



## Historical Perspective

## Precision-engineered metal and metal-oxide nanoparticles for biomedical imaging and healthcare applications



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## ABSTRACT

The growing field of nanotechnology has witnessed numerous advancements over the past few years, particularly in the development of engineered nanoparticles. Compared with bulk materials, metal nanoparticles possess more favorable properties, such as increased chemical activity and toxicity, owing to their smaller size and larger surface area. Metal nanoparticles exhibit exceptional stability, specificity, sensitivity, and effectiveness, making them highly useful in the biomedical field. Metal nanoparticles are in high demand in biomedical nanotechnology, including Au, Ag, Pt, Cu, Zn, Co, Gd, Eu, and Er. These particles exhibit excellent physicochemical properties, including amenable functionalization, non-corrosiveness, and varying optical and electronic properties based on their size and shape. Metal nanoparticles can be modified with different targeting agents such as antibodies, liposomes, transferrin, folic acid, and carbohydrates. Thus, metal nanoparticles hold great promise for various biomedical applications such as photoacoustic imaging, magnetic resonance imaging, computed tomography (CT), photothermal, and photodynamic therapy (PDT). Despite their potential, safety considerations, and regulatory hurdles must be addressed for safe clinical applications. This review highlights advancements in metal nanoparticle surface engineering and explores their integration with emerging technologies such as bioimaging, cancer therapeutics and nanomedicine. By offering valuable insights, this comprehensive review offers a deep understanding of the potential of metal nanoparticles in biomedical research.

## 1. Introduction

Nanotechnology is the integration of nanoscale science, technology, and engineering, typically in the range of 1 and 100 nm [1]. These materials exhibit distinctive physical and chemical properties, making them ideal for applications across multiple fields, including engineering, medicine, chemistry, biology, physics, and materials science. Nanomaterials can be classified based on their composition, structure, and properties, primarily into naturally occurring and artificially synthesized human-made materials [2]. Each category has unique characteristics and properties. Naturally occurring nanomaterials exist in nature without human

intervention and can be found in various sources, such as corals, calcium phosphate crystals in bone matrices, and viruses [3,4]. These materials often form through natural processes such as weathering, volcanic eruptions, or biological processes. Which serve as inspiration for the advancement of new technologies. In contrast, synthetic nanomaterials are intentionally created by humans using various methods and techniques. Nanoscale materials can be classified into five families: metal, carbon, polymer, ceramic, and nanocomposite materials [5]. These materials are produced using techniques such as chemical synthesis, sol-gel, wet precipitation, microemulsion, sonication, vapor deposition, or physical milling. Synthetic nanomaterials with a metal base encompass

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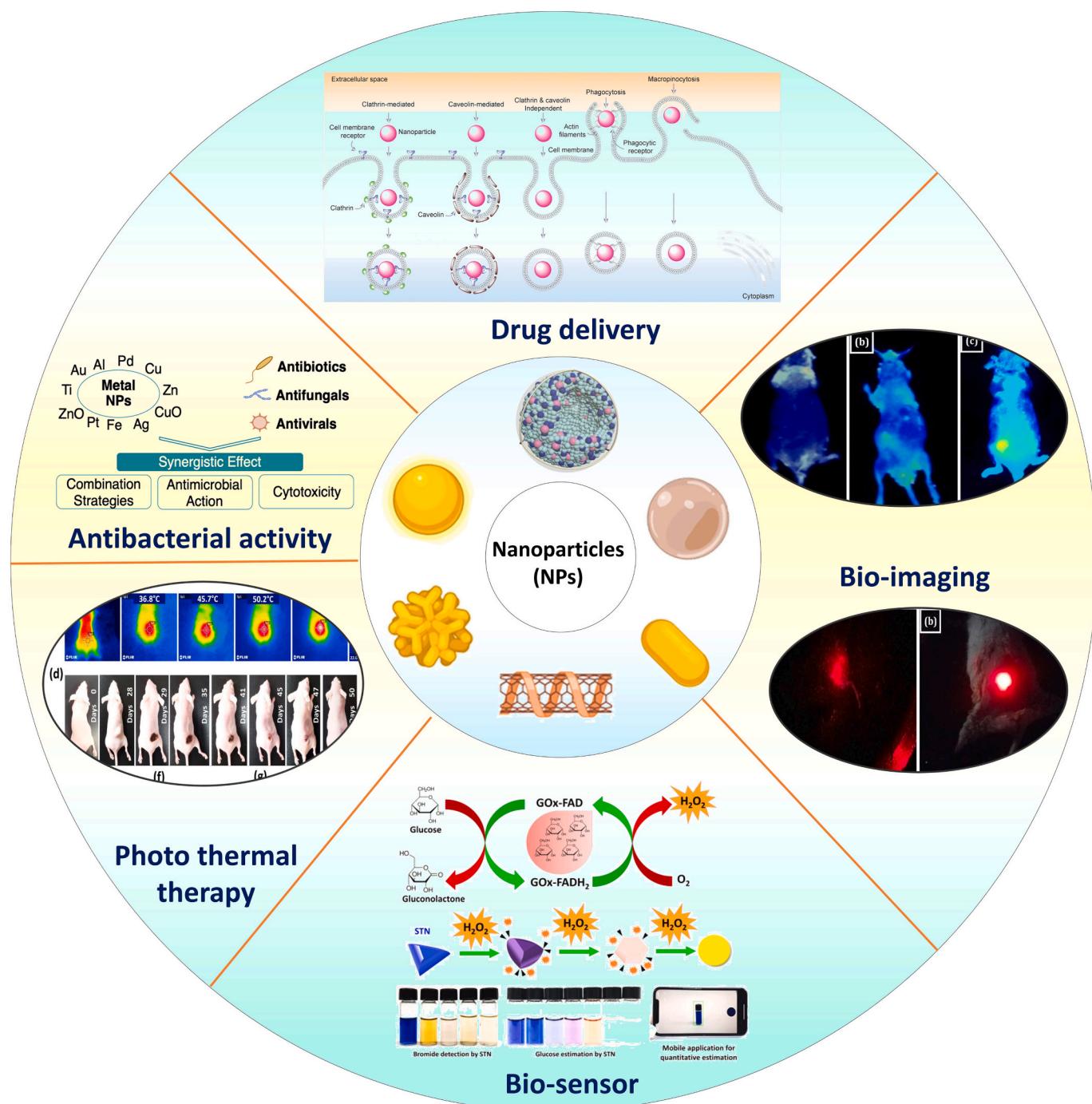
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nanosized variants of (Fe), Cu, Al, Pt, Ag, Au, and Zn [4,6–9]. These metal nanoparticles find significant applications in biomedical research, offering promising opportunities for diagnostics, imaging, drug delivery, and regenerative medicine [10]. Carbon-based nanomaterials constitute a diverse group primarily composed of carbon atoms. These materials have been utilized in the production of batteries and ultrasensitive sensors [11]. Dendrimers, nanoscale polymers built from branching components form meticulously organized three-dimensional, tree-like structures formations. Also known as arborols or starburst polymers-dendrimers can encapsulate drugs within their interior cavities and deliver them to targeted cells or tissues. The controlled release of drugs from dendrimers can be achieved by modifying their structure or

utilizing stimuli-responsive properties [12]. Nanocomposites involve the integration of diverse nanomaterials, including metallic, ceramic, polymeric, and carbon-based substances. This amalgamation enhanced the attributes of the underlying material, leading to enhanced mechanical, thermal, electrical, biological, and optical properties [13–15]. As mentioned above, nanoparticles offer a broad spectrum of uses in the field of biomedicine. Lately, a burgeoning fascination with employing these nanostructures in a range of biomedical applications, such as biosensors, photoablation therapy, hyperthermia, biological imaging, and precise drug delivery has been observed [16].

The historical progress in metal nanoparticles in biomedicine reflects the convergence of scientific understanding, technological



**Fig. 1.** Schematic illustration of metal and metal-oxide nanoparticles for different biomedical applications. The figures were reprinted with permission from Elsevier, Springer Nature, ACS. [24–28].

advancements, and clinical applications. From ancient remedies to cutting-edge therapies, the versatile and impactful roles of metal nanoparticles in healthcare have been evident throughout the history. The use of metals in medicinal practices has ancient origins millennia ago. Historical societies, including the Greeks and Egyptians, used metallic compounds such as Cu, Ag, and Au in various forms to treat wounds and illnesses. In the late 19th century, Faraday et al. initiated the study of colloidal Au, consisting of tiny Au particles suspended in a liquid, laying the foundation for further exploration into the properties and potential applications of metal nanoparticles in medicines. In the early 20th century, Mie and Rayleigh studied metal nanoparticles in colloidal suspensions [17]. The development of photography relies on the properties of Silver nanoparticles (AgNPs), which are crucial for capturing and preserving images. In the mid-20th century, researchers began exploring the capacity of Au nanoparticles (AuNPs) for drug delivery. The use of nanoparticles as carriers of therapeutic agents has gained popularity in recent years. During the 1980s and 1990s, researchers began investigating the application of AuNPs in treating cancer [18]. Studies demonstrated their potential for selectively delivering drugs or heat to tumor cells. Around the same time, noble metals such as Au and Ag garnered attention because of their distinct optical characteristics, making them suitable for various imaging techniques, including surface-enhanced Raman spectroscopy and photoacoustic (PA) imaging [19]. In the early years of the 21st century, pioneering work demonstrated that Au nanoparticles could absorb and transform light into thermal energy, resulting in the development of photothermal therapy for cancer treatment [20]. Ongoing studies have contributed to the development of various techniques for synthesizing and functionalizing metal nanoparticles, allowing precise control over their dimensions, shapes, and surface properties. Recently, several metal nanoparticle-based therapies and diagnostics have entered clinical trials. Notable examples include Au nanoparticles for cancer treatment and bio-imaging, as well as PA imaging, and iron oxide nanoparticles for enhancing magnetic resonance imaging (MRI) contrast. Investigations persist in exploring the possibilities of metal nanoparticles in fields such as targeted drug transportation, gene therapy, biosensing, and tissue regeneration (Fig. 1).

The state-of-the-art in the application of metal and metal-oxide nanoparticles highlights their significant potential in various biomedical fields, including drug delivery, imaging, diagnostics, and therapy. Metal nanoparticles such as gold (Au) and silver (Ag) are renowned for their unique optical properties, especially surface plasmon resonance, which makes them ideal for imaging and photothermal therapy. Iron oxide ( $\text{Fe}_3\text{O}_4$ ) nanoparticles are extensively utilized in magnetic resonance imaging (MRI) due to their magnetic properties. Metal-oxide nanoparticles like zinc oxide (ZnO) and titanium dioxide ( $\text{TiO}_2$ ) are also gaining attention for their photocatalytic and antibacterial properties, which are beneficial in both medical and environmental applications.

Metal nanoparticles offer several advantages over other nanoparticles such as ceramics or polymers, particularly in their electrical, magnetic, and optical properties. Metals such as Au, Ag, and iron exhibit superior electrical conductivity, making them highly suitable for applications in electronics and conductive materials [21]. Additionally, metal nanoparticles possess strong plasmonic properties, which enhance their use in sensing, imaging, and therapeutic applications. Magnetic properties of metals like iron and cobalt make them ideal for magnetic resonance imaging (MRI) and targeted drug delivery. Metals also efficiently convert light into heat, which is advantageous for hyperthermia treatments in cancer therapy [20]. Furthermore, metal nanoparticles can be easily functionalized with various chemical groups, enhancing their targeting and compatibility in biological systems. Their superior catalytic activity and mechanical strength, combined with customizable size and shape, make them versatile for a broad range of applications, including medicine, electronics, and environmental remediation. Metal nanoparticles have several advantages over polymeric nanoparticles,

especially in terms of mechanical strength, thermal and electrical conductivity, and catalytic properties [22]. Metals offer superior mechanical strength and durability, making them suitable for robust applications. They are also more stable at high temperatures and pressures and can be functionalized with various ligands for enhanced targeting in drug delivery. The dense nature of metal nanoparticles allows for more compact and potent formulations, making them more effective in certain biomedical applications. Despite these advantages, metal nanoparticles have disadvantages compared to ceramic/polymeric nanoparticles. One significant concern is their potential for toxicity, which poses risks in medical and environmental applications. Metals are also prone to oxidation and corrosion, which can limit their stability and effectiveness over time. Environmental impact is another concern, as metal nanoparticles can accumulate and potentially cause ecological harm. Additionally, metal nanoparticles are prone to rapid aggregation, reducing their effectiveness and stability in biological environments [23]. Stability issues in complex biological environments, potential cytotoxicity at higher concentrations, and higher likelihood of interacting with non-target cells further limit their applicability. Regulatory and safety concerns due to these factors make the use of metal nanoparticles subject to strict scrutiny.

The plasmonic effects of metal nanoparticles refer to the synchronized movement of electrons in response to incident electromagnetic radiation. This phenomenon arises from the unique electronic structure of metals, specifically the presence of free electrons in their conduction bands [29]. When these free electrons are perturbed by an external electric field, they collectively move in resonance with the incident light, generating strong local electromagnetic fields. The coordinated movement of free electrons within a metallic nanoparticle is known as a surface plasmon resonance (SPR). It occurs at a specific frequency determined by the metal's composition, size, shape, and the dielectric constant of the surrounding medium. SPR causes the absorption and dispersion of light, leading to distinctive optical characteristics in metal nanoparticles. Metal nanoparticles have the capability to absorb and disperse light much more efficiently than their bulk counterparts due to SPR. This effect is particularly pronounced in noble metals like Au and Ag, commonly used for their strong plasmonic effects within the range of the visible and near-infrared. When nanoparticles are significantly smaller than the wavelength of incoming light, the plasmon resonance occurs at the nanoparticle's surface. This is referred to as localized surface plasmon resonance (LSPR). Resulting in highly enhanced electric fields near the nanoparticle's surface.

## 2. Methods for synthesizing nanoparticles

Nanoparticles have garnered considerable interest in biomedical applications due to their distinctive physicochemical characteristics, tunability, and versatile functionalities. The significance of shape and size of the synthesized nanoparticles are the most important characteristics for biomedical applications (Table 1). At the nanoscale, the introduction of shape anisotropy has emerged as a powerful strategy, unlocking access to novel properties and functionalities. This remarkable capability empowers researchers to explore and harness the potential of intricate nanomaterials, propelling advancements across diverse applications and paving the way for exciting developments in the field of nanotechnology. The ability to tailor nanoparticles with such precision has opened up exciting opportunities in various fields, particularly in nanomedicine, catalysis, and electronics. The rational design and precise engineering of nanoparticles have become crucial for maximizing their performance and exploiting their unique properties.

One of the primary approaches discussed in this review is the bottom-up method, wherein nanoparticles are formed from individual atoms or molecules, enabling precise control over their dimensions and composition [30]. Chemical vapor deposition (CVD) stands as a versatile and effective approach for fabricating nanostructures. In the realm of microelectronics, CVD has served as a prominent technique for many

**Table 1**

Metal and metal-oxide nanoparticles with different shapes sizes and properties for biomedical application.

No	Nanoparticle	Size (nm)	Shape	Application	Referent
1	Au	From a few to >100 nm	Spheres	Imaging, radiation dose enhancement Imaging, treatment of cancer patients Antioxidant, antibacterial, and wound healing Surface plasmon resonance (SPR) sensing, Surface-enhanced Raman scattering (SERS) Conjugating biomolecules with utilizing Au—S bond for biosensing	[47]
2	Au	50–150	Spherical		[48]
3	Au	20	Nanosphere		[49]
4	Au	30–60	Nanostar		[50]
5	Au	32–43	Nanorod		[51]
6	Au nanoparticles with carbapenem Au nanoparticles	35, 70, and 200 nm	Not mention	Delivery vehicle	[52]
7		20–30	Not mention	Potent drug delivery vehicles	[53]
8	Ag	10–100	Spheres	Plasmatic and sensing, catalysis; antimicrobial Analytical devices (SERS); catalysis	[54,55]
9	Ag	200–300	Flower-like	Treating urinary tract infections	[56–58]
10	Ag	8.6 ± 1.2	Not mention	Biotechnology and biomedical industry	[59]
11	Ag	11	Spherical	Disrupting cell wall/membrane integrity and destroying DNA	[60]
12	Ag	Diameter: 60	Triangular	Biomedical devices and topical wound coatings	[61]
13	Ag	<10 nm	Spherical	Wound treatment	[62]
14	Chitosan-stabilized Ag nanoparticles	11.9	Spherical	Drug delivery	[63]
15	Ag nanoparticles on graphene oxide	5	Not mention	Cancer therapy	[64]
16	Magnetic Fe <sub>3</sub> O <sub>4</sub> nanoparticles	18	Not mention	Disinfection of imaging systems	[65]
17	Octahedron iron oxide nanocrystals	14 and 22	Not mention	Photo-thermal therapy	[66]
18	Graphene/iron oxide-based	15.0 ± 2.0	Methicillin-resistant	Antimicrobial therapy	[67]
19	ZnO	Not mention	Not mention		[68]
20	ZnS	2–25	Not mention	Not mention	[69]

**Table 1 (continued)**

No	Nanoparticle	Size (nm)	Shape	Application	Referent
21	NiO	9.69	Not mention	As coating for biomedical applications	[70]
22	Al <sub>2</sub> O <sub>3</sub>	30–80	Not mention	Regulation of antibiotic release	[71]
23	TiO <sub>2</sub>	15–20	Not mention	Not mention	[72]
24	Pt	1–2	Not mention	Biomedical applications, particularly therapeutics	[73]
25	Cu	2	Not mention	Affordable and potent nontraditional antibiotics	[74]
26	MgO	100–200	Not mention	As coatings for medical implants	[75]
27	MgO	25	Not mention	Ecofriendly antimicrobial nanomaterial for biomedical applications	[76]
28	MgO	20	Not mention	Preparation of infection-free medical devices	[77]
29	Pd	1.5	Not mention	and implants Catalyst and antimicrobial agent	[78]
30	Se	55.0	Not mention	Prevent food spoilage, cosmetics, pharmaceuticals	[79]
31	MoO <sub>3</sub>	Not mention	Not mention	Against hospital acquired infections	[80]
32	Graphene quantum dots	7.1 ± 0.6	Not mention	Two-photon photodynamic therapy	[81]
33	Ni(OH) <sub>2</sub> / ZnO	130 ± 20	Not mention	Biosensing	[82]
34	C/Co <sub>3</sub> O <sub>4</sub>	10 ± 2	Not mention	Biosensing	[83]
35	Mn <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> core-shell	58	Not mention	Biosensing	[84]

years and continues to be a compelling method today, capable of overcoming challenges posed by contemporary technologies [31]. The CVD method offers numerous benefits over other nanostructure development and manufacturing techniques. Notably, it provides the finest degree of control, enabling precise manipulation of nanostructure size, shape, and composition [32]. This method enables large-scale fabrication of 2D nanostructures with high purity, excellent crystal quality, and minimal substrate flaws. The resulting materials are dense and pure, with the regulation of process parameters providing control over crystal structure, orientations, and surface morphology of the nanostructures [33]. The CVD process is highly repeatable, ensuring consistent results. Its excellence in material adherence and homogeneity on substrates enables the deposition of coating with complex shapes. The nanostructures produced through CVD exhibit exceptional hardness, robustness, and purity [34]. Additionally, the rate of growth is easily adjustable, and the classical CVD approach offers an affordable processing expense, making it an appealing and cost-effective choice for producing nanostructures for various applications [35]. While the method offers several advantages over alternative techniques for the same applications, the CVD method also presents some notable disadvantages. For instance, materials need to be transferred from deposited substrates for further evaluation, adding complexity and cost to the process [36]. Additionally,

some precursors used in CVD can be hazardous, flammable, or expensive, posing safety and economic challenges. Various CVD variations may increase fabrication costs, limiting their widespread application [37]. While the CVD method holds significant promise for nanostructure synthesis, mitigating these disadvantages is essential for its broader implementation in various industries and research fields. Techniques such as chemical vapor deposition, sol-gel, and precipitation methods have been widely explored for fabricating nanoparticles with well-defined sizes and compositions. These approaches offer immense potential for designing nanoparticles for targeted drug delivery, as well as for enhancing the catalytic activity in various chemical reactions [38].

The top-down approach involves the controlled reduction of larger materials to synthesize nanoparticles [39]. Top-down techniques involve the partitioning bulk materials to generate nanostructured counterparts. Such methods encompass mechanical milling, etching, sputtering, laser ablation, and electro-explosion [40]. The most straightforward and efficient technique process of the top-down approach is ball milling, which generates nanoparticles by attrition. Mechanical milling is a cost-effective and versatile method that facilitates the production of nanoscale materials from bulk substances [41]. It is particularly beneficial for creating blends of various phases and plays a vital role in fabricating nanocomposites. This method is extensively applied in the creation of aluminum alloys reinforced with oxides and carbides, protective spray coatings resistant to wear, and nanoalloys based on, copper, aluminum, magnesium, nickel, and various other types of nanocomposite materials [40]. Through mechanical milling, researchers can harness its potential to meet the growing demands of sustainable and high-performance nanotechnology applications.

