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Nanozymes as Emerging Catalytic Nanomaterials for Tissue Engineering and Regenerative Medicine

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Abstract

Tissue engineering and regenerative medicine have advanced considerably through biomaterial-based strategies, yet conventional biomaterials often lack the ability to actively regulate the regenerative microenvironment. Excessive oxidative stress, chronic inflammation, bacterial infection, and poor vascularization remain major obstacles to successful tissue repair. Nanozymes have recently emerged as promising catalytic nanomaterials that mimic natural enzymes while offering high stability, tunable catalytic activity, and easy synthesis. Their enzyme-like activities regulate reactive oxygen species, oxygen homeostasis, immune responses, and antibacterial processes, thereby promoting tissue regeneration. Incorporating nanozymes into biomaterials such as hydrogels, electrospun fibers, injectable matrices, and 3D-printed scaffolds combines structural support with dynamic catalytic functions. This review summarizes advances in nanozyme-based biomaterials, emphasizing catalytic mechanisms, scaffold integration, and applications in bone, skin, cartilage, neural, cardiac, and vascular tissue engineering. It also discusses current challenges, including biosafety, catalytic control, scalable production, and clinical translation, while highlighting future opportunities for multifunctional nanozymes and intelligent biomaterials.

Keywords: Nanozymes; Tissue engineering; Regenerative medicine; Catalytic biomaterials; Reactive oxygen species; Hydrogels

1. Introduction

Tissue engineering and regenerative medicine have emerged as interdisciplinary fields that integrate biomaterials, stem cells, engineering technologies, and molecular biology to repair or regenerate damaged tissues and organs. Unlike conventional therapies that mainly alleviate symptoms, regenerative strategies aim to restore tissue function by recreating a favorable microenvironment that regulates cell behavior, extracellular matrix (ECM) remodeling, angiogenesis, and immune responses [1].

Over the past two decades, significant advances have been made in the development of biomaterial-based scaffolds, including hydrogels, electrospun nanofibers, porous ceramics, biodegradable polymers, and three-dimensional (3D)-printed constructs [2-4]. These scaffolds provide structural support for cell adhesion and proliferation while serving as carriers for bioactive molecules. However, most conventional biomaterials remain biologically passive and have limited ability to respond to the dynamic microenvironment after implantation [5-7].

Following tissue injury, excessive production of reactive oxygen species (ROS), inflammatory cell infiltration, bacterial infection, and insufficient vascularization create a hostile microenvironment that compromises tissue regeneration. Although physiological levels of ROS participate in intracellular signaling, prolonged oxidative stress induces DNA damage, mitochondrial dysfunction, extracellular matrix degradation, and chronic inflammation, ultimately impairing tissue repair. In addition, hypoxia resulting from poor vascularization reduces stem cell survival, inhibits angiogenesis, and delays tissue remodeling, particularly in large engineered tissues and chronic wounds [8,9].

These limitations have shifted the focus from passive scaffolds toward bioactive biomaterials capable of actively regulating the regenerative microenvironment. Among these strategies, nanozymes have attracted considerable attention as artificial enzyme-like nanomaterials with intrinsic catalytic activities [10, 11]. Since the discovery of the peroxidase-like activity of Fe_3O_4 nanoparticles in 2007 [12], nanozymes have rapidly evolved into an important class of catalytic nanomaterials owing to their high stability, tunable catalytic properties, cost-effective synthesis, and structural versatility [13, 14]. Depending on their composition and surface engineering, nanozymes can mimic the activities of catalase (CAT), superoxide dismutase (SOD), peroxidase (POD), oxidase (OXD), glutathione peroxidase (GPx), and several other natural enzymes, enabling them to regulate oxidative stress, generate oxygen, eliminate pathogens, and modulate inflammatory signaling [15].

Compared with natural enzymes, nanozymes exhibit superior physicochemical stability, longer biological activity, and greater resistance to harsh environmental conditions, making them attractive candidates for regenerative medicine [10,16]. More importantly, their integration into biomaterials such as hydrogels, electrospun fibers, bioinks, cryogels, and 3D-printed scaffolds has led to the development of multifunctional catalytic platforms capable of continuously regulating the local microenvironment. Recent studies have demonstrated that nanozyme-based biomaterials can promote angiogenesis, enhance stem cell survival, stimulate macrophage polarization toward the pro-regenerative M2 phenotype, reduce bacterial infection, and facilitate extracellular matrix remodeling, thereby improving the repair of bone, skin, cartilage, neural, and cardiovascular tissues [17-19].

Although numerous reviews have discussed the physicochemical characteristics or general biomedical applications of nanozymes, their specific roles as catalytic components in tissue engineering remain less comprehensively addressed. Therefore, this

review summarizes the classification, catalytic mechanisms, and biological functions of nanozymes, with particular emphasis on their incorporation into advanced biomaterials for tissue engineering and regenerative medicine. In addition, current challenges, recent advances, and future perspectives for the clinical translation of nanozyme-based regenerative therapies are discussed.

2. Nanozymes: Definition, Classification and Catalytic Mechanisms

2.1 Evolution and Fundamental Characteristics of Nanozymes

Natural enzymes are highly efficient biocatalysts that regulate nearly all physiological processes through remarkable substrate specificity and catalytic activity. However, their clinical application is often limited by poor stability, susceptibility to denaturation, high production costs, and short biological half-life, particularly under complex physiological conditions. These limitations have encouraged the development of artificial enzyme mimics with improved stability and broader biomedical applicability [20-22].

A major milestone in this field was achieved in 2007 when Gao and co-workers [12] reported that magnetite (Fe_3O_4) nanoparticles possess intrinsic peroxidase-like activity comparable to horseradish peroxidase. This discovery introduced the concept of nanozymes, nanostructured materials capable of catalyzing enzyme-like reactions without incorporating biological enzymes. Since then, nanozymes have attracted increasing attention owing to their excellent physicochemical stability, scalable synthesis, tunable catalytic properties, and structural diversity, making them promising alternatives to natural enzymes in biomedical applications [14, 16] (Fig. 1).

