International Journal of Nanomedicine
Dovepress
Taylor & Francis Group

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REVIEW

Nanozyme-Based Anti-Inflammatory Strategies in Cardiovascular Disease Management: Clinical Prospects and Challenges

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Abstract: Cardiovascular disease (CVD) is the leading cause of death and disability worldwide. Research indicates that inflammatory responses and oxidative stress mediated by reactive oxygen species (ROS) are hallmark pathological mechanisms of CVD. Traditional anti-inflammatory drugs, though widely used, have limitations such as lack of targeting, low systemic delivery efficiency, and significant side effects. Nanozymes are a class of nanomaterials with enzyme-like activity, and their breakthrough applications offer new directions for the prevention and treatment of CVD. In the treatment of cardiovascular diseases, nanozymes demonstrate unique advantages: they can achieve local targeted delivery and ROS scavenging, and can also regulate the inflammatory microenvironment through multi-mechanism interventions. However, despite their promising applications, nanozymes still face challenges such as optimizing catalytic selectivity, improving biological targeting efficiency, and verifying long-term safety. This article will review the mechanisms of action of nanozymes in inflammation regulation and summarize their applications in cardiovascular diseases.

Keywords: nanozyme, inflammation, reactive oxygen species, cardiovascular, target delivery

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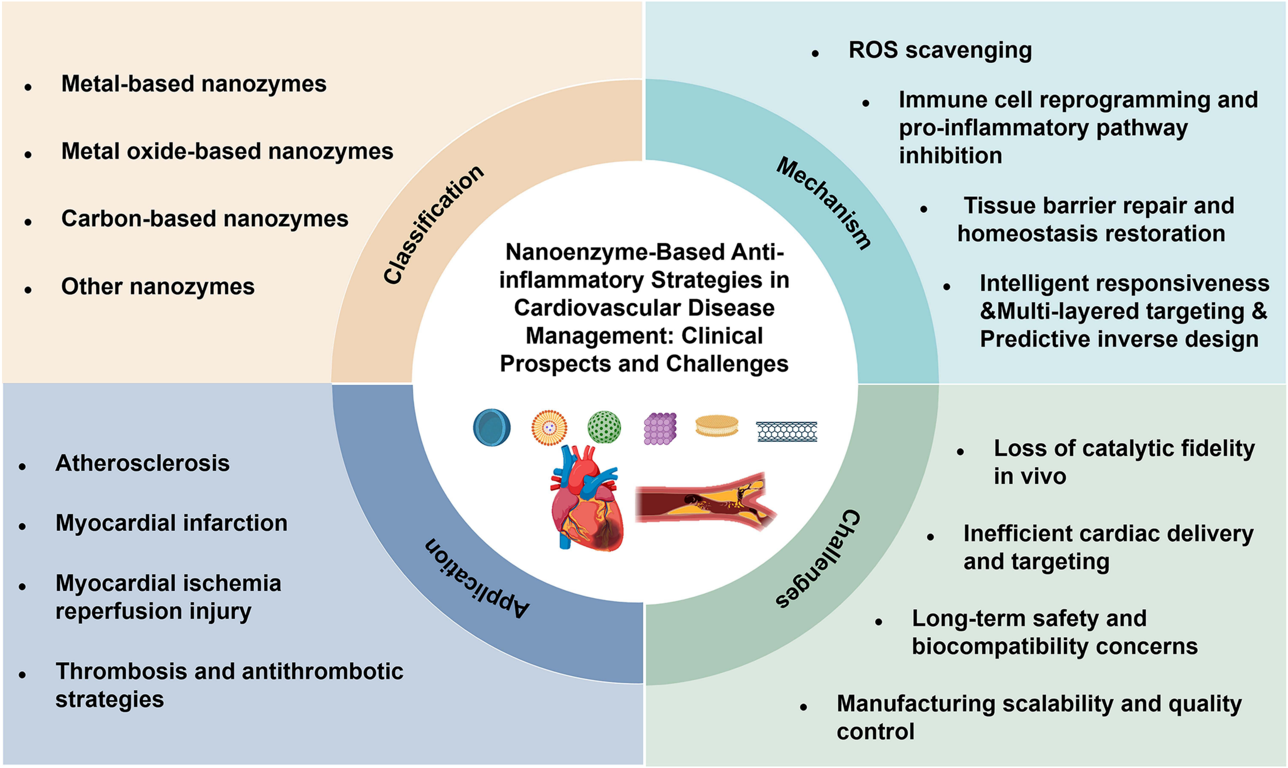
Introduction

