REVIEW

Anisotropic transition metal–based nanomaterials for biomedical applications

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Abstract
Transition metal–based nanoparticles have attracted more and more attention in biomedicine, owing to their special characteristics that arise from finite-size and surface effects, such as intense and broad light absorption, strong oxidation ability, catalytic activity, and robust mechanical properties. Researches on transition metal–based nanoparticles and their clinical applications have been, so far, mainly focus on the spherical shape. However, many efforts have been made to develop different anisotropic shapes to increase their physicochemical properties and biological activity. In this regard, it would be of great benefit to elaborate the recent developments, especially over the past 20 years, on the synthesis of anisotropic transition metal–based nanomaterials and their unique shape-dependent properties, mechanism, as well as superiority and limitations in biomedicine, such as drug delivery, disease therapy, and resonance imaging. Here, we will summarize in detail the mechanism and advantages of three main shape categories of anisotropic transition metal–based nanomaterials in biomedical applications, including one-dimensional (e.g., nanowire), two-dimensional (e.g., nanosheet), and three-dimensional (e.g., nanorod, nanocube, and nanoflower) anisotropic shapes. In addition, the critical challenges and prospects of this field will be also proposed and discussed.

KEYWORDS
anisotropic transition metal–based nanomaterials, biomedical application, one-dimensional, two-dimensional, three-dimensional

1 INTRODUCTION

Many studies are addressing deficiencies in the treatment and diagnosis of diseases. Compared to conventional medicine, nanomedicine is the research field of applying nanotechnology to develop high-performance biomedical tools.1,2 Up to now, nanomaterials have received attention in many biomedical applications due to their adjustable shape and size; excellent electrical, mechanical, and optical characterizations; and corrosion and oxidation resistance.3 Currently, different nanocarriers are broadly studied in the biomedical field such as novel cancer treatments, targeted drug delivery, detection, diagnosis, and imaging.4,5
Among these various nanomaterials, the transition metals-based nanoparticles show not only the common unique characterizations of nanostructures but also some specific physical and chemical properties, such as high thermal and chemical stability, excellent photocatalytic activity, and electronic and optical properties. Transition metals are d-block elements that contain 3–12 groups in the periodic table, whose d-shell layers are in the filled state and can form coordination complexes. Thus, transition metal–based nanomaterials are usually centered on metal atoms that are bound to surrounding molecular or anionic arrays. Owing to their special characterizations, such as finite-size effects, intense and broad light absorption, catalytic activity, and low cytotoxicity, they have been widely used in the biomedical field such as drug delivery, chemoprevention and adjunct therapy, multiplexed imaging diagnosis, and various disease therapy.

The shape or anisotropy is found to show a profound effect on the properties of nanomaterials, including physical, chemical, and physiological characteristics. Precise control of their morphology plays a decisive role in the regulation of their properties and shows a following great effect on the various physicochemical and biomedical applications. However, many of the transition metal–based nanomaterials used in the clinic or studied in the laboratory to date are spherical in shape. In recent years, transition metal–based nanoparticles with anisotropic morphologies have also been rapidly developed and applied in various biomedical applications. Numerous elaborate approaches have been explored utilizing different shapes of nanoparticles to tailor their physical, chemical, and biological properties. In addition, controlling the anisotropic shape can also influence the cytotoxicity, cellular uptake, targeted delivery, biodistribution, and pharmacokinetics of nanoparticles. Thus, we can design and construct the future nanoparticles with special morphology that presents the expected function. Also, it is necessary to understand the intrinsic relationships between nanoparticles with different anisotropic shapes and their physical, chemical, and biomedical properties to obtain predictable insights and clear strategies.

Here, we review applications of anisotropic transition metal–based nanomaterials in biomedical fields, such as drug delivery, bioimaging, biosensors, and diseases therapy (Figure 1). Herein, we highlighted the importance of three main shape categories of utilization of anisotropic transition metal–based nanoparticles, including one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) structures, as alternative biomedicine for effective disease treatment (Table 1). The review was concluded with advantages and further deliberations on the key challenges of anisotropic transition metal–based nanomaterials in biomedical applications.

## 2 1D TRANSITION METAL–BASED NANOMATERIALS WITH ANISOTROPIC SHAPE FOR BIOMEDICAL APPLICATIONS

1D nanomaterials are regarded as ideal materials for directional electron transport because of their orientation in a certain direction. They are the smallest dimensional structures that can be used for effective electron and exciton transport, such as field-effect transistors, resonant tunneling diodes, and other nanoelectronic devices. In the past decade, considerable studies have been done on certain 1D transition metal–based nanoparticles, such as gold, titanium, copper, and iron, which provide a solid foundation for the design of potential in biomedical applications.

