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Title

Novel Advancements in Nanomaterials-Based Contrast Agents Across Multimodal Imaging and Theranostic Applications

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Abstract

Nanomaterials offer significant potential for non-invasive multimodal imaging due to their multifunctionality and tunable nanoscale features. Advances in their design and conjugation with organic and inorganic materials have enhanced their production and utility. Functionalizing nanoparticles (NPs) with imaging agents enables high-contrast imaging with spatial precision. Plasmonic NPs, lanthanide NPs, semiconductor-based quantum dots (QDs), and biogenic NPs have been employed as contrast agents for sensitive and specific imaging. Diseases such as cancer, neurological, gastrointestinal, and cardiovascular conditions demand early diagnosis for effective therapy. Therefore, functionalized NPs are employed to enhance molecular imaging by penetrating cells and targeting biomolecules, improving imaging modalities like positron emission tomography (PET), X-ray computed tomography (CT), near-infrared fluorescence (NIRF), magnetic resonance imaging (MRI), and photoacoustic imaging (PAI). This review highlights novel NP applications for image-guided surgery and treatment, emphasizing their role in combining imaging techniques for precision diagnostics. Challenges such as clinical translation and toxicity are discussed, underscoring the need for further research. NP-based contrast agents have emerged as an effective tool for bridging the gap between traditional diagnostics and personalized treatments, enabling real-time therapeutic monitoring and early stage theranostics.

Keywords: Nanoparticles; Multimodal Imaging; Contrast Agents; Molecular Diagnostics; Theranostics

1. Introduction

Non-invasive imaging technologies offer sophisticated visualization aimed at early-stage disease diagnosis without entering and damaging the local body tissues due to which they have drawn significant attention in both biological and medical imaging [1]. Unlike invasive methods, non-invasive imaging avoids direct contact with organs or tissues, thus reducing complications, improving repeatability, and enabling longitudinal studies. Contrast agents enhance the performance of imaging modalities by increasing the specificity and sensitivity which is essential for tracking the activity of disease and their response to certain therapeutics [2]. The application of diverse range of imaging tools has broadly expanded from anatomical imaging to including functional and molecular imaging, thereby enhancing the accuracy of diagnosis and effectiveness of therapeutics. The use of molecular probes has not only resulted in the generation of high-resolution images of anatomical structures, but also aided in determining

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tissue permeability and organ perfusion [3]. Conventional contrast agents, such as iodinated compounds and gadolinium-based agents, have long been used to enhance anatomical imaging by altering the physical properties of tissues [4 5]. While conventionally synthesized contrast agents have enabled high-contrast imaging at the macro level, achieving micro-level imaging required for visualizing dynamic behaviors and specific cellular functions still remains challenging. In recent years, stimuli-responsive nanoprobes capable of activating their imaging signals only in specific tumor microenvironments, such as acidic pH or hypoxic regions, have gained significant interest for improving signal-to-noise ratios and minimizing off-target effects [6 7]. Magnetic particle imaging has also emerged as an excellent modality exploiting the superparamagnetic properties of iron oxide NPs offering radiation-free and highly sensitive detection for quantitative theranostic applications [8]. Other than this, hybrid nanoplatforms integrating organic, inorganic, and biological components have also played a significant role in offering multifunctionality for simultaneous multimodal imaging and combinatorial therapies [9]. Genetically engineered and endogenously produced contrast agents have surpassed conventional ones, emerging as essential tools for probing specific molecules in pathophysiological conditions. Genetically engineered contrast agents are biologically encoded reporter proteins that are genetically modified to emit optoacoustic signals or produce chromophores that emit such signals to offer more benefits than exogenous contrast agents for prolonged duration [10]. Diverse range of contrast agents such as ferritin [11], luciferase [12], fluorescent proteins [10], aquaporins [13], have been used across different imaging modalities for longitudinal imaging. On the other hand, endogenously produced contrast agents are designed to be synthesized inside the body by cells, often through the introduction of specific reporter genes which means that, unlike conventional exogenous agents, there is no need to repeatedly administer chemical contrast media, which can cause toxicity, immune reactions, or off-target effects. For example, reporter enzymes such as β-galactosidase, tyrosinase, or synthetic enzymes can catalyze the production or accumulation of paramagnetic or diamagnetic metabolites that alter local MRI signal intensities [14 15]. This provides a way to visualize gene expression or metabolic activity directly within target tissues. The use of gas vesicles (GVs) as air-filled protein nanostructures naturally produced by certain microbes like cyanobacteria or archaea is yet another good example of endogenous contrast agents. Researchers have designed novel genetically encoded acoustic reporters by transferring the genetic machinery for GVs production into mammalian cell [16]. These GVs scatter ultrasound waves, generating strong acoustic contrast precisely at the sites where engineered cells produce them. Notably, GVs are synthesized by the body cells only, there is no need for repeated administration of synthetic

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microbubbles or external NP emulsions, which typically have short circulation times and may pose safety concerns [17] [18].

Nano-sized imaging and fluorescent materials are rapidly emerging as practical revolutionary tools for improving disease diagnosis across a broad spectrum of *in vivo* imaging techniques [19]. These agents provide a sensitive approach for non-invasive diagnostics because of their unique surface attributes which can be fabricated with a diverse range of targeting agents capable of high-contrast imaging. Latest advancement in the versatility of nanoprobes has enabled the functioning of novel imaging tools surpassing the intrinsic drawbacks of conventional diagnostics in the field of clinical diagnostics and bio-imaging at molecular level [20]. The electromagnetic and optical properties of a diverse range of NPs including plasmonic NPs, lanthanide NPs, semiconductor-nanocrystal based QDs and biogenic NPs have confronted a plethora of biomedical imaging-based applications **(Table 1)**. The co-delivery of therapeutic and diagnostic agents into a single NP have enabled the development and application of novel theranostic tools in biomedical sector. NP-encapsulated theranostic agents hold great promise in real-time monitoring of the intracellular accumulation, targeted delivery to specific tissue/organs and controlled release of the drug, resulting in increased efficacy and decreased side-effects. For example, in a recent study a glutathione-responsive nano prodrug was designed where drug release and fluorescence signal are tightly coupled, allowing simultaneous real-time visualization of intracellular uptake and therapeutic action [21]. NPs can serve as excellent contrast agents for imaging purpose because of their small size, surface properties and ultrasensitive detection. Despite rapid progress, challenges such as long-term safety profile, bioaccumulation, and standardized large-scale synthesis still need to be addressed before wide clinical translation of NP-based contrast agents.

This article aims to provide a detailed overview of the evolving role of nanomaterials, such as plasmonic NPs, lanthanide NPs, QDs, and biogenic NPs in biomedical imaging and theranostics. Furthermore, the review emphasizes the potential of the nanomaterials for early detection of complex diseases, including neurological, cardiovascular, gastrointestinal disorders, and cancer. Specifically, we highlight the application of NPs as multimodal contrast agents in different imaging techniques like PET, X-Ray CT, NIRF, MRI and PAI to enhance the diagnostic accuracy. We emphasize ongoing research efforts to harness the potential of the nanomaterials for early detection of complex diseases. Moreover, we have also reviewed recent advancements in nanomaterial-based combinatorial image-guided therapies, promises and

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perspectives on the ongoing development of early theranostics for improved patient-centred outcomes.

2. Types of Nanomaterials-Based Bioimaging Agents

2.1 Diagnostic Potential of Plasmonic NPs

Plasmonic NPs are metal-based nanoformulations, typically composed of gold, silver, or copper, that exhibit localized surface plasmon resonance (LSPR) phenomenon where conduction electrons collectively oscillate in response to light resulting in intense optical properties such as enhanced absorption and scattering, which are widely exploited in imaging and biosensing applications [22]. Plasmonic NPs have revolutionized biomedical and clinical imaging by enhancing the resolution, specificity, and sensitivity of diagnostic techniques. When these NPs interact with light, their conduction electrons undergo collective oscillations, leading to significant absorption and scattering at specific resonance frequencies thereby resulting in the production of strong electromagnetic fields. The enhanced electromagnetic fields generated by LSPR can enhance the signals in imaging modalities leading to improved sensitivity and resolution [23]. These NPs have emerged as potent candidates in the field of nanotechnological sciences due to their physical and chemical properties, such as small size, high surface-area-to-volume ratio, ease of functionalization, and tunable properties. This tunability facilitates the development of multimodal imaging agents that can operate across different imaging platforms, providing comprehensive diagnostic details [24]. Metallic NPs are categorized as clusters or colloidal particles depending on the crystal lattice and particle size ranging from 1-100 nm [25]. The size of NPs is mainly governed by its synthesis technique, which can be adjusted by modifying the temperature, pH, ratio of the reactants and concentration of the solvent [26]. Apart from this, the type and quantity of ligands used during synthesis also play a crucial role in controlling nucleation and growth dynamics [27]. The unique optoelectronic and light scattering properties of these NPs make them suitable to be exploited for diagnostic and therapeutic resulting in controlled release of theranostic agent. The application of metallic NPs in different imaging modalities including PET, CT scan, ultrasound (US), surface enhanced Raman spectroscopy (SERS), PAI and MRI has led to the advancement in the real-time diagnosis and treatment of various diseases. In this context, gold NPs (AuNPs), silver NPs (AgNPs), and copper NPs (CuNPs) offer unique advantages for specific imaging modalities. In a recent research, colloidal AuNPs in conjugation with arginine-glycine-aspartic acid (RGD) peptides have been used to perform optical coherence tomography (OCT) and photoacoustic

