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Nanozyme-based catalytic therapeutics: Applications in infectious diseases, cancer therapy, and bone regeneration

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ABSTRACT

Nanozymes are nanomaterials with enzyme-like catalytic activities that have rapidly advanced in the biomedical field in recent years due to their high stability, low cost, and catalytic versatility. As promising alternatives to natural enzymes, nanozymes have demonstrated unique advantages in infection control, cancer therapy, and tissue regeneration. This review systematically summarizes key advances in recent years in nanozyme-based catalytic therapeutics. We focus on their mechanisms and applications in combating bacterial, viral, and fungal infections *via* membrane lipid peroxidation, protein/genome damage, and biofilm disruption; in cancer treatment through chemodynamic therapy (CDT), tumor microenvironment modulation, and multimodal synergistic strategies; and in bone regeneration through antioxidant, anti-inflammatory, and osteoinductive functions. Moreover, we highlight the integration of nanozymes with hydrogels, scaffolds, and microrobotic systems to enhance therapeutic outcomes. Finally, current challenges such as targeting specificity, *in vivo* catalytic control, biosafety, and clinical translation are discussed to provide a comprehensive roadmap for future research and clinical development in catalytic nanomedicine.

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1. Introduction

Nanozymes, a class of nanomaterials with enzyme-like catalytic activities, have emerged as powerful tools in biomedicine due to their intrinsic physicochemical stability, low production cost, and facile surface modification [1–3]. Compared with natural enzymes, nanozymes offer better resistance to denaturation, longer shelf life, and tunable catalytic properties, making them attractive candidates for therapeutic applications [1,4].

Infectious diseases, cancer, and tissue degeneration remain major clinical challenges globally. Conventional therapeutic approaches, such as antibiotics and chemotherapeutic agents, are often limited by drug resistance, severe side effects, and poor targeting efficiency [1,5,6]. In this context, nanozymes provide a non-traditional strategy for disease intervention by catalytically generating reactive oxygen species (ROS) or modulating redox balance, thereby inducing pathogen destruction, tumor ablation, or tissue repair [7–9]. Recent studies have expanded the biomedical utility of nanozymes into multiple domains. In infectious diseases, nanozymes can mimic peroxidase (POD) [10,11], oxidase (OXD) [12,13], or haloperoxidase (HPO) [14,15] activity to catalytically generate ROS that inactivate bacteria, viruses, or fungi through lipid peroxidation, protein oxidation, or biofilm disruption [5,16,17]. In cancer therapy, nanozymes have been harnessed in chemodynamic therapy (CDT), which leverages tumor microenvironment (TME)-specific reactions (*e.g.*, Fenton or Fenton-like processes) to generate cytotoxic $^{\bullet}OH$ from endogenous H_2O_2 [18,19], and can be further potentiated through integration with photothermal, photodynamic, or chemotherapy strategies [20,21]. Meanwhile, in the context of bone regeneration, antioxidant nanozymes alleviate oxidative stress and inflammation in bone defects while promoting osteogenic differentiation of stem cells [9,22]. Furthermore, nanozymes can be embedded within biomaterial systems

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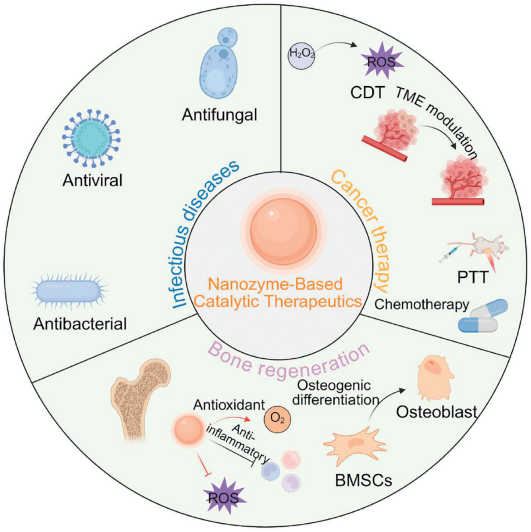


Fig. 1. Schematic summary of the overall framework of nanozyme-based catalytic therapeutics, illustrating their biomedical applications in three major disease contexts: infectious diseases, cancer therapy, and bone regeneration.

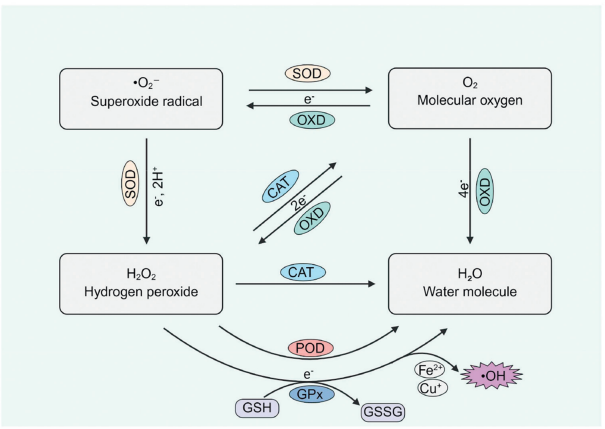


Fig. 2. Schematic illustration of the catalytic mechanisms of representative oxidoreductases. The diagram depicts the enzymatic pathways mediated by five major oxidoreductases including POD, CAT, OXD, SOD, and GPx, which are involved in the regulation of ROS through both generation and elimination mechanisms.

such as hydrogels, scaffolds, or microrobots to enhance targeting, retention, and responsiveness in complex physiological environments [23–26]. More recently, nitric oxide (NO) synthase (NOS)-like nanozymes have also been explored, which catalyze the release of NO to modulate hypoxia, improve vascular function, and enhance radiosensitization, broadening the therapeutic scope beyond ROS-mediated actions. To reliably compare nanozyme performance across materials and systems, standardized kinetic evaluation protocols have been established, most notably the ones proposed in Nature Protocols (2018, 2024) [27,28]. These methods enable quantification of Michaelis–Menten parameters (K_m, V_{max}) and turnover numbers (K_{cat}), ensuring reproducible and meaningful assessment of nanozyme activity.

However, despite these promising developments, challenges remain, particularly in achieving controlled catalytic activity *in vivo*, minimizing off-target effects, and ensuring long-term biosafety. Moreover, as nanozymes advance toward clinical translation, scaling up production, understanding regulatory requirements, and addressing ethical and environmental implications will be critical steps for their therapeutic adoption. In just two decades, the topic of nanozymes development has become a highly transversal field of biomedical research (Fig. S1 in Supporting information). In this review, we summarize the recent progress of nanozyme-based catalytic therapeutics over the past several years, focusing on their mechanisms and biomedical applications in infectious diseases, cancer therapy, and bone regeneration (Fig. 1). We also highlight emerging enzyme-mimetic modalities such as NOS-like activity, discuss standardized evaluation of catalytic kinetics, and examine key barriers to clinical translation, offering insight into the future of this dynamic field.

2. Classification, catalytic mechanisms, and performance enhancement strategies of nanozymes

Nanozymes represent a diverse class of catalytic nanomaterials, including metal nanoparticles (NPs), metal oxides, carbon-based nanostructures, metal organic frameworks (MOFs), and composite or hybrid systems. Their enzyme-like catalytic properties arise from finely tuned physicochemical characteristics such as composition, surface functionality, and nanostructure morphology. To date, nanozymes have been reported to mimic all six classes of natural enzymes, namely oxidoreductases, hydrolases, lyases, isomerases, transferases, and ligases, with oxidoreductase-like nanozymes being the most extensively investigated. Over 30 distinct enzyme-mimetic activities have been identified, with POD-like nanozymes being the earliest discovered and most widely studied. Other commonly observed activities include those resembling OXD, catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) (Fig. 2). Notably, certain nanozymes exhibit pH-responsive or multi-enzyme mimetic behaviors. For instance, iron oxide (Fe_3O_4) NPs demonstrate POD-like activity under acidic conditions by catalyzing the conversion of hydrogen peroxide into hydroxyl radicals (•OH), while functioning as CAT mimics to generate oxygen at neutral pH. Moreover, some nanozymes are designed to mimic multifunctional enzymes found in nature, which possess both antioxidant and regulatory functions. These multifunctional nanozymes integrate multiple catalytic activities (*e.g.*, POD-, CAT-, SOD-, and GPx-like) within a single nanostructure, enabling cascade or synergistic redox reactions. This design not only enhances therapeutic efficiency but also recapitulates the versatility and adaptability of natural enzymes in maintaining redox homeostasis and immune modulation.