Unlike conventional nanomaterials that primarily serve as passive carriers or structural components, nanozymes actively participate in catalytic reactions within the biological microenvironment. Through rational control of composition, morphology, crystal structure, surface chemistry, and defect engineering, their catalytic performance can be precisely tailored for different therapeutic purposes. Consequently, nanozymes have evolved from simple enzyme substitutes into multifunctional catalytic nanoplatforms with applications ranging from biosensing and antimicrobial therapy to cancer treatment and regenerative medicine [23,24].

2.2 Classification of Nanozymes Based on Catalytic Activity

Nanozymes are commonly classified according to the enzyme activity they mimic (Fig. 2), which is also the most practical classification for biomedical and tissue engineering applications [25,26].

Peroxidase (POD)-like nanozymes, represented by iron oxide nanoparticles [27], copper oxide nanostructures [28], vanadium oxide nanowires [29], and metal–organic framework (MOF)-based systems [30], catalyze substrate oxidation in the presence of hydrogen peroxide. Their ability to generate reactive intermediates has been extensively exploited for antibacterial therapy, biosensing, and infection control in regenerative biomaterials.

Catalase (CAT)-like nanozymes decompose hydrogen peroxide into water and oxygen, thereby reducing oxidative stress while simultaneously relieving local hypoxia. Cerium oxide [31], manganese dioxide [32], platinum nanoparticles [33], and Prussian Blue nanozymes [34] are among the most extensively studied catalysts in this category and have shown considerable promise for enhancing angiogenesis and tissue regeneration.

Superoxide dismutase (SOD)-like nanozymes convert superoxide radicals into less reactive species, protecting cells against oxidative damage. Cerium oxide and manganese oxide nanoparticles are particularly attractive

because they exhibit both SOD- and CAT-like activities, enabling efficient regulation of intracellular redox homeostasis [35].

Other nanozymes exhibit oxidase (OXD)- or glutathione peroxidase (GPx)-like activities, contributing to antibacterial effects, maintenance of redox balance, and mitochondrial protection. Because many nanozymes possess multiple enzyme-like activities simultaneously, they can regulate several biological pathways through coordinated catalytic processes rather than a single reaction mechanism [36].

2.3 Classification of Nanozymes Based on Their Composition

The rapid advancement in nanozyme research has catalyzed the emergence of innovative nanozyme materials. These can be categorized into four main types: metal compound nanozymes, metallic nanozymes, carbon-based nanozymes, and organic framework nanozymes (Fig. 3) [37]. The catalytic mechanism of metal compound nanozymes primarily stems from variations in the redox potential, whereas the activity of metallic and carbon-based nanozymes largely depends on surface-mediated adsorption, activation of catalytic substrates, and electron transfer processes. In contrast, the catalytic performance of organic framework nanozymes is heavily reliant on their porous architectures, the spatial distribution of active sites, and their capabilities in electron transfer.

2.4 Catalytic Mechanisms and Factors Affecting Nanozyme Activity

The catalytic behavior of nanozymes differs fundamentally from that of conventional nanoparticles because they actively accelerate biochemical reactions by facilitating electron transfer and reducing activation energy. Depending on their composition, catalytic activity may arise from reversible redox cycling between different oxidation states, oxygen-vacancy-mediated reactions, Fenton or Fenton-like chemistry, and efficient adsorption and activation of substrate molecules [14,15].

For example, cerium oxide nanozymes continuously switch between Ce^{3+} and Ce^{4+} states, allowing sustained scavenging of reactive oxygen species, whereas manganese dioxide nanozymes catalyze hydrogen peroxide decomposition to generate oxygen under hypoxic conditions (Fig. 4). Iron oxide nanozymes mainly exhibit peroxidase-like activity through Fenton-related reactions and are widely investigated for antibacterial and catalytic therapeutic applications (Fig. 5) [38].

The catalytic efficiency of nanozymes is strongly influenced by particle size, morphology, crystal structure, surface area, oxygen vacancies, elemental doping, and surface functionalization. These parameters regulate substrate adsorption, electron transfer efficiency, and reaction kinetics, providing opportunities to optimize catalytic performance for specific regenerative applications [14,15,39].

2.5 Nanozymes as Catalytic Biomaterials for Tissue Engineering

Recent advances in tissue engineering have shifted biomaterial design from passive structural scaffolds toward catalytically active systems capable of regulating the biological microenvironment. In this context, nanozymes have emerged as key functional components because they continuously modulate oxidative stress, oxygen availability, inflammatory signaling, and antimicrobial activity through enzyme-like catalytic reactions [40].

Integration of nanozymes into hydrogels, electrospun nanofibers, bioinks, cryogels, and 3D printed scaffolds has enabled the development of multifunctional biomaterials that not only provide mechanical support but also actively direct cellular behavior. By reducing oxidative damage, promoting angiogenesis, regulating macrophage polarization, and enhancing extracellular matrix remodeling, these catalytic

biomaterials establish a regenerative microenvironment that favors functional tissue repair. This concept, often referred to as “catalytic microenvironment engineering”, represents a promising strategy for developing the next generation of intelligent biomaterials for regenerative medicine [17,41,42].

3. Catalytic Mechanisms of Nanozymes in Tissue Engineering

3.1 Reactive Oxygen Species (ROS) Scavenging

Maintaining redox homeostasis is essential for successful tissue regeneration. Under physiological conditions, ROS act as signaling molecules that regulate cell proliferation, migration, differentiation, and tissue remodeling. However, excessive ROS production after tissue injury or inflammation disrupts this balance, leading to oxidative stress that damages proteins, lipids, DNA, and mitochondria. Persistent oxidative stress also impairs stem cell viability, suppresses ECM synthesis, inhibits angiogenesis, and prolongs inflammation, ultimately compromising tissue repair [43].

Although endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) play key roles in maintaining cellular redox balance, their therapeutic application is restricted by poor stability, rapid degradation, and limited activity under physiological conditions. Nanozymes have emerged as attractive alternatives because they retain enzyme-like catalytic activity while exhibiting superior physicochemical stability, prolonged catalytic function, and greater resistance to environmental changes [44].

