

Nano-theranostics: A novel platform in drug therapy

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Abstract

A fundamental component of customized medicine, theranostics is a therapy approach that combines therapeutics and diagnostics with the goal of increasing drug efficacy and safety while also monitoring treatment response. It will require significant advancements in predictive medicine. Theranostics is linked to tailored drug administration based on test results as well as a diagnostic that screens patients for potential adverse drug reactions. Early diagnosis and treatment have benefited from the designed nanoparticles with unique physicochemical characteristics. This allows treatments to be delivered and the detection method to be employed concurrently, not just before or after treatment but throughout the entire regimen. The development of nanotechnology presents more opportunities for theranostics applications using nanoparticle engineering, and it has demonstrated encouraging outcomes, particularly in cancer therapy when compared with conventional treatments.

Keywords: Customized Medicine; Theranostics; Nanoparticles; Diagnostic Imaging; Tailored Drug; Cancer therapy

1. Introduction

A paradigm change in the understanding of disease prognosis and effective therapeutic techniques to combat the repercussions of chronic health has been brought about by the application of nanotechnology in biomedicine and healthcare settings. A versatile platform for quick and early diagnosis of illness progression is offered by nano-based systems [1].

The term “theranostics,” coined by John Funkhouser in 2002, refers to the simultaneous integration of diagnosis and therapy and refers to an assemblage of diagnostic tools and appropriate therapeutic measures under a single platform [2, 3].

Nanotheranostics is to apply and further develop nanomedicine strategies for advanced theranostics, i.e., to apply and further develop various nanocarriers such as polymer conjugations, micelles, liposomes, dendrimers, inorganic and metal nanoparticles, carbon nanotubes, nanoparticles of biodegradable polymers for controlled, sustained and targeted co-delivery of diagnostic and therapeutic agents for better theranostic effects and fewer side effects. The aim is to diagnose and treat the disease at an early stage, when the disease is most likely to be curable or at least treatable. Nanotheranostics can be promising even for fatal diseases, such as cancer, cardiovascular diseases, and AIDS, thereby saving resources and enhancing the quality of life for patients. Nanomedicine, defined as the application of nanotechnology to diagnose, treat, and prevent diseases at the cellular and molecular level, can also be efficient for the development of theranostic candidate to combine diagnosis and therapy simultaneously [4,5,6]. The notable advantages of theranostic approach are selectivity, low toxicity, target-specificity, and tenability [7].

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Several internal markers influence theranostic functional modalities, such as variations in pH, compliance with redox reactions, cellular enzymatic level, and response from genetic materials [8].

The concept of theranostics is critical due to its potential as a next-generation personalized medicine. It allows a series of sequential steps, such as early detection and diagnosis of disease, disease prognosis, therapy selection, and therapeutic efficacy monitoring, with high precision selectivity [9].