2.1. Metal-based nanozymes

Noble metal and transition metal NPs represent a classical category of nanozymes with well-established catalytic activities and physicochemical stability. Metal-based nanozymes generally exhibit surface plasmon resonance (SPR) properties, along with excellent optical behavior, efficient photothermal conversion capabilities, and high chemical stability [3,23,29]. These NPs have been shown to exhibit multiple oxidoreductase-mimicking activities, including OXD, POD, CAT, SOD and GOx functions [30–34]. For instance, Au and Pt NPs can catalyze the oxidation of chromogenic substrates such as 3,3′,5,5′-tetramethylbenzidine (TMB) in the presence of H_2O_2 under acidic conditions, where the intermediate oxidized species (O*) mediates POD-like activity without free radical involvement [35,36]. Conversely, under alkaline conditions, these NPs promote the decomposition of H_2O_2 into water and oxygen, exhibiting CAT-like behavior [37,38].

Pt-based nanozymes, in particular, display both CAT and SOD-like activities due to their redox-active surfaces and high affinity for peroxide substrates. Their antioxidant properties make them attractive candidates for scavenging ROS in oxidative stress-related pathologies. Recent developments have focused on alloying noble metals to enhance their catalytic performance. For example, a PtCo core-shell nanozyme, featuring a PtCo alloy core encased

in graphitic carbon, exhibited significant OXD-like activity by catalyzing the conversion of molecular oxygen into ROS under acidic conditions [39]. Surface functionalization with bacterial-targeting ligands such as carboxyphenylboronic acid (CPB) enabled selective accumulation at bacterial infection sites, enhancing therapeutic specificity.

Researchers have systematically investigated the catalytic mechanisms of metal-based nanozymes, particularly focusing on the POD and CAT activities of Au, Pt, and Pd, using both theoretical calculations and experimental validation [40]. Under acidic or neutral conditions, H_2O_2 adsorbs onto the Au(111) surface and undergoes dissociation to form a highly reactive oxygen intermediate (O^*), which facilitates oxidation of adjacent substrates, consistent with POD-like activity. Under basic conditions, hydroxyl groups preferentially occupy the active sites on the Au(111) surface, inhibiting POD activity but promoting CAT-like behavior through the formation and release of molecular oxygen (O_2). These surface intermediates not only serve as catalytic centers but also regulate the enzyme-mimicking specificity of the nanozyme. Moreover, noble metal nanozymes have demonstrated OXD- and SOD-like activities by interacting with triplet oxygen ($^3O_2$) and superoxide anion ($^{\bullet}O_2^-$), respectively. Adsorption of $^3O_2$ onto the metal surface facilitates electron transfer into its antibonding orbitals, leading to spin conversion and dissociation into O^* species capable of oxidizing substrates. In the case of SOD-like activity, superoxide anions in aqueous environments can be protonated into perhydroxyl radicals ($HO_2^{\bullet}$), which upon adsorption undergo structural rearrangement and generate O_2^* and $H_2O_2^*$, recapitulating the native dismutation process of superoxide radicals. Theoretical studies further suggest that the catalytic efficiency of noble-metal nanozymes increases with the adsorption energies of H_2O_2 and $^3O_2$ on the metal surface [41]. Despite widespread reports on enzyme-like catalysis by metal-based nanozymes, a detailed understanding of their mechanistic pathways remains limited. Comprehensive mechanistic studies combining surface science, spectroscopy, and computational modeling are essential to guide the rational design of nanozymes with high catalytic selectivity and biomedical efficacy.

2.2. Metal oxide-based nanozymes

Transition metal oxides and cerium oxide (CeO_2) are widely studied in the field of nanozymes due to their diverse redox properties, high surface energy, and large specific surface areas, which together endow them with multiple enzyme-mimetic activities, including those of POD, OXD, CAT, and SOD [42,43]. Among them, Fe_3O_4 NPs were the first nanozymes reported and remain prototypical POD mimics [44]. Fe_3O_4 can catalyze the oxidation of standard horseradish POD (HRP) substrates such as TMB, *O*-phenylenediamine (OPD), and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), yielding chromogenic products in acidic media [27,44]. The POD-like activity of Fe_3O_4 is attributed to its surface Fe^{2+}/Fe^{3+} redox cycling, which promotes Fenton-like reactions generating $^{\bullet}OH$ from H_2O_2. Density functional theory (DFT) studies have revealed a three-step mechanism involving H_2O_2 chemisorption onto iron oxide surfaces, followed by stepwise electron transfer and removal of surface-bound hydroxyl species [45]. This mechanistic insight supports the application of Fe_3O_4 nanozymes in antibacterial and CDT.

CeO_2 is another prominent nanozyme material, distinguished by its mixed valence states (Ce^{3+}/Ce^{4+}) and high density of oxygen vacancies. These properties enable CeO_2 to emulate both CAT and SOD activities. Mechanistically, H_2O_2 binds to Ce^{4+} ions near oxygen vacancies, undergoing a redox transformation where two electrons are transferred to Ce^{4+}, generating Ce^{3+} and O_2, followed by homolytic cleavage of the O-O bond and release of H_2O [46,47]. Although initial models proposed single-step catalytic cycles, more recent computational studies suggest a bi-H_2O_2 associative mechanism as the most thermodynamically favorable for CeO_2 and Co_3O_4 nanozymes [3,48]. Furthermore, CeO_2 has demonstrated POD-like activity not only due to its ability to stabilize high-valent cerium intermediates and mediate efficient electron transfer, but also because H_2O_2 molecules can adsorb near oxygen vacancies enriched with Ce^{4+}, where electron transfer reduces Ce^{4+} to Ce^{3+} while decomposing H_2O_2 to generate $^{\bullet}OH$ radicals. During this process, Ce^{3+} is subsequently reoxidized to Ce^{4+}, completing a catalytic cycle that underlies its POD-like functionality [46]. The SOD-like function arises from the interaction of Ce^{3+} with $^{\bullet}O_2^-$ and its conversion to O_2 and H_2O_2, driven by redox cycling [49]. Manganese-based oxides, particularly MnO_2 and Mn_3O_4, also exhibit diverse enzyme-mimicking activities due to their redox-active behavior. MnO_2 primarily functions as a CAT mimic, decomposing H_2O_2 into O_2 and thereby alleviating tumor hypoxia [50]. Moreover, manganese oxides demonstrate SOD-mimetic activity by catalyzing the dismutation of superoxide radicals. These processes are mechanistically explained by models such as coupled electron transfer, the Langmuir-Hinshelwood mechanism, the Eley-Rideal mechanism, and refined catalytic cycles involving surface-bound intermediates [3,51]. Furthermore, MnO_2 can oxidize intracellular glutathione (GSH), disrupting cellular antioxidant defenses and amplifying oxidative stress.

In summary, the catalytic mechanisms of metal oxide nanozymes are governed by surface active sites, oxygen vacancy structures, and electron-transfer kinetics. The Fenton-like reactions of Fe_3O_4, the valence switching mechanism of CeO_2, and the O_2-generating and thiol-oxidizing functions of MnO_2 collectively demonstrate diverse strategies by which metal oxide nanozymes mimic natural oxidoreductases to modulate ROS, offering broad therapeutic and diagnostic potential.

2.3. Carbon-based nanozymes

Carbon-based nanozymes have attracted significant attention due to their intrinsic physicochemical tunability, biocompatibility, and rich surface functionalities. These materials include graphene oxide (GO), reduced graphene oxide (rGO), carbon nanotubes (CNTs), carbon quantum dots (CQDs), graphene quantum dots (GQDs), and fullerenes. They exhibit enzyme-like activities primarily through modulation of surface electronic states, defect engineering, and dopant-induced activation. Typically, carbon-based nanozymes exhibit POD, OXD, CAT, and even SOD-like activities, depending on their structural features and surface groups [52,53].

Among these, CQDs and GQDs are prominent POD mimics due to their abundant edge sites, oxygen-containing functional groups, and quantum confinement effects. These structural motifs facilitate H_2O_2 adsorption and activation through electron transfer processes, leading to the production of $^{\bullet}OH$ that oxidize chromogenic substrates such as TMB, OPD and ABTS [54,55]. The catalytic mechanism involves adsorption of H_2O_2 at defect sites or doped heteroatoms (*e.g.*, N, S, or B), followed by electron transfer and bond cleavage, mimicking the HRP-like activity [56–59]. In GO and rGO systems, the POD-like behavior is enhanced by structural defects and π–π conjugated domains that facilitate charge separation. Furthermore, transition metal doping (*e.g.*, Fe, Co, or Mn) into the carbon matrix significantly amplifies catalytic activity by introducing redox centers and Fenton-like reaction pathways [60,61]. These doped carbon nanozymes exhibit bifunctional behavior, simultaneously mimicking POD and CAT activities under different pH conditions [62]. CNTs and fullerenes also display OXD- and SOD-like activities by virtue of electron-rich conjugated frameworks. For instance, oxygen molecules can be adsorbed and activated on CNTs surfaces, undergoing partial charge transfer that drives the oxidation of substrates without the need for H_2O_2, analogous to OXD

enzymes [63]. The delocalized π-electron system and curvature-induced strain in fullerenes, such as C_{60}, endow them with exceptional radical scavenging capabilities [64]. These structural features allow fullerenes to act as radical "sponges", efficiently adsorbing and neutralizing ROS through electron transfer processes. Such properties underpin their SOD-like activity, whereby $^{\bullet}O_2^-$ are converted into molecular O_2 and H_2O_2. Notably, C_{60} derivatives have demonstrated stronger antioxidant performance than many traditional radical scavengers, highlighting their potential as effective SOD mimetics for oxidative stress modulation [65,66]. This antioxidant mechanism is fundamentally governed by the electron-accepting ability and high affinity of fullerenes toward ROS, enabling them to participate in catalytic redox cycling while maintaining structural stability.

