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Recent developments and prospects of inorganic nanozymes for biomedical applications

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The development of inorganic nanozymes has revolutionized the field of nanotechnology by providing a new class of catalytic materials that exhibit enzyme-like activities. Compared with traditional natural enzymes, nanozymes have broad application prospects in the field of biomedicine due to their higher chemical stability, stronger environmental adaptability, and ability to maintain their activity under extreme conditions. To provide a comprehensive overview of the recent progress made in this field, herein, an overview of inorganic nanozymes for biomedical applications is provided. In this review, the structure, synthesis methods, and catalytic mechanism of inorganic nanozymes are summarized. Subsequently, the latest progress of various inorganic nanozymes for the applications in biomedicine is reviewed, including diagnostic applications, therapeutic applications and drug delivery systems. Then, the recent developments in the modification and multifunctionalization of novel inorganic nanozymes are discussed. Finally, the challenges and prospects of inorganic nanozymes in the field of biomedicine are highlighted and pointed out. We hope that this timely review can further advance this promising field.

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1. Introduction

Natural enzymes, as a class of extremely important biological catalysts, have long been known for their exceptional substrate specificity and catalytic efficiency, enabling chemical reactions within organisms to proceed efficiently and specifically under physiological conditions.[1,2] However, their practical utility in industrial and biomedical settings is significantly hampered by their inherent limitations. Natural enzymes exhibit poor stability, with their activity readily compromised by environmental fluctuations in temperature, pH, and pressure.[3] Furthermore, their susceptibility to other proteolytic degradation presents additional challenges.

To overcome the above-mentioned limitations, some alternative enzyme mimics like enzymatic hybrid nanoflowers and

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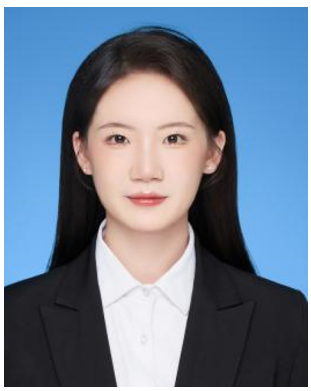

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nanozymes have been actively explored.[4] Nanozymes combine the intrinsic properties of nanomaterials with enzyme-like catalytic functions, which have the ability to convert catalytic substrates because of the presence of specific nanostructures with similar active sites or charge/electron transfer.[5] The term "nanozymes" was coined by Scrimin and co-workers in 2004 in their work focusing on the synthesis of triazacyclononane/Zn^{2+}–gold nanoparticles and their catalytic behavior in the transphosphorylation reaction.[6] In 2007, the discovery of inherent peroxidase-like activity in inert ferromagnetic nanoparticles led to the in-depth and sustained exploration of nanozymes.[7]

Compared with natural enzymes, artificial nanozymes have been demonstrated to exhibit enhanced stability, simplified manufacturing, and superior durability.[8] More notably, some non-biological processes can also be catalyzed by nanozymes.[9] As a type of nanozyme, inorganic nanozymes can achieve higher stability and adjustable enzyme activity than organic nanozymes, making them more suitable for industrial and commercial applications.[10–12] Consequently, research efforts dedicated to advancing the design and applications of inorganic nanozymes have surged considerably in recent years (Scheme 1).

1.1 Characteristics of inorganic nanozymes

Inorganic nanozymes are a class of enzyme mimics predominantly composed of metal or metal oxide nanoparticles or their composites with other materials.[13] The advantages of metal nanoparticles and functionalized polyoxometalates are combined in inorganic nanozymes.[14] These nanomaterials are engineered to exhibit specific enzyme-like activities and emulate the activity of specific natural enzymes, such as peroxidase-like, oxidase-like, catalase-like, or superoxide dismutase-like activities.[15] Crucially, their catalytic performance is primarily governed by their physicochemical properties, such as size, shape, surface characteristics, and nature of the core material.[16]

1.1.1 Catalytic activity. The hallmark of inorganic nanozymes is their capacity to efficiently catalyze specific chemical reactions, mimicking the function of their natural counterparts.[17] These diverse reactions include oxidation, reduction, and hydrolysis. For instance, copper/cobalt-based metal sulfide nanoparticles exhibit peroxidase- and oxidase-like activities, which are capable of generating reactive oxygen species (ROS) to exert bactericidal effects.[18] Similarly, zinc-implemented oligopeptide-based bionanozymes demonstrating with intrinsic hydrolase-like activity, which have been proven to hydrolyze *p*-nitrophenyl esters (*e.g. p*-NPA, *p*-NPH, and *p*-NPS).[19]

1.1.2 Size-dependent properties. The catalytic performance and activity of inorganic nanozymes are profoundly influenced by intrinsic nanoscale factors, particularly their size, morphology, and surface properties.[20] Among them, size-dependent behavior is a key manifestation in enhancing their catalytic efficiency.[21] Ultrasmall cerium-based metal–organic frameworks (Ce-MOFs) fabricated in aqueous solution exhibited 3–15-times higher hydrolytic activity than that of its bulk counterparts, which is attributed to its more densely distributed active sites.[22] The peroxidase-like activity of a graphene quantum dot–TiO_2 nanotube hybrid nanozyme was demonstrated by carrying out the catalytic oxidation of the chromogenic substrate 3,3′,5,5′-tetramethylbenzidine in H_2O_2. Its porous morphology and periodic structure provide unobstructed channels for reactants and products as well as acceptable reproducibility.[23]

1.1.3 Surface modification and functionalization. To further improve the catalytic properties of inorganic nanozymes and target specific reactions, their surface can be engineered with various functional groups.[24] These modifications serve to enhance critical attributes including solubility, biocompatibility, and reaction specificity.[25] Qiulan Li *et al.* designed a nanocomposite with multi-enzyme-like activities to solve the problem of diabetic wounds. Consequently, diabetic wounds were healed through a pH-switchable glucose-initiated cascade reaction with glucose oxidase, owing to the intrinsic-,

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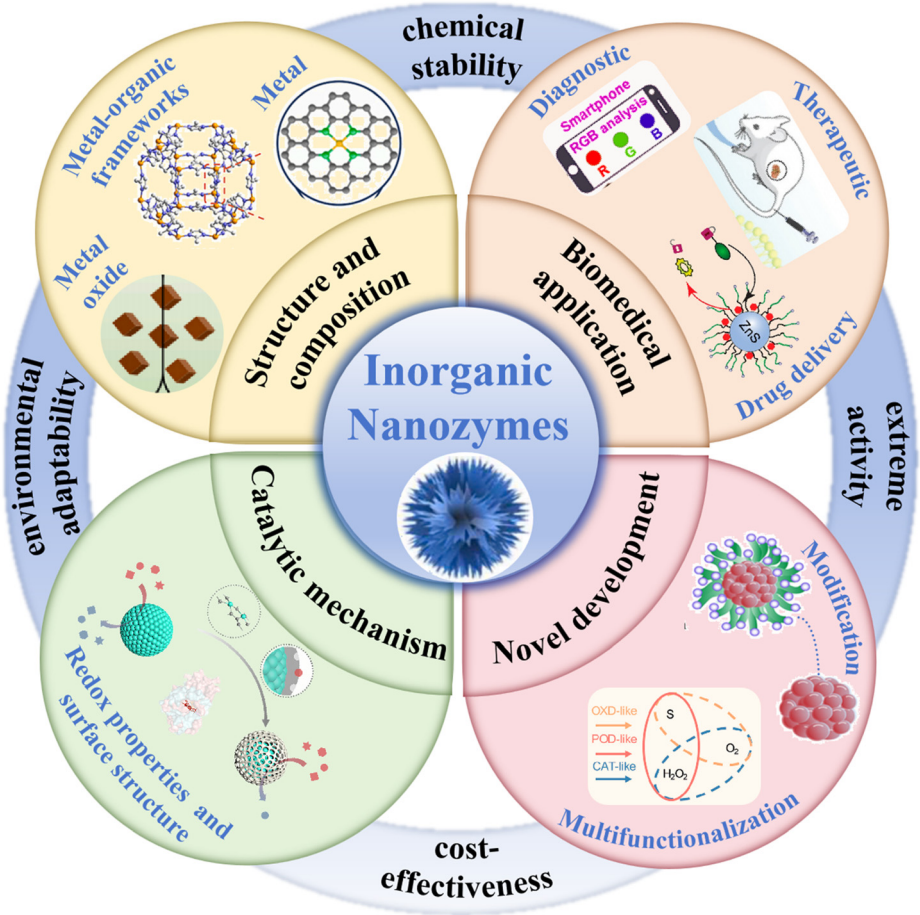

Scheme 1 Schematic of the development of inorganic nanozymes and their applications in the biomedical field. The light-yellow region (inner circle) presents the various structures and compositions of inorganic nanozymes (reproduced from ref. 68 with permission from Elsevier, Copyright 2024; ref. 22 with permission from Elsevier, Copyright 2024; and ref. 41 with permission from Elsevier, Copyright 2024). The light-green region (inner circle) shows the catalytic mechanism of inorganic nanozymes (reproduced from ref. 30 with permission from the American Chemical Society, Copyright 2024). The light-pink region (inner circle) presents the multifunctionalization and modification of novel inorganic nanozymes (reproduced from ref. 86 with permission from Wiley, Copyright 2023). The light-orange region (inner circle) shows their diverse biomedical applications (reproduced from ref. 83 with permission from The Royal Society of Chemistry, Copyright 2022; ref. 49 with permission from Elsevier, Copyright 2022; ref. 148 with permission from Journal of the American Chemical Society, Copyright 2022). The surrounding blue region (outer circle) presents the advantages of inorganic nanozymes.

peroxidase-, oxidase-, catalase- and superoxide dismutase-like activities on the nanocomposite.[26] Moreover, a nickel-based single-atom–metal-cluster biocatalyst with excellent water solubility, colloidal stability, and target specificity was developed for inducing tumor ferroptosis.[27] Xiao Han *et al.* synthesized a biomimic and translational cerium vanadate nanozyme to treat glioblastoma and repair brain damage after ionizing radiation. The nanozyme was observed to exhibit excellent pH dependence, *i.e.*, potent superoxide dismutase enzyme activity in a neutral environment and peroxidase enzyme activity in an acidic environment (Fig. 1).[28]

1.2 Comparative advantages of inorganic nanozymes

As discussed above, inorganic nanozymes have emerged as promising alternatives to overcome the inherent limitations of natural enzymes.[29] Compared to their traditional counterparts, the distinct advantages of inorganic nanozymes are mainly reflected in the their catalytic activity, enhanced stability, and cost-effectiveness/synthetic scalability.[30]

1.2.1 Catalytic activity. As biopolymers composed of amino acids, traditional natural enzymes generally exhibit high specificity.[31] Their specificity arises from their complex three-dimensional active sites, which are capable of precisely recognizing and transforming specific substrates.[32] Alternatively, inorganic nanozymes mimic the catalytic activity of enzymes through nanoscale engineering.[33] Compared with traditional enzymes, inorganic nanozymes typically possess superior surface activity and higher catalytic efficiency during the catalytic process due to their larger specific surface area and abundant active sites.[34] Fe_3O_4@polydopamine was introduced to augment the oxidase-like activity of an MnO_2-based nanozyme. The excellent performance of this nanozyme is attributed to its

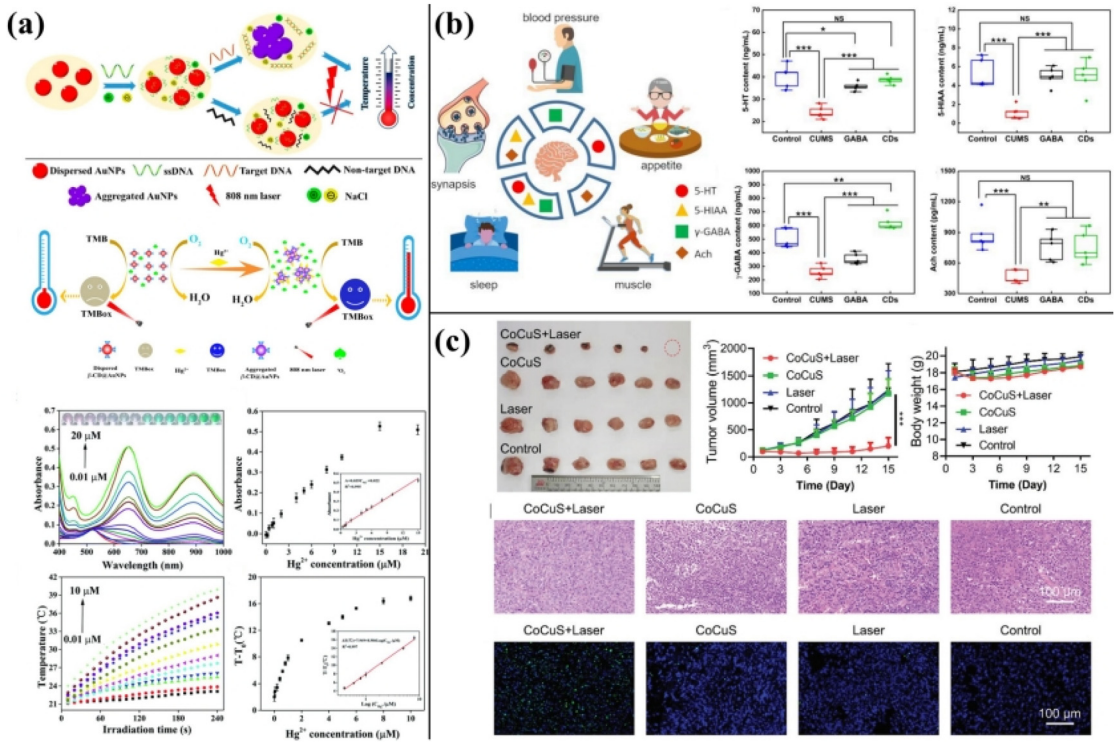

Fig. 1 (a) Multifunctional nanozyme-enabled assays. Reproduced from ref. 13 with permission from the American Chemical Society, Copyright 2022. (b) Illustration of the effects of four neurotransmitters, namely, serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), γ-aminobutyric acid, and Ach, on the hippocampus. Reproduced from ref. 15 with permission from the American Chemical Society, Copyright 2024. (c) Antitumor effect *in vivo* after different treatments. Reproduced from ref. 83 with permission from The Royal Society of Chemistry, Copyright 2022.

magnetic purification, stabilizer-free interfaces, and efficient singlet oxygen conduction.[35] A $CuMnO@Fe_3O_4$ (CMF) core–shell nanozyme was also developed to promote the antitumor activity of tumor-specific nanozymes and avoid the inactivation and oxidation of copper-based nanozymes (Fig. 2).[36]

