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REVIEW PAPER

The state of the art metal nanoparticles in drug delivery systems: A comprehensive review

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ABSTRACT

There has been a growing curiosity and enthusiasm surrounding recent advancements in nanotechnology, electromagnetism, and optics. This interdisciplinary collaboration encompasses fields such as nanomaterials, nanoelectronics, and nanobiotechnology, which often overlap in their applications. One area that has attracted significant attention is the use of metal nanoparticles (MNPs), which has resulted in notable advancements in medicine. MNPs hold the promise of significantly boosting drug delivery efficacy, reducing unwanted side effects, and enhancing delivery precision. They also have applications in diagnostics, the development of biocompatible materials, and the exploration of nutraceuticals. Using metal nanoparticles in drug delivery provides benefits such as increased stability, prolonged circulation time, enhanced distribution, and precise targeting. The field of nanobiotechnnolgy has facilitated the creation of eco-friendly approaches, referred to as green synthesis, for the production of MNPs. MNPs offer improved stability and targeted release in drug delivery, while also providing a more sustainable alternative to chemical synthesis. This review aims to address the challenges and prospects of utilizing MNPs in drug delivery, with a specific focus on sustainable approaches for fabricating and modifying metal nanocarriers. It also explores the application of various MNPs in drug delivery systems (DDSs).

Keywords: *Antibacterial activity, Drug delivery systems, Green synthesis, Metallic nanoparticles, Nanosystems*

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INTRODUCTION

Nanotechnology, a swiftly advancing field, has achieved notable progress across diverse scientific areas like biology, chemistry, physics, medicine, and pharmacy [1]. In response to increasing concerns about the environment, there has been a shift towards green chemistry and the development of environmentally friendly biological methods for creating nanoparticles [2-4].

However, the biological synthesis of metal nanoparticles presents challenges in complexity, time consumption, and cost. Achieving successful cultivation of cells and purification of nanoparticles under sterile conditions requires expertise in technology and practical microbiology [5-8]. Both metallic and nonmetallic nanoparticles possess distinct characteristics that make them valuable in various biological and therapeutic applications [9]. The small size of metallic nanoparticles enables them to interact precisely with biomolecules on the surface and within cells, allowing for precise targeting [10].

Magnetic materials, specifically, possess distinctive properties among nanoparticles and are extensively utilized in the field of biomedicine. Extensive research has focused on magnetic nanoparticles with external diameters smaller than 100 nm, which can be categorized into two groups: metals and their compounds, including alloys, oxides, and ferrites [11].

Iron (II, III) oxide nanoparticles, commonly referred to as magnetite (Fe_3O_4), have generated substantial interest. Magnetite stands out from other iron oxides due to its composition of both divalent (Fe^{2+}) and trivalent (Fe^{3+}) iron ions. In magnetite, the octahedral site comprises a combination of Fe^{2+} and Fe^{3+} ions surrounded by six oxygen atoms, while the tetrahedral site consists solely of Fe^{3+} ions surrounded by four oxygen atoms. Importantly, magnetite demonstrates both ferromagnetic properties and remarkable

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electrical conductivity [12, 13].

Nanostructured DDSs have revolutionized chemotherapy by addressing the limitations of conventional methods. These systems allow for the control of drug properties, such as release profile and solubility, resulting in improved drug quality and reduced side effects [14]. Nanostructured materials, with their organelle-like size, facilitate effective uptake by cells and targeted delivery of drugs [15]. Biologically synthesized metal nanoparticles are versatile for drug delivery, encapsulating hydrophilic and hydrophobic drugs for various therapeutic uses. They can enhance chemotherapy by targeting cancer cells and minimizing damage to healthy tissues, including the heart [16, 17]. In summary, nanostructured DDSs have demonstrated effectiveness in reducing side effects, improving drug efficacy, and enhancing patient response to treatment. Ongoing research aims to refine these methods further and explore new possibilities for targeted and controlled drug delivery in disease treatment [18-20]. MNPs have attracted considerable attention because of their remarkable optical properties, notably surface plasmon resonance (SPR), enabling precise light manipulation. This unique characteristic puts them as highly desirable candidates for an extensive variety of health care activities (Fig. 1).

Surface modifications could improve pharmacokinetics, and recent findings suggest that noninvasive drug delivery methods have the potential to target brain malignancies [21-23]. Researchers are exploring MNPs as drug carriers to enhance cancer therapy outcomes by improving specificity and targeting brain tumors effectively while minimizing side effects. Smart drug delivery systems are being developed to precisely deliver treatments to tumor sites based on their unique features, reducing impact on healthy tissues [24].

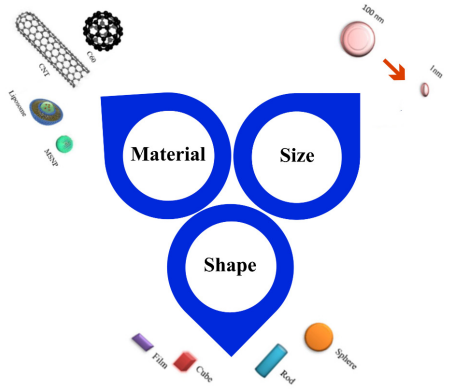

Fig. 1. The dimensions, morphology, composition of the nanoparticles

MNPs are essential for linking targeting agents to specific disease locations, enabling accurate drug delivery while minimizing adverse effects. Their extensive surface area holds potential for therapeutic use in cancer, diabetes, inflammation, antiviral therapy, and cellular-level diagnostics and treatments [25-27].

This study explores different methods for producing MNPs, encompassing physical, chemical, and biological techniques. It highlights the unique characteristics of MNPs that render them suitable for medical purposes like surface alteration and precise drug delivery to cancer cells. The research also addresses challenges and prospects for the clinical adoption and FDA endorsement of nanoparticle-driven therapies, emphasizing the significance and versatility of MNPs in diverse applications.

Methods of synthesizing MNPs

Nanoparticles can be synthesized through two primary methods: top-down and bottom-up. Top-down involves reducing larger particles using ultrasonic energy or dispersing metal vapor, while bottom-up entails gradual atom or nanostructure formation through supersaturation and nucleation [29]. Various techniques like chemical reduction, microemulsions, thermal decomposition, and sonochemical synthesis have been explored, but they may pose environmental concerns due to high temperatures and potential harm to organisms [30]. Researchers are now focusing on eco-friendly composite nanomaterials, with plant-based sources like roots, fruits, leaves, stems, and flowers emerging as sustainable options for MNP production [31]. This approach is simple, rapid, and efficient, offering advantages over traditional methods and aligning with sustainable chemistry principles by prioritizing environmental compatibility and reducing the use of toxic substances [32]. Plant-based nanotechnology is gaining traction in fields such as nanomedicine and drug delivery systems, leveraging natural plant compounds with established medicinal histories [33].

MNP synthesis

Generally, the synthesis of MNP can be categorized into three groups: physical methods, chemical methods, and biological/microbial approaches. Fig. 2 clarifies this particular category,

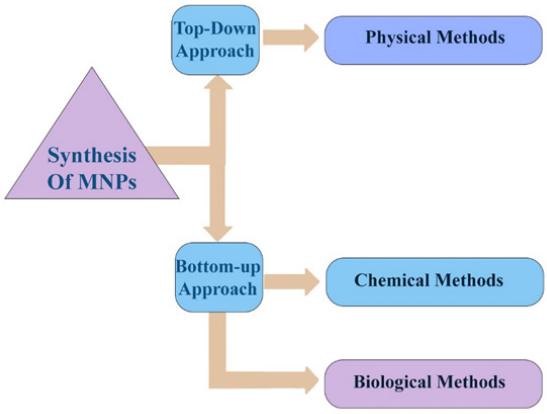

Fig. 2. Classification of synthesis methods for MNPs and their key features

and the subsequent section provides a brief explanation of each specific method employed [34].

Physical methods of synthesis

Mechanical milling

Mechanical milling is a straightforward and efficient method for manufacturing metal nanoparticle (MNP) powders. This process finds extensive applications in the synthesis of various materials using different starting chemicals, and it is especially effective in creating metallic granular alloys. Different mill types, such as shaker mills and planetary mills, can be employed for mechanical milling. The production of MNPs through mechanical milling is regulated by various parameters [35].

Electron beam lithography

Electron beam lithography utilizes an electron beam (e-beam) to convert iron particles into iron oxides (Fe_3O_4). This intricate technique involves precisely guiding the e-beam across a surface that is coated with iron particles, resulting in the creation of nanoscale iron oxide nanoparticles. Electron beam lithography is generally regarded as a cost-effective technology for manufacturing durable NPs, while also offering excellent flexibility for various applications [36].

Gas-phase deposition

The gas phase deposition method is a commonly used technique for researching the synthesis of metal nanoparticles. In this method, molecular precursors, covered in a layer of gold, are deposited onto an alumina substrate. This technique is known for its cost-effectiveness and efficiency in nanoparticle synthesis [37].

Vapour deposition and patterning

Magnetic particles can be produced during the gas-phase deposition process by generating a smooth layer and filling vacancies in a given model. Several vapor deposition processes such as laser ablation, sputtering, evaporation, and electrodeposition are used to deposit the required material in order to create these particles. This approach has been proven to have the capability of producing nanoparticles of exceptional quality [38].

Electrical explosion of wires

In this technique, a metallic wire is vaporized by applying a strong electric current. The metal nanoparticles produced using this method exhibit remarkable purity and a unique spherical arrangement. This methodology offers significant advantages as it not only demonstrates an environmentally friendly approach, but also ensures no harmful effects on the surrounding environment [39].

Chemical methods of synthesis

Spray pyrolysis

In this method, the reactor is utilized for converting the solution into a gaseous state. As the solution undergoes this transformation, the resultant droplets slowly solidify and develop into solid particles, assisted by elevated temperatures. By employing this approach, it becomes possible to obtain metal nanoparticles with enhanced magnetic and photocatalytic properties [40].

Laser pyrolysis

In this approach, the carbon dioxide laser emits thermal energy, which then permeates the surrounding atmosphere, enabling the gases to intermingle. This technique enhances the morphological characteristics of nanoparticles while also simultaneously augmenting the crystal structure and electrical conductivity [41].

Co-precipitation

The co-precipitation approach is widely recognized as the most effective and precise method for producing superparamagnetic iron oxide nanoparticles (SPIONs) with an average size of less than 50 nm. This process involves chemical reactions occurring in a homogeneous aqueous solution, where controlled growth and production

of uniform iron hydroxide particles are vital. The magnetism properties of MNPs are also influenced by the temperature at which they are annealed. Albalah et al. found that annealing temperatures between 900 and 1000°C yield the most promising results [42].

Thermal decomposition

In this method, it is crucial to operate within the temperature range of 150 to 300 °C. Utilizing organic solvents with a high boiling point enhances the efficiency of the process. Additionally, these solvents ideally exhibit a boiling temperature ranging from 250 to 300 °C. Numerous researchers have accomplished the synthesis of metal nanoparticles with superior quality using this technique [43].

Microemulsion

In this approach, for instance, two distinct fluids, water and oil, exhibit non-mixing behavior. Microemulsions essentially depict a balanced dispersion in which two (immiscible) liquids coexist within a single phase while remaining stable. By utilizing microemulsions, it becomes possible to effectively dissolve liquids that inherently resist combination due to their thermodynamic stability and considerable surface area. Furthermore, this technique enables precise monitoring of the structure and morphology of the particles [44].

Hydrothermal/solvothermal method

This technique utilizes a high temperature of 200°C and a high pressure exceeding 13790 kPa to produce magnetic nanoparticles. The role of temperature in this process is critical, as it leads to the contraction of the particles. The hydrothermal method enables effective control and observation of the intricate structures, particle size, and overall shape of nanoparticles [42].

Sol-gel method

Initially, the molecules undergo a transformation, forming a sol within an aqueous solution. Subsequently, during the condensation and polymerization stage, they come together to create a gel structure, forming a connected network. If a crystalline arrangement is required, extra heat must be added during this process. This method allows for altering the chemical composition to adapt to any modifications in the reaction kinetics, serving a significant purpose [43].

Polyol method

This technique effectively prevents nanoparticles from clustering, which results in a highly crystalline structure. It provides a viable alternative to the sol-gel method and is commonly utilized in medical imaging applications. Additionally, the addition of a surfactant in this technique impacts the surface charge of the nanoparticles [44].