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microscopy (PAM) for the observation of choroidal neovascularization [28]. Furthermore, thiol-capped AuNPs synthesized from Turkevich method have also displayed high contrast in spectral photon counting CT (SPCCT), providing a proof-of concept as an ideal candidate for contrast imaging of cancer [29]. Moreover, gold nanospheres have also been used as PAI contrast agents for high contrast imaging of breast cancer [30]. The application of AgNPs as contrast imaging agent and biosensors is also of considerable interest to many researchers. The plasmonic properties of silver is better than that of gold as it experiences lower optical losses and delivers enhanced performance in plasmonic applications [31]. There is significant demand of AgNPs in light-based nanotechnologies that involve production and regulation of light through surface plasmon resonance (SPR). Due to their optical properties influenced by extinction coefficient, size and wavelength, AgNPs are widely utilized in imaging, photocatalysis, and biosensing applications, enabling trace detection of certain elements and facilitating the study of biological interactions and *in vivo* monitoring techniques [32]. Recent research has reported the fabrication of silver-iron oxide NPs (AgIONPs) that binds specifically and effectively to thrombus due to which it has been exploited as PAI and NIRF bimodal contrast imaging agent and photothermal therapeutic agent for thrombosis [33]. Likewise, in a computational simulation based finding it was observed that polyvinyl alcohol coated silver triangular nanoprisms were used for PAI and photothermal therapy of breast cancer in mouse models [34]. Apart from the utilization of monometallic NPs, infusion of an additional metal often leads to enhanced performance because the introduction of intermetallic polar bonds and structural irregularities increases the number of active sites. Additionally bimetallic NPs tend to form intricate structures comprising of core-shell, hollow or porous structures that further leads to improved SPR effects [35]. In a research, doxorubicin-functionalized bimetallic gold-core palladium-shell nanocomplex (Au@PdNDs.PEG/DOX) was designed for demonstrating theranostic effect against breast cancer enabling multimodal plasmon-based intracellular imaging alongside potent cytotoxic activity [36]. In another study, Fe–Au core–satellite NPs synthesized via pulsed laser ablation have been investigated for their multifunctional potential, serving both as bimodal MRI and CT contrast agents, and as effective sensitizers for photothermal therapy of cancer [37]. Likewise, polyethylene glycol (PEG)ylated AgNPs and AuNPs synthesized by one pot chemical reduction method have been used for CT imaging agent and radiosenistizing agent for the treatment of oral carcinomas [38]. The use of bimetallic NPs in cancer therapy is still in its early stages and will require extensive future research to unlock their full potential, particularly in advancing novel formulations and expanding applications into areas like gene therapy and immunotherapy. Conclusively,

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plasmonic NPs offer a unique platform for their exploitation as versatile tools due to their ability to bind with several ligands, therapeutic agents and radioisotopes, opening up the prospect of therapeutic administration and multimodal imaging. However, despite their promising applications, challenges such as toxicity, aggregation, and size-related limitations must be addressed to ensure the safe and effective use of these NPs in clinical settings. The dearth of certain noble metallic NPs may be attributed to their high price and limited availability. Despite the latest developments in the field of nano-imaging, the effect of long-term exposure of metallic NPs to patients is still unknown. Detailed research and comprehensive experimental data are required to figure out the ecological safety and biological efficacy of metallic NPs. The future of metallic NPs in clinical imaging holds great promise, particularly in the realms of theranostics, where diagnostic imaging and therapy are integrated into a single treatment regimen.

2.2 Optimization of Lanthanide NPs for Multimodal Luminescence Imaging

Lanthanides, a group of 15 rare-earth elements from atomic numbers 57 to 71, are characterized by partially filled 4f orbitals that impart them with unique optical and paramagnetic properties due to which they have emerged as versatile platforms for multimodal imaging applications. Their paramagnetic nature and the presence of unpaired 4f electrons enhance contrast in imaging which increase the relaxation of surrounding protons, improving MRI sensitivity [39]. Moreover, these materials display exceptional photonic characteristics, including upconversion and downshifting which refer to the emission of ultraviolet or visible light and near-infrared (NIR) light, respectively, upon NIR excitation [40]. This optical versatility in combination with their inherent X-ray attenuation properties, makes lanthanide NPs exceptionally suitable for integrated multimodal imaging. They are highly suitable for bioimaging due to their sharp emission peaks and long luminescence lifetimes, which allow for time-gated detection and significantly reduce background noise [41]. Their emission arises from electronic f–f transitions that have low absorption coefficients due to which an external chromophore is typically used to harvest excitation energy and transfer it non-radiatively to the lanthanide ion, triggering luminescence [42]. The emitted light spans a broad spectral region, ranging from ultraviolet (e.g., Gd^{3+}), through visible wavelengths (e.g., Tm^{3+}: blue, Tb^{3+}: green, Dy^{3+}: yellow, Sm^{3+}: orange, Eu^{3+}: red), to the near-infrared region (e.g., Pr^{3+}, Nd^{3+}, Ho^{3+}, Er^{3+}, Yb^{3+}), enabling their exploitation across different imaging modalities [43]. For example, PEGylated terbium nanorods that were designed in a recent investigation displayed high X-ray attenuation and strong green luminescence for MRI and X-ray CT imaging in mouse model [44]. In another research, sodium

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lanthanide tungstate-based NPs $NaDy(WO_4)_2$ and $NaHo(WO_4)_2$ were employed as bimodal contrast agents for *in vivo* CT and high-field MRI exhibiting significant biocompatibility and tumor accumulation via enhanced permeability and retention effect [45]. Recently, researchers also developed biocompatible lanthanide vanadate core–shell–shell NPs $DyVO_4$@YVO_4@Nd-doped $GdVO_4$ as a multimodal system offering dual T_1–T_2 MRI contrast and strong NIR luminescence, with optimized relaxivity and decreased quenching through layered structural design [46]. However, incorporating multiple lanthanide ions can result in undesirable energy transfer, resulting in luminescence quenching. For example, recent work on Yb^{3+}–Tm^{3+} co-doped systems shows that back energy transfer from Tm^{3+} activators to Yb^{3+} sensitizers significantly weaken the upconversion emission, and that spatially segregating these ions in core–shell–shell structure effectively reduces this quenching [47]. While many studies have displayed significant biocompatibility of lanthanide nanomaterials in animal models, comprehensive evaluations of their long-term safety profile, including aspects like water solubility, cytotoxicity, and excretion pathways, still need to be addressed [48]. The functionalization of lanthanide NPs often involves complex synthesis processes, which can affect scalability and reproducibility, posing challenges for clinical translation [49]. The existing challenges can be addressed by optimizing the structure of NP to control energy transfer pathways, precise selection of dopant concentrations to prevent quenching, and improving surface modification techniques for better biocompatibility and targeted delivery. Additionally, advancing synthesis methods for the formation of stable lanthanide NPs and integrating them with contrast agents can further enhance their effectiveness in multimodal imaging and disease diagnosis.

