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Enzyme-Mimic Nanomaterials in Biomedicine: Catalytic Mechanisms, Functional Platforms, and Translational Potential.

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ABSTRACT

The emergence of enzyme-mimicking nanomaterials (nanozymes) represents a transformative development in biomedical research, offering catalytic versatility, enhanced stability, and cost-effective scalability compared to natural enzymes. This review consolidates current advances in the design, synthesis, and biomedical deployment of nanozymes, particularly those based on noble metals, metal oxides, and functional nanocomposites. A systematic comparative analysis was conducted across diverse studies to elucidate the catalytic mechanisms, structural-functional relationships, and environmental adaptability of these nanomaterials.

The literature was critically evaluated with emphasis on the physicochemical factors governing nanozyme activity such as particle size, surface ligands, and crystal facets and their modulation strategies. Trends indicate that noble metal nanoparticles (e.g., Au, Pt, Pd) and metal oxides (e.g., Fe_3O_4, CeO_2, V_2O_5) exhibit peroxidase, oxidase, and catalase-like functions, with performance often surpassing their biological counterparts under physiological conditions. Moreover, 2D nanomaterials and Prussian blue analogues demonstrate significant promise as tunable catalytic platforms.

Functionally, nanozymes are proving integral in areas such as tumor theranostics, antibacterial therapy, antioxidation, and bioorthogonal catalysis. Applications range from in situ ROS modulation for cancer treatment to programmable catalysis in cellular imaging and drug activation. Despite these advances, challenges remain in enhancing substrate specificity, minimizing cytotoxicity, and fully elucidating mechanistic pathways.

In conclusion, nanozymes hold substantial potential to reshape therapeutic and diagnostic modalities. Future research must focus on integrating simulation-driven design, expanding the scope of enzyme mimicry, and ensuring biosafety in complex biological environments. Addressing these gaps could accelerate the clinical translation of nanozyme-based technologies, establishing them as cornerstone tools in next-generation biomedical applications.

Keywords: Nanozymes, Catalysis, Theranostics, Antioxidants, Nanomedicine

INTRODUCTION

In recent years, the field of nanobiotechnology has witnessed a paradigm shift with the advent of enzyme-mimicking nanomaterials, commonly referred to as nanozymes (Pant et al., 2024). These synthetic

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nanostructures, capable of replicating the catalytic functions of natural enzymes, have garnered considerable attention due to their exceptional stability, tunable activity, and cost-efficient production. Unlike their biological counterparts, which often suffer from structural fragility, limited reusability, and environmental sensitivity, nanozymes offer robust catalytic performance under a broad range of physiological and environmental conditions. This has positioned them at the forefront of biomedical research, where there is a growing demand for smart, adaptive, and multifunctional materials capable of addressing complex diagnostic and therapeutic challenges (Nagendran et al., 2024).

The significance of nanozymes extends far beyond their chemical novelty. Their integration into biomedical applications ranging from tumor imaging and targeted therapy to antimicrobial treatment, antioxidant intervention (Tao et al., 2020; Zhong et al., 2023), and in vivo bioorthogonal catalysis marks a critical advancement in translational nanomedicine. These materials are not only enhancing the precision and efficiency of existing clinical protocols but also enabling entirely new therapeutic paradigms, such as hypoxia-tolerant photodynamic therapy and stimuli-responsive drug activation within the tumor microenvironment. Moreover, their potential in combating antibiotic resistant pathogens and mitigating oxidative stress opens avenues for addressing pressing public health concerns (Li et al., 2025).

Despite these promising developments, a number of critical knowledge gaps persist. Current literature often presents fragmented insights into the structure activity relationships, catalytic mechanisms, and regulatory factors that govern nanozyme behaviour. In particular, the heterogeneity in material composition, particle morphology, and surface chemistry across studies complicates the establishment of universal design principles. Furthermore, while several proof-of-concept studies have demonstrated the feasibility of nanozyme based systems, their long-term biocompatibility, in vivo kinetics, and molecular-level interaction pathways remain incompletely understood (Aldrich et al., 2023).