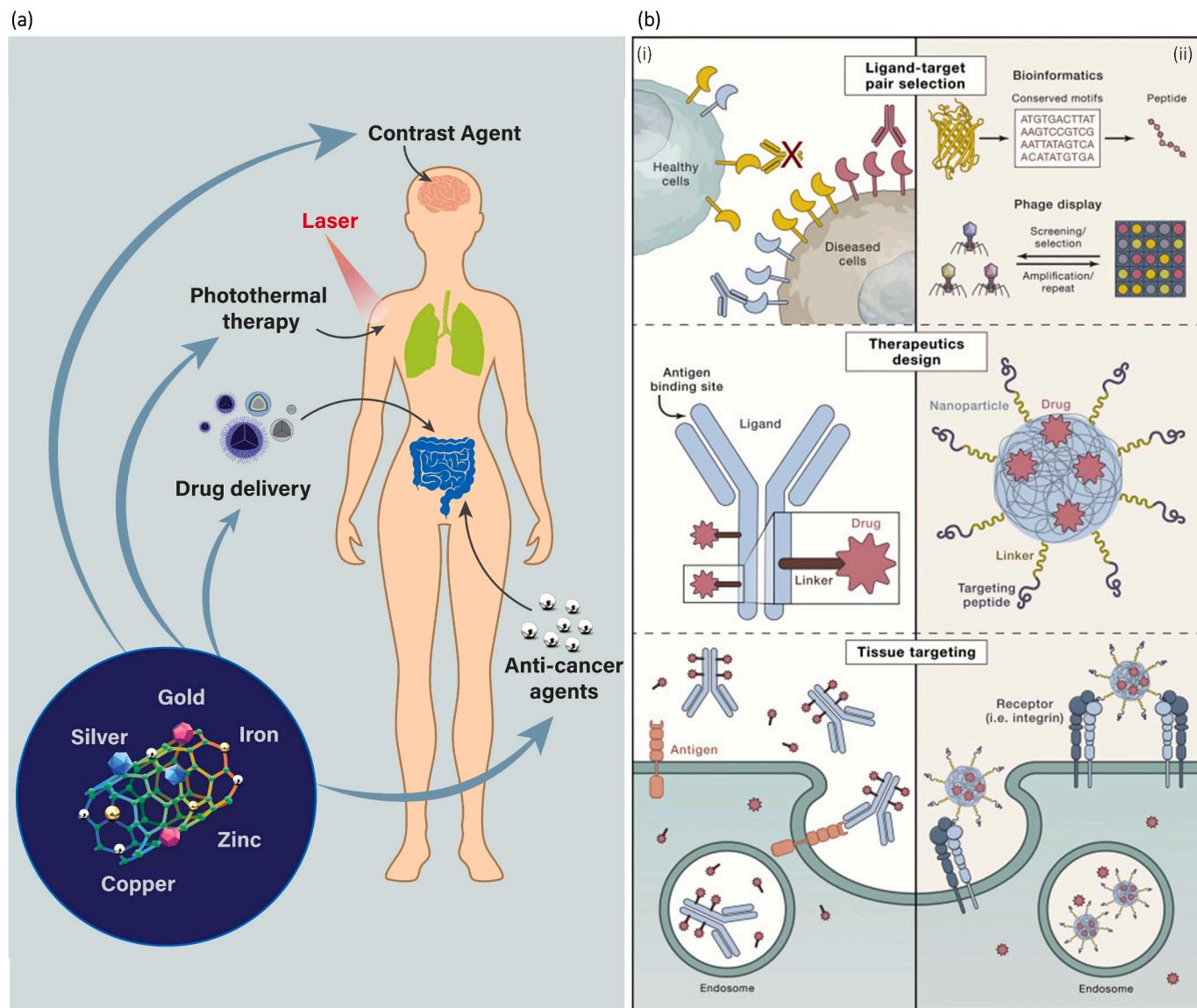
Recent advances in the fabrication of complex nanostructured metal nanoparticles, templates, and surfactants have emerged as valuable tools for controlling the shape and size of nanostructures. Template-assisted synthesis, utilizing porous templates with specific geometries, enables the production of nanoparticles with precise dimensions. Surfactants serve as stabilizing agents, preventing nanoparticle agglomeration and providing a means to tune their surface properties [42]. These strategies are critical for designing nanoparticles with enhanced biocompatibility and controlled release profiles in drug delivery applications. The synthesis of nanoparticles is significantly influenced by reaction parameters. Factors such as temperature, pressure, and solvent choice can significantly influence the nucleation and growth processes, leading to variations in nanoparticle size and shape [41]. Understanding the interplay of these parameters is essential for achieving reproducible and scalable synthesis methods. Recent advancements in nanotechnology have also contributed to precise nanoparticle synthesis. Microfluidics, for instance, enables the controlled mixing of reactants in microchannels, resulting in highly uniform nanoparticles with tailored properties [43]. Sonochemistry, which harnesses energy from acoustic cavitation, has shown promise in producing nanoparticles with narrow size distributions and unique morphologies [44]. Despite remarkable progress in nanoparticle synthesis techniques, challenges persist in achieving absolute control over every aspect of nanoparticle design. The potential toxicity of certain nanoparticle formulations, especially in medical applications, raises concerns that demand thorough investigation [45]. Additionally, the scalability of some synthesis methods remains an issue, hindering large-scale production [46].

## 2.1. Importance of precision engineering in metal nanoparticle design

Precision engineering plays a vital role in the design and development of nanoparticles, especially within the field of nanomedicine. Here, precise control over the size, shape, composition, and surface properties of nanoparticles is essential for their intended applications [10]. This discussion highlights the importance of precision engineering in metal nanoparticle design, emphasizing its impact on metal nanoparticle functionality, therapeutic efficacy, and safety. Size and Shape Control: Precision engineering enables the fabrication of nanoparticles with well-

defined sizes and shapes, significantly influences their behavior and interactions with biological systems. For example, the size of nanoparticles can dictate their biodistribution, cellular uptake, and clearance mechanisms. Certain shapes, such as rods or discs, exhibit distinct properties and targeting capabilities compared to spherical nanoparticles [85]. Exacting manipulation of size and form empowers scientists to customize nanoparticles for particular purposes, such as delivering drugs to specific sites or facilitating imaging. Nanoparticle surfaces can be modified with various functional groups or coatings to enhance their stability, biocompatibility, and targeting abilities. Precision engineering techniques enable the precise control of surface chemistry, allowing for the attachment of targeting ligands, drugs, or imaging agents [86]. Surface modification also plays a vital role in reducing unwanted interactions with proteins and cells, thereby improving metal nanoparticle circulation time and reducing off-target effects. Composition and Hybrid Systems: Precision engineering allows for the design and synthesis of metal nanoparticles with complex compositions and hybrid structures. By precisely controlling the arrangement of different materials or integrating multiple functionalities, researchers can create nanoparticles with enhanced properties and synergistic effects [87]. For instance, combining inorganic and organic components can lead to improved stability, controlled release, or multimodal imaging capabilities. Precision engineering of nanoparticles allows for the design of highly effective therapeutic systems. By precisely controlling parameters such as drug loading, release kinetics, and targeting capabilities, nanoparticles can deliver drugs to the desired site of action, enhancing therapeutic outcomes while minimizing side effects. Precision engineering techniques also enable the development of nanoparticles with improved safety profiles, such as reduced toxicity or immunogenicity [88]. Precision engineering plays a vital role in nanoparticle design, enabling precise control over size, shape, surface properties, composition, and functionality. By harnessing these capabilities, researchers can tailor metal and metal-oxide nanoparticles for specific applications, enhance therapeutic efficacy, and improve the safety profile of nanomedicine systems. Continued advancements in precision engineering techniques will further drive innovation in metal nanoparticle design and accelerate the translation of nanotechnology into clinical practice.

Targeted drug delivery is an important biomedical application in which nanoparticles can be designed to carry and deliver drugs directly to specific cells, tissues, or organs in the body [89,90]. They can encapsulate drug molecules, protecting them from degradation and improving their stability, solubility, and bioavailability. This targeted drug delivery approach can increase treatment efficacy, minimize side effects, and reduce the required dosage [91]. At present, iron oxide nanoparticles serve as the primary reservoir of magnetic materials utilized for transporting anticancer medications to specific target regions [92]. Another critical biomedical application of nanoparticles is Hyperthermia therapy (HT) refers to a treatment method in which the temperature in a specific area of the body is increased beyond normal levels, aiming to attain a therapeutic outcome [93]. Hyperthermia is a technique presently employed within the field of medical oncology to address cancerous regions. It operates by inducing necrosis in cancer cells through elevating cell temperatures to the range of 42–45 °C. The objective of hyperthermia is to concentrate the treatment effects in a specific area while minimizing damage to healthy tissue [94]. The primary characteristic of hyperthermia involves a form of cellular discrimination, stemming from the heating of tissue that effectively focuses on cancerous cells [95]. Magnetic hyperthermia is a cancer treatment technique, wherein tumors are targeted with iron oxide nanoparticles and subsequently heated using alternating magnetic fields [96]. Various types of nanoparticles have been employed for bio-imaging, including metal nanoparticles such as Au and Ag, metal-oxide nanoparticles like Iron Oxide ( $Fe_3O_4$ ), and semiconductor nanocrystals such as quantum dots (QDs) and magnetic quantum dots (MQDs) (Fig. 2a,b) [97–99]. These advantages include high levels of biosafety,



**Fig. 2.** Represents different aspects related to the interaction of metal nanoparticles with cellular components and their utilization in cancer therapy and drug delivery. (a) Schematic illustration of metal nanoparticles for different therapeutic applications. (b) Highlights of tissue-specific targeting strategies mediated by antibodies and peptides. Antibody-mediated targeting involves selecting antibodies that bind specifically to antigens highly expressed on target cells while showing minimal expression in normal tissues. Peptide-mediated targeting strategies utilize bioinformatics and molecular tools like phage display to identify biomimetic targeting peptides (Reprinted with permission from Elsevier, 2020) [101]. Metal nanoparticles could be conjugated with target-specific antigen-antibody peptides for targeted drug delivery applications.

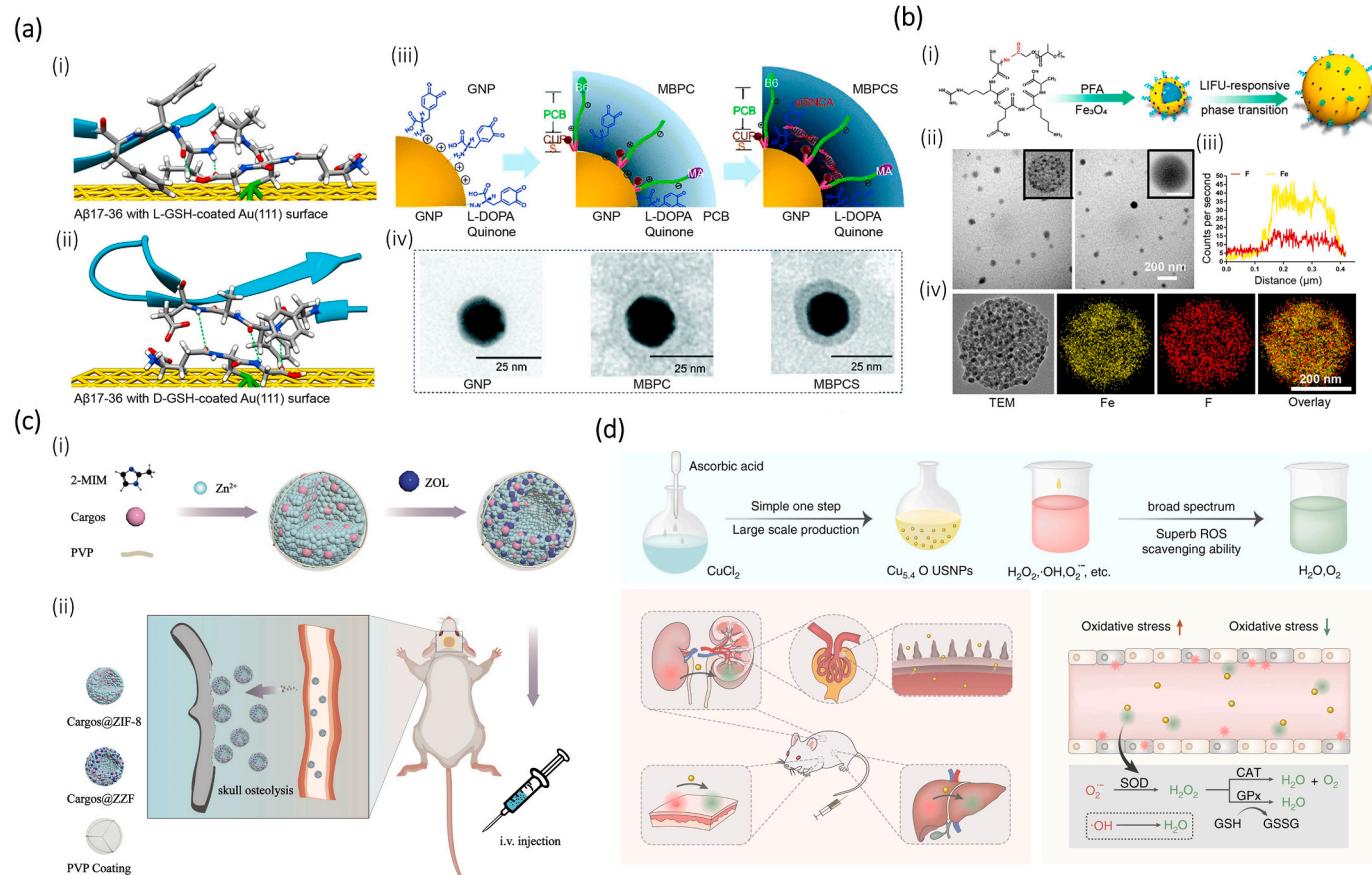
the ability to penetrate deep tissues, and the selective targeting of tumor cells for destruction. Biomacromolecules, especially antibodies, serve as crucial targeting agents in various drug delivery platforms. Recombinant monoclonal antibodies (mAbs) possess inherent specificity and strong binding affinity, typically with a  $K_D$  coefficient in the sub-nanomolar range. They can also be conjugated with metal nanoparticles for targeted therapeutic purposes. Subsequently, mAbs are extensively employed in the development of antibody-drug conjugates (ADCs) or immunoconjugates. These constructs comprise the antibody, which targets an overexpressed antigen or receptor on the cell surface, along with an active therapeutic agent (warhead), and a chemical linker facilitating their conjugation (Fig. 2c) [100,101]. Metal and metal-oxide nanoparticles serve as valuable tools in biomedical research, frequently utilized for bioimaging applications. Bioimaging techniques concentrate on studying biological interactions involving nanoparticles, providing powerful tools for investigating biomolecular pathways within cells, diagnosing diseases, and delivering therapeutics [102]. With the help of

imaging techniques, researchers have significantly advanced their understanding of complex biological processes, enabling visualization of cellular events with high spatial and temporal resolution. Nanoparticle biosensors play a crucial role in biomedical research, offering powerful tools for detecting and analyzing biomolecules with high sensitivity and specificity. These biosensors use mostly the unique properties of metal nanoparticles to enhance the capabilities of traditional biosensing techniques, enabling researchers to study complex biological processes, diagnose diseases, and develop innovative biomedical applications. In biomedical research, metal/metal-oxide nanoparticle biosensors have made significant contributions across various fields and applications [103]. In cancer research, they aid early detection and imaging of tumors, while in neuroscience, they monitor brain functions and neurological disorders. Metal/metal-oxide nanoparticle biosensors are also used in infectious disease studies, regenerative medicine, environmental toxicology, and drug screening. Their versatility and adaptability render them indispensable for advancing medical discoveries and

personalized medicine approaches [104]. Metal nanoparticle photothermal therapy, or metal-oxide nanoparticle-assisted photothermal therapy (PTT), is a promising biomedical approach that utilizes light-absorbing nanoparticles to generate localized heat and selectively destroy target cells. In this method, biocompatible nanoparticles, often made of gold or carbon-based materials, are targeted to specific cells and tissues [105–107]. When exposed to light, these nanoparticles efficiently absorb energy and convert it into heat, leading to the destruction of targeted cells while sparing surrounding healthy tissues [108,109]. Nanoparticle PTT holds potential for cancer treatment, antimicrobial applications, gene editing, drug delivery, and real-time imaging in biomedical research [110,111]. Its ability to achieve precise and non-invasive therapeutic effects makes it an exciting area of study with significant clinical implications.

Liu et al. presented a straightforward method for fabricating a switchable polymer-gold nanoparticle system capable of delivering genes and chemical drugs (referred to as gene-chem) in a programmable manner [112]. This nanoparticle system exhibits switchable properties, facilitating improved CT imaging and coordinated neuronal restoration along the delivery pathway to specific diseased cells. The development of this delivery system, with precise conversion capabilities, holds great potential as a robust gene-chem co-delivery platform for precise brain disease therapy. In this study,  $\text{Fe}^{3+}$  responsive gold nanoparticles

(GNPs) were prepared using levodopa as a reducer and CTAB as a stabilizer, resulting in a wine-red clear solution. The  $\text{Fe}^{3+}$  sensitivity of the prepared GNPs was attributed to the complexation between  $\text{Fe}^{3+}$  ions and quinone groups. Upon incubation with various ions present in the physiological environment, prodrug polymers BPC, MPC, and PC were incubated with GNPs in an aqueous phase, leading to the formation of MBPC through thioether-GNP interactions via ligand exchange. Following centrifugation and washing, brown precipitates were obtained and subsequently re-suspended to prepare MBPC, resulting in a decrease in zeta potential from 63.4 mV (GNP) to 22.0 mV, and an increase in nanoparticle diameter from 14.7 nm (GNP) to 63.4 nm (Fig. 3c iii & iv). Pan et al. (2022), reported to overcome this, a novel bone-targeting nano-drug delivery system was developed, combining zoledronate (ZOL) with zeolitic imidazolate framework-8 (ZIF-8) nanoparticles. These ZZF nanoparticles were synthesized at room temperature in water, preserving the activity of biomacromolecules. This unique synthesis method enabled ZZF nanoparticles to possess both encapsulation ability and pH-responsive release from ZIF-8, along with excellent bone-targeting performance from ZOL. With its simple preparation and biomacromolecule-friendly drug delivery, this nano platform holds promise for treating various bone-related diseases (Fig. 3c). Oxidative stress is linked to various inflammatory diseases, yet effective clinical treatments are limited. Nanomaterials that mimic enzymes



**Fig. 3.** Represents different nanoparticles designed for brain-targeted drug delivery. (a) Depicts carbon and gold nanoparticles, including simulated A $\beta$ 17-36 structures with L- and D-glutathione-coated Au(111) surfaces obtained from molecular docking simulation, along with schematic representations and TEM images of mazindol-B6 peptide-PCB-S-curcumin-siRNA (MBPCS) and intermediate products [112,119] [120] (Reprinted with permission from Nature Portfolio, 2020; Royal Society of Chemistry, 2019; and Amer Chemical Soc, 2019). (b) Showcases iron oxide nanoparticles, silica nanomaterials, biomimetic nanomaterials, and Cas9/RNA nanoparticles, with schematic illustrations and TEM images of Fe $_3$ O $_4$  nanoparticles-PLGA-perfluoro hexane (PFH) nanoparticles with CREKA peptides and their elemental mapping results (Reprinted with permission from Amer Chemical Soc, 2019) [121]. (c) Illustrates the construction of Cargas@ZZF nanoparticles and their osteolytic area targeting ability in a calvaria resorption mouse model (Reprinted with permission from Nature Portfolio, 2022) [122]. (d) Presents the therapeutic potential of Cu $5.4$ O ultra-small nanoparticles in treating ROS-related diseases, highlighting their multiple enzyme-mimicking and broad-spectrum ROS scavenging abilities synthesized through a simple and green method (Reprinted with permission from Nature Portfolio, 2020) [123]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(nanozymes), possessing robust reactive oxygen species (ROS) scavenging capabilities and biocompatibility, show potential for treating inflammation associated with ROS. Liu et al. (2020) reported a simple one-step method to produce ultrasmall CuSO<sub>4</sub> nanoparticles (CuSO<sub>4</sub> USNPs) with multiple enzyme-mimicking properties and broad-spectrum ROS scavenging ability. These CuSO<sub>4</sub> USNPs, mimicking catalase, superoxide dismutase, and glutathione peroxidase enzymes, protect against ROS-induced damage at low doses, improving results in cases of acute kidney injury, acute liver injury, and wound recovery. Their ultrasmall size allows rapid renal clearance, ensuring biocompatibility. The protective effect and biocompatibility of Cu<sub>5.4</sub>O USNPs offer potential for clinical treatment of ROS-related diseases and the advancement of nanozyme development (Fig. 3d). Targeted therapy and imaging are areas of great interest in biomedical research, particularly in cancer treatment and diagnostic imaging. Although nanomedicine offers extensive applications and advantages, it is not devoid of limitations. Here are some of the current challenges in targeted therapy and imaging. A primary challenge in traditional cancer treatment arises from the limited selectivity of chemotherapeutic drugs towards cancerous cells. Ensuring that the therapeutic agent or imaging probe reaches the specific target site in the body is a critical challenge. An additional drawback related to the utilization of nanoparticles is the occurrence of unexpected interactions among nanoparticles within the body. Our body has various biological barriers, such as the blood-brain barrier and the extracellular matrix, which can hinder the delivery and effectiveness of therapeutic agents or imaging probes [113]. Another challenge in targeted therapy and imaging is related to the heterogeneity of tumors. Tumors consist of various cell types with different genetic and molecular profiles, rendering it challenging to pinpoint a single target that would effectively target all tumor cells [114]. Researchers are exploring the concept of combination therapy, where multiple agents are used simultaneously to target different aspects of the tumor and overcome this heterogeneity. The issue of nanoparticle toxicity raises concerns in nanomedicine [115]. While nanomaterials hold great promise, their potential adverse effects on healthy tissues and organs need to be thoroughly investigated. It is crucial to understand the long-term effects of these nanoparticles on the human body to ensure their safety and avoid any unforeseen complications [116]. Current imaging techniques, such as CT and magnetic resonance imaging (MRI), have limitations in terms of resolution, sensitivity, and specificity [117]. Researchers are working on developing innovative imaging modalities, such as molecular imaging and metal/metal-oxide nanoparticle-based contrast agents, to improve early detection and accurate diagnosis of diseases. Ethical considerations also play a significant role in nanomedicine [118]. As technology advances, questions arise concerning the responsible use of nanomedicine and its potential impact on society. Issues like accessibility, affordability, and equity in healthcare need to be addressed to ensure that these cutting-edge treatments and diagnostics are available to all who can benefit from them. Despite these challenges, the field of nanomedicine continues to evolve rapidly, driven by the dedication of researchers and the promise of revolutionizing healthcare. Collaborations between scientists, clinicians, and industry partners are vital to overcome these obstacles and pave the way for more effective and personalized treatments and diagnostics in the future. By addressing these challenges, targeted therapy and imaging can truly transform the landscape of biomedical research and bring us closer to conquering some of the most formidable diseases, including cancer.

### 3. Targeted therapy using metal/metal-oxide nanoparticles

This technique has been used to improve the precision and efficiency of drug delivery using nanoparticles. Metal and metal-oxide band nanoparticles offer several advantages, including small size, large surface area, and tunable properties, making them suitable for targeted drug delivery applications [124]. Nanoparticle targeting can be broadly categorized into two main approaches: passive and active. Passive

targeting relies on the unique properties of nanoparticles to accumulate in specific areas through mechanisms such as enhanced permeability and retention (EPR) effect [125]. The EPR effect exploits leaky blood vessels and impaired lymphatic drainage commonly found in tumors, allowing the passive accumulation of nanoparticles in the tumor microenvironment [126]. Strategies to enhance passive targeting include optimizing the size, shape, and surface characteristics of nanoparticles to maximize their EPR-mediated accumulation.

