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Optically active organic and inorganic nanomaterials for biological imaging applications: A review

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ABSTRACT

Recent advancements in the field of nanotechnology have enabled targeted delivery of drug agents in vivo with minimal side effects. The use of nanoparticles for bio–imaging has revolutionized the field of nanomedicine by enabling non-invasive targeting and selective delivery of active drug moieties in vivo. Various inorganic nanomaterials like mesoporous silica nanoparticles, gold nanoparticles, magnetite nanoparticles graphene–based nanomaterials etc., have been created for multimodal therapies with varied multi–imaging modalities. These nanomaterials enable us to overcome the disadvantages of conventional imaging contrast agents (organic dyes) such as lack of stability in vitro and in vivo, high reactivity, low–quantum yield and poor photo stability. Inorganic nanomaterials can be easily fabricated, functionalised and modified as per requirements. Recently, advancements in synthesis techniques, such as the ability to generate molecules and construct supramolecular structures for specific functionalities, have boosted the usage of engineered nanomaterials. Their intrinsic physicochemical properties are unique and they possess excellent biocompatibility. Inorganic nanomaterial research has developed as the most actively booming research fields in biotechnology and biomedicine. Inorganic nanomaterials like gold nanoparticles, magnetic nanoparticles, mesoporous silica nanoparticles, graphene–based nanomaterials and quantum dots have shown excellent use in bioimaging, targeted drug delivery and cancer therapies. Biocompatibility of nanomaterials is an important aspect for the evolution of nanomaterials in the bench to bedside transition. The conduction of thorough and meticulous study for safety and efficacy in well-designed clinical trials is absolutely necessary to determine the functional and structural relationship between the engineered nanomaterial and its toxicity. In this article an attempt is made to throw some light on the current scenario and developments made in the field of nanomaterials in bioimaging.

1. Introduction

The advancements of imaging modalities are constantly being pushed by the compelling and desperate need for early detection and diagnosis. Detailed and faster results in imaging of tissue lesions and microstructures using nontoxic contrast agents with elongated retention/circulation time is a major challenge in the current scenario (Han et al., 2019). Nanotechnology plays a major role in offering possibilities for enhanced imaging. Nanoparticles as imaging contrast agents are one of the most promising and highly beneficial to clinical practice. The first and crucial step in clinical practice is the early disease diagnostics and detection (Ryvolova et al., 2012). Medical imaging technology time and again plays the most significant role in the early diagnosis, detection and therapeutic response assessment of various diseases. Since the origination of X-ray technology various other non-intrusive methodologies have been originated. These techniques have been successfully adapted to various fields ranging from clinical diagnosis, drug discovery and cell biology. Significant advancements in the fields of information technology, electronics, image processing and nanotechnology have benefitted the biomedical imaging research to a great extent (Murray et al., 2000).

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The use of fluorescent probes has rendered feasibility to view specific biological in viable and nonviable specimen. The synthesis of fluorescing luminescent engineered nanoparticles is contemplated to be constitutive to the evolution of next set of theranostic imaging technologies (Mahmood, 2004).

Ultrasound imaging (USI), magnetic resonance imaging (MRI), positron emission tomography (PET), Computed tomography (CT), optical imaging (OI), and emission of a single photon CT (SPECT) are non-intrusive optical imaging techniques that have been developed and are currently in use (Högemann and Basilion, 2002; Pomper MG, 2004). Each of these techniques differs in terms of various factors like resolution, sensitivity, and time for data accession, complexity and monetary cost. In general, various techniques in imaging are only supplementary and the choice of technique depends on the sample in question. Light microscopy (luminescence and fluorescence imaging) has been the go−to technique for imaging of biological specimens and is at present inviting significant interest as various technological advancements provide significantly improved capabilities. MRI has seen a remarkable growth in medical diagnostics specifically for soft tissues. Multifunctional nanoparticles are a step forward in MRI−based soft tissue imaging. Multimodal nanoparticles are created by incorporating a paramagnetic ion and a luminescent core into the same interface (Kircher et al., 2003; Santra et al., 2005). Thus, the multimodal nanoparticles can be detected by MRI and OI in a simultaneous manner. The advantage of using such particles is the increased sensitivity due to optical detection and ability to obtain a 3−D image of biological micro and nanostructures and processes at cellular level (Faiz Kayyem et al., 1995; Moats et al., 1997).

Light is arguably one of the most versatile radiation used in imaging due to its nonintrusive nature and ability to bring about a contrast by interference, coherence, intensity, polarization, wavelength, (Dunn et al., 2001; Tearney et al., 1997) nonlinear effects and lifetime. Various optics based imaging techniques have utilized interaction of various physical parameters of light with tissues (Alivisatos, 2004; Licha and Olbrich, 2005; Ntziachristos et al., 2005; Rudin and Weissleder, 2003; Weissleder and Ntziachristos, 2003). Fluorescence microscopy has evolved as one of the most significantly relevant imaging techniques among the many accessible optical imaging techniques. The intrinsic fluorescing capacity of the fluorophore determines optical fluorescence which is depicted in Fig. 1.

When a quantum of specific energy hits the fluorophore, it excites electrons and pushes them to a higher energy level (S1, S2), from the ground state. Since various electrons possess various vibrational and rotational energies, the shift to a singlet state necessitates a move to a higher electrical state with a corresponding rotational or vibrational energy. During this process, a part of the electrons energy is lost, most typically through a nonradioactive thermal decay as a result of which a photon at lower energy is emitted. The Stokes shift is the difference in wavelength between the excitation wavelength and the wavelength of the emitted light. In fluorescence imaging technique, an external light source emits the energy which is captured and absorbed by the imaging dyes introduced by injection near the tissue or tumour site. This light energy is instantaneously reemitted with a lesser energy and longer wavelength, which is then captured by the detector. Auto fluorescence, scattering of light and high absorption by tissue haemoglobin in the mid-visible band are all common constraints to optical imaging of any tissue. Varied penetration depths can be attained by altering the wavelength of light employed and the fluorophore used (Graves et al., 2004; Licha et al., 2001; Ntziachristos et al., 2004). For example, tissue chromospheres i.e., deoxy− and oxyhaemoglobin, strongly absorb photons in the UV−vis spectral range within the first few micrometres of tissue thickness, thus limiting the penetration of the photons. On the other hand, due to minimal surface tissue absorbency in the specific spectral region, near−IR light of 650−900 nm, achieves the greatest tissue penetration (Graves et al., 2005, 2003).

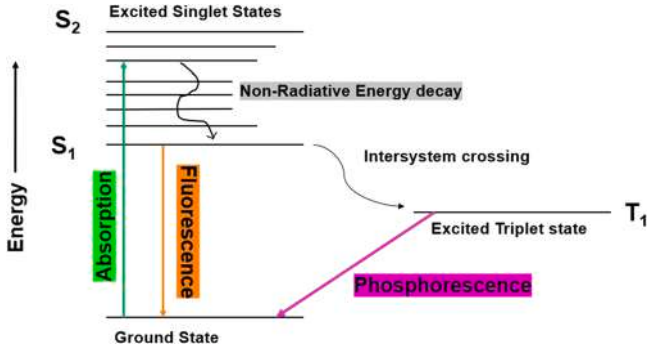

Fig. 1. The Jablonski diagram.