1.2.2 Enhanced stability. A major limitation of traditional enzymes is their susceptibility to denaturation under non-physiological conditions such as elevated temperatures, extreme pH, and harsh solvents, restricting their practical utility in demanding environments.[37,38] In contrast, inorganic nanozymes, composed of inorganic materials such as metals and metal oxides, exhibit strong thermal stability, chemical resilience, and broader environmental adaptability.[39] It has been reported that a new Fe/N-doped chitosan-chelated carbon dot-based nanozyme showed superior stability in a wide pH (1–12) and temperature (20–90 °C) range. At the same time, the nanozyme also displayed

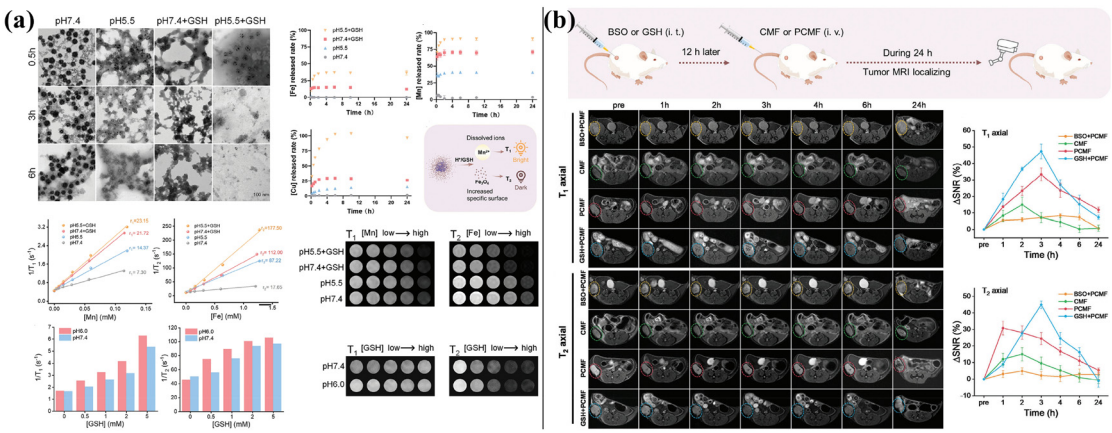

Fig. 2 The T1–T2 dual-modal MRI dynamic activation of CMF. (a) TEM images observation: the morphology changes of CMF after different treatments. (b) The release curves of Fe, Mn, and Cu ions from CMF under different conditions. Reproduced from ref. 36 with permission from Wiley, Copyright 2023.

8.8-times higher peroxidase activity than horseradish peroxidase.[40] Furthermore, the problem of insufficient catalytic activity of nanocatalysts within the acidic tumor microenvironment has been solved by integrating Rh single-atom nanozymes with photothermal therapy, which exhibited higher catalytic efficiency under weakly acidic conditions (pH = 6.0) than neutral conditions (pH = 7.4).[41]

1.2.3 Cost-effectiveness and synthetic scalability. The production of traditional enzymes often requires complex biological extraction and purification processes, posing significant challenges for large-scale applications.[42] In contrast, the methods for the synthesis of inorganic nanozymes are generally simpler and easier to scale up (*e.g.* sol–gel synthesis, heat treatment, or chemical vapor deposition). Furthermore, the raw materials employed in the synthesis process are generally more abundant and less expensive.[43] Consequently, inorganic nanozymes present obvious advantages in terms of cost and production scalability, especially in industrial applications where they can be mass-produced to reduce overall costs.

1.3 Applications of inorganic nanozymes

The discovery of inorganic nanozymes has fundamentally challenged the long-held view of inorganic nanomaterials as biologically inert, revealing their intrinsic biological effects and advancing the field of enzyme mimics.[44] Combining the high catalytic activity of natural enzymes with exceptional stability and cost-effectiveness, the research field of nanozymes has gradually expanded since they were first reported in 2007, mainly including environmental remediation, industrial catalysis, and biomedicine.[45,46]

1.3.1 Environmental remediation. Owing to the capability of inorganic nanozymes to efficiently catalyze a wide variety of reactions, such as oxidation, reduction, and hydrolysis, they play a key role in tackling environmental challenges.[47] Lixian Wang *et al.* developed a nanozyme@PA membrane by embedding peroxidase-like Cu-FeTCPP nanosheets into a PA layer for dye/salt separation in textile industry wastewater. The presence of a thinner and porous enhanced active layer in the nanoscale structure resulted in a higher water flux and selective rejection of dyes and ions.[48] A bimetallic carbon dot nanozyme with efficient peroxidase-mimicking activity has been successfully engineered for dual-mode monitoring of the gaseous pollutant methyl mercaptan in the atmosphere. The gaseous pollutant methyl mercaptan can be specifically converted to H_2O_2 with the assistance of alcohol oxidase, and then oxidized to color under the catalysis of nanozymes.[49] In addition, recent studies have also shown point-of-care testing technologies based on nanozymes in detecting various environmental pollutants, including phenolic, antibiotic residues, pesticide residues, toxic ions, and pathogenic bacteria.[50]

1.3.2 Industrial catalysis. Owing to their robust stability and tunable catalytic properties, inorganic nanozymes present compelling alternatives to conventional homogeneous and heterogeneous catalysts in industrial catalysis.[51] Nanozymes have been shown to catalyze reactions such as oxidation, hydrogenation, and carbon–carbon bond formation under mild conditions, which are valuable in chemical and fuel synthesis.[52] Some nanozymes (such as: FeCo-Prussian blue analogue nanoparticles and FeN_3P-single-atom nanozymes) can lead to boosted alcohol yields and promote the growth of

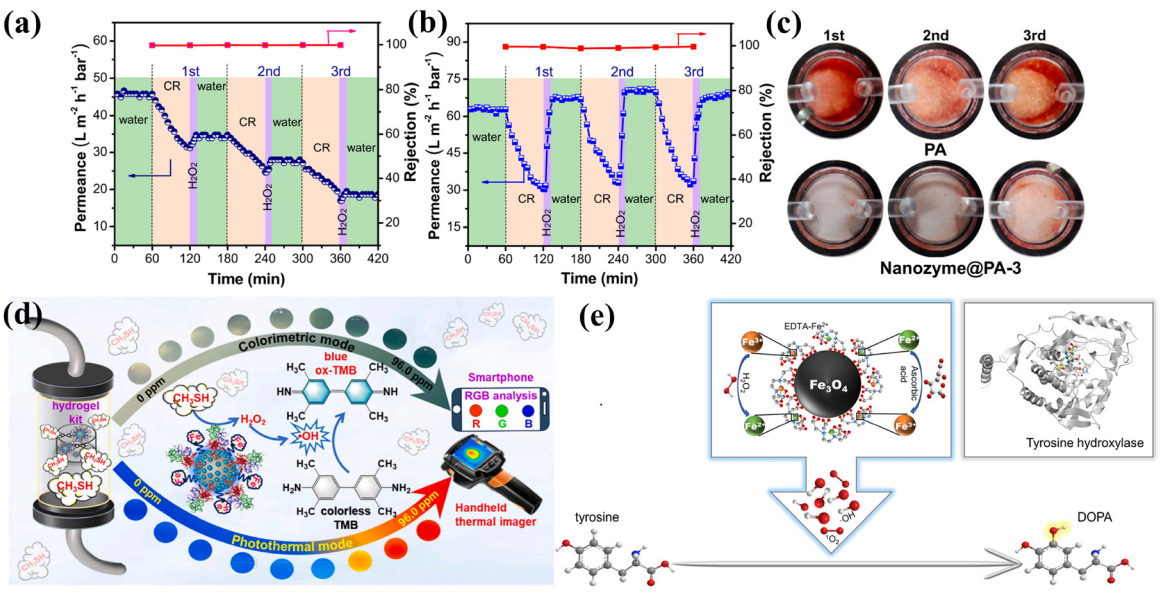

Fig. 3 Applications of inorganic nanozymes. Water permeance and CR rejection of PA membrane (a) and nanozyme@PA-3 membrane (b), and digital pictures of the tested membranes (c) in fouling cleaning cycles. Reproduced from ref. 48 with permission from Elsevier, Copyright 2025. (d) Diagram of the AOX-assisted Fe&Cu@CD nanozyme-based agarose portable hydrogel kit for enzymatic cascade catalytic H_2O_2-self-supplying colorimetric and photothermal signal synergistic amplification to achieve the onsite visual monitoring of the atmospheric CH_3SH around a waste pile. Reproduced from ref. 49 with permission from Elsevier, Copyright 2024. (e) Schematic of the reaction process for the hydroxylation of tyrosine to DOPA by the Fe_3O_4@EDTA–Fe^{2+} nanozyme. Reproduced from ref. 54 with permission from the American Chemical Society, Copyright 2022.

Saccharomyces cerevisiae cells, which is primarily attributed to their ability to suppress the production of reactive oxygen species (ROS).[53] Another study synthesized nanozymes by anchoring ethylenediaminetetraacetic acid (EDTA)-Fe^{2+} onto Fe_3O_4 magnetic nanoparticles for the synthesis of l-3,4-dihydroxyphenylalanine. The coordination structure composed of EDTA-Fe^{2+} complexes on the nanozyme is similar to the catalytic site of tyrosine hydroxylase, exhibiting an excellent catalytic performance and reusability in the conversion of tyrosine to L-DOPA.[54] The size-dependent properties and ease of surface functionalization inherent to nanozymes allow precise optimization of their catalytic activity and selectivity, making them highly efficient and reusable catalysts for diverse industrial processes (Fig. 3).[55,56]

1.3.3 Biomedical applications. In the field of biomedicine, inorganic nanozymes have emerged as powerful alternatives to natural enzymes. Their unique advantages of enhanced stability under physiological conditions, tunable catalytic activity, and potential for multifunctionality endow them with broad prospects across numerous medical domains (biosensing, antibacterial therapy, drug delivery, and anti-tumor).[57] The specific mechanisms and recent advances in these diverse biomedical applications will be discussed in detail in subsequent chapters of this review.

In summary, inorganic nanozymes have rapidly evolved into a class of multifunctional catalytic materials. Continued research advances and the development of increasingly sophisticated nanozyme systems are poised to unlock novel pathways for their integration in practical applications.

2. Types of inorganic nanozymes

2.1 Structure and composition

To date, inorganic nanozyme systems have been constructed from diverse nanomaterials. Notably, a single nanozyme can exhibit multiple enzyme activities (such as catalase-, peroxidase-, oxidase-like activities) under different conditions.[58] Based on their primary composition, inorganic nanozymes can be roughly divided into three main types, including metal-based, metal oxide-based, and metal–organic framework (MOF)-based nanozymes.[59]

2.1.1 Metal-based nanozymes. Over the past years, metal-based nanomaterials (Au, Ag, Pt and bimetallic alloys) have been extensively investigated with various enzyme-like properties due to the saturated atoms on their surface acting as active sites.[60] For instance, Au–Bi bimetallic nanoparticles demonstrate both glucose oxidase-like and peroxidase-like activities. Their glucose oxidase-like activity catalyzes the oxidation of glucose to produce gluconic acid and H_2O_2, contributing to tumor starvation therapy, while simultaneously elevating intracellular H_2O_2 levels. Subsequently, the peroxidase-like activity of Bi nanoparticles catalyzes the decomposition of H_2O_2 into highly cytotoxic hydroxyl radicals ($^{\bullet}OH$). Furthermore, the combination of bimetallic nanoparticles under NIR-II laser irradiation can exhibit a strong synergistic photothermal effect. Critically, the generated $^{\bullet}OH$ can enhance the sensitivity of cancer cells to photothermal therapy by suppressing the expression of heat shock proteins. Conversely, photothermal therapy also can promote the generation of $^{\bullet}OH$, thus establishing a mutually reinforcing cycle that significantly augments the combined efficacy of photothermal therapy (PTT) and chemodynamic therapy.[61] Additionally, the porous (Au core)@(Pt shell) nanozymes (Au@PtNEs) prepared by Bao Gao *et al.* showed highly efficient and robust peroxidase-mimetic activity. During the detection process, hydrogen peroxide oxidizes 3,3′,5,5′-tetramethylzidine (TMB), which is catalyzed by the prepared nanozyme to generate a measurable colorimetric signal. This approach offers a new platform for detecting Gram-positive pathogenic bacteria.[62]

2.1.2 Metal oxide-based nanozymes. Metal oxide-based nanozymes encompass nanoparticles comprised of metal oxides that mimic the catalytic functions of natural enzymes, where their catalytic performance is primarily governed by their surface structure, composition, and size.[63] The catalytic activity of metal oxide nanozymes can be compared to that of natural enzymes, which typically rely on a metal center to facilitate electron transfer.[64] In metal oxide nanozymes, metal ions within the oxide lattice can undergo redox cycling, thus providing active sites for catalysis.

Pioneering work in 2007 identified that Fe_3O_4 nanoparticles possess intrinsic peroxidase-like activity, which was systematically investigated.[65] Fe_3O_4 catalyzes the H_2O_2-dependent oxidation of chromogenic substrates such as TMB, following a ping-pong catalytic mechanism. Since then, numerous other metal oxide nanostructures have been reported to possess enzyme-like properties. For example, MnO_2 exhibits stable dual enzymatic activities in the treatment of tumors. Mn^{2+} catalytically decomposes endogenous substances (often accompanied by glutamate consumption) to generate O_2 and highly toxic $^{\bullet}OH$, thus alleviating tumor hypoxia and killing tumor cells.[66] Another typical example was $NiFe_2O_4$ nanoparticles, which mimic peroxidase-like activity to detect herbicide residues in the presence of H_2O_2.[67] CeO_2 was also taken as an example to show peroxidase-like activity, which is primarily governed by the Ce^{3+}/Ce^{4+} pairs on its surface. During the glucose detection process in a serum sample, the generation of superoxide radicals ($O_2^{\bullet-}$) from H_2O_2 and the oxidation of TMB to ox-TMB can be catalyzed by Mn/CeO_2 nanozyme at the same time.[68] In addition, oxides such as CO_3O_4, V_2O_5 and CuO are also known to possess multiple enzyme-like properties, including catalase-like, and superoxide dismutase-like properties.[69,70] Although the detailed mechanisms underlying these catalytic reactions are subjects of ongoing investigation, key factors influencing the efficiency and selectivity of metal oxide-based nanozymes are well-recognized, including the metal oxidation state, nanoparticle size, and specific surface characteristics.

