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Nanozymes-Enabled Advanced Healthcare Materials

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In recent years, the field of nanozyme research has experienced exponential growth, driven by the quest to develop robust, cost-effective, and multifunctional alternatives to natural enzymes. Nanozymes, defined as nanomaterials with intrinsic enzyme-mimicking catalytic activities, have emerged as versatile tools in biomedical applications, addressing critical challenges in disease diagnosis, prevention, and treatment. The ability of these materials to operate under harsh and complicated physiological conditions, combined with their tunable catalytic properties and ease of functionalization, has opened new frontiers in healthcare and nanomedicine.

Advances in nanotechnology and materials science have significantly contributed to the understanding and enhancement of nanozyme functions. The research and design of nanozymes have shifted focus from serendipitous discoveries toward more systematic approaches, leveraging machine learning, theoretical calculations, and mechanistic studies to design nanomaterial structures with tailored catalytic functionalities. As summarized by Fan et al. (202401576), computational modeling now plays a pivotal role in predicting and designing the properties of nanozymes, facilitating the demand-driven creation of nanozymes with improved catalytic efficiency for specific biomedical applications. Furthermore, Zong et al. (202401836) emphasized the fundamental role of electron transfer, a core mechanism in chemical reactions and enzymatic catalysis, in the design and synthesis of nanozymes. They explored strategies to modulate electron transfer processes, providing insights into how these adjustments can precisely regulate the catalytic activity and specificity of nanozymes. Optimizing preparation methods, simplifying synthesis processes, and enhancing nanoscale precision control are crucial for the further development of nanozymes. Metal–organic frameworks (MOFs), featuring porous structures formed by the coordination of metal ions or clusters with organic ligands, offer unique advantages such as tunable structures, high specific surface areas, and porous channels. Zhao et al. (202402066) reviewed the methodologies for utilizing MOF materials as multifunctional building blocks to construct nanozymes and discussed their potential applications in biomedicine. Furthermore, Yu et al. (202402630) focused specifically on Fe—MOFs, highlighting recent advancements in synthesis routes, surface engineering, and shaping techniques. Reaction selectivity is critical for ensuring precise catalysis in the presence of multiple substrates and products. Novel approaches, such as heterojunction strategies and hybrid materials, have been employed to fine-tune the catalytic selectivity of nanozymes. For example, Co_3O_4-MnO_2 systems have demonstrated selective peroxidase (POD)- and catalase (CAT)-like activities (202400401), whereas high-entropy alloy nanozymes with diverse active sites show promise in redox regulation and inflammation control (202402005).

Since their discovery, nanozymes have evolved from simple enzyme-mimicking particles to sophisticated multifunctional systems capable of mimicking complex enzymatic cascades. For example, Liu et al. (202401581) designed an ultrasmall $Ce_{12}V_6$ cluster exhibiting excellent glutathione peroxidase (GPx)-, superoxide dismutase (SOD)-, and POD-like activities, which has a remarkable ability to scavenge reactive oxygen species (ROS). Multiple enzyme-induced cascade catalysts are particularly critical for managing complex pathological conditions, such as wound healing, which involves multiple stages, including hemostasis, inflammation, proliferation, and remodeling. To address this issue, Huang et al. (202402393) developed a novel H_2O_2 self-supplying nanocomposite (M/C/AEK) comprising MoS_2 decorated with CaO_2 synthesized at ambient temperature and encapsulated in an AEK hydrogel. The MoS_2/CaO_2 nanocomposite induces cascade POD-like and CAT-like activities to generate toxic hydroxyl radicals, while the released Ca^{2+} ions and keratin facilitate the healing process. In a different approach, Gao et al. (202401580) encapsulated aFGF within MnO_2—Au—$mSiO_2$@Janus nanoparticles and formulated them into a hydrogel. This nanozyme system effectively mimics CAT and SOD activities, catalyzing the decomposition of ROS while generating oxygen. Furthermore, the controlled release of aFGF promotes tissue regeneration and angiogenesis, facilitating the transition of wounds from the inflammatory phase to the proliferative phase. The efficacy of the

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hydrogel in modulating macrophage polarization, enhancing fibroblast proliferation, and stimulating angiogenesis has been experimentally validated, thereby significantly promoting diabetic wound healing. As research on multienzyme cascades continues to advance, Cai et al. (202401834) summarized and discussed the application of immobilized multienzyme/nanozyme cascade catalysis in biosensing. Additionally, Cao et al. (202402372) expanded the concept of multienzyme cascade catalysis into artificial cascade catalytic systems and introduced the novel concept of "mimicomes" for the first time. This review comprehensively outlines the evolution and development of different types of mimicomes over recent decades, highlights the persistent challenges in multifunctional mimicry design, and discusses their potential applications, offering valuable insights into their future prospects.

Owing to their high catalytic efficiency, stability, cost-effectiveness, and scalability, nanozymes exhibit tremendous potential in fields such as medicine, the chemical industry, food, agriculture, and the environment. In this special issue, we focus primarily on the biomedical applications of nanozymes, particularly in disease diagnosis and therapy. Shao et al. (202401677) demonstrated that, compared with traditional Au—NPs, the POD-like catalytic activity of PGM—NPs significantly enhances the detection sensitivity of PGM—NP-based colorimetric lateral flow assays (CLFAs). This improvement in sensitivity is particularly crucial for disease diagnosis, as the concentration of corresponding biomarkers is often extremely low in the early stages of disease. In addition to CLFA, these nanozymes can be integrated with other biological components for target detection. Tian et al. (202401630) reviewed representative applications of nanozyme-molecule conjugates in disease diagnosis, highlighting emerging trends in nanozyme-supported biomedical diagnostics and addressing associated challenges.

