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Metallic Nanoparticles in Imaging and Therapy: An overview

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Nanoparticles are tiny particles that have been extensively utilized in fields such as medicine, electronics and environmental science. A common trend in nanoparticle applications is the use one specific nanoparticle type for a particular application. Therefore, several types of nanoparticles have been researched and proposed for a specific application. It was noticed that producing core-shell, multi-layered and/or composite nanostructures enable the versatile use of such structures in multiple applications. Such scenarios are often called as multimodal applications where nanoparticles serve multiple roles, such as imaging and therapy. Metallic nanoparticles are suitable candidates for multimodal applications. In addition, they could be employed in various applications including imaging, drug delivery applications, medical technologies, water cleaning applications, storage device applications. Multimodal applications are special cases where nanoparticles possess both diagnostic and therapeutic characteristics, commonly referred to as theranostics. The use of nanoparticles in theranostic applications is a growing trend with various nanoparticles and nanocomposites were extensively discussed in the literature. In this regard the use of magnetic nanoparticles having great potential in imaging and therapy applications are also encouraging and their unique potential also renders them highly suitable candidates for theranostic applications. In this short report, we aim to provide insights into the state of art and illustrate specific applications of metallic nanoparticles and magnetic nanoparticles used in imaging and therapy.

Keywords: *Metallic nanoparticles; Imaging applications, Therapy applications; Theranostics; Magnetic nanoparticles*

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1. Introduction

Nanostructures are tiny materials with size ranging from few nanometres to a hundred nanometres. Such materials exhibit fascinating properties which enables them to be used in several applications in various fields. Due to their high surface area/volume ratio, nanomaterials exhibit enhanced electrical, optical, catalytical, magnetic and optoelectronic properties and these properties have been found to be superior to those of bulk materials [1]–[5]. Such properties could be altered by varying different parameters such as particle size, shape, and crystal structure materials [1]–[3]. Alteration of chemical structure can also modify the overall nanoparticle characteristics. In this regard, combining different molecules, producing core-shell and multilayer structures, and fabricating composite or alloy-like structures may be excellent alternatives [6], [7]. To achieve this, a wide range of materials can be considered. For instance, organic-based nanostructures predominantly comprise carbon-based nanomaterials. Notably, special forms like fullerene (C60), carbon nanotubes, and graphene have gained significant popularity. Moreover, various inorganic-based nanostructures and nanoparticles have been extensively studied and reported in the literature and metallic nanoparticles can be noted as prominent example. For example, Zn-based nanoparticles have been extensively investigated owing to their catalysis, optical and optoelectronic properties, on the other hand, Cu based nanoparticles exhibit good electrical and optoelectronic properties, and they were often used for catalytic, antibacterial, and anti-fungal activities [8]–[12]. Indeed, Ag-based nanoparticles display remarkably similar characteristics to Cu-based nanoparticles. Ti- and Pt-based materials have been used in optic and optoelectronic applications, they were also used in catalytical applications. Cd nanoparticles have been extensively studied in the various application including electrical, optoelectronic applications battery technologies, detector and solar harvesting device applications [13], [14].

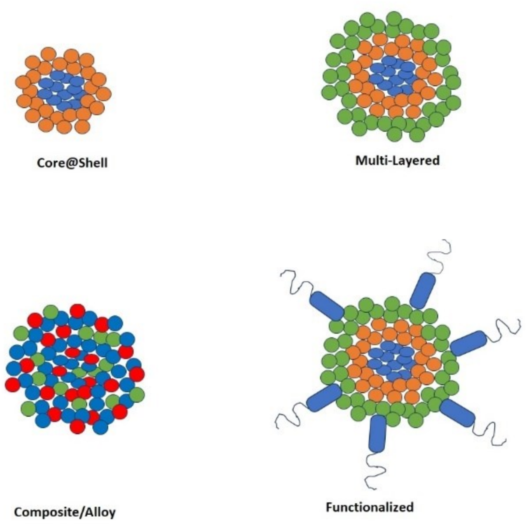

Figure 1: Illustration of basic nanoparticle structures (core-shell, multi-layered, composite and/or alloy, and functionalized nanostructures).

Au-based materials have often been preferred in catalysis, drug delivery and imaging applications. Among metals, materials with magnetic characteristics have gained significant attention and they have been extensively utilized in magnetic storage devices, sensors, and various other applications. Additionally, the use of the magnetic nanoparticles in therapeutic, imaging, and diagnostic applications has allowed the implication of nanoparticles for medical purposes [15]. It was obtained that magnetic nanoparticles are suitable candidate for medical applications. In early 2000s, there was considerable effort in the literature to apply magnetic nanoparticles, especially iron oxide nanoparticles, for cancer therapy and magnetic hyperthermia applications [15], [16]. It is known that iron oxide-based nanoparticles at smaller size exhibit superparamagnetic characteristics which enables them to be used as weighting agent for MRI applications. Beside Fe based nanoparticles, contrast enhancement properties of Co, Ni, Eu, Yb and Gd based nanoparticles and nanostructures were also evidenced [15].

