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REVIEW

Preclinical Advances in Functionalized Nanozymes for Periodontitis: From Antibacterial Action to Tissue Regeneration

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Background: Periodontitis is a chronic infectious disease caused by bacteria, which leads to destruction of periodontal tissues, tooth loss, and systemic complications. Conventional treatments often fail to counteract the suppression of periodontal tissue regeneration caused by the persistent inflammatory microenvironment.

Scope: This review focuses on the application of functionalized nanozymes in the treatment of periodontitis, covering the classification of nanozymes, their mechanisms of action, and recent advances in nanozyme-based therapeutic strategies.

Key Findings: Functionalized nanozymes, with their multiple bioactivities including antibacterial, antioxidant, and osteogenic stimulation, represent a promising complement to existing therapeutic approaches. Their sophisticated designs enhance biofilm eradication, modulate immune responses, and facilitate tissue regeneration, thereby overcoming key limitations of existing periodontal treatments.

Conclusion: Functionalized nanozymes, particularly motor-based composite nanozymes, show great promise for periodontitis treatment due to their self-propulsion and multifunctional design (antibacterial, antioxidant, osteogenic). However, long-term biosafety, especially metal-ion accumulation, remains the key bottleneck for clinical translation. With continued optimization and standardized safety evaluation, these nanozyme platforms may open a new precision therapy avenue for drug-resistant refractory periodontitis.

Keywords: periodontal therapy, nanozymes, antibacterial, reactive oxygen species, immune modulation, regeneration

Introduction

Periodontitis is a chronic inflammatory disease caused by bacterial infection. Fundamentally, the pathology involves a dysregulated host immune response to pathogens like Porphyromonas gingivalis. This excessive inflammation releases a flood of reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and pro-inflammatory cytokines, ultimately leading to the degradation of periodontal ligament collagen, resorption of alveolar bone, tooth loss, and compromised systemic health.[1,2] According to the GBD 2021 data, periodontitis affected approximately 62% of dentate adults (severe periodontitis: 23.6%), with over 1 billion people worldwide suffering from severe periodontitis (1.067 billion; 95% UI: 0.897–1.235), representing an age-standardized prevalence of 12.50% (95% UI: 10.53–14.49).[3,4] Although mechanical debridement combined with antibiotic therapy is the current standard of care, its efficacy is often compromised by the complex periodontal tissue architecture, resilient biofilms, and the escalating challenge of antibiotic resistance.[5–7] Critically, conventional therapies often fail to reverse inflammation-induced tissue damage or promote functional regeneration. Importantly, the control of inflammation and the regulation of the immune microenvironment are crucial for the subsequent bone healing process.[8,9] Therefore, developing novel precision therapies that can simultaneously eradicate pathogens and restore periodontal tissue homeostasis has become a critical priority. Nanomaterials, characterized by their distinctive

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properties such as a high surface-area-to-volume ratio, customizable chemistry, and responsiveness to stimuli, effectively address these challenges.[10] Among various nanomaterials, nanozymes are advanced nanomaterials with multiple natural enzyme-mimicking catalytic activities, which offer a potentially promising new approach to tackling this problem.[11,12] Their distinct advantage lies in a dual-action mechanism that addresses both pathogenic elimination and tissue restoration. On one hand, by mimicking peroxidase (POD) or oxidase activities, nanozymes can catalyze the generation of ROS to efficiently eradicate pathogens within deep biofilms.[13] On the other hand, their superoxide dismutase (SOD)- and catalase (CAT)-like activities enable them to precisely scavenge excessive pathological ROS in the tissue, thereby breaking the vicious cycle of oxidative stress, mitigating inflammation, and creating a favorable immune microenvironment for tissue self-repair.[14] Based on current preclinical evidence from in vitro experiments and rodent models, this dual functionality shows notable potential to address the long-standing issue of simultaneously achieving bactericidal effect and anti-inflammatory regeneration in periodontitis treatment.

Rapid advancements in materials science have rendered nanozymes increasingly powerful and controllable in their functionality. For instance, integrating self-propulsive capabilities into nanozymes to form nanomotors enables effective biofilm penetration and enhances antibacterial activity.[15,16] Despite this progress, existing reviews—including those by Hosseini Hooshiar et al[5] and Liu et al[17]—have primarily focused on the general antibacterial effects of nanozymes across various oral infectious diseases. A comprehensive review systematically covering the application of functionalized nanozymes specifically for periodontitis remains lacking. In particular, no previous review has systematically summarized advanced functionalized designs such as self-propelled nanomotors and gas-generating systems, nor has any integrated the triple bioactivities of antibacterial, antioxidant, and osteogenic properties into a holistic framework for periodontitis. In light of this, the present review aims to summarize recent advances in functionalized nanozymes as therapeutic agents for periodontal disease, evaluate their potential for clinical translation, dissect current challenges, and outline future research directions.

A structured literature search was conducted for this narrative review to identify and synthesize studies on functionalized nanozymes for periodontitis treatment. PubMed, Web of Science, Scopus, and Google Scholar were searched to ensure broad coverage and minimize omission of relevant reports. The search included all literature published up to 31 May 2026, with iteratively refined terms such as "nanozymes", "periodontitis", "artificial enzymes", "antibacterial", "immune modulation", "bone regeneration", "nanomotors", and "periodontal therapy". In line with the nature of a narrative review, studies were selected based on their relevance and contribution to the thematic synthesis rather than on formal quantitative inclusion criteria; only peer-reviewed articles published in English were considered.

Potential Mechanisms in Periodontal Treatment and Classification of Nanozymes

Nanozymes are synthetic nanomaterials that emulate the catalytic functions of natural enzymes. Functionally, they do not act as static catalysts but rather switch between opposing redox roles in a microenvironment-dependent manner: under inflammatory conditions characterized by acidity and elevated H_2O_2, they function as pro-oxidant antimicrobial agents, whereas in contexts of excessive oxidative stress or during the resolution phase, they act as antioxidant anti-inflammatory mediators to restore immune homeostasis in periodontal treatment.[18]

- Antimicrobial (Pro-oxidant) Mechanism: In the weakly acidic (pH ≈ 5.5–6.5) and H_2O_2-rich milieu of active periodontal inflammation, nanozymes typically mimic peroxidase (POD)-like activity. They catalyze Fenton- or Fenton-like reactions to convert endogenous H_2O_2 into highly cytotoxic hydroxyl radicals ($^{\cdot}OH$).[19,20] This burst of ROS directly disrupts microbial membrane integrity, oxidizes proteins and DNA, and ultimately eradicates pathogens. Concurrently, metal ions such as Cu^{2+} and Zn^{2+} released from the nanozyme scaffold exert synergistic antibacterial effects.[21]
- Anti-inflammatory (Antioxidant) Mechanism: As inflammation progresses or in microenvironments with neutral pH and accumulated superoxide ($^{\cdot}O_2^-$), nanozymes shift toward antioxidant behavior. They mimic a cascade of endogenous antioxidant enzymes: superoxide dismutase (SOD)-like activity converts $^{\cdot}O_2^-$ into H_2O_2 and O_2;

catalase (CAT)-like activity further decomposes H_2O_2 into harmless H_2O and O_2; and glutathione peroxidase (GPx)-like activity reduces cytotoxic lipid peroxides.[22] This coordinated scavenging re-establishes redox balance, dampens chronic inflammation, and supports tissue repair.

In summary, as illustrated in Figure 1, nanozymes orchestrate a sequential and synergistic therapeutic cascade against periodontitis through four interconnected stages: (1) Antibacterial action: Nanozymes first target and eliminate periodontal pathogens by catalyzing the generation of cytotoxic reactive oxygen species (ROS), such as hydroxyl radicals via peroxidase-like activity and/or releasing antimicrobial metal ions (eg., Ag^+, Zn^{2+}), thereby disrupting biofilm integrity and halting ongoing microbial stimulation. (2) ROS scavenging: Once pathogen burden is reduced, nanozymes can switch to an antioxidant mode, mimicking the enzymatic cascade of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) to neutralize excess ROS, restore redox homeostasis, and alleviate oxidative stress in the inflamed tissue. (3) Immune modulation: By mitigating oxidative damage and preserving mitochondrial function, nanozymes promote the polarization of macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory, pro-repair M2 phenotype, thus reprogramming the local immune microenvironment toward resolution and homeostasis. (4) Tissue regeneration: Finally, the sustained release of osteogenic ions, particularly Cu^{2+}, along with other bioactive cues directly stimulates osteoblast differentiation and activity, fostering alveolar bone formation and enabling functional regeneration of the periodontal complex.