Non-thermal plasma methods

In this particular approach, the bond between functional groups and material surfaces is enhanced. Moreover, this technique is acknowledged as a sustainable methodology. Ions and electrons, which play an active role in this interaction, are produced through the plasma process. The utilization of gas energy in this procedure is substantial, as the gas temperature surpasses 4000 Kelvin [40-42].

Biological methods

The primary objective of green nanotechnology is to restore the environment to its natural state using these methods[43]. Extensive research has been conducted on the biocompatibility of MNPs, specifically zero-valent iron, magnetite, and maghemite. Microbes and plants, owing to their genetic variability and the presence of specific enzymes, offer a range of pathways for MNP production. Microorganisms are capable of producing inorganic compounds both internally and externally, typically on a nanoscale and with distinct morphological characteristics. Additionally, plant components such as extracts, barks, tissues, and exudates have emerged as viable options for generating metal nanoparticles [44-46]. These techniques offer several advantages, including higher yield, improved reproducibility and scalability, and greater control over particle size [47].

Traditional methods for synthesizing MNPs are in need of more sustainable and environmentally friendly manufacturing strategies. This need arises from concerns regarding the use of dangerous chemicals, excessive energy consumption, and the production of hazardous waste. In order to tackle these challenges, experts are actively exploring alternative methods that are more environmentally friendly and promote sustainability [48]. One approach currently under investigation is green synthesis, which involves using natural or ecologically friendly reducing agents, such as plant extracts, biomolecules, or

microbes, to create MNPs. This strategy seeks to reduce or eliminate the use of toxic chemicals, thereby minimizing the generation of hazardous waste. Another method being researched is microwave-assisted synthesis, which utilizes microwave irradiation to expedite the synthesis process of MNPs [49]. Microwave assistance offers several advantages, including reduced reaction times, improved energy efficiency, and greater control over particle size and shape. Additionally, electrochemical synthesis is being examined as a sustainable means of producing MNPs[50]. Scientists are exploring environmentally friendly methods for manufacturing MNPs, including green synthesis, microwave-assisted synthesis, and electrochemical synthesis, to minimize environmental harm and enhance sustainability. The aim is to unlock the full potential of MNPs in biological applications while reducing their ecological footprint [51].

Synthesis of MNPs from biological source

From bacteria and actinomycetes

Certain bacteria and actinomycetes have the remarkable ability to transform toxic metal ions into harmless nanoparticles [52]. This unique capability makes them highly valuable for nanoparticle synthesis, as they offer efficient and precise control over the process. For example, *Streptacidiphilus durhamensis* HGG16n has been employed to produce silver nanoparticles ranging in size from 8 to 48 nm [53]. *Bacillus endophytes* and *Deinococcus radiodurans* have demonstrated the capacity to generate silver nanoparticles, while *Pseudomonas stutzeri* AG259 uses NADH-linked reductase for the synthesis of larger silver nanoparticles. *Pseudomonas aeruginosa* can also create various nanoparticles intracellularly, including Pd, Ag, Rh, Ni, Fe, Co, Pt, and Li nanoparticles [54]. Researchers are focusing on synthesizing nanoparticles like palladium, platinum, and tellurium. Palladium and platinum nanoparticles in the size range of 2 to 7 nm have been successfully produced using PV-4 and *Shewanella loihica. Bacillus subtilis* from gold mines has the ability to generate silver nanoparticles with high activity against gold ion toxicity. Actinomycetes like *Rhodococcus actinomyces* and *Streptacidiphilus durhamensis* have been utilized for silver nanoparticle synthesis. Actinomycetes such as *Streptomyces griseoruber* and *Streptomyces capillispiralis* [55].

From fungi and yeast

The use of fungi for nanoparticle synthesis provides a simple and effective method. Fungi, in comparison to bacteria, demonstrate higher tolerance and activity towards iron [53]. They also have the ability to accumulate metal ions, resulting in the production of fine nanoparticles. For instance, at a temperature of 30 °C, Trichoderma viride rapidly generates gold nanoparticles (AuNPs) that exhibit catalytic properties and potent antibacterial effects [54]. Meituku et al. successfully fabricated well-dispersed and stable nanoparticles utilizing white rot fungi and Schizophyllum [54]. Candida albicans extract has been employed to prepare highly crystalline gold and silver nanoparticles that have a uniform size distribution [52]. The marine fungus *Aspergillus terreus* has been utilized to synthesize selenium nanoparticles (SeNPs) ranging in size around 500 nm. Kitchin et al. described the *in vitro* creation of gold nanoparticles using *Rhizopus oryzae*, with potential applications in biomedicine and biocatalysis [38]. Yeasts can collect and accumulate harmful metallic ions via the surroundings [54]. Wagmeier et al. have successfully synthesized silver nanoparticles using Candida utilis NCIM 3469, resulting in spherical nanoparticles ranging in size from 20 to 80 nm. These nanoparticles exhibit antibacterial properties against infections such as *Staphylococcus aureus* [11]. In a 2016 study conducted by Eugenio et al., the yeast Candida lusitaniae was isolated from a bacterial gut and shown to produce silver nanoparticles ranging in size from 2 to 10 nm [55].

From virus

Bacteria have become useful instruments in nanotechnology, facilitating the synthesis of nanoconjugates and nanotechnology using nanoparticles of metal. These nanoparticles have numerous potential in delivering medications and prevention of cancer. Bacterial kind' specific structural characteristics and steady metabolism make them safe, easy to cultivate, and not harmful for human organisms [56]. Cao et al. used the red clover necro mosaic viruses to produce nanoparticles with regulated DOX release in tumor therapy. Similarly, Le et al. investigated the use of potato-associated virus X particles as carriers to deliver doxorubicin in the treatment of cancer. The results of this study highlight the exciting possibilities of bacterial-based nanotechnology in

Table 1. Microbe-engineered nanoparticles

Sample	Size	Metal	Ref.
Fusarium oxysporum	20–40	Au	[12]
Shewanella loihica PV-4	2–7	Pd, Pt	[53]
Rhizopus oryzae	----	Au	[44]
Candida lusitaniae	2–10	Ag	[53]
Pseudomonas stutzeri AG259	200	Ag	[8]
Vibrio alginolyticus	50–100	Ag	[17]
Candida albicans	60–80	Ag	[35]
Rhodopseudomonas capsulata	10–20	Au	[49]
actinobacteria, Streptacidiphilus durhamensis	8–48	Ag	[29]
Pseudomonas aeruginosa	----	Pd, Ag, Rh, Ni, Fe, Co, Pt, Li	[13]
actinobacteria Rhodococcus NCIM 2891	10	Ag	[50]
Streptomyces griseoruber, Streptomyces capillispiralis Ca-1	----	Cu	[51]
Schizophyllum radiatum	----	Ag	[52]
Candida utilis NCIM 3469	20-80	Ag	[54]

medicines (Table 1) [53].

From plants (Toxicity of green nanoparticle)

Plants contain bioactive compounds such as alkaloids, flavonoids, and phenolic acids that act as reducing agents, anti-inflammatory agents, and stabilizers for the synthesis of MNPs. The process of MNPs synthesis involves activation, thermodynamic stability, and removal steps. The concentration of plant extracts, as well as temperature and pH, affect the properties and size of the resulting nanoparticles [57]. Researchers have successfully synthesized silver nanoparticles (AgNPs) using an extract from ragweed leaves, which is rich in other bioactive compounds. The size and shape of nanoparticles, such as copper nanoparticles (CuNPs), can vary from 5 to 25 nm and form different structures depending on the reaction temperature [58]. pH also plays a crucial role in determining the shape and size of nanoparticles. For example, when *Rhodopsudomonas* capsules were used to synthesize gold nanoparticles (AuNPs) at a pH of 7, they had a spherical shape. However, changing the pH to 4 resulted in the formation of nanoplates, as demonstrated in a study by He et al [59]. A further significant factor influencing nanoparticle dimensions and forms is time of exposure. Raising the biological response rate may minimize the size and width of the composite nanoparticles (Table 2) [60].

Table 2. Plant-derived environmentally friendly nanoparticles

Plant	Size (nm)	Metal	Ref.
Andrographis paniculata	40-60	Ag	[13]
Brassica oleracea	36.00	Ag	[50]
Camellia sinensis	9-17.5	ZnO	[51]
Sapium sebiferum	2-14	pd	[52]
Spinacia oleracea	40.90	ZnO	[54]
Alternanthera dentate	50-100	Ag	[13]
Euphorbia nivulia	----	CuO	[50]

Synthesis of greener MNPs approach (Green synthesis)

The incorporation of green chemistry principles into sustainable development has received significant attention in the past 15 years. When producing nanomaterials, three key factors to consider are the use of environmentally friendly solvents, ensuring worker safety, and minimizing environmental impact. Traditional pharmaceutical processes frequently require expensive and toxic chemicals, but biosynthetic methods have developed as an appropriate and ecologically acceptable approach to nanoparticle synthesis for clinical purposes [54]. Researchers from around the world are actively collaborating to develop green nanotechnology techniques that can produce non-toxic and beneficial products. Nanoparticles have minimal toxicity, high compatibility, and biodegradability, making them highly promising in the fields of biology and medicine [52]. Metal nanoparticles, in particular, demonstrate diverse targeting and response mechanisms, enabling them to infiltrate the human body, bind to nucleic acids, and modulate cellular functions [55]. Despite the advantages of green nanoparticle synthesis methods, there are limitations. For example, plant extracts cannot be genetically engineered to selectively produce specific nanoparticles. To overcome these limitations and enhance future productivity, researchers are exploring collaborations with plant genetics to unlock the full potential of green

nanotechnology [50].

Plant extracts such as *turmeric*, *aloe vera*, *green tea*, *neem*, and *grape* are used in green synthesis to reduce and stabilize nanoparticles during the synthesis process. The nanoparticles created have unique characteristics depending on the particular plant extract used. For example, silver nanoparticles derived from *turmeric* extract have strong antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* infections[56]. They also have antioxidant and anti-inflammatory effects. On the other hand, gold nanoparticles produced from aloe vera extract have significant antioxidant activity and could potentially be used in wound treatment. Furthermore, they exhibit antibacterial properties against various bacteria and fungi [57].

The use of *green tea* extract in the synthesis of silver nanoparticles has produced remarkable antibacterial properties against both Gram-positive and Gram-negative bacteria. Additionally, these silver nanoparticles have antioxidant capabilities and show promise in cancer treatment due to their cytotoxic effects on cancer cells[58]. In contrast, neem extract has been used in the production of zinc oxide nanoparticles that exhibit significant antibacterial activity against various diseases. Furthermore, these nanoparticles have anti-inflammatory and antioxidant properties and are effective at eliminating mosquito larvae, making them suitable for vector control applications [59]. Grape extract has been employed in the manufacturing of silver nanoparticles that possess antioxidant activity and show potential for wound healing. These nanoparticles also have antibacterial properties against various infections, including *methicillin-resistant Staphylococcus aureus* (MRSA). Green synthesis, which harnesses the unique characteristics of these plant extracts, offers a sustainable and environmentally friendly method of nanoparticle production. This method holds promise in multiple sectors, including health and environmental science [60].

Plant-based green synthesis

Plant-based green synthesis is a rapidly developing and highly promising technology for the production of metal nanoparticles. This innovative approach harnesses the natural reducing properties of plant extracts to transform metal ions into MNPs, offering notable advantages compared to traditional synthesis methods [61].

Streamlined procedure

The technique of plant-based green synthesis is simple and straightforward. It involves the combination of metallic salts with extracts produced from various plant components, such as leaves, stems, and seeds. The reducing agents contained in these plant extracts help in lowering the concentration of metal ions, resulting in the creation of MNPs [62].

Eco-friendliness

One significant advantage of using plant-based green synthesis is its environmental sustainability. Unlike traditional synthesis processes, which frequently include toxic chemicals, this methodology makes use of natural and renewable resources. Plant extracts work as reducing agents, avoiding the need for dangerous chemicals and reducing the production of harmful waste materials [63].

Biocompatibility

MNPs generated utilizing plant-based green techniques have exceptional biocompatibility. Using plant extracts guarantees that MNPs are devoid of toxic residues or pollutants, making them suitable for a wide range of biological applications, including drug delivery, imaging, and diagnostics [64].