Among transition metal–based nanoparticles, Ti-based nanoparticles have been exploited for genetic and tissue engineering, manufacturing healthcare products, bioimaging, and the treatment of diseases such as cancer, owing to their admirable photocatalytic ability, good biocompatibility, and low toxicity. Zhang and co-workers prepared the composite nanofibers of polyvinylpyrrolidone (PVP) and TiO₂ nanowires by electrospinning on the surface of a silicon wafer with tetra butyl titanate and PVP as precursors (Figure 2A). After calcination to remove the polymer template, the obtained TiO₂ nanowires with a diameter of 100–300 nm were used to capture circulating tumor cells in cancer patients’ blood samples after salinization and antibody modification. In Liu and colleagues’ study, a series of Ni–Ti and Ni(OH)₂ layered double hydroxide (Ti–Ni LDH) have been designed and prepared through hydrothermal method with diverse Ti/Ni ratios on nitroso surface. Cellular study demonstrated that the Ti–Ni LDH could inhibit tumor cells viability effectively with relative low/no side effects to normal cells. Meanwhile, highly reactive oxygen species (ROS) level and intracellular nickel content were also demonstrated in tumor cells, verifying that tumor cells’ death might be caused by nickel ions intake.

Except for Ti-based nanoparticles, 1D copper-based nanomaterials have also been extensively studied in biomedical fields. This is because that copper-based nanoparticles exhibit strong absorption in the NIR region, highly efficient for thermal therapy, and strong fluorescence signal for optical imaging. Besides, they are also used as the versatile drug delivery vehicle. Fan et al. developed a Cu₂O-nanowire monocrystal nanocatalysis in cells as shown in Figure 2D. Such Cu₂O-nanowire...
monocrystal could also be utilized for different applications in environmental remediation, biosensing, and biotechnology.\textsuperscript{37} In another interesting work, a facile method for large-scale and controllable preparation of Cu$_2$O nanowires was reported. These Cu$_2$O nanowires have been reported to be used as a peroxidase, demonstrating the remarkable catalytic activity, which provided opportunities to them to function as enzymes for future biomedical applications.\textsuperscript{38}

Gold nanowires are usually considered as a promising candidate in the area of bioelectrocatalysis due to their high surface-to-volume ratios and other special properties.\textsuperscript{39,40} Wu et al. developed a sensitive amperometric nanobiosensor by the glucose oxidase-integrated gold nanowires arrays. Such nanobiosensor could realize glucose detection with a wider linear range and much lower detection limit.\textsuperscript{41} In another representative work, Au nanowires were used as template for the enzyme immunoassay to detect cytokeratin-7. Such Au nanowires showed enhanced selectivity and sensitivity for tumor biomarkers' detection.\textsuperscript{42}

Besides, Yang et al. reported a new kind of inorganic nanoprodrug, tellurium nanowires (TeNWs), which could cause TeO$_6^{5-}$ for tumor chemotherapy with high selectivity.\textsuperscript{43} The reaction of TeNWs and intracellular H$_2$O$_2$-produced toxic TeO$_6^{5-}$ thus enhanced the tumor ROS level. In addition, the glutathione (GSH) inside of tumor cells could react with the obtained TeO$_6^{5-}$ and decrease the level of GSH and in another aspect increase the ROS levels in the tumor. Losic and co-workers produced an iron oxide nanowire via a biofilm waste by bacteria and found it could be used for cancer therapy application. The magnetic and structural characterization demonstrated that their magnetic properties, aspect ratio, and nanoscale structure are comparable with artificial NW, verifying that these iron oxide nanowires were capable for cell internationalization and drug delivery.\textsuperscript{44} Zhao et al. prepared the PEGylated W$_{18}$O$_{49}$ nanowires via a simple solvothermal-based method with a mixture of poly(ethylene glycol) and ethanol as the solvent. These nanowires with low cytotoxicity, low cost, high photothermal conversion efficiency, and small size verified...

**FIGURE 1** Schematic diagram of various anisotropic transition metal–based nanomaterials for biomedical applications
TABLE 1  A summary of anisotropic transition metal–based nanomaterials for biomedical applications