2.3 Emerging Applications of Semiconductor-based QDs as Contrast Agents

Semiconductor nanocrystals, commonly referred to as QDs, are nanoscale imaging probes known for their excellent optical, structural, electrical, and magnetic properties, due to which they have shown encouraging advancements in the field of non-invasive clinical imaging. The pertinent favourable properties of QDs include size-tunable fluorescence, enhanced signal brightness, photobleaching resistance, adjustable light emission, and synchronized excitation of several fluorescence colours [50]. While conventional QDs are typically composed of cadmium or lead based metals, recent advances have shifted focus toward less toxic alternatives such as copper indium sulfide ($CuInS_2$) [51], indium arsenide (InAs) [52], silver sulfide (Ag_2S) [53], indium phosphide (InP) [54], silicon nanocrystals [55], and biogenic carbon QDs to improve biocompatibility and clinical relevance. A single light source may concurrently excite multiple

colours of QDs with slight spectrum overlapping offering substantial benefits for ultrasensitive detection of target molecule. The optical properties of QDs are largely affected by any alteration in core size, shell coating, surface chemistry and composition. The structure of the QDs has a core which is semiconducting in nature with fluorescent and optical properties. The core is coated with shell which protects it from nonradiative recombination thereby resisting photobleaching and improving the brightness and stability of QDs which is essential for high contrast and enhanced bio-imaging [56]. Additionally, surface coating strategies are especially critical when using heavy-metal-based cores to reduce toxicity and prevent leaching, although these materials are gradually being replaced by non-heavy-metal-based QDs due to regulatory and safety concerns [57] [20]. Any variation in core composition and size can result in customized emission profile with a precise maximum anywhere from ultraviolet (UV) to NIR electromagnetic spectral region. The ability of QDs to be tailored for specific imaging modalities has led to their growing use in diagnostics, particularly in fluorescence imaging, multiplexed imaging, and *in vivo* tracking. The narrow emission spectra of QDs allow for precise wavelength discrimination, which is crucial in multi-colour imaging and multiplexed assays. The uptake of modified QD conjugates with multifunctional capabilities offers a significant time and cost advantage over single-colour assays which results in the identification of complex cellular proteins in patient samples. QD-labeled cells hold great promise for intricate detection and real-time monitoring of phenotypic and functionals abnormalities in diseased condition offering systemized patient-centred diagnosis and treatment. For instance, recently carboxyl-modified QDs were used for image-guided high resolution detection of bone fracture by the aid of NIR-IIb fluorescence imaging [58]. Lead/cadmium sulfide QDs (PbS@CdS QDs) were also used for fluorescence-guided surgical removal of tumor in a recent investigation [59]. Likewise, zinc-doped silver telluride QDs (Zn: Ag_2Te QDs) were used for non-invasive imaging of cerebral vasculature of mice after brain injury [60]. Moreover, a bimodal QD-based nanoprobe has also been used for fluorometric MRI of mesenchymal stem cells for the detection of adipogenic differentiation in a recent research [61]. QDs have also been used to broaden the horizon of multiphoton fluorescence for multiplex imaging of subcortical structures of brain [62]. Recent research has expanded beyond traditional Cd-based QDs to exploring safer semiconductor nanocrystals. In a study, researchers have designed eco-friendly, non-toxic Cd-free glyco-$CuInS_2$ QDs with dual visible/NIR emission and significant tumor penetration, making them effective and affordable fluorescent bio-probes for *in vivo* cancer imaging [63]. Recent investigations have also developed silicon QDs for *in vivo* fluorescence imaging of osteosarcoma, leveraging their photoluminescence and favourable safety profile [64].

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Another study has revealed that the fabrication of carbon QDs from agro waste biomass served as excellent contrast agents for fluorescence imaging because of their significant biocompatibility [65]. Moreover, to address the toxicity of Cd-based QDs and weak photoluminescence of other Cd-free alternatives, a group of researchers have designed bright and biocompatible *in vivo* tumor-targeting Cd-free SiO_2@InP QDs@SiO_2 NPs by compactly embedding InP/ZnS QDs in silica, demonstrating their potential as superior fluorescent nanoprobes for bioimaging [66]. Currently, QDs are being rigorously exploited for multimodal imaging because of their charge transfer property for the emission of NIR fluorescence. In addition, efforts are being made to use QDs for MRI as well. QDs can be incorporated with magnetic materials (such as iron oxide), resulting in magnetic QDs that provide dual-modal imaging (optical and magnetic). Efforts are being made to conjugate QDs semiconductor nanocrystals which exhibit comparable imaging performance without the heavy-metal-related toxicity concerns. By tagging QDs with radioisotopes, they can be used for non-invasive, whole-body imaging, which is particularly valuable for cancer diagnostics, monitoring, and treatment planning. In theranostic applications, QDs are being investigated for their ability to combine both diagnostic imaging and therapeutic functions. Functionalized QDs can deliver therapeutic agents, such as drugs or genes, to specific tissues while simultaneously enabling real-time imaging to monitor the treatment's efficacy. However, it would be challenging to fabricate specific QDs for different medical conditions surpassing the current non-specific imaging agents. The chemical stability of the core structure can be improved by refining the shell and surface coating techniques, resolving the toxicity issues that QDs continue to encounter. These enhanced NIR QDs can eventually replace existing conventional imaging modalities allowing their advancement from preclinical to clinical conditions, opening up new avenues for disease diagnosis and therapy. While QDs have remarkable potential in clinical imaging, challenges remain. One of the main concerns with QDs, especially those based on cadmium (CdSe, CdTe), is their potential toxicity. The heavy metals used in some QDs can be cytotoxic and pose a risk of accumulation in tissues. To address this, researchers have focused on developing less toxic alternatives, such as core-shell QDs, where the toxic core is encapsulated by a biocompatible shell. The use of QDs in clinical settings therefore requires careful evaluation of their safety, biocompatibility, and long-term effects. Regulatory agencies such as the FDA have stringent requirements for the clinical use of nanomaterials, and more research is needed to establish clear guidelines. Large-scale production of QDs with consistent quality for clinical applications remains another challenge. Efforts are underway to design QDs with safer core materials, such as silica, graphene oxide, and carbon-based QDs, which are less

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toxic than traditional cadmium-based QDs. Enhancing the targeting capabilities of QDs through better functionalization with biomolecules will improve their specificity and reduce off-target effects. The integration of QDs with therapeutic agents could create multifunctional nanoplatforms that can be used for diagnosis, therapy, and monitoring, revolutionizing personalized medicine. Despite the above-mentioned challenges, ongoing research continues to address limitations, making QDs a promising tool for early disease diagnosis, real-time imaging, and personalized medicine. As the field progresses, the development of safer, more efficient QDs will likely pave the way for their widespread use in clinical settings.

2.4 Advancement of Biogenic NPs in Multimodal Imaging

In recent years, researchers and scientific community are becoming more interested in the quest for alternative large-scale technologies that are both economical and eco-friendly. One such technology is green synthesis, which is now being employed in applications that are both medically and ecologically acceptable. Biogenic NPs based imaging contrast agents have seen remarkable advancements in the field of multimodal imaging, offering improved specificity and versatility in visualizing biological processes. These agents leverage natural or biological materials to provide contrast in multiple imaging modalities, allowing for a more comprehensive understanding of pathophysiology of disease. Their ability to integrate with different imaging techniques has opened new avenues for more accurate diagnosis, real-time treatment monitoring, and research in various biomedical sectors. Biogenic nanomaterials have shown encouraging developments in the field of molecular imaging surpassing the limitations of conventional imaging modalities resulting in reduced toxicity and enhanced efficacy. Broadly, these nanomaterials can be categorized as either intrinsically biogenic, produced directly by living organisms or biofabricated via green synthesis routes using biological extracts as reducing and stabilizing agents [67]. Both classes are increasingly integrated into advanced imaging and theranostic platforms. For instance, AgNPs synthesized from the ethanolic leaf extract of *Zinnia elegans* were used as potent theranostic agents for non-invasive NIR-mediated imaging and cancer therapeutics [68]. Cysteamine–folic acid coated AgNPs synthesized from the leaf extract of *Coffea arabica* was used as a potent contrast agent for CT imaging of cancer cells [69]. Dextran-fabricated cerium oxide (Dex-CeO_2) NPs have been used as CT contrast agent for the imaging of gastrointestinal (GI) tract and inflammatory bowel disease (IBD) [70]. Beyond metal-based examples, biological entities themselves, such as oncolytic bacteria have been exploited for image-guided disease therapy paving the way for considerable development in the field of nanotheranostics [71]. For example, *Staphylococcus*

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aureus cells used for the synthesis of silver selenide QDs (Ag_2Se QDs) with catalase have been used as photoacoustic agent in bioimaging [72]. Additionally, bacterial magnetosomes have been engineered for MRI-guided tumor targeting and hyperthermia due to their high magnetization and biocompatibility [73]. Moreover, naturally secreted exosomes have gained traction as endogenous nanoscale vesicles were employed as MRI/CT contrast agents that have demonstrated image guided photothermal therapy against cancer [74]. In addition to this, plant virus NPs have also been exploited to be used as multimodal imaging contrast agents with therapeutic potential [75]. Complementary to these, lipid and polymer-based nanomaterials have also been used as novel contrast agents to assemble complex imaging modalities. For instance, lipid-coated iron oxide (Fe_3O_4) NPs have been used as MRI contrast agent in a latest investigation [76]. Terpolymer-lipid based manganese dioxide (MnO_2) NPs have also been used as MRI agent for enhanced tumor detection [77]. Furthermore, a DNA-based lipid nanodevice was endogenously designed for high contrast imaging of miRNA in tumor cells [78]. In addition to this AS1411 aptamer and RGD fabricated chitosan-based poly(lactic-co-glycolic acid) (PLGA) NPs were used for real-time imaging and co-delivery of docetaxel paving the way for novel theranostics [79]. Despite being ecofriendly and sustainable, biogenic nanomaterials frequently require large scale culture and tedious synthesis methods. Even though the precise mechanisms underlying biogenic synthesis are still unreliable, ongoing research aims to shed light on this process and has revealed novel capabilities of green synthesis routes with enormous potential for plethora of biomedical applications.