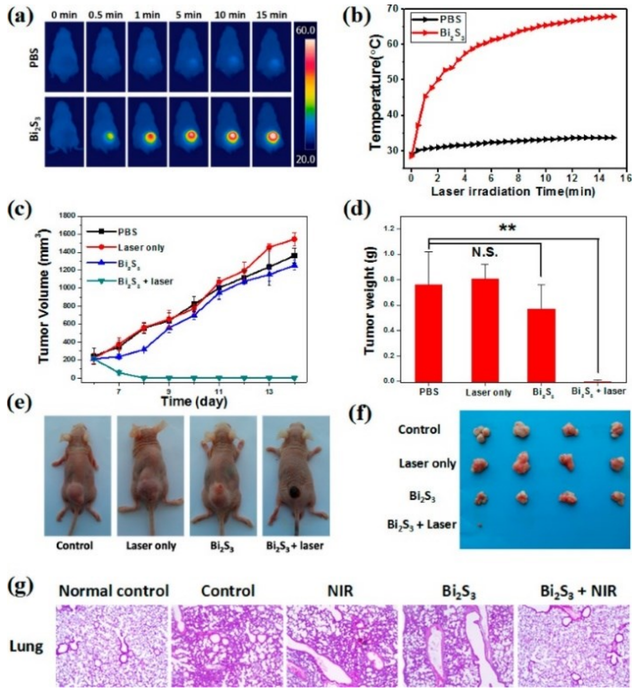

Figure 2: Application of Bi_2S_3 nanoparticles for theranostic purposes [19].

The idea of combining the two important medical parameters, therapy, and diagnostic, in a single nanostructure and/or a molecule is groundbreaking. Utilizing a single nanostructure for multiple applications could revolutionize medical approaches. This proposal give birth to the concept of theranostic materials [17]. The concept of the theranostic defines the case where single molecule and/or nanoparticle could cure and diagnose a disease. Therapy and diagnosis can occur either simultaneously or consecutively, and the order of these process is not crucial, as one can be prior to other. Hence, the key objective is to achieve the synthesis of specialized materials with unique forms, possessing multimodal functionality by incorporating both therapeutic and diagnostic characteristics. Such materials can generally consist of more than one material, as well as the metal and its oxide. The structures of these materials can be classified as core-shell, multilayer or composite (see Figure 1). The combination of multiple materials in a single form enables the synthesis of nanoparticles with desired theranostic characteristics, facilitating their application for various purposes. Produced nanomaterials could be functionalized and or decorated with special molecules or nanoparticles where certain characteristic properties of the nanoparticles could be enhanced, or nanoparticles could obtain targeted drug delivery characteristics [18].

2. Nanomaterials in imaging applications

In late 90s, medical potential of the nanoparticles was noticed, and it was seen that certain types of nanomaterials could be used for the imaging applications [20]. Different types of imaging methods were used in the medical sciences. Common imaging methods are X-ray imaging, magnetic resonance imaging (MRI), magnetic particle imaging (MPI), X-ray computed tomography (CT), ultrasonography, infrared imaging, etc [15], [21]. Such methods were mostly used for the diagnostic purposes, and to meet those criteria, various types of nanoparticles were proposed.

In early 2000s, it was illustrated that some nanoparticles enhance that X-ray contras and therefore, they can be used in the X-ray based imaging methods such as X-ray imaging and X-ray computed tomography [22]. It should be noted that to enhance the X-ray imaging materials with high X-ray attenuation was used. In this regard, Au-based materials step forward. Au-based materials have high X-ray attenuation potential and therefore, it was illustrated in many reports that Au-based nanoparticles has X-ray enhancement characteristics [23], [24]. Moreover, Bi-based materials exhibit similar characteristics to Au based materials where high X-ray contrast enhancement were obtained [25]. Bi-based materials were also exhibit photothermal characteristics where applications of a light in specific wavelength enhances the temperature of the material [19].

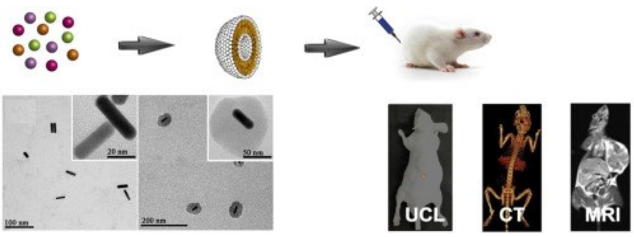

Figure 3: Illustration shows the application of nanoparticle contrast agents used for multimodal imaging.[15]

Thus, especially cancerous cells could be treated using photothermal characteristics of nanoparticles (see Figure 2). Such a case makes Bi-based materials a suitable candidate for theranostic applications where therapy and diagnostic could meet in a single material. It should be noted that Bi does not exhibit a specific magnetic characteristic; hence, Bi itself could not be used in magnetic imaging applications. Ta-and W-based material were also used in the X-ray imaging applications regarding their high atomic number which make them a suitable candidate for contrast enhancer in X-ray based applications [26], [27]. Such materials were also used in infrared based imaging applications. Si-based materials exhibit fluorescent properties and therefore they were preferred in fluorescent imaging based applications [28], [29]. Producing Au@Si core-shell structures were previously reported for multimodal imaging applications where contrast enhancement in X-ray computed tomography and fluorescence imaging techniques were obtained [28], [29]. Most of the mentioned materials were used as contrast enhancement agents or multimodal imaging agents, which means they can be utilized for single and/or multiple imaging applications (See Figure 3). For example, magnetic based nanocomposites were often used for X-ray computed tomography/ magnetic resonance imaging applications. For this purpose, mostly iron-based nanoparticles or nanocomposites were often employed to provide MRI imaging enhancement [6], [30] . The core was mostly covered with a high X-ray attenuating material like gold , bismuth etc. The outer shell was mostly covered with organic, or silica based material where dual or multimodal imaging contrast enhancement agents were obtained [15].