Fine regulation of size and form

Using plant-based green synthesis techniques provides for fine control over the size and form of the MNPs produced. Scientists can acquire desired MNP properties by altering parameters such as metal salt concentration, pH levels, temperature, and reaction length. This control is critical for tailoring the features of MNPs to specific applications [65].

Cost-effectiveness

Plant-based green synthesis is a cost-effective method for producing MNPs. Plant extracts are readily available, and the synthesis process does not require costly equipment or complex techniques. As a result, plant-based synthesis provides an enticing alternative to existing methods, especially for large-scale manufacturing [66].

Adaptability

Plant-based green synthesis is applicable to an extensive variety of metals, including iron, gold,

copper, silver and gold. This versatility allows for the development of several types of MNPs with diverse properties and prospective applications. To summarize, plant-based green synthesis is a potential and emerging strategy to producing MNPs [67].

It has various advantages, including simplicity, environmental friendliness, compatibility with biological systems, exact control over size and shape, cost-effectiveness, and flexibility. As scientists refine and perfect this technique, it is predicted to have a substantial influence on the development of sustainable and environmentally friendly methods for MNP synthesis, particularly in biomedical applications [68].

Unique properties of metal nanoparticles (MNPs) for biomedical applications

Due to their exceptional qualities, metal nanoparticles serve as excellent options for various biomedical applications, such as delivering medications, conducting imaging procedures, and aiding in medical diagnoses. These remarkable attributes can be succinctly encapsulated as follows:

Enhanced surface area

Due to their miniature dimensions, magnetic nanoparticles (MNPs) possess a remarkable ratio of surface area to volume. This substantial surface area offers ample prospects for the incorporation and tailoring of medications. Consequently, it significantly amplifies drug loading efficiency and facilitates more potent engagements with biological molecules. Ultimately, this leads to precise drug administration and enhances the overall therapeutic results [69].

Magnetic nanoparticles

MNPs, particularly gold and silver nanoparticles, have a unique phenomenon known as SPR. Once electrically conducting electrons inside MNPs are exposed to light, they vibrate in unison, a phenomenon known as SPR. These MNPs use the SPR phenomenon to scatter and absorb light at different wavelengths, which makes them very useful in imaging, photothermal therapy, and biosensing, among other uses [70].

Optical attributes

MNPs have distinct visual features due to their size and shape. Gold nanoparticles, for example, can display a variety of vibrant colors depending on their size and structure, a phenomenon known as localized surface plasmon resonance (LSPR). These optical properties have tremendous potential for use in imaging, biosensing, and therapeutic applications [61].

Magnetic response

MNPs, like iron oxide nanoparticles, have intrinsic magnetic characteristics that allow them to respond to external magnetic fields. This distinguishing feature enables precise control and guiding of MNPs to specific parts of the body. The application of an external magnetic field directs MNPs to the desired location, enhancing medicine concentration in the targeted area while reducing systemic adverse effects [64].

Surface modification

MNPs have an amazing ability to change their surface to satisfy the needs of various biomedical applications. Attaching functional groups to the surface of MNPs, such as polymers, peptides, or targeting ligands, allows for precision medication delivery to desired regions or specific interactions with biological components. Furthermore, these surface changes can improve biocompatibility, stability, and inhibit MNP aggregation, ensuring the safe and effective administration of therapeutic medicines [62].

Catalytic characteristics

Some metal nanoparticles, particularly platinum nanoparticles, have extraordinary catalytic properties. This particular characteristic has major medical implications, including drug synthesis, enzyme mimicking, and targeted therapy. Metal nanoparticles are versatile instruments in biomedicine due to their combination of outstanding characteristics. Their vast surface area, SPR, optical characteristics, magnetic behavior, and ability to change surface properties allow for precise drug delivery, imaging, and diagnostics, resulting in improved therapeutic efficacy and patient outcomes. Researchers are constantly studying and improving the use of metal nanoparticles in a variety of medicinal applications, paving the path for novel and effective therapeutics [67-70].

Surface functionalization for drug delivery

Surface modification has significance in nanotechnologies and innovation because it allows for the design and production of nanomaterials. The primary goal of surface modification is to

improve the stability of nanoparticles and prevent them from clumping together. Additionally, there is a need to enhance the biocompatibility, wetting properties, adhesion, and toxicity of MNPs before they can be effectively used in drug delivery. Noble metals are often modified through the incorporation of compounds such as nitriles, phosphines, disulfide ligands, carboxylic acids, amines, and thiol groups [71]. Organosulfur compounds have gained significant attention due to their strong affinity for noble metals like silver, gold, copper, platinum, mercury, and iron. The strong bonding facilitated by sulfur-metal interactions ensures the formation of stable bonds. Moreover, long-chain polymers like polyethylene glycol (PEG) are utilized for surface modification to minimize protein binding and decrease the uptake of nanoparticles by phagocytes. The unique physicochemical properties of PEG make it a valuable polymer for enhancing the therapeutic properties of nanoparticles, resulting in reduced accumulation in non-target organs and minimizing off-target effects [72].

The purposeful modification of the outer layer of MNPs has resulted in substantial advances in the field of medication delivery, allowing for more precise and successful therapies. Surface engineering enables MNPs to accomplish regulated drug release, targeted distribution to specific tissues, and overcome biological and histohematic obstacles. These advancements have significantly improved the efficiency and safety of MNP-based DDSs, opening up new opportunities for their use in cancer therapy and other biomedical sectors [73]. Surface changes provide unprecedented control over the rate of medication release. Drug release can be initiated by encapsulating MNPs loaded with pharmaceuticals within polymers that respond to changes in pH or temperature. *In vitro* release testing can help determine the pace and degree of medication release. The functionalization of the MNP surface enables precise targeting. MNPs can be targeted to certain cell receptors or tissues by adding ligands such as antibodies or peptides, minimizing the likelihood of off-target effects. Targeted delivery's efficiency can be proven through *in vitro* cell binding tests and *in vivo* research on how MNPs are disseminated throughout the body. Biodistribution refers to the transportation and accumulation of chemicals, such as nanoparticles, in various organs or tissues, as well as their length of existence in those

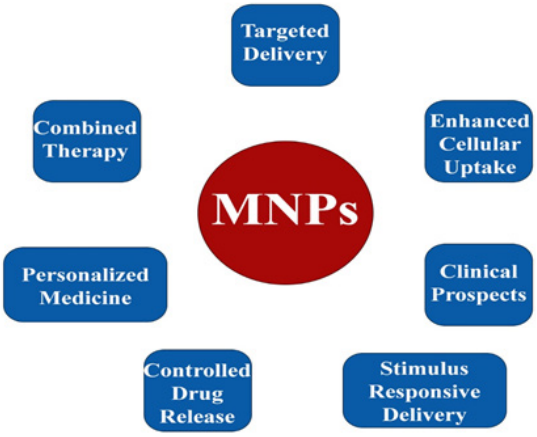

Fig. 3. A notable research direction in the field of functionalized magnetic nanoparticles involves their utilization in targeted drug delivery

locations [74]. Fig. 3, illustrates the noteworthy research conducted on functionalized magnetic nanoparticles and their utilization in targeted drug delivery [64-75].

Chitosan-based nanoparticle compositions, such as chitosan/ferromagnetic scaffolds, have shown promising results in tissue engineering and regeneration. This is principally due to the strong interaction between chitosan's amino groups ($-NH_2$) and the polymeric covering of magnetic nanoparticles. The chitosan coating also helps to inhibit the further oxidation of magnetite Fe_3O_4 to hematite Fe_2O_3 [75].

Surface-modified MNPs have shown promise in clinical trials for cancer treatment, among other applications. However, moving these complex tools from laboratory testing to clinical practice requires comprehensive safety assessment, precise strategy optimization, and scalable production processes. Functionalized particles effectively resolve various possible disadvantages and toxicity concerns connected to conventional nanoparticles, notably the development of reactive oxygen species (ROS) creation, targeted distribution, and biodegradability [76].

Bigan et al. developed pH-sensitive silica nanoparticles with magnetic properties. These nanoparticles were additionally enhanced with folic acid functional groups. To improve their performance, the nano system was coated with methacrylate using transfer polymerization. Fig. 4, illustrates the resulting nano system. Importantly, the surface modification involving metal nanoparticles facilitated targeted drug delivery. Moreover, as shown in Fig. 4, the presence of silica nanoparticles, metal nanoparticles, and folic acid groups contributed to

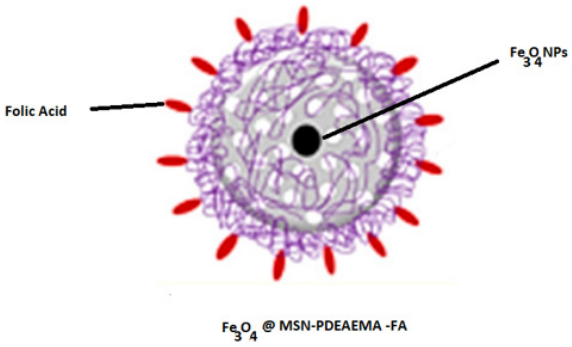

Fig. 4. depicts the grafting of folic acid-capped poly(2-(diethylamino)ethyl methacrylate) brushes onto the surfaces of magnetic mesoporous nanoparticles of silica by SI-ARGET ATRP

improved imaging characteristics. This combination is essential for improving the nanosystem's imaging characteristics [77].

Table 3 contains a collection of modified nanoparticles that have been developed for the purpose of drug delivery. MNPs' biocompatibility may vary depending on their composition and surface functionalization, as certain coatings or functional groups have the potential to cause toxicity or immunological responses. As a result, it is critical to conduct rigorous biocompatibility assessments [78].

Certain surface coatings have the potential to create inflammation, which can result in localized

Table 3. A significant research direction in the realm of modified magnetic nanoparticles is their application in targeted medication delivery

Nanoparticles	Drugs/ Active Agent	Activity and result	Ref.
Au/Fe_3O_4 NPs functionalized with L-cysteine and dithiol-terminated polyethylene glycol (PEG(SH)2)	Luciferase (enzyme)	Functionalized Au/Fe3O4 nanoparticles with L-cysteine, PEG(SH)2, and luciferase enzyme maintain 48% of their catalytic and light emission function in the presence of CysAuNPMag	[40]
Citrate-functionalized superparamagnetic iron oxide nanoparticles	SPIONs@citrate	SPIONs@citrate, functionalized with citrate, exhibit enzymatic and light emission functions, while maintaining 48% activity in the presence of CysAuNPMag. These nanoparticles also possess antitumor properties and the potential for magnetized transport of immune cells	[28]
Magnetic nanoparticles (MNPs) of Fe_3O_4/ Chitosan (CS)	MNP-CS-TEL is a telmisartan-conjugated magnetic nanoparticle. Telmisartan is an angiotensin II receptor blocker (ARB)	Telmisartan (TEL), an angiotensin II receptor blocker (ARB), is conjugated to Fe_3O_4/Chitosan (CS) magnetic nanoparticles (MNPs) to create MNP-CS-TEL, a targeted cancer-fighting medication. The CS coating is confirmed by FTIR and TGA analysis, and TEL is linked to the MNPs through an amide linkage between CS's amino groups and TEL's carboxylic groups. The efficacy of this formulation is evaluated on PC-3 prostate cancer cells	[35]
CCo nanoparticles are obtained through the carbon-coating of cobalt nanoparticles	The functionalization of the nanoparticles with sulfonated arene derivatives is achieved through an aqueous in situ diazotization reaction	Coating cobalt nanoparticles with carbon enables functionalization with sulfonated arene derivatives, leading to enzymatic acceleration and their application as a reusable blood thinner through chemical bonding on the graphene-like layer	[44]
Fe_3O_4/ SiO_2-NH2	Azide-functionalized *E. Coli*	Fe3O4/SiO2-NH2 nanoparticles are functionalized with azide groups and used to immobilize azide-functionalized E. coli bacteria for biomedical applications and catalysis, achieving an 83% immobilization efficiency with 94% recovery of activity	[25]
Fe_3O_4@SiO2@SBA-15 labeled FA	Doxorubicin	Biocompatible mesoporous magnetic nanocarriers (Fe_3O_4@SiO_2@SBA-15) labeled with folic acid are being investigated for the efficient internalization and pH-sensitive delivery of doxorubicin in the treatment of breast cancer	[66]
GSH-capped Au-Mag NPs for surface modification	Biomedical applications	Au-Mag-GSH nanoparticles: biomedical potential, non-toxic	[70]
$NiFe_2O_4$	Serum albumin	NiFe2O4 nanoparticles exhibit high capacity (916 mg BSA/g) for protein immobilization using immobilized metal affinity chromatography (IMAC) with serum albumin, following a Langmuir isotherm model	[72]
$MnFe_2O_4$/ Citrate-stabilized/ lipid	Doxorubicin	Lipid-coated MnFe2O4 nanoparticles exhibited improved drug release compared to citrate-coated MnFe2O4 nanoparticles in theranostic dehydropeptide-based supramolecular magnetogels, suggesting their potential for drug delivery and release applications	[78]
Cs-f-SiO_2@Fe_3O_4	Silymarin	Functionalized magnetic nanoparticles (Cs-f-SiO_2@Fe_3O_4) demonstrated anticancer and antioxidant properties, containing 99-120 mg of Silymarin (active component) per gram of nanoparticles, as determined using the Folin-Ciocalteu method	[78]
hematite (_αFe_2O_3)/ Polylactic acid	----	Stimuli-responsive polylactic acid (PLA)/αFe2O3 nanocomposites, incorporating hematite (_αFe_2O_3) nanoparticles, have demonstrated potential for biomedical applications, such as 3D printing and cardiovascular stents, due to their ability to respond to external stimuli and exhibit desirable properties for these specific applications.	[79]
Fe_3O_4/ PEI	Dopamine (DA), self-polymerized	Fe_3O_4/PEI Dopamine (DA) nanoparticles are stable hydrophilic gene vectors with magnetic properties and enhanced stability for efficient DNA delivery	[80]
Fe_3O_4/ Oleic-acid/ Nylon-6	Doxorubicin (Dox)	Fe_3O_4/Oleic-acid/Nylon-6 nanoparticles enable effective and pH-responsive delivery of doxorubicin (Dox) to target specific cell lines	[81]