2. Conventional contrast agents for Imaging and their limitations

The most frequently used fluorophores are organic fluorescent dyes. Carboxyfluorescein−diacetatesuccinimidyl ester and fluorescein isothiocyanate dyes have been commonly used in various biological applications. These dyes are commonly used to tag antibodies and molecules used in the staining of cells or organelles (Lyons and Parish, 1994; Weston and Parish, 1990). The problem with using these organic dyes however outweighs the benefits. The main limitation to using conventional contrast agents are,

i. They are extremely vulnerable to photobleaching, which can occur rapidly (Fig. 2). They are unable to emit fluorescence over extended periods of time. This makes them unfit for bioimaging investigations over long periods of time (Chan et al., 2002; Walker et al., 1998).
ii. Organic fluorescing molecules are unsuitable for concurrent multicolour imaging because most organic dyes have a broad emission spectrum that can interfere and overlap with other fluorophores' emission spectrum. The excitation wavelength of each fluorophore is different. As a result, using multiple excitation sources becomes important.
iii. Local chemical environment and factors such as pH, interacting ions, etc can alter and interfere with the Emission or excitation.
iv. Overlapping of emission from dyes can occur over auto fluorescence from tissues. Low quantities of fluorophores such as nicotinamide (NAD [H]), collagen, flavins and elastin cause auto fluorescence in tissues. These molecules give a background fluorescence which occurs in the same region as the fluorescence of organic dyes. Most dyes that fluoresce in the visible area suffer from this limitation. Externally administered fluorochromes that fluoresce in the near-infrared range, such as the cyanine class of dyes, are increasingly being employed in fluorescence imaging to bypass this constraint (Lin et al., 2003). Nevertheless, most common dyes that possess fluorescence emission beyond ~850 nm suffer from low quantum yield, low brightness and insufficient photostability (Frangioni, 2003; Kim et al., 2004).

3. Optically active nanomaterials

Many nanoprobes have been engineered and used in bioimaging of tissues and treatment of diseases ranging from cancer to cardiovascular and inflammatory illnesses (Lim et al., 2012). Functionality of optically active nanoparticles depends on reliable and precise fabrication techniques. Various methods of synthesis of nanomaterials are discussed in Table 1. Optics-responsive inorganic and organic nanoparticles (Fig. 3) as imaging contrast agents for bioimaging applications have been elaborated below.

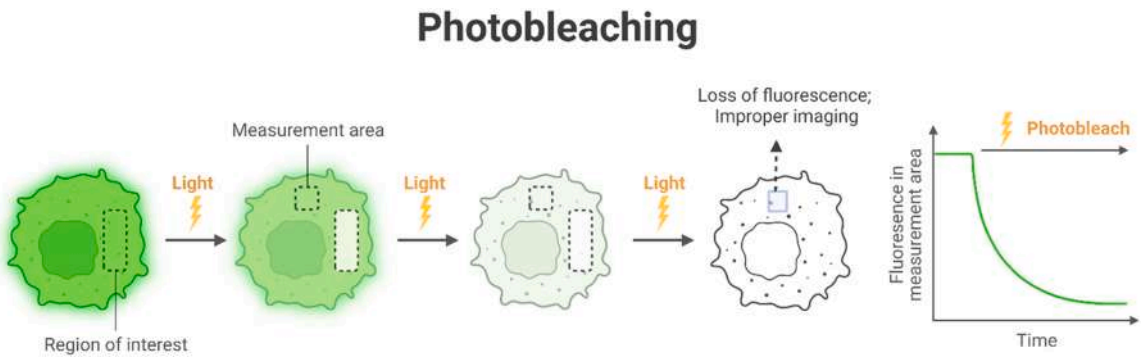

Fig. 2. Fluorescence loss due to photobleaching.

3.1. Inorganic nanoparticles as imaging contrast agents

Inorganic nanoparticles which are optically active are those which are capable of producing fluorescence or light dispersed under appropriate optical excitation by means of an inorganic material. Several optically active inorganic nanoparticles are used in optical bioimaging.

3.1.1. Magnetic nanoparticles

Magnetic nanoparticles have achieved considerable reactivity due to their imminent application in optical, magnetic and electronic mechanisms (Thorek and Tsourkas, 2008). They were extensively used to extend the platforms to target molecular imaging and theranostic purposes which take advantage of magnetic nanomaterial characteristics. Because of certain unique properties such as biocompatibility, less toxicity, distinct surface chemistry and other promising pharmacokinetic properties in blood and persistent tissue retention times. Generally, Magnetic have been used in single or multimodal imaging techniques (Huang et al., 2016; Lee et al., 2015). Besides the new expansions in molecular imaging and the growing demand for specific and effective imaging for identification and treatment, there is a revitalised advantage in emerging Iron oxide nanoparticles aimed at utilization in biomedical imaging.

There are various methods of preparing magnetic nanoparticles like physical, chemical and biological methods and each synthetic pathway has advantages and disadvantages. Physical synthetic methods such as ball milling, gas/aerosol deposition, electron beam lithography, laser-induced pyrolysis and pulsed laser ablation were simple to implement, it's difficult to control the size of the particles that may leads to various shapes. Chemical methods are efficient and simple which includes co-precipitation, thermal decomposition, hydrothermal, sol-gel, and micro emulsion. The synthesized nanoparticles have irregular shapes and they depend on the reagents used, temperature and pH. The biological means such as the use of magnetotactic bacteria are depicted by suitable reproducibility and scalability, which are also cost effective and produces great yield (Creţu et al., 2021).

There are few works reported that surface modification or functionalization of magnetic nanoparticles which are referred to as iron oxide core magnetite shells consists of Iron oxide (Fe_3O_4), Superparamagnetic iron oxide nanoparticles, Iron oxide nanoparticles, and Ultrasmall Superparamagnetic Iron oxide nanoparticles along with biologically compatible materials that has been used for imaging purposes (Ansari et al., 2019; Zhu et al., 2018). There are various shell coatings (Radhakrishnan et al., 2016) that have been used as encapsulation materials of proteins such as albumin (Vismara et al., 2017), gelatin (Murata et al., 2017), collagen (Belkahla et al., 2020) or polysaccharides like chitosan (Balan et al., 2015), alginate (Castelló et al., 2015), dextran (Naha et al., 2015), starch (Tudorachi et al., 2018), etc. This has been used for different imaging applications of MRI, PET, CT, SPECT and optical imaging (Fig. 4). In addition, the research is quite necessary to expose their ability as a potential candidate for the ingenious functionalization of metallic oxide nanomaterials to bioimaging.

3.1.2. Gold nanoparticles

Among metallic nanoparticles, silver and gold nanoparticles are most often investigated for biomedical applications. In the case of silver nanoparticles (SNPs), the area of application is restricted due to its toxic effects (Asharani et al., 2011, 2008). The unique features such as biocompatibility, optical property which is size dependent and stability were identified as the extraordinary benefits of gold nanoparticle (GNPs) to focus towards bioimaging (Bansal et al., 2020). There are various optical bioimaging techniques that are based on GNPs such as Localized Surface Plasmon Resonance (LSPR) imaging, Surface-Enhanced Raman Spectroscopy (SERS) imaging and Luminescence imaging (Kang et al., 2020).

Apart from the above characteristics, the use of GNPs in biomedical imaging techniques such as X-ray CT, dark field microscopic imaging, photoacoustic imaging, magnetic resonance imaging, and fluorescence imaging are widely accepted (Cole et al., 2015). The functionalization or the modification of GNPs with chemicals or biomolecules are useful for the diagnosis of diseases as imaging in the mode of probe (De Juan-Franco et al., 2013). Several studies have investigated the exploitation of GNPs as theranostic cancer probes, because of their exceptional optical characteristics which are not perceived in massive gold formulations. GNPs have incredible prospective for use as convenient fluorescent, probes that are non−bleaching as well as contrast agents for both *in−vitro* and *in−vivo* bioimaging (Aydogan et al., 2010; Cheng et al., 2015).

The GNPs possess unique optical properties and ease surface alteration ability makes GNPs ideal for bioimaging applications (Meir and Popovtzer, 2018; Repenko et al., 2018). In recent years, GNPs have drawn attention among the researchers due to their unique physicochemical features. GNPs are optically and electronically active, chemically stable, biologically compatible and adaptable to all functionality that depends on their size and shape. These unique properties of gold nanoparticles have immense possibilities to be used in various biomedical applications. A new approach focused on CT as an imaging technique and GNPs as contrast agent, has gained significant attention in its potential therapeutic application (Meir and Popovtzer, 2018).