3. Functionalization of nanoparticles and targeting a specific organ or tissue

It was addressed by various reports that nanoparticles have great potential to be used in imaging and therapy applications. It should be noted that nanoparticles with contrast enhancement and/or therapy characteristics could be applied using various methods. Intravenous, subcutaneous or oral applications or direct applications are some standard applications [18]. In intravenous application, nanoparticles are applied inside the blood stream where nanoparticle could travel through the cardiovascular system. In subcutaneous application, nanoparticles are applied under the skin, and they are expected to disperse around the region. In oral application, nanoparticles are swallowed and expected to be transfer in body via digestion system. In direct application, nanoparticles are applied directly to an organ or a tissue where implication is desired. All mentioned methods are uncontrolled since uncontrolled contrast enhancement of therapy could be obtained by different tissues. Moreover, nanoparticles could affect or damage different organs or tissues. For this purpose, nanoparticles were decorated with specific molecules or structures that enable to reach or target a particular organ or a tissue, enhancing the nanoparticle's effect on that specific organ or tissue. Decoration process is special procedure nanoparticles were commonly covered with organic shell. The shell enhances the stability of the nanoparticles and enables core to be decorated with functionalized molecules [31]. Organic shells also reduce the toxicity of the nanoparticles which minimize the potential toxic damage to the kidneys or livers. For example, PEG (polyethylene glycol) is one of the most common organic materials which was used to cover the metallic nanoparticles. PEG is quite stable and has low toxicity and it could be in taken by cells. It also serves as a good buffer for attaching different organic function groups. Besides, PAMAM (polyamidoamine), PEI (Polyethyleneimine), EDTA (Ethylenediaminetetraacetic acid), DTPA (Diethylenetriaminepentaacetic acid), and certain peptides are common organic molecules used to cover the magnetic nanoparticles as buffers for nanoparticles functionalization [32]–[37].

To target specific organ and/or a tissue, nanoparticle with organic shell should be functionalized. Functionalization of the nanoparticle is a specialized procedure in which a specific receptor protein or molecule is attached to the outer shell for specific applications. One of the most common targeted tissues is cancer tissues where imaging quality is crucial for a successful diagnosis. Therefore, functionalizing nanoparticles with antibodies is popular approach. Different groups functionalized their nanoparticles with anti-HER2 molecule to target breast carcinoma [32], [38]. Similarly, some groups decorated gold nanoparticles with anti-EGFR molecules to target human squamous cells [39]. Another targeted nanoparticle imaging application is for arteries. It is a common case that arteries tend to congest due to high cholesterol and stress. To detect the congestion or track the inner arterial structure targeted applications were proposed where antibodies tend to stick to inner arterial plaques were proposed. Several researchers have successfully managed to functionalize the gold nanoparticles with HDL molecule, which manage to stick on inner arterial plaques and enhance the contrast for X-ray based imaging techniques [40]. Various molecules have been explored for targeting digestion and intestinal system. Among them, folic acid has been one of the most successful molecules which was used to target intestinal system [41]–[43]. Moreover, it was reported that folic acid-functionalized gold nanoparticles can enhance the tomography contrast in specific regions. Additionally, Several reports illustrate that folic acid-functionalized nanoparticles have also successfully enhanced the tomography contrast of breast carcinoma in intravenous applications [41], [44] . It is also evidenced that folic acid functionalized nanoparticles managed to enhance the contrast for HeLa cervical cancer cells [41].

4. Multi-purpose nanoparticles

Multi-purpose nanoparticles can be used in more than one purpose and certain nanoparticles could be used in more than one imaging methods and they are often referred to as dual imaging or multipurpose imaging contrast agents. However, multipurpose term is also used for nanoparticles which can be used for both imaging and therapy. Nanoparticles which are used in imaging and therapy also referred as theranostic nanoparticles. Theranostic term is derived from therapy and diagnostics where imaging and curing capability is expected. For this purpose, various types of nanoparticles were previously reported and among those, metallic nanoparticles have important role[15]. Especially, magnetic nanoparticles have a significant attention since they could be used in diagnostic and therapy such as MRI contrast agent, MPI and magnetic nanoparticle hyperthermia. Iron- or iron oxide-based nanoparticles, which display superparamagnetic features at smaller size, are one of the most popular and one of the most researched nanoparticle and nanocomposite types [30], [45] . Besides, Bi and rare earth element based nanoparticles were also addressed in the literature for multimodal and theranostic characteristics [15].