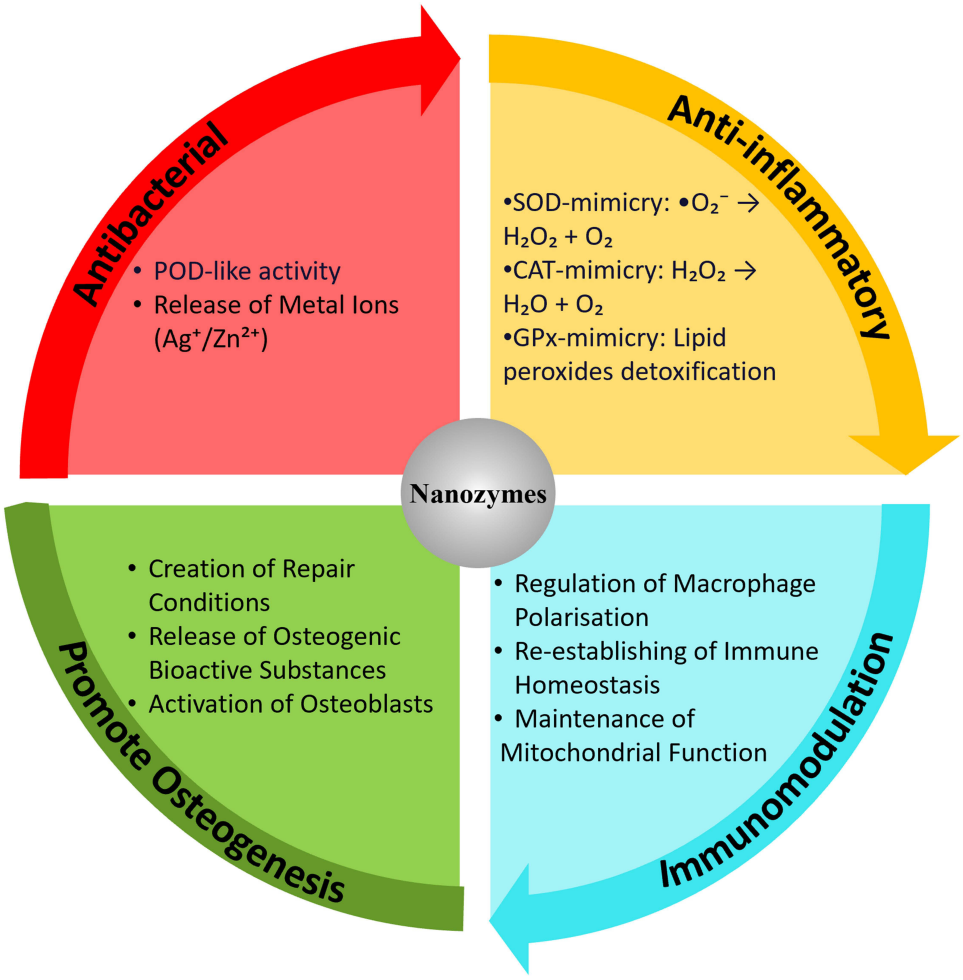

Figure 1 Schematic illustration of the cascade therapeutic mechanism of functionalized nanozymes in periodontitis treatment.

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Table 1 Classification of Nanozymes Based on Material Composition

Nanozyme	Representative Example(s)	Key Features	Challenges	References
Metal-Based Nanozymes (MNPs)	CeO_2	Superior SOD and CAT mimicry	Potential for cytotoxicity	[23,24]
		Multienzyme activity	Long-term accumulation of heavy metal ions	
		Tunable activity		
	Fe_3O_4	Strong POD-like activity	PH-dependent activity	[25]
		Biocompatible	Limited intrinsic multifunctionality without modification	
		Multifunctional platform		
Carbon-Based Nanozymes (CNMs)	Graphdiyne (GDY)	Biocompatible	Lower catalytic potency	[26,27]
		Optical and electrical features		
	Graphene Quantum Dots (GQDs)	High stability and conductivity		
MOF-Based Nanozymes (MNOFs)	Zeolitic Imidazolate Framework-8 (ZIF-8)	High surface area	Synthesis complexity	[28,29]
		Tunable activity	Stability concerns	
		Drug loading capability	High cost	
Composite Nanozymes	Metalloprotein nanozymes	Synergistic properties	Synthesis complexity	[30]
		High stability		

Based on their constituent materials, nanozymes are divided into four main categories: metal-based nanozymes (MNPs), carbon-based nanozymes (CNMs), metal-organic framework-based nanozymes (MNOFs), and composite nanozymes. Each category offers a distinct set of advantages and challenges (Table 1).

Metal-Based Nanozymes (MNPs)

Metal-based nanozymes (MNPs), primarily composed of transition metals and their oxides, represent the most established and extensively investigated class of nanozymes. Their catalytic activity originates from the intrinsic redox properties of the constituent metals and the unique electronic and crystalline structures of their nanoparticle surfaces.[22] Key advantages of MNPs include their high stability, tunable catalytic activity, low production costs, and amenability to large-scale fabrication. These features are largely attributed to their stable crystal lattices and the adjustable valence states of the metal ions, which facilitate efficient electron transport during redox reactions.

A prominent example is cerium dioxide (CeO_2), which effectively scavenges ROS such as $^{\cdot}O_2^-$ and H_2O_2 through a dynamic Ce^{3+}/Ce^{4+} redox cycle.[23] CeO_2 nanozymes exhibit both superoxide dismutase and catalase-like activities, enabling the scavenging of diverse reactive oxygen species (ROS). A representative illustration of their tunable catalytic activity can be observed in the construction of core–shell structures such as CeO_2@ZIF-8. Through such architectures, researchers can precisely modulate the surface Ce^{3+}/Ce^{4+} ratio, thereby significantly enhancing the ROS elimination capacity.[24] Despite their therapeutic potential, a significant barrier to clinical translation remains concerns about cytotoxicity and long-term bioaccumulation, leading to heavy metal deposition.

Similarly, other metal oxides like Fe_3O_4 mainly simulate POD, which catalyzes the production of ·OH from H_2O_2 in an acidic environment to kill bacteria. The biocompatibility of Fe_3O_4 nanoparticles is relatively good. The drawback is

that the activities of POD-like mimetic enzymes are highly dependent on local H_2O_2 concentration and pH. In the deep part of the periodontal pocket, the concentration of H_2O_2 may be insufficient, resulting in its "deactivation".[25]

Carbon-Based Nanozymes (CNMs)

Carbon-based nanozymes (CNMs) are a class of nanomaterials composed predominantly of carbon elements. This category includes diverse structures such as carbon nanotubes, graphene oxide (GO), fullerenes, graphdiyne (GDY), graphene quantum dots (GQDs), and carbon quantum dots (CQDs). CNMs are distinguished by several key properties: a large specific surface area, excellent biocompatibility, and superior electron transport capabilities.

The catalytic activity and selectivity of these materials can be precisely engineered by tailoring their surface chemistry and structural features. Furthermore, many CNMs exhibit remarkable optical and electrical properties, making them ideal for the development of multifunctional theragnostic platforms. For example, Graphdiyne (GDY), with its unique sp–sp^2 hybridized carbon network, exhibits high photothermal conversion efficiency in the near-infrared region. It has adjustable catalytic activity. Its highly conjugated structure and electronic properties are conducive to catalytic reactions, and it can also serve as an excellent carrier to enhance the performance of the composite nanozyme. Its electron-rich surface can be loaded with metals like iron (Fe) to create peroxidase-like active sites, which catalyze the conversion of H_2O_2 into cytotoxic $^{\cdot}OH$ radicals.[26]

Graphene Quantum Dots (GQDs) effectively quench various radicals through efficient electron transfer. Their antioxidant capacity is directly related to the density of surface functional groups, such as carboxyls. GQDs also exhibit strong, tunable fluorescence, making them highly suitable for integrated imaging and therapeutic applications.[27]

Given that carbon is a naturally abundant element, CNMs represent a more cost-effective and environmentally sustainable alternative to metal-based nanozymes for nanozyme synthesis.[31] It has good biocompatibility, but its catalytic activity and the diversity of enzyme-mimicking types are usually inferior to those of MNPs.