Photoacoustics imaging is a versatile biomedical imaging (BI) tool for deep tissue imaging with immense significance for clinical visualization application. Repenko et al. (2018) demonstrated the melanin shells around the GNPs geometrics (from spheres to star and rods) improved the Photoacoustic (PA) competence. The melanin coatings reduced the cell toxicity as bioidentical surface coating (Repenko et al., 2018). The melanin coated GNPs display the powerful particles for in vivo PA imaging, particularly to be used as gastrointestinal PA imaging probes. The presence of the melanin coating completely avoided the cell death in case of gold rods. The cell viability improved over 90 % (melanin coating) and considerably improved cell proliferation in case

Table 1
Various methods of nanomaterial synthesis in Top Down and Bottom Up Approaches (Biswas et al., 2012)(Khan et al., 2017).

Approach to Synthesis	Techniques Used	Salient Features
Top-Down Approach	Optical Lithography	Dependable degree of resolution at high throughputs, long-established micro/nanofabrication tool specifically for chip manufacture.
	E beam Lithography	A widely used technique and equipment for nanofabrication that produces desired shapes for < 20 nm nanostructures in research environments.
	Block Co-polymer Lithography	A low-cost, high-throughput approach that works well for large-scale, densely packed nanostructures that allows for the fabrication of a variety of nanostructure shapes, including spheres, cylinders, and lamellae by parallel assembly.
	Soft and nanoimprint Lithography	Making ultra-small features (<10 nm) with a simple, efficient tool for nanofabrication based on pattern transfer.
	Scanning Probe Lithography	High resolution chemical, mechanical, and molecular nanopatterning capabilities, precisely controlled nanopatterns in resists for transfer to silicon, and the capacity to handle large molecules and individual atoms.
Bottom-Up Approach	Atomic layer deposition	By depositing one atomic layer at a time, it is possible to achieve atomic level accuracy, pinhole-free nanostructured films over broad surfaces, high reproducibility, and adhesion since chemical bonds are formed at the first atomic layer.
	Molecular Self assembly	Allows for the self-assembly of atomically precise nano systems by producing deep molecular nanopatterns with a width of less than 20 nm.
	Sol-gel nano synthesis	A low-cost approach for creating a wide range of nanomaterials, including multicomponent materials (glass, ceramic, film, fibre, and composite materials). Usually difficult to regulate synthesis, not easily scalable, and the subsequent drying procedures.
	Vapour deposition (Physical and Chemical)	Adaptable nanofabrication tool for the creation of nanostructured materials, like complex multicomponent nano systems (such as nanocomposites), controlled simultaneous deposition of a variety of materials, such as metal, ceramics, semiconductors, insulators, and polymers, high purity nanofilms, a scalable process, and the potential to deposit porous nanofilms

Table 2
Inorganic nanomaterials and organic nanomaterials with optical activities and their applications in biological imaging.

Type of Nanomaterial	Application in Imaging	Reference
Lanthanide nanoparticles	Fluorescence Imaging Contrast Agents	(Ren et al., 2020)
TADF dye doped silica NPs		(Crucho et al., 2020)
NaTb $(WO_4)_2$ nanomaterials		(Munirathnappa et al., 2020)
Gold nanoparticles	Computed Tomography	(Wen et al., 2013)
Bismuth nanoparticles		(Kinsella et al., 2011)
CaP nanomaterials		(Kollenda et al., 2020)
Magnetite iron oxide nanoparticles	Magnetic Resonance Imaging	(Arsalani et al., 2019); (Maity and Agrawal, 2007)
Chitosan derived glycolipid nanoparticles		(Zhao et al., 2020)
Hyaluronic acid nanoparticles	Positron Emission Tomography and Single Photon Emission	(Lee et al., 2015)
Aluminium oxide nanoparticles	Computed Tomography	(Pérez-Campaña et al., 2012)

of silica−core gold−shell particles (SiAuMel) and Gold nano stars (AustarsMel). The surface modification of melanin coatings with biomedical identification motifs may contribute to targeted imaging probes for accurate detection and localization in order to acquire biomedically pertinent molecular data. Kang et al. (2020) synthesised nano porous GNPs by implementing pulsed electrochemical deposition procedure utilizing an anodic aluminium oxide template for repeated Ag−Ag−Au nano segments and succeeding selective Ag phase etching. The internal porous structure of nano porous GNPs displayed a 15 nm gap size. The surface of nano porous GNPs was altered with mercaptosuccinic acid and mercaptopropionic. The mercaptosuccin acid altered nano porous GNPs displayed light triggered drug releasing for doxorubicin (Kang et al., 2020). Their study suggested that light irradiation on the nano porous GNPs induce local photothermal heating to cause the doxorubicin to be released form the nano porous GNPs. The in-vivo fluorescence imaging study showed that mercaptopropionic altered nano porous GNPs effectively functioned for controlled release of doxorubicin in mouse during light irradiation. The light triggered releasing may be useful for drug delivery and in vivo photothermal therapy.

In recent times, different coatings of GNPs have been developed for targeting the macrophages due to their unique optical properties, biocompatibility and less cytotoxicity. One of the important parameters in macrophage targeting is the nanorod brightness, choosing of nanorods aspect ratio and determines the sensitivity of an imaging system. Two photo luminescence microscopy is another common bio-imaging approach that overcomes the challenges posed by certain optical imaging techniques like auto-fluorescence of living tissues. The high spatial resolution with 3D images can be obtained from luminescence microscopy. Wang et al., 2013 used a laser scanning Two−photon luminescence (TPL) microscope to study the TPL characterization of nanorods with four different aspect ratio of nanorods with surface plasmon resonance at 700, 756, 844 and 1060 nm, respectively (Wang et al., 2013). Among the four wavelengths studied the nanorods with surface plasmon resonance at 756 nm were observed to be strongest TPL signal. Their study suggested that GNPs are the promising imaging contrast agent for Two−photon luminescence and the brightness of the nanorods for specific application can be known by comparison of TPL brightness, Two photon action cross section and TPL emission spectrum. The gold nanostructures with various morphologies functions as contracts agents and are also suitable for photoacoustic imaging (Xi et al., 2012). Gold nanocages have been used in variety of nanomedicine applications due to their unique properties. Photoacoustic tomography (PAT) is a powerful bio−imaging technique and Au nanocages are known to improve the PAT efficacy (Xia and Xia, 2014). PAT represents a unique and low cost approach to determine the angiogenic status of cancers such as head, neck, breast, skin etc before or during the therapy specifically antiangiogenic treatment, using angiogenesis as the origin of treatment, as an indication of disease recurrence (Pan et al., 2011). PAT contrast agents have been documented based on dyes (Wang et al., 2005; Xie et al., 2005); GNPs, nanocages (Pan et al., 2010; Yavuz et al., 2009).

Yang et al., 2007 reported Au nanorods as contrast agent (intravascular) for Photoacoustic tomography imaging in rat model (imaging of cerebral cortex and sentinel lymph nodes) (Yang et al., 2007). Kim et al., 2010 demonstrated the use of [NIe^4, D−Phe^7] −α−melanoma stimulating hormone conjugated Au nanocages as contrast agent for in-vivo