2.1.3 Metal–organic framework (MOF)-based nanozymes. Metal–organic frameworks (MOF) represent a highly ordered, porous crystalline materials formed by the coordination of metal ions or clusters with organic ligands (Fig. 4).[71] Due to

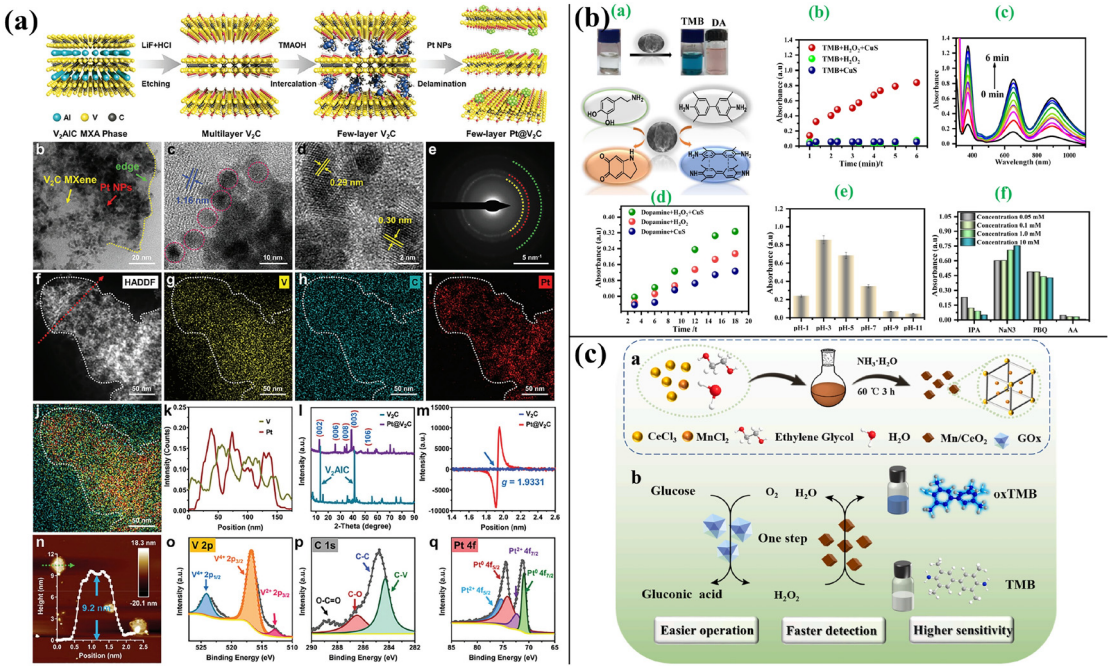

Fig. 4 Structure and composition of inorganic nanozymes. (a) Platinum nanoparticle-regulated V2C MXene nanoplatforms. Reproduced from ref. 135 with permission from Wiley, Copyright 2024. (b) CuS antioxidant nanozymes. Reproduced from ref. 119 with permission from the American Chemical Society, Copyright 2023. (c) Metal oxide nanozymes. Reproduced from ref. 68 with permission from Elsevier, Copyright 2024.

their remarkable tunability, large surface areas, and adjustable porosity, MOFs have garnered significant attention in various fields, including gas storage, separation, drug delivery, and catalysis.[72] Recently, an exciting research frontier has emerged at the intersection of MOF and enzyme-like catalysis, leading to the development of MOF-based nanozymes. These materials leverage the inherent advantages of MOFs, while exhibiting catalytic functions analogous to natural enzymes.

For example, Yin hui Yi *et al.* synthesized a Pt-NP/Fe-MOF hybrid material, consisting of platinum nanoparticles (Pt NPs) integrated with a metal–organic framework (MIL-88B-NH_2, Fe-MOF). The superior peroxidase-mimicking activity of the hybrid material for catalyzing the oxidation of TMB is attributed to the synergistic catalysis effect of Pt-NPs and Fe-MOF. Specifically, electron transfer from Pt to Fe accelerates the Fe^{2+}/Fe^{3+} redox cycling within the MOF, significantly enhancing the peroxidase-like performance. Notably, the affinity of Pt-NPs/Fe-MOF for the substrate TMB and H_2O_2 exceeds that of natural horseradish peroxidase.[73] MOF nanozymes also demonstrate significant potential in biomedical applications, particularly in modulating oxidative stress and inflammation. Yuan Tian *et al.* investigated the effect of the MOF-818 nanozyme on antioxidant and anti-inflammatory functions. The role of MOF-818 can be summarized as the following two points: (1) eliminating excessive intracellular ROS and improving cell viability and (2) blocking the recruitment and entry of macrophages and reducing the number of inflammatory macrophages.[74] Based on this, an MOF-818-2 with a higher Cu (II) loading was reported. Compared with other copper-based mimics reported previously, CN-MOF-818 was observed to exhibit enhanced oxidase-mimicking activity and stability.[75] As research progresses, further exploration into the synthesis, design, and optimization of MOF nanozymes will likely unlock novel opportunities for their use in various industrial, environmental, and medical fields.

2.2 Synthesis methods

Inorganic nanozymes can be synthesized on a large scale *via* simple and scalable methods, which are more cost-effective than natural enzymes at the same time.[76] The most prevalent synthesis strategies include chemical reduction, hydrothermal/solvothermal methods, template-assisted synthesis, co-precipitation, and biomineralization.[77] These approaches allow precise control of the nanomaterial size, shape, composition, and structure, which directly influence their catalytic performance.

2.2.1 Chemical reduction. Chemical reduction is one of the most widely employed techniques, particularly for the synthesis of metallic nanoparticles.[78] This approach involves reducing metal salt precursors using appropriate reducing agents under controlled conditions. For instance, Pt–Mn nanostructures are synthesized by reacting platinum(II) acetylacetonate and manganese acetate with hexadecyl trimethylammonium bromide as a reductant and stabilizer. Nanoparticles with different sizes can be obtained by adjusting the reaction conditions (*e.g.* temperature, concentration, and duration), followed by reduction, washing, centrifugation, and drying.[79] Although the chemical reduction method is relatively

simple and cost-effective, one of its main limitations is the potential for the aggregation of nanoparticles over time, which may lead to a decrease in catalytic activity.[80] Additionally, the synthetic process may require the use of toxic reducing agents, which could pose environmental concerns.

2.2.2 Hydrothermal and solvothermal. The hydrothermal (aqueous solvent) and solvothermal (non-aqueous solvent) methods are extensively used for synthesizing metal oxide-based inorganic nanozymes.[81] These methods utilize elevated temperature and pressure to induce the crystallization of metal oxide nanoparticles.[82] An illustrative example is the synthesis of temperature-augmented multifunctional CuCoS nanoparticles. Their preparation was completed by reacting in a kettle at 180 °C for 24 h.[83] These methods facilitate the production of high-quality nanoparticles with well-defined structures. However, they often require specialized equipment, high energy consumption, and long synthesis times.

2.2.3 Template-assisted synthesis. Template-assisted synthesis is a strategy that utilizes templates, such as porous materials, hard or soft molds, and biological templates, to direct the formation of inorganic nanozymes.[84] This method allows the creation of complex nanostructures (*e.g.* nanoparticles, nanorods, nanowires, and hollow nanospheres) with high surface areas and specific shapes.[85] For example, a nitrogen-doped carbon-supported copper single-atom nanozyme with freely switching specificity abilities was synthesized *via* template-assisted polymerization. In this strategy, the precursor material ($Cu(NO_3)_2{\cdot}6H_2O$) was deposited onto the surface of the KCl template, followed by transformation into the target structure.[86] The main challenges of template-assisted synthesis is the complexities of template fabrication and the need for meticulous control over the deposition and subsequent template removal processes.

2.2.4 Co-precipitation. Co-precipitation is particularly suitable for the synthesis of metal oxide nanozymes.[87] It involves the simultaneous precipitation of multiple metal species from a solution to form composite nanoparticles. A recent study prepared an acid-based metallo-supramolecular nanoassembly through the precipitation method. Nanoparticles with peroxidase- and glutathione oxidase-like activities were obtained by placing a mixed DMSO solution of indocyanine green, platinum chloride, curcumin, and Fmoc-*S*-methyl-L-cysteine in deionized water overnight and then aging.[88] This method allows the synthesis of nanoparticles with relatively uniform size distributions. However, one of the limitations of this method is the lack of control over the morphology of the nanoparticles.

2.2.5 Biomineralization. Biomineralization is an innovative approach that utilizes biological systems (*e.g.* bacteria, fungi, and plants) to catalyze the formation of inorganic nanoparticles (Fig. 5).[89] This approach offers potential for eco-friendly synthesis under mild conditions. Biomineralization within Mn-MOF has been shown to modulate the catalytic capacity and pore characteristics. Biomineralization-derived Mn_3O_4 exhibits enhanced peroxidase/oxidase-like activity and increased pore size/volume compared to pristine Mn-MOF.[90] However, the scalability is often limited by the complexity of the biological systems involved, and the process may require long reaction times.

Based on the above-mentioned content, the structural characteristics, synthesis methods, advantages and disadvantages in the synthesis process of different inorganic nanozymes are summarized in Table 1. Understanding the fundamental principles governing these diverse synthesis strategies is paramount for rationally designing inorganic nanozymes with superior catalytic properties and enhanced stability. Future research efforts should focus on developing more sus-

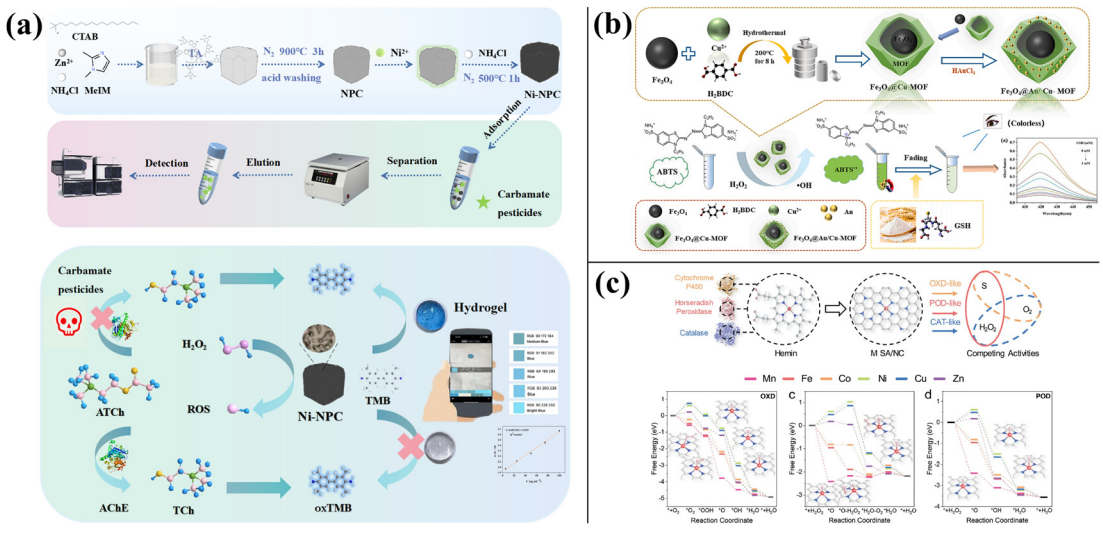

Fig. 5 (a) Ni-NPC synthesis, adsorption process, and scheme of colorimetric sensing platform for CMP assay based on Ni-NPC. Reproduced from ref. 80 with permission from the American Chemical Society, Copyright 2024. (b) Schematic of the Fe_3O_4@Au/Cu-MOF-based $ABTS^{\cdot+}$ turn-off colorimetric system for the detection of glutathione. Reproduced from ref. 82 with permission from Elsevier, Copyright 2023. (c) SAzymes with competing multiple enzyme-like activities. Reproduced from ref. 86 with permission from Wiley, Copyright 2023.

Table 1 Structural characteristics, synthesis methods, and the advantages and disadvantages of the synthetic processes of different inorganic nanozymes

Types	Structural characteristics	Synthesis methods	Advantages	Disadvantages
Metal based	Saturated atoms on the surface acting as active sites	Chemical reduction	Simple; cost-effective	Aggregation; toxic reducing agents
Metal oxide based	Metal ions within the oxide lattice as active sites	Hydrothermal and solvothermal Co-precipitation	High-quality; well-defined structures Uniform size distributions	High energy consumption; long synthesis times Lack of control over the morphology
Metal–organic frameworks (MOF) based	Porous structure provides a larger specific surface area as the site for contact	Biomineralization	Eco-friendly; mild-conditions	Complexity of the biological system; long reaction times

tainable, scalable and precisely controllable synthesis methodologies to further advance the catalytic performance and broaden the applicability of inorganic nanozymes.

2.3 Catalytic mechanism

The catalytic mechanism of inorganic nanozymes is different from that of traditional enzymes (Fig. 6). It is primarily driven by the redox properties of metal ions and the surface structure of nanoparticles, modulated by intrinsic physicochemical properties including metal center, surface structure, and nanoparticle size.[91,92] The focus of attention is mainly on the redox properties, active sites, and factors affecting their catalytic efficiency.

Inorganic nanozymes frequently exhibit redox-active properties due to the ability of metal ions to exist in multiple oxidation states, which enables the transfer of electrons during catalysis.[93] The mechanism of Fe_3O_4 nanozymes with POD-like activity has been displayed, where the interior Fe^{2+} and surface Fe^{2+} simultaneously affect their enzyme activity through electron transfer. The slow oxidation of Fe_3O_4 simultaneously with the catalytic reaction occurs during the electron transfer process.[94]

The catalytic activity of inorganic nanozymes is closely linked to the structure of their active sites, which are primarily located on the surface of the nanoparticles.[95] The surface area-to-volume ratio plays a critical role in determining the catalytic efficiency, given that a larger surface area provides more active sites for reactions.[96] This principle can be exemplified by the Ag/Fe_3O_4@h-BN nanozyme with enhanced removal efficiency in the detection and removal of As(v) compared to other materials. This is mainly attributed to its large specific surface area and porous characteristics after doping Ag and Fe_3O_4, which could enhance the diffusion and mass transfer, and expose binding sites on the pore walls.[97] Additionally, the specific arrangement of metal ions on the nanoparticle surface influences the reactivity and selectivity of the nanozyme.[98]

The surface structure of metal oxide nanoparticles also plays a role in modulating their catalytic properties. The presence of surface defects, such as oxygen vacancies and undercoordinated metal ions, can enhance the reactivity of the nanoparticle surface by providing additional active sites for catalysis.[99] In MoO_3-based organic/inorganic superlattices, rich oxygen vacancies have been introduced into their final structure. Oxygen vacancies can not only provide enhanced adsorption sites for O_2 activation, but also promote the transfer of electrons from Mo to O_2, generating $^{\bullet}O^{-}$, similar to the function of natural oxidase.[100]

The size of inorganic nanozymes has a profound effect on their catalytic activity.[101] Smaller nanoparticles generally exhibit superior catalytic efficiency due to their increased surface-area-to-volume ratios and available active sites. Researchers have demonstrated that cerium oxide nanoparticles (4.5, 7.8, 23 and 28 nm) exhibit enhanced catalase-like and superoxide dismutase-like activity at smaller size.[102] The size effect of Pd–Ir core–shell nanoparticles on peroxidase-like activities were also verified by Zheng Xi *et al.* In the case of the peroxidase-like activities of individual nanoparticles, larger particle size will result in the enhanced catalytic effects. The area-specific catalytic activity in the size range of 3.3–9.8 nm is similar but inversely proportional after the size reached 13.0 nm. In addition, the detection sensitivities in ELISA of biomarkers increases as the particle size decreases.[103] Abhishek Sahu *et al.* proved that the catalase-like and superoxide dismutase-like activity in porphyrin was associated with its size. Compared to hemin-conjugated chitosan and free hemin, higher enzymatic activities and stability were observed in hemin-conjugated heparin due to its more stable and smaller (<50 nm) self-assembled nanostructure.[104] Furthermore, the size of nanoparticles can influence their electronic structure, given that the energy levels of the metal ions may shift with changes in particle size.