Metal-Organic Frameworks-Based Nanozymes (MNOFs)

Metal–organic frameworks (MOFs) serve as the foundation for MNOFs, a class of synthetic nanozymes. Their catalytically active metal nodes directly participate in electron transfer and can be functionalized by selecting various metals, ligands, or incorporating functional groups like amino and carboxyl moieties.[32]

MNOFs offer significant advantages, including abundant functional sites, tunable pore architectures, and a high surface area. These features allow for the accommodation and exposure of additional active sites, thereby improving substrate selectivity and catalytic efficiency. The structural diversity of MOFs provides a versatile platform for designing nanozymes with a wide range of enzyme-mimetic activities. Furthermore, MOFs support controlled release and efficient drug loading, enabling the development of multifunctional therapeutic platforms.

For instance, the introduction of copper ions into Zeolitic Imidazolate Framework-8 (ZIF-8) creates a bimetallic nanozyme with significantly enhanced peroxidase-like activity. This nanozyme mimics POD activity to generate ROS, which, in synergy with the released Cu^{2+} and Zn^{2+} ions, produces potent antibacterial effects.[28] Similarly, introducing cobalt ions into the ZIF-8 framework to construct a zinc-cobalt bimetallic organic framework (Zn/Co-MOF) not only reduces metal ion leakage but also enhances multi-enzyme-like antioxidant activity, effectively scavenging reactive oxygen species and promoting osteogenic differentiation via activation of the Wnt pathway.[29]

Another paradigm for enhancing MOF-based nanozyme activity lies in engineering both the physical structure and surface chemistry. The creation of a hierarchical pore system—where macropores enable rapid molecular diffusion and meso-/micropores host abundant active sites—directly addresses mass-transfer limitations and increases catalytic efficiency. Parallel to this, -NH_2 functionalization of the MOF surface (eg., yielding HMUiO-66-NH_2) enhances its interfacial properties, improving biocompatibility and circulatory stability. Functionally, this advanced nanozyme not only scavenges ROS to mitigate oxidative stress but also contributes to bone repair by reprogramming the immune microenvironment, for instance, through polarizing macrophages toward a pro-regenerative phenotype, thereby creating a favorable milieu for tissue regeneration.[33]

Some MOF-based nanozymes have poor chemical stability in water, acids, bases or physiological environments, which may lead to structural collapse and loss of activity. The intrinsic catalytic activity of many MOF-based nanozymes

is still lower than that of natural enzymes or noble MNPs, and complex structural design is required to enhance it. The complex structure makes large-scale preparation difficult: it is costly, has poor repeatability, and it is difficult to ensure consistency between batches.

Composite Nanozymes

Composite nanozymes are defined as nanozymes composed of two or more distinct nanomaterials or functional components. By integrating the advantageous properties of different materials, these nanozymes exhibit enhanced stability, biocompatibility, and adaptability within complex biological environments.

A notable example is polyphenol-metal nanozymes, which offer unique benefits. The strong metal-chelating capacity of polyphenols effectively anchors and stabilizes metal ions, overcoming common issues of aggregation and deactivation. Additionally, polyphenols provide excellent biocompatibility, antioxidant, and antibacterial properties, which synergize with the intrinsic enzyme-mimetic catalysis of the metal ions.

For instance, researchers have synthesized copper-based nanozymes (CuNCs) by coordinating copper ions with salvianolic acid B (SalB), a polyphenol compound with established antioxidant and pro-angiogenic activities.[34] The unique copper–phenolic hydroxyl coordination structure in SalB-CuNCs facilitates the valence transition of copper, enhancing its cascade-like enzyme-mimetic catalytic activity and conferring potent oxidative stress alleviation. Concurrently, SalB's inherent bioactivity imparts significant pro-angiogenic effects to the composite nanozyme.

To further optimize nanozyme biocompatibility, some researchers have combined metal catalytic centers with protein scaffolds, which markedly reduces cytotoxicity while retaining antioxidant activity. Over the past decade, a variety of metalloprotein nanozymes have been synthesized using diverse metals and proteins, such as MoS_2@Au-HSA, Au/Ru-FTn, Cu-BSA, Hemin@BSA-ZIF8, and Mn-BSA. In the design by Ou et al, a polyphenol-coordinated bimetallic nanozyme was constructed using bismuth (Bi), copper (Cu), and tannic acid (TA). The introduction of Bi played a critical role in modulating the electronic structure of the nanozyme, thereby significantly enhancing its reactive oxygen species (ROS) scavenging capacity. Furthermore, the complex was integrated with bovine serum albumin (BSA), which improved the structural stability and biocompatibility of the resulting artificial metalloprotease. Both in vitro and in vivo experiments demonstrated that the final product, CuBi-TA@BSA, exhibits remarkable biocompatibility along with excellent pro-angiogenic, anti-inflammatory, and antioxidant properties. However, the scalable production of such nanozymes remains a significant challenge.[30]

Advances in Functionalized Nanozymes for Periodontal Therapy

The complex clinical course of periodontitis necessitates a multi-faceted therapeutic approach. Conventional single-functional nanozymes often fail to achieve the simultaneous objectives of pathogen eradication, oxidative stress modulation, and tissue regeneration. To overcome these limitations, researchers have developed advanced multi-component systems that synergize to create integrated antibacterial, antioxidant, and osteogenic platforms. This has led to the development of several classes of functionalized nanozymes, enabling significant improvements in the spatiotemporal precision and controllability of treatment (Table 2).

Multifunctional Synergistic Therapeutic Nanozymes

Through modular design, these nanozymes integrate two or more therapeutic modules onto a single platform to concurrently address the multiple pathological processes of periodontitis.[41,42] For example, copper-based nanozymes (CuNZs) exert antibacterial effects by releasing Cu^{2+} ions, further compromising the integrity of bacterial cell walls and membranes. In addition, CuNZs can catalyze Fenton-like reactions, converting H_2O_2 into ·OH, which induce irreversible lipid peroxidation and consequent damage to bacterial membranes. Beyond their antibacterial properties, CuNZs contribute to immunomodulation by maintaining a balanced M1/M2 macrophage ratio and downregulating the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), thereby mitigating inflammation and facilitating tissue regeneration.[43–45] Meng et al[46] constructed a copper-doped Prussian blue nanozyme (CuPB) by incorporating Cu^{2+} ions into the Prussian blue framework. This engineered nanozyme not only effectively scavenges multiple ROS and suppresses inflammatory responses, but also promotes osteogenic differentiation of bone marrow mesenchymal stem

Table 2 Advances in Functionalized Nanozymes for Periodontal Therapy

Category	Representative Nanozyme [With Ref.]	Therapeutic Outcomes (Antibacterial/Anti-Inflammatory/ Bone Regeneration)	Animal Model & Follow-Up
Multifunctional synergistic	Yolk–shell CRNCs: CuO core for osteogenesis promotion, RuO_2 shell for antioxidant activity[35]	**Anti-bact**: NR **Anti-inflam**: 63.2% ($O_2^{\cdot-}$) at 20 μg/mL **Bone**: CEJ-ABC: 1.1mm→ 0.7mm, BV/TV: 25% → 40%	Rat periodontitis, 4 weeks
Targeted delivery	Core-shell DMUP: Mn-silica for multi-enzyme antioxidation, $UBI_{29–41}$ peptide for pathogen-targeted enrichment[36]	**Anti-bact**: 99.9% (*P. gingivalis*), 95.7% (*E. coli*), 63.5% (*S. aureus*) **Anti-inflam**: 79.3% ($O_2^{\cdot-}$) at 200 μg/mL **Bone**: Attachment Loss: 0.7 mm → 0.07mm, BV/TV:24.2%→76.1%	Rat periodontitis, 4 weeks
Endogenous responsive	TM/BHT/CuTA hydrogel: ester bonds cleaved by MMP-9 for on-demand nanozyme release[37]	**Anti-bact**: > 90% (*P. gingivalis, A. viscosus, S. aureus*, and *E. coli*) **Anti-inflam**: 70% ($O_2^{\cdot-}$) at 50 μg/mL **Bone**: CEJ-ABC: 1.1 mm → 0.6mm, BV/TV:28% → 40%	Rat periodontitis, 2 weeks
Exogenous responsive	Au@CeO_2-DMF: Au enables potent photothermal modulation, facilitates DMF release, and enhances CeO_2 antioxidant activity[38]	**Anti-bact**: nearly 100% (*E.coli, S.aureus*) **Anti-inflam**: 40% ($O_2^{\cdot-}$) at 50 μg/mL **Bone**: Bone loss: 0.8 mm → 0.2mm, BV/TV: 50% → 80%	Rat periodontitis, 3 weeks
Nanomotors (Micro-Nanorobots)	J-CeM@Au: half Au-sputtered Ce-doped MSN achieves NIR-driven thermophoresis[39]	**Anti-bact**: 95% (*P. gingivalis*), 79% (*F. nucleatum*) **Anti-inflam**: 40% ($O_2^{\cdot-}$) at 100 μg/mL **Bone**: CEJ-ABC: 1.0mm → 0.6mm, BV/TV:60% → 80%	Rat periodontitis, 2 weeks
Gas-generating	MSN-Au@CO: CO-releasing platform for bacterial respiration inhibition[40]	**Anti-bact**: >99.9% (*S. aureus, E. coli*), 99% (*P. gingivalis*) **Anti-inflam**: Intracellular SOD activity increased by 10% **Bone**: CEJ-ABC: 0.7 mm → 0.5mm, BV/TV:20% → 30%	Rat periodontitis, 1 week

cells (BMSCs) through activation of the PI3K-Akt signaling pathway. In a rat model of diabetes-associated periodontitis, local administration of CuPB nanozyme downregulated the expression of pro-inflammatory cytokines such as TNF-α and significantly reduced alveolar bone loss.