Cardiovascular diseases (CVDs) persist as the formidable leading cause of global mortality. The scale of this crisis is underscored by World Health Organization data, which attributes approximately 19.8 million deaths—nearly 32% of global mortality in 2022—to these conditions.[1] At the cellular level, we observe that this devastation is rarely an isolated event but rather the result of pan-vascular damage driven by a relentless "inflammation-oxidative stress" axis.[2–4] Consequently, clinical consensus now suggests that the effective regulation of local cardiac inflammation and the alleviation of oxidative stress are not merely symptomatic treatments, but fundamental strategies for improving prognosis and arresting disease progression.[5]

Given this pathophysiological complexity, how have we historically approached pharmacological intervention? Clinical practice has long relied on broad-spectrum anti-inflammatory agents, such as glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs).[6–10] While effective in principle, the therapeutic window of these drugs is frequently narrowed by systemic toxicity and rapid metabolic clearance.[11–13] To circumvent these pharmacokinetic hurdles, the field has gravitated toward controlled-release delivery platforms—including liposomes, polymeric nanoparticles, and inorganic carriers—designed to enhance bioavailability.[14–18] A compelling illustration of this evolution is the modification of berberine: while its intrinsic cardioprotective potential is hampered by poor solubility, its encapsulation within PEG-modified long-circulating liposomes has been shown to facilitate passive targeting to inflamed myocardium.[19] This

https://doi.org/10.2147/IJN.S568282
Received: 17 September 2025
Accepted: 13 February 2026
Published: 27 February 2026

Graphical Abstract



strategy preserves cardiac function while minimizing systemic exposure, yet it highlights a persistent limitation: these carriers remain passive vehicles, relying entirely on the efficacy of the loaded cargo.

Is it possible, then, to engineer a material that transcends the role of a passive carrier to become an active therapeutic agent? This question has catalyzed the emergence of nanozymes, a class of nanomaterials that possess intrinsic, enzyme-like catalytic activities.[20–22] Unlike traditional nanomedicine that acts solely as a transport vessel, nanozymes integrate targeting capabilities with the ability to specifically modulate the oxidative and inflammatory microenvironment.[23–28] By mimicking the active sites of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), these materials can efficiently scavenge ROS and modulate macrophage polarization.[29–32] This dual functionality represents a paradigm shift, allowing for the direct mitigation of inflammatory damage through catalytic processes rather than stoichiometric consumption.[33] In atherosclerotic models, researchers have noted that nanozymes like Prussian blue do not simply “carry” anti-inflammatory drugs; they function as integrated platforms for ROS scavenging, lipid regulation, and cellular rejuvenation.[34]

To appreciate the engineering triumph of nanozymes, one must first consider the biological benchmark they strive to emulate: the natural enzyme. Natural enzymes are marvels of evolution, achieving high substrate specificity through precise steric and electronic complementarity within a hydrophobic active pocket.[35–37] However, our observations in biotechnological applications reveal that this precision comes at a cost: natural enzymes are plagued by instability, prohibitive purification costs, and sensitivity to the harsh conditions typical of large-scale manufacturing.[38] Nanozymes address these inherent vulnerabilities by catalyzing reactions through surface-mediated processes that can be rationally tuned via size, morphology, and composition.[39–41] Thus, rather than serving as a mere substitute, nanozymes offer a robust, complementary catalytic paradigm that combines the functional integration of enzymes with the stability and economy of inorganic materials.