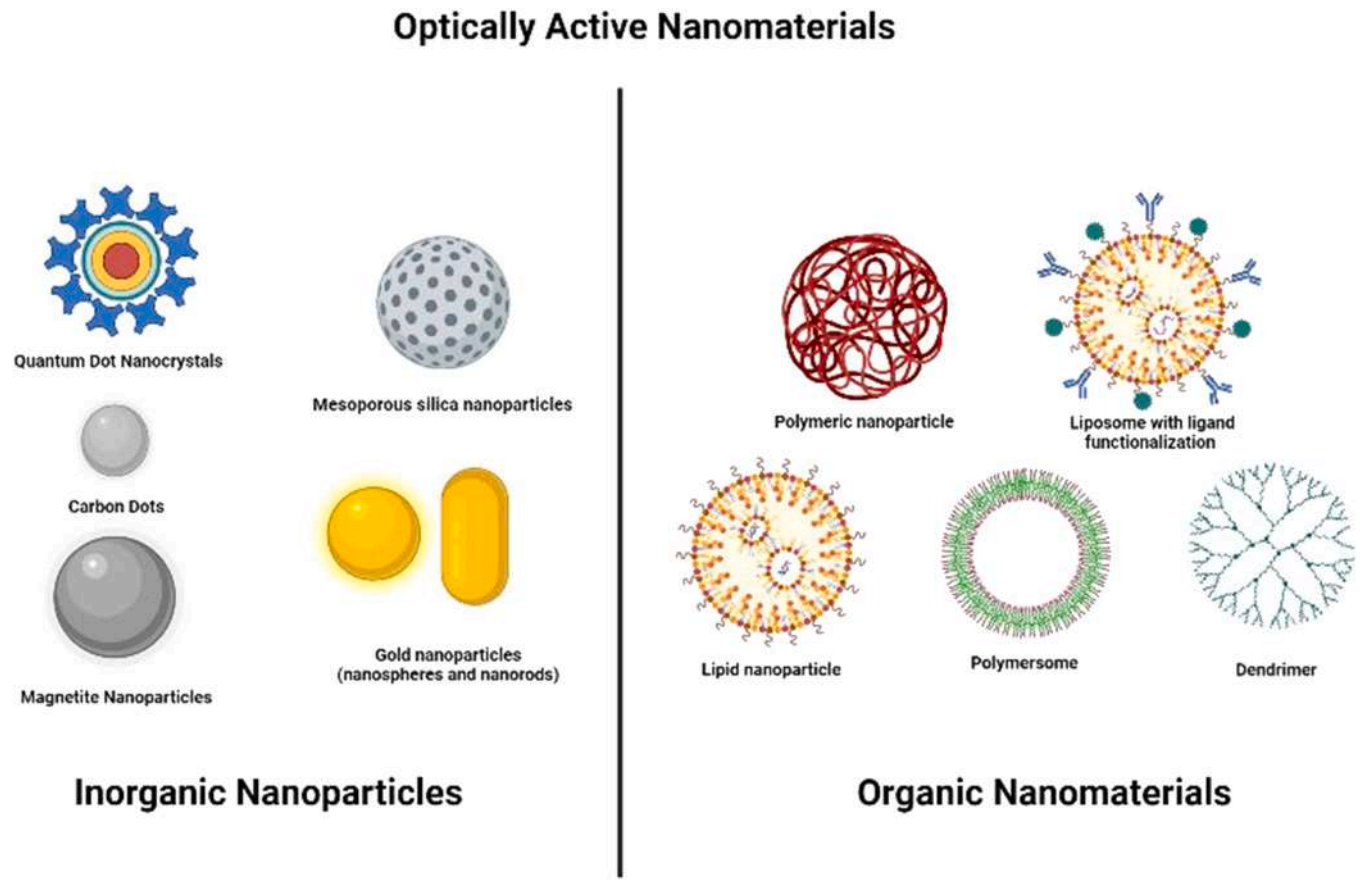

Fig. 3. Inorganic and organic optically active nanomaterials.

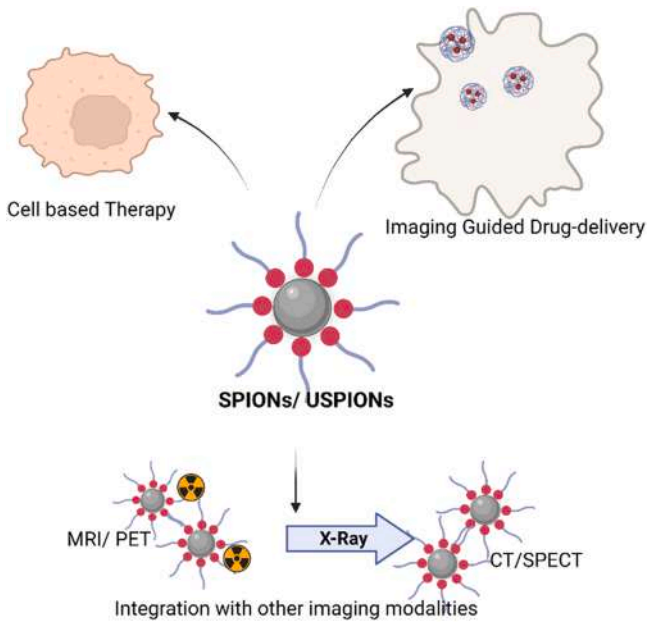

Fig. 4. Applications of super paramagnetic and ultrasmall super paramagnetic iron oxide nanoparticles (SPIONs/USPIONs).

Photoacoustic tomography imaging of melanomas (Kim et al., 2010).

Immunoelectron microscopy is one of the finest techniques for identifying and localizing the proteins in the cells and tissues (De Paul et al., 2012). In immunoelectron microscopy technique GNPs labelled antibodies are used to detect the particular antigens within the samples. Recently, biomedical investigators used GNPs for optical microscopic imaging. Wang et al. (2014) reported the Rose Bengal conjugated gold nanorods in-vivo for internalization of GNPs in oral cancer cells (Wang et al., 2014).

Another popular bio−imaging technique is magnetic resonance imaging (MRI). The 3D anatomical images with high resolution are obtained. The drawbacks from old MPI machine were long duration for scanning. The modern MRI machines have significantly reduced the time of scanning and the scanning of whole body is done in few minutes. Gadolinium based contrast agents have been extensively used to acquire magnetic resonance images. Gadolinium chelates based magnetic resonance imaging have be reported promising for improving MRI imaging (Perry et al., 2020).

3.1.3. *Mesoporous silica nanoparticles*

As previously stated, one of the most pressing issues with organic fluorescent agents is quick and rapid photobleaching. Various photochemical reactions happening in the cellular environment can lead to the degradation of the dye (Jaiswal et al., 2003; Song et al., 1995). A method that is in use and is the most effective in maximising the stability in-vitro and in vivo is the encapsulation of the dye in a ceramic matrix. This method minimizes exposure to oxygen thereby increasing chemical stability thereby allowing modification of shell surface to enhance hydrophilicity and cellular uptake. Currently various methods that are being used for encapsulation comprise incorporation of the dye in PNA oligomers nucleic acid, lipid micelles (Zheng et al., 2002), and encapsulation in polymer or silica matrices (Bagwe et al., 2004).

Colloidal mesoporous silica nanoparticles (MSNPs) are a group of inorganic vehicles that are of high significance in dye/drug delivery. They possess controllable morphologies and mesostructures that can be readily functionalised and are highly biocompatible, thus making them

suitable candidates for bio-therapeutic and biomedical applications (Popat et al., 2011; Wu et al., 2011) (Fig. 5). MSNPs possess more silanol groups on their surface making them hydrophilic; the ease of functionalization by various chemical moieties/groups enables in achieving sustained holding/release of the loaded molecules. The high pore capacity and huge internal surface area of mesoporous materials facilitate an increased loading of molecules. They also prevent the escape of molecules by rapid dissolution in an aqueous environment. This ensures efficiency and effective loading of drugs into the delivery system and increases the chances of drug reaching their specific therapeutic target. In addition, the large pore size of the MSNPs is advantageous in improving the delivery of hydrophobic anti−cancer molecules. This is of great importance because the effectiveness and efficiency of such drug molecules may be limited by their poor solubility in water (Li et al., 2012). The MSNPs can be functionalised on both the interior and exterior surfaces, improving the drug delivery and a plethora of functionalities. One of the primary aspects that contribute to MSNPs' wide functionalization capacities is their increased surface area−to−volume ratio and mesoporosity. Organic molecules such as dyes, drugs etc. can be bound to the silanol group on the exterior surface by means of electrostatic or covalent interactions. Also, the MSNP surface can be reinforced with vectors that are active targeting to increase the targeted nature of drug delivery and reduce tissue damage. Furthermore, research has been carried out on functionalization of the interior surface with specific load molecules such as drugs, dyes, proteins and nucleic acids for theranostic purposes (Li et al., 2012; Margolese et al., 2000; Solberg and Landry, 2006).