Overall, the catalytic mechanisms of carbon-based nanozymes are largely governed by defect density, dopant species, and interfacial electronic structures. By tailoring these features, carbon-based nanozymes can be engineered to perform single or multiple enzyme-mimetic functions with high catalytic efficiency, offering broad applicability in biosensing, cancer therapy, wound healing, and antibacterial treatments [52,53,67].

2.4. MOF-based and composite nanozymes

Further details on MOF-based and composite nanozymes are provided in Section 1 (Supporting information).

3. Applications

Owing to their unique catalytic activities, structural tunability, and favorable biocompatibility, nanozymes have demonstrated broad translational potential across diverse biomedical domains. In particular, infectious diseases, cancer therapy, and bone regeneration represent critical pathological conditions characterized by dysregulated redox signaling, aberrant immune responses, or impaired tissue remodeling. These are scenarios in which functional nanozymes can exert precise catalytic modulation. By mimicking oxidoreductase activities such as POD, CAT, SOD, and OXD, nanozymes can regulate reactive oxygen or nitrogen species, reshape inflammatory microenvironments, or amplify oxidative stress, thereby enhancing therapeutic efficacy or supporting tissue repair. This section provides a comprehensive overview of recent advances in nanozyme-based interventions for bacterial, viral, and fungal infections, tumor-targeted catalysis, and bone tissue regeneration. Emphasis is placed on catalytic mechanisms, material engineering strategies, and preclinical outcomes.

3.1. Applications in infectious diseases

Infectious diseases caused by bacterial, viral, and fungal pathogens continue to pose a significant global health burden, further exacerbated by the rapid escalation of antimicrobial resistance (AMR), which compromises the efficacy of many frontline therapeutics [68]. Without the development of alternative strategies, drug-resistant infections are projected to result in more than 10 million deaths annually by 2050 [69,70]. In this context, nanozyme-based catalytic therapeutics have emerged as a promising anti-infective modality that departs from conventional antibiotics by leveraging *in situ* catalytic processes to neutralize pathogens [71]. Nanozymes, defined as nanomaterials with intrinsic enzyme-like activities, can generate reactive species or catalyze biochemical reactions at sites of infection, thereby eliminating microbes *via* mechanisms distinct from those of traditional antimicrobials [5,7].

One of the most widely explored approaches involves the catalytic generation of ROS. POD-mimicking nanozymes can catalyze the conversion of endogenous hydrogen peroxide into highly cytotoxic $^{\bullet}OH$, while OXD-like nanozymes generate $^{\bullet}O_2^-$ from molecular oxygen. These ROS species cause extensive oxidative damage to bacterial membranes, intracellular proteins, and nucleic acids, overwhelming microbial defense mechanisms [11,72]. In addition to ROS-mediated mechanisms, certain nanozymes exhibit other antimicrobial functions. For instance, CeO_2 nanozymes with phospholipase-like activity can disrupt bacterial and biofilm membranes by degrading phospholipids, resulting in direct physical damage to pathogens [73]. Furthermore, nanozymes embedded with abiotic catalysts have enabled bioorthogonal activation of prodrugs, allowing for site-specific transformation of non-toxic precursors into active antimicrobial agents. This approach has shown efficacy in delivering antibiotics locally and inhibiting biofilm formation [74]. These multifaceted catalytic mechanisms confer broad-spectrum antimicrobial activity to nanozymes, enabling effective targeting of a wide range of pathogens, including multidrug-resistant bacteria, viruses, and fungi [69,75]. In the following subsections, we summarize recent advances in the application of nanozymes for antibacterial, antiviral, and antifungal therapies, and outline how these catalytic nanoplatforms are contributing to the development of next-generation anti-infective strategies.

3.1.1. Antibacterial nanozymes

Bacterial infections, ranging from localized wounds to systemic diseases, continue to pose significant clinical challenges, particularly in the context of increasing antimicrobial resistance. Among emerging strategies, nanozyme-based antibacterial platforms have emerged as highly promising candidates, primarily through the catalytic generation of ROS [5,71]. POD-like nanozymes, such as iron oxide-based systems, can convert endogenous H_2O_2 into highly cytotoxic $^{\bullet}OH$ within the acidic microenvironments of infection sites, resulting in effective bacterial eradication and biofilm disruption. For instance, a Fe_3O_4/CuO_x composite nanozyme demonstrated potent POD-mimicking activity and broad-spectrum antibacterial efficacy against both Gram-positive and Gram-negative pathogens, along with the degradation of associated biofilms [76]. Given that bacterial infections are frequently characterized by local acidosis and elevated H_2O_2 levels, these systems can be self-activated *in situ*, generating ROS precisely at the sites of infection. Building upon these principles, multifunctional nanozyme platforms have been developed to further enhance spatial control, catalytic efficiency, and therapeutic outcomes. In a recent study, Qian's group developed a GOx-like nanozyme platform consisting of gold NPs (AuNPs)-modified zeolitic imidazolate framework-8 (ZIF-8) loaded with Ag_2S quantum dots, which was integrated into an injectable thermoresponsive hydrogel for the treatment of periodontitis. The nanozyme catalyzed glucose to generate H_2O_2 *in situ*, which under near-infrared (NIR) irradiation triggered enhanced ROS production for potent antibacterial effects, achieving nearly 100% bacterial inhibition under combined laser and glucose stimulation, while also promoting osteogenic differentiation and periodontal tissue regeneration (Fig. 3) [23]. Meanwhile, Liang's group developed a multifunctional $NiCo_2O_4$ nanozyme with a bioinspired spiky surface morphology, which achieved synergistic antibacterial effects by physically disrupting bacterial membranes and catalytically generating ROS through its POD-like activity [77]. This integrated antimicrobial strategy significantly enhanced biofilm eradication and infection control while minimizing the risk of drug resistance.

To further enhance therapeutic precision, nanozymes have been incorporated into targeted delivery systems. Pathogen-specific targeting is critical to avoid damage to host tissues and commensal microbiota. Zhang *et al.* designed a core–shell PtCo@graphitic nanozyme functionalized with C_{18}-PEG-boronic acid (CPB) to selectively target *Helicobacter pylori* through glycan-mediated inter-

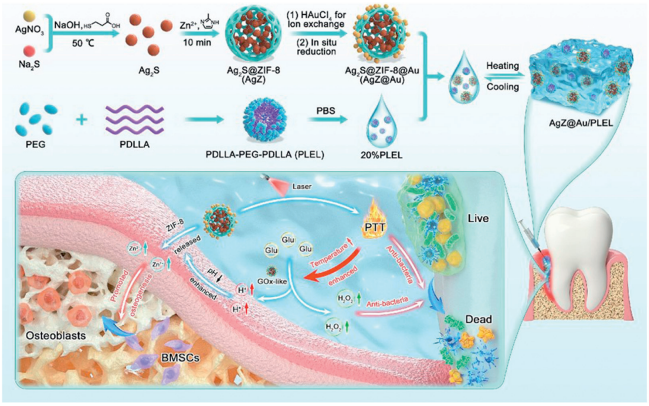


Fig. 3. A multifunctional AgZ@Au/PLEL hydrogel for antibacterial bone regeneration. The photothermal and catalytic activities enable ROS generation and antibacterial effects, while simultaneously promoting osteogenesis at the bone defect site. Copied with permission [23]. Copyright 2025, Elsevier.

actions [39]. Under acidic gastric conditions, the OXD-like activity of the nanozyme catalyzed $^{\bullet}O_2^-$ generation, leading to the effective eradication of *Helicobacter pylori* in infected mice while sparing commensal gut microbiota. Notably, its therapeutic efficacy was comparable to that of standard triple antibiotic therapy, with minimal off-target effects. Another innovative application involves the *in situ* activation of antimicrobial prodrugs *via* bioorthogonal catalysis. Rotello *et al.* developed a mannose-functionalized AuNPs system embedded with an iron-porphyrin complex (FeTPP), which selectively accumulated in macrophages infected with *Salmonella via* mannose receptor-mediated uptake [78]. Once internalized, the FeTPP catalyst converted a non-toxic prodrug of ciprofloxacin into its active form, effectively reducing intracellular bacterial load without harming host cells (Fig. S2A in Supporting information). This strategy represents a catalytic "Trojan horse" approach for the targeted elimination of intracellular pathogens and overcoming barriers related to drug penetration and resistance.