#### 3.1. Active targeting

Active targeting involves incorporating ligands or targeting moieties onto the surface of nanoparticles. These ligands specifically recognize and bind to receptors or biomarkers overexpressed on the target cells, facilitating the selective delivery of the drug payload [127]. Various ligands, such as antibodies, peptides, aptamers, and small molecules, can be conjugated or attached to the nanoparticle surface to achieve active targeting [128]. Active targeting approaches, such as ligand-receptor interactions and antibody-conjugated nanoparticles, are widely utilized to enhance the specificity and efficiency of drug delivery to the desired target sites. Ligand-receptor interactions involve the use of ligands, molecules capable of binding to specific receptors on the surface of target cells or tissues. Ligands include peptides, small molecules, aptamers, or other targeting moieties that possess high affinity and specificity for their respective receptors [129]. By conjugating these ligands onto the surface of nanoparticles, the resulting ligand-functionalized nanoparticles can selectively recognize and bind to corresponding receptors on target cells. This binding initiates a series of events that facilitate active targeting. Upon internalization, the nanoparticles can then release the encapsulated drug payload within target cells, enhancing therapeutic efficacy while minimizing off-target effects [130]. Antibody-conjugated nanoparticles represent prominent examples of active-targeting approaches. Antibodies are highly specific and can recognize specific antigens or receptors that are overexpressed on the surface of target cells, such as cancer cells [131]. Conjugating antibodies onto the surface of nanoparticles allows the resulting antibody-conjugated nanoparticles to selectively bind to the target cells through antigen-antibody interactions. This facilitates the targeted delivery of drugs to desired cells, while minimizing exposure to healthy cells. Antibody-conjugated nanoparticles have several advantages. Antibodies provide high target specificity and affinity, enabling precise targeting of desired cells. They can also serve as carriers for various payloads, including small-molecule drugs, therapeutic proteins, nucleic acids, and imaging agents [127]. Additionally, antibody-conjugated nanoparticles can exploit mechanisms of antibody-mediated immune responses, such as antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, to enhance their therapeutic effects [132]. Active targeting approaches based on ligand-receptor interactions and antibody-conjugated nanoparticles offer enhanced selectivity and improved drug delivery efficiency compared to passive targeting strategies [133]. They enable direct delivery of therapeutic agents directly to the desired cells or tissues, thereby increasing treatment efficacy and reducing systemic toxicity [134]. These approaches hold significant promise for various applications, including cancer therapy, targeted imaging, and precision medicine.

#### 3.2. Passive targeting

Passive targeting approaches, specifically the EPR effect, are employed to achieve targeted drug delivery by utilizing the distinctive characteristics of tumor vasculature. The EPR effect is a phenomenon found in solid tumors, characterized by leaky blood vessels and poor lymphatic drainage [126]. Owing to abnormal angiogenesis and increased vascular permeability, tumors exhibit an irregular and disorganized vasculature with gaps between endothelial cells, allowing for the extravasation of macromolecules and nanoparticles [135]. In passive

targeting approaches that utilize the EPR effect, nanoparticles with specific properties, such as size, surface charge, and hydrophilicity/hydrophobicity, are designed to exploit tumor vasculature [136]. These nanoparticles are engineered to have a size approximately in the range of 10–200 nm, enabling them to passively accumulate in tumor tissues while avoiding rapid clearance by the reticuloendothelial system [137]. Upon intravenous administration, nanoparticles circulate in the bloodstream, and their small size allows them to extravasate through gaps in leaky tumor blood vessels [138]. This extravasation is facilitated by impaired lymphatic drainage within tumors, hindering the clearance of extravasated nanoparticles. Once accumulated within the tumor microenvironment, nanoparticles can release their drug payload over an extended, improving the local drug concentration at the tumor site [139]. This passive accumulation of nanoparticles in tumors through the EPR effect enhances drug delivery efficiency, reduces systemic toxicity, and increases the therapeutic index of anticancer drugs.

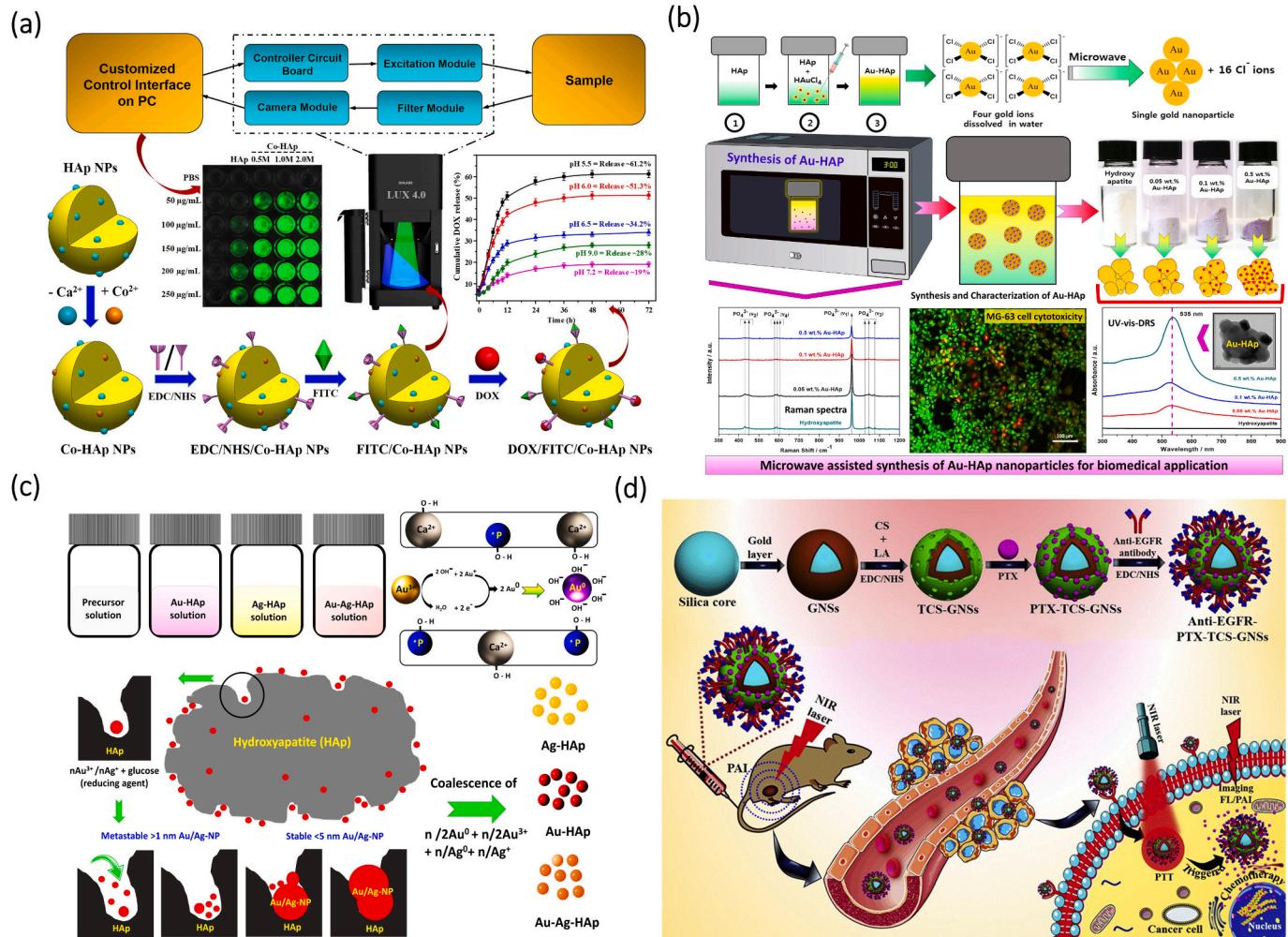
The EPR effect is influenced by various factors, including tumor type, size, stage, and nanoparticle properties [140]. Tumor heterogeneity, variable EPR expression, and limited penetration into the tumor core pose challenges in achieving optimal passive targeting. Therefore, ongoing research is focused on developing nanoparticles with improved tumor specificity and circulation stability to further exploit the EPR effect. Passive targeting approaches based on the EPR effect have shown promise in preclinical and clinical studies on various types of solid tumors [141]. However, the extent of the EPR effect can vary between tumors and patients, and significant EPR-mediated accumulation is not exhibited by all tumors [142]. This variability has led to the exploration of combination strategies, such as combining passive targeting with active targeting approaches, to enhance drug delivery to specific tumor cells and overcome the limitations associated with passive targeting alone.

### 3.3. Drug delivery and therapeutic activity

Overcoming biological barriers for efficient drug delivery is a critical aspect of developing effective therapies. The human body possesses several natural barriers that can impede the delivery of therapeutic agents to their intended targets. Understanding and overcoming these barriers is crucial to enhance drug delivery efficiency and improve treatment outcomes. One significant biological barrier is the epithelial barrier, which includes various surfaces such as the skin, respiratory tract, gastrointestinal tract, and blood-brain barrier [143]. These barriers are designed to protect the body from harmful substances but can also limit the absorption and penetration of drugs. Strategies to overcome epithelial barriers involve the use of drug delivery systems that can bypass or penetrate these barriers [144]. Nano metals with appropriate size, surface modifications, and targeting ligands can enhance drug transport across epithelial barriers. Additionally, physical methods such as sonoporation, electroporation, or microneedle-based techniques can create temporary openings in the barrier, allowing drug entry [145]. Another significant challenge is posed by the systemic circulation, which can lead to rapid drug clearance and degradation. The reticuloendothelial system (RES) and the mononuclear phagocyte system (MPS) play essential roles in clearing foreign particles and drugs from circulation [146]. To overcome this barrier, strategies involve the development of drug carriers with stealth properties, such as polyethylene glycol (PEG) coatings, which can reduce recognition and clearance by the RES/MPS. Doan et al. (2022) explore the biomedical potential of metallic cobalt-doped hydroxyapatite (Co-HAp) nanomaterials, synthesized via a co-precipitation method [147]. The substitution of  $\text{Ca}^{2+}$  ions with smaller  $\text{Co}^{2+}$  ions in the crystal structure of pure HAp is a crucial modification that enhances the functionality of these nanoparticles. This ionic substitution generates additional space within the crystal lattice, facilitating increased drug loading capacity. Computational modeling supports this structural enhancement, showing that the Co-HAp nanostructured system provides more space compared to the original Ca-HAp system. This

theoretical insight is corroborated by BET and FE-TEM analyses, which illustrate the improved surface morphology and structural characteristics of the Co-HAp nanoparticles. The modified crystal structures not only allow for increased drug (DOX) and dye (FITC) loading but also enhance the fluorescence properties of the nanoparticles. Specifically, with 2.0 mol% cobalt, the fluorescence signal peaks at 79.89% at a concentration of 250  $\mu\text{g}/\text{mL}$ , which is 2.5 times higher compared to pure HAp. This enhanced fluorescence is crucial for imaging applications, as it allows for more precise and clear visualization of the nanoparticles within biological systems. The DOX-loaded Co-HAp nanoparticles exhibit a pH-dependent drug release profile, with approximately 61.2% of the drug released in an acidic environment. This is particularly advantageous for cancer treatment, as the acidic microenvironment of tumor tissues can trigger the release of the therapeutic agent, thereby increasing the efficacy of the treatment while minimizing systemic side effects. The *in vitro* imaging and drug delivery results highlight the promising characteristics of the synthesized Co-HAp nanoparticles for biomedical applications. The enhanced drug loading capacity, superior fluorescence properties, and biocompatibility make these nanoparticles ideal candidates for cancer therapy (Fig. 4a).

In cancer research, traditional therapies such as chemotherapy, radiotherapy, and surgery are effective but often induce severe side effects, particularly during metastasis. ROS play a crucial role in cancer biology; while low levels regulate normal cellular functions, excessive ROS can lead to diseases like cancer by disrupting cellular redox balance and triggering processes like apoptosis, autophagy, necrosis, and ferroptosis. Some cancers show a synergistic response to ROS production combined with radiation therapy. Herbal-synthesized AgNPs have demonstrated significant inhibition of lung cancer cells through ROS-induced damage to cellular membranes and macromolecules [148]. Nanoparticles combining metals and metal-oxides can act as catalysts for generating ROS in tumor cells, enhancing therapies like photodynamic therapy (PDT) and chemodynamic therapy (CDT); examples include  $\text{ZnFe}_2\text{O}_4$  NPs, which act as semiconductor photocatalysts under ultraviolet (UV) and near-infrared (NIR) light to produce ROS [149]. Turning to diabetes, oxidative stress is critical in the progression of Type 2 diabetes (T2D), influenced by genetic factors and lifestyle choices. Traditional treatments such as insulin and metformin can have side effects, while metal and metal-oxide nanoparticles (MNPs/MONPs) may contribute to oxidative stress, potentially causing toxicity [150]. Nanoparticles like  $\text{CeO}_2$  possess antioxidant properties due to their surface oxygen vacancies, offering potential therapeutic benefits in managing T2D-related oxidative stress. Nanoparticles such as curcumin and ZnONPs target specific pathways related to diabetes, with studies showing promise for AuNPs and AgNPs in alleviating diabetic complications in animal models. In addressing neurodegenerative disorders, ROS are implicated in conditions like Alzheimer's disease (AD) and Parkinson's disease (PD). AD involves amyloid  $\beta$  ( $\text{A}\beta$ ) misfolding and aggregation exacerbated by metal ions like  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$ , which contribute to neurotoxicity [151]. Strategies targeting  $\text{A}\beta$ -metal complexes, such as surface-modified selenium (Se)/ruthenium (Ru) nanoparticles with L-Cys, have shown potential in reducing  $\text{A}\beta$  aggregation, inhibiting ROS production, and decreasing neurotoxicity in cell models. Conversely, copper oxide nanoparticles (CuONPs) have been observed to increase  $\text{A}\beta$  levels and induce neuronal apoptosis, suggesting potential neurotoxic effects in disorders like AD [152]. Mondal et al. (2019) synthesized metal gold nanoparticles (Au) loaded onto hydroxyapatite (HAp) surfaces using a rapid microwave-assisted synthetic technique, followed by collagen coating for use in biomedical [153]. The Au-HAp-Col nanoparticles exhibited a notable drug-loading efficiency, with a maximum of approximately 58.22% for 0.1 wt% Au-HAp-Col nanoparticles. This high efficiency can be attributed to the synergistic interaction between Au, HAp, collagen, and DOX molecules, facilitated by the rapid and uniform microwave-assisted synthesis method. The electrostatic interactions between these components play a critical role in achieving this high drug-loading capacity. The drug release kinetics of



**Fig. 4.** Illustrates different preparation methods and interactions of nanoparticles for biomedical applications. (a) Depicts the schematic preparation of a fluorescence-conjugated nanostructured cobalt-doped hydroxyapatite platform designed for imaging-guided drug delivery applications (Reprinted with permission from Elsevier, 2022) [147]. (b) Showcases the rapid microwave-assisted synthesis of Au-HAp nanoparticles for biomedical applications (Reprinted with permission from Elsevier, 2018) [153]. (c) Presents a schematic representation of interactions between zero-valent metal nanoparticles (Au/Ag/Au-Ag) and metal apatite (Au-HAp/ Ag-HAp/ Au-Ag-HAp) (Reprinted with permission from Elsevier, 2018) [4]. (d) Outlines the creation of anti-EGFR-PTX-TCS-GNSs for near-infrared fluorescence/photoacoustic (PAI) dual-modal imaging-guided chemo-photothermal synergistic therapy (Reprinted with permission from Elsevier, 2019) [154].

the maximum drug-loaded nanoparticles (0.1 wt% Au-HAp-Col-DOX) revealed a maximum drug release efficiency of about ~53% at pH 4.5. This pH-dependent release is particularly advantageous for cancer therapy, as the acidic microenvironment of tumor tissues can trigger the release of DOX, ensuring targeted delivery to cancer cells while minimizing systemic side effects. The controlled release behavior emphasizes the potential of these nanoparticles for effective and efficient drug delivery systems. Biocompatibility studies using MG-63 osteoblast-like cell lines indicated that Au-HAp nanoparticles are non-cytotoxic up to a 0.1 wt% Au loading. However, a slight increase in toxicity was observed at 0.5 wt% Au loading. This finding highlights the importance of optimizing the concentration of Au in the nanoparticle formulation to maintain biocompatibility. Electron microscopy studies of MG-63 cells seeded on scaffold materials coated with Au-HAp-Col nanoparticles showed excellent cellular attachment, growth, and proliferation. The collagen coating further enhances biocompatibility and supports cellular interactions, making these nanoparticles promising candidates for a wide range of biomedical applications (Fig. 4b). Hyehyun et al. (2018) utilized a biomimetic approach to synthesize human and environmentally friendly Au and Ag nanoparticles loaded onto pristine hydroxyapatite (HAp) for biomedical applications [4]. Extensive structural and morphological characterization of the synthesized Au-HAp, Ag-

HAp, and Au-Ag-HAp (bimetallic) nanoparticles was conducted using a range of techniques. X-ray diffraction (XRD) confirmed the crystalline structure of the nanoparticles, while spectroscopic analyses (UV-vis, DRS, FTIR, and zeta potential) provided insights into their optical properties and surface chemistry. The BET surface area and pore size analyzer, along with electron microscopy (FE-TEM, FE-SEM), revealed detailed information about the surface morphology, porosity, and nanoscale features of the particles. These comprehensive characterizations underscore the successful synthesis of well-defined and stable metal-hydroxyapatite nanoparticles. The biological activity of the synthesized nanoparticles was assessed using osteoblast-like MG-63 cell lines and antibacterial tests with *Escherichia coli* (*E. coli*). The MTT assay and fluorescence imaging (AO/PI staining) demonstrated that Au-HAp, Ag-HAp, and Au-Ag-HAp nanoparticles exhibited low cytotoxicity towards MG-63 cells, indicating their biocompatibility and potential for safe biomedical applications. The structural stability, biocompatibility, and antimicrobial properties of these nanoparticles position them as promising candidates for various biomedical applications. Specifically, the ability of Ag-HAp nanoparticles to combat *E. coli* highlights their potential use in treating bone infections such as osteomyelitis. Their application could significantly reduce postoperative infections and enhance the success rates of surgical implants and bone grafts (Fig. 4c)

[4]. Manivasagan et al. (2019) introduced a novel multifunctional nanocarrier, anti-epidermal growth factor receptor antibody-conjugated and paclitaxel-loaded thiol chitosan-layered gold nanoshells (anti-EGFR-PTX-TCS-GNSs), for cancer combination therapy and imaging [154]. The synthesized anti-EGFR-PTX-TCS-GNSs exhibit several crucial properties that enhance their potential as a theranostic agent. The biocompatibility and biosafety of these nanocarriers were confirmed, demonstrating their suitability for in vivo applications. The broad near-infrared (NIR) absorbance and photostability of the gold nanoshells are particularly noteworthy, as these characteristics enable effective photothermal therapy (PTT) and precise imaging capabilities. The thiol chitosan coating not only improves the stability and dispersibility of the gold nanoshells but also facilitates a fast and laser irradiation-controllable drug release, optimizing the delivery and therapeutic efficacy of paclitaxel (PTX). The conjugation of anti-EGFR antibodies to the nanocarriers significantly enhances their targeting efficiency towards cancer cells expressing the epidermal growth factor receptor (EGFR). The dual-modal imaging capabilities, combining fluorescence and photoacoustic imaging (PAI), provide a robust mechanism for visualizing tumors. The anti-EGFR-PTX-TCS-GNSs demonstrated remarkable anti-cancer efficiency in both in vitro and in vivo studies. In vitro experiments showed significant cytotoxicity against cancer cells, attributable to the combined chemophotothermal effects. The in vivo studies further confirmed the therapeutic potential, where laser irradiation of the anti-EGFR-PTX-TCS-GNSs led to substantial tumor damage, effectively killing tumor cells. The photoacoustic imaging capabilities of the nanocarriers provided clear visualization of tumors, reinforcing their role as a powerful PAI contrast agent. The histological analysis and TUNEL assay results were compelling, showing a significant increase in apoptotic cells within the tumor tissue treated with anti-EGFR-PTX-TCS-GNSs under laser irradiation. This confirms the successful induction of apoptosis, a key mechanism for effective cancer therapy. The heavy damage observed in tumor tissues further validates the potential of this nanocarrier system as a potent cancer treatment modality (Fig. 4d).

The cellular barrier is another obstacle to efficient drug delivery. Cell membranes possess a selective permeability that limits the entry of hydrophilic or large molecules [155]. Various techniques have been developed to enhance cellular uptake, such as the use of cell-penetrating peptides (CPPs) or receptor-mediated endocytosis. These approaches enable targeted delivery and intracellular release of therapeutic agents [156]. Additionally, stimuli-responsive drug delivery systems can be designed to release drugs in response to specific cellular cues, such as changes in pH, redox potential, or enzyme activity [157].

### 3.4. Antimicrobial activity

Antibiotic overuse has led to a surge in antimicrobial resistance, posing a major challenge in healthcare. Multi-drug-resistant strains, such as those in the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*), are on the rise, causing millions of infections and thousands of deaths annually. Recent efforts focus on developing new, long-lasting broad-spectrum drugs to combat resistance, with nanomaterials, particularly metal nanoparticles, showing promise in vitro studies for applications in drug delivery and tissue engineering. While the antibacterial properties of metal nanoparticles are well-known, their exact mechanisms are still under study. Proposed mechanisms involve physical and chemical interactions causing structural damage and interference with vital metabolic pathways. Key factors influencing metal NP antibacterial activity include size, shape, surface properties, and functionalization. Nanotechnology offers a means to design nanoparticles with optimal characteristics for reduced cytotoxicity and enhanced biocompatibility.

(i) Electrostatic Interactions of metal nanoparticles: Both Gram-positive and Gram-negative bacteria have negatively charged cell walls. Positively charged metal nanoparticles interact favorably with

surface-modified metal these bacteria due to electrostatic attraction, (ii) Membrane Damage and ROS Production: Contact with nanoparticles leads to membrane damage, causing cell wall depolarization. This modifies the wall's charge, making it more penetrable and ultimately destroying it. (iii) ROS are produced as a result. Alavi et al. (2023) reported the diverse mechanisms by which metal and metal-oxide nanoparticles exert their anticancer and antimicrobial effects, including direct cell membrane damage, biofilm inhibition, and the induction of ROS and reactive nitrogen species (RNS) [148]. ROS, like peroxides and hydroxyl radicals, are produced through the release of metal ions from nanoparticles, playing a pivotal role in cell demise. Techniques such as photodynamic therapy (PDT) leverage photosensitizers to trigger ROS production, while nanoparticles can also provoke ROS generation through mechanisms like the Fenton reaction. These ROS can induce various cellular alterations, including protein damage and lipid peroxidation, leading to programmed cell death. Nonetheless, maintaining ROS levels within a balanced range is crucial for cellular homeostasis. To target cancer cells specifically and reduce collateral damage to healthy cells, metal and metal-oxide nanoparticles are tailored with antibodies or natural compounds. Surface modifications with bioactive agents aim to mitigate ROS and RNS effects, yielding nanoformulations that are both biocompatible and biodegradable. However, the genotoxic potential of metallic nanoparticles may rise with smaller sizes and heightened ROS production, necessitating cautious dose determination. In essence, the review delineates recent strides and hurdles in crafting innovative nanoformulations centered on ROS and RNS generation.