This review is therefore both timely and necessary. It seeks to provide a consolidated and critical account of the diverse classes of nanozymes, with particular emphasis on their synthetic strategies, catalytic performance modulation, and emerging roles in biomedicine. By integrating findings from recent investigations including noble metal nanoparticles, metal oxides, 2D materials, and Prussian blue analogues this article aims to delineate the fundamental principles guiding nanozyme functionality and to highlight translational opportunities and unresolved challenges.

The objective of this review is to synthesize current advances in enzyme-mimicking nanomaterials and assess their biomedical applications through a comprehensive, mechanistically informed lens, thereby offering direction for future research and development in this rapidly evolving domain.

Objectives

1. To critically synthesize the recent advancements in the design, synthesis, and catalytic behaviour of enzyme-mimic nanomaterials, with emphasis on their structure function relationships and physicochemical regulation.
2. To evaluate the biomedical relevance of nanozymes across domains such as tumor theranostics, antibacterial therapy, antioxidation, and bioorthogonal catalysis, highlighting their multifunctionality and advantages over natural enzymes.
3. To identify existing challenges such as toxicity, specificity, and in vivo biostability and propose future directions that integrate interdisciplinary strategies for enhancing the clinical translatability of nanozyme-based platforms.

Enzyme Mimic Nanomaterials

Enzyme-mimic nanomaterials, or nanozymes, are a class of synthetic nanostructures engineered to replicate the catalytic functions of natural enzymes. These materials exhibit activities such as oxidase, peroxidase, catalase, and superoxide dismutase, yet they surpass biological enzymes in terms of stability, cost-efficiency, and environmental tolerance. Their unique physicochemical properties derived from nanoscale dimensions, surface tunability, and multifunctional architectures enable applications across diagnostics, therapeutics, and biosensing.

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This section critically examines two major categories of nanozymes: noble metal nanoparticles and metal oxide-based systems, emphasizing their mechanisms, biomedical relevance, and translational challenges (Lai et al., 2025; Xu et al., 2025; S. Zhang et al., 2025).

Noble Metal Nanoparticles with Catalytic Behaviours

Noble metal nanoparticles (NMNPs), particularly those composed of gold (Au), silver (Ag), platinum (Pt), and palladium (Pd), have emerged as a pivotal class of nanozymes owing to their superior catalytic versatility, surface modifiability, and electron transfer dynamics. Their intrinsic enzyme-like activities have been harnessed for a range of biomedical applications including tumor diagnostics, pathogen detection, and therapeutic modulation of reactive oxygen species (ROS) (Kashtiaray et al., 2025a; Malekzad et al., 2016).

Catalytic Functionality and Mechanisms

Among NMNPs, Au nanoparticles (AuNPs) were among the first reported to exhibit oxidase-mimetic behaviour, notably in glucose oxidation. The mechanistic basis lies in their ability to adsorb electron-rich substrates and mediate oxygen activation via surface complexes, facilitating redox transformations similar to those of glucose oxidase (Sen et al., 2024a). This process is highly pH-dependent and regulated by the nanoparticle's surface chemistry. Notably, DNA-functionalized AuNPs demonstrated stereoselective catalysis, exhibiting enantioselective oxidation of glucose isomers a functionality unattainable by most natural enzymes.

Ag nanoparticles similarly demonstrate peroxidase and oxidase like activity. Electron spin resonance spectroscopy has revealed their ROS generating capabilities during hydrogen peroxide decomposition, implicating AgNPs in potential antimicrobial and biosensing functions (He et al., 2011). Their catalytic output is highly responsive to environmental parameters such as pH and ionic species. For instance, the presence of Hg^{2+} ions dramatically enhance their catalytic response in chromogenic assays, a feature exploited in metal ion detection platforms.