Among antioxidant nanozymes, cerium oxide (CeO_2) has been extensively investigated owing to its reversible Ce^{3+}/Ce^{4+} redox cycling, which enables both SOD- and CAT-like activities. Other nanozymes, including Mn_3O_4, platinum, selenium, and Prussian Blue nanoparticles, also efficiently scavenge ROS and contribute to restoring intracellular redox homeostasis [34,35]. Unlike conventional antioxidants that are consumed during redox reactions, nanozymes continuously catalyze ROS elimination, providing sustained protection against oxidative damage.

Beyond direct ROS scavenging, nanozymes influence several redox-sensitive signaling pathways involved in tissue repair, including the Nrf2, NF-κB, MAPK, and PI3K/Akt pathways. Regulation of these pathways reduces inflammatory cytokine production, preserves mitochondrial function, enhances stem cell survival, and promotes matrix synthesis, thereby creating a microenvironment that supports regeneration rather than chronic inflammation [45].

The therapeutic efficacy of antioxidant nanozymes is further enhanced when they are incorporated into biomaterial platforms such as hydrogels, electrospun nanofibers, injectable matrices, and three-dimensional scaffolds. These hybrid systems provide localized and sustained catalytic activity, protecting transplanted cells from oxidative injury while facilitating angiogenesis, macrophage polarization toward the M2 phenotype, and ECM remodeling. Such catalytic regulation has demonstrated promising outcomes in bone regeneration, cartilage repair, skin wound healing, and other regenerative applications, highlighting ROS modulation as one of the fundamental mechanisms through which nanozymes improve tissue repair [46].

3.2 Oxygen Generation and Hypoxia Alleviation

Insufficient oxygen supply is a major barrier to tissue regeneration, particularly during the early stages after scaffold implantation when vascularization is still limited. Hypoxia compromises cellular metabolism, stem cell survival, extracellular matrix deposition, and angiogenesis, thereby delaying tissue repair in applications such as bone regeneration,

chronic wound healing, and ischemic tissue reconstruction [47].

Catalase-like nanozymes have emerged as an effective strategy to overcome this limitation by catalytically decomposing endogenous hydrogen peroxide into water and molecular oxygen. Unlike conventional oxygen-releasing materials, which provide only transient oxygen delivery, these nanozymes continuously generate oxygen in response to locally available hydrogen peroxide, enabling sustained regulation of tissue oxygenation while simultaneously reducing oxidative stress. Manganese dioxide (MnO_2), cerium oxide (CeO_2), platinum nanoparticles, and Prussian Blue nanozymes are among the most extensively investigated catalytic systems for this purpose [34,35].

Beyond correcting hypoxia, oxygen generation directly influences several biological processes essential for tissue repair. Improved oxygen availability enhances mitochondrial ATP production, promotes endothelial cell migration and angiogenesis, stimulates collagen synthesis, and supports the proliferation and differentiation of progenitor cells. Consequently, catalytic oxygen generation contributes not only to improved cell survival but also to more efficient tissue remodeling and functional regeneration [48-50].

The therapeutic efficacy of oxygen-generating nanozymes has been further enhanced through their incorporation into hydrogels, porous scaffolds, injectable biomaterials, and three-dimensional printed constructs. In these hybrid systems, continuous oxygen generation creates a favorable microenvironment that accelerates wound closure, promotes vascularization, and improves bone regeneration and ischemic tissue repair. Similar benefits have also been reported in cardiac and neural tissue engineering, where localized oxygen production improves stem cell survival, preserves mitochondrial function, and supports functional recovery following ischemic injury [51-53].

Because catalase-like nanozymes simultaneously consume hydrogen peroxide while releasing oxygen, they integrate oxidative stress regulation with hypoxia alleviation within a single catalytic process. This dual function represents a major advantage over conventional oxygen-delivery strategies and highlights the value of catalytic biomaterials for engineering regenerative microenvironments capable of supporting long-term tissue repair [10, 11].

3.3. Antibacterial Catalysis

Bacterial infection remains a major challenge in tissue engineering, particularly in chronic wounds, orthopedic implants, dental biomaterials, and skin substitutes. Microbial adhesion to implanted biomaterials promotes biofilm formation, which protects bacteria from host immune responses and conventional antibiotics, resulting in persistent inflammation, impaired angiogenesis, and delayed tissue regeneration [54].

Nanozymes have emerged as promising antibacterial agents because they eliminate microorganisms through catalytic reactions rather than conventional antibiotic release. Among them, peroxidase-like nanozymes are the most extensively investigated. In the presence of hydrogen peroxide, they catalyze the generation of highly reactive oxygen species, particularly hydroxyl radicals, which disrupt bacterial membranes, proteins, and nucleic acids while effectively damaging biofilm structures. This catalytic mechanism provides broad-spectrum antibacterial activity and may reduce the risk of antimicrobial resistance associated with prolonged antibiotic use [15,20].

In addition to direct bacterial eradication, antibacterial nanozymes improve tissue regeneration by limiting infection-induced inflammation. Reduced bacterial burden decreases the production of pro-inflammatory cytokines, promotes the transition toward a regenerative microenvironment, and facilitates fibroblast proliferation,

angiogenesis, and extracellular matrix deposition. Consequently, infection control and tissue repair occur simultaneously through a coordinated catalytic process [55].

The therapeutic potential of antibacterial nanozymes has been further enhanced by their incorporation into hydrogels, electrospun nanofibers, implant coatings, and injectable biomaterials. These hybrid systems provide localized and sustained antimicrobial activity while avoiding continuous antibiotic release, thereby minimizing systemic toxicity and maintaining long-term protection against bacterial contamination. Such multifunctional biomaterials are particularly promising for chronic wound management and implant-associated infections, where effective infection control is essential for successful tissue regeneration [30, 46, 48].

