The theranostic potential of chalcogenide NPs is largely responsible for their growing popularity. Most theranostic nanoconstructs comprise a scaffold and a tethered diagnostic component and are characterized by complex synthesis procedures and the challenge of achieving a balance between diagnostic and therapeutic components for effective impact. However, chalcogenide NPs are a unique nanoplatform where both diagnostic and therapeutic properties are contained in a single NP unit, and alongside chalcogen NPs, such as SeNPs and SNPs, which have demonstrated bioactivity under certain conditions, their delivery capacity positions them as viable candidates in the development of multifunctional nanomedicines for clinical applications. Equally attractive is the biogenic synthesis advantage of this class of NPs, with evidence associating the capping of biogenic chalcogen and chalcogenide NPs with their diverse therapeutic properties and capacity to mitigate debilitating pathological conditions. Besides their ease of synthesis and stability, the biogenic synthesis of chalcogen and chalcogenide NPs significantly improves biocompatibility, alleviating concerns associated with the application of inorganic NPs in clinical scenarios.

While studies focusing on the preparation of inorganic NPs for clinical applications are in their advanced stages, research on certain chalcogen and most chalcogenide NPs are still quite elementary. Of the 75 NPs currently in clinical trials, liposomal and polymeric NP-based nanomedicines are in the majority, while only 5 involve metallic NPs, with no chalcogen or chalcogenide included. At any rate, the progressive cultivation of ideas centred on the development of chalcogen and chalcogenide nanomedicines should produce candidates for clinical testing in the near future.

However, the existing challenges and limitations require due attention. For instance, the tunability of NP size and shape, which is achievable through adjustments of one or more physical factors such as temperature or pH in chemical synthesis procedures, is not feasible in certain biogenic processes, especially where living organisms are involved.

Another limitation is the synthesis time and yield, which are lower in most cases compared to what is obtainable by chemical synthesis procedures. Attempts to improve NP yield in some of these organisms may require alterations at the genetic level, which features complex procedures with significant cost implications.

Moreover, there is a paucity of information on the clearance properties of most chalcogenide nanoformulations. The general reservation about inorganic NPs is their tendency to accumulate in vital organs and tissues where they pose significant toxicity risk. Generally, the size and the charge of inorganic nanoparticles influence their fate *in vivo*. NPs with hydrodynamic sizes <6 nm can easily scale the filtration-size threshold of the glomerulus. NPs with hydrodynamics sizes between 6 and 8 nm are more affected by surface charge with cationic nanoparticles more likely transverse the glomerular basement membrane due to its highly negative charge, while NPs >8 nm are taken up by the reticuloendothelial system (RES) and stored in the lungs, liver, spleen, bone marrow, and the lymphatic system. Aside from the possible toxicity implications of prolonged storage in the organs and tissues making up the RES, reports have suggested that the prolonged accumulation of NPs with optical properties such as chalcogenides may interfere with diagnostics and bioimaging. For instance, QDs have been reported to remain optically responsive for more than 100 days *in vivo*. This necessitates more studies on the impact of long-term accumulation and the potential approaches to modulating clearance *in vivo*.

So far, the vast potential application of chalcogen and chalcogenide NPs, which includes their use in biosensor design, as theranostic agents with application in photothermal and photodynamic therapies, and in bio-imaging applications such as X-ray, NIR fluorescent imaging, photoacoustic imaging, and multimodality imaging, positions this class of NPs as veritable tools in cancer management, subject to advances in their development. Further incursions into their performance *in vivo* involving various preclinical models may assuage questions on toxicity and the side effects of long-term accumulation and facilitate their progress to clinical applications. In addition, given the advantages of biogenic synthesis highlighted in this review, the development of cost-effective methods to improve the quantum

yield of biogenic synthesis, which is a disadvantage, will improve the chance of large-scale production for future clinical use.

Going forward, we anticipate that the surging interest in this class of NPs, initiated by their significant biocompatibility and versatility in diagnostics, therapy, and imaging, will drive the improvement of existing biogenic and characterization procedures toward the production of chalcogens and chalcogenide NPs with broader applicability in medicine.

Data Availability

This is a review paper, and no data are available.

Conflicts of Interest

The authors declare that there are no potential conflicts of interest.

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References

[1] F. Masood, "Polymeric nanoparticles for targeted drug delivery system for cancer therapy," *Materials Science and Engineering: C*, vol. 60, pp. 569–578, 2016.

[2] S. Parveen, R. Misra, and S. K. Sahoo, "Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 8, no. 2, pp. 147–166, 2012.

[3] A. Bolhassani, "Potential efficacy of cell-penetrating peptides for nucleic acid and drug delivery in cancer," *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, vol. 1816, no. 2, pp. 232–246, 2011.

[4] S. K. Murthy, "Nanoparticles in modern medicine: state of the art and future challenges," *International Journal of Nanomedicine*, vol. 2, no. 2, pp. 129–141, 2007.

[5] H.-Y. Wang, X.-W. Hua, F.-G. Wu et al., "Synthesis of ultrastable copper sulfide nanoclusters via trapping the reaction intermediate: potential anticancer and antibacterial applications," *ACS Applied Materials & Interfaces*, vol. 7, no. 13, pp. 7082–7092, 2015.

[6] F. A. Devillanova and W.-W. Du Mont, *Handbook of Chalcogen Chemistry: New Perspectives in Sulfur, Selenium and Tellurium*, Royal Society of Chemistry, London, UK, 2013.

[7] P. K. Bajpai, S. Yadav, A. Tiwari, and H. S. Virk, "Recent advances in the synthesis and characterization of chalcogenide nanoparticles," in *Solid State Phenomena*Trans Tech Publications, Freienbach, Switzerland, 2015.