| Dimensions | Nanostructures | Transition metals | Synthetic methods | Applications | Ref. |
|------------|----------------|-------------------|-------------------|-------------|-----|
| 1D         | Nanowires      | Ti                | Electrospinning and calcination | Circulating tumor cells capture | 32  |
|            |                | Cu                | Hydrothermal method | Cancer palliation therapy | 33  |
|            |                | Au                | One-pot hydrothermal method | Biosensing | 37  |
|            |                |                   | Solvothermal method | Peroxidase-like activity | 38  |
|            |                |                   | Electro-deposition | Glucose detection | 41  |
| 2D         | Nanosheets     | Bi                | Solution-based method | Tumor PTT | 52  |
|            |                | Mo                | Solution-based method | Tumor PTT and PDT | 53  |
|            |                | Pd                | Chemical exfoliation method | Tumor PTT-chemical therapy | 56  |
|            |                |                   | Solution process | Detection intracellular behaviors | 57  |
|            |                |                   | Solvothermal method | Tumor PTT | 64  |
|            |                |                   | Solvothermal method | Tumor PTT | 65  |
|            |                |                   | Mo chemical exfoliation method | Tumor radiotherapy | 95  |
|            |                |                   | Solution process | Detection intracellular behaviors | 57  |
| 3D         | Nanorods       | Bi                | Solvothermal method | Intracellular H₂O₂ detection | 74  |
|            |                | Fe                | Solvothermal method | Drug delivery | 97  |
|            |                | Zn                | Solvothermal method | Drug delivery | 97  |
|            |                |                   | Low-temperature solution method | Tumor radiotherapy | 95  |
|            |                |                   | Two-step reaction method | Magnetic resonance imaging | 98  |
|            |                |                   | Biogenic one step procedure | Inhibit the growth of human pathogens | 99  |
|            |                |                   | Controlled synthesis approach | Antimicrobial activity | 105 |
|            |                | Cu                | One-step solid state reaction | Tumor PDT | 103 |
|            |                |                   | High-temperature reaction | Photocatalytic antibacterial therapy for E. coli | 104 |
|            |                |                   | Controlled synthesis approach | Antimicrobial activity | 105 |
|            |                | Mn                | Galvanic replacement reaction | Tumor PTT | 115 |
|            |                |                   | Galvanic replacement reaction | Tracking of cancer cells | 116 |
|            |                |                   | One-pot method | Detection of IgG | 117 |
|            |                |                   | Wet precipitation technique | Nonenzymatic electrochemical sensor | 120 |
|            |                |                   | Combined effort of electrochemical and thermal annealing reactions | Photocatalytic activity and glucose detection | 121 |
|            |                |                   | Kirkendall effect method | Synergetic tumor chemo/PTT/PDT | 122 |
|            |                | Mn                | Surfactant-assisted synthesis under microwave-heating condition | MRI | 126 |
TABLE 1  (Continued)

| Dimensions | Nanostructures | Transition metals | Synthetic methods | Applications | Ref. |
|------------|----------------|------------------|-------------------|--------------|------|
|            |                |                  | One step reaction | MR/fluorescence-based imaging | 127  |
|            |                |                  | Thermal decomposition | T1 contrast agent for cancer diagnosis | 128  |
| Nanoflowers| Mo             | Two-step microwave-assisted solvothermal method | MRI and tumor PTT | 140          |
|            |                | Hydrothermal method | Tumor PTT, PDT, and chemodynamic therapy | 141          |
|            |                | One-pot hydrothermal route | Antibacterial effects for wound healing | 142          |
| Ag         | Bimolecular synthetic approach |                 | Antibacterial activity for *P. aeruginosa, S. faecalis, and E. coli* | 143          |
|            | One-pot, seed- and surfactant-free synthetic method |                 | Cancer cell targeting and surface-enhanced Raman scattering imaging | 144          |
| Cu         | Reflux condensation approach |                 | Intracellular pH sensing | 145          |
|            | *Dodonaea angustifolia* (DA) extract synthesis |                 | Antimicrobial agent for *E. coli* and *S. aureus* | 146          |
|            | Biosynthetic method |                 | Photocatalytic antimicrobial agent | 147          |
| Triangle-shaped nanostars | Te | One-pot hydrothermal method | Tumor RT and immunotherapy | 152          |
| Octapod nanoparticles | Fe | Thermal decomposition method | MRI | 153          |
| Angular-shaped nanoparticles | Fe | One-pot method | MRI/FI | 154          |

great potential for NIR-induced photothermal therapy of cancer.45

3  | **2D TRANSITION METAL–BASED NANOMATERIALS WITH ANISOTROPIC SHAPE FOR BIOMEDICAL APPLICATIONS**

Compared with 1D nanoparticles, 2D transition metal–based nanomaterials with unique plate-like structures show extraordinary physicochemical properties and large surface areas, which draw great attention in the biomedical field. What is more, the 2D nanomaterials with large surface area are potential for drug delivery systems. In addition, the X-ray attenuation and optical properties of 2D transition metal–based nanomaterials can also be applied for PTT or RT of diverse diseases. Moreover, 2D nanomaterials could be utilized as multifunctional nanomaterials for cancer theranostics through integrating and utilizing other functional nanoparticles and their inherent physical properties.

3.1  | **Nanosheets**

In recent years, many kinds of 2D layered transition metal (including Bi, Mo, W, Pd, and Ru) dichalcogenides have been studied for biomedical applications.46–48 Bismuth-based nanosheet is a type of 2D layered topological insulators with superior photovoltaic and photoelectric properties,49–51 which has drew great attention in biomedical applications due to the remarkable biocompatibility and bioactivity. Chu and co-workers in their work have designed and synthesized the Bi2Se3 ultrathin nanosheets used in cancer PA imaging-guided PTT. More importantly, these Bi2Se3 nanosheets could be excreted from the body in 30 days.52 In 2018, our group prepared a hyaluronic acid-polypyrrole hybrid-modified bismuth selenide nanodish, which was loaded with photosensitizer
zinc phthalocyanine (Bi$_2$Se$_3$@HA-doped PPy/ZnPc) to act as the theranostic nanoplatform for cancer therapy.\textsuperscript{53} Such nanodish could serve as a CT/PA imaging-guided PTT/PDT/RT-triple combined therapy.