Pt nanoparticles, known for their catalytic robustness, mimic peroxidase activity effectively. Their reactivity can be fine-tuned through control over particle morphology, ligand chemistry, and size. Studies have shown that ultrasmall Pt nanocubes exhibit strong thermal and pH tolerance, making them suitable for physiological applications. Moreover, DNA templating strategies allow size and activity modulation, providing an added layer of control over catalytic kinetics and substrate affinity (Abdelhamid et al., 2020; Sen et al., 2024b).

Pd nanoparticles extend this paradigm by offering tunable oxidase and catalase-like activities. The catalytic behaviour is facet-dependent; Pd (111) surfaces exhibit superior redox capabilities compared to higher-energy surfaces. Ligand modification further alters their solubility and interaction profiles, expanding their usability in aqueous biological media. Pd-based nanozymes have been deployed in bioassays for cancer biomarkers and even demonstrated dual functionalities acting both as sensors and therapeutic agents (R. Zhang et al., 2025a).

Biomedical Relevance and Translational Insights

The utility of noble metal nanozymes in medicine hinges on their ability to function under biologically relevant conditions. For instance, Au@Pt core-shell nanoparticles have been integrated into ELISA platforms with performance metrics rivaling traditional horseradish peroxidase (HRP). Furthermore, programmable Au assemblies, directed by DNA nanotechnology, have facilitated single-particle catalytic imaging a significant step toward real-time, intracellular biochemical monitoring (Shamsabadi et al., 2024).

In antimicrobial strategies, AgNPs exhibit selective bactericidal action when modulated with external ions or surface ligands, showing promise in infection control and biosafety applications. Pt nanozymes, on the other hand, contribute to glucose monitoring in diabetic diagnostics and have been adapted for blood-based clinical assays (Sen et al., 2024c).

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Synthesis Strategies and Challenges

Despite these advancements, the synthesis of NMNPs with consistent size, shape, and surface chemistry remains a bottleneck. Wet-chemical routes often lead to heterogeneous populations, which can result in variable catalytic activity. Advances in biomolecule-assisted synthesis particularly using DNA or peptides have improved control over morphology and biocompatibility. However, scalability and batch reproducibility remain significant challenges (Desai et al., 2025).

Another major consideration is the biocompatibility and potential toxicity of noble metals upon long-term exposure. While surface modifications (e.g., PEGylation) mitigate immunogenicity and improve circulation time, systematic in vivo studies are still required to understand biodistribution, clearance, and chronic effects (Santhanakrishnan et al., 2024).

Current Trends and Future Directions

The field is now pivoting toward hybrid nanozyme systems where NMNPs are embedded within or conjugated to responsive platforms, such as hydrogels, photosensitive polymers, or smart vesicles. Such systems allow spatiotemporal control of enzymatic activity opening up avenues for stimuli-triggered therapeutic interventions. Moreover, efforts to combine catalytic and plasmonic properties are pushing the boundaries of integrated diagnostics and therapy, particularly in the realm of cancer theranostics (Cao et al., 2023).

In summary, noble metal nanoparticles offer a unique platform for enzyme mimicry, distinguished by their robustness, tunability, and multifunctionality. While their biomedical potential is profound, further refinement in design strategies and safety evaluation is essential to transition these materials from laboratory to clinic (Bayda et al., 2020; Truong et al., 2024).

Metal Oxide Nanoparticles with Catalytic Behaviours

Metal oxide nanoparticles constitute another major class of nanozymes with remarkable enzyme-like functions, offering catalytic activities that span peroxidase, catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) mimetics. Their versatile redox properties, chemical stability, and scalable synthesis have positioned them as compelling alternatives to natural enzymes, particularly in biomedical contexts requiring sustained functionality under physiological stress or complex biofluid environments (X. Wang, 2022; R. Zhang et al., 2022).