[8] W. Fischer, "A second note on the term "chalcogen"," *Journal of Chemical Education*, vol. 78, no. 10, p. 1333, 2001.

[9] N. Shevchenko, M. Steinhart, and E. Tomšík, "Single-step preparation of mono-dispersed sulfur nanoparticles for detention of copper," *Journal of Nanoparticle Research*, vol. 21, no. 11, p. 246, 2019.

[10] R. M. Tripathi, R. P. Rao, and T. Tsuzuki, "Green synthesis of sulfur nanoparticles and evaluation of their catalytic detoxification of hexavalent chromium in water," *RSC Advances*, vol. 8, no. 63, pp. 36345–36352, 2018.

[11] M. Rai, A. P. Ingle, and P. Paralikar, "Sulfur and sulfur nanoparticles as potential antimicrobials: from traditional medicine to nanomedicine," *Expert Review of Anti-infective Therapy*, vol. 14, no. 10, pp. 969–978, 2016.

[12] S. Shankar, L. Jaiswal, and J.-W. Rhim, "New insight into sulfur nanoparticles: synthesis and applications," *Critical Reviews in Environmental Science and Technology*, vol. 51, no. 20, pp. 2329–2356, 2020.

[13] F. Maiyo and M. Singh, "Selenium nanoparticles: potential in cancer gene and drug delivery," *Nanomedicine*, vol. 12, no. 9, pp. 1075–1089, 2017.

[14] L. Castro, J. Li, F. González, J. A. Muñoz, and M. L. Blázquez, "Green synthesis of tellurium nanoparticles by tellurate and tellurite reduction using aeromonas hydrophila under different aeration conditions," *Hydrometallurgy*, vol. 196, Article ID 105415, 2020.

[15] M. Xiao and L. Yang, "Binary and ternary metal chalcogenide materials and method of making and using same," US Patent, 2014.

[16] S. Ahmed, M. Ahmad, B. L. Swami, and S. Ikram, "A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: a green expertise," *Journal of Advanced Research*, vol. 7, no. 1, pp. 17–28, 2016.

[17] A. G. Ingale and A. N. Chaudhari, "Biogenic synthesis of nanoparticles and potential applications: an eco-friendly approach," *Journal of Nanomedicine and Nanotechology*, vol. 4, pp. 1–7, 2013.

[18] A. L. Rogach, *Semiconductor Nanocrystal Quantum Dots*, Verlag, Berlin, Germany, 2008.

[19] J. Mal, Y. V. Nancharaiah, E. D. Van Hullebusch, and P. N. L. Lens, "Metal chalcogenide quantum dots: biotechnological synthesis and applications," *RSC Advances*, vol. 6, no. 47, pp. 41477–41495, 2016.

[20] S. O. Kasap, *Principles of Electronic Materials and Devices*, McGraw-Hill, New York, NY, USA, 2006.

[21] R. E. Hummel, *Electronic Properties of Materials*, Springer Science & Business Media, Berlin, Germany, 2011.

[22] G. T. Einevoll, "Confinement of excitons in quantum dots," *Physical Review B*, vol. 45, no. 7, pp. 3410–3417, 1992.

[23] L. Brus, "Electronic wave functions in semiconductor clusters: experiment and theory," *Journal of Physical Chemistry*, vol. 90, no. 12, pp. 2555–2560, 1986.

[24] A. Khare, A. W. Wills, L. M. Ammerman, D. J. Norris, and E. S. Aydil, "Size control and quantum confinement in Cu2ZnSnS4 nanocrystals," *Chemical Communications*, vol. 47, no. 42, pp. 11721–11723, 2011.

[25] E. Marino, T. E. Kodger, J. B. ten Hove, A. H. Velders, and P. Schall, "Assembling quantum dots via critical casimir forces," *Solar Energy Materials and Solar Cells*, vol. 158, pp. 154–159, 2016.

[26] Y. Zhang, Y. Liu, C. Li, X. Chen, and Q. Wang, "Controlled synthesis of Ag2S quantum dots and experimental determination of the exciton Bohr radius," *Journal of Physical Chemistry C*, vol. 118, no. 9, pp. 4918–4923, 2014.

[27] S. Chand, N. Thakur, S. C. Katyal, P. B. Barman, V. Sharma, and P. Sharma, "Recent developments on the synthesis, structural and optical properties of chalcogenide quantum dots," *Solar Energy Materials and Solar Cells*, vol. 168, pp. 183–200, 2017.

[28] S. V. Kershaw, A. S. Susha, and A. L. Rogach, "Narrow bandgap colloidal metal chalcogenide quantum dots: synthetic methods, heterostructures, assemblies, electronic and

infrared optical properties," *Chemical Society Reviews*, vol. 42, no. 7, pp. 3033–3087, 2013.

[29] A. M. Smith and S. Nie, "Chemical analysis and cellular imaging with quantum dots," *Analyst*, vol. 129, no. 8, pp. 672–677, 2004.

[30] S. Jadoun, R. Arif, N. K. Jangid, and R. K. Meena, "Green synthesis of nanoparticles using plant extracts: a review," *Environmental Chemistry Letters*, vol. 19, no. 1, pp. 355–374, 2020.

[31] S. S. Salem and A. Fouda, "Green synthesis of metallic nanoparticles and their prospective biotechnological applications: an overview," *Biological Trace Element Research*, vol. 199, pp. 1–27, 2020.

[32] P. Korde, S. Ghotekar, T. Pagar, S. Pansambal, R. Oza, and D. Mane, "Plant extract assisted eco-benevolent synthesis of selenium nanoparticles-a review on plant parts involved, characterization and their recent applications," *Journal of Chemistry Reviews*, vol. 2, pp. 157–168, 2020.