Before the effective application of MSNPs in drug delivery systems, investigating their cellular uptake and cytotoxicity becomes ultimately necessary. The uptake of MSNPs and their significant biocompatibility were confirmed using both healthy cell lines and cancer cell lines (Lu et al., 2007; Radu et al., 2004). Many researchers have proven that cellular uptake and cytotoxicity of MSNPs depend upon factors like surface charge, particle shape, size and functional groups present (Vivero-Escoto et al., 2010; Wu et al., 2011). Non modified 100 nm MSNPs showed no cytotoxicity up to 100 mg mL^{-1}. Therefore, therapeutic treatments can be safely done with a lower concentration range (Lu et al., 2010; Meng et al., 2010; Thomas et al., 2010).

3.1.4. *Quantum dots*

Quantum Dots (QDs) have become a major group of imaging probes in addition to general multi-purpose nanodevice platforms for engineering (Zrazhevskiy et al., 2010). There are several routes of synthesis of QDs out of which top-down which include molecular beam epitaxy, ion implantation, and lithography and bottom-up that includes wet-chemical and vapor−phase methods are generally preferred (Bera et al., 2010). They have discrete benefits compared to conventional luminous natural dyes in both chemical and biological studies with respect to integrate emission spectrum, indicate brightness, and photostability (Liu et al., 2011; Liu et al., 2011). Hence, due to the adaptable luminophores property, its influence on numerous fields of advanced biology with QDs extensively applied as tags and diverge agents in in vitro and in vivo bioimaging (Jeong et al., 2016). Quantum dots, especially semiconductor quantum dots, are one of the most intriguing photoluminescent nanomaterials with a lot of potential in cancer nanomedicine (Yao et al., 2018). ZnS quantum dots appear intriguing,

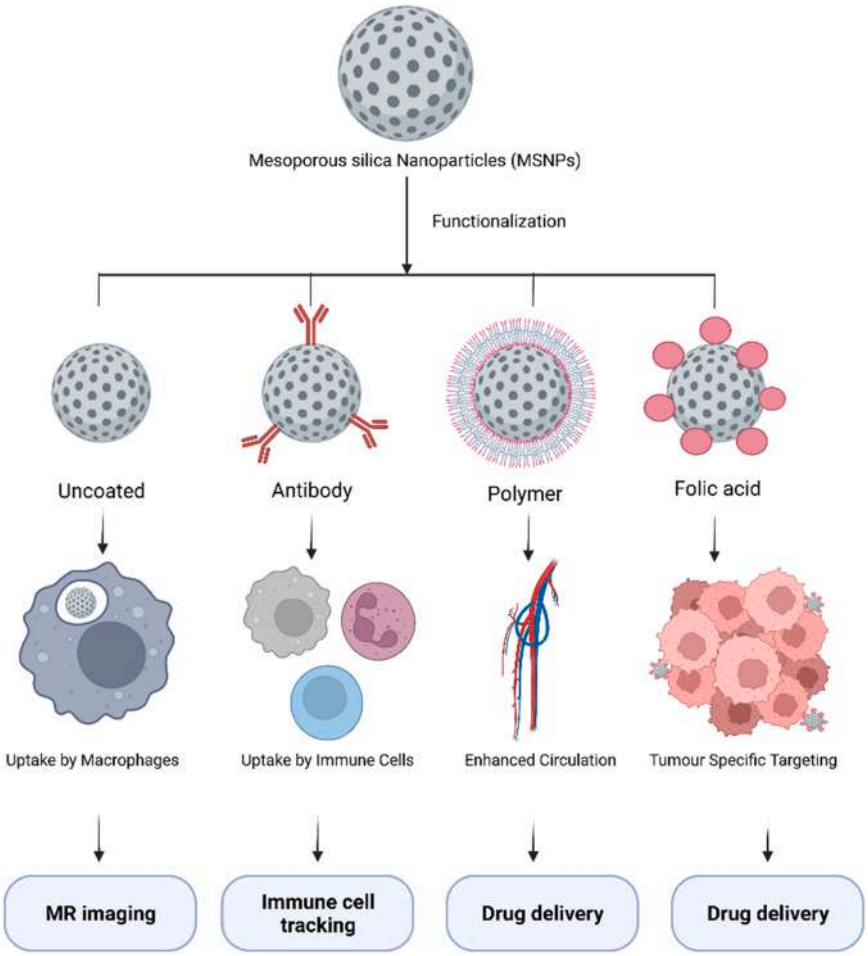

Fig. 5. Functionalization of mesoporous silica nanoparticles and their uses.

because of its visible light emission, biocompatibility, and ability to be synthesized using a variety of surface capping agents (Ramanery et al., 2014). Pure or doped ZnS nanoparticles are employed in a number of applications, including biomedical luminous nanoprobes, nano−photocatalysts, optical nano-sensors, and fluorescence resonance energy transfer processes (Caires et al., 2020). In a study, green synthesized ZnS quantum dots were used as photoluminescent nanoprobes for bioimaging brain cancer cells (Caires et al., 2020). Bioconjugates made of Ag−In−S@ZnS coupled with ZIKA virus was designed and developed for the first time which gives insights on the interaction profile of the ZIKA virus−nanoparticle conjugates with VERO cells and serves as a nanoplatform to elucidate the infection mechanisms and host cell response (Carvalho et al., 2020). Quantum dots are also presumed to be a leading tool in the fluorescent diagnostics of cancer and other acute conditions.

3.1.5. *Black phosphorous nanomaterials*

Black phosphorus (BP) nanosheets and nanodots make up the majority of BP nanomaterials. Among them, phosphorene, a two-dimensional BP nanosheet with just a few layers, has garnered a lot of interest lately. Over decades of research and development, a variety of approaches have been developed for the synthesis of BP nanosheets, including the top-down method and the bottom-up method. These techniques include mechanical cleavage and liquid-phase exfoliation procedures (such as chemical vapour deposition and wet-chemistry techniques) (Qiu et al., 2018). In recent years, a new 2D substance called BP, each layer of which is also known as phosphorene, has appeared. High anisotropy due to its wrinkled structure along the zigzag and armchair directions, a direct and layer-dependent band gap (Ep) from 0.2 eV (bulk state) to 3.2 eV (monolayer), in contrast to semi-metallic graphene, and, in particular, a strong sensitivity to oxygen and water in conjunction with visible light, which leads to poor stability under ambient conditions, are just a few of the key differences between BP and graphene (Xing et al., 2018). BP's weak environmental stability is its greatest shortcoming. The fascinating physical properties of it under ambient conditions are deteriorating mostly as a result of its degradation. As a result, numerous efforts have been made to shield BP against airborne deterioration. Recent studies, however, have shown that this trait of quick degradation is a significant benefit when using BP as a photothermal agent for photothermal therapy (PTT) against cancer (Xie et al., 2020; Zhou et al., 2016). In the field of biomedicine, accurate tumour identification and successful therapy are crucial and essential. Metal phosphide/phosphate nanomaterials were demonstrated to be appropriate for tumour imaging, including MRI, fluorescence imaging (FI), photo acoustic imaging (PAI), and tumour treatments (CDT, PTT, and PDT). BP nanoparticles, phosphorus-containing dendrimers, and metal phosphide/phosphate nanomaterials have all been used in the treatment of tumours, tumour imaging, and neurological disorders (Tang et al., 2020).

4. Organic nanomaterials

In recent years, there is an exponentially increasing interest in the development of organic nanomaterials for biomedical applications. Engineered nanoparticles have gained significant interest due to their versatile medical applications in vaccination, cancer therapy, diagnostic imaging procedures and drug delivery (Virlan et al., 2016). Polymer dots have been identified as an intriguing class of fluorescence probes in bioimaging and biosensing. Polymer dots are advanced nanomaterials that generally display enhanced fluorescence brightness and photo stability. These type of fluorescent nanoparticles are commonly used in sub fluorophore groups such as C ¼ N, C ¼ O, N ¼ O instead of fluorophore groups and have a promising potential as new fluorescent material (Zhong et al., 2018). The main advantage of these polymer dots can be low or minimal toxicity, non−degradable, rapid emission rate and high fluorescence brightness and so they possess explicated potential for vast applications in biomedical fields like cell labelling, bioimaging, cancer phototherapy, lymph node mapping, drug delivery and biosensing (Solhi and Hasanzadeh, 2019).