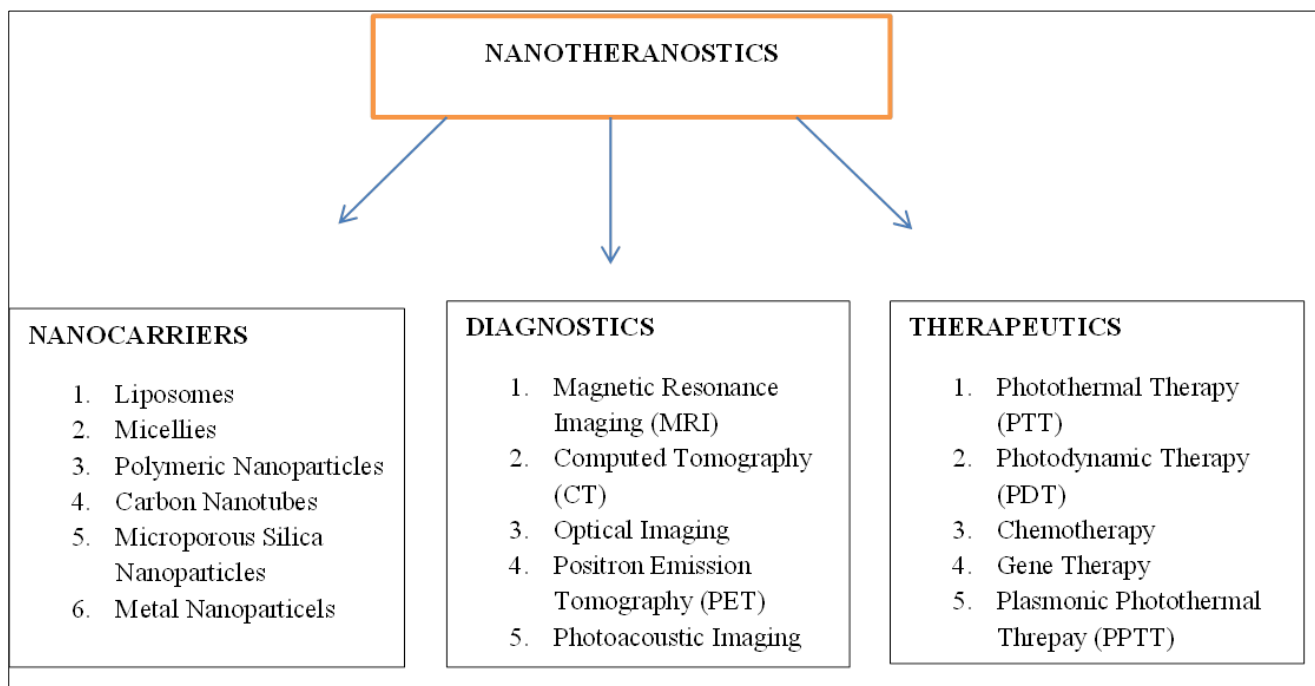


Figure 1 A schematic overview of the concept of nanotheranostics

Differential class nanomaterials, including magnetic, carbon- and silica-based, metal- and polymeric-based, and silica-based nanomaterials, demonstrated bimodal uses from both the perspective of diagnosis and treatment. Specifically, semiconductor quantum dots (QDs), organic and polymeric nanomaterials, and metal-based nanoparticles with high plasmon resonance (HPR), and light-emitting and light-responsive nanomaterials have drawn a lot of interest as effective and affordable theranostics agents [10].

Carbon-based nanomaterials are thought to have revolutionary properties for biomedical applications because of their distinct structural dimensions, distinct physicochemical properties, simplicity of functionalization, enhanced biocompatibility, and, most crucially, their wide spectrum of one-photon properties [11].

Polymeric nanoparticles, in addition to carbon-based nanomaterials, and their amalgamation with diverse nanomaterials have introduced an additional side to nanomaterial-mediated theranostics concerning multifarious functional characteristics [12].

When employed as contrasting agents in near-infrared (NIR), two-photon, and photoacoustic imaging, the conjugated polymeric nanoparticles' chemistry strictly permits multimodal imaging of deeply placed tissues with spatial resolution. Therefore, it was discovered that conjugated polymeric nanoparticles had a role in the early detection of illness. Additionally, it has been noted that these conjugated nanomaterials affect therapeutic modalities like photothermal therapy (PTT) and photodynamic therapy (PDT), which are thought to be important in non-invasive cancer therapies due to their earlier clinical approval and may therefore be helpful in the management of cardiovascular diseases [13,14].

A variety of traditional diagnostic techniques, including optical imaging, computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), photoacoustic tomography, and ultrasound, are using nanomaterials as efficient contrasting agents [15].

Nanoparticles (NPs) themselves may also act as multifunctional agents due to their unique properties; for instance, gold (Au) has many unique properties like surface functionalization, plasmon resonances, photo thermal ablation, and ease of detection [16].

Surface plasmon resonance (SPR) is a process that may be detected quantitatively and optically, wherein input light is transformed into both absorbed and dispersed components. The optical qualities are provided by the scattered component, and the thermal effect is provided by the absorbed portion. Real-time molecule binding kinetics analysis is done with it. It needs a very small amount of material and is a label-free, very sensitive detection approach. While other methods, such as Enzyme-linked Immunosorbent Assay (ELISA), simply provide the binding affinity, surface plasmon resonance (SPR) provides the binding kinetics, or the on-and-off phenomena, which is dependent on the association and dissociation of molecules. The limited sensitivity of plasmon resonant Nanoparticles (NPs) caused by background scattering by cells and tissues is their only drawback [17, 18].

Photothermal (PT) techniques can be used to enhance the quality of the images. Electromagnetic radiation, most commonly in the near-infrared (NIR) range, is employed in photothermal treatment (PTT). Heat is produced upon absorption of near-infrared range photons. The neighboring cells are killed by this heat. This method has previously been effectively applied to eradicate metastasized cancer cells in addition to localized malignant cells [19].