Li et al[35] constructed yolk-shell structured copper-ruthenium nanocapsules (CRNCs) using CuO as the core by modifying its surface with a RuO_2 layer. This core-shell configuration allows the RuO_2 shell to physically protect the CuO core, thereby enhancing the nanozyme's overall stability and biocompatibility. Within the acidic, ROS-rich microenvironment, the encapsulated CuO core serves as a responsive reservoir for Cu^{2+} release, thereby stimulating osteogenesis and angiogenesis. Simultaneously, the RuO_2 shell functions as an antioxidant nanozyme, reducing inflammation, modulating macrophage polarization, and scavenging ROS. Thus, CRNC nanozymes effectively integrate antioxidant activity, angiogenesis enhancement, and osteogenesis stimulation to address inflammation, vascular dysfunction, and bone tissue damage in periodontitis concurrently. Despite these encouraging results, the ion leakage toxicity of conventional metal-based nanozymes still limits their clinical translation. Studies have shown that doping with multiple metal elements can effectively reduce ion leakage. For example, Zhang et al[47] fabricated a manganese ferrite nanozyme hydrogel (MFZ@PG) by introducing manganese ions into an iron-based nanozyme system. The incorporation of manganese effectively enhanced structural stability and reduced metal ion release, significantly improving biosafety; cell viability remained at 99.5% even at 200 mg/L, with a hemolysis rate below 5%. Meanwhile, manganese doping

enhanced multienzyme-like activity, enabling 82.5% scavenging of superoxide anions and efficient elimination of H_2O_2. Moreover, MFZ@PG promoted osteogenic differentiation via the ZBP1/β-catenin signaling pathway, increasing ALP activity to 92.7% and matrix mineralization to 89.7% compared with the oxidative stress group. In a rat periodontitis model, local administration of MFZ@PG significantly reduced alveolar bone resorption, decreasing the CEJ-ABC distance from 894.4 μm to 487.5 μm and increasing bone volume fraction (BV/TV) from 38.5% to 66.8%.

Targeted Delivery of Nanozymes

Targeted design is a critical strategy for enhancing local therapeutic efficacy and minimizing systemic toxicity by ensuring specific accumulation at the disease site. Current research focuses on two primary targeting approaches.

Immune Cell Targeting

This strategy functionalizes nanozymes to specifically recognize macrophage membrane receptors, enabling ligand-receptor-mediated internalization.[48] This allows for precise modulation of macrophage polarization (M1/M2) to remodel the immune microenvironment. Han et al[49] designed cerium dioxide nanoparticles functionalized with a targeting A2 DNA aptamer. This aptamer confers selective targeting toward macrophages, promoting efficient cellular internalization of the nanoparticles and enhancing their anti-inflammatory and immunomodulatory functions. Cai et al[50] utilized bacterial outer membrane vesicles (OMVs), which can recognize the highly expressed CD64 and CD14 receptors on the surface of M1 macrophages, to modify gold nanocages (AuNCs), preparing hybrid nanoparticles (AuNC-OM) that can selectively target M1 macrophages. AuNC-OM can selectively target M1 macrophages without affecting the phagocytosis of M2 macrophages. Animal studies have demonstrated that this material can protect against lipopolysaccharide (LPS)-induced bone resorption in a mouse model.

Pathogen-Specific Recognition

This approach incorporates pathogen-associated molecular pattern (PAMP) recognition elements to achieve enhanced retention within the biofilm microenvironment. For instance, the bacteria-targeting peptide Ubiquitin 29–41 (UBI29-41) has been conjugated to manganese-based nanozymes, facilitating precise localization to bacterial membranes.[36] Another strategy leverages outer membrane vesicles (OMVs) derived from *Fusobacterium nucleatum*, a keystone bridging organism in periodontal biofilms, to functionalize ternary chalcogenide $AgBiS_2$ nanoparticles.[51] These OMVs retain native bacterial adhesins on their surface, including RadD, AidA, and CmpA (which bind to early colonizers like *Streptococcus gordonii*) as well as RadD, Fap2, and FomA (which recognize late colonizers such as *Porphyromonas gingivalis*). By mimicking the natural co-aggregation behavior of *F. nucleatum*, the OMV-coated nanoparticles selectively anchor to diverse periodontal pathogens through these specific ligand–receptor interactions, thereby achieving precise targeting within polymicrobial biofilms. Simultaneously, the OMV cloak provides biomimetic camouflage, enabling the nanoparticles to evade immune surveillance and passively migrate alongside dispersing bacteria. This dynamic mobility allows the therapeutic agents to track pathogen spread to newly colonized niches, effectively intercepting biofilm expansion at its source. Both in vitro and in vivo studies have validated the exceptional biofilm-eradicating and periodontitis-treating efficacy of this biomimetic platform.

Despite the promise of targeted nanozyme systems, several key challenges remain. Non-specific protein adsorption in saliva and gingival crevicular fluid forms a protein corona that masks targeting ligands, reducing binding specificity and efficiency.[52] Moreover, most targeting strategies, though effective in cell models, suffer from rapid immune clearance in vivo, leading to lower targeting efficiency and retention than observed in vitro. To address these limitations, biomimetic membrane-coating strategies have been developed. For instance, Li et al[53] constructed a periodontal ligament stem cell membrane-camouflaged MnO_2 nanozyme (MnO_2@hPM). The membrane coating, enriched with PDLSC-affinity biomolecules and hypoxia-educated functional proteins, enables active targeting of inflamed PDLSCs, neutralization of pro-inflammatory cytokines, scavenging of excessive ROS, and restoration of osteogenic potential in inflammation-impaired PDLSCs. In an experimental periodontitis model, MnO_2@hPM effectively accumulated at the disease site, significantly alleviated inflammation, and reduced alveolar bone loss.

Endogenous Stimulus-Responsive Nanozymes

To address the challenges of dynamic regulation and limited precision, smart responsive nanozymes have been developed. These systems precisely sense and respond to specific signals (eg., pH, ATP, enzymes) within the periodontal microenvironment, enabling targeted delivery and on-demand release.[54]

Enzyme-Responsive

The TM/BHT/CuTA hydrogel incorporates ester bonds that are susceptible to hydrolysis by enzymes such as MMP-9, which are overexpressed in inflammatory environments. This design enables the on-demand release of CuTA nanozymes, which exhibit SOD and catalase activities to mitigate oxidative stress and provide antibacterial, anti-inflammatory, and osteogenic properties.[37]

ATP-Responsive

The Mg/Zn-MOF system is designed to be activated by extracellular adenosine triphosphate (ATP), triggering the selective release of magnesium and zinc ions. This process inhibits the expression and activation of Gasdermin D, preventing the release of pro-inflammatory factors and halting the inflammatory cascade.[55]

pH-Responsive

Sulfur quantum dots (SQDs) exhibit a pH-dependent dual-mode catalytic capability. Within the acidic inflammatory milieu, they trigger a SOD- POD cascade to generate bactericidal ROS. Conversely, under neutral conditions, their activity dynamically switches to a SOD- CAT cascade, which decomposes H_2O_2 into water and oxygen to produce anti-inflammatory effects.[56] Similarly, Du et al[57] developed a high-entropy alloy (HEA) nanozyme (PtPdRuRhIr) with pH-switchable enzyme-mimetic activities. Under acidic conditions, H^+ in the solution preferentially binds to the ·O intermediate to generate ·OH, thereby exhibiting potent peroxidase-like activity for bacterial killing. Under neutral conditions, the ·O intermediate reacts with another H_2O_2 molecule, rearranges, and releases O_2 and H_2O, effectively scavenging reactive oxygen species (ROS). In a rat periodontitis model, local administration of this HEA nanozyme significantly reduced the cementoenamel junction–alveolar bone crest (CEJ-ABC) distance from approximately 1.3 mm to 0.5 mm and increased the bone volume fraction (BV/TV) from 40% to 80%. Moreover, its small size (approximately 68 nm) enables rapid renal clearance; ICP-MS analysis showed only trace accumulation of HEA metal elements in the kidneys and liver on day 1, with nearly complete clearance by day 3.