#### 3.4.1. Antimicrobial effects of metal nanoparticles

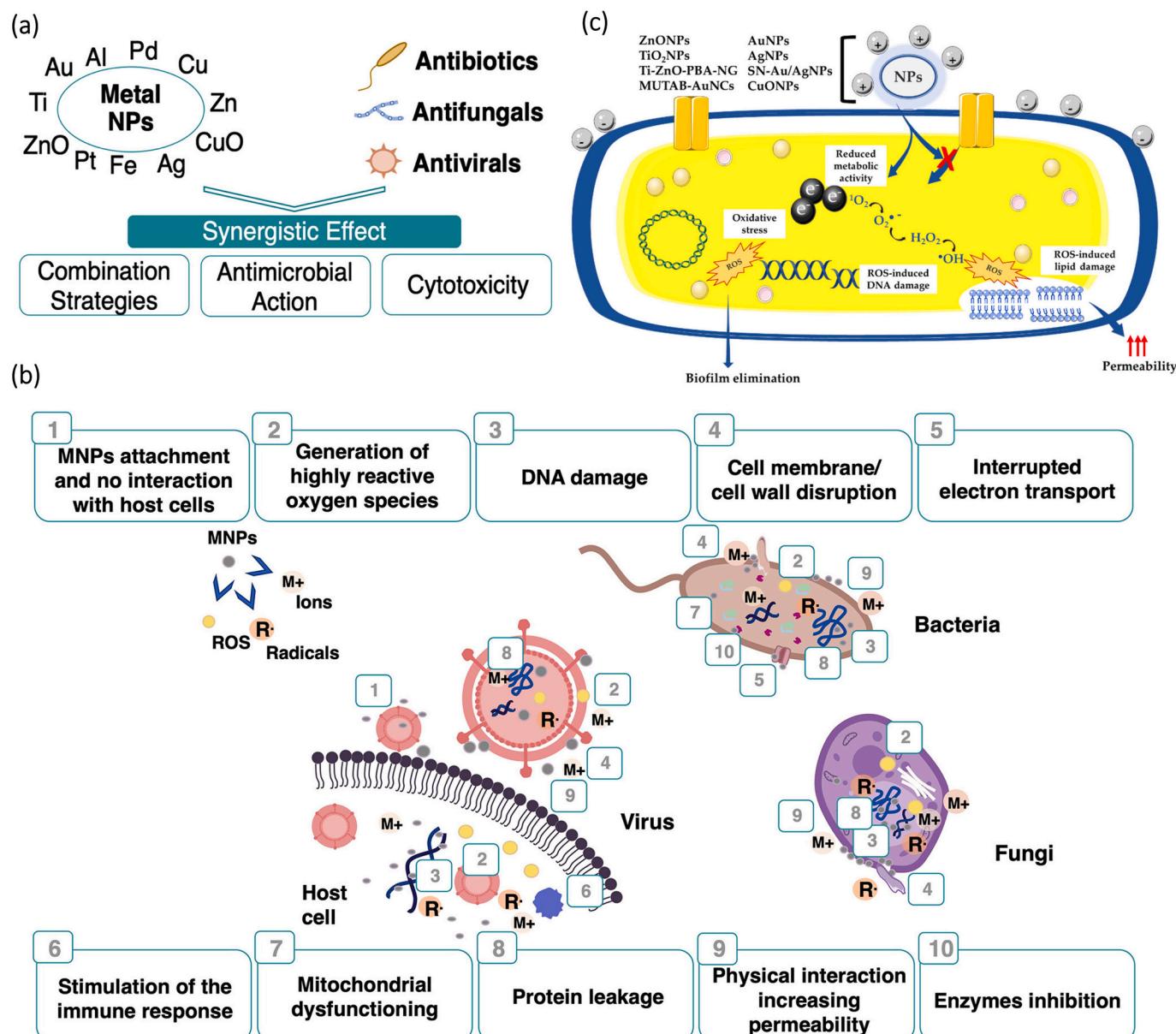
Metal and metal-oxide nanoparticles exhibit effective antibacterial properties primarily by generating ROS. When these nanoparticles interact with bacterial cells, they initiate ROS production, including superoxide radicals ( $O_2\bullet-$ ), hydroxyl radicals ( $\bullet OH$ ), and hydrogen peroxide ( $H_2O_2$ ). This process typically occurs through electron transfer from the nanoparticle surface to molecular oxygen, forming superoxide radicals. Additionally, metal ions leached from the nanoparticles can catalyze the Fenton reaction, leading to the creation of highly reactive hydroxyl radicals. Inside bacterial cells, ROS accumulation induces oxidative damage to crucial cellular components such as lipids, proteins, and nucleic acids, resulting in cell membrane disruption, DNA impairment, and cell death. Additionally, the small size and large surface area of these nanoparticles facilitate their interaction with bacterial membranes, heightening their antibacterial effectiveness. This mechanism underscores the potential of metal and metal-oxide nanoparticles in combating bacterial infections and advancing antimicrobial strategies.

Alavi et al. (2022,2023) reported various approaches to enhance the antibacterial properties of metallic nanoparticles, taking into account the structural variances between Gram-negative and Gram-positive bacteria [158,159]. Initially, AuNPs were modified with phenylboronic acids, resulting in improved binding with lipoteichoic acid (LTA) and lipopolysaccharide (LPS) in Gram-positive and Gram-negative bacteria, respectively. The antibacterial effectiveness varied based on the ratio and density of amine- and thiol-tethered phenylboronic acids, with evenly distributed coatings demonstrating broader antibacterial action. Additionally, natural compounds sourced from plants, fungi, and bacteria were utilized in synthesizing AuNPs, displaying significant antibacterial efficacy against *Staphylococcus epidermidis* and *Escherichia coli*. Moreover, modifying nanoparticles with positively charged materials like chitosan derivatives enhanced interaction with bacterial cell walls and membranes, disrupting their integrity and impeding bacterial growth. The degree of chitosan charge density influenced its interaction with bacterial lipid membranes, where high density resulted in dispersion on the lipid bilayer, and low density led to significant membrane penetration and structural disruptions. These strategies present promising avenues for combating bacterial infections by tailoring metallic nanoparticles to target specific bacterial structures effectively.

The antibacterial properties of copper oxide nanoparticles (CuO NPs) operate through multiple mechanisms. These nanoparticles adhere to bacterial membranes via electrostatic forces, resulting in membrane destabilization. Within the bacterial cell wall, functional groups like amines and carboxyls interact with copper or copper oxide, causing harm to the wall's integrity. While the precise antibacterial mechanism of CuONPs remains incompletely understood, it is thought that the release of copper ions from the nanoparticles, along with the subsequent production of ROS, plays a pivotal role. These processes impede DNA replication and protein synthesis in bacteria, thereby exerting antimicrobial effects and circumventing antibiotic resistance. CuO NPs can induce breaks in single-stranded DNA, influence gene expression, and induce substantial alterations in bacterial chromosomal DNA structure. Furthermore, these nanoparticles disrupt genes governing transcription and replication mechanisms, modulate gene promoter activity and base sequences, and interfere with the function of RNA polymerase,

ultimately culminating in bacterial demise. The generation of ROS through direct and indirect interactions with metal or metal-oxide nanoparticles can affect genes associated with oxidative stress and antioxidant production. Moreover, the size of nanoparticles impacts their genotoxicity, with smaller particles generating more ROS and demonstrating greater genotoxic effects compared to their larger counterparts.

Ag nanoparticles adhere to the cell wall, leading to ion passage and cell death. Magnesium oxide ( $MgO$ ) nanoparticles and magnesium hydroxide ( $Mg(OH)_2$ ) nanoparticles cause cell death by adsorbing onto the cell wall. Nanoparticles must be small enough to cross the cell membrane for cellular uptake. Small AgNPs (smaller than 10 nm) are effective due to membrane damage and penetration. Au nanoparticles inhibit ribosome subunits, alter membrane function, and affect ATPase activity to combat *E. coli*. Ions released from nanoparticles can interact with cellular components, including proteins and nucleic acids.



**Fig. 5.** Represents the synergistic effects of metal nanoparticles and commercially available antimicrobial agents. (a) Illustrates the combined impact (Reprinted with permission from Amer Chemical Soc, 2022) [28], while (b) Highlights the antibacterial outcomes attributed to oxidative stress induced by various metal-based nanoparticles such as AuNPs, AgNPs, CuNPs, ZnONPs, TiO<sub>2</sub>NPs, and others. These nanoparticles generate ROS and singlet oxygen ( $^1O_2$ ), contributing to antimicrobial activity (Reprinted with permission from Amer Chemical Soc, 2022) [28]. (c) Provides insight into how metal nanoparticles act as antimicrobial agents (Reprinted with permission from MDPI, 2021) [161].

Environmental conditions, such as pH and NP dissolution rate, significantly influence NP antimicrobial activity. Metal NP ions can lead to DNA condensation and even double-stranded DNA breakdown. Ribeiro et al. (2022) discuss the wide array of clinical applications facilitated by nanotechnology, particularly focusing on metal nanoparticles and their unique antimicrobial properties, which are crucial for novel medical devices [28]. Combining metal nanoparticles with commercial antimicrobial drugs presents opportunities to enhance effectiveness and mitigate drawbacks associated with individual drug use. Metal nanoparticles conjugates serve as efficient drug delivery systems, extending drug circulation, improving targeting, and reducing toxicity while broadening the antimicrobial spectrum. The study highlights common strategies for combining metal nanoparticles with clinically used antimicrobial agents and provides insights into their synergistic effects, mechanisms of action, and cytotoxicity (Fig. 5a, b). The medium in which nanoparticles are dispersed can affect ion release, impacting NP lifespan and antimicrobial activity. The production of ROS, whether inside or outside bacterial cells, disrupts cellular functions, ultimately resulting in cell death. Metal nanomaterials like Ag, ZnO, and TiO<sub>2</sub> increase ROS production. These mechanisms highlight the diverse ways in which metal nanoparticles exert their antibacterial effects, with potential implications for various biomedical applications. Mammari et al. (2022) address the urgent need for effective antimicrobial agents to combat multidrug-resistant (MDR) bacteria, a growing public health concern [160]. Metal-based nanoparticles offer promise due to their ability to target and kill bacteria through various mechanisms, including the induction of oxidative stress through ROS production. This review focuses on the characterization of metal-based nanoparticles' ability to induce oxidative stress in MDR bacteria, highlighting their potential as future antibacterial drugs. Metal-based nanoparticles, including Au, Ag, Fe, and others, have demonstrated antimicrobial activity by inhibiting bacterial growth and biofilm formation, making them valuable tools in combating infectious diseases. Studies have elucidated the antimicrobial mechanisms of metal-based nanoparticles, which involve interactions with bacterial surfaces, membrane destabilization, ROS generation, and modulation of signal transduction pathways (Fig. 5c).

#### 4. Imaging applications of nanoparticles

##### 4.1. Contrast agents for various imaging modalities (e.g., MRI, CT, PET, optical imaging)

Imaging applications of nanoparticles as contrast agents have revolutionized the field of medical imaging by providing enhanced visualization and diagnostic capabilities across various imaging modalities, including magnetic resonance imaging (MRI), positron emission tomography (PET), CT, and optical imaging. Nanoparticles have distinct physicochemical properties that make them ideal candidates for imaging applications. They can be engineered to exhibit high stability, biocompatibility, and specific targeting capabilities, allowing for precise imaging of anatomical structures or molecular processes within the body [162].

**MRI:** In MRI, nanoparticles can serve as contrast agents by altering the magnetic properties of surrounding tissues. Superparamagnetic iron oxide nanoparticles (SPIONs) are frequently used in MRI as T2-weighted contrast agents. When injected into the body, SPIONs create local magnetic field distortions, leading to signal voids and darkening of the surrounding tissue in MRI images. This allows for the detection of pathological areas or specific cellular targets [163]. **CT imaging:** Utilizes X-rays to produce detailed anatomical images. Nanoparticles with high X-ray attenuation properties, such as gold nanoparticles or iodine-based nanoparticles, can be administered as contrast agents [164]. These nanoparticles enhance the X-ray absorption, resulting in increased contrast in CT images. They enable the visualization of blood vessels, tumors, and other anatomical structures with improved sensitivity and specificity [165]. Xu et al. (2021) present a strategy for creating

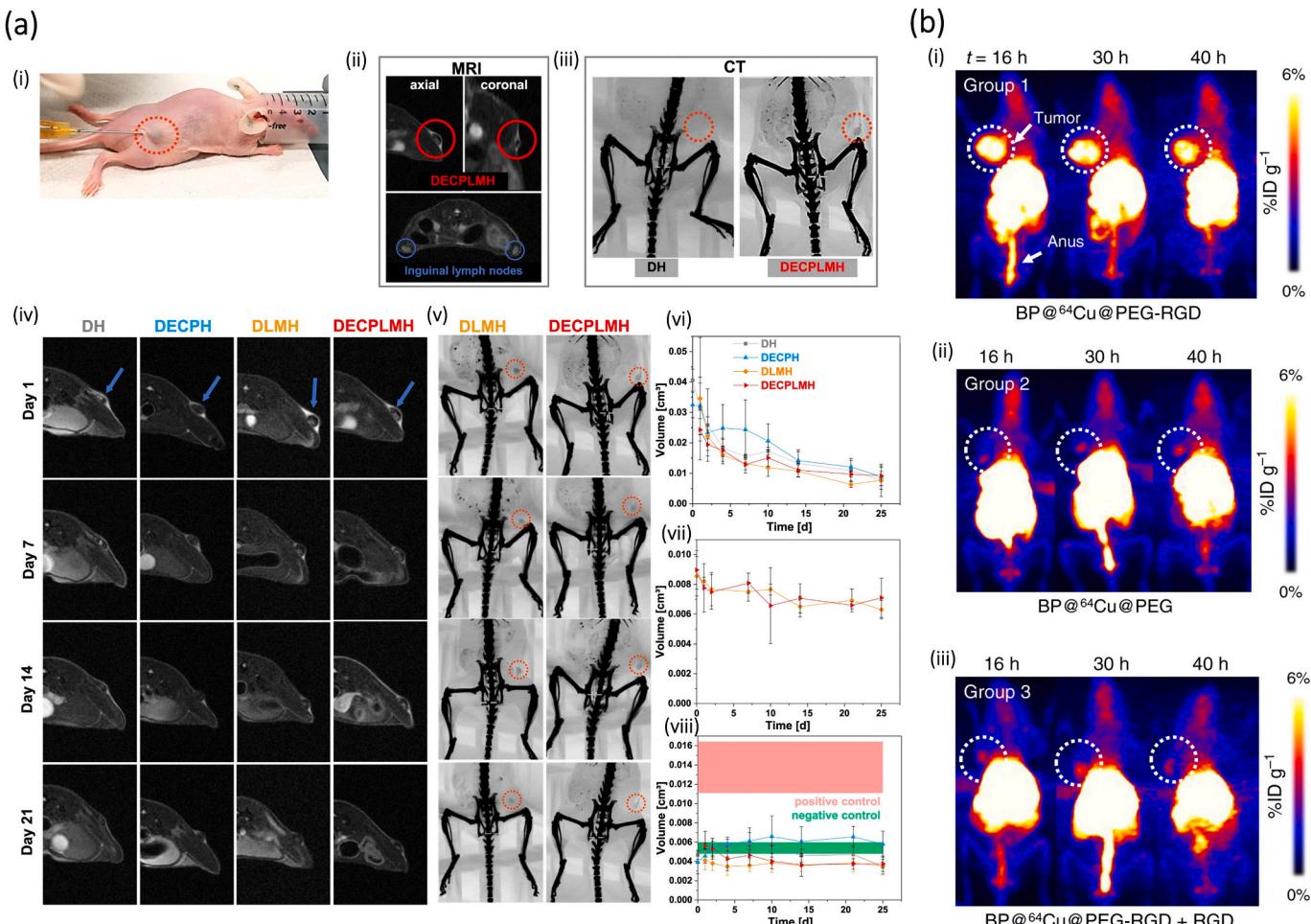
biomimetic electroconductive liquid metal hydrogels by synthesizing complex polymer networks (Fig. 6a). The approach involves assembling four precursors with different functional groups to form hydrogel adhesives, enabling the combination of materials with diverse properties. These hydrogels exhibit notable adhesive strength, heightened electroconductivity, and favorable cytocompatibility in vitro, coupled with exceptional compatibility in vivo, along with high biocompatibility in vivo. The reversible networks display self-healing and shear-thinning properties, facilitating 3D printing and minimally invasive injection for in vivo experiments. Biocompatibility assessment involves subcutaneous injection in immunocompetent mice, followed by ex vivo histological analysis and in vivo imaging techniques such as MRI, IR fluorescence imaging, and small animal µCT [166]. **PET imaging:** Involves the use of radioactive tracers to detect molecular and metabolic processes in the body [167]. Radiolabeled metal nanoparticles can serve as PET contrast agents by carrying radioactive isotopes. These nanoparticles can be tailored to target specific biomarkers or accumulate in specific tissues, enabling the visualization and quantification of biological processes or specific disease markers [168]. Hu et al. (2020) present a novel approach to reconcile the trade-off between photothermal stability and degradation of photothermal agents (PTAs) for cancer photothermal therapy (PTT) (Fig. 6b). They demonstrate that incorporating Cu<sup>2+</sup> into black phosphorus (BP) nanostructures enhances both photothermal stability and degradation of BP. This incorporation also enables chemodynamic therapy (CDT)-enhanced PTT and positron emission tomography (PET) imaging using metal ion 64Cu<sup>2+</sup> for real-time tracking in vivo. The research presents a novel photothermal ablation (PTA) solution and demonstrates the proof-of-concept application of BP-based materials in combination cancer therapy enhanced by PET-guided drug delivery and CDT [169].

##### 4.2. Optical properties of nanoparticles for fluorescence and photoacoustic imaging

The optical properties of metal nanoparticles play a crucial role in various imaging techniques, including fluorescence and PI imaging. Metal nanoparticles, particularly those of noble metals such as Au and Ag, exhibit unique optical phenomena at the nanoscale and can be harnessed for imaging applications. Fluorescence imaging relies on the emission and detection of light to visualize specific molecular or cellular events. Owing to their unique plasmonic properties, metal nanoparticles can serve as an excellent fluorophore. When excited by light of a specific wavelength, metal nanoparticles LSPR, resulting in a strong electromagnetic field enhancement near the nanoparticle surface. This enhanced electromagnetic field can significantly enhance the fluorescence emission of nearby fluorophores, leading to an enhanced sensitivity and signal-to-noise ratio in fluorescence imaging. This phenomenon, known as metal-enhanced fluorescence, allows for more highly sensitive detection of biomolecules, cellular processes, and disease markers [170]. In addition, Metal nanoparticles can also serve as fluorescence quenchers. By bringing the fluorophore close to the nanoparticle surface, energy transfer occurs, leading to fluorescence quenching. This quenching effect can be utilized to design nanoparticle-based sensors for the detection of various analytes or probing molecular interactions [171]. By modulating the distance between the fluorophore and nanoparticle surface, the quenching efficiency can be controlled, providing a versatile tool for fluorescence imaging applications.