In actuality, photothermal treatment (PTT) is an evolution of photodynamic therapy. A photosensitizer, such as porfimer sodium, is used in photodynamic therapy. This photosensitizer is administered intravenously. Cells in the body absorb photosensitizers. Nonetheless, compared to cancer cells, normal body cells release photosensitizer more quickly. Therefore, only diseased cells retain the majority of photosensitizers after 24 to 72 hours, and only cancerous cells are exposed to radiation when the body is exposed to a laser beam with a particular wavelength. Reactive oxygen species (ROS), which photosensitizer creates, destroy neighboring cells [20].

However, while photodynamic therapy (PDT) is limited by its dependency on oxygen, photothermal therapy (PTT) offers several advantages. The issue with Photothermal (PT) approaches is that they require greater laser-induced temperatures, which can be harmful to cells and molecules. In contrast, photothermal treatment (PTT) has superior penetration and can be utilized to treat deep tumors and cancer metastases [16].

The nanomaterials facile manufacturing, distinct physicochemical properties, and dual uses made them a novel platform for diagnosing and redefining treatment approaches for a range of long-term medical disorders, including neurodegenerative illnesses, cancer etc [21].

2. Biomarkers for Theranostics

There is no difference between molecular markers and biomarkers. While biomarkers have been used in therapeutic settings since antiquity, current research efforts are concentrated on the discovery and creation of molecular biomarkers that have the potential to reliably identify diseases in their early stages, predict treatment responses to stimuli, and forecast prognosis. An external or internal stimulus could be used for nanotheranostics [22].

External stimulus is commonly used as imaging biomarkers. Imaging biomarkers offer several advantages like patient convenience, noninvasive procedure, and highly intuitive. By imaging biomarkers one can get both qualitative and quantitative data. It includes computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), near-infrared spectroscopy (NIR) that responds to magnetic field, temperature, ultrasound, light, or electric pulses, Nuclear Imaging Agents [23].

Considering the limitations of external stimuli, numerous internal stimuli such as glucose concentrations, pH differences, redox reactions, Hypoxia, Nucleic Acids (i.e., DNAs or RNAs) as Bioresponsive Switches and other ions/small biomolecules are more efficient for the designing of smart drug delivery systems [16].

3. Types of Nanomaterials Used in Nanotheranostics

There are different types of nanomaterials as shown in Figure 2 and these are most commonly used as they are having good results in both therapeutics and diagnostics.