Although endogenous stimulus-responsive nanozymes have shown promising potential in vitro, their clinical translation may still face some notable challenges. Among these, the discrepancy in response thresholds between in vitro and in vivo conditions could be a particularly prominent issue. In vitro studies typically employ well-controlled signal concentrations (eg., specific pH, ATP levels, or enzyme activities), whereas the actual levels of these signals in the periodontal microenvironment are often lower and more variable. This may lead to suboptimal nanozyme sensitivity and, consequently, compromise therapeutic efficacy to some extent. To address this potential limitation, exploiting kinetic differences among catalytic materials to construct temporally sequenced therapeutic systems could be a feasible strategy. For instance, natural molecules with slower catalytic kinetics, such as polydopamine (PDA), could be used as reactive oxygen species (ROS) scavengers. During the early infection phase, the antibacterial module requires rapid generation of high ROS levels to eliminate pathogens; the slow catalytic rate of PDA may allow it to avoid interfering with this process. Once the infection is controlled and inflammation enters the resolution phase, PDA may gradually and persistently scavenge residual ROS, thereby alleviating oxidative stress and creating a more favorable microenvironment for tissue regeneration.[58]

Exogenous Stimulus-Responsive Nanozymes

Recent advances in multifunctional nanozyme systems leverage the synergy between photothermally triggered responses and chemodynamic activities, demonstrating great potential for antibacterial therapy. The core strategy involves the rational design of materials that enable spatiotemporally controlled antibacterial action through light, allowing therapeutic effects to be confined to irradiated areas in an on-demand manner.[59–62] This synergy not only enhances efficacy but also minimizes off-target effects. The GDY-Fe@HA-DA hydrogel system integrates graphdiyne-iron (GDY-Fe)

nanosheets into a hyaluronic acid-dopamine (HA-DA) matrix. This composite exhibits high photothermal conversion efficiency, rapidly reaching 40–50 °C under low-power NIR irradiation (0.5 W cm^{-2}). Concurrently, under inflammatory acidic conditions (pH 5.5–6.5), the Fenton activity of the GDY-Fe nanosheets is markedly enhanced, promoting the generation of hydroxyl radicals (·OH) and oxygen (O_2). The ·OH effectively disrupts bacterial membranes (eg., in Porphyromonas gingivalis), while the O_2 release alleviates local hypoxia to suppress anaerobic bacteria. The HA-DA matrix forms a uniform, porous network through catechol-mediated cross-linking, providing excellent tissue adhesion, mechanical tunability, and a stable carrier for the GDY-Fe nanosheets. This design enables spatiotemporally synergistic antibacterial action through combined chemodynamic (CDT) and photothermal (PTT) therapies.[26]

Another representative system, AuAg@PC-Fe nanoparticles, utilizes a metal–phenolic network (MPN) coating strategy. The core consists of gold–silver alloy (AuAg) nanoparticles enveloped by a dense MPN layer formed through Fe^{3+}–catechol coordination. Under 808 nm near-infrared light (2.5 W cm^{-2}), the localized surface plasmon resonance effect of the AuAg alloy yields a pronounced photothermal effect, effectively eradicating pathogens via localized heating. The MPN coating further imparts enzyme-like antioxidant properties, scavenging excessive ROS and neutralizing $ABTS^{+}$ radicals, thereby mitigating oxidative stress and suppressing pro-inflammatory factor release. This dual photothermal–antioxidant functionality not only enhances the broad-spectrum antibacterial efficacy of the nanoparticles (achieving inhibition rates exceeding 90% against Escherichia coli and Staphylococcus aureus), but also modulates macrophage polarization from the M1 to M2 phenotype, supporting transition to a reparative inflammatory microenvironment.[63]

Li et al[38] synthesized a multifunctional yolk–shell nanozyme, Au@CeO_2-dimethyl fumarate (DMF). As shown in Figure 2, the complementary functions of gold and cerium dioxide confer potent photothermal modulation, with rapid heating under near-infrared irradiation, which promotes DMF release and augments the antioxidant activity of CeO_2. Au@CeO_2-DMF is capable of restoring mitochondrial function and rebalancing immune responses, thereby achieving sustained anti-inflammatory effects. In vivo studies have demonstrated that Au@CeO_2-DMF treatment suppresses inflammatory responses and promotes alveolar bone regeneration in models of periodontitis.

Photo-responsive nanozymes hold great promise for periodontitis therapy, but excessive generation of reactive oxygen species (ROS) may exacerbate local oxidative stress and pose risks to host cells. An ideal strategy is to endow nanozymes with a "switchable" function: generating ROS for potent bactericidal action under light irradiation, while scavenging ROS to alleviate inflammation and promote tissue repair in the absence of light. For example, Li X. et al[64]

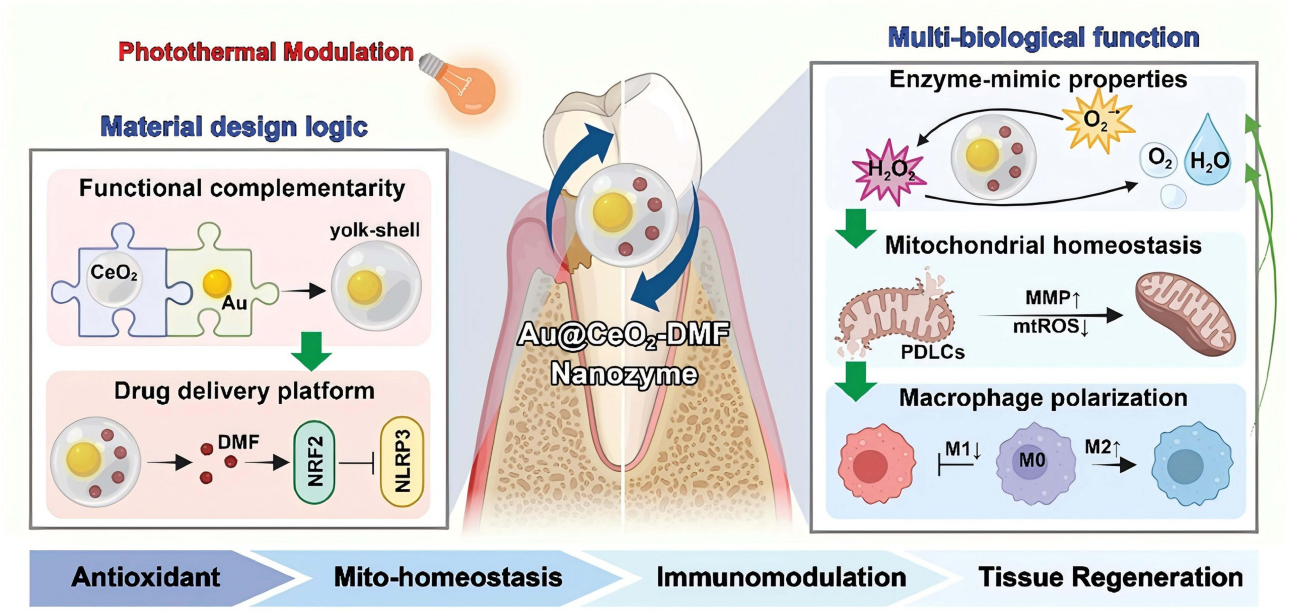

Figure 2 NIR-controlled material design of Au@CeO_2–DMF enabling triple-therapy for periodontitis via antioxidant activation, mitochondrial restoration, and immunomodulation. ↑ means significantly increased expression, ↓ means significantly decreased expression. Reproduced with permission from ref.[38] Copyright 2025, Wiley.

designed a near-infrared (NIR) light-responsive copper-cerium bimetallic oxide nanozyme ($CuCeO_2$). Under NIR irradiation, the nanozyme activates its peroxidase-like activity to produce ROS, which, together with the photothermal effect, achieves potent antibacterial activity against *Porphyromonas gingivalis*, with an inhibition rate of 98.69 ± 0.23% and a minimum inhibitory concentration (MIC) of 25 μg/mL. In the absence of NIR light, $CuCeO_2$ exhibits intrinsic enzyme-like activities that effectively scavenge ROS, alleviate cellular oxidative stress, and promote osteogenic differentiation. In vivo animal experiments demonstrate that $CuCeO_2$ significantly inhibits alveolar bone loss and shows excellent blood compatibility (hemolysis <5%). This dual-mode strategy, "ROS generation for sterilization under light, ROS scavenging for anti-inflammation without light", may represent a promising avenue for the clinical translation of photo-responsive nanozymes. Nevertheless, to advance toward clinical application, future efforts might focus on elucidating the precise mechanism underlying the switch between light-induced ROS production and dark-state ROS clearance. A deeper understanding of this mechanism could ultimately facilitate on-demand and accurate dual-mode switching.