Catalytic Mechanisms and Functional Diversity

The prototypical metal oxide nanozyme is magnetite (Fe_3O_4), first reported to exhibit intrinsic peroxidase-like activity under mild conditions. Its catalytic behaviour stems from the Fenton-like reaction between Fe^{2+}/Fe^{3+} redox pairs and hydrogen peroxide (H_2O_2), generating reactive hydroxyl radicals. Notably, the catalytic output is particle size-dependent, with smaller nanoparticles displaying higher activity due to increased surface-to-volume ratio and surface defect density. Beyond spherical forms, morphology-specific variants such as truncated octahedrons have shown superior catalytic performance due to the enhanced exposure of active crystal facets (L. Gao et al., 2007a).

Fe_3O_4-based nanozymes have been applied in biosensing platforms, immunoassays, and choline detection systems. Their ferromagnetic properties further facilitate recovery and reuse, enhancing their appeal for diagnostic and therapeutic devices. However, their activity is often nonspecific and can be influenced by surface fouling in biological media, highlighting the need for surface functionalization or protective coatings (L. Gao et al., 2007a).

Cerium oxide nanoparticles (CeO_2), or nanoceria, represent a distinctive category of SOD- and catalase-mimicking nanozymes. Their unique redox-switching capability between Ce^{3+} and Ce^{4+} oxidation states allow them to scavenge superoxide radicals and decompose H_2O_2, maintaining redox homeostasis in cells. This regenerative redox cycling enables continuous catalytic activity, mimicking the function of antioxidant enzymes.

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However, Ce^{3+} content on the surface is highly sensitive to synthetic conditions, and improper surface oxidation can severely impair catalytic performance.

PEGylation of nanoceria has emerged as a successful strategy to enhance their dispersion in aqueous media,

improve biocompatibility, and preserve Ce^{3+} surface content. Moreover, nanoceria's catalytic activity can be regulated through interactions with biomolecules such as DNA, which when adsorbed, can inhibit surface redox reactions introducing possibilities for smart regulation in biosensing or targeted therapy (Abokyi et al., 2020).

Manganese dioxide (MnO_2) and its derivatives (e.g., Mn_3O_4) offer another line of redox-active nanozymes. MnO_2 nanoparticles have demonstrated dual oxidase and peroxidase activities and have been deployed in colorimetric immunoassays, wound disinfection, and antioxidant therapies. Their GPx-like activity has been used to modulate oxidative stress, with applications in neuroprotection and anti-inflammatory treatments. Like Fe_3O_4, MnO_2 nanozyme activity is structure-dependent, and biological performance improves with protein templating or surface engineering, as seen in bovine serum albumin-stabilized formulations.

Vanadium pentoxide (V_2O_5) nanowires also stand out for their GPx-like activity. Their catalytic efficiency depends not only on their size and aspect ratio but also on the dominant exposed crystal facet, with the {010} surface showing the highest reactivity. Density functional theory (DFT) simulations have elucidated the facet-dependent electron transfer processes, aligning experimental findings with theoretical predictions. V_2O_5 nanozymes have shown effectiveness in intracellular ROS regulation, offering therapeutic benefits in degenerative and inflammatory diseases (Alrobaian, 2023).

Biomedical Applications and Functional Integration

Metal oxide nanozymes are finding expanding roles in tumor theranostics, antimicrobial treatments, and oxidative stress management. Their ability to catalyze ROS production or scavenging in situ enables dual functionality: pro-oxidant strategies for cancer therapy and antioxidant strategies for cellular protection.

In tumor applications, Fe_3O_4 and MnO_2 nanozymes have been employed for enhanced imaging and targeted therapy. When conjugated with tumor-targeting ligands or embedded in stimuli-responsive platforms, they can amplify oxidative stress within the tumor microenvironment, selectively inducing apoptosis. Simultaneously, their inherent MRI contrast-enhancing properties or colorimetric responses facilitate real-time monitoring (Mohapatra & Park, 2023).