Recently, molybdenum (Mo)-based nanosheets have drawn great interest because of their remarkable mechanical, biological, physicochemical, and electrical properties.\textsuperscript{54,55} In a representative work, the researchers have facilitated the PEG-modified molybdenum disulfide (MoS$_2$) nanosheets by the chemical exfoliation strategy and used such nanosheets as highly efficient drug nanocarriers.\textsuperscript{56} In another study, the intracellular behavior of MoS$_2$ nanosheets was studied by Zhu et al. through HeLa and MCF-7 cells (two cancer cell lines) and human aortic endothelial cells (a normal cell line).\textsuperscript{57} It was found that MoS$_2$ nanosheets could exit cells via exocytosis after entering cells by endocytosis, which was less efficient in cancer cells. Therefore, MoS$_2$ nanosheets preferably accumulated in tumor cells rather than in normal cells. Beyond that, MoS$_2$ nanosheets have also shown the capability enabled by their photocatalytic properties in the semiconducting phase and antibacterial effect induced by other biological properties.\textsuperscript{58–62}

Palladium (Pd) nanosheets are a type of 2D nanomaterials with changeable NIR region localized surface plasmon resonance (LSPR) absorption. The freestanding hexagonal Pd nanosheets were synthesized by Zheng and co-workers in 2009, which exhibited a blue color, tunable, well-defined NIR region LSPR peak.\textsuperscript{53} Pd nanosheets showed enhanced PT stability in comparison of Au and Ag nanomaterials, which is able to generate stronger PT effect to kill tumor cells. Low cellular uptake is a major limitation of the nanomaterials; to fix this issue, silica-coated Pd ultrathin nanosheets were designed by Zheng et al.\textsuperscript{64} Due to the enhanced cellular uptake efficiency, such silica-modified Pd nanosheets could remarkably improve in vitro tumor cell killing efficiency. Zheng et al. also used the uniform Pd nanosheets to synthesize the silver-modified Pd (Ag@Pd) core–shell nanoplates.\textsuperscript{65} These synthesized core–shell nanoplates shown superior PT stability and changeable LSPR absorption among NIR region.

There have been other types of other transition metal-base nanosheets also showing great potential in biomedical yield. For instance, Zhou et al. synthesized a new monolayer LDH-loaded ruthenium (Ru) hybrid (Ru(Cby)$_2$/mLDH) biosensor, which could be significantly exclusive to cancer hypoxic microenvironment. Such nanomaterials could be used as light-switchable supra-molecular theranostic agents for tumor in vivo imaging and photodynamic therapy (PDT).\textsuperscript{66} In another interesting work, researchers have developed a novel organic-base-driven intercalation and delamination approach to synthesize...
Ti₃C₂ nanosheets with multilayer and monolayer. Compared with certain other advanced 2D nanomaterials, such Ti₃C₂ exhibited a much higher extinction coefficient at a wavelength of 808 nm (Figure 3). Ti₃C₂ 2D nanomaterials with a higher PT conversion efficiency (30.6%) were also studied by Chen and co-workers for the use in cancer PTT. Besides, a series of diverse metal ions (such as Ni²⁺, Mn²⁺, Fe³⁺, Co²⁺, and Gd³⁺) doped WS₂ nanomaterials using a bottom-up solution method were reported by Liu and co-workers. In this work, Gd³⁺-doped WS₂ nanomaterials were applied to realize PA/CT/MRI triple-modal imaging-guided combined antitumor therapy. Through mild hyperthermia-induced intratumor blood flow, such nanoflakes can efficiently enhanced cancer oxygen level, which is desired to overcome the limitations of radiotherapy during combined therapy due to hypoxia.

### 3.2 Nanotriangles

In contrast to other shapes of nanoparticles, because of special local curvature, sharp vertices and edges, and larger surface-to-volume ratio, nanotriangles possess the remarkable cellular internalization and high drug loading capacity. What is more, certain types of nanotriangles exhibited high absorptions in both the first near infrared (NIR-I) regions and the second near infrared (NIR-II) regions due to their special morphology, which is beneficial to produce hot electrons in a much deeper tumor site.