or broad reactions that are uncomfortable or lead to serious consequences. People may also develop adverse reactions that range from minor skin irritation to severe anaphylaxis. While other medical devices or implants may cause interference, the behavior of magnetic nanoparticles (MNPs) in the body is of greater concern. In the case of targeted medication delivery, if the mechanisms responsible for guiding the MNPs are not accurate enough, unexpected effects on neighboring healthy tissues may occur, posing a risk [79].

The clustering of nanoparticles (NPs) in specific microenvironments might exacerbate the aforementioned effects and potentially produce blood vessel obstructions or emboli. To guarantee proper dosing and distribution, MNPs' release characteristics must be thoroughly assessed. An high amount might be harmful, whilst an insufficient dose results in poor treatment[80]. Fig. 5 depicts key areas for future improvement, such as ensuring compatibility and minimizing toxicity, ensuring long-term stability, facilitating a smooth transition to clinical settings, achieving precise control, enabling multifunctionality, understanding the relationship between structure and function, improving *in vivo* behavior and targeting accuracy, integrating various imaging techniques, and exploring areas of interest beyond biomedicine [81].

One approach that has received a lot of interest is PEGylation, which involves attaching PEG molecules to the surface of nanoparticles. This surface modification provides various benefits for medication delivery [82]. First, PEGylation improves the stability of Metall NPs by limiting their tendency to assemble and preventing interactions with biological components. This increased stability guarantees that the nanoparticles effectively deliver medications to their intended destination. PEGylation also extends the circulation duration of metallic NPs in the bloodstream [83]. When PEG molecules are attached, they form a protective coating around the nanoparticles, reducing their identification and clearance by the immune system. This prolonged circulation provides greater accumulation at the desired target spot [84].

Furthermore, PEGylation reduces the possibility of the immune system reacting to Metall NPs, making these nanoparticles less likely to elicit an immunological response. This is critical to ensuring that Metall NPs are biocompatible with the body and do not cause adverse reactions. The addition of PEG molecules on the surface of Metall NPs improves their compatibility with the body [85]. PEG is a polymer that is widely employed in pharmaceutical formulations and medical devices because of its ability to interact with the human body. This modification to the nanoparticles' surface improves their overall safety by lowering their toxicity potential. Furthermore, PEGylation can be employed to modulate medication release from metallic nanoparticles [86].

Drugs can be released in response to specific stimuli, such as changes in pH, temperature, or enzyme activity, by modifying PEG molecules with breakable linkers. This controlled release technique allows for focused drug administration, increasing therapy efficacy [87]. In conclusion, PEGylation is a surface modification strategy that enhances the stability, length of time in circulation, compatibility with the body, and controlled release capabilities of Metall NPs. This alteration is critical for improving the efficacy and safety of medication delivery systems that target specific locations [81].

Metallic nanoparticles for the targeted delivery to tumor cells

In the past few years, scientists have accomplished significant advances in the investigation of drug nanocarriers that include metal nanoparticles, with the objective of

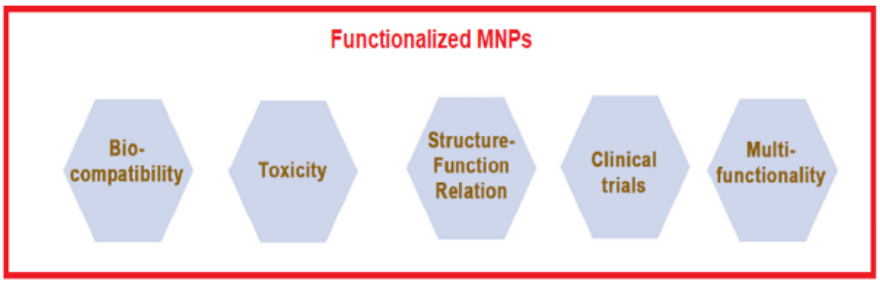

Fig. 5. The important elements and characteristics that must be considered by future MNP nanoplatforms to ensure effective utilization in biomedical applications and other fields

delivering treatment directly to the tumor site. Metallic nanoparticles have immense promise and can be successfully used to improve cancer treatment [82]. The use of metallic nanoparticles enhances the drug's ability to penetrate the tumor microenvironment and also improves the effectiveness of the treatment process. Many medications have been developed to improve cancer treatment, but they have limitations in terms of their effectiveness and potential toxicity. The precise administration of the medication results in the drug infiltrating the tumor environment, while preventing any undesired impact on healthy tissues [83].

Targeted medication delivery is accomplished by integrating specific targeting ligands onto MNPs, which bind to tumor cell receptors and improve the delivery of nanoparticle medicines to solid tumor masses [61, 62].

This strategy lowers the possibility of inadvertent damage to healthy tissues while allowing targeted delivery of anticancer medications to the precise location of the tumor, which has major benefits for the treatment of cancer [36].

Furthermore, metallic NPs' high surface-area-to-volume ratio allows for extensive chemical alterations, which can improve cellular absorption, protect the anticancer drug in biological settings, and increase overall bioavailability [63]. By using metallic nanoparticle systems, therapeutic benefits and the penetration of effective medications can be increased, which lowers the toxicity associated with traditional therapies (Fig. 6) [84].

Metallic nanoparticulate DDSs can selectively deliver anticancer medications to tumor cells while limiting drug buildup in healthy organs [36, 66–70]. The development of MNPs for targeted tumor treatment has resulted in substantial advances in cancer therapies [71]. These metallic nanoparticles have the potential to improve the selectivity of medication delivery to tumor cells while reducing toxicity to nearby healthy cells [72]. Metallic NPs can be used to treat cancer at the cellular and subcellular levels, decreasing side effects and boosting treatment efficacy [17]. Comprehensive research is required to assure the safe and effective use of metallic nanoparticles (NPs) in cancer therapies. These research should focus on examining the systems and organs.

Moreover, the variety of cancerous tissues found in patients holds significant significance as it profoundly influences the efficiency of nanocarriers.

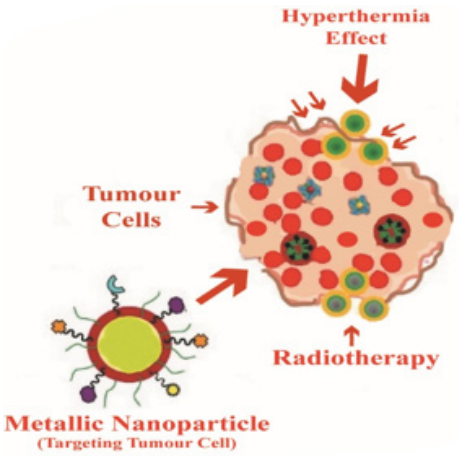

Fig. 6. Metallic nanoparticles (NPs) have multifunctional capabilities in cancer therapy, acting as therapeutic agents to induce hyperthermia, radiotherapy, gene silencing, and drug delivery for enhanced cytotoxicity

Hence, this crucial aspect must be duly considered while crafting nanoplatform DDSs [77,78].

Metallic nanoparticles in drug delivery

MNPs possess unique properties that make them highly promising in the field of nanotechnology, specifically in the area of targeted drug delivery. MNPs exhibit optical properties and can be easily modified to bind to specific targets and biomolecules via various interactions [17]. This enables the transportation of a wide range of therapeutic agents, including antibodies, nucleic acids, antibiotics, and peptides. Additionally, MNPs offer advantages such as improving the water solubility of hydrophobic drugs, increasing the time they remain in circulation in the bloodstream, and reducing renal excretion. The use of multifunctional nanoparticles further enhances their potential by facilitating the simultaneous transport of bioactive substances and therapeutic agents, enabling precise targeted delivery through modifications of ligands, and proving effective in cancer diagnosis and treatment. These advancements are depicted in Fig. 7 [81].

The distribution of drugs has three basic goals: quick delivery of drugs to the intended place, minimal influence on healthy tissue or the human body, and regulated dispersion of the drug to prevent excessive intake or overdose. MNPs have emerged as a promising strategy to achieve these goals. Consequently, researchers have been focusing on optimizing the coating of MNPs to regulate drug loading, delivery, and release at

Fig. 7. Benefits of targeted drug delivery system

specific locations [37]. Coating MNPs enhances biocompatibility and enables drug synthesis, while successful drug delivery relies on controlled release and targeted delivery. These factors can be achieved through active and passive targeting strategies. Passive targeting takes advantage of the unique characteristics of tumor blood vessels, which often exhibit irregularities and leaks due to rapid tumor growth. MNPs are designed to pass through these openings, facilitating efficient penetration into the tumor and making them particularly beneficial for cancer therapy. On the other hand, active targeting involves attaching different ligands to MNPs that specifically bind to cell surface receptors, promoting the transportation and subsequent release of drugs at the desired site [79]. MNPs have gained attention for their potential in disease detection, diagnosis, and treatment. FDA-approved nanodrugs based on metal nanoparticles show improved efficiency in drug release, bioavailability, and targeted delivery, while reducing side effects. By controlling factors such as size, shape, surface chemistry, and degradation, MNPs can be safely absorbed without causing harm to healthy tissue, making them promising candidates for cancer therapy (Table 4) [50-74].

Table 5 provides a summary of key nanoparticles and their various biological applications for effectively targeting biological cells [20-60].

Metal nanoparticles have demonstrated an extensive spectrum of uses in medicine, leading to substantial advances in nano-biotechnology. Table 6 displays various metal oxide nanoparticles that demonstrate substantial antibacterial properties [60-84].

In this study, we will highlight the numerous medication delivery uses of metal or metal oxide nanoparticles produced through chemical synthesis. The applications are summarized in Table 7 [70-90].