###### 4.2.1. Photoacoustic imaging

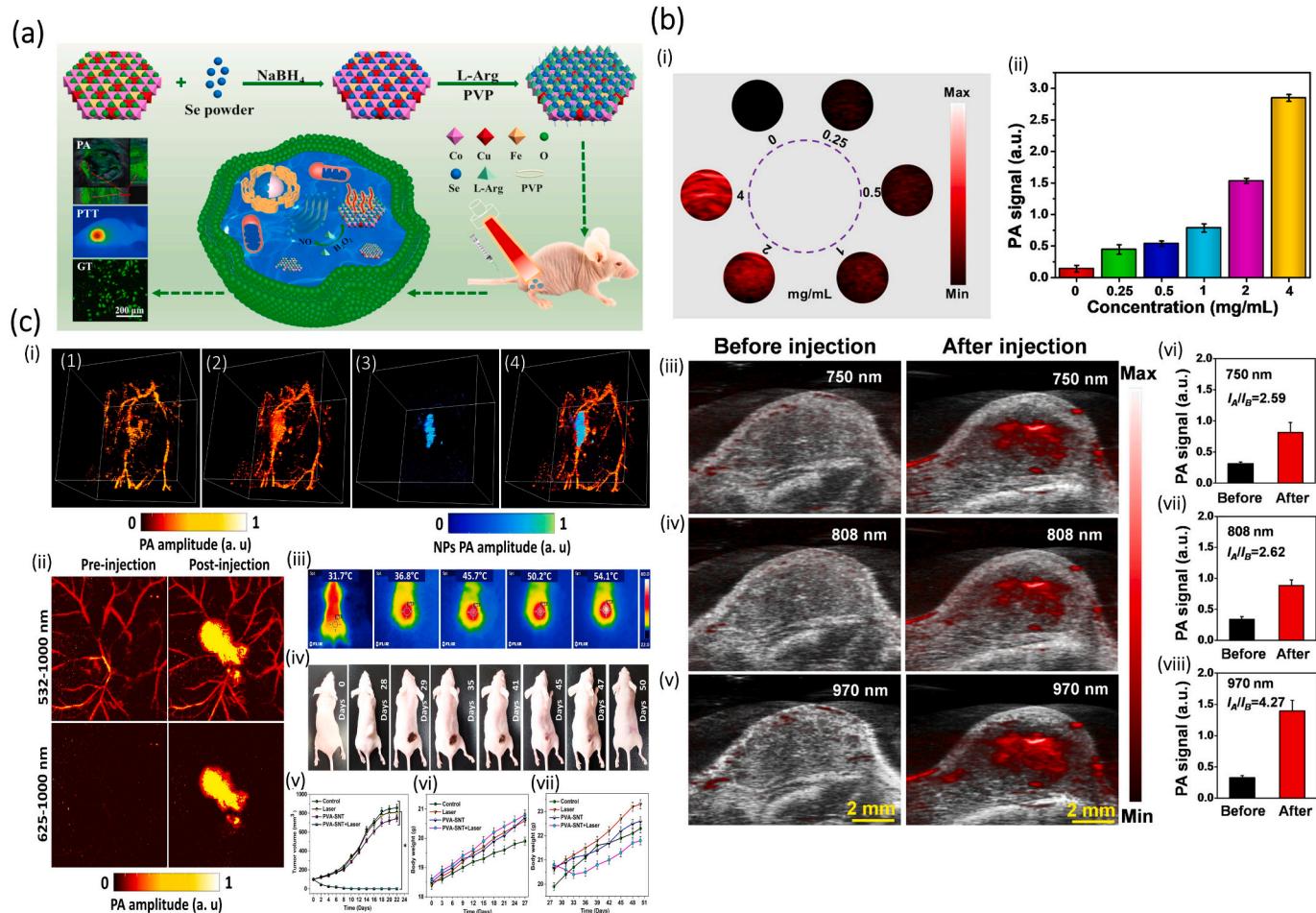
Metal nanoparticles exhibit strong light absorption properties and efficiently convert absorbed light energy into heat [172]. When irradiated with short laser pulses, metal nanoparticles experience rapid thermal expansion and generate acoustic waves, which can be detected and converted into high-resolution images. This photoacoustic effect allows for deep tissue penetration and imaging with excellent spatial resolution [173]. Gold nanoparticles, in particular, are widely used in



**Fig. 6.** Displays various imaging modalities and their application in assessing the efficacy of DECPLMH hydrogels and BP@64Cu@PEG-RGD nanoparticles. (a) Showcases exemplary images depicting the subcutaneous injection of DECPLMH, along with MRI and CT images illustrating the hydrogels and inguinal lymph nodes. Hydrogel volume estimation using MRI and CT is presented, along with inguinal lymph node size at the injection site (Reprinted with permission from Nature Portfolio, 2021) [166]. (b) Illustrates maximum intensity projection (MIP) PET images of B16F10 tumor-bearing mice at different time points after the intravenous injection of BP@64Cu@PEG-RGD nanoparticles (Reprinted with permission from Nature Portfolio, 2020) [169].

photoacoustic imaging due to their strong light absorption in the near-infrared (NIR) region, which matches the optical window of biological tissues [30]. Wu et al. (2021) developed an ultrathin metal Cu-loaded CoCuFe-selenide (CCFS) system for synergistic photothermal and gas therapy (PTT/GT) [174]. The CCFS-PVP-L-Arg (CPA) nanocomposite exhibited strong light absorption in the near-infrared (NIR) region, achieving a remarkable photothermal conversion efficiency of 72.0% (pH 7.4) and 81.0% (pH 5.4). Additionally, NO release from CPA was initiated by the decomposition of L-Arg in the tumor microenvironment, enabling localized gas therapy. In vitro studies demonstrated 91.8% apoptosis of HepG2 cells, while in vivo experiments demonstrated the total eradication of tumors when exposed to NIR irradiation. This represents the first instance of defect-induced high-efficiency PTT combined with targeted GT (Fig. 7a). Chen et al. (2021) developed a novel ultrasound-assisted liquid-reduction synthesis method to produce PEGylated indium nanoparticles (metal In nanoparticles) [175]. These nanoparticles served as efficient contrast agents for enhancing multi-wavelength photoacoustic imaging and second near-infrared (NIR-II) photothermal therapy in 4 T1 breast tumors. The metal In nanoparticles exhibited robust optical absorption spanning the NIR-I to NIR-II regions and demonstrated a high photothermal conversion efficiency of 41.3% at 1064 nm, surpassing conventional NIR-II photothermal agents. Upon injection into the tumor, the photoacoustic intensities experienced a significant increase, highlighting their exceptional multiwavelength

contrast capability for photoacoustic imaging. PEGylated In nanoparticles achieved efficient ablation of 4 T1 tumors under NIR-II laser irradiation, showing promising biocompatibility in vitro and in vivo. (Fig. 7b). Mondal et al. (2022) synthesized polyvinyl alcohol-coated silver triangular nano-prism (PVA-SNT) nanoparticles with drug-free, aiming for theranostic applications. These nanoparticles exhibited heightened photothermal activity against triple-negative breast cancer in a mouse model, attributed to their enhanced near-infrared absorbance and excellent contrast efficiency, biosafety, and photostability [27]. Both in vitro and in vivo experiments validated their potent anticancer efficacy and photoacoustic imaging-guided photothermal treatment capability. A standardized dose of  $140 \mu\text{g} \cdot \text{mL}^{-1}$  PVA-SNT nanoparticles, coupled with  $1.0 \text{ W} \cdot \text{cm}^{-2}$  laser irradiation for 7 min, demonstrated efficacy in managing triple-negative breast cancer. The integration of computational simulations with experimental approaches offers valuable insights into the efficiency and usability of plasmonic nanoparticles in future nano-biomedical research, providing accurate estimates of plasmonic heat generation (Fig. 7c). The optical characteristics of metal nanoparticles can be additionally adjusted by managing their size, shape, and surface characteristics. The plasmonic properties of metal nanoparticles strongly depend on these factors, allowing for precise control over their optical characteristics [176]. By engineering metal nanoparticles with specific sizes and shapes, their absorption and scattering spectra can be tailored to match the desired imaging wavelength,



**Fig. 7.** (a) Depicts the preparation process of the CPA nanocomposite for photoacoustic (PA) image-guided synergistic photothermal therapy (PTT) and gene therapy (GT) (Reprinted with permission from Elsevier, 2021) [174]. In (b) (i), *in vivo* 3D PA imaging of tumor tissues in MDA-MB-231 tumor-bearing nude mice is depicted before and after injection of PVA-SNT, with images obtained using different wavelength filters. In (ii), 2D PA imaging of tumor tissues is shown before and after injection of PVA-SNT. (iii) Displays an infrared (IR) thermal image during photothermal treatment, with laser irradiation applied for 7 min. (iv) Shows representative photographs of tumor-bearing mice at various stages from tumor induction to complete healing. (v) Presents tumor volume measurements of different groups post-PTT treatments. (vi) Depicts the body weight of mice before PTT treatments, and (vii) shows the body weight after PTT treatments (Reprinted with permission from Amer Chemical Soc, 2021) [175]. In (c), (i) demonstrates photoacoustic images of gradient concentrations of NP dispersions and DI water, while (ii) shows the corresponding photoacoustic intensity. (iii–v) Depict photoacoustic images of tumor regions captured using various excitation wavelengths, and (vi–vii) present the corresponding photoacoustic intensity of tumor regions (Reprinted with permission from Elsevier, 2021) [27].

maximizing imaging sensitivity and specificity.

#### 4.3. Multimodal imaging using nanoparticles for improved diagnostic accuracy

Multimodal imaging using metal nanoparticles has emerged as a powerful approach to improve the diagnostic accuracy of various medical imaging techniques. By integrating different imaging techniques, including MRI, CT, positron emission tomography (PET), and optical imaging, with metal nanoparticles as contrast agents, the strength of each modality can be leveraged to provide complementary information and enhance diagnostic capabilities [177]. Metal nanoparticles, particularly those crafted from noble metals, such as Au or Ag, exhibit distinctive optical and magnetic characteristics, rendering them ideal candidates for multimodal imaging applications [178]. These nanoparticles can be functionalized and tailored to exhibit specific properties suitable for multiple imaging modalities simultaneously.

In multimodal imaging, metal nanoparticles serve as versatile contrast agents, providing enhanced signal intensity, sensitivity, and spatial resolution across different imaging techniques [179]. For instance, Au nanoparticles are used in CT imaging because of their

strong X-ray attenuation properties, resulting in increased contrast and improved detection sensitivity. Simultaneously, these nanoparticles can be designed to exhibit fluorescent properties, enabling their use in optical imaging. By incorporating radioactive isotopes, such as Ga-68 or Cu-64, metal nanoparticles can also serve as PET contrast agents, allowing molecular imaging and quantitative analysis of biological processes [180]. Metal nanoparticles can be engineered to respond to magnetic fields, rendering them suitable for utilization in MRI. Superparamagnetic iron oxide nanoparticles are commonly used in MRI because of their ability to generate contrasting signals on T2-weighted images [92]. When used alongside other imaging modalities, such as CT or optical imaging, metal nanoparticles provide complementary insights into both anatomical structures and functional tissue properties, thereby improving diagnostic accuracy. Multimodal imaging approaches utilizing metal nanoparticles offer several advantages. First, they allow for the integration of different imaging modalities, each possessing unique advantages, thereby furnishing comprehensive and accurate diagnostic information [181]. Second, the ability to simultaneously acquire data from multiple modalities reduces the need for separate imaging sessions, improving patient comfort and convenience [182]. Third, combining different imaging techniques can offset the

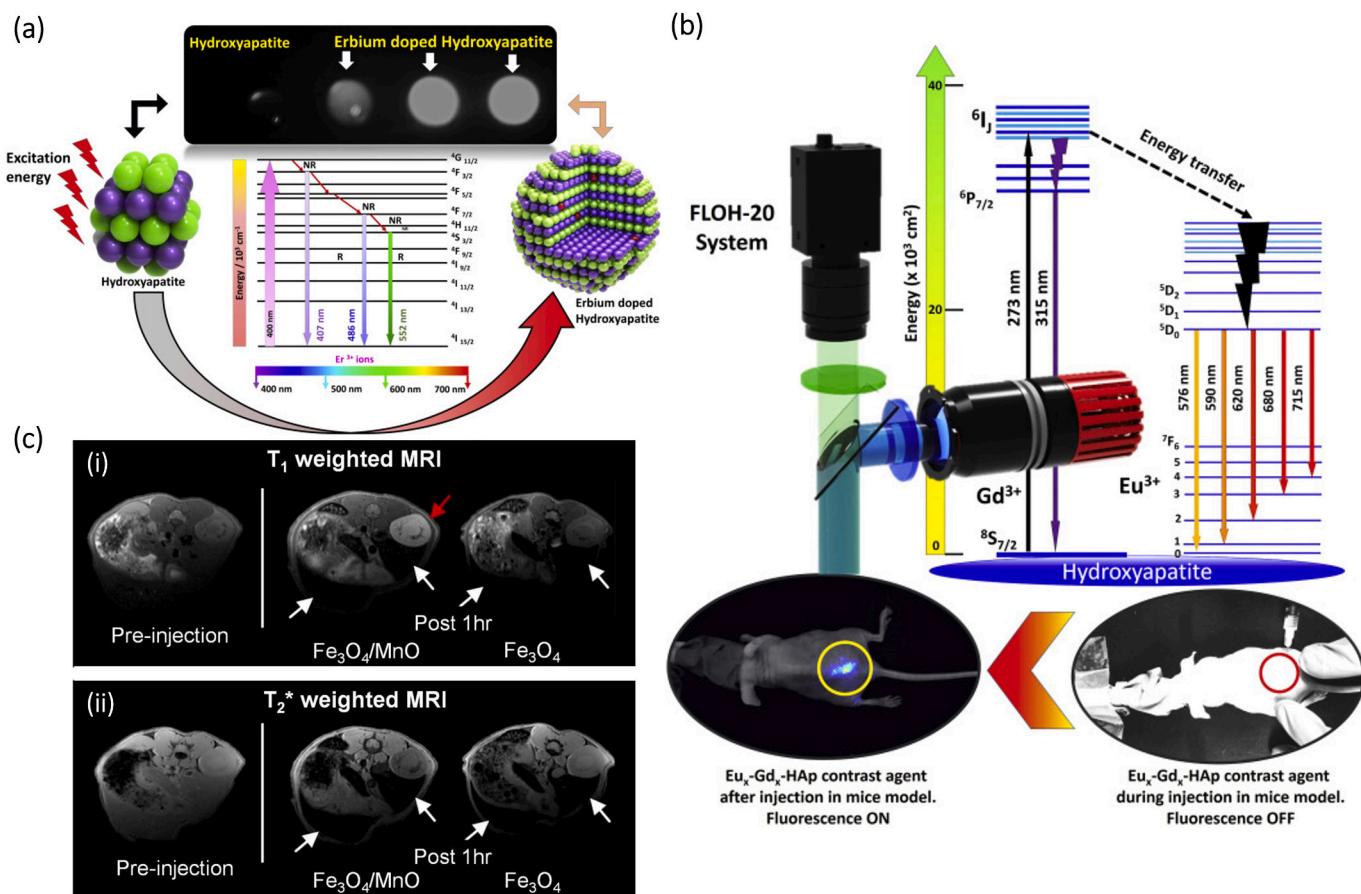
limitations and artifacts present of individual modalities, resulting in improved image quality, sensitivity, and specificity [183]. Utilizing metal nanoparticles as multimodal imaging contrast agents, allow medical professionals to gain a comprehensive understanding of the structural, functional, and molecular characteristics of tissues and disease sites. This approach holds significant promise for various clinical applications, including cancer detection, cardiovascular imaging, neuroimaging, and targeted drug delivery. Ongoing research and development in the field of multimodal imaging using metal nanoparticles continue to advance our ability to diagnose diseases accurately and develop personalized treatment strategies [184].

#### 4.4. In vivo imaging

##### 4.4.1. Optical imaging

including fluorescence and bioluminescence, relies on the emission and detection of light to visualize specific molecular and cellular events [185]. Nanoparticles with fluorescent or bioluminescent properties, such as quantum dots or up-conversion nanoparticles, can be employed as contrast agents [186]. These nanoparticles emit light signals that can be detected and analyzed to provide detailed information on cellular processes, tissue morphology, and disease markers. In addition to their inherent imaging properties, nanoparticles can be surface-functionalized with targeting ligands or biomolecules to improve specificity and enable molecular imaging. By conjugating targeting moieties onto the nanoparticle surface, such as antibodies, peptides, or aptamers, nanoparticles can selectively bind to specific receptors or biomarkers,

allowing for targeted imaging and improved diagnostic accuracy [187]. The use of nanoparticles as contrast agents across different imaging modalities has expanded the capabilities of medical imaging, providing enhanced sensitivity, specificity, and multiplexing [180]. Advancements in multifunctional nanoparticles that combine imaging, drug delivery, and therapeutic functionalities hold great promise for personalized medicine and precision diagnostics. Mondal et al. (2020) fabricated luminescent lanthanide Er-doped hydroxyapatite (Er-HAp) using a simple wet-chemical precipitation method [188]. The synthesized nanostructured materials, characterized by their chemical composition, morphology, optical properties, and biological effects, exhibited an elongated morphology with a size distribution of <50 nm (Fig. 8a). Photoluminescence studies revealed distinct emission bands corresponding to different transition states. In vitro studies with osteoblast-like cells confirmed the non-toxic luminescent behavior of the synthesized nanomaterials. Real-time monitoring of metal nanoparticle behavior in vivo has become a crucial area of research in nanomedicine. This involves tracking and understanding the dynamic interactions, biodistribution, and fate of metal nanoparticles within living organisms to provide valuable insights into their therapeutic efficacy, safety, and potential applications. The ability to monitor metal nanoparticles in real-time is essential for assessing their behavior, such as circulation time, tissue distribution, and clearance kinetics. This enables researchers to understand how nanoparticles interact with biological systems, including their cellular uptake by cells, accumulation in specific tissues or organs, and eventual elimination from the body [189]. This information is vital for optimizing nanoparticle design, dosage, and



**Fig. 8.** Illustrates various aspects related to the materials and imaging techniques discussed in the study. (a) Shows a schematic representation of erbium-doped hydroxyapatite as a luminescent bioactive material (Reprinted with permission from Elsevier, 2020) [188]. (b) Depicts a schematic of Eux-Gdx-HAp nanoparticles as a contrast agent (Reprinted with permission from Elsevier, 2020) [191]. (c) Features T1- and T2\*-weighted abdominal MR images of a nude mouse pre- and post-intravenous administration of  $\text{Fe}_3\text{O}_4/\text{MnO}$  dumbbell and  $\text{Fe}_3\text{O}_4$  nanocrystals. The kidneys exhibit enhanced brightness only with  $\text{Fe}_3\text{O}_4/\text{MnO}$  dumbbell nanocrystals, while both  $\text{Fe}_3\text{O}_4$  and  $\text{Fe}_3\text{O}_4/\text{MnO}$  dumbbell nanocrystals cause the liver to become dark (Reprinted with permission from Elsevier, 2012) [194].

administration routes. Several imaging techniques have been employed for real-time monitoring of metal nanoparticles *in vivo*. Optical imaging methods, such as fluorescence imaging or bioluminescence imaging, utilize the fluorescence or bioluminescence properties of nanoparticles to visualize their localization and movement in real time [190]. These techniques provide high spatial resolution and are suitable for surface imaging or tracking nanoparticles near the surface of the body. Mondal et al. (2020) extended their significant research by developing biocompatible luminescent bioimaging agents for biomedical applications. By doping rare earth ions ( $\text{Gd}^{3+}$  and  $\text{Eu}^{3+}$ ) into a flexible hydroxyapatite (HAp) structure, they achieved enhanced luminescence properties [191]. The wet co-precipitation method employed for doping resulted in nanocrystals ( $\text{Eu}_{x}\text{-Gd}_{x}\text{-HAp}$ ) with excellent structural and thermal stabilities. Characterization techniques confirmed the hexagonal crystal structure and large surface area of the prepared nanomaterials. Enhanced luminescence, attributed to “Gd-Eu” co-doping, was observed under specific excitation wavelengths. *In vitro* and *in vivo* studies demonstrated the biocompatibility and imaging capabilities of the  $\text{Eu}_{x}\text{-Gd}_{x}\text{-HAp}$  nanocrystals, indicating their potential as contrast agents for fluorescence imaging in biomedicine (Fig. 8b). Advanced imaging techniques such as PA imaging, intravital microscopy, and multiphoton microscopy provide high-resolution imaging at the cellular and subcellular levels. Vy et al. (2019) demonstrated that CS-stabilized porous flower-shaped Pd (CFP) nanoparticles could effectively enter tumors through an improved EPR mechanism or receptor-mediated binding [192]. This makes CFP nanoparticle-based PA imaging suitable for identifying different tumor types. PA signals acquired from CFP nanoparticle-treated cells showed intense signals correlating with nanoparticle concentration, indicating their potential as a tumor imaging agent. These findings suggest that CFP nanoparticles hold promise for PA imaging of tumors (Fig. 8c). *In vivo* imaging techniques such as MRI, PET, and single-photon emission CT are also employed for live monitoring [165]. Metal nanoparticles can be labeled with radioactive isotopes or paramagnetic agents, enabling their detection and quantification using these imaging modalities. These techniques offer deep tissue penetration and whole-body imaging capabilities, allowing researchers to track nanoparticle behavior at a systemic level [193]. Ho Im et al. (2013) developed  $\text{Fe}_3\text{O}_4/\text{MnO}$  hybrid nanocrystals as dual magnetic resonance (MR) contrast agents with both T1 and T2 contrast-enhancing abilities [194]. *In vitro* and *in vivo* studies showed that these nanocrystals exhibited negative T2 contrast and positive T1 contrast, respectively, upon the release of  $\text{Mn}^{2+}$  ions in a low pH environment. This results in organ-specific contrast enhancement on both T1- and T2-weighted MR scans. *In vivo* MR of a hepatocellular carcinoma (HCC) model showed synergistic dual contrast effects, facilitating the detection of HCC with high conspicuity (Fig. 8d). These approaches allow the direct visualization of metal nanoparticles and their interactions with specific tissues, cells, or even organelles in real time. They offer valuable insights into nanoparticle behavior, including intracellular trafficking, interactions with cellular components, and cellular responses [195]. Real-time monitoring of the behavior of metal nanoparticles *in vivo* has significant implications for various biomedical applications. It helps elucidate the mechanisms of nanoparticle-mediated drug delivery, targeted therapy, and imaging enhancement. It also aids in understanding the nanoparticle-induced toxicity, potential side effects, and immune responses [196]. Real-time monitoring enables the optimization of nanoparticle properties and delivery strategies, leading to improved therapeutic outcomes and personalized medicine approaches [197].