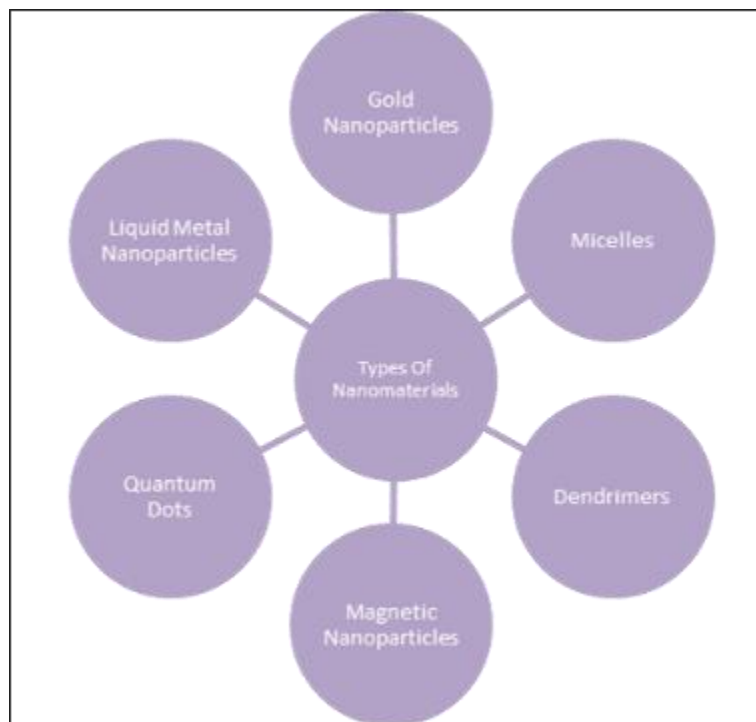


Figure 2 Types of Nanomaterials used in Nanotheranostics

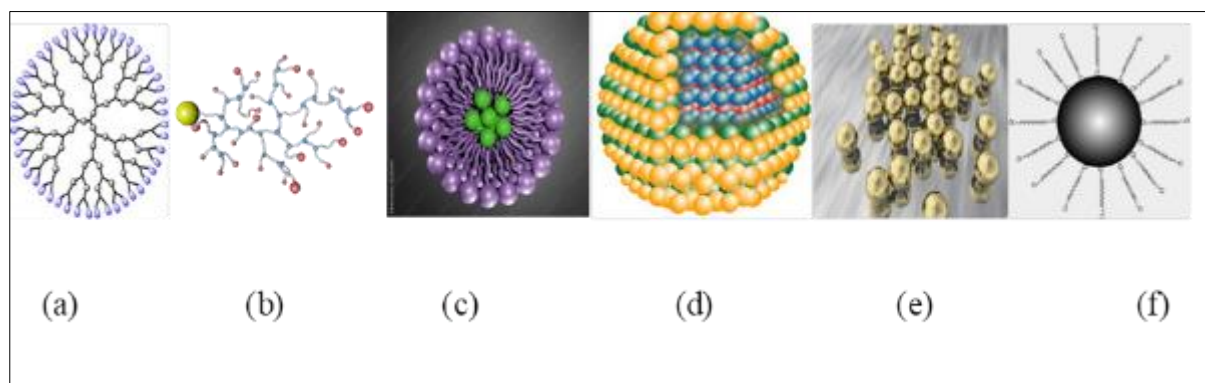


Figure 3 Diagrammatic Illustration Of Nanocarriers a)Dendrimers ,b)Polymers ,c)Micelle ,d)Quantum Dots ,e)Gold Nanoparticles ,f)Magnetic Metal Nanoparticles

4. Metallic Nanoparticles

Metallic nanoparticles are the foundation of the majority of nanoformulations utilized in contemporary theranostic applications. Because of their distinctive physical and chemical characteristics, metals including gold (Au), silver (Ag), zinc (Zn), and titanium (Ti) have so drawn a lot of interest for use as theranostics agents [24].

Their physiochemical capabilities are enhanced by their increased surface area and high surface-area-to-volume ratio, which makes them particularly useful for cancer treatments. Additionally, theranostic agents are ideal options with improved biocompatibility toward the living system due to their simplicity of surface synthesis. One of the main characteristics of metallic nanoparticles in comparison to their bulk state is surface plasmon resonance (SPR). As such, it has evolved into a fingerprint feature and an x-factor for image-guided metallic nanoparticle medicine delivery [25, 26, 27, 28].

It is possible to think of metallic nanoparticles as a lattice of ionic cores with conduction electrons traveling nearly freely inside the lattice structure. Because of this, nanoparticles can be exposed to electromagnetic light, which intensifies the collective vibrations of conductive electrons and causes surface plasmon resonance. Other optical materials will scarcely be able to achieve this resonant optical feature caused by the excitation of metallic nanoparticles. The metallic NP's charge, size, shape, and surrounding medium all have a direct impact on surface plasmon resonance. Because of this, several metallic nanoparticles (NPs) with particular plasmonic characteristics are being employed in theranostic applications [29].

Metallic nanoparticles can have numerous ligands coated on their surface, such as folic acid (FA), biotin, paclitaxel (PTX), and polyethylene glycol (PEG), which can be used as effective theranostic drugs, particularly for cancer treatments as they improve biocompatibility. As a result, metallic nanoparticles (NPs) have found widespread application as imaging agents in image-guided medication administration, photoacoustic imaging (PA), and computed tomography imaging (CT). Furthermore, medication delivery guided by images can also be used as therapeutic agents in radiotherapy (RT), photodynamic therapy (PDT), and photothermal therapy (PTT) [16].

4.1. Gold Nanoparticles

Gold nanorods, gold nanoshells, and gold nanocages are just a few examples of the unusual forms and sizes that can be achieved in gold nanoparticle synthesis. The optical and thermal properties of gold nanoparticles that are important for theranostics are explained by particular shifts in the localized surface plasmon resonance (LSPR), which is caused by changes in the shape and size of the particles. Gold-based nanomaterials exhibit substantial vibrational energy when excited with a laser energy tailored to the particular localized surface plasmon resonance (LSPR), leading to high temperatures that are beneficial for tissue ablation. Photothermal therapy can be used to ablate tumor tissue when gold nanoparticles are directed towards a specific tumor site, especially in areas that are challenging to operate on. Moreover, localized surface plasmon resonance (LSPR) bands can be tuned towards the near infrared region (NIR) to take advantage of biological tissue's optical window and pierce deeply into the tissue to fully utilize LSPR's *in vivo* capabilities. Apart from their therapeutic applications, gold nanoparticles possess potent fluorescent-quenching properties due to the presence of localized surface plasmon resonance (LSPR), which can be employed to identify particular molecular biomarkers. Due to their high atomic number and x-ray absorption coefficient, gold nanoparticles can also be used as radiation sensitizers or computed tomography imaging agents. When used in conjunction with proven surface conjugation techniques, gold nanoparticles can function as efficient nanotheranostics [30].