Furthermore, nanozymes have been utilized to target biofilms and polymicrobial communities. Koo and colleagues developed a dextran-coated iron oxide NP-glucose OXD (Dex-IONP-GOx) nanozyme to eradicate *Streptococcus mutans* in dental caries (Fig. S2B in Supporting information) [79]. In the sugar-rich, acidic biofilm environment, glucose OXD converted glucose into gluconic acid and H_2O_2, while the Fe_3O_4 core generated $^{\bullet}OH$ to damage bacterial cells. Dextran ligands enabled selective binding to *Streptococcus mutans*, ensuring targeted killing without affecting commensal species like *Streptococcus oralis* [80]. In rodent models, topical application of this nanozyme reduced tooth decay without detectable toxicity. Smart, stimuli-responsive nanozymes have also been engineered to respond to pathogen-specific signals. One design encapsulated a Pt nanozyme and GOx in a hyaluronic acid shell for treating *Staphylococcus aureus*-infected diabetic wounds (Fig. S2C in Supporting information) [81]. The Pt nanozyme, conjugated with an aptamer targeting *Staphylococcus aureus* [82], was released upon bacterial hyaluronidase-mediated hydrogel degradation. In the glucose-rich diabetic wound environment, GOx generated H_2O_2 and lowered pH, thereby enhancing the POD-like activity of the Pt nanozyme. This system demonstrated enhanced antibacterial efficacy and accelerated wound healing in diabetic mice, with negligible impact on surrounding healthy tissue. While ROS-based antibacterial mechanisms are dominant, alternative strategies are gaining attention. For example, a polyacrylic acid-coated CeO_2 nanozyme was reported to mimic phospholipase activity, hydrolyzing bacterial membrane phospholipids directly without requiring ROS generation [73]. This approach showed potent antibacterial effects against diverse pathogens while maintaining excellent biocompatibility, offering a ROS-independent route for bacterial eradication.

In summary, nanozyme-based antibacterial strategies offer unique advantages in targeting microbial infections through catalytic amplification of oxidative stress or site-specific prodrug activation. These platforms hold considerable promise for addressing antibiotic resistance and achieving precision antimicrobial therapy. To this end, it is important to consider the structural differences between Gram-positive and Gram-negative bacteria, as they influence the response to nanozyme-mediated therapies. Gram-positive bacteria, with their thick peptidoglycan layer and lack of an outer membrane, are more permeable and generally more susceptible to ROS-mediated damage. In contrast, the outer membrane of Gram-negative bacteria, rich in lipopolysaccharides, provides additional protection, making them relatively more resistant to oxidative stress and nanozyme-based treatments. These structural differences underscore the need to tailor nanozyme design and dosage to specific bacterial pathogens to achieve optimal therapeutic efficacy.

3.1.2. Antiviral nanozymes

Building on the success of nanozyme-based antibacterials, researchers have expanded nanozybiotic catalytic therapy to target viral and fungal pathogens. These nanozymes exhibit broad-spectrum antimicrobial activity through reactive catalysis, offering a mechanism that differs from traditional drugs and is less susceptible to the development of resistance [83]. This approach is particularly valuable given the inherent challenges in treating viruses and fungi. Rapid viral mutations frequently reduce the efficacy of small-molecule antivirals or vaccines, while fungal pathogens are characterized by limited drug targets and increasing resistance to existing therapies [5]. By catalyzing the *in situ* production of ROS or other biocidal agents, nanozymes can inactivate pathogens without requiring specific molecular recognition [75]. This enables sustained efficacy against rapidly evolving viral strains and difficult-to-treat fungal species. In the following sections, we summarize recent advancements in antiviral nanozyme therapeutics. These are presented in parallel with bacterial nanozyme applications, highlighting key mechanisms such as lipid peroxidation of viral or fungal envelopes and ROS-induced damage to proteins or genetic material, along with representative examples.

Antiviral nanozymes neutralize viruses through either direct or indirect mechanisms. In the direct approach, nanozymes catalytically disrupt viral structures by generating ROS *via* POD- or OXD-like activity [8]. Enveloped viruses are particularly vulnerable, as ROS can induce lipid peroxidation of the viral envelope, leading to compromised membrane integrity and impaired function of surface proteins required for host cell entry [84]. Non-enveloped viruses, which lack a lipid membrane, can instead be affected through catalytic cleavage of capsid proteins or oxidative damage to their protein shells and genomes [16]. Indirect antiviral mechanisms involve modulation of the host cellular environment to inhibit viral replication [5]. These catalytic processes mimic the oxidative burst of immune cells and cause irreversible damage to key viral components, including membranes, proteins, and nucleic acids, thereby rendering the virions non-infectious. Representative antiviral nanozymes include iron oxide-based POD mimics, commonly referred to as IONzymes [84]. These nanozymes catalyze the decomposition of H_2O_2 into $^{\bullet}OH$, which in turn induces lipid peroxidation of viral envelopes, disrupting membrane integrity and associated surface glycoproteins. Qin *et al.* reported that Fe_3O_4 nanozymes exhibited potent virucidal activity against 12 subtypes of influenza A virus (H1–H12), underscoring their broad-spectrum antiviral potential (Fig. S3A in Supporting information) [84]. In addition, Mn-based MOF nanozymes (nMnBTC) have demonstrated

OXD-like catalytic behavior and retained robust antiviral efficacy at subzero temperatures (−20 °C), making them well-suited for cold-chain sterilisation applications (Fig. S3B in Supporting information) [85].

Another promising strategy involves the *in situ* generation of highly reactive halogen oxidants. Oxygen-deficient CeO_2 nanorods (CeO_{2-x}), functioning as HPO mimics, catalyze the reaction of H_2O_2 and bromide ions to yield hypobromous acid, a potent virucidal agent capable of nonspecifically oxidizing viral proteins, lipids, and genomes (Fig. S3C in Supporting information) [86]. *In vitro* studies confirmed that CeO_{2-x} nanorods effectively inactivated human coronavirus OC43 (HCoV-OC43) with excellent biocompatibility at therapeutic concentrations. To address non-enveloped viruses, protease-mimicking nanozymes have also been developed. For example, Xu *et al.* designed chiral copper sulfide NPs ($Cu_{1.96}S$) functionalized with D-penicillamine, which exhibited light-responsive proteolytic activity, selectively cleaving viral capsid proteins under green light irradiation [16]. This bioorthogonal system successfully disrupted the capsid of tobacco mosaic virus (TMV), thereby preventing infection. Such artificial protease strategies offer a novel route for the inactivation of structurally resilient non-enveloped viruses. In addition to directly disrupting viral structures, modulation of the host microenvironment has emerged as a crucial indirect antiviral approach. Xu *et al.* synthesized a cauliflower-like manganese dioxide nanozyme (MnO_2 Cfs) with multiple enzymatic activities (SOD-, CAT-, and GPx-like), capable of scavenging various ROS species including H_2O_2, $^{\bullet}OH$, and $^{\bullet}O_2^-$ (Fig. S3D in Supporting information) [17]. *In vitro*, MnO_2 Cfs alleviated virus-induced cytopathic effects, suppressed the expression of proinflammatory cytokines (*e.g.*, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL-8), and significantly inhibited the replication of duck Tembusu virus (DTMUV) and the expression of its virulence-associated proteins. *In vivo*, intravenous administration of MnO_2 Cfs markedly attenuated virus-induced tissue injury, body weight loss, and mortality in infected ducklings, demonstrating strong therapeutic efficacy and favorable biosafety. The nanozyme exerted its protective effect by rebalancing the redox state and modulating innate immune responses during early-stage infection, highlighting its potential as a host-directed nanotherapeutic for treating virus-associated inflammatory diseases.

Collectively, antiviral nanozymes achieve broad-spectrum, efficient, and biocompatible therapeutic effects through either direct virion disruption or indirect regulation of host immunity and redox homeostasis. These mechanistically diverse and complementary strategies provide a solid foundation for the rational design of next-generation nanozyme-based antiviral agents.