Against this backdrop of rapid technological evolution, this review aims to synthesize the current landscape of nanozyme applications in cardiovascular medicine. Emerging evidence suggests that these catalytic nanomaterials exert their therapeutic effects through a multipronged mechanism involving ROS scavenging, anti-inflammatory modulation, and endothelial restoration. To provide a rigorous analysis of these mechanisms and the barriers to clinical translation—such as catalytic selectivity and biosafety—we conducted a review. By filtering a dataset of 511 articles retrieved from major databases (including PubMed and Web of Science) down to 197 pivotal studies, we have constructed a narrative that not only highlights the promising trajectory of nanozyme technology but also critically evaluates the "bottlenecks" that must be overcome for precise cardiovascular anti-inflammatory therapy to become a clinical reality. (Figure 1)

Classification and Synthesis of Nanozymes

Classification of Nanozymes

The management of ROS constitutes a fundamental biological paradox: while essential for signaling, their accumulation—specifically superoxide anions (O2-), hydroxyl radicals (OH·), and hydrogen peroxide (H_2O_2)—precipitates severe oxidative stress.[42] Nature resolves this through a sophisticated cascade of enzymes, utilizing SOD to disproportionate toxic radicals, CAT to decompose the resulting peroxide, and Glutathione Peroxidase (GPx) to clear lipid peroxides.[43–45] However, the translation of these natural proteins into therapeutic agents is frequently stalled by their intrinsic fragility and stringent storage requirements. This limitation has catalyzed the search for robust alternatives, leading to the emergence of nanozymes—nanomaterials engineered to mimic these catalytic active sites with superior stability. Based on their physicochemical composition, these biomimetic catalysts are broadly categorized into metal-based, metal oxide-based, and carbon-based nanozymes.

Metal-Based Nanozymes

Metal-based nanozymes, composed of zero-valent metals, alloys, or metallic clusters, mimic natural enzymes through accessible surface active sites and tunable electronic structures.[46] Their high surface-to-volume ratios allow for precise optimization via ligand coordination, defect engineering, and hetero-interface construction, facilitating efficient substrate