3.4. Immunomodulation and Macrophage Polarization

The immune response plays a central role in determining the outcome of tissue regeneration. Following injury, macrophages orchestrate the inflammatory process by eliminating pathogens and cellular debris while regulating subsequent tissue repair. Although an initial pro-inflammatory response is essential for healing, prolonged inflammation disrupts tissue homeostasis, impairs stem cell function, and often results in fibrosis or chronic non-healing wounds [56].

Macrophages exhibit remarkable phenotypic plasticity, ranging from the pro-inflammatory M1 phenotype to the pro-regenerative M2 phenotype. Successful tissue repair depends on the timely transition from M1 to M2 macrophages, which promotes angiogenesis, extracellular matrix remodeling, and tissue reconstruction. However, excessive oxidative stress, hypoxia, and persistent infection frequently interfere with this transition and sustain a chronic inflammatory microenvironment [57].

Nanozymes regulate immune responses primarily through catalytic modulation of the local redox balance. By scavenging excessive reactive oxygen species and attenuating oxidative stress, antioxidant nanozymes suppress inflammatory signaling pathways such as NF-κB while promoting macrophage polarization toward the M2 phenotype. This catalytic regulation reduces the production of pro-inflammatory cytokines and enhances the secretion of regenerative mediators, thereby creating an immune microenvironment that supports cell survival and tissue regeneration. When incorporated into biomaterial scaffolds, immunomodulatory nanozymes further enhance regenerative outcomes by simultaneously regulating oxidative stress, inflammation, and oxygen homeostasis. This coordinated catalytic activity accelerates angiogenesis, extracellular matrix deposition, and functional tissue remodeling, highlighting immunomodulation as one of the key mechanisms underlying the therapeutic potential of nanozyme-based biomaterials in regenerative medicine [58,59].

3.5. ECM Remodeling and Angiogenesis

Successful tissue regeneration depends on coordinated ECM remodeling and rapid vascularization, both of which are essential for restoring tissue structure and function. However, persistent oxidative stress and chronic inflammation disrupt these processes by impairing fibroblast and endothelial cell activity, promoting collagen degradation, and inducing excessive matrix metalloproteinase (MMP) activation, ultimately delaying tissue repair [8, 9].

Nanozymes facilitate ECM remodeling by maintaining redox homeostasis and protecting resident cells from oxidative damage. Their antioxidant activity preserves fibroblast function, enhances collagen synthesis, and limits excessive MMP-mediated matrix degradation, thereby supporting the formation of a stable and organized extracellular matrix. At the same time, catalase-like nanozymes improve local oxygen availability, while antioxidant

nanozymes preserve endothelial cell viability and promote the expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), collectively enhancing neovascularization and tissue maturation. The incorporation of nanozymes into hydrogels, porous scaffolds, and other regenerative biomaterials has been shown to increase vascular density, improve collagen deposition, and accelerate tissue remodeling in models of skin, bone, and cardiac repair. These findings demonstrate that nanozymes actively coordinate structural reconstruction by simultaneously promoting angiogenesis and balanced ECM remodeling, thereby creating a regenerative microenvironment favorable for long-term functional recovery [43,60].

3.6. Catalytic Microenvironment Engineering

Recent advances in regenerative medicine have shifted the focus from developing bioactive scaffolds to engineering regenerative microenvironments capable of actively directing tissue repair. Within this framework, nanozymes have emerged as multifunctional catalytic components that simultaneously regulate multiple biological processes rather than targeting a single pathological factor [10,15].

Following tissue injury, oxidative stress, hypoxia, persistent inflammation, bacterial infection, and extracellular matrix disruption collectively impair tissue regeneration. Because these events are closely interconnected, therapeutic strategies aimed at only one pathway often produce limited outcomes. By integrating multiple enzyme-like activities within a single nanoplatform, nanozymes can concurrently regulate redox homeostasis, oxygen availability, immune responses, antimicrobial defense, and matrix remodeling, thereby establishing a microenvironment that supports cell survival and functional tissue regeneration [11,40].

When incorporated into advanced biomaterials, nanozymes transform conventional scaffolds into dynamic catalytic systems that continuously interact with surrounding tissues. Instead of serving solely as structural supports or passive carriers, these biomaterials actively modulate cellular behavior, promote angiogenesis, facilitate macrophage polarization toward regenerative phenotypes, and enhance extracellular matrix reconstruction throughout the healing process. This concept of catalytic microenvironment engineering represents an important step toward the development of intelligent biomaterials capable of orchestrating tissue regeneration through sustained biochemical regulation [61].

4. Nanozyme-Integrated Biomaterials

The therapeutic performance of nanozymes can be substantially improved through their integration into biomaterial platforms. Although free nanozymes exhibit excellent catalytic activity, their direct administration is often limited by rapid diffusion, short retention at the target site, and reduced local bioavailability. Incorporation into biomaterials not only prolongs catalytic activity but also provides structural support, enhances local retention, and enables sustained modulation of the regenerative microenvironment. Consequently, nanozyme-integrated biomaterials have emerged as promising multifunctional systems that combine the architectural role of scaffolds with catalytic regulation of tissue repair [17,42].

Depending on the target tissue and therapeutic requirements, nanozymes have been incorporated into hydrogels, electrospun nanofibers, injectable matrices, and 3D printed scaffolds. These hybrid materials preserve the desirable physicochemical properties of conventional biomaterials while introducing catalytic functions that regulate oxidative stress, oxygen homeostasis, inflammation, and bacterial infection, thereby improving the regenerative potential of engineered tissues [18,41].

4.1 Nanozyme-Integrated Hydrogels

Hydrogels are among the most widely investigated carriers for nanozymes because of their high water content, porous architecture, and structural similarity to the extracellular matrix. Encapsulation of nanozymes within hydrogel networks prevents nanoparticle aggregation, prolongs catalytic activity, and enables localized ROS regulation at the injury site. In addition to reducing oxidative stress and inflammation, catalase-like nanozymes incorporated into hydrogels continuously generate oxygen, thereby improving cell survival and angiogenesis under hypoxic conditions. These catalytic hydrogels have demonstrated encouraging outcomes in chronic wound healing, diabetic ulcers, bone regeneration, and cartilage repair [60 , 17].