For anti-bacterial applications, nanozymes such as MnO_2 and CeO_2 demonstrate high catalytic activity in generating bactericidal species (e.g., hydroxyl radicals) or disrupting bacterial redox balance. Importantly, these systems maintain activity in biofilm-associated infections, where conventional antibiotics often fail. Recent designs incorporate charge-switchable or light-responsive elements to modulate selectivity toward Gram-positive or Gram-negative bacteria.

Antioxidant therapies also benefit from metal oxide nanozymes. Mn_3O_4 and V_2O_5 nanoparticles have been shown to attenuate oxidative damage to DNA, proteins, and lipids, supporting their role in combating oxidative-stress-related pathologies such as neurodegeneration, cardiovascular disease, and aging-related dysfunction (Jiang et al., 2022).

Limitations and Design Challenges

Despite significant progress, several issues temper the clinical translation of metal oxide nanozymes. First, their catalytic specificity remains lower than that of natural enzymes, limiting their utility in highly selective biochemical processes. Second, concerns persist regarding their long-term accumulation and potential toxicity, particularly for materials like V_2O_5 and Mn-based systems. Although surface modifications (e.g., PEG, biomolecule coatings) improve compatibility, comprehensive toxicological assessments remain limited (Chen et al., 2013; Qu et al., 2014).

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Another challenge lies in standardizing activity assays. Disparities in experimental conditions such as pH, buffer composition, and substrate concentrations complicate direct comparisons across studies. Moreover, the impact of protein corona formation in vivo on catalytic activity is underexplored and could significantly alter functionality (Liu et al., 2021).

Emerging Directions

Emerging trends in metal oxide nanozyme research include the development of hybrid platforms that integrate multiple enzymatic activities (e.g., SOD + GPx + catalase), enabling synergistic effects in complex oxidative environments. Molecular imprinting techniques and bio-inspired coatings are being investigated to enhance substrate specificity and reduce off-target effects. Simultaneously, computational modelling and machine learning are aiding in predictive design, allowing researchers to tailor nanoparticle composition and morphology for optimized catalytic profiles.

In conclusion, metal oxide-based nanozymes offer a rich landscape of catalytic functionalities with substantial potential in biomedical science. Their adaptability, tunability, and multifunctionality continue to drive innovation, though further refinement in biocompatibility, specificity, and regulatory understanding will be essential for their successful integration into clinical practice (Z. Wang et al., 2025).

Other Nanomaterials with Catalytic Behaviours

Beyond noble metals and metal oxides, a diverse range of nanomaterials including carbon-based nanostructures, two-dimensional (2D) materials, Prussian blue analogues, and metal–organic frameworks (MOFs) have been identified as potent enzyme mimics. These materials expand the functional landscape of nanozymes by offering novel surface chemistries, structural tunability, and unique physicochemical interactions with biological substrates.

Graphene oxide (GO), a widely studied carbon-based nanomaterial, demonstrates intrinsic peroxidase-like activity largely attributed to its surface carboxyl and carbonyl groups. These functionalities create catalytic sites capable of facilitating hydrogen peroxide decomposition and substrate oxidation in colorimetric assays. Unlike transition metal-based nanozymes, the catalytic mechanisms in carbon materials are often governed by electron transfer processes localized at defect sites or functional groups, enabling reaction pathways distinct from metal-centered catalysis. This difference allows for broader environmental adaptability and pH tolerance, which are valuable for biosensing and diagnostic platforms (Yusuf et al., 2022).

Similarly, other 2D nanomaterials like molybdenum disulfide (MoS_2) have gained attention due to their layered structure and ability to catalyze ROS generation. MoS_2 exhibits peroxidase-like behaviour that can be exploited for photothermal antimicrobial therapies and oxidative stress modulation. Its surface can also be functionalized with polymers or biomolecules to enhance specificity and biocompatibility.