4.1. Iron- and Iron oxide-based multi-purpose nanoparticles

Iron oxide nanoparticles are one of the most common magnetic nanoparticles used in the medical applications and they exhibit superparamagnetic properties at certain sizes. Pure iron nanoparticles also generate significant interest because of their high saturation magnetization. As a result, core-shell structures are of great interest, as they offer the opportunity to stabilize core materials with a shell or synthesize multipurpose characteristics by using different materials in the core and shell. Iron@iron oxide core-shell nanoparticles are among the most commonly synthesized examples, where the iron core is protected against oxidation by a few nanometres thick oxide shell [46] Also, in order to obtain multipurpose characteristic, there are many examples that used iron oxide as a core materials and Au, Ag and organic polymers etc. [30], [47]. Having superparamagnetic characteristics enable iron oxide nanoparticles to be used in MRI imaging applications as a weighting agent where enhanced contrast can be obtained for different modes [48]. Moreover, iron or iron oxide nanoparticles can be used as a therapy agent for magnetic nanoparticle hyperthermia which is a trending topic for cancer therapy and cancer related research.

Iron oxide – Au nanocomposites are trending nanostructures which were often studied for primary X-ray computed tomography / MRI contrast agent. Such composite structures were also used in cancer therapy [30]. For example, PEG coated Au-Fe alloys were reported for CT/ MRI/ SERS (Surface Enhanced Raman Scattering) applications where nanoparticles were intravenously (iv) applied. Gold decorated nanoparticles were reported for dual imaging [49]. Hybrid Au-Fe_3O_4 nanoparticles were reported for cancer imaging for CT/MRI imaging for breast cancer [50]. Gold/polypyrole@Fe_3O_4 nanoparticles were reported for guided thermal therapy and applications [51]. Gold and ferro ferric oxide nanoparticles coated by polypyrole (Ppy@Fe3O4/Au) was reported with their theranostic characteristics [52].

Bismuth-iron oxide composites were also used in CT/MRI dual imaging applications as contrast enhancement and MRI weighting agent [53]. PEG modified Fe@Bi_2S_3 were also reported for dual imaging and thermal-radiotherapy capabilities [54]. The nanocomposites could manage to enhance the contrast for both CT and MRI, it can also absorb the light at near infrared light where thermal therapy characteristics could be achieved. Anti-Her2 Antibody decorated Fe:Pt NP nanoparticles were managed to target MBT2 tumour and managed to enhance the contrast for CT/MRI [55].

4.2. Bismuth based multi-purpose nanoparticles

Bismuth-based nanoparticles are widely used for X-ray computed tomography since bismuth has high X-ray attenuation and high atomic number. Additionally, they were reported for absorbing near infrared radiation and increases the inner temperature which makes them a suitable candidate for photothermal applications [56]. Therefore, producing bismuth-based nanoparticles and nanocomposites have great potential for multi modal and theranostic applications.

Previously, Bi:Fe nanoparticles were reported for targeting cancer cells where photothermal therapy and dual imaging applications[53]. Similarly, PEG modified Fe:Bi nanoparticles were used to target cancer cells as well [54]. Bi nanospheres were reported for CT imaging and chemo-photothermal therapy [57]. Functionalizing the Bi-based nanoparticles helps them to target a specific target or molecule. Antibody-functionalized drug-loaded bismuth sulphur@mesoporus silica (Bi_2S_3@mPS) core-shell nanoparticles were reported for targeted imaging and breast cancer therapy [58]. Decorating and loading bismuth nanoparticles with specific drugs were also used to achieve theranostic characteristics. Doxorubicin is a special molecule used for the cancer treatment. Different reports illustrate that doxorubicin loaded Bi nanoparticles were reported for theranostic characteristics where cancer imaging and cancer therapy achieved [59]. Bi nanoparticles were also reported for multimodal imaging agents for CT and multispectral optoacoustic tomography [19]. Oleic acid modification was also used for Bi nanoparticles for tumour targeting, X-ray tomography contrast enhancement and photothermal therapy applications [19]. Similarly, 1,2-dilauroyl-sn-glycero-3-phosphocholinemodified (DLPC-modified) bismuth nanoparticles (Bi@DLPC NPs) reported for theranostic and photothermal therapy applications [60].

4.3. Rare earth metal based multi-purpose nanoparticles

Rare earth metals are materials which find application in different fields such as telecommunication, LED applications, storage device applications, display applications, sensor applications, etc. Such materials have high atomic number and high X-ray attenuation; therefore, they can be used as contrast enhancement agent for X-ray computed tomography imaging applications. Yb, Eu, Gd and Er are popular rare earth materials used for the multipurpose imaging and theranostic applications. Such rare earth based materials also exhibit magnetic characteristics; therefore, they have potential to be used in MRI and magnetic hyperthermia applications [61]–[63].

They are mostly used as a shell or chelate to enhance the magnetic characteristics of the nanocomposites [64]. However, some works reports nanocomposites consisting of solely rare earth elements where multipurpose imaging and therapy properties were achieved [65]. Chelate and/or shell based magnetic enhancement was used as MRI weighting and/or magnetic hyperthermia characteristics [66]. Moreover, rare earth material based nanoparticles were often referred as upconverting nanoparticles for different reports and used for optical imaging and guided photothermal therapy applications [67], [68].

Covering the surface of the rare earth metal based nanoparticles and nanocomposites with and organic molecule is a common method to enhance the stabilization. Moreover, such organic cover reduces the toxicity, and it can be used to functionalize the nanocomposites. PEG is the one the most popular organic molecule which was repeatedly reported in the literature [63]–[65], [69]. Rare earth element based nanoparticles and nanocomposites are often functionalized for targeted applications since functionalization of nanoparticles help them to target a specific organ or a tissue [27], [70]–[72].