One of the most recent advancements in the creation of value−added goods from bioenergy and biochar production is the fabrication of carbon−based nanomaterials (Plácido et al., 2019a). The synthesis and purification of carbon containing nanomaterials from biochar or microalgae by employing chemical depolymerisation and solvent extraction methods has been reported too (Plácido et al., 2019b). These nanomaterials were investigated as a transducer for the detection of heavy metal ions in aqueous systems and cellular imaging. The fluorescence emitted by microalgal biochar−derived carbon nanomaterials was found to be quenched by four heavy metal ions: Ni (II), Pb (II), Cd (II), and Cu (II). The results suggest that the biochar−derived carbonaceous nanomaterials were suitable as a bioimaging probe for yeast cell bioimaging and had varied fluorescence intensity and the localisation depending on the yeast cells. The intensity of the signals and absence of toxicity make them most suitable for bioimaging applications (Plácido et al., 2019a). Graphene, a two−dimensional substance with a sheet−-like faveolated structure, has sparked a tremendous amount of interest in both basic and applied research. Due to its distinctive optical and electrical features, as well as a tunable band gap, 2D black phosphorus has recently gained popularity. Black phosphorus nanodots of size < 20 nm was reported to serve as a candidate for bioimaging. The so formed nanodots were found to be stable in aqueous solution and degraded in phosphate buffered saline. They showed little or minimal cytotoxicity *in−vitro*, making them a suitable candidate for drug delivery or intracellular tracking systems as bioimaging agents using blue and green fluorescence (Lee et al., 2016).

Self-assembled organic molecules made of paclitaxel conjugated near-infrared brominated boron−dipyrromethenes synthesized via nanoprecipitation method was used as an efficient bioimaging agent for cervical tumours and showed no systemic toxicity (Zhang et al., 2018). Emission tunable probes via one step hydrothermal reaction using terbium (III) doped self−activated luminescent hydroxyapatite were synthesized with the assistance of trisodium citrate which holds significant promise in luminescence and bioimaging (Wang et al., 2021).

In comparison to the traditional natural fluorophores and semi−conductor QDs, the recently developed carbon quantum dots, which belongs to nanocarbon family, are exclusive in terms of facile surface functionalization, chemical inertness, resistance to photobleaching, etc. (Xu et al., 2004). CDs can be synthesised from a wide variety of precursors such as chemical and eco−friendly resources such as glucose, ascorbic acid, gelatin, chitosan, sugarcane juice, watermelon peel, etc. Surface modification of CDs by functionalisation that are obtained using polyethylene glycol, thiols, etc., for bioimaging application (Dong et al., 2012).

Carbon dots were also assessed for optical bioimaging applications, including their cellular absorption and fluorescence luminosity within the cell (Li et al., 2012). Fluorescence imaging of the in vivo mouse model using commercially available CdSe−ZnS QDs was compared (Cao et al., 2012). Additional research on uses such as combining carbon dots with bioactive substances for exclusive in vivo targeting and their applications in cancer diagnosis and angiography could be envisaged.

Organic–inorganic hybrid NPs of PANI@$W_{18}O_{49}$ with uniform morphology and PANI@$W_{18}O_{49}$ @Fe_3O_4 with magnetic targeting were synthesized by hydrothermal method in a study for combined synergistic photothermal therapy and chemotherapy for cancer. It was found that the hybrid NPs not only did not affect the photothermal properties of $W_{18}O_{49}$, but also improve its antioxidant properties, which made the synthesized NPs more suitable for PTT as a photothermal agent than $W_{18}O_{49}$ itself (Yang et al., 2021).

5. Bioimaging using nanomaterials

5.1. Nanoparticles in fluorescence imaging

Fluorescent nanoparticles are potential devices in biochemical, bio-analytical, and medicinal fields for optical data storage and other technical applications. Fluorescent imaging with engineered nanoparticles has become widely used in a variety of clinical and biological applications, including gene therapy, drug delivery, and also in bio sensing, to investigate cellular dynamics and interactions (Grunert et al., 2018). The majority of current medical and biological fluorescence imaging technologies rely on dye markers, which have limitations in terms of light emission per molecule and photostability. These drawbacks are solved by nanoparticles, which provide strong and stable fluorescence. In a study, engineered NIR−IIb fluorescence of Er−based lanthanide nanoparticles were reported for through−skull targeted imaging of orthotopic glioma which demonstrated to possess greater potential in imaging-guided surgery of tumour (Ren et al., 2020). The field of organic light emitting diodes that provide a long-lived delayed fluorescence component for sensing oxygen content, measuring local temperature, or imaging has been revolutionised by thermally activated delayed fluorescence (TADF). A facile method demonstrated the synthesis of TADF dye doped silica nanoparticles that are effectively internalized by human cells even at low incubation concentrations, localized in the cytosol and enabled fluorescence live cell imaging (Crucho et al., 2020). An electrostatic complex nanoparticle has been designed to serve as a fluorescence switch for selective cell imaging. The fluorescence of the complex nanoparticle can be modulated by light irradiation and those with good fluorescence performance were employed for selective cell marking and imaging applications (Peng et al., 2020). Scheelite like NaTb $(WO_4)_2$ nanoparticles has been reported to exhibit particle size dependent optical properties which emit green fluorescence. The nanoparticles synthesized showed excellent biocompatibility in HeLa cells and it is reported to be a promising candidate for its role as a biomarker for cell imaging applications (Munirathnappa et al., 2020).

5.2. Nanoparticles for CT imaging applications

The structural and morphological qualities of the sample under investigation can be determined using X−ray CT in 3−D. It is essentially used in clinical and medical applications to diagnose the diseases that occur in different parts of the body (Aslan et al., 2020). Contrast agents based on tiny molecular molecules are frequently employed for better CT imaging; however, they have significant drawbacks such as a short half−life, renal toxicity at relatively high concentrations, and non−−specificity. Recent advances in nanotechnology have paved way for various nano systems for numerous applications. In a study, multifunctional gadolinium−loaded dendrimer−entrapped GNPs were synthesized and were reported to show excellent dual mode MRI−CT imaging performance in-vivo. These complexes were anticipated to show promising results in cancer diagnosis at an early stage with high accuracy and sensitivity (Wen et al., 2013).

Bismuth, due to its high atomic number, density and good X−ray attenuation, is a suitable candidate to be a contrast agent. Polyvinyl pyrrolidone (PVP) coated chemically synthesized bismuth nanoparticles provided excellent contrast amplification which was reported to be significantly greater than commercial iodine based products in the market. Internal organ visibility was improved without causing any significant cytotoxicity (Rabin et al., 2006). In addition, functionalization of bismuth nanoparticles with antibody possessed tissue targeted drug delivery applications (Kinsella et al., 2011). Intravenous injection of radiolabelled/tagged nanoparticles enhanced the contrast of the tumorous tissue and was found to be cleared up in renal pathway (Fig. 6).

Calcium phosphate nanoparticles were fabricated to visualize its biodistribution in-vivo by quantitative small animal positron emission tomography for several application routes. The results revealed that post intra−venous injection; the nanoparticles entered the lungs rapidly and gradually were redistributed into the spleen and liver. However, while following the intra muscular route of injection the nanoparticles remained mostly at the injection site which provides a new insight for the persistent activity of the nanoparticle in treatment (Kollenda et al., 2020).