Nanomotors for Enhanced Biofilm Penetration (Micro-Nanorobots)

The dense extracellular polymeric substance (EPS) matrix in biofilms presents a major barrier to penetration. To address this, nanozyme-based nanomotors are engineered with self-propulsion capabilities, which enhance their mobility and improve penetration through the biofilm.[65]

Chemical-Driven Nanomotors

Their propulsion leverages endogenous pathological fuels from the disease microenvironment, exemplified by elevated H_2O_2 in inflammatory sites. Researchers have developed a yolk-shell structured microrobot with a single-end opening, in which copper single atoms are anchored on carbon nitride (denoted as Y-CuSA/CN). This design enables self-propulsion by decomposing locally elevated hydrogen peroxide at inflammatory sites to generate oxygen bubbles. The microrobot achieves a velocity of 17.2 μm/s and a diffusion rate of 7.2 $\mu m^2/s$, significantly enhancing its biofilm penetration capability. During movement, it catalytically produces ROS, exerting potent antibacterial effects. Both in vitro and in vivo tests validated its efficacy in biofilm eradication.[66] In a separate study, sputter-fabricated Janus Ag–MnO_2 nanomotors, which propel via oxygen bubbles from catalytic H_2O_2 decomposition, demonstrated high bactericidal efficacy (>97%) against periodontal pathogens and effective treatment of periodontitis in mice.[67] Another research strategy combined targeting function with nanomotor activity by fabricating folic acid-modified, photosensitizer-loaded CeO_2 nanoparticles with dual specificity for bacteria and M1 macrophages. This system not only eliminates bacteria via PTT but also scavenges ROS and produces O_2 to enhance diffusion and ameliorate hypoxia. The clearance of ROS further induces a phenotypic switch in macrophages from M1 to M2, resulting in inflammation resolution and tissue regeneration.[68]

Light-Driven Nanomotors

These systems convert optical energy into autonomous motion through mechanisms such as self-thermophoresis and photothermally induced bubble propulsion. Self-thermophoresis occurs when asymmetric light absorption creates a temperature gradient, generating a thermophoretic flow from hotter to cooler regions that drives directional movement. Alternatively, intense photothermal effects can trigger the formation and ejection of gas bubbles—for instance, through localized thermal decomposition of surrounding media or onboard fuel—providing thrust via bubble recoil. Both mechanisms enable precise, fuel-free propulsion under remote optical control. For instance, the Janus-structured J-CeM@Au nanomotor utilizes asymmetrically modified gold nanoparticles to generate a pronounced thermophoretic effect under NIR irradiation (Figure 3). This propels the nanomotor at speeds up to 45 μm/s, and the resulting mechanical forces disrupt the biofilm EPS, increasing nanozyme penetration depth from 20 μm to 50 μm. The NIR laser provides the energy for propulsion and activates the nanomotor's antibacterial properties, allowing it to penetrate biofilms and kill bacteria. Additionally, the nanomotor's ability to scavenge ROS can modulate the immune response and create a regenerative environment, promoting the healing of periodontal tissue.[39]

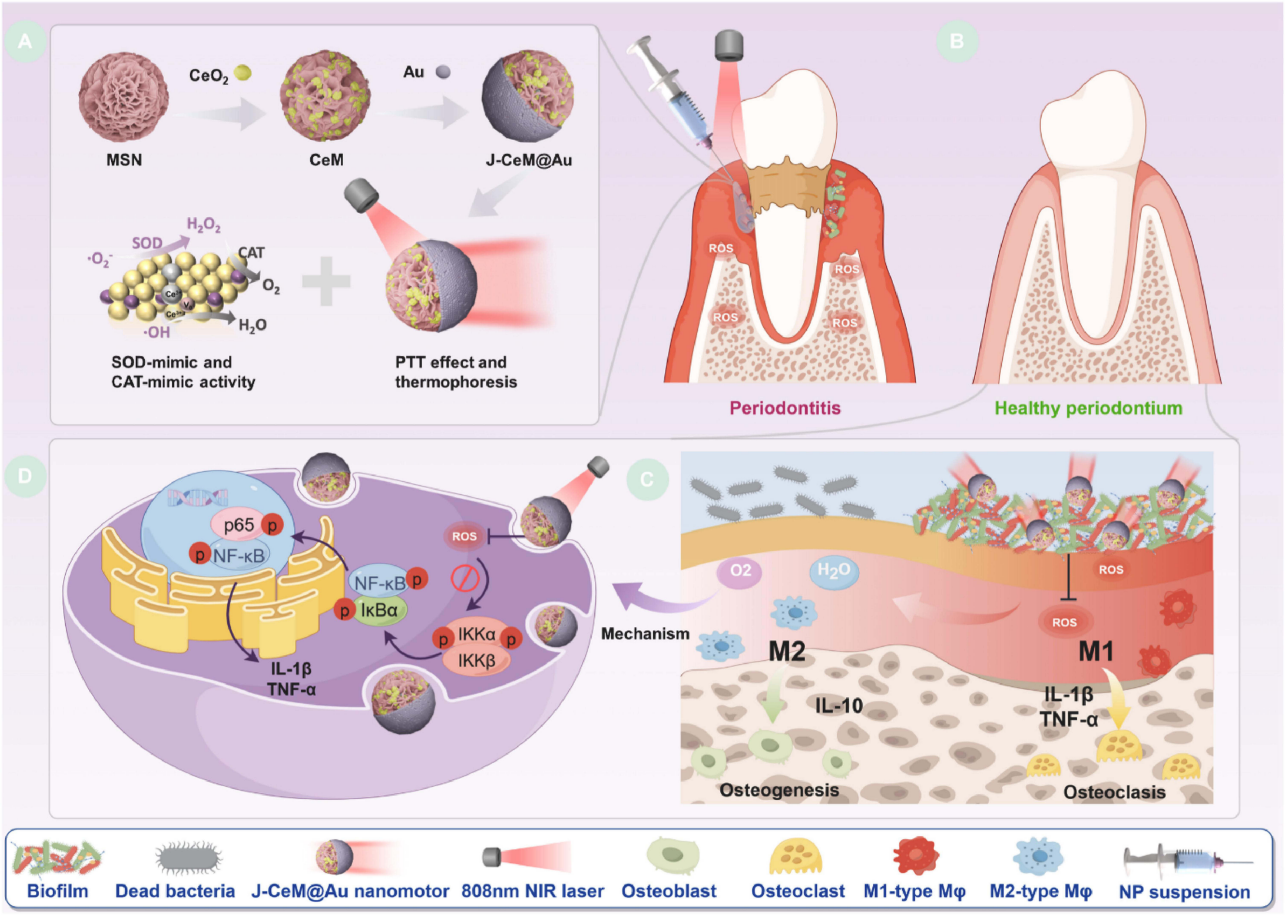

Figure 3 The synthesis process and therapeutic mechanism of J-CeM@Au. (**A**) Illustration for the preparation process of J-CeM@Au. (**B** and **C**) Illumination of the multifunctional J-CeM@Au for accelerating periodontitis healing by biofilm eradicating and ROS scavenging. (**D**) Mechanisms for the immunomodulation of J-CeM@Au. ↓ means reduced ROS levels. Adapted from ref,[39] published under the CC BY-NC-ND 4.0 license.