Conclusion

Medical potential of the nanoparticles is addressed by different works. In this report, we try to overview and address the imaging and therapy implications of metallic nanoparticles. It has been illustrated that various types of nanoparticles can be used in imaging and therapy applications. Combining different type of materials with each other and producing composite like structures allow them to be used in dual or multipurpose applications. Functionalization of such nanoparticles help nanoparticles to targeted imaging and therapy applications. Therefore, they have great potential to be used in imaging and imaging and therapy.

References

[1] A. Więckowski, E. R. E. Savinova, and C. G. Vayenas, *Catalysis and electrocatalysis at nanoparticle surfaces*, 1st ed. New York: Marcel Dekker, 2003.

[2] M. M. Koç and G. E. Ragkousis, "AFM induced diffusion of large scale mobile HOPG defects," *Appl. Nanosci.*, vol. 9, no. 7, 2019.

[3] I. Khan, K. Saeed, and I. Khan, "Nanoparticles: Properties, applications and toxicities," *Arabian Journal of Chemistry*, vol. 12, no. 7. Elsevier B.V., pp. 908–931, 01-Nov-2019.

[4] X. Xu, C. Xu, J. Dai, J. Hu, F. Li, and S. Zhang, "Size dependence of defect-induced room temperature ferromagnetism in undoped ZnO nanoparticles," *J. Phys. Chem. C*, vol. 116, no. 15, pp. 8813–8818, Apr. 2012.

[5] C. Hariharan, "Photocatalytic degradation of organic contaminants in water by ZnO nanoparticles: Revisited," *Appl. Catal. A Gen.*, vol. 304, no. 1–2, pp. 55–61, May 2006.

[6] S. Aktas *et al.*, "Control of gas phase nanoparticle shape and its effect on MRI relaxivity," *Mater. Res. Express*, vol. 2, no. 3, p. 105356, 2015.

[7] S. M. Janib, A. S. Moses, and J. A. MacKay, "Imaging and drug delivery using theranostic nanoparticles," *Adv. Drug Deliv. Rev.*, vol. 62, no. 11, pp. 1052–1063, Aug. 2010.

[8] A. Makalesi and N. Aslan, "Synthesis and Characterization of ZnO@Fe3O4 Composite Nanostructures by Using Hydrothermal Synthesis Method," *Turkish J. Nat. Sci.*, vol. 11, no. 1, pp. 95–101, Mar. 2022.

[9] S. UYAR, B. COŞKUN, M. İLHAN, and M. M. KOC, "Optoelectronic Properties of ZnO:TiO2 Nanocomposite Thin Films," *J. Mater. Electron. DEVICES*, vol. 5, no. 1, pp. 21–27, Sep. 2021.

[10] M. M. Koc, "Photoelectrical properties of solar sensitive CuO doped carbon photodiodes," *J. Mol. Struct.*, vol. 1208, p. 127872, May 2020.

[11] J. Li, W. Liu, Y. Ding, L. Liu, F. Li, and Q. Li, "Composition modulation of Cu/Cu2O/CuO nanoparticles supported on carbon for p-nitrophenol reduction," *Korean J. Chem. Eng. 2019 366*, vol. 36, no. 6, pp. 851–859, Jun. 2019.

[12] M. Elango, M. Deepa, R. Subramanian, and A. Mohamed Musthafa, "Synthesis, Characterization, and Antibacterial Activity of Polyindole/Ag–Cuo Nanocomposites by Reflux Condensation Method," *Polym. - Plast. Technol. Eng.*, vol. 57, no. 14, pp. 1440–1451, Sep. 2018.

[13] M. İlhan, M. M. Koç, B. Coşkun, M. Erkovan, and F. Yakuphanoğlu, "Cd dopant effect on structural and optoelectronic properties of TiO2 solar detectors," *J. Mater. Sci. Mater. Electron.*, vol. 32, no. 2, pp. 2346–2365, Jan. 2021.

[14] N. Aslan *et al.*, "Ti doped amorphous carbon (Al/Ti-a:C/p-Si/Al) photodiodes for optoelectronic applications," *J. Mol. Struct.*, vol. 1155, pp. 813–818, 2018.

[15] N. Aslan, B. Ceylan, M. M. Koç, and F. Findik, "Metallic nanoparticles as X-Ray computed tomography (CT) contrast agents: A review," *J. Mol. Struct.*, vol. 1219, p. 128599, Nov. 2020.

[16] H. Shao *et al.*, "Magnetic nanoparticles and micronmr for diagnostic applications," *Theranostics*, vol. 2, no. 1. Ivyspring International Publisher, pp. 55–65, 2012.

[17] F. Chen, E. B. Ehlerding, and W. Cai, "Theranostic Nanoparticles," *J. Nucl. Med.*, vol. 55, no. 12, pp. 1919–1922, Dec. 2014.

[18] M. M. Koç, N. Aslan, A. P. Kao, and A. H. Barber, "Evaluation of X-ray tomography contrast agents: A review of production, protocols, and biological applications," *Microsc. Res. Tech.*, vol. 82, no. 6, 2019.

[19] J. Liu *et al.*, "Bismuth Sulfide Nanorods as a Precision Nanomedicine for in Vivo Multimodal Imaging-Guided Photothermal Therapy of Tumor," *ACS Nano*, vol. 9, no. 1, pp. 696–707, Jan. 2015.