Prussian blue nanoparticles (PBNPs), known for their multienzyme mimicry particularly peroxidase, catalase, and SOD-like activities exhibit strong redox activity across a broad pH range. Their iron-cyanide framework facilitates electron relay mechanisms, enabling efficient ROS scavenging and oxidative stress management in biomedical applications. Unlike many other nanozymes, PBNPs demonstrate exceptional catalytic efficiency and low toxicity, positioning them as promising agents for inflammation therapy and biosensing (Gunatilake et al., 2021).

Despite their advantages, challenges persist. Carbon-based and MOF nanozymes often suffer from limited catalytic turnover rates compared to metal-based counterparts. Additionally, their catalytic activity may be highly sensitive to structural defects, surface oxidation, or biomolecule adsorption, complicating reproducibility. Nevertheless, innovations such as ligand-directed assembly, hybrid nanostructures, and computational design are rapidly improving their functional performance (Gunatilake et al., 2023).

In sum, these alternative nanomaterials introduce new catalytic mechanisms and application modalities into the enzyme-mimetic domain. Their structural diversity and functional versatility present powerful opportunities for

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developing next-generation nanozymes tailored for complex biomedical and environmental systems (Gunatilake et al., 2025).

Biomedical Applications of Enzyme Mimic Nanomaterials

The emergence of nanozymes as synthetic enzyme mimics has ushered in a transformative era in biomedical science. Their catalytic adaptability, physicochemical stability, and biofunctionality under physiological conditions make them attractive candidates for therapeutic and diagnostic applications. This section explores the major biomedical domains where nanozymes have shown pronounced utility.

Tumor Theranostics

Enzyme-mimicking nanomaterials have become pivotal agents in cancer theranostics, offering a unique convergence of diagnostic imaging and therapeutic efficacy. Central to their functionality is the ability to modulate the tumor microenvironment (TME) through catalytic generation of reactive oxygen species (ROS), particularly via peroxidase or oxidase-like reactions that exploit elevated endogenous hydrogen peroxide levels within tumours. This catalytic ROS amplification induces oxidative stress selectively in malignant cells, leading to apoptosis without harming adjacent healthy tissue.

Beyond cytotoxicity, nanozymes are employed to reverse hypoxia, a common feature of solid tumours that impairs conventional treatments. Catalase-mimicking nanomaterials decompose H_2O_2 into oxygen, thereby enhancing photodynamic therapy (PDT) and radiotherapy outcomes. Some nanozymes are further functionalized with photosensitizers or chemotherapeutic agents to enable synergistic therapy leveraging catalytic oxygen production to potentiate drug efficacy (R. Wang et al., 2025).

Nanozymes have also shown remarkable potential in tumor imaging. Magnetic metal oxide nanozymes (e.g., Fe_3O_4) provide contrast in magnetic resonance imaging (MRI), while plasmonic metal-based nanozymes (e.g., Au@Pt) enable high-resolution optical imaging. Their integration into stimuli-responsive platforms allows targeted release and catalytic activation only within the TME, enhancing specificity and minimizing systemic toxicity.

Collectively, nanozymes serve as multifunctional agents capable of targeted delivery, catalytic activation, and image-guided therapy offering a modular and intelligent alternative to traditional single-function cancer treatments (Kashtiaray et al., 2025b).

Anti-bacteria

Nanozymes have emerged as innovative antimicrobial agents capable of addressing bacterial resistance and biofilm-associated infections through catalytic generation of bactericidal species. Their primary mechanism involves peroxidase-like activity, wherein nanozymes catalyze the decomposition of H_2O_2 into highly reactive hydroxyl radicals (•OH), effectively disrupting bacterial membranes, proteins, and genetic material.