4.2 Electrospun Nanofibrous Scaffolds

Electrospun nanofibers closely mimic the fibrous architecture of native extracellular matrix and provide a favorable substrate for cell adhesion, proliferation, and migration. Functionalization of these scaffolds with nanozymes converts passive structural matrices into catalytically active biomaterials capable of continuously regulating oxidative stress and inflammatory responses. Studies have shown that nanozyme-containing electrospun scaffolds enhance osteogenic differentiation, reduce bacterial colonization, and promote vascularization, making them attractive candidates for skin, bone, and vascular tissue engineering [62].

4.3 Injectable Biomaterials

Injectable biomaterials offer a minimally invasive strategy for treating irregular tissue defects and can undergo *in situ* gelation after administration. Incorporating nanozymes into injectable hydrogels enables localized catalytic therapy with prolonged retention at the injury site, leading to sustained ROS scavenging, oxygen generation, and immunomodulation. Furthermore, these systems can simultaneously deliver stem cells, therapeutic proteins, or bioactive molecules, providing synergistic effects that enhance tissue regeneration in applications such as myocardial repair, cartilage regeneration, spinal cord injury, and chronic wound healing [63].

4.4 Three-Dimensional Printed Scaffolds

Three-dimensional printing enables the fabrication of patient-specific scaffolds with precisely controlled architecture and mechanical properties. Integration of nanozymes into printable biomaterials has expanded the functionality of these constructs beyond structural support by introducing continuous catalytic regulation of the local microenvironment. Experimental studies indicate that nanozyme-containing 3D-printed scaffolds reduce oxidative stress, promote angiogenesis, and enhance bone regeneration while allowing spatial control over nanozyme distribution according to tissue-specific requirements [3,42,53].

4.5 Emerging Multifunctional Biomaterial Platforms

Recent advances have led to multifunctional biomaterials that combine nanozyme catalysis with complementary therapeutic strategies. Examples include bioinks for 3D bioprinting, self-healing hydrogels, microneedle patches, and stimuli-responsive systems capable of releasing therapeutic agents in response to changes in ROS levels, pH, or enzymatic activity. The incorporation of stem cells, extracellular vesicles, or growth factors into these catalytic platforms further enhances regenerative outcomes by simultaneously regulating oxidative stress, inflammation, angiogenesis, and extracellular matrix remodeling. These developments illustrate the transition from passive scaffolds to intelligent biomaterials capable of actively orchestrating tissue regeneration through catalytic microenvironment engineering [64].

5. Applications of Nanozymes in Tissue Engineering

The catalytic versatility of nanozymes has enabled their application across a broad range of tissue engineering strategies. By regulating oxidative stress, inflammation, oxygen homeostasis, and antibacterial activity, nanozyme-based biomaterials create a regenerative microenvironment that enhances cell survival, tissue remodeling, and functional recovery. Their integration with advanced scaffolds has shown promising outcomes in the regeneration of bone, skin, cartilage, neural, cardiac, and vascular tissues (Fig. 6) [10,17,37,40].

5.1 Bone Tissue Engineering

Bone tissue engineering represents one of the most extensively explored applications of nanozymes. Large bone defects are frequently associated with excessive oxidative stress and chronic inflammation, both of which impair osteogenic differentiation and delay healing. Incorporation of antioxidant nanozymes, particularly cerium oxide- and manganese oxide-based systems, into bioceramics, collagen matrices, hydrogels, and three-dimensional printed scaffolds has been shown to promote mesenchymal stem cell differentiation, stimulate osteogenic markers such as Runx2 and ALP, enhance angiogenesis, and accelerate new bone formation. These findings demonstrate that catalytic regulation of the bone microenvironment is an effective strategy for improving bone regeneration [4-6,19,37,42,53].

5.2 Skin Tissue Engineering and Wound Healing

Chronic wounds, especially diabetic ulcers, are characterized by persistent inflammation, bacterial infection, excessive ROS accumulation, and impaired vascularization. Nanozyme-based wound dressings effectively address these challenges through multiple catalytic mechanisms, including ROS scavenging, oxygen generation, and antibacterial activity. When incorporated into hydrogels or electrospun dressings, nanozymes promote macrophage polarization toward the M2 phenotype, stimulate angiogenesis, enhance collagen deposition, and accelerate re-epithelialization, resulting in faster wound closure and improved tissue remodeling compared with conventional wound dressings [51,65,66].

5.3 Cartilage Tissue Engineering

The avascular nature of articular cartilage limits its regenerative capacity following injury or degeneration. Nanozymes help preserve cartilage homeostasis by reducing oxidative stress, suppressing inflammatory signaling, and protecting chondrocytes from apoptosis. Incorporation of catalytic nanoparticles into injectable hydrogels and cartilage scaffolds has been reported to maintain collagen type II and aggrecan synthesis, inhibit matrix metalloproteinases, and improve extracellular matrix deposition, thereby enhancing cartilage regeneration and offering promising therapeutic potential for osteoarthritis [67,68].

5.4 Neural Tissue Engineering

Oxidative stress and neuroinflammation are major contributors to neuronal degeneration after traumatic brain injury, spinal cord injury, and peripheral nerve damage. Owing to their antioxidant and anti-inflammatory activities, nanozymes reduce neuronal apoptosis, preserve mitochondrial function, and promote axonal regeneration. Their incorporation into nerve guidance conduits, conductive biomaterials, and injectable hydrogels has improved neural stem cell survival, reduced glial scar formation, and enhanced functional recovery in preclinical studies [69,63].

5.5 Cardiac Tissue Engineering

The ischemic microenvironment following myocardial infarction is characterized by severe oxidative stress, inflammation, and inadequate oxygen supply, which markedly limit cardiac repair. Nanozyme-based

biomaterials alleviate these pathological conditions by scavenging ROS, generating oxygen, and protecting cardiomyocytes against oxidative injury. Injectable hydrogels containing catalytic nanozymes further provide localized and sustained therapeutic activity, improving stem cell survival, angiogenesis, and cardiac function while reducing adverse ventricular remodeling [52, 70].