3.1.3. Antifungal nanozymes

Fungal infections are particularly difficult to treat, primarily due to the limited availability of safe antifungal agents and the high structural similarity between fungal and host cells [87]. Pathogenic fungi typically possess robust cell walls, form invasive hyphae and biofilms, and exhibit increasing resistance to frontline antifungal drugs such as azoles and polyenes [88,89]. In addition, existing antifungal agents are often associated with high toxicity and show limited efficacy in immunocompromised patients. These challenges underscore the urgent need to develop novel antifungal strategies that can selectively eliminate fungal pathogens while minimizing damage to host tissues. Nanozyme-based antifungal therapy offers a promising alternative. This strategy involves catalytic reactions, such as the generation of ROS, to disrupt fungal cell structures and their associated biofilms. Due to the nonspecific nature of ROS-induced damage to biomacromolecules, fungi are less likely to develop resistance through conventional mechanisms [90]. Recent studies have demonstrated that various nanozymes with POD-mimicking activity exhibit broad-spectrum antifungal efficacy *in vitro* [88,91,92]. For example, nitrogen- and iodine-doped carbon dots (I-CDs) and Ce-based MOF (AU-1) have been shown to catalyze ROS production and inhibit the growth of "*Candida albicans*" (a yeast-like fungus), as well as filamentous fungi such as "*Aspergillus flavus*" and "*Aspergillus niger*" [92,93]. These preliminary findings suggest that catalytic nanozymes can effectively overcome fungal antioxidant defenses by locally generating high concentrations of ROS, resulting in cell wall and membrane disruption, oxidative DNA damage, and eventual fungal cell death. This enables efficient antifungal treatment.

Numerous nanozyme systems have demonstrated potent antifungal efficacy in preclinical models of fungal infection. Meanwhile, Yang's group reported that Cu/I-CDs nanozymes efficiently catalyze ROS generation in the presence of H_2O_2, effectively eradicating *Candida albicans* and disrupting its biofilm matrix [94]. In a murine model of vulvovaginal candidiasis (VVC), topical application of Cu/I-CDs nanozymes led to rapid fungal clearance without inducing noticeable toxicity or inflammation (Fig. S4A in Supporting information). Compared to untreated controls, treated animals showed a significant reduction in fungal burden and tissue inflammation, underscoring the therapeutic potential of the system. Another study introduced a reduced GO-supported iron sulfide nanozyme composite (rGO@FeS_2) for treating vaginal Candida infections [95]. This nanozyme possessed stable POD-like activity and was capable of *in situ* ROS generation upon local administration, which led to effective fungal eradication. Notably, the treatment spared commensal vaginal microbiota such as Lactobacillus and did not damage epithelial cells. The system's selectivity is attributed to the spatially confined ROS burst within the fungal biofilm, which dissipated rapidly to minimize off-target effects (Fig. S4B in Supporting information). For cutaneous superficial fungal infections, nanozyme-based therapies have also shown encouraging progress. Wang *et al.* developed a dissolvable microneedle (MN) patch incorporating a copper sulfide (CuS) nanozyme and antifungal peptide PAF-26 for the treatment of dermal mycoses [96]. The CuS nanozyme exhibited dual OXD- and POD-like activities. Upon application, the MNs painlessly penetrated the skin, releasing the nanozyme and peptide into the infected lesion. The CuS nanozyme catalyzed local ROS production, while the peptide disrupted fungal membranes, resulting in synergistic antifungal activity. In a murine model of Candida skin infection, this patch achieved rapid fungal clearance, reduced inflammation, and promoted near-complete healing (Fig. S4C in Supporting information). The solid-state nature of the patch allowed for controlled release and spatially localized therapy, making it particularly well-suited for site-specific applications. To address deep-seated or anatomically concealed fungal infections, researchers have developed actively navigable "nanozyme robots". A recent study reported a microrobotic antifungal platform composed of magnetic iron oxide nanozymes configured into microscale robots. These robots were magnetically guided to the infection site, where they generated a concentrated ROS burst and achieved complete fungal eradication within approximately 10 min (Fig. S4D in Supporting information) [25]. This microrobotic system offered precise delivery, penetration through biofilm barriers, and access to tissue crevices that are otherwise difficult to treat with conventional antifungals, presenting a promising solution for persistent biofilm-associated fungal infections and abscesses.

In summary, these advances underscore the potential of nanozyme-based strategies for the treatment of both superficial and invasive fungal infections. By integrating catalytic platforms with precise delivery systems, nanozymes offer a versatile, biocompatible, and effective therapeutic modality for overcoming the current limitations in antifungal therapy.

3.2. Applications in cancer therapy

The intricate pathophysiology of cancer presents multiple avenues for nanozyme-enabled therapeutic interventions. Tumor tissues are typically characterized by a dysregulated microenvironment, including elevated levels of endogenous antioxidants (*e.g.*, GSH), high concentrations of H_2O_2, low pH value and hypoxic conditions [97,98]. Leveraging these pathological hallmarks, nanozymes can be rationally designed to remodel the TME or directly induce cancer cell death through catalytic redox reactions. Two principal therapeutic modalities have been widely explored. Firstly, pro-oxidant nanozyme therapy utilizes nanozymes with POD- or OXD- like activities to convert endogenous substrates such as H_2O_2 or O_2 into highly ROS, inducing oxidative damage to malignant cells [99,100]. Secondly, oxygen-generating nanozymes, CAT mimetic systems, decompose H_2O_2 into molecular oxygen, alleviating intratumoral hypoxia and enhancing the efficacy of oxygen-dependent treatments such as photodynamic therapy (PDT) [101–103]. These strategies can be further potentiated *via* combination with conventional modalities, including chemotherapy and radiotherapy, or integrated with advanced therapeutic approaches such as photothermal therapy (PTT) and PDT to achieve synergistic therapeutic outcomes.

A critical design consideration in nanozyme-based cancer therapy is ensuring selective tumor targeting while minimizing collateral damage to healthy tissues, as non-specific ROS production may pose systemic toxicity risks [1]. To this end, nanozymes have been engineered with active targeting ligands such as folic acid [104], ferritin [104], RGD peptides [105], or monoclonal antibodies [106], or optimized in terms of size and surface charge to exploit the enhanced permeability and retention (EPR) effect of tumor vasculature [1,107]. In addition to their single therapeutic functionalities, theranostic nanozymes have emerged as multifunctional platforms integrating diagnosis and treatment in cancer therapy. These systems combine enzymatic activities (*e.g.*, POD, CAT, OXD and SOD) with imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) for real-time therapeutic monitoring [108,109]. For example, biodegradable copper/manganese silicate nanozymes catalyze H_2O_2 to produce $^{\bullet}OH$ and O_2, enhancing PDT while enabling dual-modal MRI/CT imaging [110]. This integration allows for spatiotemporally controlled and personalized cancer treatment strategies. The following section highlights recent advances in nanozyme-based CDT, modulation of the TME, multimodal combination strategies and emerging NOS-like nanozymes for precision oncology applications.

3.2.1. CDT and ROS-mediated tumor killing

CDT is a tumor-selective strategy that catalytically transforms mild endogenous substrates into highly cytotoxic species within the TME [111]. A well-established mechanism involves Fenton or Fenton-like reactions, frequently mediated by nanozymes [112]. For instance, Fe-based nanozymes can exploit elevated levels of H_2O_2 (about 50–100 μmol/L in tumors) to generate $^{\bullet}OH$, which cause oxidative damage to cancer cells [113,114]. This strategy utilizes the tumor's own metabolic byproducts as reactants for therapeutic purposes. A notable advancement in CDT is the development of cascade nanozyme systems that self-supply H_2O_2, thereby overcoming the limitation of insufficient H_2O_2 levels in certain tumors. Xue *et al.* developed a biomimetic hollow nanozyme (CoO@AuPt) capable of responding to multiple TME cues to enhance CDT efficacy [115]. This nanoplatform consists of a CoO core decorated with ultrasmall Au/Pt NPs, endowing it with multi-enzyme mimetic activities including CAT-, GOx-, and POD-like functions. Within the TME, the Au/Pt nanostructures catalyze the oxidation of intratumoral glucose to produce H_2O_2, which not only serves as a substrate for downstream CDT but also induces tumor starvation by glucose depletion. The generated H_2O_2 is subsequently converted into cytotoxic $^{\bullet}OH$ through Co^{2+}-mediated Fenton-like reactions and further catalysis by Au/Pt components (Fig. S5A in Supporting information). Moreover, the nanozyme effectively depletes intracellular GSH, thereby reducing ROS scavenging and amplifying oxidative stress. *In vivo* studies demonstrated that this nanoplatform achieved significant tumor suppression with minimal systemic toxicity. Importantly, the catalytic processes relieved tumor hypoxia and induced glucose deprivation, synergistically augmenting the CDT outcome. This work exemplifies a TME-activated, cascade-amplified therapeutic strategy, wherein one enzyme-mimicking function initiates and reinforces others, leading to sustained and selective ROS generation for efficient tumor eradication.