[33] S. Li, Y. Shen, A. Xie et al., "Rapid, room-temperature synthesis of amorphous selenium/protein composites using capsicum annuum L extract," *Nanotechnology*, vol. 18, no. 40, Article ID 405101, 2007.

[34] P. Paralikar and M. Rai, "Sulfur nanoparticles: biosynthesis, antibacterial applications, and their mechanism of action," *Nanobiotechnology in Diagnosis, Drug Delivery Treatment*, pp. 217–228, Wiley-Blackwell, NJ, USA, 2020.

[35] M. N. Borovaya, A. P. Naumenko, N. A. Matvieieva, Y. B. Blume, and A. I. Yemets, "Biosynthesis of luminescent CdS quantum dots using plant hairy root culture," *Nanoscale Research Letters*, vol. 9, no. 1, p. 686, 2014.

[36] M. Akbari, M. Rahimi-Nasrabadi, S. Pourmasud et al., "CdTe quantum dots prepared using herbal species and microorganisms and their anti-cancer, drug delivery and antibacterial applications; a review," *Ceramics International*, vol. 46, no. 8, pp. 9979–9989, 2020.

[37] H. Q. Alijani, S. Pourseyedi, M. Torkzadeh Mahani, and M. Khatami, "Green synthesis of zinc sulfide (ZnS) nanoparticles using tevia rebaudiana bertoni and evaluation of its cytotoxic properties," *Journal of Molecular Structure*, vol. 1175, pp. 214–218, 2019.

[38] S. R. Bera and S. Saha, "Biosynthesis and characterization of thevetia peruviana leaf extract capped CdTe nanoparticles in photoconductive and photovoltaic applications," *Materials Today Proceedings*, vol. 5, no. 2, pp. 3476–3485, 2018.

[39] P. Iyyappa Rajan, J. Judith Vijaya, S. K. Jesudoss et al., "Investigation on preferably oriented abnormal growth of CdSe nanorods along (0002) plane synthesized by henna leaf extract-mediated green synthesis," *Royal Society Open Science*, vol. 5, no. 3, Article ID 171430, 2018.

[40] Z. Moradi Alvand, H. R. Rajabi, A. Mirzaei, A. Masoumiasl, and H. Sadatfaraji, "Rapid and green synthesis of cadmium telluride quantum dots with low toxicity based on a plant-mediated approach after microwave and ultrasonic assisted extraction: synthesis, characterization, biological potentials and comparison study," *Materials Science and Engineering: C*, vol. 98, pp. 535–544, 2019.

[41] D. Cui, T. Liang, L. Sun et al., "Green synthesis of selenium nanoparticles with extract of hawthorn fruit induced HepG2 cells apoptosis," *Pharmaceutical Biology*, vol. 56, no. 1, pp. 528–534, 2018.

[42] D. Medina Cruz, W. Tien-Street, B. Zhang et al., "Citric juice-mediated synthesis of tellurium nanoparticles with antimicrobial and anticancer properties," *Green Chemistry*, vol. 21, no. 8, pp. 1982–1998, 2019.

[43] C. Ramamurthy, K. S. Sampath, P. Arunkumar et al., "Green synthesis and characterization of selenium nanoparticles and its augmented cytotoxicity with doxorubicin on cancer cells," *Bioprocess and Biosystems Engineering*, vol. 36, no. 8, pp. 1131–1139, 2013.

[44] K. Anu, G. Singaravelu, K. Murugan, and G. Benelli, "Green-synthesis of selenium nanoparticles using garlic cloves (Allium Sativum): biophysical characterization and cytotoxicity on vero cells," *Journal of Cluster Science*, vol. 28, no. 1, pp. 551–563, 2017.

[45] V. Cittrarasu, D. Kaliannan, K. Dharman et al., "Green synthesis of selenium nanoparticles mediated from ceropegia bulbosa roxb extract and its cytotoxicity, antimicrobial, mosquitocidal and photocatalytic activities," *Scientific Reports*, vol. 11, no. 1, p. 1032, 2021.

[46] S. Tang, T. Wang, M. Jiang et al., "Construction of arabinogalactans/selenium nanoparticles composites for enhancement of the antitumor activity," *International Journal of Biological Macromolecules*, vol. 128, pp. 444–451, 2019.

[47] R. Hassanien, A. A. I. Abed-Elmageed, and D. Z. Husein, "Eco-friendly approach to synthesize selenium nanoparticles: photocatalytic degradation of sunset yellow azo dye and anticancer activity," *ChemistrySelect*, vol. 4, no. 31, pp. 9018–9026, 2019.

[48] A. H. Hashem and S. S. Salem, "Green and ecofriendly biosynthesis of selenium nanoparticles using Urtica Dioica (Stinging Nettle) leaf extract: antimicrobial and anticancer activity," *Biotechnology Journal*, vol. 17, no. 2, Article ID 2100432, 2021.

[49] D. Medina-Cruz, A. Vernet-Crua, E. Mostafavi et al., "Aloe vera-mediated Te nanostructures: highly potent antibacterial agents and moderated anticancer effects," *Nanomaterials*, vol. 11, no. 2, p. 514, 2021.

[50] F. Olawale, M. Ariatti, and M. Singh, "Biogenic synthesis of silver-core selenium-shell nanoparticles using Ocimum Tenuiflorum L.: response surface methodology-based optimization and biological activity," *Nanomaterials*, vol. 11, p. 2516, 2021.

[51] K. Shivaji, S. Mani, P. Ponmurugan et al., "Green-synthesis-derived CdS quantum dots using tea leaf extract: antimicrobial, bioimaging, and therapeutic applications in lung cancer cells," *ACS Applied Nano Materials*, vol. 1, no. 4, pp. 1683–1693, 2018.