The shape of nanoparticles is another factor that can influence their catalytic properties.[105] Nanocubes, nanorods, and nanosheets of metal oxides have been found to exhibit different catalytic behaviors due to the variations in the arrangement of atoms on their surface. Yongjian Ai and coworkers in 2021 explored the influence of coordination hierarchical superstructures on peroxidase-like activity and tumor photothermal treatment. Based on this reaction system and metal–ligand cross-linking strategy, a series of structures with 0D nanospheres, 1D nanorods, and 3D hierarchical superstructures (flower-like, octopus-like, and hedgehog-like) morphologies was designed. Among them, the hierarchical superstructures exhibited higher enzyme activity and photothermal effect.[106]

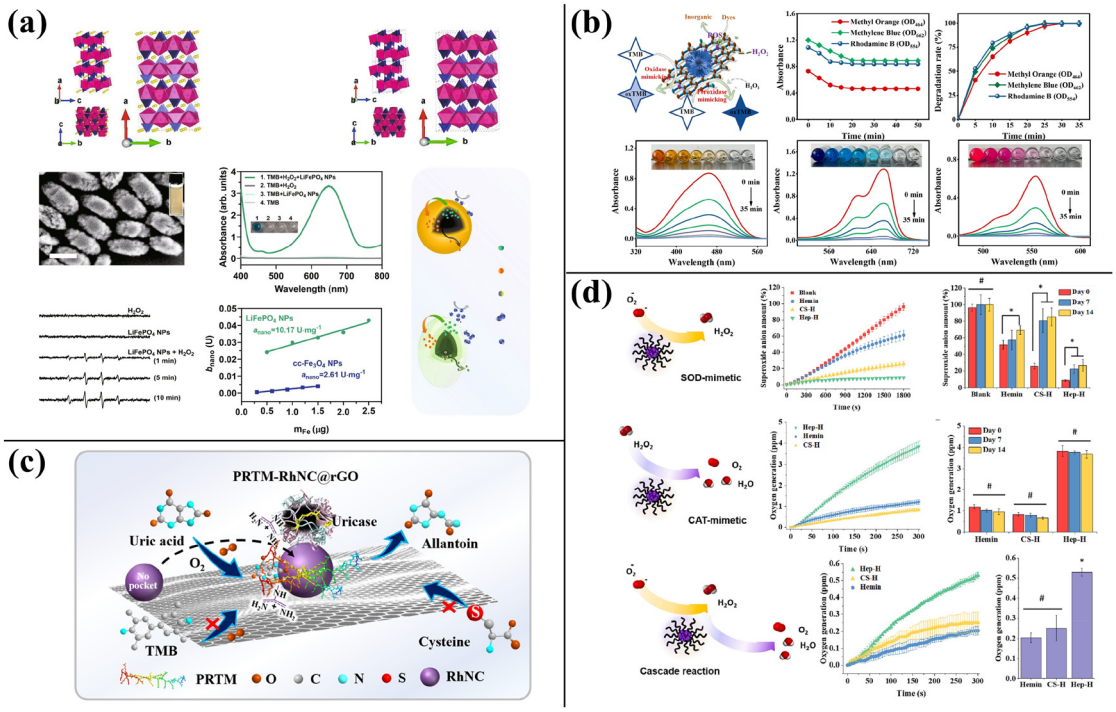

Fig. 6 Catalytic mechanism of inorganic nanozymes. (a) $LiFePO_4$ NPs as verification materials and their POD-like activity. Reproduced from ref. 94 with permission from Springer, Copyright 2022. (b) Dye degradation analysis of nanozyme with the test conditions of pH 7.0, 50 °C, 75 mg L^{-1} Ag/Fe_3O_4@h-BN, 10 mg L^{-1} dye and 0.4 M H_2O. Reproduced from ref. 97 with permission from Elsevier, Copyright 2023. (c) Schematic of the integrated PRTM-RhNC@rGO composite nanozyme with high selectivity, activity, and stability for the catalytic degradation of uric acid. Reproduced from ref. 98 with permission from the American Chemical Society, Copyright 2024. (d) SOD mimetic activity of Hep-H and CS-H that convert the superoxide anion to hydrogen peroxide. Reproduced from ref. 104 with permission from Elsevier, Copyright 2023.

3. Applications of inorganic nanozymes in the biomedical field

3.1 Diagnostic application

3.1.1 Biomarker detection. Inorganic nanozymes have emerged as powerful tools for biomarker detection, offering significant advantages over traditional methods, such as enhanced sensitivity, stability, and versatility.[107] The application of nanozymes is driven by their ability to catalyze specific reactions that can be easily detected and quantified, thus enabling the sensitive and rapid detection of biomarkers.[108] By generating colorimetric or fluorescent signals, nanozymes permit the rapid visual detection of biomarkers without complex equipment, paving the way for novel diagnostic platforms that enable the early detection and monitoring of various diseases.[109] The integration of inorganic nanozymes with advanced detection platforms (such as electrochemical, optical, and fluorescence-based sensors) further expands their application in biomarker detection.

Nanozymes exhibit potential for the low-cost and highly sensitive detection of toxic metal ions, which pose significant threats to human health and the ecosystem.[110] Congcong Lou *et al.* designed a dual-functional sensor based on an NH_2-MIL-101(Fe)@Cu/CeO_2 hybrid nanozyme to investigate Cu^{2+} and Hg^{2+} without interference. In this colorimetric sensor, Hg^{2+} inhibits the glutathione (GSH)-mediated reduction of oxidized TMB (blue → colorless) by binding surface thiol groups. Cu^{2+} quenches fluorescence *via* reaction with surface amino groups.[111] Similarly, the detection of Al^{3+} by a single-atom Ce–N–C nanozyme with phosphatase-like activity has been validated, which is attributed to the specific binding of Al^{3+} with the O atom in the nanozyme, leading to the formation of Al–O bonds and inhibition of enzyme activity.[112]

The early diagnosis and prevention of cancer can also be achieved through the detection of proteins using nanoenzymes.[113] Urinary extracellular vesicles (uEVs) are considered the most promising biomarkers for the prognosis and diagnosis of bladder cancer, but their ultra-low abundance and huge heterogeneity bring great challenges to their detection technology. Thus, to solve this problem, a platinum nanozyme with choline phosphate-grafted was presented to multiplex profile EV protein markers. Relying on the nonspecific polyvalent interactions between the "CP-inverse" phosphatidylcholine (PC) of EV and CP installed on the nanozymes, the immunoassay of nanozymes can not only be used to judge the residual tumor after bladder cancer surgery, but also used to detect and distinguish bladder cancer donors, cystitis donors and healthy donors.[114] In the same situation, diseases of the kidney and prostate can also be diagnosed by detecting acid phosphatase

in human serum. Their successful detection is due to the inhibition of acid phosphatase on the blue charge transfer complex generated by nanozyme redox TMB.[115]

Disease diagnostics can also be achieved through the nanozyme detection of nucleic acids. Mengya He established the detection of respiratory syndrome coronavirus 2 through an iron manganese silicate nanozyme. The POD-like activity was inhibited by amplification-generated pyrophosphate ions.[116]

3.1.2 Biosensors. The detection of various molecules by inorganic nanozymes endows them with special potential in the development of real-time biosensors for rapid diagnostic testing (Fig. 7).[117] The integration of inorganic nanozymes with modern detection platforms, such as electrochemical, optical, and fluorescence-based sensors, has revolutionized the field of biosensing.[118] Electrochemical sensors utilize the inherent conductivity of nanoparticles to enable real-time, label-free detection with high sensitivity. Optical biosensors leverage the catalytic properties of nanozymes to produce measurable colorimetric and fluorescent signals upon reaction with the target biomolecules, providing simple and rapid visual detection methods without complex instrumentation.

A recent study developed a biosensor comprised of crystalline CuS nanoparticles with appreciable superoxide dismutase-mimicking activity and sensitive colorimetric determination and detection of epinephrine (EP) neurotransmitters. This study achieved a linear detection range of 0–16 μm with a limit of detection at 457 nm.[119] Bin Hong and co-workers developed a smartphone-assisted paper sensor based on AuPt nanoparticle-coated enzyme–antibiotic–inorganic nanoflowers. The integrated bio-recognition and dual signal amplification capabilities of this system facilitated the rapid, highly sensitive detection of *S. typhimurium* in food samples.[120] Liming Wang *et al.* established a rapid light-controlled colorimetric sensing platform based on 5,10,15,20-tetrakis(4-carboxylpheyl) cobalt (II) porphyrin–TiO_2 nanozymes to determine H_2O_2 and amikacin in two linear stages for the first time. The biosensing relies on the change in the peroxidase-like activity of nanozymes under light irradiation to control the color reaction.[121] As the research in this field progresses, the further development of nanozyme-based biosensors holds promise for revolutionizing diagnostics and enabling more efficient, affordable, and accessible healthcare solutions worldwide.

3.2 Therapeutic application

3.2.1 Anti-tumor treatment. Unlike traditional therapeutic approaches (such as chemotherapy and radiotherapy), which often suffer from side effects and resistance, inorganic nanozymes can provide a novel, highly efficient, and targeted way to combat cancer.[122] SnSe nanosheets with catalytic-like activity can reverse the immunosuppressive acidic tumor microenvironment by degrading lactate to pyruvate.[123] Similar to antibacterial action, inorganic nanozymes can also promote tumor cell death by producing reactive oxygen species (ROS). For instance, hybrid nanozymes combining magnetic iron oxide nanoparticles (MIONs) with glucose oxidase (GOx) exploit tumor glucose metabolism, where GOx consumes glucose to generate H_2O_2, which then undergoes Fenton-like reactions with iron oxide-based nanozymes to release toxic substances, ultimately leading to tumor cell death.[124]

In addition to ROS production, the versatility of inorganic nanozymes allows effective synergy with established anticancer modalities, overcoming inherent limitations.[125] To break the poor electrical conductivity limits of electrotherapy, a novel copper-based inorganic nanozyme has been developed by encapsulating liposomes embedded in potassium chloride nanoclusters. Its anti-tumor mechanism mainly includes the following three parts: (1) the release of K^+, Cl^- and Cu^{2+} within the tumor microenvironment can improve the electrical ablation and activate the pyroptosis of cancer cells; (2) Cu^{2+} catalyzes the Fenton-like reaction, generating highly toxic $^{\bullet}OH$ to cause mitochondrial damage; and (3) electrical stimulation

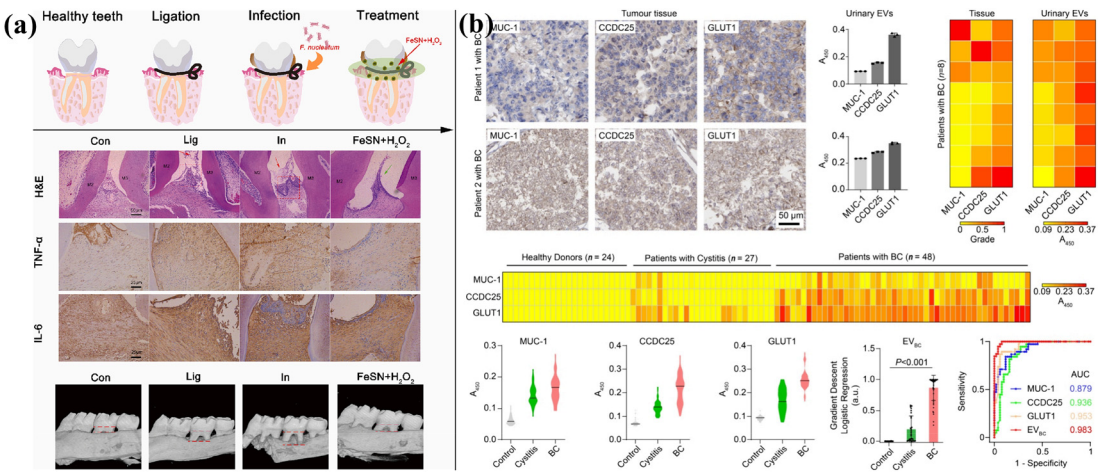

Fig. 7 Diagnostic application of inorganic nanozymes. (a) Schematic of periodontitis modeling, H&E staining of tissue sections, and 3D micro-CT reconstructed images of the maxillary molar area. Reproduced from ref. 110 with permission from Elsevier, Copyright 2023. (b) EV profiling for BC detection. Reproduced from ref. 113 with permission from the American Chemical Society, Copyright 2024.

can enhance the oxidative stress level of cancer cells by promoting the generation of hypochlorite radicals.[126]

Near-infrared light-induced photothermal therapy (PTT) is also one of the methods for ablating tumors, but the high-temperature damage to proximal tissues caused by PTT has always been a major concern. Ultra-small gold nanozymes immobilized within a metal organic framework can solve the high-temperature problem. The inhibition of tumor growth by nanozymes is mainly attributed to their glucose oxidase (GOD)-like activity and photothermal/photosensitive properties.[127] To address the hypoxia issue in photodynamic therapy (PDT), a PtBi-β-CD-Ce_6 nanoplatform was synthesized, which exhibited catalase-like activity to promote the production of O_2 through H_2O_2 conversion.[128] To overcome the H_2O_2 deficiency in the tumor ablation of chemodynamic therapy (CDT), an FePBG@GOX nanomimic was designed. Its GOx component consumes intratumoral glucose to generate H_2O_2, which is then utilized in Fe^{2+}-catalyzed Fenton reactions to produce ROS, while simultaneously depleting tumor nutrients.[129]

As research into the safety, targeting strategies, and optimization of inorganic nanozymes continues, these materials have the potential to revolutionize cancer therapy by providing highly effective, targeted treatments with minimized side effects.