5.3. Nanomaterials for MRI imaging

MRI has become one of the most extensively used and powerful tools for non−invasive clinical diagnosis. Nanomaterials have been extensively studied in the biomedical field to improve imaging tools for the diagnosis of tumours, tissue damage, and neurological problems (Wang et al., 2020; Yoo, 2012). MRI contrast agents available at present are commonly in the form of T1 positive agents of paramagnetic particles and T2 negative agents of superparamagnetic particles (Yang et al., 2011). Though the mostly used contrast agents are Gd−complexes, they pose a high risk of serious effects including systemic fibrosis of kidneys (Todd et al., 2007) and its accumulation in the brain (McDonald et al., 2015). To counteract this, lately, magnetic nanoparticles, in particular magnetite iron oxide nanoparticles are used as MRI contrast agents owing to their magnetism, insignificant toxicity and enhanced biocompatibility when compared to other magnetic nanoparticles (Arsalani et al., 2019). In addition, surface modification of these magnetite iron oxide nanoparticles can enhance the properties of biocompatibility and stability for medical applications (Maity and Agrawal, 2007).

In another study, chitosan derived glycolipid nanoparticles were reported as contrast agents for MRI imaging for the photodynamic

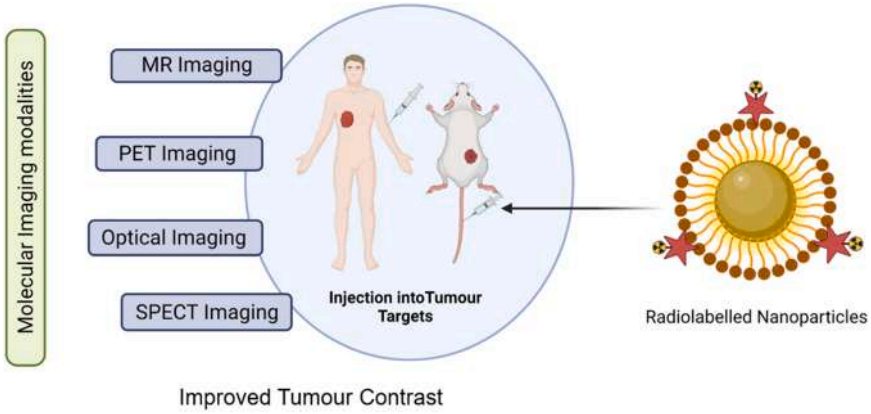

Fig. 6. Radiolabelled nanoparticles for molecular Imaging modalities.

therapy of cancer (Zhao et al., 2020). Among the polysaccharides, chitosan being a naturally occurring one has been widely reported for its high biocompatibility, flexibility and clinical efficacy (Esfandiarpour-Boroujeni et al., 2017). The chemical conjugation of octadecanoic acid and gadopentetic acid with chitosan gave rise to a polymer that self-assemble into glycolipid nanoparticles increased the MRI sensitivity as compared to the common gadolinium diethylenetriaminepentaacetic acid candidate. Moreover, it was reported that the nanoparticles showed negligible haemolysis and stability in physiological environments in addition to powerful MRI guided tumour ablation through photodynamic therapy (Kamkaew et al., 2016; Zhao et al., 2020).

5.4. PET/SPECT imaging using nanoparticles

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are the two major imaging modalities in nuclear medicine. A radioisotope is generally used as the imaging signal in both the methods. PET and SPECT are most commonly used for imaging or diagnosis of cancer and cardiovascular diseases respectively. PET has become the clinical method of choice for grading and restaging a variety of cancers, requiring the intravenous delivery of tracer amounts (typically nanomolar) of a radioactively labelled medication that is selective and specific for the target of interest. Nanoparticles can operate as signal amplifiers, leading in improved sensitivity and greater contrast indices. Their enormous surface area allows them to be functionalized with various targeting moieties, resulting in a multifunctional nanoplatform for disease detection (Goel et al., 2017). The capability for multimodality is a significant benefit of nanoprobes over standard biological moieties. Generally, nanoparticles−based functional imaging has the potential to enable early detection and prevention, and to essentially improve diagnosis, treatment and follow−up of diseases.

Hyaluronic acid nanoparticles labelled with fluorescent dyes have the potential to effectively target the atherosclerotic lesions (Lee et al., 2015). In a study, GNPs based imaging for cardiovascular diseases using SPECT proved to be promising due to their easy uptake and high X−ray sensitivity. It was also reported that the GNPs based imaging agents increased the specificity for apoptotic macrophages and reflects the exact pathologic condition of the examined specimen (Li et al., 2016). In another study, dual-functional quantum dot nanoprobes were utilized for quantitative evaluation of *in−vivo* pharmacokinetics and tumour−targeting efficacy studies using both PET and NIRF imaging (Cai et al., 2007).

Radionuclides emitting positrons can be conjugated or even inserted into carbon nanotubes for PET imaging. For instance, it was reported that 86Y−Carbon nanotubes were synthesized from amine-functionalized and water-soluble carbon nanotubes by covalently attaching multiple copies of DOTA chelates and then radiolabelling with the positron-emitting metal-ion, yttrium−86 (McDevitt et al., 2007). Nahrendorf et al. developed a dextranated 20−nm nanoparticle labelled with ^{64}Cu to yield a PET, MR, and optically detectable imaging agent (Nahrendorf et al., 2008). Recently, ^{18}O−enriched aluminium oxide (Al_2O_3) NPs were developed by irradiation with protons to yield ^{18}F-labeled NPs via the ^{18}O (p,n)^{18}F nuclear reaction(Pérez-Campaña et al., 2012).

5.5. Multimodal imaging using nanoparticles

Multifunctional nanoplatforms with multimodal imaging and cancer therapeutic abilities have gained attention in biomedical applications. Molecular imaging techniques such as OI, MRI and CT play a vital role for diagnosis in medical field (Gao et al., 2010). Nevertheless, unimodal molecular imaging techniques provide inadequate information in clinical diagnosis and scientific research (Dai et al., 2013). OI with increased sensitivity is limited owing to their relatively unsatisfactory spatial resolution (Ma et al., 2012). Also, as a non-invasive imaging method, MRI possess high spatial resolution and soft tissue contrast without any damage due to radiation; however, it sometimes shows insufficient sensitivity resulting in false images (Zhou et al., 2012). To counteract these difficulties, multimodal imaging methods have gained attention as they prove to be more efficient and provide exact information about physical and biological structures and their physiological functions (Lv et al., 2015).

The fabrication of imaging probes is crucial to the advancement of multimodal imaging. Many multimodal imaging nanoprobes have coupled optical and MR imaging such as in Gd/Fe−based QDs (Liu et al., 2011; Liu et al., 2011), Gd−based carbon dots (Chen et al., 2016) etc. The ideal candidate for optical and MR multimodal probe is Gd^{3+} ions, due to their minimal quenching efficiency and strong MRI signals. Due to the exceptional optical imaging properties, luminescent nanoprobes based on near infrared luminescence have proved to be one of the best candidates. In a study, a novel multimodal imaging nanoprobe based on near infrared luminescence nanoparticles functionalised with gadolinium complex for in-vivo MRI and NIR persistent luminescence imaging (Abdukayum et al., 2014). In another study, Maldiney et al., 2015 synthesized a multimodal bioimaging nanoprobe via Gd^{3+} co−doping into near infrared luminescence nanoparticles for MR Imaging (Maldiney et al., 2015). Apart from these near infrared luminescence nanoprobes, metallic nanoparticles like fluorescent copper sulphide nanoparticles enable both non-invasive multimodality imaging and targeting photothermal therapy of metastatic gastric cancer cells in lymph nodes examined in mice models (Shi et al., 2018).

5.6. Nanoparticles in ultrasound imaging

USI is one among the most often used diagnostic modalities in clinics, with various advantages over other imaging techniques, including quick and real-time imaging, excellent temporal and spatial resolution, low cost, no radiation risk, and easy patient access (Kang et al., 2010; Son et al., 2014). USI is most commonly utilised to perform morphological and functional examinations of soft tissues and the abdomen without the need for contrast agents. However, the assistance of contrast agents proves to provide more exact and clear USI of organs in various disease diagnosis.