[52] S. K. Torres, V. L. Campos, C. G. León et al., "Biosynthesis of selenium nanoparticles by Pantoea agglomerans and their antioxidant activity," *Journal of Nanoparticle Research*, vol. 14, no. 11, p. 1236, 2012.

[53] M. S. Ahmad, M. M. Yasser, E. N. Sholkamy, A. M. Ali, and M. M. Mehanni, "Anticancer activity of biostabilized selenium nanorods synthesized by streptomyces bikiniensis strain Ess_amA-1," *International Journal of Nanomedicine*, vol. 10, pp. 3389–401, 2015.

[54] P. Bao, Z. Chen, R.-Z. Tai, H.-M. Shen, F. L. Martin, and Y.-G. Zhu, "Selenite-induced toxicity in cancer cells is mediated by metabolic generation of endogenous selenium nanoparticles," *Journal of Proteome Research*, vol. 14, no. 2, pp. 1127–1136, 2015.

[55] C. Xu, L. Qiao, Y. Guo, L. Ma, and Y. Cheng, "Preparation, characteristics and antioxidant activity of polysaccharides and proteins-capped selenium nanoparticles synthesized by lactobacillus Casei ATCC 393," *Carbohydrate Polymers*, vol. 195, pp. 576–585, 2018.

[56] S. Kumar, M. S. Tomar, and A. Acharya, "Carboxylic group-induced synthesis and characterization of selenium

nanoparticles and its anti-tumor potential on Dalton's lymphoma cells," *Colloids and Surfaces B: Biointerfaces*, vol. 126, pp. 546–552, 2015.

[57] G. Huang, Z. Liu, L. He et al., "Autophagy is an important action mode for functionalized selenium nanoparticles to exhibit anti-colorectal cancer activity," *Biomaterials Science*, vol. 6, no. 9, pp. 2508–2517, 2018.

[58] X. Fu, Y. Yang, X. Li et al., "RGD peptide-conjugated selenium nanoparticles: antiangiogenesis by suppressing VEGF-VEGFR2-ERK/AKT pathway," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, no. 6, pp. 1627–1639, 2016.

[59] M. H. Yazdi, M. Mahdavi, B. Varastehmoradi, M. A. Faramarzi, and A. R. Shahverdi, "The immunostimulatory effect of biogenic selenium nanoparticles on the 4T1 breast cancer model: an in vivo study," *Biological Trace Element Research*, vol. 149, no. 1, pp. 22–28, 2012.

[60] P. Bao, S.-C. Chen, and K.-Q. Xiao, "Dynamic equilibrium of endogenous selenium nanoparticles in selenite-exposed cancer cells: a deep insight into the interaction between endogenous SeNPs and proteins," *Molecular BioSystems*, vol. 11, no. 12, pp. 3355–3361, 2015.

[61] L. A. Ba, M. Döring, V. Jamier, and C. Jacob, "Tellurium: an element with great biological potency and potential," *Organic and Biomolecular Chemistry*, vol. 8, no. 19, pp. 4203–4216, 2010.

[62] F. Danhier, O. Feron, and V. Préat, "To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery," *Journal of Controlled Release*, vol. 148, no. 2, pp. 135–146, 2010.

[63] E. R. DeLeon, Y. Gao, E. Huang et al., "A case of mistaken identity: are reactive oxygen species actually reactive sulfide species?" *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, vol. 310, no. 7, pp. R549–R560, 2016.

[64] S.-M. Tang, X.-T. Deng, J. Zhou, Q.-P. Li, X.-X. Ge, and L. Miao, "Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects," *Biomedicine and Pharmacotherapy*, vol. 121, Article ID 109604, 2020.

[65] A. Vernet Crua, D. Medina, B. Zhang et al., "Comparison of cytocompatibility and anticancer properties of traditional and green chemistry-synthesized tellurium nanowires," *International Journal of Nanomedicine*, vol. 14, pp. 3155–3176, 2019.

[66] H. Vahidi, F. Kobarfard, A. Alizadeh, M. Saravanan, and H. Barabadi, "Green nanotechnology-based tellurium nanoparticles: exploration of their antioxidant, antibacterial, antifungal and cytotoxic potentials against cancerous and normal cells compared to potassium tellurite," *Inorganic Chemistry Communications*, vol. 124, Article ID 108385, 2020.

[67] Y. Li, J. Pan, K. Jiang et al., "Preparation of elemental tellurium nanoparticles - sucrose sol and its antioxidant activity in vitro," *Journal of Wuhan University of Technology-Materials Science Edition*, vol. 28, no. 5, pp. 1048–1052, 2013.

[68] R. L. O. R. Cunha, I. E. Gouvea, and L. Juliano, "A glimpse on biological activities of tellurium compounds," *Anais da Academia Brasileira de Ciências*, vol. 81, no. 3, pp. 393–407, 2009.

[69] D. Bhowmick, S. Srivastava, P. D'Silva, and G. Mugesh, "Highly efficient glutathione peroxidase and peroxiredoxin mimetics protect mammalian cells against oxidative damage," *Angewandte Chemie*, vol. 127, no. 29, pp. 8569–8573, 2015.

[70] X. Lu, G. Mestres, V. Singh et al., "Selenium- and tellurium-based antioxidants for modulating inflammation and effects on osteoblastic activity," *Antioxidants*, vol. 6, no. 1, p. 13, 2017.

[71] W. Huang, L. He, J. Ouyang et al., "Triangle-shaped tellurium nanostars potentiate radiotherapy by boosting checkpoint blockade immunotherapy," *Matter*, vol. 3, no. 5, pp. 1725–1753, 2020.