In another approach, sodium nitroprusside was incorporated into Prussian blue nanoparticles to construct an integrated system in which NIR-irradiated Prussian blue induces photothermal heating, accelerating nitric oxide release from sodium nitroprusside and enhancing biofilm penetration via gaseous propulsion. Combined with its inherent photothermal antibacterial activity, the system achieves potent antibacterial effects. Additionally, the ROS-scavenging capacity of Prussian blue contributes to immunomodulation and supports periodontal tissue regeneration.[69]

Despite the promising biofilm-penetrating ability of nanomotors in vitro, their clinical translation faces practical challenges. The limited availability of endogenous fuels (eg., H_2O_2) in the periodontitis microenvironment often fails to sustain self-propulsion, while light-driven systems alone are constrained by inadequate tissue penetration, making it difficult to activate nanomotors in deep periodontal pockets or furcation areas. To address these limitations, current research has been shifting toward synergistic strategies, such as constructing hybrid light–chemical propulsion systems that enable rapid activation in superficial tissues under near-infrared light while relying on local chemical fuels to sustain motion in deeper regions. Another complementary approach involves designing fuel self-supply systems, for instance, by loading glucose oxidase (GOx) onto nanomotors to convert locally abundant glucose into H_2O_2 in situ, thereby providing a continuous energy source.[70] These efforts are expected to enhance the adaptability and therapeutic efficacy of nanomotors within the complex in vivo environment.

Gas-Generating Nanozymes

The hypoxic microenvironment of periodontal pockets (pO_2 < 5 mmHg) fosters the growth of anaerobic bacteria such as Porphyromonas gingivalis, posing a significant challenge in periodontitis management. Gas-generating nanozymes have

emerged as an innovative strategy to reshape this microenvironment and enhance antibacterial efficacy by in situ gas production. Early efforts focused on augmenting local oxygen levels; for example, platinum nanoparticle-modified PCN-222 (Pt@PCN-222) leverages catalase-like activity to convert endogenous hydrogen peroxide into water and oxygen, thereby relieving hypoxia and promoting both photodynamic and peroxidase-like antibacterial activity. This dual mechanism not only suppresses anaerobic bacterial proliferation but also alleviates oxidative stress and supports tissue repair.[71]

To address the limitations of deep infection treatment, Wang et al[72] developed an integrated system (CeCycn-$Cu_{5.4}O$) comprising spontaneous oxygen-producing cyanobacteria as carriers for the photosensitizer Ce6, and ultrasmall catalase-mimicking $Cu_{5.4}O$ nanoparticles ($Cu_{5.4}O$ USNPs). The cyanobacteria continuously generate oxygen through photosynthesis, thereby overcoming the hypoxia limitation of traditional photodynamic therapy (PDT). This enhanced oxygen supply, combined with the catalase-like activity of $Cu_{5.4}O$ USNPs, enables effective anaerobic biofilm eradication upon laser irradiation and promotes rapid tissue repair, presenting a promising strategy for disinfecting deep periodontal pockets.

Beyond oxygen, other therapeutic gases such as carbon monoxide (CO), nitric oxide (NO), molecular hydrogen (H2), and hydrogen sulphide (H_2S) have demonstrated potential in periodontal therapy.[73] Researchers have engineered nanozyme platforms capable of controlled, localized gas release, often integrating photodynamic or photothermal modalities for spatiotemporal precision. Such multimodal designs offer synergistic antibacterial, anti-inflammatory, and tissue-reparative benefits, which are particularly advantageous for drug-resistant periodontitis.

A notable example is the carbon monoxide-enhanced multienzyme hybrid platform (MSN-Au@CO), comprising gold nanoparticles conjugated to mesoporous silica and loaded with a carbonyl manganese CO donor.[40] The gold nanoparticles exhibit glucose oxidase-like activity, generating hydrogen peroxide and gluconic acid, followed by peroxidase-like conversion of H_2O_2 into hydroxyl radicals for effective bacterial killing. Simultaneously, H_2O_2 triggers CO release, which inhibits bacterial respiration and further enhances therapeutic efficacy, as demonstrated in diabetic periodontitis models (Figure 4).

Hydrogen sulphide-based systems have also shown promise. Li et al[74] synthesized a mesoporous silica-copper composite (DM/Cu^{2+}-CuS), which responds to glutathione in the biofilm microenvironment for selective H_2S release. This design ensures controlled peroxidase-like and bactericidal activity while the generated H_2S modulates inflammation

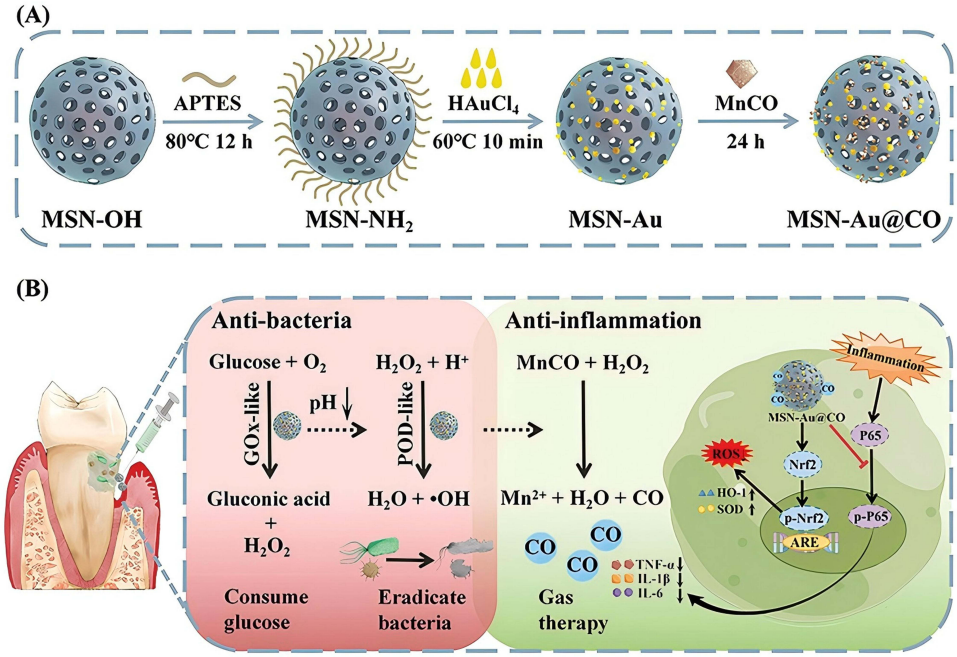

Figure 4 (**A**) Schematic illustration of the construction of MSN-Au@CO. (**B**) The mechanisms of the cascade reaction present antibacterial and antiinflammation effects in the treatment of diabetic periodontitis. In the nanozyme cascade reaction, MSN-Au@CO consumes glucose to generate ˙OH, which eradicates periodontal bacteria. In addition, the resultant CO enhances MSN-Au to reduce inflammation by inhibiting P65 nuclear translocation and increasing the antioxidant ability by promoting Nrf2 nuclear translocation. ↑ means significantly increased expression, ↓ means significantly decreased expression. Reproduced with permission from ref.[40] Copyright 2024, Wiley.

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and, together with copper ions, promote angiogenesis. However, excessive gas release poses risks of toxicity and adverse effects such as cellular damage. To mitigate this, controlled-release strategies, such as pH-responsive MOFs loaded with CO-releasing molecules, are being developed to ensure effective antibacterial action without exceeding safe gas concentrations.[75]

Clinical Relevance and Future Perspectives

To accurately assess the translational potential of functionalized nanozymes for periodontitis treatment, they should be compared not only with conventional mechanical debridement and antibiotics but also with other non-traditional strategies that have a longer history of clinical translation. Antimicrobial peptides (eg., LL-37) exhibit rapid bactericidal activity and immunomodulatory effects but suffer from high production costs, susceptibility to protease degradation, short half-life, inhibition by physiological salt concentrations and saliva, as well as cytotoxicity.[76,77] Photodynamic therapy alone relies on an external light source with limited tissue penetration, requires repeated treatments, shows inconsistent efficacy against key pathogens, and cannot directly modulate inflammation or promote bone regeneration.[78,79] Probiotics/postbiotics (eg., *Lactobacillus reuteri*) may modestly improve bleeding on probing and clinical attachment levels, but their effects are highly strain-specific, diminish after discontinuation, and lack ROS-scavenging or osteogenic capacity.[80,81] Other established nanomaterial strategies, such as chlorhexidine-loaded mesoporous silica, enable sustained local release and enhanced biofilm penetration but lack intrinsic multi-enzyme activity.[82] By contrast, functionalized nanozymes—particularly nanomotors and cascade catalytic systems—integrate deep biofilm penetration, ROS scavenging, immune microenvironment remodeling, and pro-osteogenic activity into a single platform, offering unique advantages in the full-course regulation of periodontitis. Nevertheless, their clinical translation faces major challenges, including insufficient long-term biosafety, potential cumulative toxicity of metal ions, unclear metabolic clearance pathways, and the absence of standardized toxicological evaluation frameworks.[17,83] For example, accumulation of metal ions such as Cu^{2+} can trigger local toxic responses, including NLRP3 inflammasome activation and apoptosis of gingival epithelial cells.[84] Although the use of degradable carriers, biomimetic coatings, and natural biomaterials (eg., chitosan, hyaluronic acid) may mitigate toxicity risks to some extent, a systematic framework to assess the dose-dependent effects of nanozymes on immunomodulation is still lacking, and their metabolic clearance via hepatic and renal pathways remains to be elucidated.