As a type of representative 2D nanoparticles, Au-based nanotriangles have been used in biological, medical, and pharmaceutical applications. Especially, because of significant photoelectric and thermoelectric properties, Au-based nanotriangles can be acted as PT agents. For example, Liz-Marzán et al. reported a series of 50–150 nm Au nanotriangles. The obtained Au nanotriangles shown a high shape yield (>50%) and high monodispersity (<3% standard deviation). Due to the unique optical properties and high quality, such Au nanomaterials could be applied as efficient nanoplasmonic devices. In another case, with gold triangular nanoprisms (AuTNPs) as probes Wang et al. developed a novel approach for living cells’ H₂O₂ detection through dark-field scattering spectroscopy (Figure 4A). Besides, some study reported that...
the novel write-once plasmonic memories and plasmonic logic chips could also be achieved by etching AuTNP. In our recent work, SO$_2$ prodrug-loaded Au–Ag hollow nanotriangles were developed, which could enhance mitochondrial Bax expression and generate SO$_2$ for deep cancer therapy within the acidic tumor microenvironment.

Besides 2D gold nanostructures, copper-based nanotriangles are emerging as another kind of candidate because of their good electrical and optical properties, low cytotoxicity and cost, and a wide range of prospective and well-established applications in lots of fields (biological imaging, drug delivery carriers, chemical sensors, and solar cell devices). Based on the fact that precursor of copper dialkyl dithiophosphate could be decomposed in oleylamine, a CuS nanotriangle was obtained by Chen and co-workers via a solvothermal approach. Besides, with the existence of halide ions, Tao et al. designed and synthesized the nanotriangular CuS resulting from the oil-soluble disk-shaped nanocrystal intermediates Ostwald ripening (Figure 4F–L). Nanocrystals composed of CuS exhibited semimetallic behavior and were also capable of supporting LSPR in the NIR wavelengths, which could be used as potential photothermal agents in vivo.

Through a nanosphere lithography and co-deposition process, patterned and composition-graded nanotriangle arrays with multilayered Ag–Cu were obtained by Zhao et al. recently. Index sensitivity of the obtained nanotriangles increased along with the layers number, demonstrating that the graded boundaries could enhance plasmon resonance sensing, which further confirmed that the PTT effect for diseases could be regulated by the nanostructure shape following treatment need. In another interesting work, through nanosphere lithography technique, the gold nanotriangle and vanadium dioxide (VO$_2$) hybrids’ sandwich nanostructure (VO$_2$/Au/VO$_2$) was synthesized by Guo group. Through changing near-field permittivity of the Au nanotriangle, this work exhibited tunable LSPR via VO$_2$ phase transition external thermal stimuli. These findings verified that such sandwich nanostructure is one effective method to build a tunable resonance responses plasmonic structure, which could be tailored by varying the hybrid structures’ bottom and top phase materials properties. In Lu’s work, the experimental research on ZnO nanoparticles array acoustic vibrations with diverse Ga doping concentration was presented through femtosecond pump–probe technique. Through pulsed laser deposition and nanosphere lithography methods, the obtained nanotriangle materials have different sizes (190, 232, and 348 nm). The study is helpful to evaluate the elastic characteristics and crystal structure distortion of doped nanomaterials with optical methods. Moreover, it also offers a ZnO-based optoelectronic devices complementary thermal management approach.
4 | 3D TRANSITION METAL–BASED NANOMATERIALS WITH ANISOTROPIC SHAPE FOR BIOMEDICAL APPLICATIONS

Except for 1D and 2D transition metal–based nanomaterials, 3D transition metal–based nanomaterials with unique structures have broad application prospects in biomedical fields. Over the past decade, these “next-generation” nanomaterials have received more and more attention and a lot of efforts have been devoted to exploring their unique biomedical applications. These transition metals (including Bi, Te, Zn, Au, Ag, Mn, Cu, Pt, etc.) based 3D nanomaterials have been widely evolved into various nanostructures, such as nanorods, nanocubes, nanoflowers, and so on.

4.1 | Nanorods

In the past two decades, nanorods attracted much attention due to their special rod-like shape-induced unique properties and their possibility to become building blocks for future life science applications. Compared with normal spherical nanoparticles, more advantages of this nanostructure are generally accepted, such as increased ability for cell internalization, high drug loading capacity, and easy functionalization process. Recently, various transition metals, including Bi, Fe, Zn, and so on, have been shaped into nanorod structures.

4.1.1 | Bismuth-based nanorods

As a biologically nonreactive heavy metal, Bi-based nanoparticles have gained much interest in biomedical field, owing to excellent characterizations, such as low toxicity, desirable catalytic activity, and favorable antibacterial activity. Among these various morphologies, Bi chalcogenides (e.g., Bi sulfide [Bi$_2$S$_3$]) nanorods have been extensively studied. In 2015, Zhao et al. first used Bi$_2$S$_3$ nanorods as a therapeutic agent for imaging-guided tumor therapy (Figure 5A). In this paper, prepared Bi$_2$S$_3$ nanorods were about 10 nm in diameter and 50 nm in length, which were constructed by a solvothermal approach under the temperature of 150°C for 10 h. In their following research, they additionally explored the imaging capabilities of Bi$_2$S$_3$ nanorods for noninvasive imaging of gastrointestinal (GI) tract. The in vivo results proved that Bi$_2$S$_3$ nanorods were multi-modal contrast agents to detect their biodistribution in GI tract by CT and photoacoustic tomography imaging. Recently, Wang et al. prepared a kind of biomimetic Bi$_2$S$_3$ nanorods, which were camouflaged by a platelet membrane to enhance their ability of immune escape for tumor RT. These Bi$_2$S$_3$ nanorods were approximately 100 nm in length and 15 nm in diameter, which were prepared by solvothermal method. The results proved that the as-prepared Bi$_2$S$_3$ nanorods had a good cancer therapeutic efficiency.