Unlike conventional antibiotics, nanozymes do not rely on specific metabolic pathways, thereby minimizing the risk of resistance development. Their activity can be modulated by environmental pH, metal ions, or external stimuli (e.g., light), enabling context-specific bacterial killing. This is particularly advantageous in heterogeneous infections where Gram-positive and Gram-negative bacteria coexist.

Recent designs incorporate charge-switchable nanozymes that preferentially interact with specific bacterial surfaces based on cell wall composition. Light-activated nanozymes further enhance selectivity, enabling programmable targeting through differential surface charge modulation and controlled ROS generation (Javed et al., 2025).

In addition to planktonic bacteria, nanozymes effectively target biofilms complex microbial communities notoriously resistant to antibiotics. Their catalytic activity facilitates biofilm penetration and oxidative degradation of the extracellular matrix, exposing embedded bacteria to immune clearance or secondary therapeutics.

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The biocompatibility and durability of nanozymes make them suitable for wound healing applications, surgical coatings, and antimicrobial textiles. As resistance to conventional agents rises, nanozymes provide a robust, tunable, and mechanistically distinct platform for antibacterial intervention (Ge et al., 2024).

Antioxidation

In biological systems, maintaining redox homeostasis is vital for cellular integrity. Nanozymes capable of mimicking antioxidant enzymes such as superoxide dismutase (SOD), catalase, and peroxidase have demonstrated promise in mitigating oxidative stress associated with numerous pathologies, including neurodegeneration, cardiovascular disorders, and chronic inflammation.

SOD-mimicking nanozymes catalyze the dismutation of superoxide anions ($O_2^{-}\bullet$) into hydrogen peroxide, which is subsequently decomposed by catalase-like nanozymes into oxygen and water thus neutralizing two major classes of ROS in a cascade fashion. Cerium oxide (CeO_2) nanoparticles are notable in this regard, with their reversible Ce^{3+}/Ce^{4+} redox cycling enabling continuous ROS scavenging under physiological conditions (X. Gao et al., 2024).

These antioxidant nanozymes offer enhanced stability compared to natural enzymes, remaining active across broader pH and temperature ranges. Moreover, their surface can be engineered to enable intracellular delivery and organelle-specific localization, allowing targeted protection of mitochondria or nuclei from oxidative insults.

In preclinical models, nanozymes have been shown to prevent DNA damage, lipid peroxidation, and protein oxidation hallmarks of oxidative pathology. Their integration into nanocarriers or hydrogels has further improved tissue retention and therapeutic efficacy.

Nonetheless, modulation of catalytic activity remains essential to avoid over-suppression of physiological ROS, which are involved in signalling processes. Therefore, rational design of nanozymes with feedback-regulated or stimuli-responsive behaviour is key to their safe and effective use in antioxidation therapies (L. Gao et al., 2007b).

Bioorthogonal Catalysis

Bioorthogonal catalysis involves chemical reactions that proceed within living systems without perturbing native biochemical processes. In this context, nanozymes serve as artificial catalysts capable of mediating selective transformations such as prodrug activation or fluorophore release within targeted biological niches.

Encapsulated metal catalysts within functionalized nanoparticles (e.g., Au or Pd nanozymes) can be engineered for bioorthogonal transformations, leveraging their robustness and structural confinement to maintain catalytic activity in the crowded intracellular environment. These systems mimic natural allosteric regulation by using surface ligands or host–guest interactions to gate substrate access, thus preventing off-target effects (Huang et al., 2019).

One significant application is the in-situ activation of therapeutics such as cleavage of protective groups from prodrugs triggered by the nanozyme at the disease site. This localized catalysis enhances drug efficacy while reducing systemic exposure. Similarly, non-fluorescent precursors can be converted into imaging probes in vivo, allowing real-time visualization of biological processes or disease progression.

The stability of nanozymes under oxidative, proteolytic, and variable pH conditions ensures functionality in complex biological environments, such as tumours, inflamed tissues, or infection sites. Light-activated or pH-responsive nanozymes offer additional layers of control, enabling temporal precision in catalysis (Bird et al., 2021).