[20] L. Babes, B. Denizot, G. Tanguy, J. J. Le Jeune, and P. Jallet, "Synthesis of Iron Oxide Nanoparticles Used as MRI Contrast Agents: A Parametric Study," *J. Colloid Interface Sci.*, vol. 212, no. 2, pp. 474–482, Apr. 1999.

[21] N. Panagiotopoulos *et al.*, "Magnetic particle imaging: Current developments and future directions," *Int. J. Nanomedicine*, vol. 10, pp. 3097–3114, Apr. 2015.

[22] J. F. Hainfeld, D. N. Slatkin, T. M. Focella, and H. M. Smilowitz, "Gold nanoparticles: a new X-ray contrast agent," *Br. J. Radiol.*, vol. 79, no. 939, pp. 248–253, Mar. 2006.

[23] C. Kojima, Y. Umeda, M. Ogawa, A. Harada, Y. Magata, and K. Kono, “X-ray computed tomography contrast agents prepared by seeded growth of gold nanoparticles in PEGylated dendrimer,” *Nanotechnology*, vol. 21, no. 24, p. 245104, Jun. 2010.

[24] G. Chen, J. Zhang, and S. Yang, “A novel method for the synthesis of Au nanoparticles incorporated amorphous hydrogenated carbon films,” *Electrochem. commun.*, vol. 9, no. 5, pp. 1053–1056, May 2007.

[25] R. Karaçam, N. K. Yetim, and M. M. Koç, “Structural and Magnetic Investigation of Bi2S3@Fe3O4 Nanocomposites for Medical Applications,” *J. Supercond. Nov. Magn.*, vol. 33, no. 9, pp. 2715–2725, Sep. 2020.

[26] X. Wang, C. Wang, and S. Anderson, “Fabrication of hydrogel particles with tantalum oxide nanoparticle payloads as computed tomography contrast agents,” *Transducers Eurosensors XXVII 17th Int. Conf.*, pp. 426–429, 2013.

[27] Y. Cheng *et al.*, “Ultrathin Tellurium Oxide/Ammonium Tungsten Bronze Nanoribbon for Multimodality Imaging and Second Near-Infrared Region Photothermal Therapy,” *Nano Lett.*, vol. 19, no. 2, pp. 1179–1189, Feb. 2019.

[28] N. Kurnaz Yetim, F. Kurşun Baysak, M. M. Koç, and D. Nartop, “Characterization of magnetic Fe3O4@SiO2 nanoparticles with fluorescent properties for potential multipurpose imaging and theranostic applications,” *J. Mater. Sci. Mater. Electron.*, vol. 31, no. 20, pp. 18278–18288, 2020.

[29] P. Huang *et al.*, “Folic acid-conjugated silica-modified gold nanorods for X-ray/CT imaging-guided dual-mode radiation and photo-thermal therapy,” *Biomaterials*, vol. 32, no. 36, pp. 9796–9809, 2011.

[30] L. Sun *et al.*, “Theranostic application of mixed gold and superparamagnetic iron oxide nanoparticle micelles in glioblastoma multiforme,” *J. Biomed. Nanotechnol.*, vol. 12, no. 2, pp. 347–356, Feb. 2016.

[31] J. Wallyn *et al.*, “A new formulation of poly(MAOTIB) nanoparticles as an efficient contrast agent for in vivo X-ray imaging,” *Acta Biomater.*, vol. 66, pp. 200–212, Jan. 2018.

[32] L. E. Cole, T. L. McGinnity, L. E. Irimata, T. Vargo-Gogola, and R. K. Roeder, “Effects of bisphosphonate ligands and PEGylation on targeted delivery of gold nanoparticles for contrast-enhanced radiographic detection of breast microcalcifications,” *Acta Biomater.*, vol. 82, pp. 122–132, Dec. 2018.

[33] P. Kesharwani, K. Jain, and N. K. Jain, “Dendrimer as nanocarrier for drug delivery,” *Prog. Polym. Sci.*, vol. 39, no. 2, pp. 268–307, Feb. 2014.

[34] N. Bingwa and R. Meijboom, “Evaluation of catalytic activity of Ag and Au dendrimer-encapsulated nanoparticles in the reduction of 4-nitrophenol,” *J. Mol. Catal. A Chem.*, vol. 396, pp. 1–7, Jan. 2015.

[35] O. Kaygili, T. Ates, S. Keser, A. A. Al-Ghamdi, and F. Yakuphanoglu, “Controlling of dielectrical properties of hydroxyapatite by ethylenediamine tetraacetic acid (EDTA) for bone healing applications,” *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.*, vol. 129, pp. 268–273, Aug. 2014.

[36] W. Liao *et al.*, “Bi-DTPA as a high-performance CT contrast agent for in vivo imaging,” *Biomaterials*, vol. 203, pp. 1–11, May 2019.

[37] L. Tzounis and S. Logothetidis, “Fe3O4@SiO2 core shell particles as platforms for the decoration of Ag nanoparticles,” in *Materials Today: Proceedings*, 2017, vol. 4, no. 7, pp. 7076–7082.

[38] J. F. Hainfeld, M. J. O’Connor, F. A. Dilmanian, D. N. Slatkin, D. J. Adams, and H. M. Smilowitz, “Micro-CT enables microlocalisation and quantification of Her2-targeted gold nanoparticles within tumour regions,” *Br. J. Radiol.*, vol. 84, no. 1002, pp. 526–533, Jun. 2011.