#### 4.4.2. Biosensing

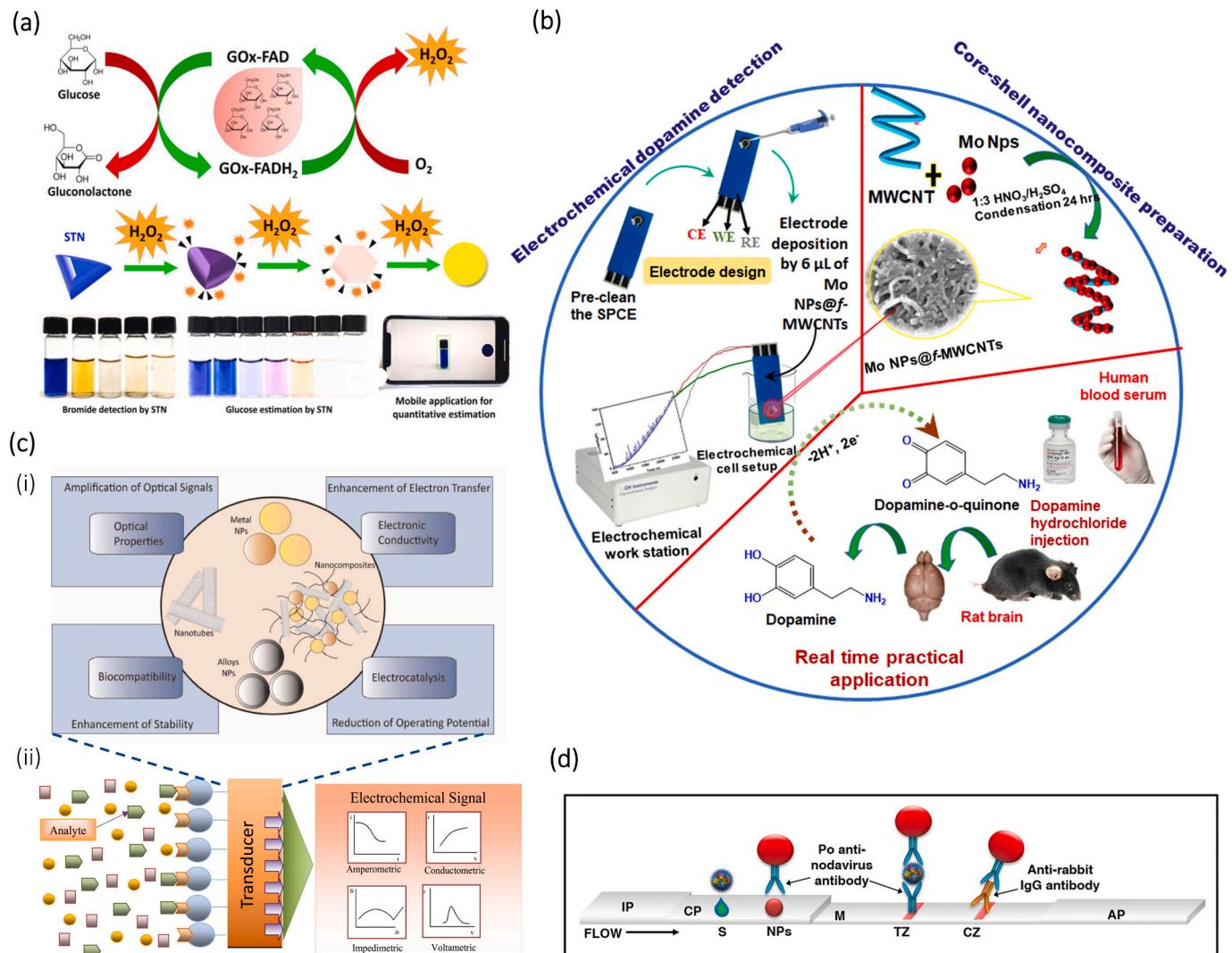
Metal nanoparticles, including gold and silver, are widely utilized in biosensor applications owing to their distinctive optical, electronic, and catalytic attributes. These nanoparticles serve as highly effective platforms for immobilizing biomolecules, such as antibodies or DNA probes, enabling specific binding interactions with target analytes. The elevated surface area-to-volume ratio of metal nanoparticles amplifies the

sensitivity of biosensors, enabling the detection of low concentrations of biomolecules. The customizable surface chemistry of metal nanoparticles permits the tailoring of biosensors for diverse applications in medical diagnostics, environmental observation, and food safety. Mondal et al. (2022) developed a simple and cost-effective method using colloidal metal silver triangular nanoprism (STN) for the colorimetric estimation of glucose and bromide [26]. Glucose sensing relied on distinct color changes induced by glucose oxidase enzymatic oxidation of STN, while bromide detection was achieved using STN alone. A reference color scale enabled direct estimation of glucose concentrations by visual inspection, and a smartphone-based app employing YOLOv3 deep-learning algorithm enhanced accuracy. Increasing analyte concentrations led to a gradual blue-shift of the localized surface plasmon resonance (LSPR) peak of STN and decreased absorbance. Experimental results demonstrated high accuracy in estimating urine glucose levels, with detection limits of 0.010 mg/mL for glucose and 0.005 mg/mL for bromide ions. This non-invasive and highly selective sensing technique holds promise for point-of-care diagnostics or environmental monitoring (Fig. 9a). Keerthi et al. (2019) developed a highly sensitive dopamine (DA) biosensor for early disease diagnosis [198]. They successfully synthesized self-supported functionalized multi-walled carbon nanotubes (f-MWCNTs) embedded with molybdenum nanoparticles (Mo NPs@f-MWCNTs) with an average diameter ranging from 40 to 45 nm. This hybrid nanocomposite exhibited exceptional electrochemical performance, particularly in dopamine (DA) detection. Characterization techniques including XRD, Raman, FE-SEM, HR-TEM, and EDX confirmed the morphological and structural features of the hybrid nanomaterial. Electrochemical impedance spectroscopy, cyclic voltammetry, and amperometry were employed to investigate the sensor's performance. The biosensor showcased a remarkably low detection limit of 1.26 nM, coupled with an outstanding linear response spanning from 0.01  $\mu\text{M}$  to 1609  $\mu\text{M}$ . Additionally, it exhibited a commendable sensitivity of  $4.925 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-2}$ . Real sample analysis of rat brain, human blood serum, and DA hydrochloride injection validated the sensor's stability and reliability for real-time DA detection (Fig. 9b). Metal nanoparticles are widely used in biosensor applications due to their unique properties that enable highly sensitive and selective detection of biomolecules (Fig. 9c). Metal nanoparticles, such as Au and Ag, exhibit SPR, which causes strong absorption and scattering of light at specific wavelengths. This property is exploited in optical biosensors for label-free detection of biomolecular interactions [199]. Metal nanoparticles can be functionalized with various biomolecules, such as enzymes, antibodies, aptamers, or DNA probes, to specifically capture target analytes. This allows for highly selective detection of biomolecules in complex samples [200]. Toubanaki et al. (2020) developed a paper lateral flow biosensor (LFB) for rapid detection of nodavirus, a pathogen causing significant losses in the aquaculture industry [201]. The prototype LFB utilized polyclonal antibodies conjugated to gold nanoparticles for signal visualization. This assay facilitated the detection of nodavirus virions in fish samples within 30 min, providing a robust, cost-effective, and precise detection method. Optimization of key parameters improved detection efficiency and minimized non-specific interactions. This biosensor holds promise for commercial development as a convenient tool for disease monitoring in aquaculture facilities, potentially streamlining procedures and enhancing environmental safety (Fig. 9c).

## 5. Challenges and future directions

### 5.1. Safety considerations and toxicity of nanoparticles in biomedical applications

Safety considerations and the toxicity of metal nanoparticles are critical aspects that need to be carefully addressed when considering their biomedical applications. Although metal nanoparticles have immense potential for various therapeutic and diagnostic purposes,



**Fig. 9.** Depicts different sensor designs and detection mechanisms used in various applications. (a) Describes the detection mechanism of a colorimetric sensor for glucose utilizing Surface-Textured Nanoparticles (STN) in a label-free and reagent-free manner (Reprinted with permission from Elsevier, 2022) [26]. (b) Illustrates the fabrication process of a core-shell Mo NPs@f-MWCNTs hybrid nanocomposite and its electrochemical electrochemical assessment for the detection of neurotransmitters in biological samples (Reprinted with permission from Nature Portfolio, 2019) [198]. (c) Provides characteristics and roles of nanomaterials in biosensor applications, along with a diagram illustrating the structure of a biosensor (Reprinted with permission from Elsevier, 2016) [200]. (d) Explains the principle of a nanoparticle-based lateral flow biosensor for detecting nodavirus virions involves the integration of various components, including the immersion pad (IP), conjugation pad (CP), diagnostic membrane (M), and absorbent pad (AP). A side view of the biosensor illustrates these components, although not to scale, to demonstrate their spatial arrangement and functionality in facilitating the detection process (Reprinted with permission from Nature Portfolio, 2020) [201].

understanding their potential adverse effects is crucial to ensure their safe use in biomedical settings. One of the primary concerns regarding the safety of metal nanoparticles is their potential toxicity. The small size and expandable surface area of nanoparticles may lead to heightened reactivity and interactions with biological systems. Certain metal nanoparticles, such as those made from Ag, Au, or Cd-based materials, have been shown to exhibit toxicity in vitro and in vivo under specific conditions. Therefore, establishing the safe concentration ranges and exposure limits for metal nanoparticles is crucial to minimize potential adverse effects. Another challenge lies in the biodistribution and clearance of metal nanoparticles within the body. The behavior of nanoparticles in biological systems, including their circulation time, tissue accumulation, and potential long-term retention, must be thoroughly investigated. Understanding the fate and clearance pathways of metal nanoparticles is crucial for evaluating their potential accumulation in vital organs and their adverse effects on systemic homeostasis. In addition, the potential for metal nanoparticles to induce immunological responses is significant. Interactions between nanoparticles and the

immune system can lead to inflammatory reactions or immune cell activation. Notably, assessing the immunological response induced by metal nanoparticles and evaluating potential long-term consequences on the immune system are essential. Standardized protocols for evaluating the safety of metal nanoparticles are crucial for accurate assessment. Comprehensive studies, involving in vitro models, animal models, and human trials, are necessary to evaluate the safety profiles of metal nanoparticles thoroughly. These studies should encompass various aspects, including biocompatibility, cytotoxicity, genotoxicity, immunotoxicity, and long-term effects on organs and tissues. The physicochemical attributes of metal nanoparticles, including their dimensions, morphology, surface charge, and modifications, can significantly influence their safety profiles. Meticulously evaluating these parameters is crucial to understand their effects on the interactions between metal nanoparticles and biological entities.

## 5.2. Regulatory hurdles and clinical limitations

Regulatory hurdles and clinical limitations present significant challenges to the successful and effective translation of metal nanoparticles for biomedical applications. The regulatory landscape governing the utilization of nanoparticles in medicine is complex and continuously evolving, requiring careful adherence to guidelines and regulations to ensure patient safety and product efficacy. One of the primary regulatory challenges is the absence of standardized protocols and guidelines specifically tailored to metal nanoparticles. While regulatory agencies have typically established guidelines for conventional drugs and medical devices, the unique properties and behaviors of nanoparticles require additional consideration. The characterization, safety assessment, and efficacy evaluation of metal nanoparticles must align with regulatory requirements, which can be challenging owing to the diverse nature of nanoparticle formulations and applications. Another barrier to the translation of metal nanoparticles into clinical practice is the necessity for comprehensive toxicity evaluation and risk assessment. One of the foremost clinical limitations is the potential toxicity of metal and metal-oxide nanoparticles. These nanoparticles can exhibit cytotoxic effects, generate ROS, and cause oxidative stress, leading to cell damage and inflammation. The long-term biocompatibility and potential accumulation of nanoparticles in vital organs, such as the liver, spleen, and kidneys, pose serious concerns. Ensuring that these nanoparticles do not induce chronic toxicity or adverse immune responses is crucial for their clinical use. The biodistribution and clearance of metal nanoparticles in the body are critical factors that impact their clinical application. Nanoparticles may accumulate in non-target tissues, leading to unintended side effects. The inability to predict and control their biodistribution accurately can hinder their effectiveness and safety. Furthermore, the clearance of nanoparticles from the body through renal or hepatic pathways must be thoroughly understood to avoid potential toxicity from prolonged retention in the body. Regulatory bodies demand extensive data on the safety profile of metal nanoparticles, encompassing potential toxicity, biodistribution, long-term effects, and environmental impact. However, acquiring such data through preclinical studies and clinical trials can be time-consuming, resource-intensive, and expensive, thus hindering the translation process. The regulatory approval process itself is both lengthy and complex, involving rigorous scrutiny of data, including preclinical and clinical evidence, manufacturing practices, quality control, and ethical considerations. Compliance with good manufacturing practices and laboratory practices is necessary to ensure the reproducibility, reliability, and quality of nanoparticle-based products. Meeting regulatory requirements can pose significant challenges, particularly for academic researchers and small companies with limited resources and expertise to navigate the complex regulatory landscape. The cost associated with regulatory compliance and the intellectual property landscape surrounding metal nanoparticles further compound these challenges. Expenses related to conducting preclinical and clinical studies, obtaining regulatory approval, and ensuring quality control are substantial. Intellectual property challenges, such as patent protection and infringement issues, may also influence the commercial viability and investment prospects of nanoparticle-based products. Cooperation among scientists, regulatory agencies, and industry partners is vital to overcome these regulatory and translational barriers. Establishing clear regulatory guidelines specific to metal nanoparticles, streamlining the approval process, and supporting academic researchers and small companies can facilitate the translation of metal nanoparticles into clinical applications. Collaboration among stakeholders can further foster knowledge exchange, data sharing, and the development of standardized protocols for nanoparticle characterization, safety assessment, and risk evaluation (Table 2).

## 5.3. Advancements in nanoparticle surface engineering for enhanced targeting and imaging

The future direction for metal nanoparticles in biomedical applications lies in surface engineering, aimed at enhancing their targeting and imaging capabilities. Surface engineering involves modifying the surface properties of metal nanoparticles to achieve specific functionalities and improve their performance in targeting specific tissues or cells, as well as enhancing imaging modalities for better diagnostic accuracy. One promising avenue for future research is the development of surface modifications enabling targeted delivery of metal nanoparticles to specific cells or tissues. This can be achieved through the conjugation of targeting ligands, such as antibodies or peptides, onto the nanoparticle surface. These ligands can specifically recognize and bind to receptors or biomarkers present in target cells, facilitating the selective accumulation and internalization of nanoparticles. By incorporating surface-engineered targeting strategies, metal nanoparticles can be directed to disease sites with enhanced precision, thereby augmenting their therapeutic effectiveness and mitigating off-target effects. Another important aspect for future research is the improvement of imaging capabilities through surface engineering approaches. Owing to their exceptional optical properties, metal nanoparticles are considered superior contrast agents for numerous imaging modalities, including CT, MRI, optical imaging, and PET. Surface engineering techniques can be employed to improve the imaging contrast, stability, and specificity of metal nanoparticles. For example, functionalizing nanoparticle surfaces with specific dyes or fluorophores can improve their fluorescence imaging properties. Coating the nanoparticles with biocompatible materials enhances their stability and biocompatibility for in vivo imaging applications. Moreover, surface engineering can be used to develop multifunctional metal nanoparticles with combined targeting and imaging capabilities. By integrating targeting ligands, imaging agents, and therapeutic payloads onto the nanoparticle surface, these multifunctional nanoparticles can serve as theranostic agents. They allow simultaneous targeted drug delivery and real-time imaging of the therapeutic response, thus enabling personalized medicine approaches and enhancing treatment outcomes. In future biomedical applications, researchers are likely to integrate metal nanoparticles with advanced nanotechnologies such as gene editing and nanorobotics. This integration has the potential to revolutionize diagnostics, therapeutics, and personalized medicine by enabling precise targeted interventions at the molecular level.

One exciting area of research is the integration of metal nanoparticles with gene-editing technologies, such as CRISPR-Cas9. Gene editing allows precise modification of DNA sequences, offering opportunities for targeted treatment of genetic diseases. By combining metal nanoparticles with gene editing tools, the delivery of gene editing agents to specific cells or tissues may be enhanced. Metal nanoparticles can serve as carriers to protect and deliver gene editing molecules, thereby improving their stability, cellular uptake, and targeted delivery. This integration holds promise for the development of effective and precise gene therapies. Another emerging field of research is the integration of metal nanoparticles with nanorobotics. Nanorobots are tiny devices capable of navigating the body and performing specific tasks at a nanoscale level. By incorporating metal nanoparticles into nanorobots, researchers can enhance their capabilities for targeted drug delivery, imaging, and direct manipulation of biological structures. Metal nanoparticles can act as functional components of nanorobots, providing imaging contrast, surface modifications for specific interactions, and controlled release of therapeutic agents. This integration opens new possibilities for highly precise and efficient therapeutic interventions. The convergence of metal nanoparticles with other advanced technologies such as artificial intelligence (AI) holds tremendous promise. By utilizing AI algorithms in metal nanoparticle-based diagnostics or therapeutic dataset processing, researchers can identify patterns, correlations, and personalized treatment strategies. This synergy has the

potential to enhance diagnostic precision, refine treatment protocols, and ultimately elevate patient outcomes.

## 6. Conclusion

The advent of precision-engineered metal nanoparticles, spanning a wide spectrum of metal, represents a transformative force in targeted therapy and imaging, propelling medical science into a new era. Au and Ag nanoparticles, for instance, exhibit remarkable potential in photothermal therapy, whereas elements such as Mn and Gd enhance imaging techniques to unprecedented levels. Metal and metal-oxide nanoparticles, especially those incorporating Mn and Gd, have demonstrated exceptional capabilities in improving the resolution and accuracy of imaging modalities such as MRI and CT scans. These advancements facilitate early and precise diagnosis of various diseases. The implications of this technology for personalized medicine are profound and far-reaching. However, despite their promise, several hurdles hinder their widespread clinical adoption. Biological challenges, including understanding disease pathology and optimizing physicochemical properties, require further exploration. Through meticulous tailoring, these nanoparticles can be finely tuned to interact with specific cellular targets, providing, promising treatments uniquely suited to individual patients. This marks a departure from generic medical interventions towards highly specific treatments, minimizing collateral damage, and maximizing therapeutic efficacy. This review also emphasizes the importance of addressing biocompatibility and safety concerns. Comprehensive toxicity evaluations and long-term studies are essential to ensure that these metal/metal-oxide nanoparticles do not pose adverse effects when used in clinical settings. The prospects of precision-engineered metal nanoparticles in medicine are exceptionally promising. Ongoing research on new materials, fabrication techniques, and surface modifications is likely to broaden their applications. Additionally, the convergence of artificial intelligence and nanotechnology has vast potential to present innovative solutions for diagnostics, drug delivery, and therapeutic monitoring. Precision-engineered metal nanoparticles have immense potential to reshape the healthcare landscape. Their pivotal roles in targeted therapy and imaging, coupled with their promise in personalized medicine, offer a glimpse into a future where treatments are not only effective but also tailored to the unique characteristics of each patient. As research advances and technologies evolve, nanoparticles are poised to become one of the most significant contributions to human health in the 21st century. This revolution holds the promise of vastly improving the lives of countless individuals and, ushering in an era of healthcare that is as precise and it is powerful as possible.

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## CRediT authorship contribution statement

**Thi Thuy Truong:** Writing – review & editing, Writing – original draft, Investigation. **Sudip Mondal:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Vu Hoang Minh Doan:** Writing – original draft. **Soonhyuk Tak:** Writing – original draft. **Jaeyeop Choi:** Writing – original draft. **Hanmin Oh:** Writing – review & editing. **Tan Dung Nguyen:** Writing – review & editing. **Mrinmoy Misra:** Writing – original draft. **Byeongil Lee:** Writing – review & editing, Supervision. **Junghwan Oh:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

**Table 2**

List of metal-based nanomedicine formulations approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

No	Material description	Commercial name	Application	Reference
1	AuNPs	Aurimune	Targeting delivery	[202]
2	Ferumoxytol SPION with polyglucose sorbitol carboxymethylether	Ferumoxytol	Enhanced MR imaging to assess myocardial infarction	[203]
3	Iron oxide coated with dextran	Feridex	MRI diagnostic, imaging of liver lesions	[204]
4	Ultrasmall iron oxide coated with low $M_w$ dextran	Combidex	MRI	[205]
5	Iron oxide nanoparticles coated with carboxylated dextran	Resovist	MRI	[205]
6	Silicone-coated iron oxide nanoparticles	Gastromark	MRI	[205]
8	Iron oxide nanoparticles with aminosilane coating	Nanotherm	Hyperthermia in solid tumors	[205]
9	ferumoxytol	Feraheme™	Anemia	[206,207]
10	Iron dextran	Dexferrum®	Iron deficiency in CKD	[208]
11	Iron carboxymaltose colloid	Ferinject®	Iron deficient anemia	[209]
12	Sodium ferric gluconate	Ferrlecit®	Iron deficiency in CKD	[210]
13	Hafnium oxide nanoparticles	Hensify®	locally advanced squamous cell carcinoma	[211]
14	Iron dextran	Infed®	Iron deficiency in CKD	[212]
15	SPION coated with dextran	Feridex®/Endorem®	Imaging agent	[213]
16	SPION coated with silicone	GastroMARK™/Umir	Imaging agent	[213,214]
17	Iron dextran	INFed	Iron-deficient anemia	[87]
18	Iron dextran	DexFerrum	Iron-deficient anemia	[87]
19	Sodium ferric gluconate	Ferrlecit	Iron deficiency in chronic kidney disease	[87]
20	Iron sucrose	Venofer	Iron deficiency in chronic kidney disease	[87]
21	Calcium phosphate	Vitoss® (Stryker)	Bone substitute	[215]
22	Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (Heraseus Kulzer)	Ostim®	Bone substitute	[215]
23	Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (OsSatura® (IsoTis Orthobiologics))	OsSatura® (IsoTis Orthobiologics)	Bone substitute	[215]
24	Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (NanOss® (Rti surgical))	NanOss® (Rti surgical)	Bone substitute	[215]
25	Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (Zimmer Biomet)	EquivaBone®	Bone substitute	[215]
26	Dantrolene sodium	Ryanodex® (Eagle Pharmaceuticals)	Malignant hypothermia	[215]

To date, a total of approximately 100 nanomedicine-based formulations have been approved by the FDA and EMA [216].