The field is rapidly evolving, with emerging designs incorporating supramolecular assemblies, photo responsive elements, and biodegradable scaffolds. These advancements underscore the growing utility of nanozymes in non-invasive, site-specific catalysis laying the groundwork for dynamic control over therapeutic and diagnostic functions in vivo.

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CONCLUSION

The advancement of enzyme-mimicking nanomaterials, or nanozymes, represents a compelling shift in biomedical innovation, offering a synthetic route to catalytic functionality that rivals and, in many cases, exceeds that of natural enzymes. Over the past decade, significant progress has been made in engineering nanozymes with finely tuned activity profiles, environmental responsiveness, and biocompatibility. These materials, spanning noble metals, metal oxides, 2D nanostructures, and hybrid composites, have demonstrated remarkable versatility across key biomedical domains such as cancer theranostics, antibacterial therapy, oxidative stress regulation, and in vivo catalytic transformations.

Nanozymes overcome many intrinsic limitations of natural enzymes, including poor thermal stability, susceptibility to proteolysis, and narrow pH activity ranges. Their physicochemical robustness, coupled with surface modifiability and scalable synthesis, makes them ideal candidates for clinical translation and integration into multifunctional therapeutic platforms. A consistent trend across the reviewed literature is the use of nanozymes not only as catalytic mimics but also as intelligent agents capable of dual or even triple functionality diagnosis, therapy, and real-time monitoring within a single system.

The biomedical potential of nanozymes is further reinforced by their adaptability. Advances in nanostructure design, stimuli-responsive activation, and bioorthogonal catalysis are pushing the boundaries of precision medicine. The integration of nanozymes into smart delivery vehicles, biosensors, and microenvironment-sensitive platforms underscores their interdisciplinary relevance, particularly at the interface of nanotechnology, materials science, and molecular medicine.

Looking forward, the next phase of nanozyme research must focus on enhancing biological specificity, minimizing off-target interactions, and addressing long-term biosafety. Collaboration across fields including computational modelling, immunology, and regulatory science will be essential to accelerate clinical adoption. With rigorous design principles and translational foresight, nanozymes are poised to become foundational tools in next-generation biomedicine, enabling catalysis-driven solutions to some of the most complex challenges in diagnostics and therapy.

LIMITATIONS

Despite the notable progress, several limitations continue to constrain the full translational potential of enzyme-mimic nanomaterials. Chief among these is the issue of biocompatibility and potential long-term toxicity, especially for noble metal and transition metal-based nanozymes. While surface modifications can improve biostability and reduce immunogenicity, comprehensive in vivo toxicity profiling remains insufficient across much of the existing literature (R. Zhang et al., 2025b).

Another persistent challenge is the limited reproducibility and standardization in nanozyme synthesis. Variability in particle size, morphology, and surface chemistry can significantly affect catalytic behaviour, hindering batch-to-batch consistency and comparative evaluation. Moreover, while numerous studies have demonstrated efficacy in vitro, in vivo validations particularly in clinically relevant models are still sparse. The lack of controlled, large-scale clinical trials further delays regulatory approval and widespread clinical adoption (Sen et al., 2024d).

Additionally, the catalytic efficiency of many nanozymes, though high in isolated systems, can be suppressed in complex biological environments due to biomolecule adsorption, ion interference, or rapid clearance. Addressing these issues through rational design and mechanistic understanding is critical (Feng et al., 2024).

Overcoming these challenges will not only enhance nanozyme reliability but also unlock their broader application in clinical diagnostics, targeted therapy, and regenerative medicine. A coordinated effort toward safer, smarter, and more controllable nanozymes will ultimately define their role in future healthcare systems (Cordani et al., 2025).

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Conflict of Interest

All authors confirm that they have no financial, personal, or professional conflicts of interest to declare in relation to the content of this manuscript.

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