4.1.2 | Iron-based nanorods

Iron (Fe)-based nanoparticles exhibit some characterizations resulted from finite-size and surface effects, such as high magnetization and additional anisotropy contributions, and have been widely used in biomedical applications. Among Fe-based nanorods, iron oxide nanorods are the most common nanostructures. Yeh et al. constructed porous iron oxide-based nanorods with diameters of 38 ± 5 nm and lengths of 480 ± 45 nm for drug delivery, which could control the release of drugs. In this study, the low-temperature solution method was used to synthesize iron oxide-based nanorods, firstly in aqueous solution with FeCl$_3$ as precursor and then calcined to form the porous structures. In 2015, the further imaging ability of iron oxide-based nanorods was investigated by Aslam group, which were synthesized by a two-step reaction for magnetic resonance imaging (MRI). Later, Ezema et al. found a biogenic procedure for preparation of iron oxide nanorods using *Moringa oleifera* aqueous extract (Figure 5B–D). The formulated nanorods were able to effectively inhibit human pathogens even at the low concentration.

4.1.3 | Zinc-based nanorods

Compared to other Zn-based nanomaterials, ZnO nanorods are easy to prepare and stable under harsh processing conditions, which were generally considered bio-safe and biocompatible. Back in 2011, Wang et al. reported a one-step solid-state reaction to fabricate ZnO nanorods for multi-mode cancer treatment as the drug carrier and photodynamic agent simultaneously. Beyond that, the antibacterial effect of ZnO nanorods was also explored. Ding et al. compared the antibacterial ability of ZnO nanorods with several conventional antibiotics (Figure 5E and F). Compared with commonly used antibiotics, ZnO nanorods (15–22 nm, smaller than 300 nm) were able to significantly inhibit the growth of *Escherichia coli*. Recently, Berenjian et al. fabricated the ZnO nanorods by controlled synthesis using secreted carbohydrates of *Chlorella vulgaris*. In this study, the antibacterial ability of ZnO nanorods was also demonstrated.
4.1.4 | Other transition metal–based nanorods

Besides the above nanomaterials, a number of other transition metal–based nanorods also shown promises in biomedicine. Emelianov et al. developed a seedless approach to synthesize the gold nanorods (AuNRs) with the small size of $8 \times 49$ nm, which showed a NIR-II region absorbance at 1064 nm. Under nanosecond laser irradiation, this kind of small AuNRs displayed three times thermal stability and 3.5-fold photoacoustic signal than the large AuNRs ($8 \times 49$ nm). In another study, Liz-Marzán et al. reported a monodisperse polymer-coated silver nanorods (AgNRs), which were synthesized through a wet-chemistry reaction. Experimental results confirmed that these AgNRs had good optical response and therapeutic efficiency. Beyond that, Swart et al. synthesized a type of CdO nanorods by using a combustion approach. Compared with pure CdO structures, the as-prepared Zn-doped CdO nanorods had enhanced antibacterial and antifungal ability.

4.2 | Nanocubes

Nanocubes, as its name implies, possessing the cube-like shape, have been widely used for diagnosis and treatment. In contrast to spherical nanoparticles, nanostructures in cubic shape were approved to improve the imaging and therapeutic efficiency. To date, transition metal materials such as Au, Cu, Mn, and so on have been fully applied and researched.

4.2.1 | Gold-based nanocubes

Gold nanocubes (AuNCs) are a new type of nanostructures, which was first found by Xia group in 2002. In 2007, Xia et al. reported an emerging type of gold nanocages for photothermal therapy. These nanocages were synthesized using a galvanic replacement reaction between silver nanocubes, which served as sacrificial templates. Later, Xia et al. took advantage of AuNCs to track and quantify them in the target cells or tumors.
The in vivo tracking results of AuNCs with an outer edge length of approximately 50 nm offered insights into the metastasis of cancer. Recently, Liu et al. reported a lateral flow strip biosensor-based Au nanocage for IgG detection.117 Their results showed that AuNCs-based strip biosensors exhibited high sensitivity and stability without any aggregation during the conjugation process.