3.2.2 Antibacterial treatment. In recent years, the emergence of antibiotic-resistant bacteria has become a significant global health threat, driving the search for alternative therapeutic strategies (Fig. 8).[130–133] Inorganic nanozymes have emerged as promising candidates, primarily leveraging their ability to generate reactive oxygen species (ROS) under certain conditions. The ROS produced by these nanozymes, such as hydroxyl radicals ($^{\bullet}OH$), superoxide anions ($O_2^{\bullet-}$), and hydrogen peroxide (H_2O_2), play a crucial role in bacterial cell death. These ROS inflict oxidative damage on essential cellular components (*e.g.* proteins, lipids, and nucleic acids), ultimately leading to cell death.[134] An FeSN-based nanozyme can generate hydroxyl radicals through Fenton-like reactions. Bowen Shen *et al.* produced an FeSN-based nanozyme with unique antibacterial, biocompatibility and toxicity properties. Ferrous ions (Fe^{2+}) decompose H_2O_2 into highly reactive hydroxyl radicals, inducing severe oxidative damage to bacterial cells.[110] Xiaojun He *et al.* found that Pt@V_2C with OXD-like and POD-like catalytic activities could eliminate methicillin-resistant *Staphylococcus aureus* in deep-seated tissues in bacterial keratitis and subcutaneous abscess environments. This research showcases the potential of Pt@V_2C for treating bacterial keratitis and deep-seated infections.[135]

Combining inorganic nanozymes with different catalytic activities or natural enzymes can enhance their antibacterial efficacy.[136,137] To address the challenge of against nontypeable *Haemophilus influenzae*, a cascade nanozyme was designed. The cascade nanozyme consists of two parts of gold nanoparticles and vanadium pentoxide nanowires connected by dopamine, providing glucose oxidase-like activity and haloperoxidase-mimicking activity, respectively. Compared with vanadium pentoxide nanowires, the higher antibacterial efficacy of cascade nanozymes is due to the introduction and combination of dual catalytic functions, where glucose oxidase-like activity generates H_2O_2 and haloperoxidase-like activity converts H_2O_2 to the antiseptic ability.[138] Cascade nanozymes can be established not only between artificial enzymes, but also between natural enzymes and artificial enzymes. A satisfactory anti-inflammation effect was exhibited by decorating ceria nanoparticles (CeO_2) on the surface of *Spirulina platensis via* electrostatic interaction in ulcerative colitis. The combination of superoxide dismutase in biological systems and catalase in non-biological systems endows the cascade nanozymes with superior ROS elimination activity.[139]

Despite their promising antibacterial properties, the clinical application of inorganic nanozymes faces challenges related to their long-term stability, biocompatibility, and potential off-target toxicity.[140] The development of novel inorganic nanozymes with improved properties and minimized toxicity will pave the way for new strategies in combating antibiotic-resistant bacterial infections and improving public health outcomes.

3.3 Drug delivery system

Inorganic nanozymes represent a highly promising platform for advanced drug delivery, particularly in oncology and complex disease treatment, owing to their catalytic plasticity enabling controlled therapeutic release and enhanced efficacy (Fig. 9).[141,142] One of the key advantages of inorganic nanozymes in drug delivery is their ability to mimic natural enzymes and generate bioactive molecules such as reactive oxygen species (ROS) and catalyzing prodrug activation directly within the target site.[143,144] This feature can be used to facilitate the release of therapeutic agents in a controlled and localized manner, thereby overcoming many challenges associated with conventional drug delivery systems, including poor solubility, lack of targeting specificity, and systemic toxicity.[145]

Inorganic nanozymes can orchestrate therapeutic effects through catalytic cascades. For instance, Pt-engineered MIL-101 nanomedicine with a multi-step catalytic process was demonstrated. During the treatment process, the nanomedicine first catalyzes the consumption of nicotinamide adenine dinucleotide phosphate to produce O_2 and H_2O_2. The generated H_2O_2 subsequently undergoes Fenton-like reactions with iron ions to produce highly toxic $^{\bullet}OH$, and the regeneration inhibition of antioxidant glutathione synergistically drives the death of tumor cells.[146]

Nanozyme-mediated prodrug activation is also a pivotal strategy for achieving site-specific drug synthesis and localized therapy.[147] As the first prodrug used in the context of enzyme prodrug therapy, phosphate demonstrates strong efficacy and solubility advantages. Mammalian experiments have validated phosphate prodrug conversion mediated by the ceria nanozyme with phosphatase-like activity. The conversion of the phosphate prodrug into the parent chemotherapeutic can be mediated in the presence of ceria and reflected as complete release and high toxicity.[148] Similarly, surface-functionalized zinc sulfide nanoparticles loaded with ruthenium-based transition metal complexes (TMCs) can kill tumor cells. The thiol ligands released from zinc sulfide nanoparticles act as

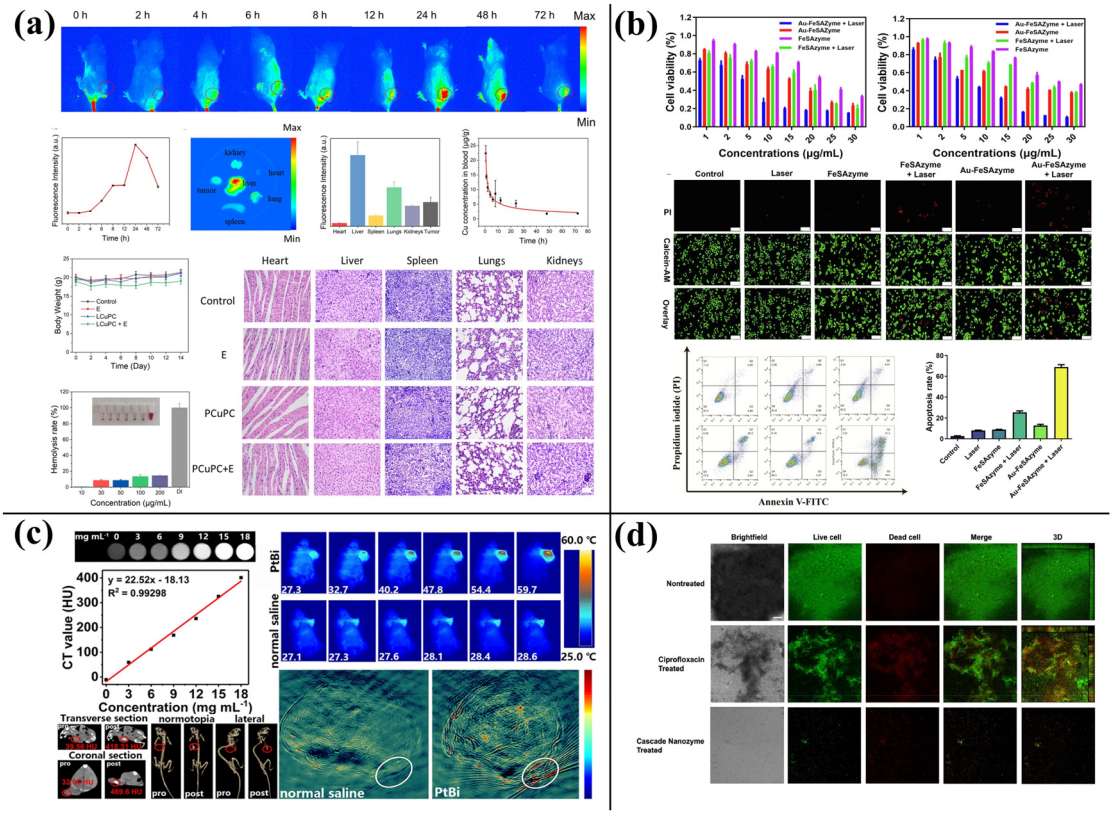

Fig. 8 Therapeutic applications of inorganic nanozymes. (a) *In vivo* biodistribution and biosafety of liposome-encapsulated copper oxide (CuO) embedded with potassium chloride nanoclusters. Reproduced from ref. 126 with permission from The Royal Society of Chemistry, Copyright 2023. (b) *In vitro* anti-cancer ability of Au-FeSAzyme. Reproduced from ref. 127 with permission from Elsevier, Copyright 2022. (c) Detection of the ability of PtBi-β-CD-Ce6 to produce O_2 and $^1O_2$. Reproduced from ref. 128 with permission from the American Chemical Society, Copyright 2022. (d) Confocal images of the nontreated NTHi biofilm and NTHi biofilm treated with the V_2O_5 NW@DPA@AuNP cascade nanozyme and ciprofloxacin, respectively, and stained with the BacTiter-Glo™ Microbial Cell Viability Assay. Reproduced from ref. 138 with permission from the Royal Society of Chemistry, Copyright 2022.

nucleophiles, thus accelerating the catalytic oxidation of ruthenium. This process facilitates the uncaging of allyl-protected molecules, thereby activating inert prodrugs into chemotherapy agents.[149]

In addition, stimuli-responsive nanozyme platforms can also enhance spatiotemporal control. Zheng Nie *et al.* constructed a pH-sensitive nanoplatform based on iron oxide (Fe_3O_4) nanospheres with platinum nanozymes for drug deliv-

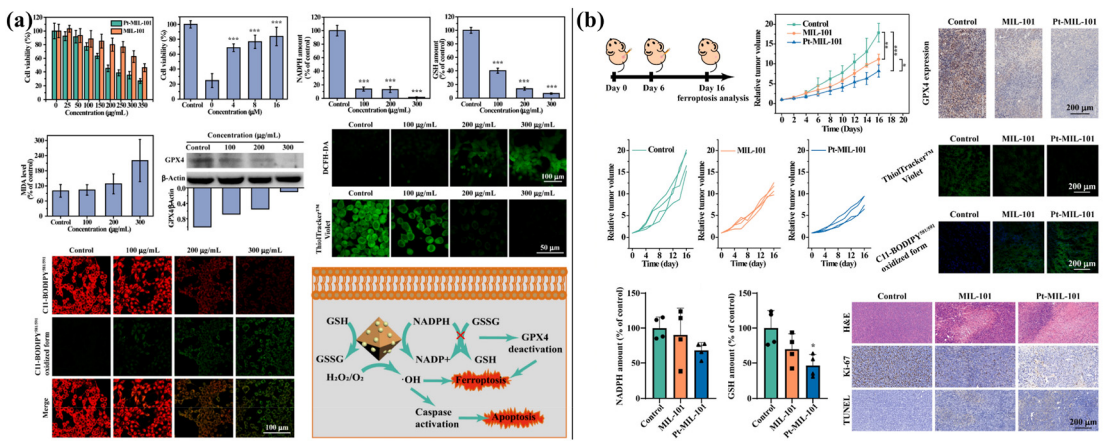

Fig. 9 Drug delivery systems based on inorganic nanozymes. (a) *In vitro* cancer cell ferroptosis evaluation of Pt-MIL-101. (b) *In vivo* ferroptosis therapy of 4T1 tumor by Pt-MIL-101. Reproduced from ref. 146 with permission from Elsevier, Copyright 2022.

ery. In the acidic tumor microenvironment (pH = 6–6.5), the efficiency of 5-fluorouracil released from the nanoplatform can reach 77.8%. This study provides a superior prospect for simultaneous drug delivery to breast tumors.[150] Hybrid systems further expand the functionality, where a doxorubicin delivery system based on poly(lactic acid-*co*-glycolic acid) grafted-Fe_2O_3 nanoparticles was reported to inhibit lung adenocarcinoma.[151]

4. Development of novel inorganic nanozymes

Inorganic nanozymes, capable of mimicking natural enzyme activities, have demonstrated broad utility across biomedicine, diagnostics, and environmental remediation.[152] Despite this promise, realizing their full potential necessitates strategic optimization of their catalytic activities, stability, biocompatibility, and specificity for targeted applications. The engineering of advanced inorganic nanozymes has emerged as a transformative frontier in the field of nanotechnology.

4.1 Strategic surface modification of inorganic nanozymes

Surface modification is pivotal in augmenting the performance and biocompatibility of inorganic nanozymes (Fig. 10).[153] The surface properties of nanoparticles dictate their interactions with biomolecules (*e.g.*, proteins, lipids, and nucleic acids), influencing their biological fate and function.[154] Modifying their surface can not only improve their catalytic efficiency but also confer desirable properties, such as hydrophilicity, biocompatibility, and targeting ability.

In the process of modifying their surface to optimize their performance, the assembly of a core–shell structure is one of the efficient means.[155] Wei Chen *et al.* constructed a core–shell-structured $Cu_2O@Mn_3Cu_3O_8$ nanozyme to achieve efficient and safe cuproptosis. $Mn_3Cu_3O_8$ as the shell can reduce the toxicity of the nuclear structure to normal tissue and show higher enzyme activity and biocompatibility at the same time. The enhanced enzyme-mimicking activity can be attributed to the better band continuity near the Fermi surface. The diverse enzyme activities (CAT-like, POD-like, and GSHOx-like activities) of nanozymes are attributed to the presence of the $Mn^{2+}/Mn^{3+}/Mn^{4+}$ and Cu^{+}/Cu^{2+} redox couples.[156]

The surface charge of nanoparticles also plays an essential role in their interaction with biological systems.[157] Modifying their surface charge can enhance their cellular uptake, alter their biodistribution, and influence their stability. Cationic surfaces tend to interact more readily with negatively charged cellular membranes to enhance their internalization, while anionic nanoparticles might show reduced toxicity and better biocompatibility. Environmentally responsive charge switching further enables targeted applications. Polydopamine-modified copper oxide nanozymes change from negatively to positively charged in acidic microenvironments, activating their peroxidase-like activity and targeting function for negatively charged bacteria. Longwei Wang *et al.* proved that piezoelectricity-produced charges can enhance the POD-like activity of MoS_2. The designed BTO/MoS_2@CA cascade nanocatalyst was composed by exposing MoS_2 nanosheets on the surface of piezoelectric tetragonal barium titanate and modifying them with cinnamaldehyde. The achievement of POD-like activity of MoS_2 under ultrasound was first reported, which is mainly attributed to the decrease in the binding energy between MoS_2 and H_2O_2, and the promoted decomposition of H_2O_2. The charge generated by ultrasonic separation piezoelectric tetragonal barium titanate will promote the combination of MoS_2 and H_2O_2, resulting in the continuous generation of –OH to kill tumors.[158]

Coating inorganic nanozymes with biocompatible polymers (*e.g.*, polyethylene glycol, polylactic acid, or polyvinyl alcohol) is beneficial to improve their stability in physiological environments and reduce their nonspecific interactions with proteins and cells, which offer advanced programmability.[159] Baoxuan Huang *et al.* developed a pH-responsive supramolecular AuP-PS nanoplatform self-assembled from porphyrin-containing block copolymers and pillar[5]arene-capped AuNPs. The dense grafting of porphyrin-containing amphiphilic block copolymers on the surface of Au-PS is attributed to the reversible host–guest interactions. The formation of supramolecular complexes is conducive to improving the biosafety of AuP-PS. The dissociation of the two different nanoparticles under different pH conditions provides a programmable coordinated treatment scheme for tumors.[160] In particular, PEGylation is a widely used strategy to enhance the solubility, circulation time, and biocompatibility of nanoparticles, making them less likely to be cleared by the immune system.