3. Nanomaterials-Driven Diagnostic Advancements in Disease Detection

3.1 Nanomaterial-Based Strategies for Brain Disease Diagnosis and Therapy

The increasing prevalence of neurological diseases has emerged as a leading cause of disability and mortality, imposing a significant need to address them in near future. A large number of patients are being diagnosed with neuropathic diseases, but complete recovery remains rare due to the irreversible loss of neurons in affected tissues. Neurological diseases encompass a wide range of conditions, including brain tumors, traumatic injuries, vascular disorders, and neurodegenerative diseases. These diseases can cause irreversible damage to the central or peripheral nervous system, underscoring the critical importance of precise diagnosis and clinical evaluation. However, present diagnostic tools are relatively elementary with limited resolution and face multiple challenges in accurately locating the site of injury which significantly hampers the ability to provide precise diagnosis and therapy. Due to their unique

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physicochemical attributes, substantial efforts have been dedicated to exploit nanomaterials in advancing research and clinical translation of neural disease theranostics. Nanomaterials can cross the blood–brain barrier (BBB) to accumulate selectively at targeted site, and enable multimodal imaging or controlled drug release. For instance, in a latest work, amyloid-β (Aβ) specific Gd^{3+}NPs (NP@SiO_2@F-SLOH) was used as NIR imaging agent of MRI for the successful real-time monitoring of Aβ level which is a prognostic biomarker of Alzheimer's disease [80]. TAT-Polyp-QL which is a colour-convertible nanoprobe was designed for fluorescent diagnosis of Parkinson's disease with enhanced specificity and sensitivity [81]. Furthermore, recently rapamycin loaded NP was used as a potent theranostic agent for improved MRI and NIR fluorescence imaging of acute ischaemic stroke facilitating precise multimodal imaging with least background interference, thereby significantly enhancing drug tracking and diagnostic precision [82]. Beyond these examples, novel magnetic-based nanotheranostics are being explored for non-invasive brain tumor imaging and magnetic hyperthermia [83]. Moreover, smart nanocarriers functionalized with targeting ligands or exosomes are also emerging as strong candidates for precise delivery of RNA therapeutics and neuroprotective agents across the BBB [84] [85]. Recent advancements have also emphasized on the development of stimuli-responsive nanomaterials to enhance brain-targeting efficiency and reduce systemic toxicity. For example, cell membrane–coated NPs, such as macrophage or neutrophil membrane camouflaged nanocarriers, have demonstrated prolonged circulation, immune evasion, and enhanced BBB penetration for precise neuroinflammatory disease imaging [86]. Moreover, efforts are underway to integrate clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) systems with nanoscale delivery carriers such as lipid NPs and exosomes to enable gene editing directly within brain tissues with simultaneous molecular imaging for precise visualization and monitoring of therapeutic gene modulation [87]. In parallel, the development of multifunctional nanorobots and magnetic field–guided NPs offer significant control over navigation and accumulation at deep brain sites [88]. These next-generation strategies, combined with advanced imaging modalities, hold promise for early-stage, non-invasive diagnosis and personalized treatment of complex brain disorders. However, their clinical translation will require extensive *in vivo* safety validation and long-term monitoring to ensure biocompatibility and therapeutic efficacy. Conclusively, nanomaterials have the ability to cross the blood brain barrier thereby allowing significant diagnosis and therapy of neurological disorders. While the research on nanomaterials for brain disease imaging remains in its early stages, it encounters significant challenges, including biosafety and clinical translation. However, with the ongoing

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interdisciplinary advancements in nanotechnology and multimodal imaging, there is strong optimism that these nanomaterials will progress from the laboratory to clinical research offering encouraging patient centred treatment options for neurological diseases.

3.2 Next-Generation Imaging Agents in Nano-Oncology

Cancer remains a significant worldwide health challenge, characterized by uncontrolled cell proliferation and metastasis, which disrupts and damage normal healthy cells. Over the past several decades, there has been significant advantage in the scientific knowledge of the molecular basis of cancer due to the rapid breakthroughs in molecular biology research. However, only a few experimental approaches have been able to withstand rigorous testing and become clinically viable. Molecular imaging is an area that has emerged from the great drive towards developing non-invasive imaging techniques to observe molecular alterations in *in vitro* and *in vivo* conditions [89]. For instance, H-ferritin-nanocaged gadolinium NPs (Gd-HFn) have been designed for MRI-based ultrasensitive detection of tumor biomarkers [90]. Carcinoembryonic antigen-conjugated fluorescent silica NPs (CEA-FSNs) were developed for immunofluorescence imaging of colorectal cancer serving as potent imaging agent for early diagnosis of colorectal cancer [91]. Glucose and casein coated ultra-small superparamagnetic iron oxide (USPIO) NPs were recently developed for their conjugation with a Cy7.5-K-8AOC-bombesin peptide for the construction of USPIO(Cy7.5)-BBN NPs. These NPs showed promising results when tested *in vivo* and *ex vivo* NIRF imaging because of their high specificity towards gastrin-releasing peptide receptors (GRPs) of pancreatic cancer [92]. Zwitterionic charge-convertible NIR cyclodextrin derivative was also fabricated with pheophorbide-conjugated ferrocene for ultra specific imaging and therapeutics of rectal cancer thus serving as a potent theranostic agent [93]. Additionally, a methylene blue-integrated fibroblast activation protein inhibitor (FAPI) nanoprobe was also constructed for enhanced PET/CT fluorescence imaging of tumor which demonstrates its potential to serve as powerful multimodal imaging agent [94]. In recent years, researchers have also focused on developing smart and stimuli-responsive nanoprobes to further improve tumor specificity and minimize off-target effects. For instance, pH-responsive polymeric nanocarriers embedded with indocyanine green (ICG) have shown promising results for real-time NIRF and PAI of acidic tumor microenvironments [95]. Moreover, enzyme-activated probes, such as matrix metalloproteinase (MMP)-sensitive iron oxide nanoclusters, have been developed to enhance MRI contrast precisely at tumor sites exhibiting high MMP expression [96]. Another noteworthy advancement is the integration of DNA nanotechnology with imaging, enabling programmable

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nanodevices that can selectively hybridize with tumor-related microRNAs and trigger a detectable fluorescence or MRI signal [97]. Researchers are also developing hybrid nanostructures combining gold nanorods (GNRs) and QDs to achieve synergistic benefits of PAI and NIRF for intraoperative tumor margin delineation [98]. NPs-based theranostic and multimodal imaging have been extensively researched as they present several opportunities to overcome the drawbacks of conventional imaging modalities. However, there are several challenges in actual clinical translations of NPs due to their intricate nanostructures including generation of immune response, safety profile, and significant differences between imaging from actual cancer patients and the current *in vivo* animal model. Therefore, prior to its clinical application, unusual adverse effects on animal models post NP administration should be examined. The sustainable development of nano-oncology in upcoming future will continue to drive next generation of cancer detection by the aid of multimodal imaging.

3.3 Multimodal Imaging Approaches in Cardiovascular Nanomedicine

The clinical practice of cardiology exploits the versatility of a wide range of NPs to aid in accurate diagnosis, risk assessment and real-time therapeutic visualization. Most of the imaging modalities provide significant details of anatomical cardiovascular structures, however, fundamental molecular processes are yet to be reflected accurately. Cardiovascular diseases present different challenges as compared to cancer biology when it comes to multimodal imaging including small and dynamic structures of cardiovascular system, short time interval between different cardiovascular processes, blood flow and presence of pathological constituents. Recent investigations have examined the application of certain NP platforms for theranostics of cardiovascular disorders. For example, a nanoplatform (CNA35-GNR/PFP@NPs) comprising of collagen targeted and lipid NP encapsulated perfluoropentane (PFP) and GNRs was constructed for the multimodal high-resolution US, CT and PAI of myocardial fibrosis [99]. A ratiometric semiconducting polymeric NP was designed for successful PAI of pneumonia-procured atherosclerotic plaque that resulted in strong photoacoustic signaling for the accurate and specific detection of superoxide anions [100]. Additionally, a novel phase change material and superparamagnetic iron oxide loaded macrophage membrane-modified biomimetic nanoprobe was used as an imaging agent for multimodal imaging of autoimmune myocarditis [101]. Moreover, silver iron oxide NPs have also been exploited for multimodal imaging and photothermal therapy (PTT) of thrombosis [33]. In addition to this, a perfluoro-crown ether payload (^{19}F-HDL) based high-density lipoprotein-derived nanotracer was used for hot-spot multimodal imaging of myeloid cell egression in