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## References

- [1] Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical-physical applications to nanomedicine. *Molecules* 2019;25:112.
- [2] Lee KX, Shamel K, Yew YP, Teow S-Y, Jahangirian H, Rafiee-Moghaddam R, et al. Recent developments in the facile bio-synthesis of gold nanoparticles (AuNPs) and their biomedical applications. *Int J Nanomedicine* 2020;275–300.
- [3] Zhou H, Lee J. Nanoscale hydroxyapatite particles for bone tissue engineering. *Acta Biomater* 2011;7:2769–81.
- [4] Kim H, Mondal S, Jang B, Manivasagan P, Moorthy MS, Oh J. Biomimetic synthesis of metal-hydroxyapatite (au-HAp, ag-HAp, au-ag-HAp): structural analysis, spectroscopic characterization and biomedical application. *Ceram Int* 2018;44:20490–500.
- [5] Fulekar M, Pathak B. Environmental Nanotechnology. CRC Press; 2017.
- [6] Kulkarni MB, Goel S. Microfluidic devices for synthesizing nanomaterials—A review. *Nano Express* 2020;1:032004.
- [7] Vo TMT, Mondal S, Nguyen VT, Park S, Choi J, Bui NT, et al. Rice starch coated iron oxide nanoparticles: A theranostic probe for photoacoustic imaging-guided photothermal cancer therapy. *Int J Biol Macromol* 2021;183:55–67.
- [8] Kim H, Mondal S, Bharathiraja S, Manivasagan P, Moorthy MS, Oh J. Optimized Zn-doped hydroxyapatite/doxorubicin bioceramics system for efficient drug delivery and tissue engineering application. *Ceram Int* 2018;44:6062–71.
- [9] Park S, Choi J, Mondal S, Vo TMT, Pham VH, Lee H, et al. The impact of cu(II) ions doping in nanostructured hydroxyapatite powder: A finite element modelling study for physico-mechanical and biological property evaluation. *Adv Powder Technol* 2022;33:103405.
- [10] Sahu T, Ratre YK, Chauhan S, Bhaskar L, Nair MP, Verma HK. Nanotechnology based drug delivery system: current strategies and emerging therapeutic potential for medical science. *J Drug Deliv Sci Technol* 2021;63:102487.
- [11] Raju CV, Cho CH, Rani GM, Manju V, Umapathi R, Huh YS, et al. Emerging insights into the use of carbon-based nanomaterials for the electrochemical detection of heavy metal ions. *Coord Chem Rev* 2023;476:214920.
- [12] Chowdhury S, Toth I, Stephenson RJ. Dendrimers in vaccine delivery: recent progress and advances. *Biomaterials* 2022;280:121303.
- [13] Bayan R, Karak N. Polymer nanocomposites based on two-dimensional nanomaterials. In: Two-Dimensional Nanostructures for Biomedical Technology. Elsevier; 2020. p. 249–79.
- [14] Mondal S, Park S, Choi J, Tran LH, Yi M, Shin JH, et al. Bioactive, luminescent erbium-doped hydroxyapatite nanocrystals for biomedical applications. *Ceram Int* 2020;46:16020–31.
- [15] Doan VHM, Nguyen VT, Mondal S, Vo TMT, Ly CD, Vu DD, et al. Fluorescence/photoacoustic imaging-guided nanomaterials for highly efficient cancer theragnostic agent. *Sci Rep* 2021;11:15943.
- [16] McNamara K, Tofail SA, Thorat ND, Bauer J, Mulvihill JJ. Biomedical applications of nanoalloys. *Nanoalloys* 2020;381–432.
- [17] Jones RR, Hooper DC, Zhang L, Wolverson D, Valev VK. Raman techniques: fundamentals and frontiers. *Nanoscale Res Lett* 2019;14:1–34.
- [18] Zottel A, Videtic Paska A, Jovcevska I. Nanotechnology meets oncology: nanomaterials in brain cancer research, diagnosis and therapy. *Materials* 2019;12:1588.
- [19] Bansal SA, Kumar V, Karimi J, Singh AP, Kumar S. Role of gold nanoparticles in advanced biomedical applications. *Nanoscale Adv* 2020;2:3764–87.
- [20] Abadeer NS, Murphy CJ. Recent progress in cancer thermal therapy using gold nanoparticles. *Nanomat Neoplasms* 2021;143–217.
- [21] Naik GV, Shalaeve VM, Boltasseva A. Alternative plasmonic materials: beyond gold and silver. *Adv Mater* 2013;25:3264–94.
- [22] Tamayo L, Palza H, Bejarano J, Zapata PA. Polymer composites with metal nanoparticles: Synthesis, properties, and applications. In: Polymer Composites with Functionalized Nanoparticles. Elsevier; 2019. p. 249–86.
- [23] Wang Z, Zhang L, Zhao J, Xing B. Environmental processes and toxicity of metallic nanoparticles in aquatic systems as affected by natural organic matter. *Environ Sci Nano* 2016;3:240–55.
- [24] Augustine R, Hasan A, Primavera R, Wilson RJ, Thakor AS, Kevadiya BD. Cellular uptake and retention of nanoparticles: insights on particle properties and interaction with cellular components. *Mater Today Commun* 2020;25:101692.
- [25] Wanás W, Abd El-Kareem SA, Ebrahim S, Soliman M, Karim M. Cancer bioimaging using dual mode luminescence of graphene/FA-ZnO nanocomposite based on novel green technique. *Sci Rep* 2023;13:27.
- [26] Mondal S, Park S, Vo TH, Choi J, Minh Doan VH, Phan DT, et al. Smart inexpensive quantitative urine glucose and contaminant bromide ion sensor based on metal nanoparticles with deep learning approach. *Mater Chem Phys* 2022;287:126289.
- [27] Mondal S, Montaño-Priede JL, Nguyen VT, Park S, Choi J, Doan VHM, et al. Computational analysis of drug free silver triangular nanoprism theranostic probe plasmonic behavior for in-situ tumor imaging and photothermal therapy. *J Adv Res* 2022;41:23–38.
- [28] Ribeiro AI, Dias AM, Zille A. Synergistic effects between metal nanoparticles and commercial antimicrobial agents: A review. *ACS Appl Nano Mater* 2022;5:3030–64.
- [29] Kuppe C, Rusimova KR, Ohnoutek L, Slavov D, Valev VK. "Hot" in plasmonics: temperature-related concepts and applications of metal nanostructures. *Adv Optical Mater* 2020;8:1901166.
- [30] Lee S, Sim K, Moon SY, Choi J, Jeon Y, Nam JM, et al. Controlled assembly of plasmonic nanoparticles: from static to dynamic nanostructures. *Adv Mater* 2021;33:2007668.
- [31] Abid N, Khan AM, Shujait S, Chaudhary K, Ikram M, Imran M, et al. Synthesis of nanomaterials using various top-down and bottom-up approaches, influencing factors, advantages, and disadvantages: A review. *Adv Colloid Interface Sci* 2022;300:102597.
- [32] Wei Q, Fu Y, Zhang G, Yang D, Meng G, Sun S. Rational design of novel nanostructured arrays based on porous AAO templates for electrochemical energy storage and conversion. *Nano Energy* 2019;55:234–59.
- [33] Baig N. Two-dimensional nanomaterials: A critical review of recent progress, properties, applications, and future directions. In: Composites Part A: Applied Science and Manufacturing; 2022. p. 107362.
- [34] Guillou O, Dash A, Lenser C, Uhlenbruck S, Mauer G. Tuning the microstructure and thickness of ceramic layers with advanced coating technologies using zirconia as an example. *Adv Eng Mater* 2020;22:2000529.
- [35] Meierhofer F, Fritsching U. Synthesis of metal oxide nanoparticles in flame sprays: review on process technology, modeling, and diagnostics. *Energy Fuel* 2021;35:5495–537.
- [36] Mavukkandy MO, McBride SA, Warsinger DM, Dizge N, Hasan SW, Arafat HA. Thin film deposition techniques for polymeric membranes—A review. *J Membr Sci* 2020;610:118258.
- [37] Shi Y, Xu H, Liu T, Zeb S, Nie Y, Zhao Y, et al. Advanced development of metal oxide nanomaterials for H<sub>2</sub> gas sensing applications. *Mater Adv* 2021;2:1530–69.
- [38] Chouke PB, Shrirame T, Potbhare AK, Mondal A, Chaudhary AR, Mondal S, et al. Bioinspired metal/metal oxide nanoparticles: A road map to potential applications. *Mater Today Adv* 2022;16:100314.
- [39] Ahmadi Tehrani A, Omranpoor MM, Vatanara A, Seyedabadi M, Ramezani V. Formation of nanosuspensions in bottom-up approach: theories and optimization. *DARU J Pharmaceut Sci* 2019;27:451–73.
- [40] Baig N, Kammakakan I, Falath W. Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. *Mater Adv* 2021;2:1821–71.
- [41] Harish V, Ansari M, Tewari D, Yadav AB, Sharma N, Bawarig S, et al. Cutting-edge advances in tailoring size, shape, and functionality of nanoparticles and nanostructures: A review. *J Taiwan Inst Chem Eng* 2023;149:105010.
- [42] Simon SM, George G, Sajna M, Prakashan V, Jose TA, Vasudevan P, et al. Recent advancements in multifunctional applications of sol-gel derived polymer incorporated TiO<sub>2</sub>-ZrO<sub>2</sub> composite coatings: A comprehensive review. *Appl Surf Sci Adv* 2021;6:100173.
- [43] Khizar S, Zine N, Errachid A, Jaffrezic-Renault N, Elaissari A. Microfluidic-based nanoparticle synthesis and their potential applications. *Electrophoresis* 2022;43:819–38.
- [44] Morsali A, Hashemi L. Nanoscale coordination polymers: Preparation, function and application. In: Advances in inorganic chemistry. vol. 76. Elsevier; 2020. p. 33–72.
- [45] Malhotra N, Lee J-S, Liman RAD, Ruallo JMS, Villaflorres OB, Ger T-R, et al. Potential toxicity of iron oxide magnetic nanoparticles: a review. *Molecules* 2020;25:3159.
- [46] Liu W, Li X, Wang C, Pan H, Liu W, Wang K, et al. A scalable general synthetic approach toward ultrathin imine-linked two-dimensional covalent organic framework nanosheets for photocatalytic CO<sub>2</sub> reduction. *J Am Chem Soc* 2019;141:17431–40.
- [47] Lee J, Chatterjee DK, Lee MH, Krishnan S. Gold nanoparticles in breast cancer treatment: promise and potential pitfalls. *Cancer Lett* 2014;347:46–53.
- [48] Zhao J, Wallace M, Melancon MP. Cancer theranostics with gold nanoshells. *Nanomedicine* 2014;9:2041–57.
- [49] Anik MI, Mahmud N, Al Masud A, Hasan M. Gold nanoparticles (GNPs) in biomedical and clinical applications: A review. *Nano Select* 2022;3:792–828.
- [50] Harder RA, Wijenayaka LA, Phan HT, Haes AJ. Tuning gold nanostar morphology for the SERS detection of uranyl. *J Raman Spectrosc* 2021;52:497–505.
- [51] Requejo KI, Liopo AV, Zubarev ER. Gold nanorod synthesis with small thiolated molecules. *Langmuir* 2020;36:3758–69.
- [52] Shaker MA, Shaaban MI. Formulation of carbapenems loaded gold nanoparticles to combat multi-antibiotic bacterial resistance: in vitro antibacterial study. *Int J Pharm* 2017;525:71–84.
- [53] Vidya S, Mutualik S, Bhat KU, Huilgol P, Avadhani K. Preparation of gold nanoparticles by novel bacterial exopolysaccharide for antibiotic delivery. *Life Sci* 2016;153:171–9.
- [54] Mahmodin L, Suharyadi E, Utomo ABS, Abraha K. Optical properties of silver nanoparticles for surface plasmon resonance (SPR)-based biosensor applications. *J Modern Phys* 2015;6:1071.
- [55] Cobley CM, Skrabalak SE, Campbell DJ, Xia Y. Shape-controlled synthesis of silver nanoparticles for plasmonic and sensing applications. *Plasmonics* 2009;4:171–9.
- [56] Khodashenas B, Ghorbani HR. Synthesis of silver nanoparticles with different shapes. *Arab J Chem* 2019;12:1823–38.
- [57] Lu Y, Zhang C-Y, Zhang D-J, Hao R, Hao Y-W, Liu Y-Q. Fabrication of flower-like silver nanoparticles for surface-enhanced Raman scattering. *Chin Chem Lett* 2016;27:689–92.
- [58] Khorshidi A, Mardazad N. Flower-like silver nanoparticles: an effective and recyclable catalyst for degradation of rhodamine B with H<sub>2</sub>O<sub>2</sub>. *Res Chem Intermediates* 2016;42:7551–8.

- [59] Lopez-Carizales M, Velasco KI, Castillo C, Flores A, Magaña M, Martinez-Castanon GA, et al. In vitro synergism of silver nanoparticles with antibiotics as an alternative treatment in multiresistant uropathogens. *Antibiotics* 2018;7:50.
- [60] Yuan Y-G, Peng Q-L, Gurunathan S. Effects of silver nanoparticles on multiple drug-resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa* from mastitis-infected goats: an alternative approach for antimicrobial therapy. *Int J Mol Sci* 2017;18:569.
- [61] Neethu S, Midhun SJ, Radhakrishnan E, Jyothis M. Green synthesized silver nanoparticles by marine endophytic fungus *Penicillium polonicum* and its antibacterial efficacy against biofilm forming, multidrug-resistant *Acinetobacter baumannii*. *Microb Pathog* 2018;116:263–72.
- [62] Siritongsuk P, Hongsing N, Thammawithan S, Daduang S, Klaynongsruang S, Tuanyok A, et al. Two-phase bactericidal mechanism of silver nanoparticles against *Burkholderia pseudomallei*. *PLoS One* 2016;11:e0168098.
- [63] Pansara C, Chan WY, Parikh A, Trott DJ, Mehta T, Mishra R, et al. Formulation optimization of chitosan-stabilized silver nanoparticles using in vitro antimicrobial assay. *J Pharm Sci* 2019;108:1007–16.
- [64] Ullah S, Ahmad A, Subhan F, Jan A, Raza M, Khan AU, et al. Tobramycin mediated silver nanospheres/graphene oxide composite for synergistic therapy of bacterial infection. *J Photochem Photobiol B Biol* 2018;183:342–8.
- [65] Namvar F, Rahman HS, Mohamad R, Baharara J, Mahdavi M, Amini E, et al. Cytotoxic effect of magnetic iron oxide nanoparticles synthesized via seaweed aqueous extract. *Int J Nanomedicine* 2014;2479–88.
- [66] Lee W-T, Wu Y-N, Chen Y-H, Wu S-R, Shih T-M, Li T-J, et al. Octahedron iron oxide nanocrystals prohibited Clostridium difficile spore germination and attenuated local and systemic inflammation. *Sci Rep* 2017;7:8124.
- [67] Pan W-Y, Huang G-C, Lin T-T, Hu H-Y, Lin W-C, Li M-J, et al. Synergistic antibacterial effects of localized heat and oxidative stress caused by hydroxyl radicals mediated by graphene/iron oxide-based nanocomposites. *Nanomed Nanotechnol Biol Med* 2016;12:431–8.
- [68] Darroudi M, Sabouri Z, Oskuee RK, Zak AK, Kargar H, Abd Hamid MHN. Green chemistry approach for the synthesis of ZnO nanopowders and their cytotoxic effects. *Ceram Int* 2014;40:4827–31.
- [69] Bayal M, Janardhanan P, Tom E, Chandran N, Devadathan S, Ranjeet D, et al. Cytotoxicity of nanoparticles—are the size and shape only matters? Or the media parameters too?: a study on band engineered ZnS nanoparticles and calculations based on equivolume stress model. *Nanotoxicology* 2019;13:1005–20.
- [70] Ezhilarasu AA, Vijaya JJ, Kaviyarasu K, Maaza M, Ayeshamariam A, Kennedy LJ. Green synthesis of NiO nanoparticles using *Moringa oleifera* extract and their biomedical applications: cytotoxicity effect of nanoparticles against HT-29 cancer cells. *J Photochem Photobiol B Biol* 2016;164:352–60.
- [71] Liu X, Tang J, Wang L, Giesy JP. Al2O3 nanoparticles promote secretion of antibiotics in *Streptomyces coelicolor* by regulating gene expression through the nano effect. *Chemosphere* 2019;226:687–95.
- [72] Ullah AMA, Tamanna A, Hossain A, Akter M, Kabir M, Tareq A, et al. In vitro cytotoxicity and antibiotic application of green route surface modified ferromagnetic TiO<sub>2</sub> nanoparticles. *RSC Adv* 2019;9:13254–62.
- [73] Gurunathan S, Jeyaraj M, Kang M-H, Kim J-H. The effects of apigenin-biosynthesized ultra-small platinum nanoparticles on the human monocytic THP-1 cell line. *Cells* 2019;8:444.
- [74] Khurana C, Chudasama B. Nanoantibiotics: strategic assets in the fight against drug-resistant superbugs. *Int J Nanomedicine* 2018;13:3–6.
- [75] MubarakAli D, Manzoor MA, Sabarinathan A, Devi CA, Rekha P, Thajuddin N, et al. An investigation of antibiofilm and cytotoxic property of MgO nanoparticles. *Biocatal Agric Biotechnol* 2019;18:101069.
- [76] El-Moslamy SH. Bioprocessing strategies for cost-effective large-scale biogenic synthesis of nano-MgO from endophytic *Streptomyces coelicolor* strain E72 as an anti-multidrug-resistant pathogens agent. *Sci Rep* 2018;8:3820.
- [77] Nguyen N-YT, Grelling N, Wetland CL, Rosario R, Liu H. Antimicrobial activities and mechanisms of magnesium oxide nanoparticles (nMgO) against pathogenic bacteria, yeasts, and biofilms. *Sci Rep* 2018;8:16260.
- [78] Hazarika M, Borah D, Bora P, Silva AR, Das P. Biogenic synthesis of palladium nanoparticles and their applications as catalyst and antimicrobial agent. *PLoS One* 2017;12:e0184936.
- [79] Mosallam FM, El-Sayyad GS, Fathy RM, El-Batal AI. Biomolecules-mediated synthesis of selenium nanoparticles using *Aspergillus oryzae* fermented Lupin extract and gamma radiation for hindering the growth of some multidrug-resistant bacteria and pathogenic fungi. *Microb Pathog* 2018;122:108–16.
- [80] Lopes E, Piçarra S, Almeida PL, De Lencastre H, Aires-de-Sousa M. Bactericidal efficacy of molybdenum oxide nanoparticles against antimicrobial-resistant pathogens. *J Med Microbiol* 2018;67:1042–6.
- [81] Jones S, Sinha SS, Pramanik A, Ray PC. Three-dimensional (3D) plasmonic hot spots for label-free sensing and effective photothermal killing of multiple drug resistant superbugs. *Nanoscale* 2016;8:18301–8.
- [82] Marie M, Manoharan A, Kuchuk A, Ang S, Manasreh M. Vertically grown zinc oxide nanorods functionalized with ferric oxide for in vivo and non-enzymatic glucose detection. *Nanotechnology* 2018;29:115501.
- [83] Haldorai Y, Choe SR, Hub YS, Han Y-K. A composite consisting of microporous carbon and cobalt (III) oxide and prepared from zeolitic imidazolate framework-67 for voltammetric determination of ascorbic acid. *Microchimica Acta* 2018;185:1–10.
- [84] Gan T, Shi Z, Wang K, Sun J, Lv Z, Liu Y. Rifampicin determination in human serum and urine based on a disposable carbon paste microelectrode modified with a hollow manganese dioxide@mesoporous silica oxide core-shell nanohybrid. *Can J Chem* 2015;93:1061–8.
- [85] Clasky AJ, Watchorn JD, Chen PZ, Gu FX. From prevention to diagnosis and treatment: biomedical applications of metal nanoparticle-hydrogel composites. *Acta Biomater* 2021;122:1–25.
- [86] Jindal AB. The effect of particle shape on cellular interaction and drug delivery applications of micro-and nanoparticles. *Int J Pharm* 2017;532:450–65.
- [87] Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 2021;20:101–24.
- [88] Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduct Target Ther* 2018;3:7.
- [89] Chenthama D, Subramanian S, Ramakrishnan SG, Krishnaswamy S, Essa MM, Lin F-H, et al. Therapeutic efficacy of nanoparticles and routes of administration. *Biomater Res* 2019;23:1–29.
- [90] Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, et al. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. *Semin Cancer Biol* 2021;69:166–77. Elsevier.
- [91] Singh AP, Biswas A, Shukla A, Maiti P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. *Signal Transduct Target Ther* 2019;4:33.
- [92] Dulńska-Litewka J, Łazarczyk A, Halubiec P, Szafrański O, Karmas K, Karczewicz A. Superparamagnetic iron oxide nanoparticles—current and prospective medical applications. *Materials* 2019;12:617.
- [93] Dunne M, Regenold M, Allen C. Hyperthermia can alter tumor physiology and improve chemo-and radio-therapy efficacy. *Adv Drug Deliv Rev* 2020;163:98–124.
- [94] Ahmed S, Rajak BL, Gogoi M, Sarma HD. Magnetic nanoparticles mediated cancer hyperthermia. In: Smart Healthcare for Disease Diagnosis and Prevention. Elsevier; 2020. p. 153–73.
- [95] Sharma S, Shrivastava N, Rossi F, Thanh NTK. Nanoparticles-based magnetic and photo induced hyperthermia for cancer treatment. *Nano Today* 2019;29:100795.
- [96] Soetaert F, Korangath P, Serantes D, Fiering S, Ivkov R. Cancer therapy with iron oxide nanoparticles: agents of thermal and immune therapies. *Adv Drug Deliv Rev* 2020;163:65–83.
- [97] Safari M. Recent advances in quantum dots-based biosensors. 2022.
- [98] Mondal S, Montaño-Prieto JL, Park S, Choi J, Doan VHM, Vo TMT, et al. Computational analysis of drug free silver triangular nanoprism theranostic probe plasmonic behavior for in-situ tumor imaging and photothermal therapy. *J Adv Res* 2022;41:23–38.
- [99] Manivasagan P, Jun SW, Hoang G, Mondal S, Kim H, Doan VHM, et al. Anti-EGFR antibody conjugated thiol chitosan-layered gold nanoshells for dual-modal imaging-guided cancer combination therapy. *J Control Release* 2019;311:26–42.
- [100] Vaughan TJ, Williams AJ, Pritchard K, Osbourn JK, Pope AR, Earnshaw JC, et al. Human antibodies with sub-nanomolar affinities isolated from a large non-immunized phage display library. *Nat Biotechnol* 1996;14:309–14.
- [101] Zhao Z, Ukidve A, Kim J, Mitragotri S. Targeting strategies for tissue-specific drug delivery. *Cell* 2020;181:151–67.
- [102] Qin M, Singh A, Wang D, Qu J, Swihart M, Zhang H, et al. Biocompatible and biodegradable inorganic nanostructures for nanomedicine: silicon and black phosphorus. *Nano Today* 2019;25:135–55.
- [103] Yang L, Patel KD, Rathnam C, Thangam R, Hou Y, Kang H, et al. Harnessing the therapeutic potential of extracellular vesicles for biomedical applications using multifunctional magnetic nanomaterials. *Small* 2022;18:2104783.
- [104] Li Z, Wang Y, Liu J, Rawding P, Bu J, Hong S, et al. Chemically and biologically engineered bacteria-based delivery systems for emerging diagnosis and advanced therapy. *Adv Mater* 2021;33:2102580.
- [105] Bommakanti V, Banerjee M, Shah D, Manisha K, Sri K, Banerjee S. An overview of synthesis, characterization, applications and associated adverse effects of bioactive nanoparticles. *Environ Res* 2022;113919.
- [106] Manivasagan P, Jun SW, Nguyen VT, Truong NTP, Hoang G, Mondal S, et al. A multifunctional near-infrared laser-triggered drug delivery system using folic acid conjugated chitosan oligosaccharide encapsulated gold nanorods for targeted chemo-photothermal therapy. *J Mater Chem B* 2019;7:3811–25.
- [107] Manivasagan P, Hoang G, Santha Moorthy M, Mondal S, Minh Doan VH, Kim H, et al. Chitosan/fucoidan multilayer coating of gold nanorods as highly efficient near-infrared photothermal agents for cancer therapy. *Carbohydr Polym* 2019;211:360–9.
- [108] Zhang Y, Xu C, Yang X, Pu K. Photoactivatable protherapeutic nanomedicine for cancer. *Adv Mater* 2020;32:2002661.
- [109] Phan TTV, Bui NQ, Cho S-W, Bharathiraja S, Manivasagan P, Moorthy MS, et al. Photoacoustic imaging-guided Photothermal therapy with tumor-targeting HA-FeOOH@PPy Nanorods. *Sci Rep* 2018;8:8809.
- [110] Song S, Shen H, Wang Y, Chu X, Xie J, Zhou N, et al. Biomedical application of graphene: from drug delivery, tumor therapy, to theranostics. *Colloids Surf B Biointerfaces* 2020;185:110596.
- [111] Santha Moorthy M, Hoang G, Subramanian B, Bui NQ, Panchanathan M, Mondal S, et al. Prussian blue decorated mesoporous silica hybrid nanocarriers for photoacoustic imaging-guided synergistic chemo-photothermal combination therapy. *J Mater Chem B* 2018;6:5220–33.
- [112] Liu L, Li Y, Liu R, Shen Q, Li Y, Shi Z, et al. Switchable nanoparticle for programmed gene-chem delivery with enhanced neuronal recovery and CT imaging for neurodegenerative disease treatment. *Materials Horizons* 2019;6:1923–9.
- [113] Sethi B, Kumar V, Mahato K, Coulter DW, Mahato RI. Recent advances in drug delivery and targeting to the brain. *J Control Release* 2022;350:668–87.
- [114] Zhang Y, Wang D, Peng M, Tang L, Ouyang J, Xiong F, et al. Single-cell RNA sequencing in cancer research. *J Exp Clin Cancer Res* 2021;40:1–17.