5.6 Vascular Tissue Engineering

Successful regeneration of engineered tissues depends on rapid vascularization to ensure adequate oxygen and nutrient delivery. Nanozymes facilitate this process by protecting endothelial cells from oxidative damage, alleviating hypoxia through catalase-like activity, and modulating inflammatory responses that support angiogenesis. Nanozyme-functionalized vascular grafts and hydrogel systems have demonstrated enhanced endothelialization, capillary formation, and tissue perfusion, highlighting their value in vascular reconstruction and in supporting regeneration of highly vascularized tissues [71,49].

6. Challenges

Despite the rapid development of nanozyme-based biomaterials, several challenges still hinder their clinical translation. Beyond demonstrating catalytic efficiency in laboratory studies, future research must address issues related to biosafety, catalytic regulation, scalable manufacturing, and regulatory approval to facilitate their application in regenerative medicine.

6.1 Biosafety and Biocompatibility

Although many nanozymes, including cerium oxide, manganese oxide, and Prussian Blue nanoparticles, have shown good biocompatibility in preclinical studies, their long-term safety remains insufficiently understood. Physicochemical characteristics such as particle size, morphology, surface chemistry, and degradation behavior can significantly influence cellular uptake, biodistribution, and biological responses. In addition, the potential accumulation of non-biodegradable nanoparticles in major organs highlights the need for comprehensive investigations into long-term toxicity, metabolism, and clearance before clinical application [72,73].

6.2 Regulation of Catalytic Activity

The catalytic performance of nanozymes is strongly influenced by the physiological microenvironment, including pH, oxygen availability, hydrogen peroxide concentration, and ionic composition. Consequently, catalytic activity observed under experimental conditions may not accurately reflect *in vivo* performance. Developing stimuli-responsive nanozymes that are selectively activated under pathological conditions while remaining inactive in healthy tissues is expected to improve therapeutic precision and minimize potential adverse effects [74].

6.3 Scalable Manufacturing and Standardization

Clinical translation also requires reproducible and large-scale manufacturing. Minor variations during synthesis can alter particle size, crystal structure, surface defects, and catalytic activity, resulting in inconsistent biological performance. Therefore, standardized fabrication protocols, robust quality-control procedures, and cost-effective production strategies are essential for ensuring batch-to-batch consistency and supporting industrial-scale manufacturing [75].

6.4 Clinical Translation and Regulatory Considerations

Most evidence supporting nanozyme-assisted tissue regeneration is currently derived from *in vitro* experiments and small-animal models, whereas clinical validation remains limited. Large-animal studies, long-term safety assessments, and well-designed

clinical trials are needed to establish therapeutic efficacy under clinically relevant conditions. Furthermore, because nanozymes combine the characteristics of nanomaterials and catalytic therapeutics, their regulatory evaluation requires standardized criteria for physicochemical characterization, biosafety assessment, manufacturing quality, and clinical performance. Close collaboration among materials scientists, clinicians, and regulatory authorities will be essential for the successful translation of nanozyme-based regenerative therapies into clinical practice.

Overall, continued advances in nanozyme engineering, biomaterial design, and regulatory science are expected to accelerate the development of safer, more efficient, and clinically applicable catalytic biomaterials for tissue engineering and regenerative medicine [76,77].

7. Future Perspectives

Nanozymes are expected to become integral components of next-generation regenerative biomaterials as advances in nanotechnology, biomaterials science, and precision medicine continue to expand their therapeutic capabilities. Future research is likely to move beyond single-enzyme mimics toward multifunctional catalytic nanoplatforms capable of simultaneously regulating oxidative stress, inflammation, oxygen homeostasis, antibacterial activity, and immune responses within a single system.

An important direction involves the development of stimuli-responsive nanozymes that selectively adjust their catalytic activity in response to pathological signals such as elevated ROS levels, acidic pH, hypoxia, or bacterial infection. These intelligent systems may provide localized and on-demand therapy, improving treatment efficacy while minimizing off-target catalytic effects. At the same time, integrating nanozymes with advanced biomaterial platforms, including injectable hydrogels, self-healing matrices, extracellular vesicles, stem cell delivery systems, and three-dimensional bioprinted constructs, is expected to generate highly adaptive regenerative microenvironments capable of responding dynamically to tissue-specific biological cues [78,79].

Emerging computational approaches are also expected to accelerate nanozyme development. Machine learning, artificial intelligence, and high-throughput computational screening can facilitate the rational design of catalytic nanomaterials with optimized composition, surface chemistry, and enzyme-like activity, thereby reducing experimental costs and shortening development cycles. Such strategies may further support the realization of personalized regenerative therapies by enabling nanozyme-based biomaterials tailored to the pathological characteristics of individual patients [80].

Overall, continued advances in catalytic nanomaterials, intelligent biomaterial design, and interdisciplinary collaboration are expected to transform nanozymes from experimental nanocatalysts into clinically applicable therapeutic platforms. Their ability to actively regulate the regenerative microenvironment positions nanozymes as promising building blocks for future tissue engineering and regenerative medicine.

8. Conclusions

Nanozymes have emerged as a promising class of catalytic nanomaterials that extend the role of conventional biomaterials from passive structural support to active regulation of the regenerative microenvironment. Through enzyme-like catalytic activities, these nanomaterials modulate oxidative stress, inflammation, oxygen homeostasis, antibacterial defense, and extracellular matrix remodeling, thereby creating conditions that support tissue repair and functional regeneration. Their superior physicochemical stability, tunable catalytic properties, and compatibility with diverse biomaterial platforms provide clear advantages over natural enzymes in regenerative applications.