4.2. Liquid Metal Nanoparticles

Researchers have been interested in light-driven liquid metal nanotransformers because they present an unusual theranostics application. This is especially true in the field of bioimaging. Because of their chemical stability and inertness to water at normal temperature, liquid metals with lower melting points, such as gallium, gallium-indium eutectic alloys, and gallium-indium-tin alloys, have been studied for bioimaging applications. Liquid metal compositions have demonstrated their advantages in relation to the photoacoustic effect recently. Furthermore, the ability of liquid metal formulations to produce heat and reactive oxygen species in the near-infrared range has made them useful for the efficient removal of cancer cells. However, a significant barrier to a broad adoption is its increased toxicity [31].

5. Magnetic Nanoparticles (MPNs)

Because they can be noninvasively viewed by Magnetic Resonance Imaging (MRI), magnetic nanoparticles can be used as nanotheranostics. High spatiotemporal resolution and deep penetration into soft tissue are provided by Magnetic Resonance Imaging (MRI); nevertheless, exogenous contrast chemicals may still be needed to improve detection sensitivity (single/noise ratio). The T1 and T2 proton relaxation times in tissue can be shortened by positive and negative contrast agents, respectively, increasing bright or dark contrast.

Super-paramagnetic iron oxide can be used as the building block for T2 contrast agents, while metal ions such paramagnetic gadolinium (Gd³⁺) and manganese (Mn²⁺ and Mn³⁺) can lengthen the T1 relaxation time and act as T1 contrast agents. The FDA has approved T1 Gd³⁺-based MRI contrast agents (such as Magnevist®, Bayer Schering Pharma, Berlin, Germany) and T2 iron oxide-based MRI contrast agents (such as Feridex® or GastroMARK®, AMAG Pharma, MA, USA). Apart from GastroMARK, the majorities of iron oxide MRI contrast agents has been withdrawn from the market and are not available in the United States. The most commonly used magnetic nanoparticles with inherent imaging capabilities for T2 contrast are iron oxide nanoparticles (IONPs).

Nanoparticle formulations containing these metallic particles, like liposomes or micelles, are becoming more and more common as drug-delivery and imaging agents with theranostic potential [32].

6. Polymeric Nanoparticles

Polymeric nanoparticles are widely recognized as a class of integrated nanocarriers for diagnosis and therapy. Copolymer self-assembly allows for the integration of numerous functional units into soluble macromolecules, resulting in the formulation of these nanoparticles. Thus, several medicinal and imaging compounds can be put into polymeric formulations. However, effective solutions are needed for polymeric nanoparticles to reduce their immunogenicity and antigenicity while increasing their residence length and stability inside the biological system. Consequently, the most popular tactic is to use PEG to alter nanocarriers. PEG acts as a barrier to protect the polymeric nanocarrier from renal clearance and steric hindrance-induced degradation [33, 34].

The synthesis of polymeric nanoparticles (NPs) frequently uses synthetic polymers like polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), poly-glutamic acid, polyglycolide, poly aspartic acid, hyaluronic acid (HA), and poly anhydride, as well as conventional natural polymers like chitosan, gelatin, albumin, and sodium alginate. Consequently, the resulting polymeric nanoparticles can be synthesized into drug-polymer conjugates, polymersomes, polyplexes, nanocapsules, nanospheres, and micelles). Additionally, the physiochemical characteristics of the polymeric nanoparticles, such as their hydrophobicity, molecular weight, polydispersity index, and crystallinity, control the kinetics of drug delivery and dissolution [35, 36].