MNPs have emerged as promising tools in DDSs

MNPs have emerged as promising tools in DDSs,

Table 4. Metallic nanoparticles as anti-cancer agents

Sample	Application	Ref.
Magnetic iron oxide NPs	Detection of leukemia	[51]
Titanium dioxide nanoparticles	Denture stomatitis	[37]
Silver nanoparticle/calcium hydroxide	Postoperative pain	[55]
Zinc oxide nanoparticles	Foot dermatoses; dental caries	[27]
Silver nanoparticle gel	Anti-bacterial	[48]
Gold nanoparticle with iron oxide silica cell	Plasmonic photothermal and stem cell therapy of atherosclerosis	[17]
Nanocrystalline silver	Pemphigus; pemphigoid	[44]
Hafnium oxide nanoparticle	Prostate adenocarcinoma	[25]
Mixture of gold and silver nanoparticles	Caries class II	[12]
Spherical gold nanoparticle	Recurrent glioblastoma or gliosarcoma undergoing surgery	[68]
Gold nanoparticle with iron oxide silica cell	Plasmonic photothermal and stem cell therapy of atherosclerosis	[17]
Iron oxide	Prostate cancer	[74]

Table 5. Various metal nanoparticles and their potential uses

Nanomaterials	Targeted sites and Application	Ref.
Gold nanoparticles	Gold nanoparticles have potential applications as radiosensitizers in cancer cells	[22]
Silver nanoparticles	The evaluation of skin penetration for silver nanoparticles	[37]
Platinum nanoparticles	The therapeutic evaluation of platinum nanoparticles in cancer cells	[45]
Silver nanoparticles / polyvinylpyrrolidone	The therapeutic evaluation of silver nanoparticles coated with polyvinylpyrrolidone in brain cancer	[17]
Platinum nanoparticles	The toxicity evaluation of platinum nanoparticles in cancer cells	[28]
Gold nanoparticles **/** iron oxide nanoparticles **/**glutathione	The application of gold nanoparticles, iron oxide nanoparticles, and glutathione as radiosensitizers in cancer cells	[44]
FeO /Si/Au	The use of FeO/Si/Au nanoparticles in photothermal therapies for head and neck cancer	[55]
Gold nanoparticles /Ag nanoparticles	The application of gold nanoparticles and silver nanoparticles in imaging therapy and photothermal therapy for cancer cells	[51]
Platinum nanoparticles /polyvinyl alcohol	The toxicity evaluation of platinum nanoparticles in the brain using polyvinyl alcohol	[60]

offering significant advantages over conventional approaches and leading to enhanced therapeutic outcomes. MNPs provide improved drug stability by acting as protective shields, preventing degradation and extending the shelf life of the drugs [91]. For example, chemotherapeutic agents encapsulated within MNPs, such as liposomes or metallic nanoparticles, are effectively shielded from degradation, resulting in increased efficacy. This enhanced stability ensures a higher concentration of the active drug reaches the intended site, ultimately leading to superior therapeutic outcomes compared to conventional pharmacological formulations [92].

Functionalizing MNPs with ligands or antibodies enables precise detection and binding to receptors that are overexpressed on the surface of target cells, making them valuable tools for targeted medication administration [93]. This targeted approach ensures that medications are selectively delivered to diseased tissues, minimizing adverse effects on healthy tissues. In contrast, conventional drug formulations lack this level of selectivity, leading to increased overall

Table 6. Various metal oxide nanoparticles and their potential applications

Nanomaterials	Application	Ref.
Manganese dioxide	Manganese dioxide: versatile applications in biocatalysis, sensing, drug delivery, and imaging	[64]
Magnesium oxide	Due to its antibacterial properties, magnesium oxide is well-suited for a range of applications that require antibacterial properties	[67]
Cerium oxide	Cerium oxide is used in bioimaging and surgical devices due to its unique properties, such as high stability, low toxicity, and excellent biocompatibility	[61]
Titanium dioxide	Titanium dioxide: antimicrobial agent, coating material, sterilization	[68]
Gold oxide	versatile applications in drug delivery, imaging, therapies, and surgical devices	[70]
Nickel (oxide)	Nickel oxide shows potential as an anticancer agent, with cytotoxic properties against cancer cells. It is being studied for use in targeted drug delivery and as a component in anticancer treatments	[80]
Magnetic iron oxide	Magnetic iron oxide has diverse applications in drug delivery, tissue repair, cellular labeling, and hyperthermia. It can be used for targeted drug delivery, tissue regeneration, cell tracking, and as a heat source for hyperthermia therapy	[77]
Iron oxide	Iron oxide is commonly used as a contrast agent in MRI scans and for environmental remediation due to its magnetic properties	[82]
Bismuth oxide	Bismuth oxide shows promise for DDSs, acting as a carrier for controlled release and targeted delivery, thanks to its unique properties and biocompatibility	[66]
Silver oxide	antimicrobial, drug delivery, gene therapies, tissue development, imaging in healthcare and biomedical fields	[67]
Calcium oxide	strong antimicrobial activity, effective in combating microbial growth and infections	[81]
Zinc oxide	Zinc oxide acts as a barrier on the skin, protecting it from the environment and UV rays. It also has soothing properties that can reduce inflammation and redness	[83]
Chromium oxide	Chromium oxide is utilized to enhance the stability of collagen. It helps to maintain the structure and integrity of collagen proteins, promoting healthy and resilient skin	[82]
Copper oxide	Copper oxide (CuO) is a versatile compound used for its antimicrobial properties and in various nonmedical applications	[84]
Silica oxide	production of insulators, gene delivery systems, catalysts, drug carriers, efficient adsorbents, filler materials	[82]
Aluminum oxide	Aluminum oxide exhibits antifungal, antibacterial, and antiviral properties	[60]

Table 7. various drug delivery applications of metal or metal oxide

Nanocarriers	Drugs	Applications	Ref.
Gold nanoparticles conjugated with folic acid	Doxorubicin	Gold nanoparticles functionalized with folic acid and loaded with doxorubicin for tumor-targeted medication delivery	[72]
Gold nanoparticles and palladium nanoparticles functionalized with polyethylene glycol	Doxorubicin	Responsive drug delivery using gold and palladium nanoparticles coated with polyethylene glycol	[78]
Silver nanoparticles embedded within a zirconium metal-organic framework	Doxorubicin	Zirconium metal-organic framework incorporating silver nanoparticles: tumor-targeted medication delivery of doxorubicin	[82]
Tungsten, iron, and gold nanoparticles coated with chitosan	Doxorubicin	Chitosan-coated tungsten, iron, and gold nanoparticles: pH and visible light-responsive drug delivery of doxorubicin	[88]
Iron oxide nanoparticles (NPs) encapsulated in silica nanoparticles	Iron	Iron oxide and silica nanoparticles for targeted drug delivery	[74]
Gold nanoparticles (NPs) functionalized with cyclic arginine-glycine-aspartate peptide	Sunitinib Malate	Gold nanoparticles deliver sunitinib malate to tumors	[85]
Iron oxide nanoparticles (NPs) decorated with graphene oxide NPs	Doxorubicin	Nanoparticles target brain for doxorubicin delivery	[89]
Zinc oxide nanoparticles functionalized with 2,3-dimethylmaleic anhydride	Phenylsulfonyl furoxan and Doxorubicin	Nanoparticles deliver drugs inside cells effectively	[90]
Iron oxide nanoparticles (NPs) coated with folic acid and galactoxyloglucan	Doxorubicin	Nanoparticles target tumors for doxorubicin delivery	[73]
Iron-gold alloy NPs functionalized with Angiopep-2 peptide	Gold - Iron	Nanoparticles deliver medication to tumors with Angiopep-2	[79]
Gold NPs supported on hollow mesoporous carbon	Doxorubicin	Enhanced doxorubicin delivery via nanoparticles, glutathione, and near-infrared light	[82]
Zinc oxide-iron oxide NPs functionalized with folic acid	Curcumin	Curcumin delivered to tumors using folic acid-functionalized zinc oxide-iron oxide nanoparticles	[84]
Gold NPs stabilized with gelatin	Methotrexate	Methotrexate delivered using gelatin-coated gold nanoparticles (NPs) with pH and temperature responsiveness	[89]
Gold NPs labeled with Technetium-99	Methotrexate	Technetium-99 labeled gold nanoparticles (NPs) for tumor-targeted drug delivery and methotrexate diagnosis	[77]
Zinc oxide NPs conjugated with N-succinyl chitosan	Curcumin	Curcumin delivered using pH-responsive zinc oxide nanoparticles (NPs) conjugated with N-succinyl chitosan	[89]
Iron oxide NPs functionalized with glutamic acid	Doxorubicin and Methotrexate	pH-responsive iron oxide NPs for targeted drug delivery and diagnosis	[90]

toxicity and potential harm to healthy organs. By leveraging the targeting capabilities of MNPs, we can enhance the therapeutic efficacy while reducing the potential for off-target effects and damage to healthy tissues [94].

In addition, MNPs offer precise control over drug release kinetics, enabling long-term and regulated delivery. This controlled release mechanism ensures optimal drug concentrations at the desired site while reducing the frequency of drug administration [95]. In contrast, conventional approaches often lead to rapid drug release, resulting in suboptimal drug concentrations and the need for frequent dosing, which can lead to fluctuations in drug levels and diminished therapeutic effectiveness. By utilizing MNPs, we can achieve more consistent and sustained drug release, enhancing the therapeutic benefits and minimizing the need for frequent dosing [96].

MNPs have the potential to revolutionize the distribution and dispersion of medications within the body, ultimately enhancing their efficacy and availability. By encapsulating medications in nanoparticles, they are shielded from enzyme degradation and exhibit greater overall stability within the body. Consequently, these medications remain in circulation for extended periods and may accumulate at the targeted site in higher concentrations [97]. This improved approach to drug distribution and elimination from the body results in superior therapeutic outcomes compared to traditional drug formulations. MNPs offer a promising avenue for optimizing drug delivery and maximizing therapeutic effectiveness [98].

MNPs also possess the capability to facilitate combination therapy by enabling the simultaneous administration of multiple medications. This approach harnesses the synergistic effects that arise when different medications interact, resulting in enhanced therapeutic efficacy. In contrast, conventional methods often require the separate administration of multiple medications, making it challenging to achieve optimal drug concentrations and potentially leading to drug interactions [99]. Additionally, MNPs offer unique features such as responsiveness to light and magnetism, making them ideal agents for imaging purposes. By leveraging these characteristics,

MNPs can serve as valuable tools for diagnostic imaging, providing valuable insights into disease progression and treatment response [100].

Integrating visible components, such as fluorescent dyes or contrast agents, within MNPs allows for real-time tracking of drug delivery and analysis of the body's response to therapy. This integration of therapy and diagnostics, often referred to as theranostics, enables the development of personalized medicine and treatment approaches that are tailored to individual patient responses [82]. By utilizing MNPs for theranostic applications, healthcare professionals can gain valuable insights into the effectiveness of treatment, monitor disease progression, and make informed decisions regarding further therapeutic interventions [85].

Indeed, the advantages of using MNPs in medication delivery systems over traditional approaches are evident. MNPs offer a range of benefits, including increased drug stability, targeted delivery, controlled release, improved drug distribution and elimination, the potential for combination therapy, and imaging capabilities [87-90] These advantages lead to enhanced therapeutic outcomes and reduced risk of adverse effects. Ongoing research and development in this field continue to demonstrate the significant potential of MNPs in improving DDSs, ultimately resulting in better patient outcomes. As scientists and healthcare professionals continue to explore and refine the use of MNPs, we can expect further advancements in this field to revolutionize medication delivery and improve patient care[91].

Various metallic nanocarriers in drug delivery systems

Silver nanoparticles

The use of silver nanoparticles (AgNPs) in precise medication administration and controlled release, notably for cancer treatment, has received substantial interest. AgNPs have special properties that make them ideal for various applications. AgNPs can be modified with particular receptors or antibodies that selectively attach to cancer cells or tumor tissues, enabling targeted medicine delivery [12]. This focused method minimizes detrimental effects on non-target locations while lowering overall toxicity in the body. Furthermore, AgNPs can take advantage of the increased permeability and retention (EPR) effect, which allows them to aggregate only in tumor tissues and deliver medications directly to cancer cells. AgNPs can also be developed to encapsulate pharmaceuticals inside their structure or coated with drug-loaded polymers, allowing for the regulated release of medicinal compounds [13]. The pace at which pharmaceuticals are released can be controlled by altering the characteristics of the AgNPs, resulting in a consistent and extended concentration of the medication at the target site.