In addition to cascade reactions that amplify ROS production, controlling the intrinsic catalytic behavior of single-component nanozymes is equally critical. In the TME, which is acidic and characterized by a H_2O_2 concentration higher than that in normal cells, iron oxide nanozymes (Fe_3O_4 NPs) exhibit a unique pH-dependent dual enzymatic activity. The POD-like activity of Fe_3O_4 nanozymes was first reported by Yan's group in 2007 [29]. Building on this finding, Gu's group later demonstrated pH-dependent dual activities (POD/CAT) in 2012, with Fe_3O_4 acting as a POD mimic under acidic conditions (pH $<$ 6.5) to catalyze Fenton-like conversion of H_2O_2 into highly cytotoxic $^{\bullet}OH$ for oxidative tumor destruction, and as a CAT mimic near neutral pH ($\sim$7.4) to decompose H_2O_2 into water and oxygen, thereby consuming the ROS substrate and potentially diminishing therapeutic efficacy [38]. This dual enzymatic behavior highlights the importance of precisely modulating local pH or catalytic activity to achieve optimal CDT outcomes. More recently, Yan's team developed a structure-engineered hybrid nanoplatform, HCFe nanozymes, capable of selectively suppressing undesired CAT-like activity while preserving or even enhancing POD-like functionality in the acidic TME [116]. This was accomplished by constructing a core–shell structure that effectively inhibited oxygen evolution and promoted $^{\bullet}OH$ generation through enhanced Fe^{2+}/Fe^{3+} redox cycling. The resulting nanoplatform exhibited potent CDT efficacy and robust tumor suppression both *in vitro* and *in vivo*. These findings underscore the critical importance of understanding and regulating dual enzyme-like activities to overcome intrinsic resistance mechanisms in catalytic tumor therapy.

In addition to ROS generation, nanozymes can also enhance CDT by depleting tumor-associated antioxidant systems, particularly GSH, a key intracellular thiol that confers resistance to ROS and chemotherapeutics. Nanozymes with GPx-like activity, such as manganese or copper based nanocatalysts, can oxidize GSH or catalyze its conversion to GSH disulfide (GSSG) [117,118], thereby disrupting the tumor's redox balance. For example, Cu^{2+}-based nanozymes have been shown to induce GSH depletion while simultaneously generating ROS, triggering ferroptosis, an iron dependent form of oxidative cell death [119].

In addition, NOS-like nanozymes have recently been explored for tumor therapy by generating generating NO, further amplifying oxidative damage (Section 4 in Supporting information). Overall, by elevating intratumoral oxidative stress while dismantling intrinsic defense mechanisms, nanozyme-based CDT represents a minimally invasive and tumor-selective approach for effective cancer therapy.

3.2.2. TME modulation and oxygen supply

Hypoxia in solid tumors is a well-recognized barrier to effective cancer therapy, particularly for PDT and radiotherapy, both of which depend on sufficient oxygen to generate ROS or induce DNA damage [120,121]. Nanozymes with CAT-like activity have been developed to alleviate tumor hypoxia by catalyzing the decomposition of endogenous H_2O_2, a byproduct of tumor metabolic repro-

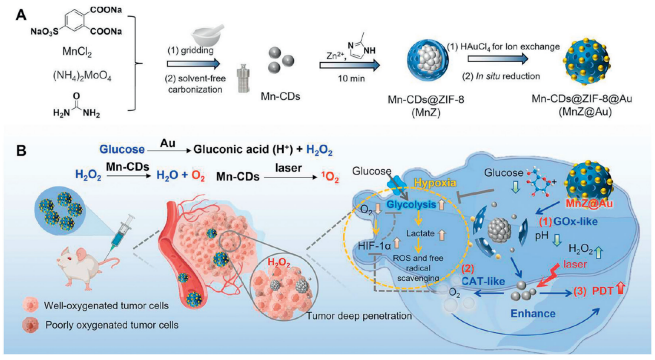


Fig. 4. CDs-based bifunctional nanosystem (MnZ@Au) exhibiting cascade catalytic activities for glucose oxidation and H_2O_2 conversion. The nanosystem alleviates hypoxia and amplifies PDT efficacy *via* GOx-like and CAT-like activities, with enhanced tumor penetration and glycolysis disruption. Copied with permission [34]. Copyright 2023, American Chemical Society.

gramming, into oxygen and water [120]. This oxygenation effect enhances the therapeutic efficacy of oxygen-dependent modalities. For instance, Zhao and Gu *et al.* developed a self-assembled single-atom ruthenium nanozyme (OxgeMCC-r SAE) to enhance PDT efficacy in hypoxic tumors [120]. The system utilized a Prussian blue analogue framework $Mn_3[Co(CN)_6]_2$ as the structural scaffold, with single-atom Ru embedded as a CAT-like catalytic center and chlorin e6 (Ce6) encapsulated as a photosensitizer, followed by stabilization with polyvinylpyrrolidone (PVP) (Fig. S5B in Supporting information). Upon accumulation in the TME, endogenous H_2O_2 was catalytically decomposed by the Ru active sites to generate molecular oxygen, thereby relieving hypoxia and facilitating enhanced generation of cytotoxic singlet oxygen ($^1O_2$) under laser irradiation. This cascade effect led to significant intracellular ROS amplification and apoptosis in 4T1 cancer cells. *In vivo*, the OxgeMCC-r SAE enabled sustained tumor oxygenation, efficient PDT-induced tumor suppression, and high-resolution MRI owing to the Mn-based T_1 contrast, all while maintaining excellent biocompatibility and minimal systemic toxicity.

In addition to alleviating tumor hypoxia, Luo *et al.* developed a cascade nanozyme system capable of modulating intratumoral glucose metabolism to potentiate PDT [34]. The platform, designated MnZ@Au, consisted of manganese-doped CDs (Mn-CDs) as a catalytic and photosensitizing core, coated with an acid-responsive ZIF-8 and further functionalized with ultrasmall AuNPs (Fig. 4). Within this architecture, AuNPs exhibited GOx-mimicking activity, catalyzing the oxidation of glucose to yield H_2O_2 and gluconic acid, which not only induced ZIF-8 degradation but also elevated local H_2O_2 concentrations. The released Mn-CDs subsequently catalyzed H_2O_2 decomposition *via* CAT-like activity, generating oxygen to overcome hypoxia and sustain PDT efficacy. Concurrently, glucose consumption and lactic acid reduction suppressed glycolytic flux, downregulating HIF-1α and GLUT1 expression in tumor cells. *In vitro* and *in vivo* evaluations demonstrated enhanced singlet oxygen generation, improved tumor penetration, and significant inhibition of tumor growth under laser irradiation. Under laser irradiation, the treatment of MnZ@Au exhibited the best tumor suppression with a decrease in tumor size and even no growth, resulting in a tumor volume of only ~4 mm^3. Furthermore, the system enabled real-time monitoring of oxygenation and metabolic modulation *via* photoacoustic and ^{18}F-FDG PET imaging. This multifunctional cascade nanozyme strategy provides a promising approach for TME remodeling and hypoxia-resistant PDT enhancement.

In addition to oxygen-supplying strategies, recent advances have introduced oxygen-independent therapeutic approaches to overcome hypoxia-related resistance. For example, a polyoxometalate (Fe_{12}-POM) nano-cluster was developed to enable oxygen-independent radiodynamic therapy (RDT) by catalyzing ·OH production through X-ray-induced metal-to-metal charge transfer [122]. This process enhances Fe^{3+}/Fe^{2+} redox cycling and dramatically amplifies ·OH generation without requiring molecular oxygen. When combined with immune checkpoint blockade (*e.g.*, PD-1 therapy), this strategy not only achieved effective tumor suppression under hypoxia but also reprogrammed the immunosuppressive TME, inducing systemic antitumor responses. These findings highlight a promising path for oxygen-independent catalytic therapies in hypoxic tumors.