Nanozymes can be divided into two categories on the basis of their overall catalytic effects: antioxidant nanozymes and pro-oxidant nanozymes. Antioxidant nanozymes, such as those with SOD-like and CAT-like activities, are suitable for treating pathological conditions associated with oxidative stress, such as neuroinflammation (202401607), oxalate kidney stones (202401574), and inflammatory bowel disease (202401994). Moreover, Shi et al. (202402763) designed MnO_x nanozymes modified with the polyphenol tannic acid and loaded them with the natural thrombolytic agent nattokinase, which possesses dual thrombolytic and antioxidant functions and has demonstrated significant protective effects in mouse models of myocardial infarction. Furthermore, many ocular diseases, such as dry eye disease, age-related macular degeneration, and glaucoma, are associated with high levels of oxidative stress and inflammation. In this context, Wong et al. (202401309) discussed recent advances in elucidating the applications of nanozymes in ocular therapy and their integration with soft materials, such as MNs, for disease management. Pro-oxidative nanozymes primarily exert their therapeutic effects by promoting the generation of ROS for tumor eradication and antibacterial applications. For example, Zhang et al. (202401362) developed a biomimetic SAE drug delivery system combined with cold exposure (CE) therapy. In this system, BPTES was loaded into mesoporous Fe-SAEs, and the compounds were encapsulated within a platelet membrane. Owing to the POD activity of the Fe-SAEs, oxidative stress was increased by the catalysis of the conversion of H_2O_2 into hydroxyl radicals. Simultaneously, the "dual starvation" effect induced by CE therapy and BPTES comprehensively inhibited the glucose supply, leading to reduced levels of glucose, adenosine triphosphate, and glutathione in the tumor microenvironment, thereby increasing the cytotoxic potential of ROS. Moreover, Li et al. (202400596) developed a catalytic nanozyme, RPC@M, using naturally derived cobalt phytate and resveratrol (Res). This nanozyme not only facilitates the breakdown of water in the tumor stroma under photoactivation to reduce tumor interstitial fluid pressure but also contributes to reducing collagen deposition, thereby decreasing tumor interstitial stromal pressure and enhancing tumor permeability. Furthermore, through its POD-like activity, the nanozyme generated abundant ROS to exert cytotoxic effects on tumor cells.

For antibacterial applications, Dong et al. (202401657) proposed a near-infrared (NIR) light-driven nanofiber membrane combining phytomedicine and nanozymes for antibiotic-free triple synergistic therapy targeting various microbial wound infections. Zhang et al. (202401602) introduced glucose-modified MoO_x (G-MoO_x) as an electron donor to reduce Ag ions, and then, Ag NPs are spontaneously deposited onto the surface of the G-MoO^+_x nanozyme without extra additives. The incorporation of Ag NPs enhances the photothermal effect and ROS generation under NIR irradiation, resulting in excellent antibacterial activity. Furthermore, Zang et al. (202401810) designed a Bi_2Se_3/PAAS hydrogel that not only demonstrated exceptionally high antibacterial activity under NIR light but also improved endothelial cell functionality, regulated glucose and lipid metabolism, and promoted the healing of infected wounds. Some studies have explored the application of nanozymes in antimicrobial strategies under specific conditions. For example, Xie et al. (202402363) designed and fabricated an intelligent hydrogel capable of responding to bacterial infection and a persistent inflammatory microenvironment, thereby remodeling and regenerating the environment to treat infectious pressure ulcers. Additionally, Tran et al. (202402306) introduced a nanozyme-shell microrobot platform that employs magnetic microcapsules with collective and adaptive mobility. These microcapsules exhibit high peroxidase-like activity, effectively catalyzing the generation of ROS from hydrogen peroxide. Notably, the microcapsule components demonstrate significant collective navigation within arching and branching constraints, enabling precise targeting of the apical region of dental roots to exert antibiofilm effects. Given the rapid development of bacterial resistance and the slow progress in new antibiotic discovery, the effectiveness of traditional antibiotics has been diminishing, necessitating innovative strategies. Xie et al. (202402659) reviewed recent advances in the application of nanozymes to combat bacterial resistance, emphasizing their design, structural characteristics, applications in combination therapy, and future prospects.

With the continuous discovery of nanozymes possessing unique biocatalytic activities, research on the in vivo applications of nanozymes has expanded from ROS regulation, which primarily involves oxidoreductase activity, to broader domains. Mouli et al. (202401629) synthesized deferoxamine, an iron chelator covalently linked to (oxidized carbon nanoparticles) OCNs, which utilizes the OCN-catalyzed reduction of NADH to NAD. This process promotes glycolytic flux and enhances mitochondrial energy under impaired conditions, thereby providing a metabolic

regulation-based therapeutic approach for traumatic brain injury. Furthermore, Li et al. (202402785) provided a comprehensive overview of NADH oxidase (NOX) nanozymes, detailing their types, functional mechanisms, biomedical applications, and future research prospects. They also discussed key challenges and directions in the development of NOX nanozymes. Another intriguing review by Swinnen et al. (202401547) highlighted the tunable properties of MOFs, which can be seamlessly integrated into proteomics workflows, facilitating applications such as protein separation, peptide enrichment, and mass spectrometry ionization.

This special issue underscores the critical role of nanozymes in biomedical research and their vast potential for transforming healthcare. The contributions featured here provide valuable insights into current trends and future directions, fostering collaboration across materials science, biochemistry, and medicine. We hope that this collection inspires further innovation in nanozyme development and application, ultimately enhancing patient care and advancing medical science.

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Conflict of Interest

The authors declare no conflict of interest.

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