- [115] Wu L-P, Wang D, Li Z. Grand challenges in nanomedicine. *Mater Sci Eng C* 2020; 106:110302.
- [116] Aengenheister L, Favaro RR, Morales-Prieto DM, Furer LA, Gruber M, Wadsack C, et al. Research on nanoparticles in human perfused placenta: state of the art and perspectives. *Placenta* 2021;104:199–207.
- [117] Woods JC, Wild JM, Welpütz MO, Clancy JP, Hatabu H, Kauczor HU, et al. Current state of the art MRI for the longitudinal assessment of cystic fibrosis. *J Magn Reson Imaging* 2020;52:1306–20.
- [118] Grunwald A. Nanotechnology—A new field of ethical inquiry? The ethics of nanotechnology. In: *Geoengineering, and Clean Energy*. Routledge; 2020. p. 17–31.
- [119] Hou K, Zhao J, Wang H, Li B, Li K, Shi X, et al. Chiral gold nanoparticles enantioselectively rescue memory deficits in a mouse model of Alzheimer's disease. *Nat Commun* 2020;11:4790.
- [120] Zhong Y, Zhang Y, Xu J, Zhou J, Liu J, Ye M, et al. Low-intensity focused ultrasound-responsive phase-transitional nanoparticles for thrombolysis without vascular damage: a synergistic nonpharmaceutical strategy. *ACS Nano* 2019;13: 3387–403.
- [121] Zhong Y, Zhang Y, Xu J, Zhou J, Liu J, Ye M, et al. Low-intensity focused ultrasound-responsive phase-transitional nanoparticles for thrombolysis without vascular damage: A synergistic nonpharmaceutical strategy. *ACS Nano* 2019;13: 3387–403.
- [122] Pan Y, Wang J, Jiang Z, Guo Q, Zhang Z, Li J, et al. Zoledronate combined metal-organic frameworks for bone-targeting and drugs deliveries. *Sci Rep* 2022;12: 12290.
- [123] Liu T, Xiao B, Xiang F, Tan J, Chen Z, Zhang X, et al. Ultrasound copper-based nanoparticles for reactive oxygen species scavenging and alleviation of inflammation related diseases. *Nat Commun* 2020;11:2788.
- [124] Liu Y, Yang G, Jin S, Xu L, Zhao CX. Development of high-drug-loading nanoparticles. *ChemPlusChem* 2020;85:2143–57.
- [125] Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. *J Pharm Pharmacol* 2019;71:1185–98.
- [126] Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K, Tekade RK. Employment of enhanced permeability and retention effect (EPR): nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. *Mater Sci Eng C* 2019;98:1252–76.
- [127] Rana A, Bhatnagar S. Advancements in folate receptor targeting for anti-cancer therapy: A small molecule-drug conjugate approach. *Bioorg Chem* 2021;112: 104946.
- [128] Alipour A, Kalashgarani MY. Nano protein and peptides for drug delivery and anticancer agents. *Adv Appl NanoBio Technol* 2022;3:60–4.
- [129] Anthony DP, Hegde M, Shetty SS, Rafic T, Mutalik S, Rao BS. Targeting receptor-ligand chemistry for drug delivery across blood-brain barrier in brain diseases. *Life Sci* 2021;274:119326.
- [130] Ali ES, Sharkeer SM, Islam MT, Khan IN, Shaw S, Rahman MA, et al. Targeting cancer cells with nanotherapeutics and nanodiagnostics: Current status and future perspectives. In: *Seminars in Cancer Biology*. vol. 69. Elsevier; 2021. p. 52–68.
- [131] Anarjan FS. Active targeting drug delivery nanocarriers: ligands. *Nano Struct Nano Objects* 2019;19:100370.
- [132] Ye QN, Wang Y, Shen S, Xu CF, Wang J. Biomaterials-based delivery of therapeutic antibodies for Cancer therapy. *Adv Healthc Mater* 2021;10:2002139.
- [133] Marques A, Costa P, Velho S, Amaral M. Functionalizing nanoparticles with cancer-targeting antibodies: A comparison of strategies. *J Control Release* 2020; 320:180–200.
- [134] Tewabe A, Abate A, Tamrie M, Seyfu A, Abdela Siraj E. Targeted drug delivery—from magic bullet to nanomedicine: principles, challenges, and future perspectives. *J Multidiscip Healthc* 2021;1711–24.
- [135] Subhan MA, Yalamarty SSK, Filipczak N, Parveen F, Torchilin VP. Recent advances in tumor targeting via EPR effect for cancer treatment. *J Personalized Med* 2021;11:571.
- [136] Cao J, Huang D, Peppas NA. Advanced engineered nanoparticulate platforms to address key biological barriers for delivering chemotherapeutic agents to target sites. *Adv Drug Deliv Rev* 2020;167:170–88.
- [137] Abbasi M, Ghoran SH, Niakan MH, Jamali K, Moeini Z, Jangjou A, et al. Mesoporous silica nanoparticle: heralding a brighter future in cancer nanomedicine. *Microporous and Mesoporous Mater* 2021;319:110967.
- [138] Tee JK, Yip LX, Tan ES, Santitewagun S, Prasath A, Ke PC, et al. Nanoparticles' interactions with vasculature in diseases. *Chem Soc Rev* 2019;48:5381–407.
- [139] Goldberg MS. Improving cancer immunotherapy through nanotechnology. *Nat Rev Cancer* 2019;19:587–602.
- [140] Ikeda-Imafuku M, Wang LL-W, Rodrigues D, Shah S, Zhao Z, Mitragotri S. Strategies to improve the EPR effect: A mechanistic perspective and clinical translation. *J Control Release* 2022;345:512–36.
- [141] Park J, Choi Y, Chang H, Um W, Ryu JH, Kwon IC. Alliance with EPR effect: combined strategies to improve the EPR effect in the tumor microenvironment. *Theranostics* 2019;9:8073.
- [142] Wu J. The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application. *J Personalized Med* 2021;11: 771.
- [143] Luiz MT, Di Filippo LD, Alves RC, Araújo VHS, Duarte JL, Marchetti JM, et al. The use of TPGS in drug delivery systems to overcome biological barriers. *Eur Polym J* 2021;142:110129.
- [144] Finbloom JA, Sousa F, Stevens MM, Desai TA. Engineering the drug carrier biointerface to overcome biological barriers to drug delivery. *Adv Drug Deliv Rev* 2020;167:89–108.
- [145] Sharma D, Arora S, Singh J, Layek B. A review of the tortuous path of nonviral gene delivery and recent progress. *Int J Biol Macromol* 2021;183:2055–73.
- [146] Di J, Gao X, Du Y, Zhang H, Gao J, Zheng A. Size, shape, charge and "stealthy" surface: carrier properties affect the drug circulation time in vivo. *Asian J Pharm Sci* 2021;16:444–58.
- [147] Doan VHM, Mondal S, Vo TMT, Ly CD, Vu DD, Nguyen VT, et al. Fluorescence conjugated nanostructured cobalt-doped hydroxyapatite platform for imaging-guided drug delivery application. *Colloids Surf B Biointerfaces* 2022;214:112458.
- [148] Alavi M, Yarani R. ROS and RNS modulation: the main antimicrobial, anticancer, antidiabetic, and antineurodegenerative mechanisms of metal or metal oxide nanoparticles. *Nano Micro Biosyst* 2023;2:22–30.
- [149] Tong G, Du F, Wu W, Wu R, Liu F, Liang Y. Enhanced reactive oxygen species (ROS) yields and antibacterial activity of spongy ZnO/ZnFe2O4 hybrid micro-hexahedra selectively synthesized through a versatile glucose-engineered co-precipitation/annealing process. *J Mater Chem B* 2013;1:2647–57.
- [150] Wang Z, Tang M. Research progress on toxicity, function, and mechanism of metal oxide nanoparticles on vascular endothelial cells. *J Appl Toxicol* 2021;41: 683–700.
- [151] Rana M, Cho H-J, Arya H, Bhatt TK, Bhar K, Bhatt S, et al. Azo-stilbene and pyridine–amine hybrid multifunctional molecules to target metal-mediated neurotoxicity and amyloid- $\beta$  aggregation in Alzheimer's disease. *Inorg Chem* 2022;61:10294–309.
- [152] Shi Y, Pilozzi AR, Huang X. Exposure of CuO nanoparticles contributes to cellular apoptosis, redox stress, and Alzheimer's A $\beta$  amyloidosis. *Int J Environ Res Public Health* 2020;17:1005.
- [153] Mondal S, Hoang G, Manivasagan P, Moorthy MS, Vy Phan TT, Kim HH, et al. Rapid microwave-assisted synthesis of gold loaded hydroxyapatite collagen nano-bio materials for drug delivery and tissue engineering application. *Ceram Int* 2019;45:2977–88.
- [154] Manivasagan P, Nguyen VT, Jun SW, Hoang G, Mondal S, Kim H, et al. Anti-EGFR antibody conjugated thiol chitosan-layered gold nanoshells for dual-modal imaging-guided cancer combination therapy. *J Control Release* 2019;311:312: 26–42.
- [155] Zhang R, Qin X, Kong F, Chen P, Pan G. Improving cellular uptake of therapeutic entities through interaction with components of cell membrane. *Drug Deliv* 2019; 26:328–42.
- [156] Kardani K, Milani A, H. Shabani S, Bolhassani A.. Cell penetrating peptides: the potent multi-cargo intracellular carriers. *Expert Opin Drug Deliv* 2019;16: 1227–58.
- [157] Van Gheluwe L, Chourpa I, Gaigne C, Munnier E. Polymer-based smart drug delivery systems for skin application and demonstration of stimuli-responsiveness. *Polymers* 2021;13:1285.
- [158] Alavi M, Kowalski R, Capasso R, Douglas Melo Coutinho H, Alencar Rose, de Menezes I. Various novel strategies for functionalization of gold and silver nanoparticles to hinder drug-resistant bacteria and cancer cells. *Micro Nano Bio Aspects* 2022;1:38–48.
- [159] Alavi M, Hamblin MR. Interaction of copper oxide nanoparticles with bacterial nucleic acids: a mini-review. *Micro Nano Bio Aspects* 2023;2:20–5.
- [160] Mammari N, Lamouroux E, Boudier A, Duval RE. Current knowledge on the oxidative-stress-mediated antimicrobial properties of metal-based nanoparticles. *Microorganisms* 2022;10.
- [161] Mammari N, Lamouroux E, Boudier A, Duval RE. Current knowledge on the oxidative-stress-mediated antimicrobial properties of metal-based nanoparticles. *Microorganisms* 2022;10:437.
- [162] Liu Z, Li S, Xia X, Zhu Z, Chen L, Chen Z. Recent advances in multifunctional graphitic nanocapsules for Raman detection, imaging, and therapy. *Small Methods* 2020;4:1900440.
- [163] Hobson NJ, Weng X, Siow B, Veiga C, Ashford M, Thanh NT, et al. Clustering superparamagnetic iron oxide nanoparticles produces organ-targeted high-contrast magnetic resonance images. *Nanomedicine* 2019;14:1135–52.
- [164] Aslan N, Ceylan B, Koç MM, Findik F. Metallic nanoparticles as X-Ray computed tomography (CT) contrast agents: A review. *J Mol Struct* 2020;1219:128599.
- [165] Ansari AA, Parchur AK, Thorat ND, Chen G. New advances in pre-clinical diagnostic imaging perspectives of functionalized upconversion nanoparticle-based nanomedicine. *Coord Chem Rev* 2021;440:213971.
- [166] Xu Y, Rothe R, Voigt D, Hauser S, Cui M, Miyagawa T, et al. Convergent synthesis of diversified reversible network leads to liquid metal-containing conductive hydrogel adhesives. *Nat Commun* 2021;12:2407.
- [167] MacRitchie N, Frleta-Gilchrist M, Sugiyama A, Lawton T, McInnes IB, Maffia P. Molecular imaging of inflammation-current and emerging technologies for diagnosis and treatment. *Pharmacol Ther* 2020;211:107550.
- [168] Perez-Medina C, Teunissen AJ, Kluzza E, Mulder WJ, Van der Meel R. Nuclear imaging approaches facilitating nanomedicine translation. *Adv Drug Deliv Rev* 2020;154:123–41.
- [169] Hu K, Xie L, Zhang Y, Hanyu M, Yang Z, Nagatsu K, et al. Marriage of black phosphorus and Cu $^{2+}$  as effective photothermal agents for PET-guided combination cancer therapy. *Nat Commun* 2020;11:2778.
- [170] Huang J, Pu K. Near-infrared fluorescent molecular probes for imaging and diagnosis of nephro-urological diseases. *Chem Sci* 2021;12:3379–92.
- [171] Semeniak D, Cruz DF, Chilkoti A, Mikkelson MH. Plasmonic fluorescence enhancement in diagnostics for clinical tests at point-of-care: A review of recent technologies. *Adv Mater* 2022;2107986.
- [172] Mantri Y, Jokerst JV. Engineering plasmonic nanoparticles for enhanced photoacoustic imaging. *ACS Nano* 2020;14:9408–22.

- [173] Liu Y, Teng L, Yin B, Meng H, Yin X, Huan S, et al. Chemical design of activatable photoacoustic probes for precise biomedical applications. *Chem Rev* 2022;122: 6850–918.
- [174] Wu J, Williams GR, Zhu Y, Hu T, Wang H, Zhao W, et al. Ultrathin chalcogenide nanosheets for photoacoustic imaging-guided synergistic photothermal/gas therapy. *Biomaterials* 2021;273:120807.
- [175] Chen Y, Wu H, Zhou H, Miao Z, Hong F, Zhao Q, et al. PEGylated indium nanoparticles: A metallic contrast agent for multiwavelength photoacoustic imaging and second near-infrared Photothermal therapy. *ACS Appl Mater Interfaces* 2021;13:46343–52.
- [176] Sarfraz N, Khan I. Plasmonic gold nanoparticles (AuNPs): properties, synthesis and their advanced energy, environmental and biomedical applications. *Chemistry Asian J* 2021;16:720–42.
- [177] Hussain Z. Toward the development of a novel diagnostic Nano-imaging platform for lung Cancer. *Nanotechnology-Based Targeted Drug Delivery Systems for Lung Cancer*. Elsevier; 2019. p. 269–92.
- [178] de la Encarnación C, de Aberasturi DJ, Liz-Marzáñ LM. Multifunctional plasmonic-magnetic nanoparticles for bioimaging and hyperthermia. *Adv Drug Deliv Rev* 2022;114484.
- [179] Yuan H, Liang H, Hou P, Li J. Advanced nanomaterials for multimodal molecular imaging. *Chem Res Chin Univ* 2021;37:840–5.
- [180] Hsu JC, Nieves LM, Betzer O, Sadan T, Noël PB, Popovtzer R, et al. Nanoparticle contrast agents for X-ray imaging applications. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2020;12:e1642.
- [181] Du J, Yang S, Qiao Y, Lu H, Dong H. Recent progress in near-infrared photoacoustic imaging. *Biosens Bioelectron* 2021;191:113478.
- [182] Ilém-Ozdemir D, Gundogdu EA, Ekinci M, Ozgenc E, Asikoglu M. Nuclear medicine and radiopharmaceuticals for molecular diagnosis. In: *Biomedical Applications of Nanoparticles*. Elsevier; 2019. p. 457–90.
- [183] Subasinghe SAS, Pautler RG, Sameer MAH, Yustein JT, Allen MJ. Dual-mode tumor imaging using probes that are responsive to hypoxia-induced pathological conditions. *Biosensors* 2022;12:478.
- [184] Tomitaka A, Kaushik A, Kevadiya BD, Mukadam I, Gendelman HE, Khalili K, et al. Surface-engineered multimodal magnetic nanoparticles to manage CNS diseases. *Drug Discov Today* 2019;24:873–82.
- [185] Jiang Y, Pu K. Molecular probes for autofluorescence-free optical imaging. *Chem Rev* 2021;121:13086–131.
- [186] Cao J, Zhu B, Zheng K, He S, Meng L, Song J, et al. Recent progress in NIR-II contrast agent for biological imaging. *Front Bioeng Biotechnol* 2020;7:487.
- [187] Gopalan D, Pandey A, Udupa N, Mutualik S. Receptor specific, stimuli responsive and subcellular targeted approaches for effective therapy of Alzheimer: role of surface engineered nanocarriers. *J Control Release* 2020;319:183–200.
- [188] Mondal S, Nguyen VT, Park S, Choi J, Tran LH, Yi M, et al. Bioactive, luminescent erbium-doped hydroxyapatite nanocrystals for biomedical applications. *Ceram Int* 2020;46:16020–31.
- [189] Mohamed NA, Marei I, Crovella S, Abou-Saleh H. Recent developments in nanomaterials-based drug delivery and upgrading treatment of cardiovascular diseases. *Int J Mol Sci* 2022;23:1404.
- [190] Liu J, Léucy T, Seguin J, Mignet N, Scherman D, Viana B, et al. Imaging and therapeutic applications of persistent luminescence nanomaterials. *Adv Drug Deliv Rev* 2019;138:193–210.
- [191] Mondal S, Nguyen VT, Park S, Choi J, Thien Vo TM, Shin JH, et al. Rare earth element doped hydroxyapatite luminescent bioceramics contrast agent for enhanced biomedical imaging and therapeutic applications. *Ceram Int* 2020;46: 29249–60.
- [192] Phan TTV, Hoang G, Nguyen VT, Nguyen TP, Kim HH, Mondal S, et al. Chitosan as a stabilizer and size-control agent for synthesis of porous flower-shaped palladium nanoparticles and their applications on photo-based therapies. *Carbohydr Polym* 2019;205:340–52.
- [193] Ge J, Zhang Q, Zeng J, Gu Z, Gao M. Radiolabeling nanomaterials for multimodality imaging: new insights into nuclear medicine and cancer diagnosis. *Biomaterials* 2020;228:119553.
- [194] Im GH, Kim SM, Lee D-G, Lee WJ, Lee JH, Lee IS. Fe<sub>3</sub>O<sub>4</sub>/MnO hybrid nanocrystals as a dual contrast agent for both T1- and T2-weighted liver MRI. *Biomaterials* 2013;34:2069–76.
- [195] Datta R, Heaster TM, Sharick JT, Gillette AA, Skala MC. Fluorescence lifetime imaging microscopy: fundamentals and advances in instrumentation, analysis, and applications. *J Biomed Opt* 2020;25:071203.
- [196] Aminabad NS, Farshbaf M, Akbarzadeh A. Recent advances of gold nanoparticles in biomedical applications: state of the art. *Cell Biochem Biophys* 2019;77: 123–37.
- [197] Tan P, Chen X, Zhang H, Wei Q, Luo K. Artificial intelligence aids in development of nanomedicines for cancer management. In: *Seminars in Cancer Biology*. Elsevier; 2023.
- [198] Keerthi M, Boopathy G, Chen S-M, Chen T-W, Lou B-S. A core-shell molybdenum nanoparticles entrapped f-MWCNTs hybrid nanostructured material based non-enzymatic biosensor for electrochemical detection of dopamine neurotransmitter in biological samples. *Sci Rep* 2019;9:13075.
- [199] Saxena U, Das Asim B. Nanomaterials towards fabrication of cholesterol biosensors: key roles and design approaches. *Biosens Bioelectron* 2016;75: 196–205.
- [200] Kurbanoglu S, Ozkan SA, Merkoç A. Nanomaterials-based enzyme electrochemical biosensors operating through inhibition for biosensing applications. *Biosens Bioelectron* 2017;89:886–98.
- [201] Toupanaki DK, Margaroni M, Prapas A, Karagouni E. Development of a nanoparticle-based lateral flow strip biosensor for visual detection of whole nervous necrosis virus particles. *Sci Rep* 2020;10:6529.
- [202] Milan J, Niemczyk K, Kus-Liśkiewicz M. Treasure on the earth—gold nanoparticles and their biomedical applications. *Materials* 2022;15:3355.
- [203] Anik MI, Hossain MK, Hossain I, Mahfuz A, Rahman MT, Ahmed I. Recent progress of magnetic nanoparticles in biomedical applications: A review. *Nano Select* 2021;2:1146–86.
- [204] Elahi N, Rizwan M. Progress and prospects of magnetic iron oxide nanoparticles in biomedical applications: A review. *Artif Organs* 2021;45:1272–99.
- [205] Cardoso VF, Francesco A, Ribeiro C, Bañobre-López M, Martins P, Lanceros-Mendez S. Advances in magnetic nanoparticles for biomedical applications. *Adv Healthc Mater* 2018;7:1700845.
- [206] Coyne DW. Ferumoxytol for treatment of iron deficiency anemia in patients with chronic kidney disease. *Expert Opin Pharmacother* 2009;10:2563–8.
- [207] Schwenk MH. Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease. *Pharmacother J Human Pharmacol Drug Ther* 2010;30:70–9.
- [208] Hood SA, O'Brien M, Higgins R. The safety of intravenous iron dextran (Dexferrum [R]) during hemodialysis in patients with end stage renal disease. *Nephrol Nurs J* 2000;27:41–3.
- [209] Lim E-A, Sohn H-S, Lee H, Choi S-E. Cost-utility of ferric carboxymaltose (Ferinject®) for iron-deficiency anemia patients with chronic heart failure in South Korea. *Cost Effect Resource Allocation* 2014;12:1–10.
- [210] Fütterer S, Andrusenko I, Kolb U, Hofmeister W, Langguth P. Structural characterization of iron oxide/hydroxide nanoparticles in nine different parenteral drugs for the treatment of iron deficiency anaemia by electron diffraction (ED) and X-ray powder diffraction (XRPD). *J Pharm Biomed Anal* 2013;86:151–60.
- [211] Germain M, Caputo F, Metcalfe S, Tosi G, Spring K, Åslund AK, et al. Delivering the power of nanomedicine to patients today. *J Control Release* 2020;326: 164–71.
- [212] Auerbach M, Pappadakis JA, Bahrain H, Auerbach SA, Ballard H, Dahl NV. Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. *Am J Hematol* 2011;86:860–2.
- [213] Wang Y-XJ, Hussain SM, Krestin GP. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. *Eur Radiol* 2001;11:2319–31.
- [214] Gil PR, Hühn D, del Mercato LL, Sasse D, Parak WJ. Nanopharmacy: inorganic nanoscale devices as vectors and active compounds. *Pharmacol Res* 2010;62: 115–25.
- [215] Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MdP, Acosta-Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol* 2018;16:1–33.
- [216] Shan X, Gong X, Li J, Wen J, Li Y, Zhang Z. Current approaches of nanomedicines in the market and various stage of clinical translation. *Acta Pharmaceutica Sinica B* 2022;12:3028–48.