3.2.3. Combined nanozyme therapies

Nanozymes can be incorporated into multifunctional nanoplatforms to achieve synergistic therapeutic effects through the combination of multiple treatment modalities. One such strategy involves coupling nanozyme-catalyzed activity with PTT. Photothermal agents, such as gold nanostructures, copper sulfide, or carbon-based materials, convert NIR light into heat to ablate tumor cells [123,124]. However, sublethal heating may trigger cellular stress responses and hinder complete tumor eradication [125]. The integration of catalytic components introduces a dual "thermal + chemical" attack, enhancing therapeutic outcomes. For instance, a ruthenium–tellurium nanozyme ($RuTe_2$) with POD-like activity was integrated with immobilized GOx into a single nanoplatform [21]. GOx catalyzed the oxidation of intratumoral glucose to generate H_2O_2, which not only fueled downstream CDT but also induced cancer cell starvation by depriving them of glucose. The $RuTe_2$ nanozyme then catalyzed a Fenton-like reaction, converting the *in situ* H_2O_2 into ·OH. This cascade system, enabled continuous and tumor-specific ROS generation. Furthermore, the platform incorporated TMB, which served as a colorimetric substrate and photothermal agent. Upon oxidation by $RuTe_2$, TMB underwent a color change and exhibited strong photothermal conversion under near-infrared irradiation. Thus, when sufficient ·OH was produced, the TMB oxidation product enabled self-triggered PTT in conjunction with CDT. *In vivo*, this multi-enzyme nanozyme system induced effective tumor ablation and stimulated antitumor immune responses that helped prevent tumor recurrence and metastasis. This work illustrates the concept of self-replenishing catalytic therapy, in which the activity of one nanozyme (GOx) drives the catalytic function of another ($RuTe_2$), forming a positive feedback loop to amplify therapeutic efficacy.

Similarly, nanozymes have been combined with conventional chemotherapeutic agents to achieve enhanced efficacy. Catalytic nanocarriers that generate ROS can sensitize tumor cells to chemotherapy. For example, doxorubicin was loaded onto Fe_3O_4/MnO_2 hybrid nanozymes with CAT- and POD-like activities. This system simultaneously generated O_2 to alleviate tumor hypoxia and produced ·OH radicals to weaken drug resistance, improving the chemotherapeutic response [126]. In a similar approach, a cisplatin prodrug was anchored onto two-dimensional copper-based MOF (CuMOF) nanozymes, forming a TME-responsive cascade nanoreactor that simultaneously triggered GSH depletion and ·OH generation under acidic and reductive conditions [20]. Upon internalization by tumor cells, the CuMOF@Pt(IV) nanoplatform released active cisplatin *via* GSH reduction to induce DNA crosslinking and apoptosis, while the released Cu^+ catalyzed intracellular H_2O_2 to generate highly toxic ·OH through Fenton-like reactions (Fig. S5C in Supporting information). This dual-function nanozyme–drug system enabled spatiotemporally coordinated oxidative and chemotherapeutic stress, effectively disrupting redox homeostasis and overcoming resistance mechanisms associated with elevated GSH levels. Meanwhile, nanozymes can facilitate or enhance antitumor immune responses, particularly when combined with PTT or immunogenic chemotherapeutic agents. The

previously described $RuTe_2$–GOx–TMB multienzyme system not only eliminated primary tumors *via* ROS and thermal damage, but also released tumor-associated antigens and danger signals to stimulate systemic immune responses against residual tumor cells and distant metastases [21]. When combined with immune checkpoint inhibitors (*e.g.*, anti-PD-1 antibodies), such nanozyme-mediated tumor cell death can convert "cold" tumors into T cell–infiltrated "hot" tumors, enhancing T cell–mediated immunoactivation [127]. Although immunotherapy is not the focus of this review, it is worth noting that catalytic nanoagents can promote *in situ* vaccination effects by releasing antigens under oxidative and thermal stress.

In addition to immune activation, nanozyme functionality *in vivo* may be compromised by biological barriers such as protein corona formation. To overcome this, Liu *et al.* designed a genetically engineered protein corona-coated cascade nanozyme system (MSN–Au/Ce6–FTn–Ru) [128]. In this system, human ferritin heavy chain (FTn) was coated onto mesoporous silica NPs to form a biomimetic "pre-formed" protein corona. This shield effectively minimized plasma protein adhesion, extended blood circulation time, and facilitated selective tumor accumulation. The system integrated GOx-like AuNPs and CAT-like Ru nanoclusters, enabling cascade reactions to deplete glucose and generate oxygen within the TME. Consequently, this strategy enhanced PDT efficacy and significantly suppressed tumor progression. This work highlights the potential of protein corona resistance to preserve catalytic functionality under physiological conditions and improve the therapeutic outcome of nanozymes. Such designs may also help maintain nanozyme-mediated immunogenic effects *in vivo*.

In summary, nanozymes represent a versatile therapeutic toolkit for cancer treatment. They can directly induce tumor cell death *via* ROS generation and membrane disruption, modulate the TME (*e.g.*, oxygenation, antioxidant depletion, pH reduction), and synergize with other modalities such as PTT, PDT, and chemotherapy.

3.3. Applications in bone regeneration

Bone regeneration and repair are often impaired by pathological oxidative stress and chronic inflammation. For example, large critical-sized bone defects or infections (osteomyelitis) create a hostile microenvironment with excessive ROS that disrupt osteogenic signaling and promote osteoblast apoptosis. Similarly, systemic disorders such as diabetes and rheumatoid arthritis produce chronic inflammation and ROS overload that delay bone healing. Radiation-induced bone injury also generates high levels of ROS, and strategies that scavenge ROS (for instance, CAT-mimetic nanozymes) can protect bone tissue from radiogenic damage. Given these factors, novel therapies that restore redox balance and resolve inflammation are needed to improve bone defect repair.

3.3.1. Antioxidant and anti-inflammatory nanozymes in bone regeneration

Oxidative stress is a major contributor to impaired bone healing, particularly under pathological conditions such as diabetes, periodontitis, and irradiation injury [26,129–132]. Nanozymes are nanomaterials with intrinsic enzyme-like catalytic activity [9,22]. Those exhibiting SOD, CAT, or GPx mimetic activity can dramatically lower ROS levels and blunt inflammatory signaling in bone. Among them, CeO_2-based nanozymes stand out for their redox-switchable Ce^{3+}/Ce^{4+} valence states and abundant oxygen vacancies, which enable the catalytic dismutation of $^{\bullet}O_2^-$ and decomposition of H_2O_2 into water and molecular oxygen [46]. Both *in vitro* and *in vivo* studies have demonstrated that CeO_2 nanozymes effectively suppress nuclear factor kappa-B (NF-κB) activation and downstream pro-inflammatory cytokine expression under oxidative stress [130,133]. For example, Coathup *et al.* synthesized ultrasmall CeO_2 NPs (~5 nm) with high Ce^{3+} content (60%) that effectively scavenged intracellular ROS and modulated macrophage polarization under both acute and chronic inflammatory conditions, while promoting osteogenic differentiation of human bone marrow MSCs (hBMSCs) in the presence of osteogenic medium (increased alkaline phosphatase (ALP) activity and expression of collagen type I (Col I), osterix (OSX), osteocalcin (OCN) and bone morphogenetic protein-7 (BMP-7) (Fig. S6A in Supporting information) [134]. Similarly, in a rat periodontitis model, CeO_2 nanozymes were found to suppress mitogen-activated protein kinase (MAPK)/NF-κB signaling, leading to decreased inflammatory cytokines, reduced osteoclast activity and preservation of alveolar bone [130]. To counteract ROS-impaired osteogenesis in diabetes, CeO_2-containing composite scaffolds have been shown to scavenge hyperglycemia-induced ROS, rescuing stem cell osteogenic capacity, restoring bone matrix synthesis, and improving trabecular bone architecture *in vivo* [129].

In summary, CeO_2-based nanozymes synergistically scavenge pathological ROS, reprogram inflammatory pathways, and promote lineage-specific differentiation, offering a powerful strategy for bone regeneration in hostile oxidative environments.

3.3.2. Nanozyme-integrated scaffolds and hybrid systems

Recent tissue-engineering scaffolds incorporate nanozymes to combine structural support with biochemical regulation. For example, hollow mesoporous bioglass scaffolds embedded with CeO_2 NPs enable staged osteoinduction: initially, the hierarchical macropores support hBMSC adhesion and infiltration, while cerium ions released from the scaffold stimulate early osteogenic signaling. Subsequently, the dual-valence Ce^{3+}/Ce^{4+} species activate the extracellular signal-regulated kinase (ERK) pathway, upregulating Runx2 and promoting extracellular matrix mineralization. *In vivo*, CeO_2-modified scaffolds enhanced collagen deposition, osteoblast formation, and bone volume restoration by orchestrating structural guidance and biochemical cues for regenerative bone formation [24]. Hydrogel delivery systems have similarly harnessed nanozyme activity. A recent design embedded dual SOD-/CAT-like nanozymes in an injectable hydrogel co-loaded with BMSCs for rheumatoid arthritis (RA) models (Figs. S6B and C in Supporting information) [136,137]. This nanozyme–hydrogel composite rapidly scavenged excessive ROS in the inflamed tissue while simultaneously generating dissolved O_2 from endogenous H_2O_2. The combined effect protected the transplanted BMSCs from ROS-induced apoptosis and hypoxia, enabling them to survive and differentiate. *In vivo*, the treatment suppressed local inflammatory cytokines and significantly improved bone regeneration and osseointegration. In other words, the nanozyme-enhanced hydrogel created a pro-regenerative niche (reducing oxidative stress and hypoxia) that allowed the stem-cell therapy to be effective [137].