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ischaemic heart disease [102]. Recent progress has also focused on the development of enzyme-responsive gold nanoclusters coated with fibrin-targeting peptides that have demonstrated enhanced sensitivity in detecting early-stage thrombi via combined photoacoustic and MRI [103]. Researchers have also developed ROS-sensitive polymeric micelles loaded with NIR dyes, enabling real-time imaging of oxidative stress within atherosclerotic plaques [104]. In another notable advancement, multifunctional exosome-mimetic nanovesicles decorated with iron oxide and fluorophores have been employed for T1-weighted MRI of inflamed endothelial regions, providing improved specificity for pathological angiogenesis [105]. Moreover, targeted lipid-polymer hybrid NPs carrying ultrasound contrast agents and PET isotopes have been tested for non-invasive assessment of myocardial ischaemia, offering both functional and molecular information in a single diagnostic session [106]. It is clearly evident that the bioavailability of imaging agents for the detection of cardiovascular diseases has significantly enhanced by the application of NP-based multimodal imaging agents. The potential to design accessible nanotracers that provide site-specific molecular imaging has been made feasible due to the specific microenvironment of cardiovascular diseases. However, in-depth research is still required to elucidate the underlying mechanism, associated pharmacokinetics and intraorganellar uptake. Additionally, comprehensive safety assessment must be conducted prior to clinical trials to minimize the level of potential side effects.

3.4 Nanomaterials-Based Advanced Imaging Approaches for Detection of Gastrointestinal (GI) Diseases

Nanomaterials have been extensively exploited for the diagnosis of GI disorders because of their ability to be conjugated with multiple imaging modalities for ultrasensitive and specific detection. Conventional techniques like digestive endoscopy and ultrasonography are mostly used to diagnose GI disorders. However, these techniques often result in discomfort, respiratory problems, allergy, and microbial infections in patients during or post investigation. The involuntary peristalsis in GI tract and densely interconnected abdominal tissues makes it challenging for the conventional techniques to diagnose GI disorders. Therefore, most of the latest research work is inclining towards the application of NP-based diagnosis in associated with wide range of multimodal imaging and contrast agents for specific biodistribution and enhanced imaging of GI disorders. For instance, dextran coated bismuth oxide NPs (Bi_2O_3-Dex NPs) were used for improved CT imaging of inflammatory bowel disease (IBD) [107]. Similarly, a bismuth-pectin based microgel network (Bi-GLUE) was designed for real time imaging of GI tract using X-RAY and MRI due to its significant mucoadhesive property [108]. Apart from

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this, in a novel work, gadolinium oxide carbonate and mesoporous silica coated GNRs (AuNR–SiO_2–Gd) was used for high contrast imaging using CT, MRI and PAI for the diagnosis of pancreatic ductal adenocarcinoma [109]. The microemulsion method was used for the construction of bimodal-polymer based NP which displayed significant high resolution imaging after being integrated with NIR fluorescence imaging and PAI of GT tract [110]. An innovative one-pot solvothermal method was used for the synthesis of PEGylated $BaGdF_5$ NPs for high contrast MRI/CT bimodal *in vivo* imaging of GI tract [111]. Recently, macrophage-membrane coated bismuth oxyiodide nanodots (BiOI@M) have been shown to provide robust X-ray/CT contrast in the GI tract with excellent biocompatibility and mucoadhesive behavior for improved lesion localization [112]. Furthermore, PEGylated AuNPs have been demonstrated to offer size-independent, high-contrast CT imaging in murine models of ulcerative colitis [113]. Another promising direction involves spectral CT imaging using bismuth or rhenium-sulfide NPs, which enable dual-energy differentiation of GI lesions and reduce artefacts, as evidenced in recent rodent studies [114]. These multifunctional nanoprobes offer higher sensitivity, rapid clearance, and clinical potential. In summary, ongoing developments of NP-based imaging modalities offer potential diagnostic approach for the early detection of GI diseases. The conjugation of nanoprobes with multiple contrast agents have not only improved the specificity but have also provided a platform for the selective accumulation of theranostic agents at the targeted site. However, multiple challenges including precise targeting, guaranteed safety and cost effectiveness are yet to be confronted for successful clinical implementation of NP-based imaging agents in gastroenterology.

4. Applications of NP-Based Contrast Agents in Advanced Bioimaging Modalities

4.1 Role of Nanomaterials in PET scanning for Molecular Imaging

PET is a highly sensitive, non-invasive radionuclide imaging modality that offers great diagnostic advantage in preclinical and clinical fields due to its ability to quantitatively visualize physiological and molecular processes. PET imaging is generally required because of the development of radiotracers that can exhibit targeted action against specific biomarkers of certain disease. In this context, nanomaterials play a pivotal role by serving as vehicles for PET isotopes and enabling improved pharmacokinetics, enhanced signal retention, and precise molecular targeting [115]. Various types of biomolecules including proteins, antibodies or lipids can serve as potent radiotracers opening the avenues for PET bioimaging by the aid of nanoprobes. For instance, radiolabeled polymeric NPs are heavily utilized for evaluating their

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biodistribution through PET scanning. In an interesting work, ^{89}Zr PLGA-NH_2 NPs labeled monocytes were used for radioactive *in vivo* cellular tracking of breast tumors as well as *Staphylococcus aureus* bacterial infection using PET imaging [116]. Moreover, anti-CD64 antibody conjugated gold and methotrexate encapsulating PLGA NPs were used for the diagnosis and therapy of rheumatoid arthritis [117]. Ga-labeled amphiphilic polymeric NPs have been used to diagnose lymph node metastasis through PET imaging [118]. Apart from this, lipid NPs are being exploited in improved PET based diagnosis of certain diseases. For example, $^{68/67}$Ga-radiolabeled sphingolipid nanoemulsions serve as a potent nanoprobe for PET imaging of breast and lung carcinoma [119]. A group of researchers have recently developed a novel nanocomplex (DOX@TLNPs) composed of tannic acid, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000 (DSPE-PEG2k), and doxorubicin, which demonstrated significant tumor targeting, sustained drug release as confirmed by PET imaging using ^{89}Zr-labeled particles, and displayed effective anticancer activity with minimal toxicity [120]. The potential of radioactive imaging agents can be significantly highlighted through the aforementioned examples and advancements. Radiolabeled positron emitters offer a platform for precise molecular imaging and substantial image-guided therapy planning of various diseases. However, there are a lot of issues that are the main roadblocks in NPs based PET imaging. For example, before the selection of a suitable NP synthesis procedure, the half-life and biological targets should be kept in mind. Secondly, the appropriate labeling strategy for ideal fabrication of NP is also a matter of concern for many researchers. Additionally, there is a need to design novel biofabricated radiolabelled NPs to minimize the toxicity during PET imaging. The stability of the radiolabel, potential toxicity, and *in vivo* fate of the NP formulation are some of the additional concerns. Last but not the least, lack of evaluation of the radiolabeled NPs accumulation in certain organs including liver and kidneys often complicates image interpretation and safety profiles. Future research should focus on optimizing biocompatible and biodegradable nanomaterials. that offer site-specific targeting, high radiolabel stability, and minimal off-target accumulation. Moreover, systematic evaluation of pharmacodynamics and organ-specific distribution is necessary for their clinical translation. Nevertheless, further investigations in this intriguing field are expected to be planned by exploiting polymeric or lipid NPs that can offer selective delivery of therapeutic agents at target sites, allowing for enhanced *in vivo* tracking using PET technology.

4.2 Optimization of Nanomaterials-Based X-Ray CT Contrast Agents for Clinical Applications

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X-Ray CT has emerged as one of the most prevalent non-invasive clinical diagnostic tools due to its low cost, optimal performance, rapid acquisition time and ability to provide high-resolution anatomical details. CT contrast agents can offer precise molecular imaging by corresponding diagnostic signals with biological processes. The specificity and sensitivity of CT imaging is directly proportional to its X-ray attenuation coefficient. However, conventional iodinated contrast agents often confer several challenges including short circulation time, nephrotoxicity, and lack of specificity. Therefore, designing nanomaterial-based CT contrast agents with improved pharmacokinetics, lower toxicity, and enhanced imaging performance is a pressing need in biomedical multimodal imaging [121]. A wide range of NPs, particularly metal NPs, have been constructed to serve as a potent CT contrast agent for specific bioimaging. For example, tantalum nanodots were synthesized for efficient CT imaging along with significant biocompatibility, good water solubility and renal clearance [122]. In addition, in an innovative research work, hydroxyapatite based nanoformulations, AuNPs and copper doped graphene oxide were separately evaluated for X-ray CT scanning. The results demonstrated that hydroxyapatite microspheres and thermally treated hydroxyapatite can serve as better contrast agents as compared to other nanoformulations [123]. Moreover, polymer-fabricated lead oxide NPs have also been designed to be used as efficient CT contrast agents to facilitate high contrast tumor imaging [124]. Despite these advances, many NP-based CT agents are still in their experimental stage due to long-term safety concerns, non-biodegradability, and potential organ accumulation. NP-based agents must display good biocompatibility, colloidal stability, suitable hydrodynamic size (<100 nm for renal clearance) [125], and less toxicity related concerns for successful clinical translation. Therefore, addressing these requirements by involving surface modification, biodegradable polymer coatings, and ligand targeted conjugation is required to enhance site-specific imaging while reducing off-target effects. Future research should focus on developing hybrid nanoplatforms that combine CT imaging with therapeutic capabilities (theranostics), evaluating long-term *in vivo* biodistribution, and complying with regulatory safety standards to to expand their applications in biomedical field.