[39] J. R. Ashton, E. B. Gottlin, E. F. Patz, J. L. West, and C. T. Badea, “A comparative analysis of EGFR-targeting antibodies for gold nanoparticle CT imaging of lung cancer,” *PLoS One*, vol. 13, no. 11, p. e0206950, Nov. 2018.

[40] T. Skajaa, D. P. Cormode, E. Falk, W. J. M. Mulder, E. A. Fisher, and Z. A. Fayad, “High-density lipoprotein-based contrast agents for multimodal imaging of atherosclerosis,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 2. Lippincott Williams and Wilkins, pp. 169–176, 01-Feb-2010.

[41] J. Lin, W. Hu, F. Gao, J. Qin, C. Peng, and X. Lu, “Folic acid-modified diatrizoic acid-linked dendrimer-entrapped gold nanoparticles enable targeted CT imaging of human cervical cancer.,” *J. Cancer*, vol. 9, no. 3, pp. 564–577, 2018.

[42] H. Wang *et al.*, “Folic acid-modified dendrimer-entrapped gold nanoparticles as nanoprobes for targeted CT imaging of human lung adencarcinoma,” *Biomaterials*, vol. 2, no. 34, pp. 470–480, 2013.
[43] P. S. Low, W. A. Henne, and D. D. Doorneweerd, “Discovery and Development of Folic-Acid-Based Receptor Targeting for Imaging and Therapy of Cancer and Inflammatory Diseases,” *Acc. Chem. Res.*, vol. 41, no. 1, pp. 120–129, Jan. 2008.
[44] K. Li *et al.*, “Arg-Gly-Asp-D-Phe-Lys peptide-modified PEGylated dendrimer-entrapped gold nanoparticles for targeted computed tomography imaging of breast carcinoma,” *Nanomedicine*, vol. 10, no. 14, pp. 2185–2197, Jul. 2015.
[45] S. Aktas, S. C. Thornton, C. Binns, and P. Denby, “Gas phase synthesis of core-shell Fe@FeO x magnetic nanoparticles into fluids,” *J. Nanoparticle Res.*, vol. 118, p. 365, 2016.
[46] C. Binns *et al.*, “Preparation of hydrosol suspensions of elemental and core-shell nanoparticles by co-deposition with water vapour from the gas-phase in ultra-high vacuum conditions,” *J. Nanoparticle Res.*, vol. 14, no. 9, p. 1136, Aug. 2012.
[47] H. Y. Park *et al.*, “Fabrication of magnetic core @Shell Fe Oxide@ Au nanoparticles for interfacial bioactivity and bio-separation,” *Langmuir*, vol. 23, no. 17, pp. 9050–9056, Aug. 2007.
[48] K. C. Barick, S. Singh, D. Bahadur, M. A. Lawande, D. P. Patkar, and P. A. Hassan, “Carboxyl decorated Fe3O4 nanoparticles for MRI diagnosis and localized hyperthermia,” *J. Colloid Interface Sci.*, vol. 418, pp. 120–125, Mar. 2014.
[49] J. Cai *et al.*, “Facile Preparation of Gold-Decorated Fe3O4 Nanoparticles for CT and MR Dual-Modal Imaging,” *Int. J. Mol. Sci.*, vol. 19, no. 12, p. 4049, Dec. 2018.
[50] J. Zhu *et al.*, “Synthesis of Au–Fe 3 O 4 heterostructured nanoparticles for in vivo computed tomography and magnetic resonance dual model imaging,” *Nanoscale*, vol. 1, no. 6, pp. 199–202, 2014.
[51] W. Feng *et al.*, “Au/Polypyrrole@Fe3O4 Nanocomposites for MR/CT Dual-Modal Imaging Guided-Photothermal Therapy: An n Vitro Study,” *ACS Appl. Mater. Interfaces*, vol. 7, no. 7, pp. 4354–4367, Feb. 2015.
[52] D. Yan *et al.*, “Facile assembling of novel polypyrrole nanocomposites theranostic agent for magnetic resonance and computed tomography imaging guided efficient photothermal ablation of tumors,” *J. Colloid Interface Sci.*, vol. 530, pp. 547–555, Nov. 2018.
[53] P. Naha, A. Al Zaki, E. Hecht, and M. Chorny, “Dextran coated bismuth–iron oxide nanohybrid contrast agents for computed tomography and magnetic resonance imaging,” *J. Mater. Chem. B*, vol. 2, no. 46, pp. 8239–8248, 2014.
[54] E. Li *et al.*, “Fabrication of PEGylated Fe@Bi2S3 nanocomposites for dual-mode imaging and synergistic thermoradiotherapy,” *Biomater. Sci.*, vol. 6, no. 7, pp. 1892–1898, Jun. 2018.
[55] S.-W. Chou, Y.-H. Shau, P.-C. Wu, Y.-S. Yang, D.-B. Shieh, and C.-C. Chen, “In Vitro and in Vivo Studies of FePt Nanoparticles for Dual Modal CT/MRI Molecular Imaging,” *J. Am. Chem. Soc.*, vol. 132, no. 38, pp. 13270–13278, Sep. 2010.
[56] N. Yu *et al.*, “Thiol-capped Bi nanoparticles as stable and all-in-one type theranostic nanoagents for tumor imaging and thermoradiotherapy,” *Biomaterials*, vol. 161, pp. 279–291, Apr. 2018.
[57] G. Ma, X. Liu, G. Deng, H. Yuan, Q. Wang, and J. Lu, “A novel theranostic agent based on porous bismuth nanosphere for CT imaging-guided combined chemo-photothermal therapy and radiotherapy,” *J. Mater. Chem. B*, vol. 6, no. 42, pp. 6788–6795, Oct. 2018.
[58] L. Li *et al.*, “Actively Targeted Deep Tissue Imaging and Photothermal-Chemo Therapy of Breast Cancer by Antibody-Functionalized Drug-Loaded X-Ray-Responsive Bismuth Sulfide@Mesoporous Silica Core-Shell Nanoparticles,” *Adv. Funct. Mater.*, vol. 28, no. 5, p. 1704623, Jan. 2018.
[59] Y. Xuan *et al.*, “High-Security Multifunctional Nano-Bismuth-Sphere-Cluster Prepared from Oral Gastric Drug for CT/PA Dual-Mode Imaging and Chemo-Photothermal Combined Therapy In Vivo,” *Adv. Funct. Mater.*, vol. 29, no. 18, p. 1900017, May 2019.
[60] C. Yang, C. Guo, W. Guo, X. Zhao, S. Liu, and X. Han, “Multifunctional Bismuth Nanoparticles as Theranostic Agent for PA/CT Imaging and NIR Laser-Driven Photothermal Therapy,” *ACS Appl. Nano Mater.*, vol. 1, no. 2, pp. 820–830, Feb. 2018.
[61] J. Ma *et al.*, “Folic Acid-Conjugated LaF