Bone injury sites are often characterized by pathological microenvironments such as elevated levels of ROS, acidic pH, and inflammatory cytokines, which severely hinder tissue repair [136]. To address this, recent advances have led to the development of smart responsive hydrogel platforms. By integrating nanozymes, these systems enable on-demand release under inflammatory or oxidative stress conditions, dynamically regulating redox balance and immune responses [138]. This strategy not only optimizes the microenvironment for stem cell survival but also significantly enhances osteogenic differentiation and tissue regeneration. For instance, Xu *et al.* developed a TM/BHT/CuTA system composed of copper–tannic acid coordination nanosheets (CuTA NSs) and TM/BHT hydrogel *via* self-assembly [139]. The hydrogel is retained at inflamed sites *via* electrostatic interactions and undergoes responsive hydrolysis in the presence of elevated matrix metalloproteinase (MMP) levels associated with periodontitis, thereby

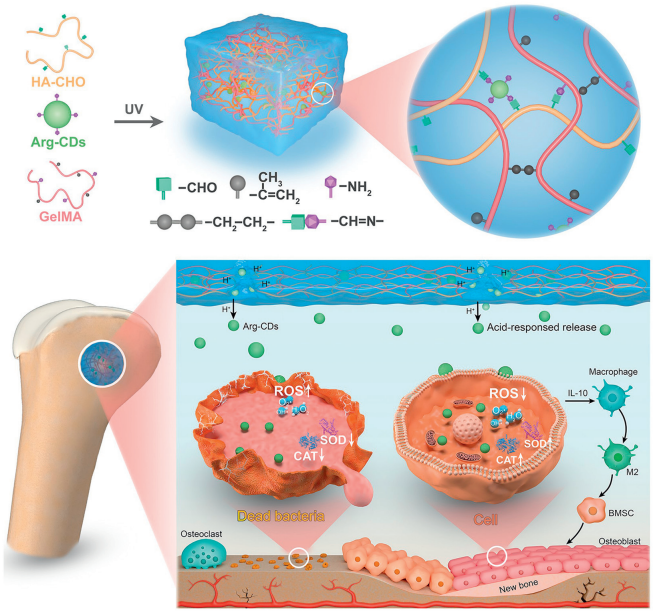


Fig. 5. A bifunctional hydrogel incorporating Arg-CDs and GelMA for simultaneous antibacterial and bone-regenerative applications. The system enhances intracellular antioxidant enzyme expression (SOD, CAT), reduces oxidative stress, promotes macrophage polarization toward the M2 phenotype, and supports osteogenesis at bone defect sites. Copied with permission [135]. Copyright 2023, American Association for the Advancement of Science.

achieving on-demand release of the CuTA nanozyme. The released CuTA exhibits both antibacterial and antiplaque activity and mimics the cascade reaction of SOD and CAT to effectively scavenge ROS. Furthermore, CuTA modulates macrophage polarization from the pro-inflammatory M1 phenotype to the reparative M2 phenotype through activation of the Nrf2/NF-κB signaling pathway, which reduces pro-inflammatory cytokine expression, increases anti-inflammatory cytokines, and upregulates osteogenic gene expression. This work highlights the potential of responsive nanozyme-loaded hydrogels to achieve multifunctional therapeutic effects in complex pathological environments.

3.3.3. Metal-free and antibacterial nanozyme systems

To avoid potential metal toxicity, metal-free nanozymes have also been developed. For instance, CDs-based NPs can mimic antioxidant enzymes and are incorporated into hydrogels or scaffolds [135,140]. These nanozymes retain potent ROS-scavenging and anti-inflammatory capacity while being inherently biocompatible. In preclinical models, polyphenol-enriched scaffolds reduce oxidative damage at the implant site, which gene-expression profiling confirms by showing upregulation of osteogenic markers (*e.g.*, Runx2, Ocn) and downregulation of NF-κB-driven inflammatory genes [140]. This transcriptomic signature correlates with accelerated bone formation in treated defects (compared to controls) [22]. In treating infected bone defects, bifunctional nanozymes that integrate ROS-scavenging with antibacterial activity present a compelling therapeutic strategy. For example, arginine-derived CDs (Arg-CDs) were engineered into an acid-responsive hydrogel platform (CHG) that selectively released the nanozyme in the acidic microenvironment of infection [135]. Upon release, Arg-CDs catalyzed excessive ROS generation in bacteria, leading to membrane disruption and cell death, while simultaneously upregulating intracellular antioxidant enzymes such as SOD and CAT in host cells, thereby mitigating oxidative stress (Fig. 5). This dual-function system not only eradicated *S. aureus* but also modulated the local immune microenvironment by inducing M2 macrophage polarization *via* IL-10 upregulation, ultimately promoting osteogenesis. Notably, the CHG + *S. aureus* group significantly promoted bone regeneration with a BV/TV value larger than 39%. The coordinated antimicrobial, immunoregulatory, and osteoinductive properties exemplify a cascade-responsive therapeutic paradigm in which the infected microenvironment dynamically activates and sustains the catalytic functions of the nanozyme, enabling both infection resolution and bone regeneration.

Overall, nanozymes are emerging as a versatile platform for bone repair. By mimicking natural antioxidant enzymes, they dynamically regulate the injury microenvironment, quenching pathological ROS, dampening inflammation, and even generating oxygen when needed [22]. Whether delivered as free NPs, embedded in scaffolds, or as part of cell–matrix composites, nanozymes have been shown to protect bone-forming cells and create pro-healing niches. This modular approach allows simultaneous targeting of multiple insults (oxidative stress, hypoxia, infection) while promoting pro-regenerative signals (angiogenesis, osteogenesis). In summary, evidence suggests that enzyme-mimetic nanomaterials hold significant translational promise for orthopedic regeneration by orchestrating the complex redox and immune environment of healing bone [22].

4. Conclusion and outlook

Nanozymes have emerged as a promising class of catalytic nanomedicines owing to their enzyme-mimicking activities, structural tunability, and intrinsic physicochemical stability. Recent advances in cascade catalysis, self-propulsion, and stimulus-responsive targeting have opened opportunities to treat complex disease microenvironments, including tumors, infections, and bone defects.

Clinical translation still faces key barriers. Precise in vivo targeting remains limited by reliance on passive accumulation; ligand-mediated active targeting (*e.g.*, RGD, folate, antibodies, aptamers), stimulus-responsive activation (endogenous pH/ROS/GSH/enzymes or exogenous light/ultrasound/magnetic fields), and biomimetic camouflage (cell membranes, PEGylation) can improve specificity and retention, while multi-ligand designs and artificial intelligence (AI)-assisted screening may further refine selectivity. Catalytic performance can be attenuated by protein corona formation, pH variation, and cofactor depletion, underscoring the need for nanozymes that retain activity under physiological conditions or can be activated in situ. Long-term biosafety and biodegradability, particularly chronic accumulation, inflammatory responses, and degradation products, require systematic evaluation.

Beyond their intrinsic catalysis, nanozymes complement combination strategies for anti-infection and bone regeneration by tuning immune responses, balancing oxidative stress, and integrating into scaffolds or hydrogels to provide structural and catalytic synergy. Priorities include engineering multifunctional "smart" platforms capable of closed-loop action from site recognition to organelle-level modulation, establishing scalable and standardized manufacturing for clinical-grade quality, and conducting rigorous preclinical studies to define pharmacokinetics, biodistribution, and efficacy. With continued innovation in design, targeting, and catalytic efficiency, nanozymes are poised to evolve into a next-generation therapeutic platform for drug-resistant infections, tumor hypoxia, and regenerative medicine.

Declaration of competing interest

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

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Dechao Yuan: Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis. **Tianying Luo:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Qiao Su:** Formal analysis, Conceptualization. **Changxing Qu:** Software, Formal analysis. **Meng Pan:** Visualization, Methodology. **Jia Xu:** Visualization, Formal analysis. **Mingyi Zhang:** Formal analysis. **Yuanchao Luo:** Formal analysis. **Renjian He:** Visualization. **Shiwei Liu:** Formal analysis. **Xiang Fang:** Formal analysis. **Hong Duan:** Writing – review & editing. **Zhiyong Qian:** Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111842.

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