[72] W. Huang, H. Wu, X. Li, and T. Chen, "Facile one-pot synthesis of tellurium nanorods as antioxidant and anticancer agents," *Chemistry - An Asian Journal*, vol. 11, no. 16, pp. 2301–2311, 2016.

[73] R. L. Puntel, D. S. Avila, D. H. Roos, and S. Pinton, "Mitochondrial effects of organoselenium and organotellurium compounds," *Current Organic Chemistry*, vol. 20, pp. 198–210, 2016.

[74] R. Pessoa-Pureur, L. Heimfarth, and J. B. Rocha, "Signaling mechanisms and disrupted cytoskeleton in the diphenyl ditelluride neurotoxicity," *Oxidative Medicine and Cellular Longevity*, vol. 2014, Article ID 458601, 21 pages, 2014.

[75] R. B. De Andrade, T. Gemelli, R. B. Guerra, C. Funchal, and C. M. Duval Wannmacher, "Inhibition of creatine kinase activity by 3-butyl-1-phenyl-2-(phenyltelluro)Oct-en-1-one in the cerebral cortex and cerebellum of young rats," *Journal of Applied Toxicology*, vol. 30, no. 6, pp. 611–616, 2010.

[76] E. Olm, A. P. Fernandes, C. Hebert et al., "Extracellular thiol-assisted selenium uptake dependent on the Xc - cystine transporter explains the cancer-specific cytotoxicity of selenite," *Proceedings of the National Academy of Sciences*, vol. 106, no. 27, pp. 11400–11405, 2009.

[77] M. C. Yarema and S. C. Curry, "Acute tellurium toxicity from ingestion of metal-oxidizing solutions," *Pediatrics*, vol. 116, no. 2, pp. e319–e321, 2005.

[78] S. Roy Choudhury and A. Goswami, "Supramolecular reactive sulphur nanoparticles: a novel and efficient antimicrobial agent," *Journal of Applied Microbiology*, vol. 114, no. 1, pp. 1–10, 2013.

[79] R. Kumar, K. K. Nair, M. I. Alam et al., "A simple method for estimation of sulphur in nanoformulations by UV spectrophotometry," *Current Science*, vol. 100, pp. 1542–1546, 2011.

[80] Y.-X. Wang, L. Huang, L.-C. Sun et al., "Facile synthesis of a interleaved expanded graphite-embedded sulphur nanocomposite as cathode of Li-S batteries with excellent lithium storage performance," *Journal of Materials Chemistry*, vol. 22, no. 11, pp. 4744–4750, 2012.

[81] P. Paralikar and M. Rai, "Bio-inspired synthesis of sulphur nanoparticles using leaf extract of four medicinal plants with special reference to their antibacterial activity," *IET Nanobiotechnology*, vol. 12, no. 1, pp. 25–31, 2017.

[82] S. Ghotekar, T. Pagar, S. Pansambal, and R. Oza, "A review on green synthesis of sulfur nanoparticles via plant extract, characterization and its applications," *Advance Journal of Chemistry B*, vol. 2, pp. 128–143, 2020.

[83] C. Galeone, C. Pelucchi, F. Levi et al., "Onion and garlic use and human cancer," *American Journal of Clinical Nutrition*, vol. 84, no. 5, pp. 1027–1032, 2006.

[84] J. M. Mates, J. A. Segura, F. J. Alonso, and J. Marquez, "Sulphur-containing non enzymatic antioxidants therapeutic tools against cancer," *Frontiers in Bioscience*, vol. 4, no. 2, pp. 722–748, 2012.

[85] F. Zahran, M. Hammadi, M. Al-dulaimi, and M. Sebaiy, "Potential role of sulfur nanoparticles as antitumor and

antioxidant in mice," *Der Pharmaceutical Letters*, vol. 10, pp. 7–26, 2018.

[86] J.-H. Kim, H.-J. Jang, W.-Y. Cho, S.-J. Yeon, and C.-H. Lee, "In vitro antioxidant actions of sulfur-containing amino acids," *Arabian Journal of Chemistry*, vol. 13, no. 1, pp. 1678–1684, 2020.

[87] R. L. Levine, L. Mosoni, B. S. Berlett, and E. R. Stadtman, "Methionine residues as endogenous antioxidants in proteins," *Proceedings of the National Academy of Sciences*, vol. 93, no. 26, pp. 15036–15040, 1996.

[88] J. Lee, H.-J. Lee, J.-D. Park et al., "Anti-cancer activity of highly purified sulfur in immortalized and malignant human oral keratinocytes," *Toxicology in Vitro*, vol. 22, no. 1, pp. 87–95, 2008.

[89] H. Liu, Y. Zhang, S. Zheng et al., "Detention of copper by sulfur nanoparticles inhibits the proliferation of A375 malignant melanoma and MCF-7 breast cancer cells," *Biochemical and Biophysical Research Communications*, vol. 477, no. 4, pp. 1031–1037, 2016.

[90] A. K. Mittal, S. Kumar, and U. C. Banerjee, "Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antitumor and antimicrobial potential," *Journal of Colloid and Interface Science*, vol. 431, pp. 194–199, 2014.

[91] N. M. Aborehab and N. Osama, "Effect of gallic acid in potentiating chemotherapeutic effect of paclitaxel in HeLa cervical cancer cells," *Cancer Cell International*, vol. 19, no. 1, p. 154, 2019.

[92] F. Sharifi, F. Sharififar, I. Sharifi, H. Q. Alijani, and M. Khatami, "Cytotoxicity, leishmanicidal, and antioxidant activity of biosynthesised zinc sulphide nanoparticles using phoenix dactylifera," *IET Nanobiotechnology*, vol. 12, no. 3, pp. 264–269, 2017.