Using photoactive chemicals, iron oxide, gadolinium, gold and iodine nanoparticles allows them to be applied in single-photon emission computed tomography, Magnetic Resonance Imaging (MRI), Computed Tomography(CT) imaging, and near-infrared imaging, in that order. For instance, 3,4-difluoro benzylidene curcumin (CDF), which has low water solubility but antibacterial, antioxidant, anti-inflammatory, and anticancer qualities, can be administered with effectiveness using polymeric dendrimers [37, 38, 39, 40].

Moreover, conjugation with other nanomaterials, such magnetic and metallic nanoparticles, enables their application in gene therapy, PTT, and PDT, among other applications. These changes allow polymeric nanoparticles to be successfully applied in disease management applications [41].

6.1. Dendrimers

Among the several polymer-based nanomaterials, dendrimers have demonstrated a great deal of promise as drug delivery nanocarriers tailored to individual tumors. Dendrimers have an exact architecture and composition, are highly branching, and have a monodispersed weight distribution [42].

Because dendrimers have significant positive charges, they can act as agents of transfection. Additionally, they can functionalize with antibodies, peptides, folate, and other targeted molecules to the surface's functional groups [43].

Although they have been widely used as medication and gene carriers, their ability to collaborate on diagnosis and treatment is made possible by the existence of functional groups. For example, delivering complexing short interfering RNA and administering gold nanostar-stabilized dendrimers enable computed tomography (CT) imaging, photothermal treatment (PTT), and tumor gene silencing. Furthermore, gadolinium-containing dendrimers can be administered to facilitate their usage as Magnetic Resonance Imaging (MRI) contrasting agents [44, 45].

It may demonstrate certain limitations for their application, despite the fact that we have defined it as a viable option for nanotheranostics. Dendrimers have the ability to interact with proteins, organelles, and cell membranes at the nanoscale. It is possible for dendrimers with cationic surface groups to interact with the lipid bilayer in a way that both increases and decreases its permeability [46, 47, 48, 49].

6.2. Micelles

Polymeric micelles have garnered significant attention in recent decades as a versatile nanosystem with the potential to treat cancer. Preclinical and clinical researches are currently successfully claiming these nanocarriers. Polymeric micelles, put simply, are spheroid nanoplateforms consisting of a hydrophobic core and a hydrophilic shell. They are particularly drawn to medical treatments because of their kinetic stability, thermodynamic stability, and large payload in smaller dimensions. Superparamagnetic IONPs and DOX-entrapped polymeric micelles with a central polymeric core can be utilized as a multipurpose agent for magnetic resonance imaging and therapeutic delivery [50, 51].

Furthermore, in cancer treatment, PEG–polylactic acid micelles can function as a three-in-one nanocarrier system for hydrophobic medications including rapamycin, 17-allylamino-17-demethoxygeldanamycin, and paclitaxel. Furthermore, they can be used as an NIR optical imaging agent because polyethylene glycol-block-poly- ϵ -caprolactone

(PEG-b-PCL) micelles are entrapped with a carbocyanine medication. Thus, these methods demonstrate the manipulation of polymeric micelles for various theranostic purposes [52].

6.3. Polymersomes

A unique class of thin-shelled capsules known as polymersomes is derived from block copolymer chemistry. Therefore, it is possible to characterize polymersomes as self-assembling nanocarriers that possess amphiphilic block copolymers and a thicker, more durable membrane than liposomes. Thus, the development of cocktails—a synergistic effect—will result from the mixing of hydrophobic medications to thicken the wall and hydrophilic pharmaceuticals into the vesicular lumen. Furthermore, polymersomes' physicochemical characteristics made them attractive as viable options for targeted medication delivery [53].

Additionally, Iron oxide nanoparticles (IONP) stabilized by lipo-polymersomes has been shown to be useful for magnetically guided gene delivery by another set of researchers. Furthermore, a number of investigations have demonstrated their potential as a nanocarrier for effective medication delivery [54].

7. Semiconducting Nanoparticles or Quantum Dots

It is now well acknowledged that nanotechnology is a multidisciplinary field in which various types of nanoparticles can be readily converted into a variety of uses [55]. Quantum dots (QDs) are better fluorescent nanocrystals that are semiconducting [56]. In light of this, Quantum dots (QDs) have advantages over molecular dyes in biological imaging and therapeutic applications due to their resistance to photobleaching [57, 58].