Recent progress in integrating nanozymes with hydrogels, electrospun nanofibers, injectable biomaterials, and 3D printed scaffolds has significantly expanded their therapeutic potential. These catalytic biomaterials have demonstrated encouraging regenerative outcomes in bone, skin, cartilage, neural, cardiac, and vascular tissue engineering by improving cell survival, angiogenesis, immunomodulation, and tissue remodeling. Such advances highlight the transition from conventional scaffold design toward intelligent biomaterials capable of dynamically interacting with the biological microenvironment.

Although several challenges, including long-term biosafety, precise regulation of catalytic activity, scalable manufacturing, and clinical translation, remain to be addressed, rapid advances in nanotechnology, biomaterials engineering, and computational material design are expected to accelerate the development of next-generation nanozyme-based therapies. Continued interdisciplinary collaboration will be essential for transforming these catalytic nanomaterials from experimental platforms into clinically applicable regenerative technologies.

Overall, nanozymes represent a versatile and rapidly evolving strategy for tissue engineering and regenerative medicine. Their unique ability to continuously regulate the local biological microenvironment positions them as key components of future catalytic biomaterials and offers new opportunities for the development of more effective regenerative therapies.

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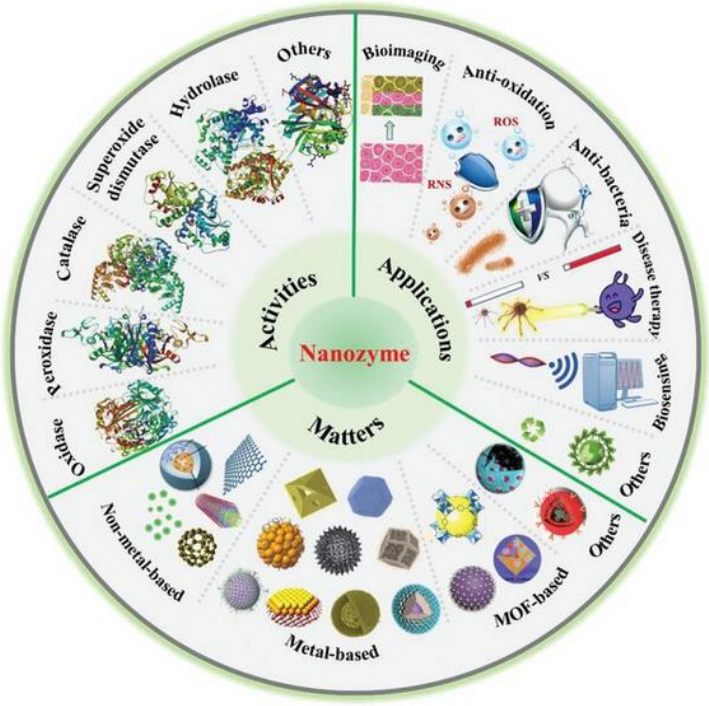


Figure 1. Fabrication matters, enzymatic activities, and bioapplications of nanozymes [11].

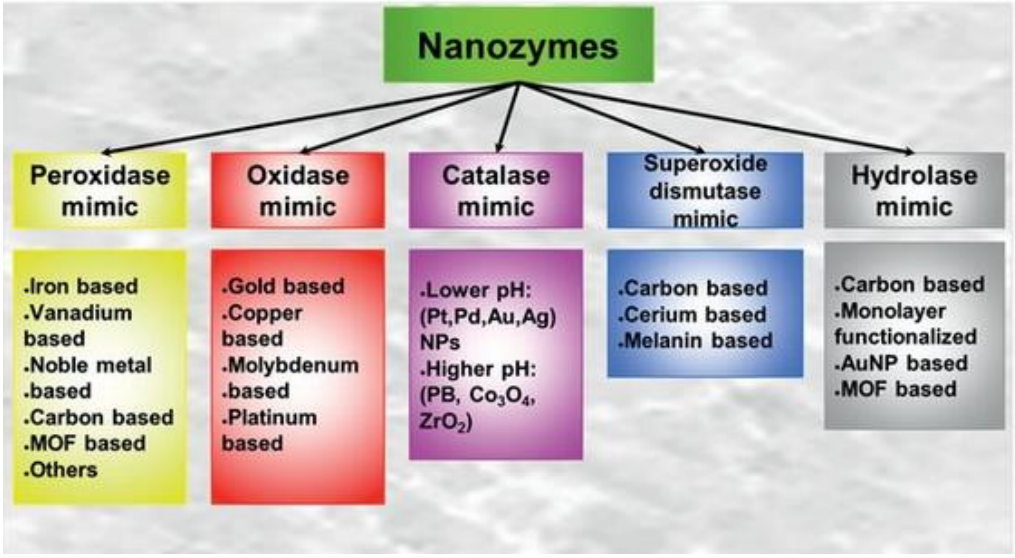


Figure 2. Classification of nanozymes based on the type of enzymatic reaction: peroxidase, oxidase, catalase, superoxide dismutase, and hydrolase mimic [25].

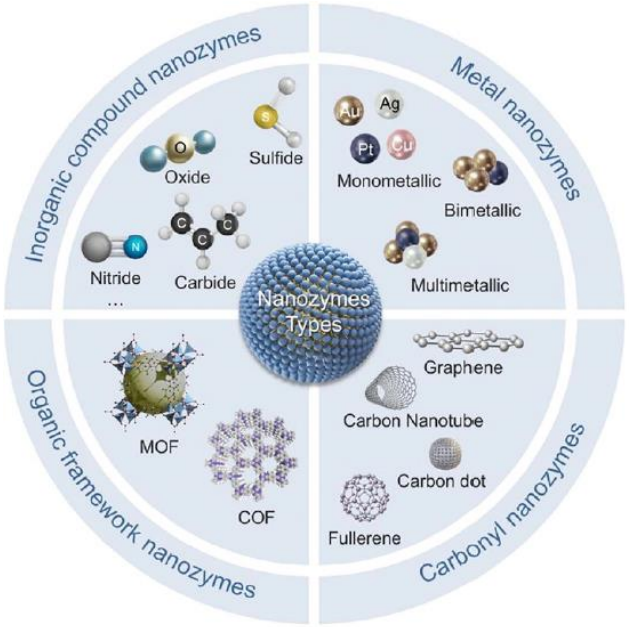


Figure 3. Several common types of nanozymes include metal compounds (e.g., metal oxides, sulfides, nitrides, and carbides), metallic nanozymes (e.g., Au, Ag, Pt, and Cu nanoparticles), carbon-based nanozymes (e.g., fullerenes, carbon quantum dots, graphene, and carbon nanotubes), and organic framework nanozymes (e.g., metal−organic frameworks and covalent organic framework nanozymes) [37].