Moreover, despite the encouraging preclinical findings, several methodological limitations must be acknowledged when interpreting these results. First, most studies employ small sample sizes, increasing the risk of type I and type II errors. Second, follow-up durations are almost uniformly short (≤4 weeks), insufficient to assess long-term biosafety, material degradation kinetics, or the stability of alveolar bone regeneration. Third, the majority of studies use only phosphate-buffered saline or untreated controls, lacking head-to-head comparisons with established clinical therapies (eg., mechanical debridement, chlorhexidine mouthwash, or locally delivered minocycline gel). Consequently, the relative therapeutic advantages of nanozyme platforms remain unclear. Fourth, the complexity of multi-component nanozyme synthesis raises concerns about inter-laboratory batch-to-batch reproducibility and scalability, yet few studies report inter-batch consistency data. These limitations do not negate the potential value of nanozymes but highlight the urgent need for more rigorous, standardized, and translationally oriented preclinical evaluation systems.

Based on the preclinical evidence, we propose a preliminary clinical translation framework that considers the unique anatomical and pathological features of periodontitis. First-in-human trials could prioritize patients with refractory chronic periodontitis who respond poorly to conventional mechanical debridement and antibiotics. Local administration into the periodontal pocket is preferred over systemic delivery to maximize local catalytic activity while minimizing off-target toxicity. A single-administration, dose-escalation Phase 0/I trial using an injectable biodegradable hydrogel formulation may be considered. The dose should be carefully titrated according to the limited volume of the periodontal pocket to ensure sustained catalytic activity, prevent excessive metal ion release, and avoid systemic exposure. This localized, low-dose, biodegradable delivery strategy appears to offer a potentially safe and feasible pathway for the clinical translation of functionalized nanozymes.

Smarter, More Precise Nanozyme Systems

- Multi-mode responsive systems: Integrate nanozyme units with NIR light, ultrasound or magnetic field triggers to realize spatiotemporal catalytic switch; guided by pathological pH, ROS and bacterial concentration in periodontal pocket, the catalytic antibacterial/antioxidant function is selectively turned on only at lesion sites, avoiding off-target injury to normal gingival tissue.[85]
- Closed-loop platforms: Developing "smart" theranostic systems that sense disease biomarkers (eg., MMP-8, IL-1β) in real time, responsively activate catalytic functions, and adjust therapy based on feedback will create truly dynamic and personalized treatments.

Rational Design and Green Synthesis

- Artificial intelligence and machine learning: Artificial intelligence has become a powerful driving force in the advancement of nanobiomedicine.[86,87] Computational methods such as machine learning that simulate the relationship between nanozyme structure and activity can accelerate the design process, enabling rapid, high-throughput screening of novel and efficient nanozymes.[88,89]
- Green manufacturing: Replace toxic organic solvents with water-phase natural ligand (tannic acid, chitosan) synthesis routes; adopt room-temperature mild preparation to lower production cost and facilitate subsequent clinical batch production.

Advanced Delivery Systems and Biocompatibility

- Formulations compatible with dental devices: Creating nanozyme formulations compatible with dental devices (eg., injectable hydrogels, light-responsive patches) ensures local enrichment at the lesion site.
- Long-term biosafety assessment: Establishing standardized systems for evaluating the long-term biosafety of nanozymes, including their effects on the immune system, metabolic clearance pathways, and potential systemic toxicity.

Ultimately, only through deep cross-disciplinary integration of materials science, catalytic engineering, clinical dentistry, and bioinformatics can functionalized nanozymes be truly upgraded from "broad-spectrum antibacterial and anti-inflammatory" agents to "precision periodontal microenvironment remodeling platforms." By leveraging local targeted delivery, smart responsive release, deep biofilm penetration, and standardized safety evaluation, nanozymes hold the potential to achieve synergistic coupling of infection control, inflammation resolution, and bone regeneration, thereby providing a next-generation precision regenerative strategy for refractory periodontitis.

Conclusion

Among the various nanozyme architectures for periodontitis treatment, motor-based composite nanozymes may represent one of the more translation-ready candidates. Leveraging self-propulsive capability, these nanozymes have demonstrated promising biofilm-penetrating ability in preclinical models, effectively overcoming the anatomical complexity of periodontal pockets and resolving the dilemma that conventional therapeutic agents cannot efficiently reach deep lesion sites. Beyond deep penetration, their integrated multifunctional design enables concurrent antibacterial action, ROS scavenging, modulation of macrophage M2 polarization, and promotion of alveolar bone regeneration, suggesting a potential advantage for comprehensive periodontal intervention. Nevertheless, long-term biosafety, especially the chronic bioaccumulation of metal ions, remains the single most pressing bottleneck hindering clinical translation. Addressing this critical challenge requires sustained and robust interdisciplinary collaboration across materials science, stomatology, and translational medicine to optimize structural design, degradability, and in vivo metabolic clearance. From a clinical perspective, patients with drug-resistant refractory periodontitis represent the most appropriate cohort for future pilot clinical trials. Based on the continuous optimization of materials and the gradual establishment of standardized safety evaluation frameworks, such nanozyme platforms may offer new perspectives for precision therapy in this patient population.

Abbreviations

ATP, Adenosine triphosphate; AuNPs, Gold nanoparticles; Bi, Bismuth; BMSCs, Bone marrow mesenchymal stem cell(s); BSA, Bovine serum albumin; CAT, Catalase; CDT, Chemical dynamic therapy; CeO_2, Cerium dioxide; CeO_2 NPs, Cerium oxide nanoparticles; circRNA, circular RNA; CNM(s), Carbon-based nanozyme(s); CO, Carbon monoxide; CQD(s), Carbon quantum dot(s); CRNCs, Copper–ruthenium nano-capsule(s); CuNZs, Copper-based nanozyme(s); DMF, Dimethyl fumarate; ETA, Electron transfer activity; EPS, Extracellular polymeric substance; FA, Folic acid; Fe_3O_4, Triiron tetraoxide; GPx, Glutathione peroxidase; GDY, Graphdiyne; GO, Graphene oxide; GQD(s), Graphene quantum dot(s); H_2O_2, Hydrogen peroxide; H_2S, Hydrogen sulphide; HMUiO-66, Hierarchical mesoporous MOF; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-alpha; MMP-9, Matrix metalloproteinase; MNOF(s), Metal–organic framework-based nanozyme(s); MNP(s), Metal-based nanozyme(s); MOF(s), Metal-organic framework(s); MPN, Metal–phenolic network; NIR, Near-infrared; NO, Nitric oxide; OMVs, Outer membrane vesicle(s); PAMP, Pathogen-associated molecular pattern; PCFs, 2TT-mC6B@CeO_2@FA nanoparticles; PDT – Photodynamic therapy; pH, potential of hydrogen; POD, Peroxidase; PTA, Photothermal agent(s); PTT, Photothermal therapy; QD(s), Quantum dot(s); ROS, Reactive oxygen species; SalB, Salvianolic acid B; SEM, Scanning electron microscopy; SOD, Superoxide dismutase; SQD(s), Sulfur quantum dot(s); TA, Tannic acid; TMA, Tyramine–methacrylamide; UBI29–41, Ubiquitin 29–41; UiO-66(Ce), Cerium-based metal–organic framework; $^{\cdot}O_2^-$, Superoxide anions; $^{\cdot}OH$, Hydroxyl radicals.

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Disclosure

The authors report no conflicts of interest in this work.

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