[93] Z. Gholami, M. Dadmehr, N. B. Jelodar, M. Hosseini, and A. P. Parizi, "One-pot biosynthesis of CdS quantum dots through in vitro regeneration of hairy roots of Rhaphanus Sativus L. And their apoptosis effect on MCF-7 and AGS cancerous human cell lines," *Materials Research Express*, vol. 7, Article ID 15056, 2020.

[94] N. Chen, Y. He, Y. Su et al., "The cytotoxicity of cadmium-based quantum dots," *Biomaterials*, vol. 33, no. 5, pp. 1238–1244, 2012.

[95] K. G. Li, J. T. Chen, S. S. Bai et al., "Intracellular oxidative stress and cadmium ions release induce cytotoxicity of unmodified cadmium sulfide quantum dots," *Toxicology in Vitro*, vol. 23, no. 6, pp. 1007–1013, 2009.

[96] S. J. Cho, D. Maysinger, M. Jain, B. Röder, S. Hackbarth, and F. M. Winnik, "Long-term exposure to CdTe quantum dots causes functional impairments in live cells," *Langmuir*, vol. 23, no. 4, pp. 1974–1980, 2007.

[97] S. Dailianis, S. M. Piperakis, and M. Kaloyianni, "Cadmium effects on ROS production and DNA damage via adrenergic receptors stimulation: role of Na+/H+exchanger and PKC," *Free Radical Research*, vol. 39, no. 10, pp. 1059–1070, 2005.

[98] A. Hoshino, K. Fujioka, T. Oku et al., "Physicochemical properties and cellular toxicity of nanocrystal quantum dots depend on their surface modification," *Nano Letters*, vol. 4, no. 11, pp. 2163–2169, 2004.

[99] W.-H. Chan, N.-H. Shiao, and P.-Z. Lu, "CdSe quantum dots induce apoptosis in human neuroblastoma cells via mitochondrial-dependent pathways and inhibition of survival signals," *Toxicology Letters*, vol. 167, no. 3, pp. 191–200, 2006.

[100] J. Lovrić, H. S. Bazzi, Y. Cuie, G. R. Fortin, F. M. Winnik, and D. Maysinger, "Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots," *Journal of Molecular Medicine*, vol. 83, pp. 377–385, 2005.

[101] J. Lovrić, S. J. Cho, F. M. Winnik, and D. Maysinger, "Unmodified cadmium telluride quantum dots induce reactive oxygen species formation leading to multiple organelle damage and cell death," *Chemical Biology*, vol. 12, pp. 1227–1234, 2005.

[102] L. Lai, J.-C. Jin, Z.-Q. Xu, P. Mei, F.-L. Jiang, and Y. Liu, "Necrotic cell death induced by the protein-mediated intercellular uptake of CdTe quantum dots," *Chemosphere*, vol. 135, pp. 240–249, 2015.

[103] K. C. Nguyen, W. G. Willmore, and A. F. Tayabali, "Cadmium telluride quantum dots cause oxidative stress leading to extrinsic and intrinsic apoptosis in hepatocellular carcinoma HepG2 cells," *Toxicology*, vol. 306, pp. 114–123, 2013.

[104] K. Kaviyarasu, K. Kanimozhi, N. Matinise et al., "Anti-proliferative effects on human lung cell lines A549 activity of cadmium selenide nanoparticles extracted from cytotoxic effects: investigation of bio-electronic application," *Materials Science and Engineering: C*, vol. 76, pp. 1012–1025, 2017.

[105] O. S. Viana, M. S. Ribeiro, A. Fontes, and B. S. Santos, "Quantum dots in photodynamic therapy," in *Redox-Active Therapeutics*, pp. 525–539, Springer, Berlin, Germany, 2016.

[106] K. V. Pavan Kumar, O. S. Nirmal Ghosh, G. Balakrishnan, P. Thirugnanasambantham, S. K. Raghavan, and A. K. Viswanath, "Green synthesis of zinc oxysulfide quantum dots using aegle marmelos fruit extract and their cytotoxicity in HeLa cells," *RSC Advances*, vol. 5, no. 22, pp. 16815–16820, 2015.

[107] A. A. P. Mansur, F. G. de Carvalho, S. M. Carvalho, L. C. de Oliveira, H. S. Mansur, and H. S. Mansur, "Carboxymethylcellulose/ZnCdS fluorescent quantum dot nanoconjugates for cancer cell bioimaging," *International Journal of Biological Macromolecules*, vol. 96, pp. 675–686, 2017.

[108] N. Tsolekile, S. Nahle, N. Zikalala et al., "Cytotoxicity, fluorescence tagging and gene-expression study of CuInS/ZnS QDS - meso (hydroxyphenyl) porphyrin conjugate against human monocytic leukemia cells," *Scientific Reports*, vol. 10, pp. 4936–5013, 2020.

[109] N. Tsolekile, S. Parani, M. C. Matoetoe, S. P. Songca, and O. S. Oluwafemi, "Evolution of ternary I-III-VI QDs: synthesis, characterization and application," *Nano-Structures & Nano-Objects*, vol. 12, pp. 46–56, 2017.

[110] J. Zhang, W. Sun, L. Yin, X. Miao, and D. Zhang, "One-pot synthesis of hydrophilic CuInS2 and CuInS2-ZnS colloidal quantum dots," *Journal of Materials Chemistry C*, vol. 2, no. 24, pp. 4812–4817, 2014.

[111] D. S. Bhattacharya, D. Svechkarev, A. Bapat, P. Patil, M. A. Hollingsworth, and A. M. Mohs, "Sulfation modulates the targeting properties of hyaluronic acid to P-selectin and CD44," *ACS Biomaterials Science and Engineering*, vol. 6, no. 6, pp. 3585–3598, 2020.