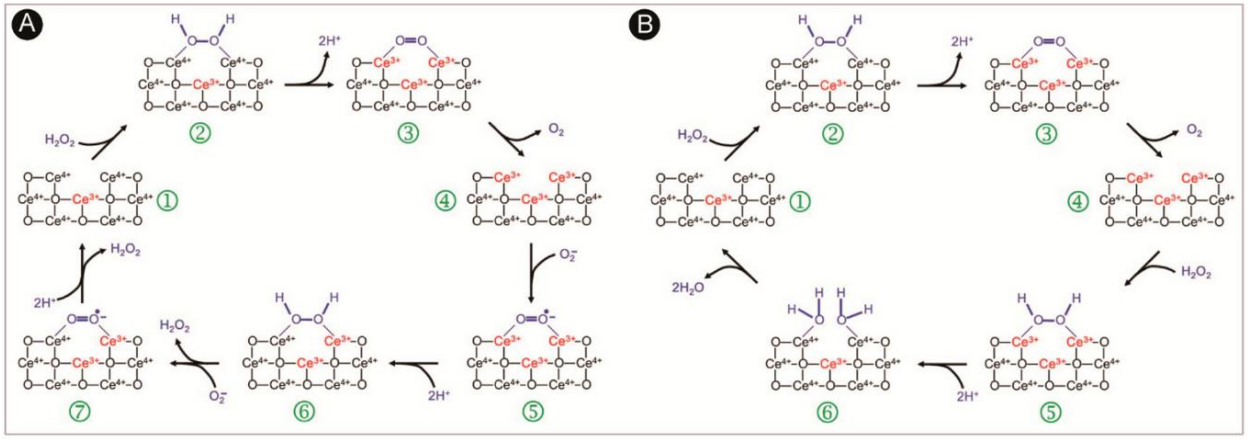


Figure 4. The proposed mechanism for the enzymatic activity of cerium-oxide nanoparticles. Mechanism for superoxide dismutase activity (A) and catalase activity (B). The oxidative half-reactions (1–4) are identical in both reactions [38].

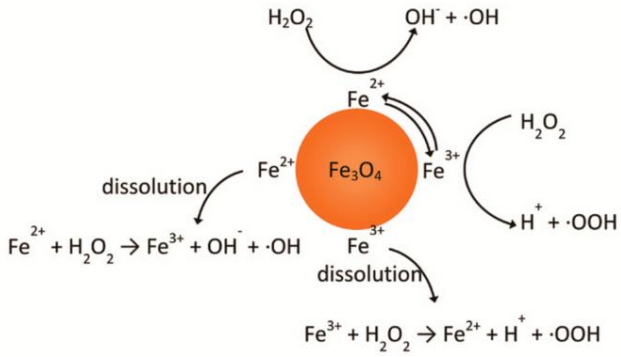


Figure 5. The proposed mechanism for the enzymatic activity of iron-oxide (Fe_3O_4) nanoparticles, including Fenton/Haber–Weiss reaction mechanisms [38].

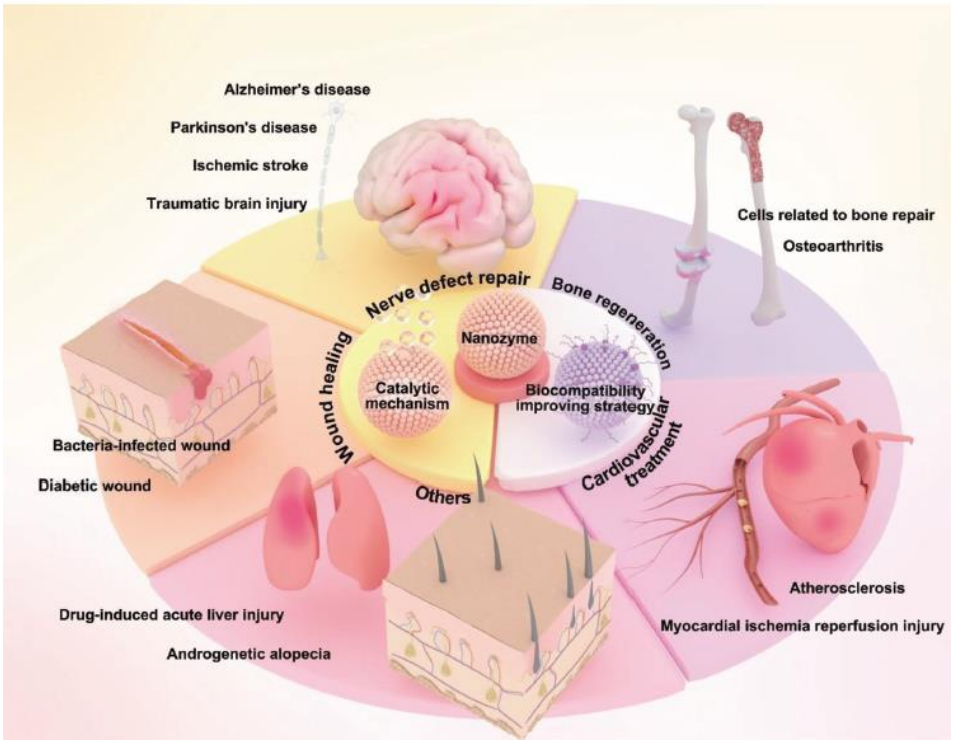


Figure 6. The schematic illustration of the applications of nanozyme for tissue engineering [10].