The ketalized maltodextrin nanoparticles for contrast enhanced USI and therapy of acute liver failure. The synthesized nanoparticles were capable of delivering therapeutic and imaging functions simultaneously to the acidic conditions found in the site of inflammation (Go et al., 2018). In another study, Min et al., 2015 developed gas generating pH-controlled calcium carbonate ($CaCO_3$) nanoparticles as diagnostic and therapeutic agents for USI and cancer therapy. The mechanism of action of mineralized nanoparticles involved acid triggered dissolution of $CaCO_3$ and subsequent CO_2 generation. The hybrid nanoparticles were reported to quicken drug release at the acidic tumour site, leading to targeted drug delivery (Min et al., 2015). Magnetic nanoparticles also play a vital role in medical diagnosis where they mostly served as imaging contrast agents. Magneto−motive ultrasound is one such imaging technique where superparamagnetic NPs are used as contrast agent. A facile and economical coprecipitation method for the synthesis of Zn−substituted magnetite nanoparticles was reported. The study showed a marked increase in magnetic properties of magnetite nanoparticles by zinc which makes it a good candidate not only as contrast agent in USI but also as a therapeutic agent in magnetic hyperthermia. GNPs that have been explored widely in biomedical research also proved to have a profound efficacy in USI. In a study, nanomolecular probe encapsulating liquid perfluoro hexane and gold nanorods targeted towards melanoma associated antigens were found to enhance USI at tumour sites (Hadadian et al., 2018).

6. Biocompatibility of nanomaterials

Biocompatibility of nanomaterials is an important aspect for the evolution of nanomaterials from laboratory to medicinal use.

Nanotoxicology is a growing paradigm that attempts to evaluate the effects of nanoparticles in order to determine out the structure and functional link between nanomaterials and toxicity. Toxicology testing and assessment are, nonetheless, a significant aspect of pre−clinical safety testing of novel medications, which is required before beginning human Phase I/II clinical trials (Ashokan et al., 2017).

Nanomaterials, particularly gold is known to be highly compatible with the human body and is regarded as safe. However, there exist various concerns on its repeated and long−term exposure. In a study, Suganya et al., 2017 reported the biocompatibility of pectin derived GNPs in-vivo at acute and sub-acute level. The results proved the biocompatibility of GNPs with no lethal effects on tested animals (Suganya et al., 2017). Various reports have reported the use of graphene−based nanomaterials for medical applications. Covalent functionalization of graphene oxide with amino acids based on amidation has proved to be biocompatible on *in−vitro* evaluation on human embryonic kidney cells. The fabricated graphene−L−methionine nanomaterial has also shown to be a potential target for drug delivery upon binding with human serum albumin (Abdelhalim et al., 2020). Carbon nanomaterials have been used in a vast array and it was of interest to investigate its biocompatibility to be used for medical applications. The importance of particle shape in toxicity was demonstrated in a study where multi-walled carbon nanotube were found to be more toxic compared to multi−walled nano−onions to human skin fibroblasts (Ding et al., 2005). In a study, where the role of dimension of carbon nanotubes were considered in dermal toxicity, the results suggested that considering multiple physicochemical parameters when evaluating cellular toxicity of carbon nanomaterials will provide accurate results on its biocompatibility (Grabinski et al., 2007). Among various nanomaterials, biodegradable polymeric nanoparticles serve as a possible alternative for drug delivery (Mattu et al., 2013), to deliver drugs, genes and proteins (Hu et al., 2013). Commonly used polymeric nanoparticles include PLGA and PLA nanoparticles which were approved by US Food and Drug Administration (FDA). It is well established that several nanomaterials are able to cross blood−brain barrier reaching several regions in the central nervous system. While some nanomaterials possess the ability to cause neuronal toxicity, inflammation and cognitive deficits, there are reports on the biocompatibility of polymeric nanoparticles to the CNS and biodegradable properties which are the important characteristics when developing efficient nanocarriers for drug delivery (Leite et al., 2015).

The most worrying concerns with regard to phosphorus-based nanoparticles and possible clinical use are their biosafety and in vivo metabolism. The most widely utilised phosphorus-containing dendrimers, polyphosphazenes and polyphosphoesters, have the potential to breakdown into non-toxic compounds (Jing et al., 2019).

7. Toxicity of nanomaterials

Most nanomaterials used in biomedical applications for imaging diagnostics and theranostics are associated with toxic effects if not used with caution. Most nanomaterials enter the environment through air, water and soil. The benefits of NPs, such as their small size, strong reactivity, and great capacity, could turn into potential hazards by causing adverse toxicity in cells and thus leading to lethality. Studies have also shown that NPs can enter living organisms by inhalation or ingestion, and they possess the ability to translocate around the body to different organs and tissues where they may exert their reactivity and bioaccumulate (Khan et al., 2019). Also, the relatively small size of nanomaterials makes it easier for the smaller organisms to ingest or uptake the nanomaterials, which over time has detrimental consequences on the organisms. The increased manufacturing and application of nanomaterials, combined with a lack of a dedicated waste management infrastructure, cause them to become a discharge. Since nanoparticles are influenced by physicochemical and other elements including the pH of the surroundings, surface charge of the material, biomass concentration, and chemical composition of the environment, environmental transformation is crucial for determining the toxicity of nanoparticles (Jadhav et al., 2021). Thus an ecotoxicological evaluation of the fate and persistence of nanoparticles becomes a crucial component of the toxicity assessments (Vineeth Kumar et al., 2022). Inorganic nanoparticles undergo a series of changes that significantly impact ecosystem's lower-level organisms. On rare instances, particle aggregation may be caused by increased surface area and charge. Metal oxide nanoparticles go through a number of transformation processes when they are discharged into an aqueous environment, including aggregation (including homogeneous and heterogeneous aggregation), adsorption, dissolution, and redox reactions. Linkages to macromolecules can happen due to numerous processes, including hydrophobic interaction, electrostatic interaction, van der Waals interaction, chelation, and ligand exchange (Wang et al., 2019).

8. Conclusion

Nano−imaging agents integrate diagnostics with therapeutics in the same platform, termed nano−theragnostic. Nanoparticles as carriers have humongous potential to incorporate various imaging and therapeutic agents to specific locations for biomedical imaging. Many categories of inorganic and organic nanoparticles have been used for biomedical imaging purposes. Most of these have been applied in tumour research. To ensure maximum bench to bedside translation of nanoparticle research, all aspects of nanoparticles, including shape, composition, surface area and charge, hydrodynamic diameter, composition, stability, solubility, delivery method, distribution, metabolism, clearance, accumulation, and potential hazardous effect, should be thoroughly studied (Choi and Frangioni, 2011). The conduct of thorough studies for efficacy and safety in well−designed clinical trials will be the most crucial and challenging component of this nanomaterial evolution. Improving target specificity with elongated fluorescence and minimal toxicity should be focussed on (Hua et al., 2018; Min et al., 2016). Moreover, the increasing significance of translational potential with relevant animal models cannot be exaggerated, without understanding the specific pharmacokinetic and pharmacodynamic profile of these agents in humans. Despite these challenges, nanoparticles possess remarkable capability as novel imaging agents for a variety of clinical applications (Sanna and Sechi, 2020; Van Norman, 2016). Further clinical translation is also hampered by the paucity of knowledge on the metabolism of nanomaterials in vivo. The current issues encourage future study of nanoparticles in imaging, PTT and PDT. For example, surface modification or the addition of liposome, erythrosome, and exosome for the encapsulation of phosphorus-based nanomaterials may significantly improve their biosafety and benefit their metabolism (Boorn et al., 2011; Fan et al., 2018). However, further research into the biosafety, cost-effectiveness, and controlled synthesis of high-quality few-layer nanomaterials with much increased efficiency, controlled size/thickness, and reduced adverse effects is imperative to finally realise clinical and translational applications of nanomaterials for therapeutic, diagnostic, or clinical applications.

CRediT authorship contribution statement

P. Sowmiya: Writing original draft, illustration, review & editing, visualization, conceptualization. **T. Stalin Dhas**: Conceptualization, writing original draft, review, editing, visualization and supervision, **D. Inbakandan** & **N. Anandakumar**: review & editing, **S. Nalini**, **K.S.U. Suganya**, **R.R. Remya**: Writing and review, **V. Karthick** and **C.M.V. Kumar**: Review & Editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

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