[112] B. Guan, R. Yan, R. Li, and X. Zhang, "Selenium as a pleiotropic agent for medical discovery and drug delivery," *International Journal of Nanomedicine*, vol. 13, pp. 7473–7490, 2018.

[113] M. Gharbavi, B. Johari, N. Mousazadeh et al., "Hybrid of niosomes and bio-synthesized selenium nanoparticles as a novel approach in drug delivery for cancer treatment," *Molecular Biology Reports*, vol. 47, no. 9, pp. 6517–6529, 2020.

[114] S. Zhao, Q. Yu, J. Pan et al., "Redox-responsive mesoporous selenium delivery of doxorubicin targets MCF-7 cells and

synergistically enhances its anti-tumor activity," *Acta Biomaterialia*, vol. 54, pp. 294–306, 2017.

[115] V. Krishnan, C. Loganathan, and P. Thayumanavan, "Green synthesized selenium nanoparticles using Spermacoce hispida as carrier of S-allyl glutathione: to accomplish hepatoprotective and nephroprotective activity against acetaminophen toxicity," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 47, no. 1, pp. 56–63, 2019.

[116] H. Xu, W. Cao, and X. Zhang, "Selenium-containing polymers: promising biomaterials for controlled release and enzyme mimics," *Accounts of Chemical Research*, vol. 46, no. 7, pp. 1647–1658, 2013.

[117] J. Huang, W. Huang, Z. Zhang et al., "Highly uniform synthesis of selenium nanoparticles with EGFR targeting and tumor microenvironment-responsive ability for simultaneous diagnosis and therapy of nasopharyngeal carcinoma," *ACS Applied Materials & Interfaces*, vol. 11, no. 12, pp. 11177–11193, 2019.

[118] S. H. Jalalian, M. Ramezani, K. Abnous, and S. M. Taghdisi, "Targeted co-delivery of epirubicin and NAS-24 aptamer to cancer cells using selenium nanoparticles for enhancing tumor response in vitro and in vivo," *Cancer Letters*, vol. 416, pp. 87–93, 2018.

[119] H. Chen, P. Li, Y. Yin et al., "The promotion of type 1 T helper cell responses to cationic polymers in vivo via toll-like receptor-4 mediated IL-12 secretion," *Biomaterials*, vol. 31, no. 32, pp. 8172–8180, 2010.

[120] Y. Xia, J. Zhong, M. Zhao et al., "Galactose-modified selenium nanoparticles for targeted delivery of doxorubicin to hepatocellular carcinoma," *Drug Delivery*, vol. 26, no. 1, pp. 1–11, 2019.

[121] T. Nie, H. Wu, K.-H. Wong, and T. Chen, "Facile synthesis of highly uniform selenium nanoparticles using glucose as the reductant and surface decorator to induce cancer cell apoptosis," *Journal of Materials Chemistry B*, vol. 4, no. 13, pp. 2351–2358, 2016.

[122] M. V. Liberti and J. W. Locasale, "The Warburg effect: how does it benefit cancer cells?" *Trends in Biochemical Sciences*, vol. 41, no. 3, pp. 211–218, 2016.

[123] B. Yu, Y. Zhou, M. Song et al., "Synthesis of selenium nanoparticles with mesoporous silica drug-carrier shell for programmed responsive tumor targeted synergistic therapy," *RSC Advances*, vol. 6, no. 3, pp. 2171–2175, 2016.

[124] X. Fang, C. Li, L. Zheng, F. Yang, and T. Chen, "Dual-targeted selenium nanoparticles for synergistic photothermal therapy and chemotherapy of tumors," *Chemistry - An Asian Journal*, vol. 13, no. 8, pp. 996–1004, 2018.

[125] S. Fu, F. Li, M. Zang et al., "Diselenium-containing ultrathin polymer nanocapsules for highly efficient targeted drug delivery and combined anticancer effect," *Journal of Materials Chemistry B*, vol. 7, no. 32, pp. 4927–4932, 2019.

[126] W. Cao, Y. Gu, M. Meineck, T. Li, and H. Xu, "Tellurium-containing polymer micelles: competitive-ligand-regulated coordination responsive systems," *Journal of the American Chemical Society*, vol. 136, no. 13, pp. 5132–5137, 2014.

[127] W. Cao, L. Wang, and H. Xu, "Selenium/tellurium containing polymer materials in nanobiotechnology," *Nano Today*, vol. 10, no. 6, pp. 717–736, 2015.

[128] F. Li, T. Li, W. Cao, L. Wang, and H. Xu, "Near-infrared light stimuli-responsive synergistic therapy nanoplatforms based on the coordination of tellurium-containing block polymer and cisplatin for cancer treatment," *Biomaterials*, vol. 133, pp. 208–218, 2017.

[129] Z. Guo, Y. Liu, X. Cheng et al., "Versatile biomimetic cantharidin-tellurium nanoparticles enhance photothermal therapy by inhibiting the heat shock response for combined tumor therapy," *Acta Biomaterialia*, vol. 110, pp. 208–220, 2020.

[130] T. Yang, H. Ke, Q. Wang et al., "Bifunctional tellurium nanodots for photo-induced synergistic cancer therapy," *ACS Nano*, vol. 11, no. 10, pp. 10012–10024, 2017.

[131] W. Cao, F. Li, R. Chen, and H. Xu, "Tellurium-containing nanoparticles for controlled delivery of cisplatin based on coordination interaction," *RSC Advances*, vol. 6, no. 96, pp. 94033–94037, 2016.

[132] F. Fan, S. Gao, S. Ji, Y. Fu, P. Zhang, and H. Xu, "Gamma radiation-responsive side-chain tellurium-containing polymer for cancer therapy," *Materials Chemistry Frontiers*, vol. 2, no. 11, pp. 2109–2115, 2018.