Furthermore, AgNPs have inherent characteristics that provide antibacterial and anticancer effects, making them attractive candidates for combination therapy. Combining medicines and AgNPs in a targeted drug delivery system can result in a synergistic effect that improves therapeutic efficacy and overcomes drug resistance [14]. Additionally, AgNPs can be employed for imaging, allowing for real-time monitoring of drug distribution during administration. Various imaging techniques can be used to visualize AgNPs, which aids in the development of treatment plans [15]. AgNPs are a powerful tool for developing more efficient and tailored cancer therapeutics due to their particular targeting of medicines to tumor locations, controlled release mechanisms, synergistic effects, and imaging capabilities. However, more research is needed to improve their qualities, assure their safety, and assess their long-term impacts [16].

Silver, a valuable metal, is widely used in the production of NPs and nanomaterials. These materials have exceptional physical properties, such as antibacterial, antibiotic, anti-inflammatory, and optical, thermal, electrical, and catalytic enhancements compared to their larger counterparts [17]. Approximately 500 tons of AgNPs are manufactured each year to meet the demands of various industries and everyday life. However, there is a need for eco-friendly synthesis methods for silver nanomaterials. AgNPs interact with bacteria, accumulate ions, deactivate cellular enzymes, and disrupt membrane permeability [18]. They also exhibit cytotoxicity by inducing apoptosis and necrosis in various cell types. Additionally, AgNPs have shown potential in mitigating the adverse effects of current treatments, such as DNA damage, ROS production, increased lactate dehydrogenase (LDH) leakage, and inhibition of stem cell differentiation. Nanoscale metal particles have emerged as promising targets for drug delivery in the field of oncology and clinical research [22]. Considering that cancer remains

a leading cause of death worldwide, extensive studies have been conducted on the anticancer properties of AgNPs. AgNPs can generate ROS and disrupt the mitochondrial respiratory chain in cancer cells, displaying promising potential against cancer [47]. Some researchers have investigated the cytotoxic effects of AgNPs on leukemia cells. For instance, Guo et al. examined the effects of PVP-coated AgNPs on acute myeloid leukemia (AML) cells, resulting in ROS generation, release of silver ions, reduced cell viability, DNA damage, and apoptosis. Sahu et al. reported significant concentration-dependent cytotoxicity of AgNPs on human hepatic (HepG2) cells across a range of concentrations [48].

El-Dib et al. developed a cost-effective and environmentally friendly method for synthesizing AgNPs using honey bees. They demonstrated the inhibitory effect of AgNPs on the viability of colon cancer Caco-2 cells. In summary, the use of AgNPs in cancer therapy and their potential for drug delivery represents a significant advancement in the field of oncology research and medicine. AgNPs have been found to inhibit the growth of various cancer cells, including Caco-2, MCF-7, and H1299. Doses of 5 to 28 g/mL of AgNPs were found to inhibit the growth of Caco-2 cells, while 20 µg/mL of AgNPs were cytotoxic to MCF-7 breast cancer cells for 48 hr [49]. AgNPs also show promise as nanocarriers for delivering anti-cancer drugs, which enhances their therapeutic effects. For example, AgNPs loaded with protocatechuic acid (PCA) have shown significant effects on cancer cell growth. These findings demonstrate the potential of AgNPs in cancer therapy. However, further research is needed to understand their effectiveness in treating infectious diseases. Overall, AgNPs have great potential as versatile tools in medicine, especially in cancer therapy and drug delivery. Recent studies have made significant advancements in the use of AgNPs for cancer therapy [50]. Researchers synthesized AgNPs conjugated with methotrexate (AgNPs-MTX), which showed superior anti-cancer effects in breast cancer cells compared to colon cancer cells. Another study developed a nanocomposite of AgNPs with graphene oxide (GO) and methotrexate (MTX-GO/AgNPs), which enhanced apoptosis induction and DNA damage in cancer cells. Biosynthetic methods were also used to create AgNPs conjugated with doxorubicin or imatinib, enabling controlled drug release and increased cytotoxicity in cancer cells. Additionally, AgNPs have shown synergistic effects when combined with existing anti-cancer drugs like gemcitabine and camptothecin, resulting in increased cytotoxicity and apoptosis induction in cancer cells. These advancements demonstrate the potential of AgNPs in revolutionizing cancer therapy, improving targeted drug delivery, and enhancing treatment outcomes [41].

Gold nanoparticles

Gold nanoparticles (AuNPs) have been extensively researched because of their potential usefulness in targeted medication administration and controlled release, particularly in cancer treatment. These nanoparticles can be engineered to connect selectively to cancer cells or tumor tissues, allowing medications to be delivered directly to the target site[16]. Modifying the surface of AuNPs improves their stability, solubility, and compatibility with biological systems. This alteration also allows for the attachment of targeted molecules or medicinal compounds, thereby increasing their efficacy.

AuNPs can be used in photothermal therapy, where they convert near-infrared (NIR) light into heat, resulting in localized hyperthermia and the destruction of cancer cells. They can also be used to control the release of therapeutic agents by encapsulating or coating drug-loaded materials on AuNPs [17-22].Additionally, their exceptional optical properties make it possible to visualize and monitor drug delivery, biodistribution, and therapeutic response [23]. AuNP-based combination therapies, when combined with traditional chemotherapy or immunotherapy techniques, can provide synergistic effects, resulting in enhanced therapeutic outcomes. Nonetheless, more research is needed to improve the characteristics of AuNPs, assure their safety, and assess their long-term impacts [24-30].

AuNPs have unique properties that make them highly valuable in medicine, particularly in drug delivery and cancer therapy. Their distinctive electrical properties enable versatile interactions with various chemicals, proteins, and nucleotides. AuNPs can effectively deliver drugs to specific targets and regulate their release, reducing side effects and minimizing harm to healthy cells. To fully utilize the potential of gold nanoparticles in medicine, it is essential to understand their distribution and accumulation in bacteria. This

requires a comprehensive understanding of nanomaterials, the use of appropriate animal models, and robust data analysis. By gaining a deeper understanding of the behavior and characteristics of gold nanoparticles, scientists can enhance their properties and improve their effectiveness in medical applications. AuNPs offer a promising approach to cancer therapy due to their ability to aggregate and exhibit size-dependent cytotoxic activity against various cell types. The exact mechanism of their anti-inflammatory effect is not fully understood, but it is believed to be associated with their interaction with negatively charged species in tumor cells and cell membranes. Furthermore, studies have shown that small AuNPs can enter cells through endocytosis.

Additionally, researchers have developed gold nanoparticles loaded with anti-inflammatory drugs as effective drug delivery vehicles in both laboratory tests and tumor models. Furthermore, AuNPs have also been used in combination with other cancer-targeting drugs, such as Herceptin, to improve the effectiveness of breast cancer treatment. For example, when combined with methotrexate, 13 nm colloidal gold nanoparticles have been shown to inhibit the growth of cancer cells [52]. *In vitro* and tumor model studies have also demonstrated the effectiveness of AuNPs loaded with anti-inflammatory drugs like sedoximab and gemcitabine as drug delivery vehicles. Additionally, AuNPs have been utilized in conjunction with Herceptin for targeting and treating breast cancer [53]. Apart from their use in drug delivery and cancer therapy, gold nanoparticles have shown potential in addressing antibiotic resistance. Gentamycin Sulfate, a commonly used antimicrobial aminoglycoside, faces challenges in penetrating cell membranes and has limited water solubility. Combining gentamicin with gold nanoparticles has been explored as a solution for treating severe microbial infections. Ampicillin-functionalized gold nanoparticles have demonstrated broad-spectrum activity against both Gram-negative and Gram-positive bacteria by exploiting ampicillin's ability to breach the bacterial cell wall. These nanoparticles effectively penetrate bacteria and eliminate ampicillin-resistant strains. Similarly, guaiac-functionalized gold nanoparticles have exhibited anti-inflammatory properties and insulin-dependent glucose uptake activity in laboratory tests [54].

Zhang Yujie et al. conducted a study in which they developed glucose-conjugated gold nanoclusters (AuNCs) that can release insulin. These AuNCs were then incorporated into microneedle (MN) patches to create glucose-responsive MN patches for delivering insulin in the treatment of type 1 diabetes. The inclusion of drug-loaded AuNC nanocarriers improved the effectiveness of the MNs and facilitated their penetration into the skin of mice [48-52]. For example, in a study, arginylglycylpartate (RGD)-conjugated methotrexate (MTX)-loaded gold/metal/gold plasmonic nanoparticles were developed for magnetic-guided chemophotothermal therapy in rheumatoid arthritis. When exposed to near-infrared (NIR) radiation, these nanoparticles generate heat in the affected area, promoting the release of MTX [55].

Palladium nanoparticles

Numerous forms of MNPs have been widely explored for use in drug delivery and controlled release, particularly in cancer treatment. Palladium nanoparticles (PdNPs) are a form of MNP. PdNPs can be modified with particular binding agents, such as targeting ligands, antibodies, or peptides, allowing them to connect specifically to cancer cells or tumor tissues [56]. This targeted binding mechanism enables for the direct distribution of medications to the designated region, boosting the effectiveness of therapy while limiting any unwanted effects on healthy tissues [57]. The surface of PdNPs can be modified by the addition of various substances, such as polymers or small molecules, to improve their stability, solubility, and compatibility with biological systems [58]. These changes can aid in the attachment of targeted agents or medicinal molecules. Furthermore, PdNPs can be designed to encapsulate medicines inside their structure or to be coated with drug payload-containing materials, allowing for regulated and prolonged release of therapeutic agents. The rate of release can be adjusted by changing the parameters of PdNPs, such as their size, shape, and surface characteristics [59].

Their magnetic qualities allow for improved imaging of tumor tissues, which aids in the diagnosis and monitoring of therapy response. PdNPs can potentially be used with other therapeutic techniques, such as chemotherapy or radiation therapy, to produce synergistic benefits[60]. Superior treatment effects can be

achieved by combining medications with PdNPs in a tailored drug delivery system [61]. To summarize, a wide range of MNPs, including palladium nanoparticles, have significant potential in cancer treatment through targeted drug delivery and controlled release. Their ability to deliver drugs selectively, capacity for surface modification, mechanisms for controlled release, capabilities for magnetic targeting, imaging capabilities, and compatibility with combination therapies. However, more research is required to improve their qualities, assure their safety, and assess their long-term consequences [62].

PdNPs have a porous structure that makes them suitable for carrying anti-inflammatory drugs. These drugs can be directly attached to PdNPs using crosslinking agents. For example, researchers have successfully developed a pH-sensitive carrier using PdNPs to deliver doxorubicin (DOX), an anticancer drug. DOX is bound to PdNPs through an acid-labile bond, enabling controlled release of the drug within endosomal compartments [18]. In a study, DOX-loaded PdNPs linked to PEGylated PdNPs via a hydrazine bond showed pH-sensitive drug release in human cervical cells (HeLa). Additionally, this model demonstrated promising anti-inflammatory effects in an *in vivo* HeLa tumor xenograft model [19]. It is important to carefully evaluate the cytotoxicity of PdNPs as independent therapeutic agents and compare them with bimodal PdNPs loaded with cancer drugs. In cell-based experiments, the combination of Chaga extract with PdNPs at a concentration of 20 µg/mL resulted in approximately 20% cell death in HeLa cells. Conversely, the use of Dox-loaded PdNPs (20 µg/mL Pd) caused around 30% cell death in HeLa cells [20].

9.4.Platinum nanoparticles

Palladium nanoparticles (PdNPs) have a porous structure that is well-suited for carrying anti-inflammatory drugs. These drugs can be directly attached to PdNPs using crosslinkers. For example, Shanti et al. have successfully developed a pH-sensitive carrier that utilizes PdNPs to deliver doxorubicin (DOX), an anticancer drug. DOX is bound to PdNPs through an acid-labile bond, allowing for controlled release of the drug within endosomal compartments [54].

In a study, PdNPs loaded with DOX and attached to PEGylated PdNPs through a hydrazine bond demonstrated pH-sensitive drug release in human cervical cells (HeLa). This model also showed promising anti-inflammatory effects in an *in vivo* HeLa tumor xenograft model. It is important to note that PdNPs themselves have inherent anti-inflammatory properties against various types of cancer, which could affect the outcomes of drug research. Therefore, it is crucial to carefully evaluate the cytotoxicity of PdNPs as standalone therapeutic agents and compare them with bimodal PdNPs loaded with cancer drugs [55].