Groups II–VI Zn (S, Se) and Cd (S, Se, Te), IV–VI Pb (S, Se), I–VI Ag₂ (S, Se), II–V Cd₃ (P, As)₂, and III–V In (P, As) are among the several Quantum dots (QDs) types that are now being successfully employed in biological sectors. Furthermore, ternary I–III–VI QDs were created for these uses, where I = Cu or Ag, III = Ga or In, and VI = S or Se [59, 60]. However, the manufacturer's preference and the intended usage may cause the composition to change. Essentially, Quantum dots (QDs) accumulate with an exterior crystal shell and a fluorescent core to protect the core from the biological system's ionization process [61].

Stable distribution in aqueous conditions, tolerance to varying pH ranges, and ideally water solubility are required for biological applications. Developments in nanotheranostics have produced efficient methods for producing Quantum dots with improved characteristics for their intended uses. Comparing semiconductor nanocrystals to the Bohr radius of their bulk materials reveals size-dependent optical characteristics. Quantum confinement enhances the band gap, which causes size-dependent Quantum dots emission and absorption spectra with band edge characteristics that shift higher energies with decreasing particle size [62,63].

Quantum dots (QDs) have exceptional optical characteristics that make them useful for biomedical applications. Their symmetrical and narrow emission profiles are good for maintaining color purity and precise emission tenability, and their broad excitation range and high molar absorption coefficients make them suitable for high-throughput detection. Moreover, resistance to photobleaching and high photoluminescence (PL) quantum yield (QY) increase the likelihood of long-term biological process tracking and observation. Furthermore, their comparatively extended photoluminescence lifetimes allow for the exclusion of autofluorescence [64].

Therefore, it has been suggested that Quantum dots (QDs) can be appreciated as multimodal contrast imaging agents that can employ infrared fluorescence, positron emission tomography, computed tomography, Magnetic resonance imaging [65].

Novel nanoparticles called quantum dots have drawn a lot of attention in their role as medicine delivery systems. Therefore, Quantum dots (QDs) can be made with various biological molecules (antibodies, peptides, and aptamers), just like the other nanoparticles covered in earlier sections of this chapter, to improve their biocompatibility for target drug delivery [66].

Antitumor drug loading using conjugated graphene Quantum dots (QDs) with folic acid was demonstrated by Wang et al. (2014). Furthermore, some research has demonstrated that QDs can be employed as a carrier molecule to deliver siRNAs—short, double-stranded small interfering RNAs—for non-drugable targets. These siRNAs can cause RNA interference, which can impede the translation of proteins. They can also be used as photostable beacons to track the delivery of siRNA [67, 68].

Therapeutic efficacy of Quantum dots (QDs) has given opportunities to apply them in photothermal (PTT) and photodynamic (PDT) therapy. While PDT needs photosensitizers to produce Reactive Oxygen Species (ROS) to destroy cancer tissues, PTT requires near-infrared (NIR) absorption platforms that can cause hyperthermia on the target region, producing cellular damage. While the findings from the above applications were encouraging, there might be issues with other NPs. For example, the depletion of oxygen in tissues can cause the efficiency of PDT to vary over time. Aside from that, heat shock brought on by hyperthermia can reduce the effectiveness of PTT by inhibiting tumor cell death. Cu₂(OH)PO₄ quantum dots, for example, have been found as viable nanoplatforms to overcome these limitations for effective disease treatments [65].

8. Conclusion

The drastic development in nanotechnology has granted a tremendous value on medical applications, especially in cancer. Hence, it requires well-improved platforms for efficient performance because dealing with biological systems is a serious process and requires to be sharply focused. One effective method to get around these restrictions is to use nanotheranostics. Nanoparticles intrinsic qualities allow them to combine therapeutic and diagnostic uses onto a single platform. As a result, by improving the drug's biocompatibility and pharmacokinetic potential for the therapies, this sets off the process for targeted drug administration. Making a diagnosis makes it possible to concentrate on and obtain accurate data for clinical purposes. The field of nanotheranostics is now making strides in real-time disease treatment monitoring, which is a major breakthrough for therapeutics. These days, there is a lot of research being done on the potential uses of quantum dots, liquid metal nanoparticles, and nanoparticles for theranostics. Although their usefulness and value are currently being discussed in many different disciplines, nanotoxicological aspects are of greater concern than their applications. Then, physicochemical characteristics like size, shape, stability, and surface functionality can cause toxicity on biological systems that also rely on extrinsic factors like organismal features like age, the type of target site, and the pH of the internal environment to which the nanoparticles are exposed. Consequently, nanotheranostics can be advanced toward next-generation therapy with the right formulation and manipulation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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