[133] C. Yan, Q. Tian, and S. Yang, "Recent advances in the rational design of copper chalcogenide to enhance the photothermal conversion efficiency for the photothermal ablation of cancer cells," *RSC Advances*, vol. 7, no. 60, pp. 37887–37897, 2017.

[134] X. Zhang, J. Wu, G. R. Williams, S. Niu, Q. Qian, and L.-M. Zhu, "Functionalized MoS2-nanosheets for targeted drug delivery and chemo-photothermal therapy," *Colloids and Surfaces B: Biointerfaces*, vol. 173, pp. 101–108, 2019.

[135] X.-R. Song, X. Wang, S.-X. Yu et al., "Co9Se8Nanoplates as a new theranostic platform for photoacoustic/magnetic resonance dual-modal-imaging-guided chemo-photothermal combination therapy," *Advanced Materials*, vol. 27, no. 21, pp. 3285–3291, 2015.

[136] M. F. Kircher, A. de La Zerda, J. V. Jokerst et al., "A brain tumor molecular imaging strategy using a new triple-modality MRI-photoacoustic-Raman nanoparticle," *Nature Medicine*, vol. 18, no. 5, pp. 829–834, 2012.

[137] Z. Li, Y. Hu, M. Chang et al., "Highly porous PEGylated Bi2S3nano-urchins as a versatile platform for in vivo triple-modal imaging, photothermal therapy and drug delivery," *Nanoscale*, vol. 8, no. 35, pp. 16005–16016, 2016.

[138] J. Liu, X. Zheng, L. Yan et al., "Bismuth sulfide nanorods as a precision nanomedicine for in vivo multimodal imaging-guided photothermal therapy of tumor," *ACS Nano*, vol. 9, no. 1, pp. 696–707, 2015.

[139] X. Jiang, Y. Han, H. Zhang et al., "Cu-Fe-Se ternary nanosheet-based drug delivery carrier for multimodal imaging and combined chemo/photothermal therapy of cancer," *ACS Applied Materials & Interfaces*, vol. 10, no. 50, pp. 43396–43404, 2018.

[140] G. Song, Q. Wang, Y. Wang et al., "A low-toxic multifunctional nanoplatform based on Cu9S5@mSiO2Core-shell nanocomposites: combining photothermal- and chemotherapies with infrared thermal imaging for cancer treatment," *Advanced Functional Materials*, vol. 23, no. 35, pp. 4281–4292, 2013.

[141] Y. Chen, Z. Hou, B. Liu, S. Huang, C. Li, and J. Lin, "DOX-Cu9S5@mSiO2-PG composite fibers for orthotopic synergistic chemo- and photothermal tumor therapy," *Dalton Transactions*, vol. 44, no. 7, pp. 3118–3127, 2015.

[142] H. Liu, H. Wang, Y. Xu et al., "Lactobionic acid-modified dendrimer-entrapped gold nanoparticles for targeted computed tomography imaging of human hepatocellular carcinoma," *ACS Applied Materials & Interfaces*, vol. 6, no. 9, pp. 6944–6953, 2014.

[143] S. Huang, Y. Wei, Z. Cheng et al., "Controllable synthesis of hollow porous silica nanotubes/CuS nanoplatform for

targeted chemo-photothermal therapy," *Science China Materials*, vol. 63, pp. 1–12, 2020.

[144] L. Zhang, Y. Li, Z. Jin, J. C. Yu, and K. M. Chan, "An NIR-triggered and thermally responsive drug delivery platform through DNA/copper sulfide gates," *Nanoscale*, vol. 7, no. 29, pp. 12614–12624, 2015.

[145] Z. Li and S. L. Wong, "Functionalization of 2D transition metal dichalcogenides for biomedical applications," *Materials Science and Engineering: C*, vol. 70, pp. 1095–1106, 2017.

[146] D. Shao, Q. Zeng, Z. Fan et al., "Monitoring HSV-TK/Ganciclovir cancer suicide gene therapy using CdTe/CdS core/shell quantum dots," *Biomaterials*, vol. 33, no. 17, pp. 4336–4344, 2012.

[147] S. Nigar and T. Shimosato, "Cooperation of oligodeoxynucleotides and synthetic molecules as enhanced immune modulators," *Frontiers in Nutrition*, vol. 6, p. 140, 2019.

[148] L. Guo, D. D. Yan, D. Yang et al., "Combinatorial photothermal and immuno cancer therapy using chitosan-coated hollow copper sulfide nanoparticles," *ACS Nano*, vol. 8, no. 6, pp. 5670–5681, 2014.

[149] Z. Karjoo, X. Chen, and A. Hatefi, "Progress and problems with the use of suicide genes for targeted cancer therapy," *Advanced Drug Delivery Reviews*, vol. 99, pp. 113–128, 2016.

[150] L. G. Eissenberg, M. Rettig, F. Dehdashti, D. Piwnica-Worms, and J. F. DiPersio, "Suicide genes: monitoring cells in patients with a safety switch," *Frontiers in Pharmacology*, vol. 5, p. 241, 2014.

[151] R. Kanwar, J. Rathee, D. B. Salunke, and S. K. Mehta, "Green nanotechnology-driven drug delivery assemblies," *ACS Omega*, vol. 4, no. 5, pp. 8804–8815, 2019.

[152] G. Chen, B. Ma, Y. Wang et al., "CuS-based theranostic micelles for NIR-controlled combination chemotherapy and photothermal therapy and photoacoustic imaging," *ACS Applied Materials & Interfaces*, vol. 9, no. 48, pp. 41700–41711, 2017.