In cell-based experiments, the combination of Chaga extract with PdNPs at a concentration of 20 µg/mL resulted in approximately 20% cell death in HeLa cells. In contrast, the use of DOX-loaded PdNPs (20 µg/mL Pd) caused around 30% cell death in HeLa cells [56].

Platinum nanoparticles (PtNPs) have received significant attention in the fields of biotechnology, nanomedicine, and pharmacology due to their unique properties and potential applications in antibiotics, disease treatments, and cancer therapy [192]. However, concerns have emerged regarding the toxicity of PtNPs, which poses a challenge for their clinical use. This necessitates the development of biocompatible PtNPs for effective cancer therapy [57].

Mukherjee et al.'s study found that PEGylated platinum nanoparticles, specifically PtNPs-DOX, showed improved DOX activity in melanoma treatment, inhibiting tumor growth in mouse models. This suggests a biological basis for PtNPs-DOX's anticancer action [20-25].

Copper nanoparticles

CuNPs' surface can be easily changed with a variety of chemicals, including polymers and tiny compounds, to improve their stability, solubility, and compatibility with biological systems. These changes also aid in the attachment of targeted molecules or medicinal compounds [16]. CuNPs can be created to include pharmaceuticals inside their structure or to be coated with drug-loaded materials. This allows for the regulated and sustained release of therapeutic substances, increasing the efficiency of medication delivery [17]. The rate of release can be controlled by altering CuNP parameters such as size, shape, and surface features. MNPs, especially CuNPs, have magnetic characteristics that can be used for magnetic targeting. CuNPs can be directed towards the tumor location using an external magnetic field, increasing their accumulation

and retention in the desired area while reducing dissemination to healthy tissues[36].Their magnetic qualities allow for enhanced imaging of tumor tissues, which aids in diagnosis and monitoring the therapy response. CuNPs can also be used with other therapeutic techniques, such as chemotherapy or radiation therapy, to achieve synergistic results [40-44]. Drugs and CuNPs can be combined to provide a tailored drug delivery system with improved therapeutic effects. Finally, certain MNPs, particularly copper nanoparticles, show potential in cancer treatment due to their targeted drug delivery and controlled release capabilities [47]. Their selective drug delivery ability, surface modification versatility, controlled release mechanisms, magnetic targeting capabilities, imaging potential, and compatibility with combination therapies make them valuable tools for developing more efficient and personalized cancer treatments. However, further research is needed to improve their qualities, verify safety, and examine their long-term consequences [45-50].

In the field of drug delivery and bioimaging, researchers have successfully developed transferrin (Tf) patterned copper nanoclusters (Tf-CuNC) that exhibit enhanced luminescence properties. These nanoclusters have been used to create spherical nanoparticles known as transferrin copper nanocluster - Dox nanoparticles (Tf-CuNC-Dox-NP) through electrostatic interaction with doxorubicin. *In vivo* evaluation of this innovative formulation in DLA (Dalton Lymphoma Acid) mice with transferrin receptor (TfR) positive tumors demonstrated superior inhibition of tumor growth and improved survival [56].

The potential of CuNPs in inhibiting human cancer and angiogenesis has also been researched. Curcumin-coated CuNPs were studied for their effects on cancer cells and compared to curcumin alone [20].

Zinc oxide nanoparticles

Zinc oxide (ZnO) nanoparticles have displayed promise in drug delivery for the treatment of cancer and diabetes. According to a study conducted by Zhang et al., ZnO nanoparticles were synthesized using a simple method and used to transport the drug daunorubicin. This combination resulted in a reduction in drug toxicity and an improvement in tumor targeting by inhibiting the generation of ROS in cancer cells [23]. Hüseyin et al. focused on the environmentally friendly synthesis of ZnO nanoparticles by utilizing a solid-phase process and encapsulating them with gum arabic. These nanoparticles exhibited anti-inflammatory properties and high compatibility as delivery systems. Additionally, they loaded hydrophobic docosahexaenoic acid onto the nanoparticles and discovered positive effects on various diabetes-related parameters in experimental mice [24]. In a separate study, John et al. investigated the effects of curcumin-zinc oxide nanoparticles encapsulated in chitosan on diabetes in mice. Administration of these nanoparticles triggered positive alterations in diabetes biomarkers without causing toxicity [25]. Ekta Yadav et al. explored the application of ZnO nanoparticles synthesized from Trianthema portulacastrum Linn. plants for their anti-inflammatory properties. These nanoparticles expedited wound healing by reducing collagen fibers, promoting tissue granulation, and exerting antioxidant effects [26].

Titanium dioxide nanoparticles

Titanium dioxide (TiO_2), also known as titania, is a metal oxide semiconductor with promising applications in drug delivery, particularly in cancer therapy. Its chemical stability, lack of toxicity, and cost-effectiveness make it highly attractive [27, 28]. TiO_2 exists in two crystal structures: rutile and anatase, with anatase being the more chemically active form. Recent research suggests that TiO_2 NPs in the anatase phase generate a higher level of ROS, which can be more detrimental to healthy cells compared to the rutile phase. It has also been observed that although rutile TiO_2 is considered less chemically active, reducing the particle size can increase its surface area and potentially pose risks. Moreover, altering the surface of TiO_2 NPs can modify their overall activity [60].

The use of TiO_2 matrices to encapsulate valproic acid enables the controlled release of the drug for various medical conditions [16]. Additionally, GA-TiO_2 and DNR-TiO_2 nanocomposites have shown increased anti-inflammatory activity in human leukemia K562 cells compared to using each drug separately [25-30].

Metal sulfide nanoparticles

Metal sulfide nanoparticles (MeSNPs) are a new type of nanomaterial composed of metal ions and sulfur compounds [30-35]. Recent research has shown that MeSNPs, which are synthesized

using specialized techniques, have excellent biocompatibility and unique physicochemical properties, making them very promising for cancer treatment. In one study, Yang et al. created polydopamine-coated hollow porous nickel sulfide (NiS) nanoparticles as carriers for the drug doxorubicin (DOX) [37]. These nanoparticles had a high encapsulation efficiency and loading rate because of the intercavity and hollow porous structure of NiS nanoparticles, as well as the interaction between DOX and polydopamine. Li et al. developed porous hollow copper sulfide (CuS) nanoparticles (H-CuS NPs) to deliver photosensitive chlorine (Ce6) and DOX to cancer cells [21]. H-CuS nanoparticles had heat-sensitive degradation properties and acted as a "seal" to keep the drug inside their structure [22]. This allowed for controlled drug release through light-induced thermal stimulation, which is beneficial for reducing non-specific drug release and improving drug availability in tumors. Hou et al. described a localized drug delivery system using copper sulfide nanoparticles, showing potential for cancer treatment and theranostics [40]. They created transferrin (Tf)-modified hollow-pore CuS nanoparticles (HMCuS NPs) for diffusion molecule retention (DMR) tumor targeting [41]. These nanoparticles diffused through the interstitial space and stayed in the tumor after peritumoral injection (PT), leading to prolonged localization and retention, reduced vascular uptake, and widespread distribution within the tumor stroma. In another study, Xie et al. synthesized two-dimensional tin sulfide nanolayers (SnS NS) with high DOX loading by electrostatically adsorbing carriers and DOX [42]. This loading capacity surpassed that achieved through traditional methods. Overall, these studies demonstrate the potential of metal sulfide nanomaterials as effective agents for cancer therapy, providing advantages such as improved drug encapsulation, controlled release, enhanced targeting, and delivery [43].

Nanoscale metal organic frameworks

Metal-organic frameworks (MOFs) have garnered significant attention as potential systems for drug delivery due to their unique structure, large surface area, expansive pore sizes, and ease of handling. In recent years, researchers have focused on miniaturizing MOFs to the nanoscale, resulting in the development of nanoscale metal-organic frameworks (NMOFs) for biomedical applications[16]. The remarkable characteristics of NMOFs, including their pore size, regular structure, and extensive surface area, allow them to efficiently adsorb molecules on their surface or within their pores. NMOFs offer advantages over traditional nanomedicine, such as structural adaptability, high loading capacity, and biodegradability [53].

Scientists are exploring the functionalization of MOFs with biomolecules to enhance their bioactivity and biocompatibility [54]. Zirconium-based MOFs have been utilized as nanocarriers for controlled delivery of ibuprofen [55]. Non-toxic metal (III)-based nano-MOFs have demonstrated the ability to transport and regulate drug release. An excellent example is Zeolitic Imidazolate Framework 8 (ZIF-8), known for its high porosity, stability, excellent biocompatibility, and pH-dependent degradability [56]. In a recent study, insulin, VEGF aptamer, and glucose oxidase were encapsulated within ZIF-8 nanoparticles for controlled drug release [56-63].

Antibacterial activity

Numerous research studies have provided evidence of the ability of nanomaterials to inhibit bacterial growth through various interactions, including cellular penetration and membrane damage[90]. Among metallic nanoparticles, silver, gold, copper, and titanium have shown remarkable antibacterial properties owing to their unique characteristics. It explores their toxicity and antibacterial efficacy in relation to their structure, dimensions, and size. In addition, it discusses the advantages of using nanoparticles in biomedical applications. Table 8 presents a summary of the antibacterial abilities of each nanomaterial[80-108].

Tumor-targeting strategies involving ligands or antibodies in nanoparticle-based therapeutics

Nanoparticle-based treatments depend on tumor-targeting strategies involving ligands or antibodies and controlled drug release mechanisms. These approaches are crucial for ensuring treatment effectiveness. Now, let's explore the intricacies of these strategies:

Interactions between ligands and receptors

Nanoparticles can be created through the use of particular ligands in which include folic acid, to go after and bind to overexpressed receptors on the surface of tumor cells. This focused method

Table 8. Antibacterial properties of nanomaterial

Nanomaterials	Size and Synthesis Method	Properties	Ref.
Silver	Silver nanoparticles synthesized at sizes of 12 nm and 65 nm using the Bacillus flexus strain	Potent antimicrobial activity against resistance	[90]
Silver	Silver nanoparticles with a size of less than 25 nm synthesized through a one-pot synthesis method	Remarkable antibacterial characteristics when it comes to inhibiting the growth of Escherichia coli and *Staphylococcus aureus*	[92]
Gold	Gold nanoparticles with a size range of 22-35 nm synthesized using a green synthesis approach involving Salicornia brachiata plant extract	Noteworthy antibacterial synergy with ofloxacin against pathogens	[100]
Gold	4 nm-sized gold nanoparticles synthesized using an organic solution-based method	High concentrations impaired cell viability, proliferation, differentiation	[102]
Copper	Copper nanoparticles synthesized via template-based electrodeposition with a size range of 20-250 nm	Vertically oriented nanotubular copper arrays significantly reduced the population of S. aureus by 99.99% within a short period of 6 hours, while showing less impact on other bacteria	[85]
Copper oxide	Green synthesis of copper oxide nanoparticles (48±4 nm) using Tabernaemontana divaricata leaf extract	CuONPs from Tabernaemontana divaricata leaves inhibited urinary tract pathogen	[95]
Copper oxide	Wet chemical synthesis of copper oxide nanoparticles with a size of 6 nm	CuO nanocrystals were found to possess bactericidal effects, primarily by causing irreversible damage to the cell membrane of bacteria	[101]
Titanium dioxide	Anodization in electrolytes for the synthesis of titanium dioxide nanoparticles with a size of 2 nm	The use of TiO2 nanotubes on a titanium substrate resulted in improved corrosion stability, while also exhibiting antibacterial activity against E. coli bacteria	[89]
Titanium dioxide	Sol-gel synthesis of titanium dioxide nanoparticles with a size of less than 10 nm	The material exposure resulted in the damage of cellular membranes due to the degradation of membrane fatty acids caused by photocatalysis	[90]
Titanium	Conventional synthesis of titanium nanoparticles with sizes ranging from 20 to 80 nm using a convectional method	In a comparative study, it was found that titanium nanotubes with a diameter of 80 nm showed the highest level of antibacterial activity among the tested nanotubes with diameters of 20, 40, and 60 nm	[92]
Zinc oxide	Zinc oxide nanoparticles (25-40 nm) synthesized using plant extract	The nanoparticles possess controllable size and shape, are cost-effective, and do not contain any harmful contaminants	[95]
Zinc oxide	30 nm zinc oxide synthesized using microwave-assisted hydrothermal method	Higher concentration of nanosized zinc oxide enhances antifungal activity due to increased anti-oxidative stress on microorganism cells	[97]
Magnesium oxide	44 nm magnesium oxide synthesis through plant-mediated calcination	Magnesium oxide nanoparticles have been found to exhibit a 65% inhibitory efficacy, potentially due to their antioxidant activity. This antioxidant activity may be attributed to the presence of bioactive components found in plant extracts	[99]
Magnesium fluoride	30 nm magnesium fluoride synthesis using a microwave-assisted method	Magnesium fluoride has been observed to penetrate bacterial infections and induce antibiofilm action. This action includes various mechanisms such as breakdown of membrane potential, binding to DNA, and enhanced lipid peroxidation. These actions contribute to the antimicrobial effects of magnesium fluoride against bacterial infections and biofilms	[104]
Titanium dioxide	5 nm titanium dioxide formation through titanium tetrabutoxide hydrolysis	Large quantities of magnesium fluoride have been found to cause liver, heart, and kidney damage in mice, as well as alterations in blood sugar and lipid levels. Further research is needed to determine its effects in humans.	[107]
Copper iodide	8 nm copper iodide reduction during coprecipitation	Copper iodide nanoparticles exhibit antibacterial activity via ROS-induced DNA damage in bacteria	[87]
Copper oxide	Copper oxide formation through thermal decomposition of 15-30 nm particles	Copper iodide nanoparticles inhibit bacteria via oxidative stress.	[108]

improves the introduction of drugs to cancer cells expressing high numbers of these receptors while limiting potential adverse impacts in normal tissue. It is an exciting development in the field of medicine and offers a promising strategy for improving the efficacy and safety of cancer treatments [88].