4.2.2 Copper-based nanocubes

Copper (Cu) is another transition metal that can be easily converted into cubic nanomaterials.118,119 Recently, Neri et al. fabricated a cuprous oxide (CuO) nanocubes-based nonenzymatic electrochemical sensor.120 In this research work, CuO nanocubes were prepared by a wet precipitation reaction. Experimental results proved that CuO nanocubes were able to detect glucose. Soni et al. also explored nonenzymatic sensing behavior of copper oxide nanocubes, which were synthesized by synergistic electrochemical and thermal annealing methods (Figure 6D–H).121 Then these as-prepared nanocubes were proved to show the excellent photocatalytic ability and glucose monitoring characterizations. In addition to CuS nanocubes, copper chalcogenide (e.g., CuS) nanocubes also exhibited a considerable application in biomedicine. Qu et al. synthesized a kind of hollow CuS nanocubes about 250–300 nm through the Kirkendall effect for synergistic chemo/PTT/PDT therapy.122 From the experimental results, hollow CuS nanocubes had a rapid NIR-triggered temperature increase and ROS production ability.

4.2.3 Manganese-based nanocubes

Recently, a number of strategies and biomedical applications of Mn-based nanocubes have been carefully investigated, such as MRI, drug delivery, and several combined treatments.123–125 Back in 2008, Lin et al.
found that Mn$^{2+}$ could be readily converted into cubic metal–organic frameworks through microwave-heating reaction, which showed high T1-weighted MRI ability for contrast-enhanced tumor imaging. After that, more and more studies have reported imaging capabilities of Mn-based nanocubes. For example, Fernandes et al. constructed Mn-containing Prussian blue nanocubes for MRI and fluorescence imaging of tumors. In another representative work, Zhao group presented a type of manganese oxide nanocubes with smaller size of about 33 nm for tumor diagnosis (Figure 6I).

4.2.4 Other transition metal–based nanocubes

Besides the above three typical transition metals, other types of nanocubes are also researched. Hyeon et al. constructed iron oxide nanocube for thermotherapy (Figure 6J). The iron oxide nanocubes were synthesized by using a nanoprecipitation process. In 2017, Tang et al. reported platinum concave nanocubes for ultrasensitive detection. In another attempt, Chen group synthesized ultrasmall copper sulfide (CuS)–ferritin (Fn) nanocages by natural mineralization of Fn, for imaging-guided PTT treatment of tumors.

4.3 Nanoflowers

Nanoflowers refer to a group of special nanostructures that have flower-like shapes in microscopic view, showing unique properties for biomedical applications. This nanostructure can react at cellular level and within the cells, showing a perfect manner for diagnosing and treating diseases in a wide range of animal and human bodies. Among these, nanoflowers produced by Mo, Zn, and Cu elements are at the forefront of research and show widespread applications.

4.3.1 Molybdenum-based nanoflowers

Among the Mo-based nanoflowers, MoS$_2$ has been studied widely in biomedicine. So far, many reports on the synthesis of MoS$_2$ nanoflowers for biomedical applications, especially for synergetic cancer therapy, have been emerged. For example, Shao et al. constructed multifunctional flower-like Mn-doped Fe$_3$O$_4$@MoS$_2$ nanoparticles using a two-step microwave-assisted solvothermal approach for diagnosis and treatment of liver cancer. The results showed that these flower-like nanostructures with an average diameter of approximately 50 nm exhibited good synergistic chemophotothermal therapeutic efficiency. In addition to the PTT efficiency, the unique catalytic therapeutic ability of MoS$_2$ nanoflowers has been studied. Huang et al. synthesized a kind of porous MoS$_2$ nanoflowers, which showed peroxidase-like activity for ROS generation. As a result, this nanosystem could achieve PA/CT imaging-guided PTT/PDT/chemodynamic therapy combined cancer treatment. Importantly, the catalytic capacity of MoS$_2$ nanoflowers could be applied for other diseases treatment. Gu et al. first prepared a biocompatible antibacterial platform based on PEG–MoS$_2$ nanoflowers, which were synthesized through a one-pot hydrothermal reaction (180°C for 12 h) (Figure 7A–C). Subsequently, the E. coli and Bacillus subtilis were applied as a biological model to explore the antibacterial effect of PEG–MoS$_2$ nanoflowers. Experimental results proved that these MoS$_2$ nanoflowers could efficiently catalyze hydrogen peroxide to produce hydroxyl radicals to kill the bacteria for the rapid healing of wound.