4.2 Multifunctionalization of inorganic nanozymes

Inorganic nanozymes exhibit diverse catalytic mechanisms, include peroxidase-, catalase-, and superoxide dismutase (SOD)-like activities, alongside more complex functionalities, such as esterase and phosphatase activities.[161] Beyond singular catalytic activity, recent research focuses on engineering multifunctional nanozymes that integrate multiple enzyme-mimicking properties within a single nanostructure (Fig. 11).[162]

Their multifunctionality leverages the unique capacity to co-localize distinct catalytic activities, enhancing their synergistic effects and application potential. A bimetallic Au–Pt nanozyme with triple-enzyme-mimicking activities was synthesized by anchoring ultrasmall Au–Pt nanoparticles onto metastable Cu_2O supports, followed by encapsulation within a Cu-MOF and surface modification with Pluronic F127 to enhance its overall hydrophilicity and biocompatibility. Nanozymes can achieve the following three-in-one functions simultaneously: (1) mimicking catalase to support O_2; (2) mimicking oxidase to produce H_2O_2; and (3) mimicking peroxidase to generate $^{\bullet}OH$. During the process, the metastable Cu_2O NPs acted as redox templates to anchor the Au–Pt nanozyme and as a copper source to realize the controllable growth of the MOF shell for preventing protein adsorption. The continuous catalytic process with multiple enzyme activities not only avoids the need for assembling multiple various natural enzymes, but also enhances the therapeutic effect on tumors,

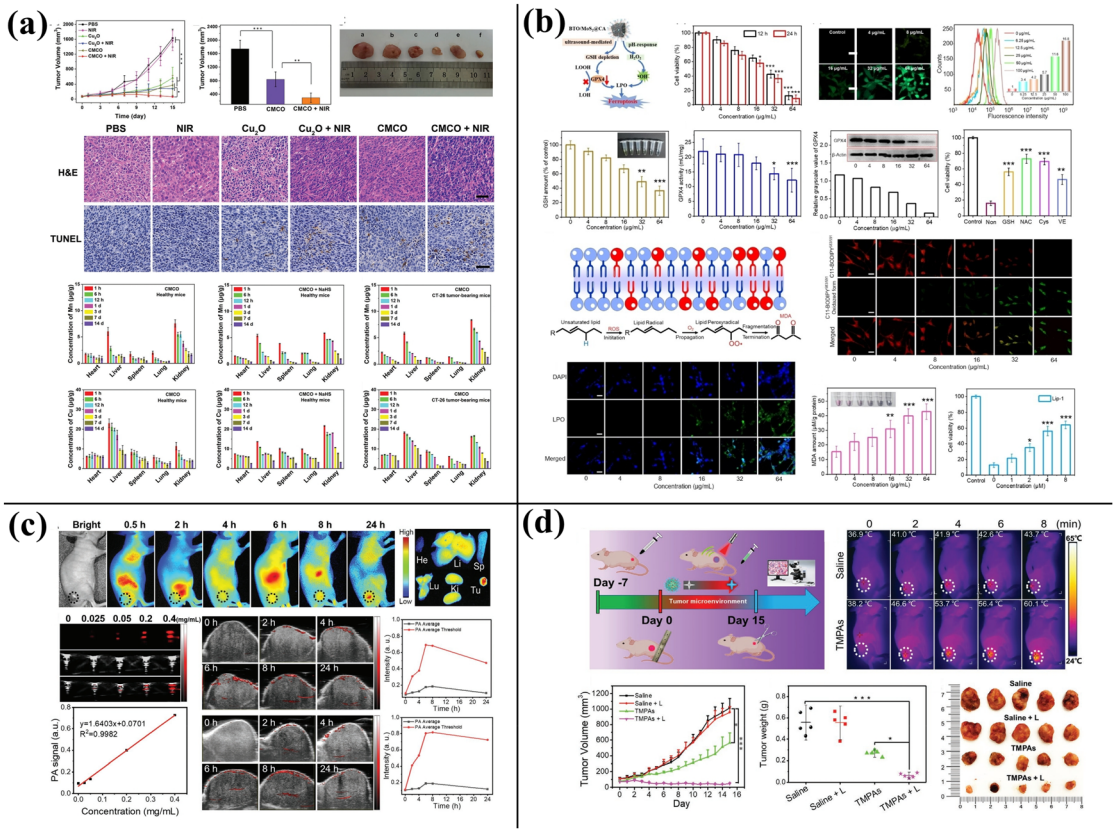

Fig. 10 (a) *In vivo* therapeutic effect of core–shell-structured $Cu_2O@Mn_3Cu_3O_8$ nanozyme. Reproduced from ref. 156 with permission from Wiley, Copyright 2022. (b) US enhancement of MoS_2 POD-like activity. Reproduced from ref. 158 with permission from Wiley, Copyright 2023. (c) Multimodal imaging of TMPAs *in vivo*. (d) Schematic of the establishment of 4T1 tumor xenografts and therapeutic outcome with TMPAs. Reproduced from ref. 159 with permission from Wiley, Copyright 2021.

while reducing the side effects.[163] Similarly, the Co^{2+}-ZIF-67 metal–organic framework nanoparticles prepared by Yi Wu also exhibited three different activities of catalase-like, oxidase-like, and peroxidase-like activities. The catalase activity of the nanoparticles is reflected in the oxidative decomposition of H_2O_2. The catalytic oxidation of dopamine to aminochrome

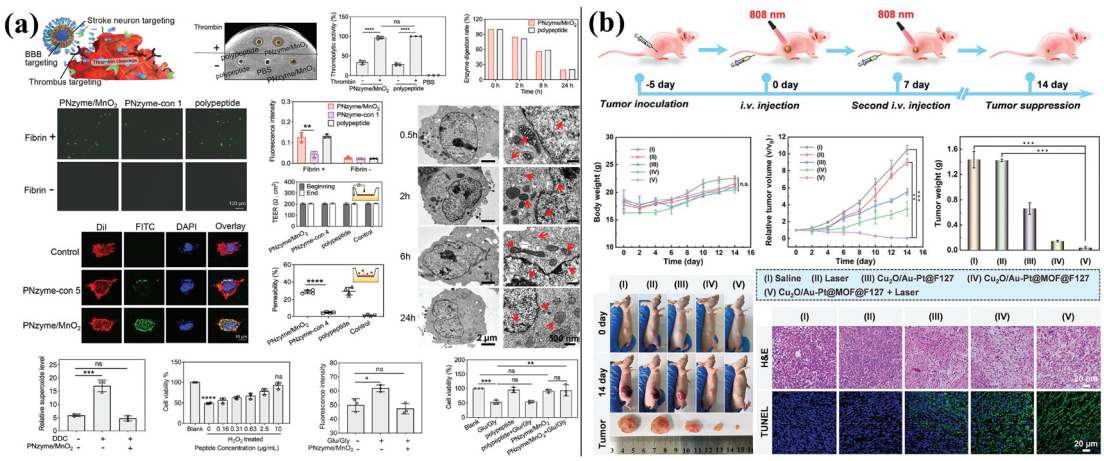

Fig. 11 Multifunctionalization of inorganic nanozymes. (a) Thrombin-"switch-on"-induced multiple levels of targeting. Reproduced from ref. 161 with permission from Wiley, Copyright 2023. (b) *In vivo* antitumor performance of "three-in-one" nanozyme composite. Reproduced from ref. 163 with permission from Wiley, Copyright 2023.

and NAD^+ represents the oxidase activity. The peroxidase activity is reflected in the generation of polyaniline. Different from the previously reported method, the synthesis of nanozyme-driven imprinted particles is different. This method produced imprinted sites near the active catalytic sites of the nanozyme, thus effectively emulating the function of the active sites of natural enzymes.[164] The arginine-rich peptide–Pt nanoparticle cluster (ARP-PtNC) nanozymes incorporate two enzymatic cascade systems. The effective degradation of uric acid and the removal of oxygen species can be achieved simultaneously in the ARP-PtNC nanozymes, where the former is due to the excellent uricase-like activity, and the latter is attributed to the two-cascade catalysis (superoxide dismutase/catalase and uricase/catalase). The prepared nanozymes show broad application prospects in gout and hyperuricemia.

At the same time, next-generation artificial enzyme cascade system5s based on a single nanozyme will continue to attract attention in the future.[165] Furthermore, inorganic nanozymes can also maintain their activity under more extreme conditions, which makes them particularly useful for industrial and environmental applications. A three-component RGPT-PdNP@rGO nanozyme with highly selective and sensitive properties was developed by integrating an Arg-rich recognition peptide for the accurate detection of UA. The RGPT-PdNP@rGO nanozyme with improved UA recognition, sensing and degrading performances provide more comprehensive information about multifunctional nanozymes for precise biomarker recognition. This study proves that the peptide-based recognition can effectively and flexibly control the structure-dependent recognition ability of composite nanozymes through simulation of the pocket-like structure of natural enzymes.[166]

5. Challenges and prospects

Although inorganic nanozymes have shown remarkable promise in biomedicine, there are still numerous scientific and translational barriers. Addressing these challenges is paramount for realizing their clinical potential.

(1) **Limited catalytic precision in biological systems**. How to further improve their catalytic efficiency, selectivity, and stability in complex environments is a key issue in current research. While offering advantages in stability, the catalytic efficiency and substrate selectivity of most inorganic nanozymes still significantly lag behind their natural counterparts in complex physiological environments. Non-specific ROS generation (common in peroxidase-mimics) causes off-target effects during anti-tumor therapy, while interference from biomolecules (*e.g.* glutathione and albumin) compromises the biosensing accuracy. This gap fundamentally limits their sensitivity in diagnostics and efficacy in therapeutics. The mechanisms underlying substrate recognition and specificity remain poorly understood for inorganic surfaces. Enhancing their activity under physiological pH, ionic strength, and in the presence of biological inhibitors is a persistent challenge.

(2) **Synthetic reproducibility and scalability.** Achieving batch-to-batch consistency during the synthesis of inorganic nanozymes remains a major barrier to their reliable performance evaluation and clinical translation. Minor variations in parameters (pH, temperature, precursor ratios, and reaction time) profoundly influence their critical physicochemical attributes (size, shape, crystallinity, surface defects, and ligand density), which are directly linked to their catalytic activity and stability. Also, scaling up their synthesis while maintaining precise control over these nanoscale features presents significant engineering challenges.

(3) **Biocompatibility and long-term toxicity.** Unlike natural enzymes, which are biocompatible and biodegradable, inorganic nanozymes are often composed of metals and metal oxides (*e.g.* Ag^+ ions from silver nanozymes and Ce^{3+}/Ce^{4+} redox cycling), which can raise concerns regarding their safety and potential toxicity *in vivo*. Current surface modification strategies (*e.g.* PEGylation) often sacrifice catalytic sites to improve safety. Consequently, ensuring the biocompatibility and reducing the toxicity of inorganic nanozymes are critical steps in their development for medical applications.

(4) **Predictability and complexity of *in vivo* behavior.** Lastly, the understanding of the biological behavior and pharmacokinetics of inorganic nanozymes *in vivo* is limited. Their performance *in vivo* is often unpredictable due to various factors such as biological fluid composition, organ distribution, and the presence of various biological barriers. For instance, the rapid adsorption of biomolecules alters their surface properties, potentially masking their catalytic sites, changing their targeting ability, and modulating their immune recognition. Their dynamic nature and composition-dependent impact on catalysis are poorly characterized. Additionally, targeted delivery to specific disease sites is hindered by physiological barriers. Passive accumulation strategies often lack efficiency and specificity. Comprehensive studies on the pharmacokinetics, biodistribution, and long-term safety of inorganic nanozymes are essential.

To overcome these challenges and fully realize the potential of inorganic nanozymes in biomedicine, future research should focus on the following.

(1) **Rational design of next-generation nanozymes.** Future efforts should prioritize the rational design of inorganic nanozymes with enhanced catalytic specificity and efficiency under physiological conditions. Focus should be on predictably boosting their catalytic efficiency and selectivity for biomedically relevant substrates. This will require integrating computational modeling and artificial intelligence (AI), such as molecular dynamics simulations, machine learning-based prediction of catalytic activity, and AI-driven material selection, to enable atomic-level engineering of active sites and enzyme-mimetic substrate. Special emphasis should be placed on mimicking natural enzyme kinetics and achieving predictable interactions with biomedical substrates.

(2) **Advanced synthesis and surface engineering.** The scalable and reproducible synthesis of inorganic nanozymes is essential for their clinical translation. Robust, scalable syn-

thetic routes with real-time monitoring need to be developed to ensure batch uniformity. Implementing multifunctional surface coatings and stimuli-responsive polymers will simultaneously enhance their biocompatibility, reduce non-specific protein adsorption, enable active targeting, and provide environmental responsiveness.

(3) Integration with emerging technologies and bioinspired systems. Nanozyme research should increasingly intersect with other advancing fields, such as bioinspired engineering and wearable sensors. Emphasis on "smart" theranostic systems that operate in response to pathological stimuli (*e.g.*, inflammation, hypoxia, or acidosis) will enhance the precision in applications such as targeted drug delivery and immunomodulation.

(4) Comprehensive *in vivo* evaluation frameworks. Establishing standardized protocols for the rigorous assessment of long-term biocompatibility, immunogenicity, and chronic toxicity in relevant disease models. Advanced imaging techniques need to integrated to spatiotemporally track the biodistribution, *in situ* catalytic activity, and clearance kinetics of nanozymes. This data is vital for predictive pharmacokinetic/pharmacodynamic modeling. At the same time, there is an urgent need to develop standardized protocols and reference materials for quantifying nanozyme activity across laboratories. Efforts should be directed toward establishing ISO-compliant assays. This will facilitate a direct comparison between studies and support regulatory approval.

(5) Bridging the gap with clinical translation. Research efforts should focus on overcoming the most critical translational barriers identified, such as GMP-compliant manufacturing, establishing robust quality control metrics, and designing clinically relevant efficacy and safety studies.

(6) Overcoming translational and regulatory barriers. A translational road map must be developed in collaboration with regulatory agencies to define a clear path from bench to bedside. Key activities include defining critical quality attributes for inorganic nanozyme-based products, designing pivotal pre-clinical and clinical trials that emphasize safety and clinically meaningful endpoints, and creating open-access databases for material safety and efficacy data.