Monoclonal antibodies can be conjugated to the surface of nanoparticles, enabling specific recognition and binding to antigens present on cancer cells

This specialized technique, called antibody-mediated targeting, enables precise identification of cancer cells. For instance, trastuzumab, an antibody designed to target the HER2 receptor, can be closely linked to nanoparticles to facilitate targeted delivery exclusively to breast cancer cells expressing the HER2 protein [89].

pH-Responsive drug delivery

pH-responsive DDSs utilize the slightly acidic environment found in tumor tissues compared to healthy tissues. By coating or loading nanoparticles with pH-sensitive polymers, these systems can undergo structural changes in response to the low pH of the tumor microenvironment. This allows for precise drug delivery to the tumor site, increasing the effectiveness of treatment while minimizing

side effects on healthy tissues[91].

Responsive DDSs

Indeed, nanoparticles can be designed to respond to different external stimuli like light, heat, or magnetic fields, enabling controlled drug release. For instance, gold nanoparticles can be modified with light-responsive molecules, enabling drug release upon exposure to specific wavelengths of light. This innovative approach offers advantages such as precise spatial and temporal control over drug release, enhancing the accuracy and effectiveness of the treatment [92].

Responsive drug delivery by enzymatic activation

Diseases like cancer often exhibit increased levels of specific enzymes, and nanoparticles can be designed to respond to these enzymes for targeted drug release. For example, in the tumor microenvironment, there is often an overproduction of matrix metalloproteinases (MMPs). The drug delivery system can be designed to detect the presence of MMPs, allowing for targeted medication release at the tumor location while reducing exposure to healthy tissues. This approach of releasing medications triggered by specific enzymes improves therapeutic outcomes by specifically targeting the damaged area [93-95].

Nanoparticles can be coated with MMP-responsive connections, allowing for localized drug release at the tumor site. This targeted approach improves drug accumulation in tumors while reducing systemic side effects. Overall, it optimizes treatment efficacy and minimizes undesired effects in nanoparticle-based therapies [96].

Obstacles to the clinical implementation of tumor-targeting nanosystems

The practical deployment of nanosystems for drug delivery faces two primary challenges

Large-scale production and investigation of their pharmacological properties. Scale-up synthesis poses a challenge in producing nanosystems on a large scale while maintaining consistent quality, repeatability, and cost-effectiveness [97]. This challenge involves the need for robust and scalable production procedures, optimization of synthesis methods, purification processes, and implementation of quality control measures. Moreover, reducing the high production costs associated with nanosystems is crucial for their widespread use in clinical settings. Addressing these challenges is essential for the successful translation of nanosystems from the laboratory to practical applications in drug delivery [98].

Pharmacological profiles examine the interactions between nanosystems and the body, encompassing biodistribution, pharmacokinetics, and biocompatibility. To mitigate any adverse effects, it is essential to evaluate potential toxicity and ensure biocompatibility [99]. Comprehending the pharmacokinetic characteristics of nanosystems, including their duration of circulation, distribution in tissues, and kinetics of drug release, is crucial for selecting optimal dosage regimens and achieving desired therapeutic effects while minimizing off-target consequences [100]. Regulatory considerations present significant obstacles. Regulatory bodies like the FDA have specific regulations and criteria for approving nanosystems as therapeutic agents. Meeting these requirements often entails extensive preclinical and clinical research to assess safety, efficacy, and quality control procedures. Such research endeavors can be time-consuming and resource-intensive [101].

Collaboration among researchers, clinicians, regulatory authorities, and industry partners is crucial to surmount these obstacles. The key objective is to enhance the synthesis process, devise scalable and efficient manufacturing techniques, minimize production expenses, conduct comprehensive analysis of pharmacological properties, and fulfill all regulatory obligations. By directly tackling these challenges, we can enhance the clinical integration of nanosystems for drug delivery, leading to safer and more potent nanomedicines that cater to a wider range of patients [102].

Real-world applications of clinical translations and FDA-approved nanoparticle-based therapeutics

Remarkable progress in nanoparticle-driven therapies has led to the approval of numerous nanomedicine products by the FDA for application in clinical settings. These validated medications, which rely on nanoparticles, present compelling proof of nanotechnology's successful integration into the realm of healthcare [70-80]. Here are several illustrations that exemplify these extraordinary breakthroughs:

Doxil (liposomal doxorubicin)

Doxil represents a liposomal formulation of doxorubicin, a widely used chemotherapy drug. Liposomes, minute particles composed of lipids,

effectively encapsulate the medication, facilitating controlled release and improved transport to the specific tumor location. Doxil, an innovative treatment harnessing the power of nanoparticles, has obtained clearance from the FDA. Its primary aim is to combat AIDS, ovarian cancer and multiple myeloma [81-85].

Abraxane (paclitaxel bound to albumin)

Abraxane presents itself as an innovative nanoparticle formulation comprising paclitaxel, a highly potent anti-cancer medication. Paclitaxel molecules are encapsulated within minuscule albumin particles, enhancing solubility and improving drug delivery characteristics. The FDA has officially approved the use of Abraxane for the treatment of pancreatic cancer ,breast cancer, and non-small cell lung tumor [86-89].

Onivyde (liposomal irinotecan)

Onivyde represents a liposomal rendition of irinotecan, a potent chemotherapy agent. The solubility and stability of irinotecan are notably enhanced through its encapsulation within lipid-based structures called liposomes. This improved formulation allows for more efficient drug distribution, ultimately resulting in heightened effectiveness and reduced adverse effects. Onivyde has been granted regulatory clearance for its application in the treatment of advanced pancreatic cancer that has metastasized to other areas of the body [90-92].

Vyxeos (liposomal daunorubicin, cytarabine)

Vyxeos represents a groundbreaking formulation that combines daunorubicin and cytarabine, two crucial chemotherapy agents employed in the management of acute myeloid leukemia (AML). The liposomal structure significantly enhances the pharmacokinetics of these medications, leading to synergistic effects and improved therapeutic results. Vyxeos has been granted approval for the treatment of specific subtypes of AML [93-95].

FDA has authorized the use of nanoparticle-based medications for the treatment of numerous cancers and other medical conditions. Their successful transition from the lab to clinical practice demonstrates the positive impact of nanotechnology in medicine. These advancements provide hope for more effective treatments, fewer side effects, and improved outcomes for patients. Ongoing research and development in this field promise the introduction of additional FDA-approved nanomedicines, expanding therapeutic options [96-99].

Future prospects and challenges

Magnetic nanoparticles (MNPs) revolutionize cancer treatment through improved drug targeting and delivery. Advantages include cancer diagnosis, targeted drug release, and transformative therapy. MNPs' interaction with light enables detection of nanometal-drug complexes, enhancing chemotherapy [100].

However, there are challenges in translating and commercializing MNPs for therapeutic use. These challenges encompass issues related to bulk production, biological considerations, safety concerns, compliance with government regulations, and overall cost-effectiveness compared to conventional treatments. MNPs are primarily targeted for cancer treatment due to their enhanced permeability and retention (EPR) effect [101].

The effectiveness of MNPs is influenced by factors such as cellular absorption and the kinetics of drug release in the target tissues. The complex and diverse synthesis techniques required for large-scale MNP production may limit their potential for clinical application, as companies prioritize quality and cost [102]. Regulatory authorities in the pharmaceutical industry actively support thorough examination of any changes in drug composition, synthesis techniques, or drug product formulation at each stage of clinical development. Understanding these relationships allows us to address the challenges associated with MNPs and actively work towards overcoming them. This, in turn, will contribute to the improvement of the therapeutic application of MNPs in cancer therapy [103].

Theranostics refers to the combined use of diagnostic and therapeutic approaches in medicine. MNPs have demonstrated remarkable imaging properties, making them suitable for both diagnosis and therapy [104]. Future advancements in this field aim to integrate different imaging modalities with MNPs, enabling real-time monitoring of medication administration, treatment response, and disease progression. This approach has the potential to revolutionize medical practices by providing personalized and precise treatment options based on real-time

information obtained through imaging [105].

Indeed, when MNPs interact with biological barriers, such as the immune system, blood-brain barrier, and clearance systems, they encounter certain challenges. However, future research aims to address these obstacles by carefully designing MNPs with surface modifications to minimize the risk of immune response, enhance their compatibility with biological systems, and improve their ability to cross biological barriers [106]. These advancements are crucial for maximizing the therapeutic potential of MNPs and ensuring their safe and effective use in medical applications [107].

Enhancing scalability and manufacturing processes is crucial for the widespread adoption of MNPs. Developing manufacturing procedures that are both scalable and cost-effective is necessary to meet the demands of large-scale production [99]. This involves optimizing synthesis methodologies, purification methods, and quality control measures to ensure repeatability, consistency, and regulatory compliance. By improving the efficiency and reliability of MNP manufacturing, we can ensure the availability of MNPs for various applications and facilitate their integration into clinical practice [100-102].

Safety and Toxicity: It is crucial to ensure the safety and comprehensively understand the toxicity of MNPs to determine their long-term effects, biodistribution patterns, and pathways of clearance [103]. To tackle any potential toxicity concerns, it is vital to explore surface modifications, biodegradable MNPs, and controlled release techniques. These measures play a significant role in minimizing the risks associated with toxicity [104].

Protecting intellectual property rights and securing financing for micro and nanoparticles in innovative medication delivery systems are crucial for their success. Collaboration among academia, businesses, and regulatory organizations is essential to enhance the commercial viability and widespread adoption of MNPs [105]. The future of MNPs in intelligent medication delivery systems appears promising, with a focus on advancements in targeted and triggered drug delivery, combination therapy, theranostics, overcoming biological barriers, obtaining regulatory approval, scalability, safety, and commercialization. Overcoming these obstacles will speed up the actual deployment and widespread use of MNPs, transforming the clinical practice of health care and increasing patient outcomes [106-108].

CONCLUSION

Nanotechnology and nanomedicine have made significant advancements in various fields, with the potential to greatly improve our quality of life. However, there is still much to learn and discover about the application of nanoscale technology in pharmacy and the progress of nanomedicine. Extensive research, especially in the area of drug delivery, is essential to enhance therapies further, making them more effective and cost-efficient. The main objective of any medical treatment is to target and treat diseases effectively while minimizing damage to healthy tissue. Metal nanoparticles are being investigated as possible means of delivering drugs due to their availability, biological compatibility, and durability. These nanoparticles offer the advantage of enhancing drug encapsulation and enabling precise delivery to specific areas, thus improving treatment outcomes. The development of metal nanoparticles is rapidly advancing in various directions, suggesting their potential as innovative tools for future drug delivery, particularly in addressing conditions like cancer, inflammation, diabetes, and immune system disorders.

CONFLICTS OF 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.

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