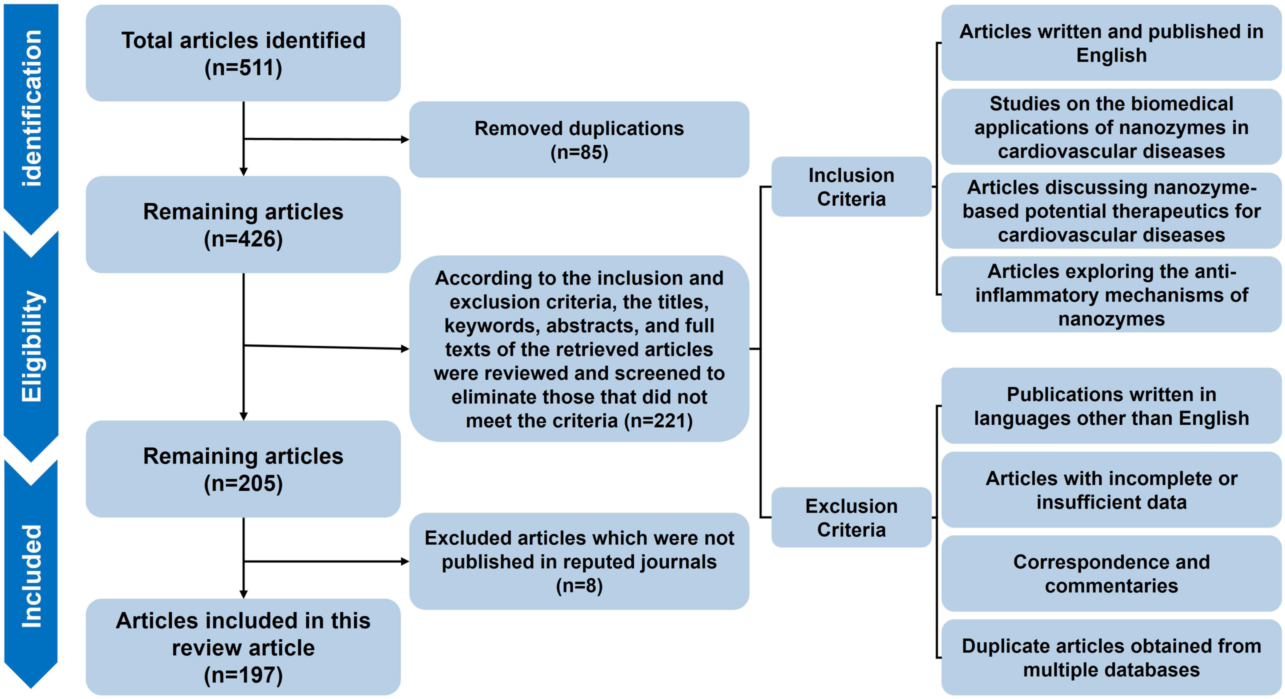


Figure 1 Flow chart of the articles in this review.

https://doi.org/10.2147/IJN.S568282

adsorption and electron transfer.[47] These modifications enable complex single- or multi-enzymatic behaviors (eg, concurrent SOD-, CAT-, and POD-like activities). Generally, these materials are divided into noble and non-noble metal categories.

Noble metal-based nanozymes, utilizing gold (Au), silver (Ag), platinum (Pt), and palladium (Pd), are distinguished by their exceptional chemical stability and catalytic activity.[48–52] Recent advances have moved beyond simple single-element systems toward functionalized and hybrid architectures. For instance, Au@Fmoc-YR nanozymes exhibit high sensitivity for glucose and plasma GSH detection in oncology settings.[53] Furthermore, bimetallic and composite structures offer synergistic advantages: Core-shell Au@Pt nanozymes regulate glycolipid metabolism by modulating hepatic gene expression, while Pd@Pt systems display triple enzyme-mimicking activities.[54,55]

Non-noble metal-based nanozymes (Fe, Cu, Mn, Ce, Zn) offer a cost-effective and biocompatible alternative.[56–63] Through structural innovation, such as the use of single-atom catalysts or metal-organic frameworks (MOFs), these materials achieve enzyme-like specificity. For example, single-atom nanozymes incorporating Fe clusters and Fe-N4 moieties demonstrate stable multi-enzymatic activity with SOD performance comparable to natural enzymes.[64] Similarly, a polydopamine-modified manganese organic framework (pDA-MNOF) mimics the SOD2 catalytic domain to protect neurons from ischemic injury.[65] Other systems exploit unique valence states for specific therapeutic outcomes; Ce-UiO-66 leverages Ce(III)/Ce(IV) sites for oxygen generation, while engineered Cu-$CuFe_2O_4$ exhibits dual CAT- and GPx-like activities for anticancer effects.[66,67] These advances highlight the potential of metal-based nanozymes as robust tools in anti-inflammatory and antitumor therapies.

Metal Oxide-Based Nanozymes

Metal oxide-based nanozymes derive their catalytic potency from surface redox couples (eg, Mn^{3+}/Mn^{2+}), oxygen vacancies, and coordinatively unsaturated sites, which collectively regulate substrate activation.[68] Compared to pure metals, metal oxides often possess richer defect chemistry, enabling diverse catalytic profiles under physiological conditions.[69] Iron and cerium oxide systems remain the most extensively investigated due to their biocompatibility and tunable valence properties.[70–74]

Iron-based nanozymes represent the foundational class of this field. The discipline of nanozymology was effectively launched in 2006 when Yan et al discovered the intrinsic peroxidase activity of Fe_3O_4 nanoparticles.[75] Since then, the scope of iron-based biocatalysts has expanded significantly. For instance, pyrite (FeS2) nanozymes were developed to exhibit dual glutathione oxidase and POD activities, achieving a catalytic efficiency (kcat/KM) for H_2O_2 over 3,000 times that of natural horseradish peroxidase. Mechanistically, the groove-like topology of FeS2 enhances substrate binding, facilitating tumor-specific apoptosis.[76] More recently, ferrihydrite ($Fe_5HO_8 \cdot 4H_2O$) nanozymes have been shown to display CAT-like activity exponentially correlated with surface iron hydroxyl (Fe-OH) abundance, maintaining stability across a wide pH range (4.0–8.7) to mitigate tumor hypoxia and sensitize radiotherapy.[77]