4.3.2 Silver-based nanoflowers

In the past years, silver (Ag) nanoflowers show great potential in biological applications. For example, Bohidar et al. proposed branched flower-like Ag nanostructured particles (SNFs), which were prepared by an interesting bimolecular method. As-prepared SNFs showed a variety of antimicrobial ability. Later, Hu et al. employed a one-pot, seedless, surfactant-free synthesis way under room temperature to synthesize a type of chitosan-coated Au–Ag nanoflowers with size of 50, 80, and 120 nm. Compared with nanospheres, these nanostructures about 80 nm exhibited stronger and more stable surface-enhanced Raman scattering signals. Recently, Hiroshi Uji-i copper (Cu) is another transition metal that can be easily converted into cubic nanomaterials prepared by gold-coated silver nanoflowers (AuAgNFs) (Figures 7D and 7E). The AuAgNFs could be able to detect pH changes in cells.
green method and then assembled them into nanoflowers by using *Dodonaea angustifolia* extract (Figure 7F). In comparison with CuO nanospindles, the antibacterial ability of CuO nanoflowers with the average diameter and length of 38 nm and 97 nm, was improved. Haque et al. also explored a biosynthetic method to synthesize flower-shaped CuO nanoparticles by *O. sanctum* leaves extract. The results demonstrate the sustainability performance of these CuO nanoflowers in the degradation of methylene blue as well as inhibition of bacteria.

### 4.3.4 Other transition metal–based nanoflowers

Besides the above typical nanoflowers, other transition metals are also researched for biomedical application. For example, Chen et al. reported a chiral gold nanoflower (GNF) through a one-pot green approach. The GNFs exhibited good biocompatibility, imaging ability, and photothermal effect. In another study, Singh and co-workers prepared the well-crystalline ZnO nanoflowers by a low-temperature (65°C) synthesis method and studied their antimicrobial effect for *E. coli* and glucose detection efficiency. ZnO nanoflowers were also found in this work to be effective electron mediators for the fabrication of efficient enzyme-free glucose sensors. In addition, Wu et al. also researched Fe3O4 nanoflowers (Fe-NFs) with controllable dimensions through a simple solvothermal way. In this work, these nanoplatforms could be able to achieve MRI-guided PTT of tumor.

### 4.4 Other nanostructures

In addition to the above nanostructures, some other 3D nanocarriers with special shapes are also studied. For example, Chen et al. constructed a triangle-shaped
tellurium (Te) nanostar (GTe-RGD) for radiotherapy. In this study, GTe-RGD was prepared by a one-pot hydrothermal way. In another work, Zhao et al. fabricated a type of morphology and size controllable octapod iron oxide nanoparticles, which could be used as imaging agents for early stage monitoring of tumor. Comparing with nanospheres, this octapod-shaped nanostructure (edge length of 30 nm) showed better MRI. Piao et al. also focused on improving MRI effect of iron oxide nanoparticles, which were prepared by stirring vigorously with a mixed solution. These nanostructures also showed excellent MRI ability.

5 SUMMARY AND PERSPECTIVES

In this review, we systematically reviewed the latest advances in transition metal–based nanomaterials with anisotropic shape for biomedical applications. Controlled synthesis of transition metal–based nanoparticles with anisotropic shape reported by diverse research groups, performance regulation via the morphology, and research progress in biological applications using anisotropic transition metal–based nanomaterials are summarized in detail. Explorations regarding the biomedical application of nanomaterials by integrating nanostructures with other functional decoration to achieve the precise and abroad applications are further discussed. Compared with other inorganic nanomaterials, transition metal–based nanomaterials have the following advantages: (1) the composition of nanomaterials can be controlled in a wide range; (2) the crystal phase, electronic structure, and other aspects can be easily controlled to improve physical and chemical properties; (3) the physical, chemical, and biological properties and even influence of the cytotoxicity, uptake, targeted delivery, biodistribution, and pharmacokinetics can be regulated by precise control of their morphology.

Although tremendous interesting studies were reported in this field in the past few years, there are still some potential challenges against these anisotropic transition metal–based nanoparticles. Lots of nanostructures with anisotropic shapes are prepared following harsh conditions and complex procedures, which significantly deteriorate the yield, productivity, and reproducibility. Therefore, how to achieve a precise and controllable synthesis of anisotropic transition metal–based nanoparticles with a large-scale yield is one of the problems we need to solve. At the same time, the green-synthesis approaches of transition metal–based nanoparticles, the determination of reactive sites, and the understanding of biological action mechanisms still need to be further studied in detail. With the help of density functional theory theoretical calculations and in situ characterization techniques, we can deeply explore the unique physical–chemical properties and reaction mechanisms, which could further expand and promote the rapid development of anisotropic transition metal–based nanoparticles application in biological fields.

Another concern is the potential long-term safety issues of the anisotropic transition metal–based nanoparticles, particularly those that are hardly biodegradable and might accumulate in the body for a long time postadministration. Despite large amounts of studies have verified that some transition metal–based nanoparticles, such as gold-based nanocubes, when under appropriate sizes and surface modification, are not conspicuously toxic both in vitro and in vivo between a specified dose range, it is still extremely hard to finally find clinical use of those transition metal–based nanoparticles, due to their unclear absorption–distribution–metabolism–excretion pathway in the body. In this case, the development of biocompatible and biodegradable transition metal–based nanoparticles for biological applications could thus have much higher value.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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