4.3 Fluorescent Nanoprobes in NIRF Imaging

NIRF imaging has drawn substantial attention in the field of multimodal imaging due to its ultra sensitivity, contrast enhancement property, and versatility resulting in the application of a wide range of fluorescent nanoprobes for capturing images of biological components. The images obtained through fluorescence are studied by the observation of several factors including transfer of resonance energy, emission spectra, intensity and lifetime of fluorescent

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agents. These factors provide insights into dynamic molecular interactions, localization, and metabolic processes within the biological system, allowing for a comprehensive understanding of cellular functions. Conventional imaging techniques often struggle with limited sensitivity, low specificity and poor spatial resolution. NIRF imaging has been reported in overcoming these limitations by enabling real-time, high-resolution imaging with reduced background autofluorescence. NIR fluorescent nanoprobes must exhibit certain critical features such as high quantum yield, excellent photostability, biocompatibility, minimal toxicity, and tunable emission within the NIR window (650–1700 nm) to function effectively in clinical bioimaging. In particular, the NIR-II window (1000–1700 nm) is now being actively investigated for superior in-depth imaging and signal-to-noise ratio [126].

In order to accomplish specific targeted bioimaging, the surface of the fluorophores or NPs are modified with proteins or ligands to make them capable of recognising prognostic biomarkers of particular disease. In a novel approach, bislactosyl-fabricated BODIPY-TPE fluorescent probe NPs (BTL-Leus) was designed for the identification of leucine aminopeptidase (LAP) through fluorescence imaging in hepatoma cells [127]. Indocyanine green loaded calcium-based carbon NPs (Ca-CNPs@ICG) have been used for NIRF imaging of tumor thereby aiding in enhanced photodynamic therapy (PDT) [128]. Furthermore, in an innovative research erbium-based lanthanide NPs were designed for fluorescence imaging mediated surgery of orthotopic glioma [129]. Fluorescent imaging is rapidly emerging as an advanced imaging technique due to substantial development in microscopy, spectroscopy and material sciences. Despite these advances, certain limitations still persist that needs to be addressed in the coming future. The selection of fluorescent materials is often complicated due to the need to balance properties such as brightness, toxicity, and *in vivo* stability. Many conventional fluorophores suffer from rapid photobleaching or short fluorescence lifetimes, limiting their use in long-term tracking. Moreover, non-specific accumulation and rapid clearance pose challenges for achieving sustained imaging at target sites. To address these issues, current research focuses on engineering novel NIR fluorophores that aim to deliver improved decay lifetimes, higher contrast ratios, and the potential for multimodal fluorescent imaging, broadening their utility in both diagnostics and theranostics.

4.4 Advancements in Nanomaterials-Based High Contrast MRI

MRI is one of the most dynamic imaging modalities known for its non-invasive nature, high spatial resolution, excellent soft tissue contrast and ability of three-dimensional imaging. MRI

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contrast agents, particularly those based on nanomaterials, have significantly enhanced the imaging of tissues by altering their magnetic properties, thereby improving diagnostic precision. The application of magnetic contrast agents has enabled the modification of intrinsic properties of tissues making the visualization flexible thereby enhancing the specificity and sensitivity of MRI **(Figure 1)**. Wide range of nanomaterials such as superparamagnetic iron oxide, paramagnetic manganese oxide, and lanthanide-based compounds are being engineered for this purpose. In an earlier study, carbon-coated iron oxide NPs (Fe_3O_4@C NPs) were used as MRI contrast agents for *in vivo* liver and kidney imaging [130]. Similarly, a manganese oxide based MRI contrast agent has also been exploited for MRI of tumor in a novel work [131]. PEGylated manganese zinc ferrite NPs have also been designed to serve as MRI contrast agent for high contrast MRI [132]. Moreover, iron oxide NPs with citric acid coating have been used for determining the effect of pH and the results revealed that acidic coating enhanced the biocompatibility and stability making it suitable to be used as high contrast MRI agent [133]. Many MRI nanoprobes are being functionalized with targeting ligands or therapeutic molecules to further improve specificity and multimodal utility. This dual-functional approach opens new possibilities in image-guided therapy. However, challenges such as long-term biocompatibility, biodistribution, clearance, and potential off-target accumulation still require deeper investigation. The understanding of magnetic effects is crucial for the development of novel MRI contrast agents. In addition to this, extensive *in vivo* research is also required to comprehend their mode of action in various organs for the purpose of MRI. Future efforts should focus on the development of biocompatible and stimuli-responsive MRI contrast agents with optimized relaxivity. Moreover, integrating artificial intelligence (AI)-assisted image analysis and predictive modeling could further enhance the clinical utility and precision of NP-based MRI platforms in personalized medicine.

4.5 Role of Nanoparticles in PAI for Enhanced Diagnosis

PAI is an emerging non-invasive full body bioimaging technique that works on the principle of optical imaging and ultrasound and offers high resolution and high contrast imaging due to deep tissue penetrability. PAI is widely used for the investigation and biodistribution of therapeutic or diagnostic agents thereby offering precise quantification of these agents inside the body **(Figure 2)**. This unique hybrid approach enables high-resolution, high-contrast bioimaging at depths beyond the reach of purely optical methods, making it highly promising for clinical diagnostics and therapy monitoring. However, the effectiveness of PAI heavily depends on the availability of exogenous contrast agents that can strongly absorb NIR light and

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exhibit minimal photobleaching with significant biocompatibility, and preferably offer multifunctional therapeutic capabilities. To address this, diverse range of NPs have been used for the purpose of fabrication of PAI contrast agents because of their intrinsic optical properties. For instance, acrylate-substituted thiadiazoloquinoxaline-diketopyrrolopyrrole polymeric NPs (PATQ-DPP) were developed as novel photoacoustic contrast agents for imaging and PTT of nasopharyngeal cancer [134]. Likewise, PLGA decorated methylene blue NPs have also been designed to serve as PAI and phototherapeutic agents [135]. Naphthalene diimide conjugated polycyclic molecule was nano precipitated with $CoFe_2O_4$ for the synthesis of NDI-S@$CoFe_2O_4$ that served as potent PAI agent for multimodal photodynamic and sonodynamic therapy [2]. Macrophage membrane-coated photoacoustic nanoprobes were developed for PAI of neuroinflammation in murine model [136]. Moreover, hyaluronic-acid-modified polydopamine NPs (PDA@HA) were constructed to serve as PAI contrast agent for the detection and real time therapeutic monitoring of endometriosis lesions [137]. While various kinds of functional nanomaterials have been investigated for enhancing high contrast PAI, there is still a need for comprehensive research on the *in vivo* safety profile of these nanomaterials. In addition to this, critical requirement for any PAI nanocomplex is also required to ensure strong and stable optical absorption with low toxicity, biodegradability, and clearance from the body to avoid long-term accumulation. Therefore, NPs should be subjected to rigorous toxicity assessment before proceeding for clinical application. Future research should focus not only on designing novel nanoformulation with optimized photoacoustic performance but also on comprehensive pharmacokinetic and regulatory assessments to overcome the challenges before clinical translation. The development of highly efficient and sensitive photoacoustic systems is a key area of research for spatial, dynamic, real-time, high contrast 3D multimodal bioimaging.