$_3$:Yb,Tm@SiO $_2$ Nanoprobes for Targeting Dual-Modality Imaging of Upconversion Luminescence and X-ray Computed Tomography," *J. Phys. Chem. B*, vol. 116, no. 48, pp. 14062–14070, Dec. 2012.

[62] A. Xia, M. Chen, Y. Gao, D. Wu, W. Feng, and F. Li, "Gd3+ complex-modified NaLuF4-based upconversion nanophosphors for trimodality imaging of NIR-to-NIR upconversion luminescence, X-Ray computed tomography and magnetic resonance," *Biomaterials*, vol. 33, no. 21, pp. 5394–5405, Jul. 2012.

[63] T. Guo *et al.*, "High-efficiency X-ray luminescence in Eu3+-activated tungstate nanoprobes for optical imaging through energy transfer sensitization," *Nanoscale*, vol. 10, no. 4, pp. 1607–1612, Jan. 2018.

[64] D. Li *et al.*, "One-Step Loading of Gold and Gd2O3 Nanoparticles within PEGylated Polyethylenimine for Dual Mode Computed Tomography/Magnetic Resonance Imaging of Tumors," *ACS Appl. Bio Mater.*, vol. 1, no. 2, pp. 221–225, Aug. 2018.

[65] Z. Liu *et al.*, "Long-circulating Gd2O3: Yb3+, Er3+ up-conversion nanoprobes as high-performance contrast agents for multi-modality imaging," *Biomaterials*, vol. 6, no. 34, pp. 1712–1721, 2013.

[66] Q. Yin *et al.*, "Biocompatible folate-modified Gd 3+/Yb 3+-doped ZnO nanoparticles for dualmodal MRI/CT imaging," *RSC Adv.* , vol. 4, no. 96, pp. 53561–53569, 2014.

[67] Z. Yi *et al.*, "PEGylated NaLuF4: Yb/Er upconversion nanophosphors for in vivo synergistic fluorescence/X-ray bioimaging and long-lasting, real-time tracking," *Biomaterials*, vol. 36, no. 35, pp. 9689–9697, 2014.

[68] X. Zhu, J. Zhou, M. Chen, M. Shi, W. Feng, and F. Li, "Core–shell Fe3O4@ NaLuF4: Yb, Er/Tm nanostructure for MRI, CT and upconversion luminescence tri-modality imaging," *Biomaterials*, vol. 18, no. 33, pp. 4618–4627, 2012.

[69] S. Zeng, M. Tsang, C. Chan, K. Wong, and J. Hao, "PEG modified BaGdF5: Yb/Er nanoprobes for multi-modal upconversion fluorescent, in vivo X-ray computed tomography and biomagnetic imaging," *Biomaterials*, vol. 33, no. 36, pp. 9232–9238, 2012.

[70] H. Sun, Q. Yuan, B. Zhang, K. Ai, P. Zhang, and L.- Lu, "Gd III functionalized gold nanorods for multimodal imaging applications," *Nanoscale*, vol. 3, no. 5, pp. 1990–1996, 2011.

[71] C. Alric *et al.*, "Gadolinium chelate coated gold nanoparticles as contrast agents for both X-ray computed tomography and magnetic resonance imaging," *J. Am. Chem. Soc.*, vol. 130, no. 18, pp. 5908–5915, May 2008.

[72] Z. Yi *et al.*, "Synergistic Dual-Modality in Vivo Upconversion Luminescence/X-ray Imaging and Tracking of Amine-Functionalized NaYbF4:Er Nanoprobes," *ACS Appl. Mater. Interfaces*, vol. 6, no. 6, pp. 3839–3846, Mar. 2014.