Cerium oxide nanoparticles are unique for their reversible Ce^{3+}/Ce^{4+} redox cycling, where a higher Ce^{3+}/Ce^{4+} ratio typically correlates with stronger SOD mimetic activity.[78,79] Advanced formulations utilize this property for complex therapeutic goals; for example, mesoporous cerium oxide (MSN-Ce@SP/PEG) integrates CAT and POD activities to inhibit tumor metastasis.[80] Additionally, self-assembling cerium systems have proven effective in suppressing inflammatory cytokines in viral pneumonia models, while calcein-modified CeO_2 serves as a probe for intracellular ROS detection.[81,82]

Emerging research focuses on other metal oxides and synergistic hybrids to maximize efficacy. Manganese-based systems, such as Mn_3O_4 nanocomposites, have been employed to promote macrophage polarization (M1 to M2) in rheumatoid arthritis.[83] To further enhance performance, researchers are engineering heterostructures like CeOx/Mn_3O_4, which couple Ce^{3+}/Ce^{4+} and Mn^{3+}/Mn^{2+} cycles with vacancy defects to achieve robust activity in high-ROS environments.[84] Similarly, copper-cerium bimetallic oxides (CuCeOx) combine antibacterial action with ROS scavenging for periodontitis treatment, demonstrating the versatility of hybrid oxide systems.[85]

Carbon-Based Nanozymes

Carbon-based nanozymes are defined by their high chemical stability, large specific surface area, and intrinsic catalytic potential. These metal-free or hybrid materials mimic POD, SOD, and CAT activities to scavenge ROS in therapeutic contexts.[86–88]

Undoped carbon nanozymes, such as carbon dots (C-dots), have demonstrated remarkable intrinsic performance, with some SOD mimics exceeding 10,000 U/mg and effectively reducing oxidative damage in ischemic stroke models.[89]

Performance can be further enhanced through doping strategies. The incorporation of metal centers into the carbon lattice—exemplified by biocompatible -Cu-O-Zn- covalently doped carbon dots (CuZn-CDs)—imparts simultaneous CAT and SOD activities for myocardial protection.[90] The next generation of carbon nanozymes focuses on advanced multi-functional systems. By integrating ferritin with carbon platforms, researchers have engineered nanostructures possessing four distinct enzymatic activities (oxidase, peroxidase, catalase, and SOD). This multifunctional approach enables targeted delivery and potent in vivo catalytic therapy, underscoring the potential of carbon materials as comprehensive theranostic platforms.[91]

Synthesis of Nanozymes

Common Synthesis Strategies

Nanozymes are typically fabricated via bottom-up chemical methods, each offering distinct control over material properties.[92–94] (Table 1)

Stability and Preservation Protocols

Ensuring the physicochemical integrity of nanozymes is a prerequisite for clinical translation. These materials are susceptible to thermodynamic degradation, including aggregation, oxidative dissolution, and ligand detachment—processes accelerated by UV irradiation, oxygen, and thermal fluctuations. Consequently, robust formulation strategies are critical. While aqueous suspensions offer experimental convenience, they are metastable; strict storage protocols (low temperature, light exclusion, inert atmosphere) are required to retard degradation. Lyophilization remains the gold standard for long-term preservation. By eliminating solvent-mediated hydrolysis and arresting particle mobility—often supplemented with cryoprotectants like trehalose—lyophilization maintains structural fidelity and maximizes shelf-life.[93,95]

Standardization of Shelf-Life and Stability Metrics

Establishing a regulatory framework for nanozyme stability remains a critical challenge in the bench-to-bedside transition. Unlike small-molecule drugs with predictable degradation kinetics, nanozymes exhibit complex, system-dependent stability profiles governed by core oxidation resistance and ligand durability. For instance, bare noble metal nanoparticles may lose activity within days, whereas cross-linked hybrid nanoflowers can retain over 70% efficacy after ten months. Therefore, generalized shelf-life metrics are insufficient. To ensure clinical viability, rigorous longitudinal monitoring of Critical Quality Attributes (CQAs)—specifically catalytic turnover, hydrodynamic radius, zeta potential, and morphological integrity—is imperative.[93,95]