5. Role of Multifunctional Nanoparticles for Image-Guided Theranostics

Disease therapy can be facilitated by multifaceted NPs with specialized multi-modal imaging abilities, which can offer a novel approach for precise diagnosis and image-guided real-time treatment. The image guided approach can aid in conventional therapy by providing low dose of therapeutic agents and its controlled release with minimal side effects and specific targeting. In recent years, novel multifunctional NP formulations have advanced the field of image-guided theranostics by integrating multimodal imaging with targeted therapies to achieve diagnostic precision and treatment efficacy while minimizing systemic toxicity. For example, novel pyropheophorbide a–bisaminoquinoline lipid NPs (PPBC LNPs) have demonstrated combined PAI and fluorescence imaging alongside potent photothermal and photodynamic

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therapy, facilitating real-time treatment monitoring and effective tumor eradication in bladder cancer models [138]. Similarly, enzyme-activatable theranostic nanomedicines designed to respond to tumor-associated enzymes such as MMP-14 and cathepsin have displayed enhanced MRI contrast and site-specific release of chemotherapeutics coupled with photothermal ablation, thereby improving treatment selectivity in case of glioblastoma [96]. Upconversion NPs (UCNPs) co-doped with lanthanides like gadolinium and iron oxide have been engineered for trimodal photoluminescence, CT, and MRI, offering high-resolution imaging and enabling precise monitoring of photoactivated tumor therapy deep within tissues [139]. Magnetic particle imaging has also recently emerged as an innovative tool for guiding magnetic fluid hyperthermia, where magnetic NPs serve dual functions as imaging tracers and localized heat sources, allowing for non-invasive, real-time mapping of treatment zones and temperature control with high spatial resolution [140]. Researchers have also designed pH-responsive nanogels encapsulating gadolinium or manganese-based MRI agents, which display enhanced relaxivity in the acidic tumor microenvironment and provide superior imaging contrast with minimal systemic toxicity due to their improved biodegradability and clearance profiles [141]. To overcome long-term bioaccumulation concerns of noble metal NPs, ultrasmall gold-in-nano architectures have been developed, where sub-5 nm gold nanoclusters are confined within biodegradable silica capsules, ensuring effective photothermal tumor ablation under near-infrared irradiation while enabling complete renal clearance post-treatment [142]. Additionally, hybrid theranostic nanoplatforms integrating gene editing systems like (CRISPR/Cas9) with MRI-visible nanocarriers have opened new avenues for real-time monitoring of gene therapy efficacy and off-target effects [143] [144]. NPs are loaded with therapeutic moieties such as antigens, cytokines, immune checkpoint inhibitors, photosensitizers, chemotherapeutic drugs, polymers or fluorophores and can be subsequently monitored for efficient imaging and theranostics. For example, an iRGD peptide-based nanocomplex for its conjugation with dual immune checkpoint inhibitors for successful crossing of blood brain barrier and offering efficient immunotherapy of glioblastoma by blocking CXCL12/CXCR4 and PD-1/PD-L1 pathways [145]. Another fascinating research has focused on the conjugation of Ag_2S QDs with Pluronic F-127 (an amphiphilic polymer) followed by its functionalization with cancer cell membrane-based adjuvant for the construction of a potent nanocomplex Ag_2S@P@M-A capable of sonodynamic immunotherapy of colon cancer [146]. Chitosan coated paclitaxel was conjugated with MoS_2 having photothermal and optical properties for combined image-guided chemotherapy and PTT of breast cancer by the aid of MoS_2@PTX-CS-K237 NP [147]. The application of NPs as multimodal contrast agents for the purpose of image guided therapy has

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also broadened its horizon in the field of précised surgical treatment. For instance, PLGA-cyclic RGD, perfluorohexane, and indocyanine green conjugated multifunctional NPs (PLGA-cRGD-PFH-ICG NPs) were designed for bimodal PET and NIRF imaging and promoting dissolution of activated platelets for the treatment of coronary microthrombosis [148]. Moreover, a polystyrene nanoprobe has also been recently designed for precise fluorescence imaging guided resection of metastatic lesions in a latest work [149]. An *in situ* spraying method was used for fluorescence guided surgery of aminopeptidase overexpressing metastatic cancer in a novel research work [150]. Furthermore, in a recent work, bi-doped iron selenide NPs were fabricated for multimodal CT and MRI guided combined PTT and chemodynamic therapy of colorectal cancer [151]. The effectiveness of nanomaterials-based image guided therapy can be evidenced by the aid of aforementioned examples and research areas. The trend towards combining multiple therapeutic modalities such as chemotherapy, immunotherapy, phototherapy, and chemodynamic therapy within a single NP system, complemented by dual or triple imaging modes, holds immense potential to revolutionize personalized treatment regimens. However, a number of challenges including half-life of NPs in blood, pre-planning of surgical process, precise targeting and safety profile of NPs still need to be resolved for high contrast multimodal imaging and theranostics of certain diseases with minimum side effects.

6. Concluding Remarks and Future Prospects

Nanomaterials-based multimodal contrast agents have drawn significant attention due to their several advantages including homogeneity, high dispersibility, stability, tunable size and functional modification ability. The versatility of wide range of NPs makes them an ideal candidate to be integrated with existing conventional imaging modalities to enhance their spatial resolution and improving the diagnostic accuracy. Herein, we have provided recent data about the novel nanomaterials-based contrast and imaging agents that have been exploited for enhancing the efficacy of different multimodal imaging techniques along with their applications in certain common diseases. The designing of high contrast NP based multimodal imaging agents is an active area of research, however, it is still challenging for many researchers to construct multifunctional low-cost contrast agents on a large scale. This is a challenging field and has a lot of room to expand before advancing the application of NP in clinical imaging. Apart from the challenges in scaling-up-processes, the characterization of NPs has also not been given significant attention by nano-engineers which has resulted in limited success in their *in vitro* and *in vivo* imaging applications. Substantial characterization of NPs is important for their delivery in adequate doses according to the sensitivity of any

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particular imaging modality, route of administration, pharmacokinetics, dispersibility and biocompatibility. The safety profile and toxicity of novel NP-based imaging moieties are yet other factors that need to be addressed for minimizing the adverse effects of imaging or theranostics. The presence of heavy transition metals restricts the application of these contrast agents in clinical bioimaging and diagnostic tests due to underlying toxicity issues. To address these complex issues, scientists and researchers from different biological backgrounds employ different assays to confirm or disprove toxicity which often results in different conclusions. Toxicological nature of any nanomaterial can be measured by ROS production, determination of lethal dose (LD_{50}) value, haemolytic assay and *in vivo* biodistribution profile. However, the application of commercial kits for *in vitro* toxicity assays is not completely valid for testing the safety profile of NPs and it is not necessary that *in vitro* results align with *in vivo* analysis. Therefore, a standard is required for testing the toxicity of all fabricated NPs and determining their potential to be conjugated with imaging or therapeutic agents. The fabrication, durability and efficacy of NP-based contrast agents highly depend on certain pharmacokinetic attributes including route of administration. Although the intravenous injection is the most preferred route of administration for the delivery of NP for bio-imaging, normal body vasculature has the tendency to limit the biodistribution resulting in delayed vascular equilibration. Additionally, certain NPs become prone to reticuloendothelial system (RES) uptake and immune clearance which makes it challenging for them to reach at the target site. Although, the clinical application of NPs is restricted due to their limited fabrication and lack of patient trials, NPs based imaging and diagnostics have paved the way to delve deeper into the pathophysiology of any disease or medical condition. It is believed that NP-based contrast agents would present a multitude of advantages including early-stage theranostics that will ultimately progress to clinical trials. Comprehensive research and innovative advancements are still required to bridge the gap between experimental results and clinical applications.

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Conflict of interest

The corresponding author on behalf of all the authors declares no potential conflict of interest.

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Table 1: Overview of Different Types of NPs with their Examples, Stage of Trial, Applications in Imaging Modalities and Theranostic Properties

S.No	Type of NPs	Examples of Nanoformulations	Stage of trial	Imaging modalities	Theranostic Properties	References
1	Metallic NPs	Fe-AuNPs	*In vivo*	MRI/CT	Theranostic agent for laser induced photothermal treatment of tumor.	37
		PEGylated Indium NPs	*In vivo*	PAI	High contrast imaging and photothermal therapy of breast tumor.	152
		Chalcone conjugated Gd chelate (Gd-DO3A-Chal)	*In vivo*	MRI/Fluorescence optical imaging	Use of amyloid beta targeting contrast agents for the detection of Alzheimer's disease	153
		Gd-based (Activation and Guidance of Irradiation by X-ray) AGuIX NPs	Phase I clinical trial	MRI	Brain tumor imaging	154
		IRDye 800CW coupled hafnium oxide (HfO_2) nanocrystals	*In vivo*	X-Ray CT/NIRF imaging	Detection of sentinel lymph nodes	155
2	Magnetic NPs	Single-nanometer iron oxide (SNIO) fabricated collagen-binding peptide (CBP) NPs	*In vivo*	MRI	Non-invasive detection of liver fibrosis	156
		Superparamagnetic iron oxide NPs (SPIONs)	*In vivo*	MRI	High contrast imaging of liver and kidney at ultra-low magnetic field (ULF)	157
		Transferrin fabricated magnetic NPs (SPIO-Tf)	*In vivo*	MRI	Magnetothermally stimulated theranostic NPs	158
		Superparamagnetic iron oxide NPs (SPIONs)	Phase II clinical trial	MRI-lymphography MRI-LG/magnetic-guided axillary ultrasound (MagUS)	Minimally invasive sentinel lymph node biopsy in breast cancer patients reducing the risk of diagnostic surgery.	159
		Ultra-small superparamagnetic iron oxide (USPIO) NPs	Clinical trial	Dynamic contrast enhanced (DCE)-weighted MRI	Detection of head and neck squamous cell carcinomas (HNSCCs)	160