In conclusion, by fostering collaboration among different fields, inorganic nanozymes can transition from bench-scale innovations to applications that redefine medicine. By addressing these multifaceted challenges through collaborative and standardized approaches, this field has the potential to develop into clinically approved frontier technology that can completely change the methods of diagnosis and treatment. As we unravel the complexities of inorganic nanozyme catalysis, these artificial enzymes may ultimately rival or even surpass the sophistication of nature's own catalysts.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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References

1 L. Ma, J. Zheng, N. Zhou, R. Zhang, L. Fang, Y. Yang, X. Gao, C. Chen, X. Yan and K. Fan, *Nat. Commun.*, 2024, **15**, 233.
2 L. Zhang, H. Wang and X. Qu, *Adv. Mater.*, 2024, **36**, e2211147.
3 X. Liu, H. Xu, H. Peng, L. Wan, D. Di, Z. Qin, L. He, J. Lu, S. Wang and Q. Zhao, *Coord. Chem. Rev.*, 2024, **502**, 215610.
4 B. Xu, S. Li, L. Zheng, Y. Liu, A. Han, J. Zhang, Z. Huang, H. Xie, K. Fan, L. Gao and H. Liu, *Adv. Mater.*, 2022, **34**, e2107088.
5 F. Wang, Y. Wang, H. Wang, G. Zhao, J. Li and Y. Wang, *Microchem. J.*, 2023, **191**, 108817.
6 H. Wei, L. Gao, K. Fan, J. Liu, J. He, X. Qu, S. Dong, E. Wang and X. Yan, *Nano Today*, 2021, **40**, 101269.
7 Q. Liu, A. Zhang, R. Wang, Q. Zhang and D. Cui, *Nano-Micro Lett.*, 2021, **13**, 154.
8 J. Razlivina, A. Dmitrenko and V. Vinogradov, *J. Phys. Chem. Lett.*, 2024, **15**, 5804–5813.
9 K. A. Abdullah, T. F. Tahir, A. F. Qader, R. A. Omer and K. A. Othman, *J. Fluoresc.*, 2025, **35**, 4973–4987.
10 Q. Tian, S. Li, Z. Tang, Z. Zhang, D. Du, X. Zhang, X. Niu and Y. Lin, *Adv. Healthcare Mater.*, 2025, **14**, 2401630.
11 A. Baranwal, S. A. Polash, V. K. Aralappanavar, B. K. Behera, V. Bansal and R. Shukla, *Nanomaterials*, 2024, **14**, 244.
12 M. Kumawat, H. Madhyastha, A. Umapathi, M. Singh, N. Revaprasadu and H. K. Daima, *Langmuir*, 2022, **38**, 1877–1887.
13 S. Li, Y. Zhang, Q. Wang, A. Lin and H. Wei, *Anal. Chem.*, 2022, **94**, 312–323.
14 X. Wang, X. Zhong, J. Li, Z. Liu and L. Cheng, *Chem. Soc. Rev.*, 2021, **50**, 8669–8742.
15 H. Jia, J. Gong, Z. Hu, T. Wen, C. Li, Y. Chen, J. Huang and W. He, *Langmuir*, 2024, **40**, 19739–19750.

16 T. G. Halmagyi, L. Noureen, A. Szerlauth and I. Szilagyi, *Dalton Trans.*, 2024, **53**, 14132–14138.
17 W. Yang, X. Yang, L. Zhu, H. Chu, X. Li and W. Xu, *Coord. Chem. Rev.*, 2021, **448**, 214170.
18 Z. Liu, R. Wu, Y. Jiang, L. Qi, J. Liu, M. Du, J. Wang, L. Liu, G. Feng and L. Zhang, *Colloids Surf., B*, 2024, **233**, 113644.
19 S. Liang, X. Wu, M. Zong and W. Lou, *J. Colloid Interface Sci.*, 2022, **622**, 860–870.
20 M. Perwez, S. Y. Lau, D. Hussain, S. Anboo, M. Arshad and P. Thakur, *Colloids Surf., B*, 2023, **225**, 113241.
21 X. Huang, *New J. Chem.*, 2022, **46**, 15273–15291.
22 X. Yuan, J. Xiong, X. Wu, N. Ta, S. Liu, Z. Li and W. Lou, *Chem. Eng. J.*, 2024, **480**, 148246.
23 B. Cakiroglu, *Mikrochim. Acta*, 2024, **191**, 268.
24 Z. Ge, Y. Zhao, J. Li, Z. Si, W. Du and H. Su, *Nanoscale*, 2024, **16**, 2608–2620.
25 K. Fan, Y. Lin and V. Bansal, *Front. Chem.*, 2021, **9**, 670767.
26 Q. Li, M. Dong, Q. Han, Y. Zhang, D. Yang, D. Wei and Y. Yang, *J. Controlled Release*, 2024, **365**, 905–918.
27 H. Liu, B. Yu, C. Zhou, Z. Deng, H. Wang, X. Zhang and K. Wang, *Mater. Today Bio*, 2024, **27**, 101137.
28 X. Han, B. Li, W. Wang, B. Feng, Q. Tang, Y. Qi, R. Zhao, W. Qiu, S. Zhao, Z. Pan, X. Guo, H. Du, J. Qiu, H. Liu, G. Li and H. Xue, *ACS Nano*, 2024, **18**, 19836–19853.
29 M. Liu, H. Yu, T. Zhao and X. Li, *Dalton Trans.*, 2023, **52**, 15203–15215.
30 H. Fan, R. Zhang, K. Fan, L. Gao and X. Yan, *ACS Nano*, 2024, **18**, 2533–2540.
31 J. Mujtaba, J. Liu, K. K. Dey, T. Li, R. Chakraborty, K. Xu, D. Makarov, R. A. Barmin, D. A. Gorin, V. P. Tolstoy, G. Huang, A. A. Solovev and Y. Mei, *Adv. Mater.*, 2021, **33**, e2007465.
32 L. Zhang, C. Zhu, R. Huang, Y. Ding, C. Ruan and X. Shen, *Front. Chem.*, 2021, **9**, 630969.
33 P. Wang, D. Min, G. Chen, M. Li, L. Tong and Y. Cao, *Front. Chem.*, 2021, **9**, 773285.
34 M. Zandieh and J. Liu, *Adv. Mater.*, 2024, **36**, e2211041.
35 Y. Gao, X. Gao, H. Hou, Z. Qu, H. Li, B. Du and P. Tang, *Sens. Actuators, B*, 2024, **404**, 135280.
36 W. Xie, Y. Gan, L. Wang, Y. Si, Q. Li, T. Song, P. Wei, Z. Wu and G. Zhang, *Small*, 2024, **20**, e2306446.
37 H. Zhu, P. Liu, L. Xu, X. Li, P. Hu, B. Liu, J. Pan, F. Yang and X. Niu, *Biosensors*, 2021, **11**, 11100382.
38 C. P. Kurup and M. U. Ahmed, *Biosensors*, 2023, **13**, 13040461.
39 X. Li, H. Zhu, P. Liu, M. Wang, J. Pan, F. Qiu, L. Ni and X. Niu, *TrAC, Trends Anal. Chem.*, 2021, **143**, 116379.
40 L. Li, D. Wang, L. Ren, T. Wang, X. Tan, F. Cui, T. Li and J. Li, *Int. J. Biol. Macromol.*, 2024, **258**, 129098.
41 N. Tao, S. Chen, S. Mahdinloo, Q. Zhang, T. Lan, Q. Saiding, S. Chen, Y. Xiong, W. Tao and J. Ouyang, *Nano Today*, 2024, **57**, 102371.
42 R. Zhang, X. Yan and K. Fan, *Acc. Mater. Res.*, 2021, **2**, 534–547.
43 Z. Mohamad and J. Liu, *ACS Nano*, 2021, **15**, 15645–15655.
44 A. Moradi Hasan-Abad, A. Shabankare, A. Atapour, G. A. Hamidi, M. Salami Zavareh and A. Sobhani-Nasab, *Front. Pharmacol.*, 2024, **15**, 1339580.
45 X. Ren, D. Chen, Y. Wang, H. Li, Y. Zhang, H. Chen, X. Li and M. Huo, *J. Nanobiotechnol.*, 2022, **20**, 92.
46 J. Shen, J. Chen, Y. Qian, X. Wang, D. Wang, H. Pan and Y. Wang, *Adv. Mater.*, 2024, **36**, 2313406.
47 A. A. P. Mansur, A. G. Leonel, K. Krambrock and H. S. Mansur, *Catal. Today*, 2022, **397–399**, 129–144.
48 L. Wang, L. Zhao, X. Xiao, X. Wang, J. Cao, H. Ye, H. Li and Y. Zhang, *Sep. Purif. Technol.*, 2025, **359**, 130551.
49 X. Gao, H. Chen, H. Qiu, Y. Zhang, J. Cheng and Y. Shen, *J. Hazard. Mater.*, 2024, **469**, 133871.
50 Q. Diao, X. Chen, Z. Tang, S. Li, Q. Tian, Z. Bu, H. Liu, J. Liu and X. Niu, *Environ. Sci.: Nano*, 2024, **11**, 766–796.
51 Y. Zhou, Y. Li, Y. Fei, M. Zhang, S. Wang, F. Li and X. Bao, *Front. Chem.*, 2021, **9**, 681566.
52 R. Xu, S. Zhang, P. Wang, R. Zhang, P. Lin, Y. Wang, L. Gao, H. Wei, X. Zhang, D. Ling, X. Yan and K. Fan, *Coord. Chem. Rev.*, 2024, **501**, 215519.
53 C. Qiao, X. Wang, Y. Gao, Y. Ma, H. Luo, S. Zhang, D. Huo and C. Hou, *ACS Appl. Nano Mater.*, 2024, **7**, 9375–9387.
54 Q. Shang, L. Zhang, C. Chen, W. Tang, M. Han, Q. Chen and W. Liu, *ACS Appl. Nano Mater.*, 2022, **5**, 2678–2687.
55 C. N. Zhu, X. Chen, Y. Q. Xu, F. Wang, D. Y. Zheng, C. Liu, X. H. Zhang, Y. Yi and D. B. Cheng, *ACS Biomater. Sci. Eng.*, 2024, **10**, 7352–7371.
56 C. Wang, H. Wang, B. Xu and H. Liu, *View*, 2020, **2**, 20200045.
57 S. Jimenez-Falcao, J. M. Méndez-Arriaga, V. García-Almodóvar, A. A. García-Valdivia and S. Gómez-Ruiz, *Catalysts*, 2022, **13**, 13010013.
58 A. A. P. Mansur and H. S. Mansur, *J. Nanotheranostics*, 2025, **6**, 4.
59 F. Wei and X. Han, *Chin. J. Anal. Chem.*, 2021, **49**, 581–592.
60 Y. Ai, Z. Hu, X. Liang, H. Sun, H. Xin and Q. Liang, *Adv. Funct. Mater.*, 2021, **32**, 202110432.
61 L. Tang, S. Wang, J. Hu, L. Meng, J. Zhang, Y. Chang, X. Ma and Y. Guo, *Colloids Surf., B*, 2025, **245**, 114188.
62 B. Gao, Y. Ding, Z. Cai, S. Wu, J. Wang, N. Ling, Q. Ye, M. Chen, Y. Zhang, X. Wei, Y. Ye and Q. Wu, *Microchim. Acta*, 2024, **191**, 438.
63 C. Cheng, H. Wang, J. Zhao, Y. Wang, G. Zhao, Y. Zhang, X. Liu and Y. Wang, *Colloids Surf., B*, 2024, **235**, 113767.
64 S. Maddheshiya and S. Nara, *Front. Bioeng. Biotechnol.*, 2022, **10**, 880214.
65 A. Sen, J. Oswalia, S. Yadav, M. Vachher and A. Nigam, *Curr. Res. Biotechnol.*, 2024, **7**, 100205.
66 J. Li, X. Cai, Y. Zhang, K. Li, L. Guan, Y. Li, T. Wang and T. Sun, *ChemistrySelect*, 2022, **7**, 202201127.
67 N. A. Omar and H. S. Jabbar, *Inorg. Chem. Commun.*, 2022, **146**, 110104.
68 J. Li, S. Wei, N. Wang, M. Yang, X. Xu, J. Tang and Z. Li, *Talanta*, 2024, **279**, 126603.