Anti-Inflammatory Mechanism of Nanozymes

While the inflammatory response is a cornerstone of host defense against injury and infection, its dysregulation—whether manifesting as chronic persistence or acute volatility—precipitates widespread systemic pathology.[96,97] This dichotomy

Table 1 Common Synthesis Strategies of Nanozymes

Methods	Overview
Chemical Precipitation/Co-precipitation	A scalable aqueous-phase route for metal oxides involving simultaneous nucleation of metal cations via precipitating agents, yielding easily processable nanoparticles.
Hydrothermal/Solvothermal Synthesis	Conducted in sealed reactors under elevated pressure/temperature. Offers superior control over crystallinity and morphology (eg, nanorods, nanoflowers), exposing active facets for maximum catalytic efficiency.[92]
Reduction Methods	Standard for noble metal nanozymes. Reduces metal salts to zero-valent nanoparticles using agents like sodium borohydride. Capping agents are essential to regulate size and prevent aggregation.[93]
Doping and Hybridization	Modulates performance beyond single-component limits. Heteroatom doping alters electronic structures/defect density. Hybridization (eg, with organic components) endows multifunctionality for theranostics.[94]
Template-Assisted Synthesis	Uses scaffolds to strictly control size and shape. Biomimetic mineralization within protein cages yields nanozymes with exceptional uniformity and biocompatibility.

is starkly illustrated in cardiovascular diseases, where the synergistic interplay of inflammation and oxidative stress drives endothelial dysfunction, thereby accelerating atherosclerosis.[98,99] At the heart of this pathology lies a self-perpetuating "oxidative stress-inflammation" cycle, driven by the bidirectional relationship between ROS and immune activation.[100] Since ROS not only amplify inflammatory signaling but are also copiously generated by activated neutrophils, disrupting this feedback loop via efficient ROS scavenging has become a therapeutic imperative.[101–105] In this landscape, nanozymes have emerged as a superior alternative to traditional small molecules, offering the intrinsic ability to mimic natural antioxidant enzymes (SOD, CAT, GPx) for direct ROS elimination.[106–108] Yet, the therapeutic potential of nanozymes extends beyond simple chemical neutralization; they actively intervene in the hierarchical "receptor recognition–cascade amplification–transcriptional regulation" signaling axis and drive the reprogramming of plastic immune phenotypes to foster inflammation resolution.[109–114]

Given this complexity, how do nanozymes achieve potent therapeutic outcomes in vivo? The answer lies not in a single mechanism, but in their ability to exert synergistic, multi-modal effects.[115,116] A case in point is the engineering of ultra-small laminin-modified platinum nanozymes (Pt@LA), which transcend simple antioxidant activity by simultaneously inhibiting the NF-κB pathway and modulating microglial polarization.[117] This concerted action enables Pt@LA to arrest the pathological cascade in intracerebral hemorrhage models, effectively preserving neurological function and inhibiting glial scar formation through a holistic intervention strategy.

Building on this multi-targeted paradigm, can nanozymes also be engineered to repair physical tissue barriers while modulating the extracellular milieu? Recent advances suggest they can.[118–120] For instance, the development of an oral copper-zinc bimetallic nanozyme (Cu-Zn@HA) demonstrates a sophisticated tripartite mechanism: it scavenges ROS to mitigate oxidative damage, repairs the intestinal barrier protein ZO-1, and facilitates the phenotypic conversion of macrophages from pro-inflammatory M1 to restorative M2 states.[121] In experimental colitis models, this comprehensive approach translated into a 19% preservation of colon length and a reduction of key inflammatory cytokines (IL-1β, TNF-α) by over 50%, all while maintaining an excellent safety profile. Beyond these direct effects, the study uncovered a remarkable capacity of nanozymes to reshape the gut microbiota—specifically restoring beneficial Lactobacillus populations—thereby illuminating new pathways for treating inflammatory bowel disease (IBD) through microbiome homeostasis.