3	Biogenic NPs	PEGylated Pemetrexed and PolyNIPAM decorated AuNPs	*In vivo*	CT contrast agent	Biocompatible and stable contrast agent for the imaging of breast tumor.	[161]
		β-cyclodextrin coated and phyllacanthone-loaded magnetic iron oxide NPs (Fe_3O_4@βCD-PHY)	*In vivo*	MRI/PAI	Theranostic application in cancer by the induction of magnetic hyperthermia.	[162]
		Prosopis farcta derived PtNPs	*In vitro*	CT	Biocompatible green contrast agents for enhanced bioimaging.	[163]
		Gd chelated anthocyanin-based NP (ANP-Gd)	*In vivo*	PAI/MRI	Multifunctional theranostic agent for image guided photothermal therapy of tumor.	[164]
		Barley leaves derived AuNPs (BL-Au NPs)	*In vivo*	CT	Biocompatible NPs with good colloidal stability and high X-Ray attenuation capacity.	[165]
4	Quantum Dots	Turmeric-derived Gd-doped carbon QDs	*In vitro*	MRI/Fluorescence imaging	Multifunctional biological contrast agents with significant cell penetration ability.	[166]
		Cysteine modified magnetic graphene oxide nanosheets conjugated cadmium telluride QDs (GO@Fe_3O_4-cys-CdTe QDs)	*In vivo*	PET/MRI	Radiolabelled imaging agent for the diagnosis of fibrosarcoma tumor.	[167]
		Iohexol conjugated mercaptopropionic acid capped Mn:ZnSe QDs (I@MPA-Mn:ZnSe QDs)	*In vitro*	CT/Fluorescence imaging	High luminescence photostable cell imaging with good X-ray attenuation ability.	[168]
		Carbon QDs conjugated rhodium NPs	*In vitro*	X-ray Fluorescence Computed Tomography (XFCT)	Highly photostable bioimaging agents with low photobleaching property.	[169]
		Dextran mimetic QDs	*In vivo*	PET/CT	Single cell imaging capacity with high resolution.	[170]

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Figure legends:

Figure 1: Diagrammatic representation of dual role of magnetic NPs as brain MRI contrast and therapeutic agents. Magnetic NPs can serve as a potent MRI contrast agent for high contrast imaging with spatial resolution for specific detection of brain tumors. In addition to this, magnetic NPs can also serve as potent therapeutic agent for the treatment of brain tumor by inducing magnetic hyperthermia. Magnetic hyperthermia results in nuclear ablation and HSP70 and HSP90 blockade leading to reactive oxygen species (ROS) mediated oxidative DNA damage.

Figure 2: Pictorial illustration of NPs-based PAI guided photothermal therapy of breast cancer. The administration of NPs results in high contrast PAI of breast cancer to provide real time monitoring of breast cancer therapy. The NPs get activated by the NIR light and results in light to heat conversion resulting in generation of ROS and temperature induced oxidative stress for photothermal ablation of tumor.

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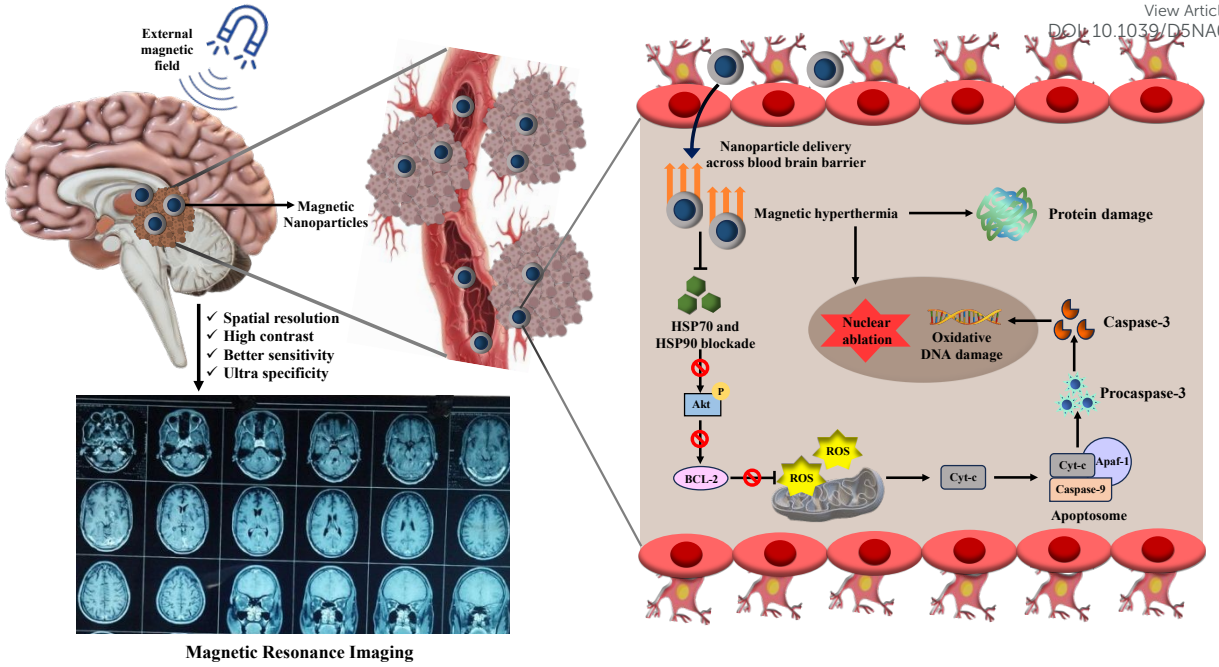

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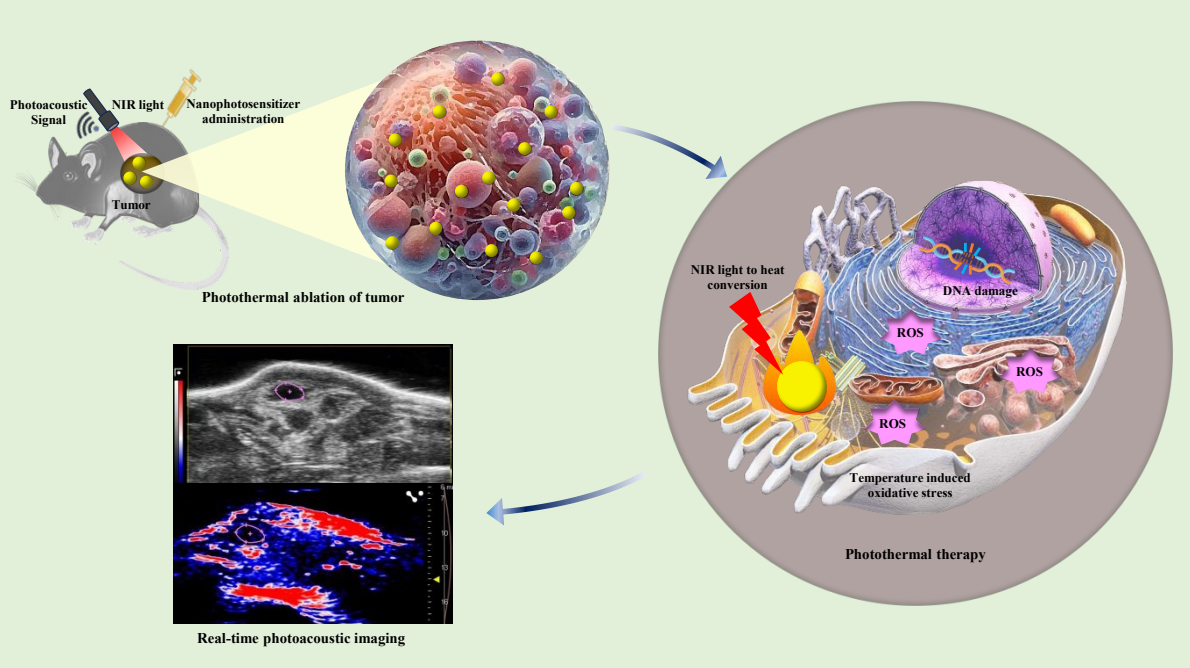

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Data Availability Statement

The data supporting the findings of this study are available within the manuscript and its supplementary materials. No additional datasets were generated or analyzed for this review article.