69 R. Li, C. Yang and Z. Li, *New J. Chem.*, 2025, **49**, 4682–4691.
70 J. Huo, J. Hao, J. Mu and Y. Wang, *ACS Appl. Bio Mater.*, 2021, **4**, 3443–3452.
71 X. Huang, S. Zhang, Y. Tang, X. Zhang, Y. Bai and H. Pang, *Coord. Chem. Rev.*, 2021, **449**, 214216.
72 X. Zhang, S. Lin, S. Liu, X. Tan, Y. Dai and F. Xia, *Coord. Chem. Rev.*, 2021, **429**, 213652.
73 Y. Yi, X. Zhou, D. Liao, J. Hou, H. Liu and G. Zhu, *Inorg. Chem.*, 2023, **62**, 13929–13936.
74 Y. Tian, Z. Ye, X. Wang, H. Guan, W. Liu, X. Duan, Y. Liu, G. Zeng and H. Liu, *Adv. Healthcare Mater.*, 2024, e2401574.
75 X. Liu, P. An, Y. Han, H. Meng and X. Zhang, *Microchem. J.*, 2024, **201**, 110559.
76 A. Ali, M. Ovais, H. Zhou, Y. Rui and C. Chen, *Biomaterials*, 2021, **275**, 120951.
77 M. K. Sarangi, L. D. Patel, G. Rath, S. S. Nanda and D. K. Yi, *Chin. Chem. Lett.*, 2024, **35**, 109381.
78 Z. Zhang, Y. Li, Z. Yuan, L. Wu, J. Ma, W. Tan, Y. Sun, G. Zhang and H. Chai, *Inorg. Chem. Front.*, 2025, **12**, 400–429.
79 B. Li, D. Xu, Y. Chen, W. Li, H. Liu, A. A. Ansari and R. Lv, *ACS Appl. Nano Mater.*, 2024, **7**, 9428–9440.
80 X. Xu, M. Ma, J. Gao, T. Sun, Y. Guo, D. Feng and L. Zhang, *Inorg. Chem.*, 2024, **63**, 1225–1235.
81 R. Wang, B. Guan, W. Wang, H. Yan, J. Jin, Y. Yang, L. Li, L. Guo and Y. Zeng, *Sens. Actuators, B*, 2025, **427**, 137178.
82 H. Guan, B. Han, B. Peng, H. Ye, Q. Zhang and D. Wang, *Microchem. J.*, 2023, **194**, 109311.
83 G. Zhu, P. Zheng, M. Wang, W. Chenb and C. Li, *Inorg. Chem. Front.*, 2022, **9**, 1006–1015.
84 J. Xia, Z. Li, Y. Ding, L. A. Shah, H. Zhao, D. Ye and J. Zhang, *Anal. Chem.*, 2024, **96**, 8221–8233.
85 Z. Wang, R. Wang, Z. Geng, X. Luo, J. Jia, S. Pang, X. Fan, M. Bilal and J. Cui, *Crit. Rev. Biotechnol.*, 2024, **44**, 674–697.
86 Y. Wu, Y. Tang, W. Xu, R. Su, Y. Qin, L. Jiao, H. Wang, X. Cui, L. Zheng, C. Wang, L. Hu, W. Gu, D. Du, Y. Lin and C. Zhu, *Small*, 2023, **19**, e2302929.
87 L. Jiang, Y. Han, S. Fernández-García, M. Tinoco, Z. Li, P. Nan, J. Sun, J. J. Delgado, H. Pan, G. Blanco, J. Martínez-López, A. B. Hungría, J. J. Calvino and X. Chen, *Appl. Surf. Sci.*, 2023, **610**, 155502.
88 L. Tu, S. Chen, Z. Yuan, Y. Xiong, B. Luo, Y. Chen, Z. Hou, S. Ke, N. Lin, C. Li and S. Ye, *J. Colloid Interface Sci.*, 2024, **663**, 810–824.
89 T. Chen, Y. Wang, K. Wang, M. Dai, Y. Duan, C. Mao and M. Wan, *Mater. Chem. Front.*, 2024, **8**, 3383–3412.
90 X. Zeng, S. Yan and B. Liu, *Microporous Mesoporous Mater.*, 2022, **335**, 111826.
91 Q. Ye, E. Yuan, J. Shen, M. Ye, Q. Xu, X. Hu, Y. Shu and H. Pang, *Adv. Sci.*, 2023, **10**, e2304149.
92 Y. Huang, J. Ren and X. Qu, *Chem. Rev.*, 2019, **119**, 4357–4412.
93 X. Shen, Z. Wang, X. Gao and X. Gao, *Adv. Mater.*, 2024, **36**, e2211151.
94 H. Dong, W. Du, J. Dong, R. Che, F. Kong, W. Cheng, M. Ma, N. Gu and Y. Zhang, *Nat. Commun.*, 2022, **13**, 5365.
95 Y. Song, C. Huang and Y. Li, *Inorg. Chem.*, 2023, **62**, 12697–12707.
96 Y. Wang, X. Zhang, Y. Dai and F. Xia, *Chem. Eng. J.*, 2023, **455**, 140811.
97 Z. Xin, K. Duan, Q. Zhuo, Q. He, X. Zhang, C. Zheng, X. Han, T. Han, Z. Fu, X. Xu and X. Zhao, *Chem. Eng. J.*, 2023, **461**, 141589.
98 Y. Liu, N. Li, K. Su, J. Du and R. Guo, *Inorg. Chem.*, 2024, **63**, 13602–13612.
99 Z. Tong, Y. Gao, H. Yang, W. Wang and Z. Mao, *View*, 2021, **2**, 20200133.
100 T. Hu, Q. Liu, Z. Zhou, W. Zhao, H. Huang, F. Meng, W. Liu, Q. Zhang, L. Gu, R. Liang and C. Tan, *Small*, 2022, **18**, e2200595.
101 J. Sheng, Y. Wu, H. Ding, K. Feng, Y. Shen, Y. Zhang and N. Gu, *Adv. Mater.*, 2024, **36**, e2211210.
102 V. Baldim, F. Bedioui, N. Mignet, I. Margaill and J. F. Berret, *Nanoscale*, 2018, **10**, 6971–6980.
103 Z. Xi, W. Gao and X. Xia, *ChemBioChem*, 2020, **21**, 2440–2444.
104 A. Sahu, K. Min, S. H. Jeon, K. Kwon and G. Tae, *Carbohydr. Polym.*, 2023, **316**, 121088.
105 S. Singh, *Int. J. Biol. Macromol.*, 2024, **260**, 129374.
106 Y. Ai, H. Sun, C. Wang, W. Zheng, Q. Han and Q. Liang, *Small*, 2022, **18**, e2105304.
107 N. K. Dega, A. B. Ganganboina, H. L. Tran, E. P. Kuncoro and R. A. Doong, *Talanta*, 2022, **237**, 122957.
108 Y. Li, *IOP Conf. Ser.: Earth Environ. Sci.*, 2021, **804**, 042018.
109 T. Sahare, N. Singh, B. N. Sahoo and A. Joshi, *Biosens. Bioelectron.: X*, 2024, **21**, 100544.
110 B. Shen, L. Yang, H. Xu, Y. Zhang, D. Ming, L. Zhu, Y. Wang and L. Jiang, *J. Colloid Interface Sci.*, 2023, **650**, 211–221.
111 C. Lou, F. Yang, L. Zhu, Q. Sun, Y. Yang and J. Guo, *Colloids Surf., A*, 2023, **677**, 132398.
112 G. Song, J. Li, Z. Majid, W. Xu, X. He, Z. Yao, Y. Luo, K. Huang and N. Cheng, *Food Chem.*, 2022, **390**, 133127.
113 Q. Li, S. Zhan, X. Yang, Z. Zhang, N. Sun, X. Wang, J. Kang, R. Du, X. Hong, M. Yue, X. Li, Y. Tang, G. Liu, Y. Liu and D. Liu, *ACS Nano*, 2024, **18**, 16113–16125.
114 Z. Wang, Y. Shao, Z. Zhu, J. Wang, X. Gao, J. Xie, Y. Wang, Q. Wu, Y. Shen and Y. Ding, *Coord. Chem. Rev.*, 2023, **495**, 215369.
115 Q. Zhang, L. Song and K. Zhang, *Mater. Chem. Front.*, 2023, **7**, 44–64.
116 M. He, X. Xu, H. Wang, Q. Wu, L. Zhang, D. Zhou, Y. Tong, X. Su and H. Liu, *Small*, 2023, **19**, e2208167.
117 S. Khan, M. M. N. Babadaei, A. Hasan, Z. Edis, F. Attar, R. Siddique, Q. Bai, M. Sharifi and M. Falahati, *J. Adv. Res.*, 2021, **33**, 227–239.

118 Z. Wang, M. Li, H. Bu, D. S. Zia, P. Dai and J. Liu, *Mater. Chem. Front.*, 2023, **7**, 3625–3640.
119 S. Ali, S. Sikdar, S. Basak, M. S. Haydar, K. Mallick, M. Mondal, D. Roy, S. Ghosh, S. Sahu, P. Paul and M. N. Roy, *Inorg. Chem.*, 2023, **62**, 11291–11303.
120 B. Hong, T. Qin, W. Wang, L. Luo, Y. Li, Y. Ma and J. Wang, *Sens. Actuators, B*, 2025, **426**, 137097.
121 L. Wang, Y. Chu, B. Cao, R. Zhang, Z. Hussain and Q. Liu, *Talanta*, 2025, **281**, 126889.
122 M. Luo, F. Zhao, Y. Wang and J. Bian, *J. Transl. Med.*, 2024, **22**, 814.
123 H. Wang, B. Wang, J. Jiang, Y. Wu, A. Song, X. Wang, C. Yao, H. Dai, J. Xu, Y. Zhang, Q. Ma, F. Xu, R. Li and C. Wang, *Molecules*, 2022, **27**, 27238552.
124 A. A. P. Mansur, H. S. Mansur and S. M. Carvalho, *Catal. Today*, 2022, **388–389**, 187–198.
125 W. He, Z. Zhang and X. Sha, *Biomaterials*, 2021, **277**, 121111.
126 X. Qin, J. Xiao, H. Li, H. Huang, H. Jin, Y. Zhang, G. Tian, G. Wang and G. Zhang, *Inorg. Chem. Front.*, 2023, **10**, 7176–7186.
127 N. Feng, Q. Li, Q. Bai, S. Xu, J. Shi, B. Liu and J. Guo, *J. Colloid Interface Sci.*, 2022, **618**, 68–77.
128 Y. Xie, M. Wang, Q. Sun, D. Wang, S. Luo and C. Li, *Inorg. Chem.*, 2022, **61**, 6852–6860.
129 Y. Yao, Z. Wang, Q. Cao, H. Li, S. Ge, J. Liu, P. Sun, Z. Liu, Y. Wu, W. Wang and J. Liu, *ACS Appl. Mater. Interfaces*, 2022, **14**, 17153–17163.
130 L. Xie, H. Wu, Y. Li, L. Shi and Y. Liu, *Adv. Healthcare Mater.*, 2024, e2402659.
131 Y. Zhang, F. Lei, W. Qian, C. Zhang, Q. Wang, C. Liu, H. Ji, Z. Liu and F. Wang, *J. Controlled Release*, 2024, **373**, 929–951.
132 M. Zhang and W. Tong, *Biomater. Sci.*, 2023, **11**, 5769–5780.
133 S. Ahmadi, K. Rahimizadeh, A. Shafiee, N. Rabiee and S. Iravani, *Process Biochem.*, 2023, **131**, 154–174.
134 B. Unnikrishnan, C. W. Lien, H. Chu and C. Huang, *J. Hazard. Mater.*, 2021, **401**, 123397.
135 X. He, Y. Lv, Y. Lin, H. Yu, Y. Zhang, Y. Tong and C. Zhang, *Adv. Mater.*, 2024, **36**, e2400366.
136 N. Singh, G. R. Sherin and G. Mugesh, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301232.
137 Q. Wang, J. Jiang and L. Gao, *Biomed. Mater.*, 2021, **16**, 042002.
138 X. Ma, J. Lang, P. Chen, W. Tang, S. Shindler and R. Yang, *Nanoscale*, 2023, **15**, 1014–1023.
139 Q. Chen, M. Cao, J. Qiao, Q. Li and X. Zhang, *Nanoscale Horiz.*, 2023, **8**, 489–498.
140 Z. Sun, J. Yao, J. Wang, R. Huang, X. Liu, F. Li, X. Jiang and W. Chen, *Inorg. Chem.*, 2022, **61**, 1169–1177.
141 G. Luo, J. Zhang, Y. Sun, Y. Wang, H. Wang, B. Cheng, Q. Shu and X. Fang, *Nano-Micro Lett.*, 2021, **13**, 88.
142 D. Jiang, D. Ni, Z. T. Rosenkrans, P. Huang, X. Yan and W. Cai, *Chem. Soc. Rev.*, 2019, **48**, 3683–3704.
143 M. Kumawat, H. Madhyastha, M. Singh, D. Jain and H. K. Daima, *Colloids Surf., A*, 2022, **650**, 129294.
144 M. Kumawat, A. Umapathi, E. Lichtfouse and H. K. Daima, *Environ. Chem. Lett.*, 2021, **19**, 3951–3957.
145 H. Li, Z. Liu, P. Zhang and D. Zhang, *Drug Delivery*, 2024, **31**, 2417986.
146 C. Wu, D. Xu, M. Ge, J. Luo, L. Chen, Z. Chen, Y. You, Y. Zhu, H. Lin and J. Shi, *Nano Today*, 2022, **46**, 101574.
147 Y. Wu, W. Chen, C. Wang and D. Xing, *Chin. Chem. Lett.*, 2024, **35**, 109096.
148 L. Li, D. Wang, L. Ren, T. Wang, X. Tan, F. Cui, T. Li and J. Li, *Int. J. Biol. Macromol.*, 2024, **258**, 129098.
149 X. Zhang, S. Lin, R. Huang, A. Gupta, S. Fedeli, R. Cao-Milan, D. C. Luther, Y. Liu, M. Jiang, G. Li, B. Rondon, H. Wei and V. M. Rotello, *J. Am. Chem. Soc.*, 2022, **144**, 12893–12900.
150 Z. Nie, Y. Vahdani, W. C. Cho, S. H. Bloukh, Z. Edis, S. Haghighat, M. Falahati, R. Kheradmandi, L. A. Jaragh-Alhadad and M. Sharifi, *Arabian J. Chem.*, 2022, **15**, 103966.
151 M. Cui, H. Zhang, F. Ouyang, Y. Guo, R. Li, S. Duan, T. Xiong, Y. Wang and X. Wang, *J. Biomed. Nanotechnol.*, 2021, **17**, 1007–1019.
152 A. Jouyban and R. Amini, *Microchem. J.*, 2021, **164**, 105970.
153 G. Wei, S. Liu, Y. Peng and H. Wei, *Chin. J. Chem.*, 2024, **42**, 1515–1522.
154 Y. Li and J. Liu, *Mater. Horiz.*, 2021, **8**, 336–350.
155 X. Zhu, N. Xu, L. Zhang, D. Wang and P. Zhang, *Eur. J. Med. Chem.*, 2022, **238**, 114456.
156 W. Chen, W. Xie, Z. Gao, C. Lin, M. Tan, Y. Zhang and Z. Hou, *Adv. Sci.*, 2023, **10**, e2303694.
157 Z. Wang, Y. Shao, Z. Zhu, J. Wang, X. Gao, J. Xie, Y. Wang, Q. Wu, Y. Shen and Y. Ding, *Coord. Chem. Rev.*, 2023, **495**, 215369.
158 L. Wang, X. Zhang, Z. You, Z. Yang, M. Guo, J. Guo, H. Liu, X. Zhang, Z. Wang, A. Wang, Y. Lv, J. Zhang, X. Yu, J. Liu and C. Chen, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217448.
159 Z. Ma, M. F. Foda, H. Liang, Y. Zhao and H. Han, *Adv. Funct. Mater.*, 2021, **31**, 202103765.
160 B. Huang, J. Tian, Z. Cui, S. Weng, W. Wang, X. Jiang and W. Zhang, *Chem. Eng. J.*, 2022, **444**, 136164.
161 Z. Wang, Y. Zhao, Y. Hou, G. Tang, R. Zhang, Y. Yang, X. Yan and K. Fan, *Adv. Mater.*, 2024, **36**, e2210144.
162 H. Yang, B. Xu, S. Li, Q. Wu, M. Lu, A. Han and H. Liu, *Small*, 2021, **17**, e2007090.
163 Y. Cheng, Y. Xia, Y. Sun, Y. Wang and X. Yin, *Adv. Mater.*, 2024, **36**, e2308033.
164 Y. Wu, Y. Qin, M. Muppidathi, R. Carmieli, M. Fadeev, W. Lei, M. Xia and I. Willner, *Adv. Funct. Mater.*, 2023, **34**, 202306929.
165 Y. Liu, Y. Qin, Q. Zhang, W. Zou, L. Jin and R. Guo, *J. Colloid Interface Sci.*, 2021, **600**, 37–48.
166 Y. Liu, N. Li, H. Zhang, D. Wei and R. Guo, *Sens. Actuators, B*, 2025, **423**, 136784.