To further augment these biological effects, current research focuses on enhancing the versatility of nanozyme platforms through synergistic drug delivery and surface engineering. By encapsulating therapeutics such as celastrol within silver-modified cerium nanoparticles (Ag-CeNP@Cel), researchers have created hybrid systems that overcome the poor solubility and systemic toxicity often associated with potent anti-inflammatory drugs.[122] This nanoplatform creates a powerful synergy: the nanoparticles scavenge ROS while the delivered cargo drives macrophage reprogramming, significantly ameliorating the microenvironment in rheumatoid arthritis. Furthermore, ensuring the clinical viability of such systems requires addressing stability and biocompatibility; thus, surface modifications with chitosan or polyethylene glycol (PEG) have become standard practice to minimize non-specific binding and hemolytic risks.[123,124]

However, passive delivery is often insufficient for complex pathologies; true precision medicine demands "intelligent responsiveness." In the context of catalytic medicine, this refers to the engineering of nanozymes that remain inert until triggered by specific pathological cues—such as acidic pH or elevated ROS—or external stimuli like light and ultrasound.[22,125,126] This spatiotemporal control is realized through stimulus-sensitive "switches" embedded in the nanozyme architecture. For example, photoresponsive Cu/Zn dual single-atom systems can achieve reversible catalytic switching with efficiencies exceeding 90%, offering on-demand activity that minimizes off-target effects.[127,128] Similarly, the integration of piezoelectric materials expands this repertoire, allowing deep-tissue activation via ultrasound stimulation.[129,130] In parallel, targeted design provides an additional axis of precision, enabling preferential accumulation and/or activation at the desired biological scale. Practically, this can be implemented via ligand-mediated active targeting (eg, hyaluronic acid–CD44 interactions), biomimetic membrane-coating strategies to enhance inflammatory tropism and immune evasion, and organelle targeting (notably mitochondria) to intercept ROS production at its source.[131–133]

Moving forward, how do we transition from serendipitous discovery to the predictable construction of such sophisticated systems? The field is increasingly pivoting toward a data-driven, rational design framework that treats nanozyme engineering as a systems biology problem. Rather than relying solely on the Enhanced Permeability and Retention (EPR) effect, emerging strategies utilize machine learning-assisted high-throughput screening to map the correlations between atomic-scale structure and therapeutic efficacy.[118] By using disease-specific parameters—such as required antioxidant capacity or mitochondrial protection—as inputs, researchers can now inversely design optimal material compositions. This rational approach has proven particularly effective in cardiovascular applications; for instance, PtIr bimetallic nanozymes and Prussian blue analogues have been successfully tailored to remodel post-infarction microenvironments by coupling ROS scavenging with mitochondrial metabolic enhancement.[134,135]

In summary, the anti-inflammatory efficacy of nanozymes is underpinned by a “tripartite” regulatory mechanism: breaking the oxidative stress cycle, reprogramming immune responses, and restoring tissue barrier homeostasis. When these intrinsic properties are coupled with intelligent responsiveness and rational, data-driven design, nanozymes evolve from simple catalysts into transformative therapeutic platforms capable of addressing the multifaceted challenges of chronic inflammatory diseases. (Figure 2)

Applications of Nanozymes in Cardiovascular Diseases

Atherosclerosis

Atherosclerosis (AS) is not merely a lipid disorder but a complex, lipid-driven pathology fueled by a self-perpetuating inflammatory feedback loop within plaque lesions. Here, the interplay of pro-inflammatory cytokines, excessive ROS, and lipid accumulation dictates the stability of the plaque.[136,137] Since persistent inflammation is the primary driver of plaque rupture, therapeutic strategies must intervene in this vicious cycle. Addressing this, He et al engineered a Prussian

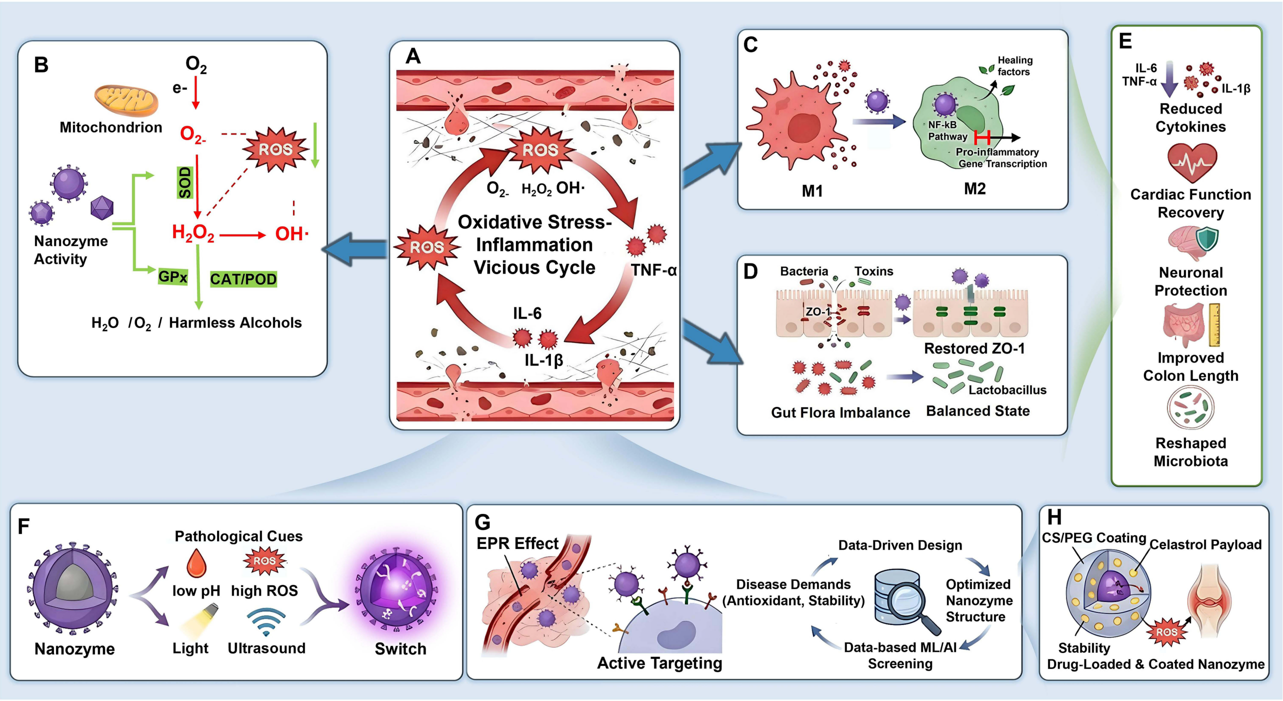


Figure 2 The trinity mechanism and intelligent design of nanozymes in anti-Inflammatory therapy. (**A**) Inflammatory tissue microenvironment, where excessive ROS and inflammatory signaling reinforce each other to form an oxidative stress–inflammation vicious cycle, accompanied by elevated pro-inflammatory cytokines (eg, TNF-α, IL-6, and IL-1β). (**B**) Direct ROS scavenging by nanozymes with multi-enzyme–mimetic activities, including SOD-, CAT-, POD-, and GPx-like catalysis, enabling stepwise detoxification of O_2^-/H_2O_2/OH• into less harmful products. Green arrows indicate nanozyme-mediated therapeutic effects, whereas red arrows denote ROS transformations. (**C**) Immune reprogramming and suppression of pro-inflammatory pathways: nanozymes promote macrophage polarization from M1 to M2 and inhibit NF-κB–mediated pro-inflammatory gene transcription while enhancing tissue-repair factors. Symbol clarification: the red inhibitory bar (**H**) denotes inhibition/suppression of the indicated process. (**D**) Restoration of barrier integrity and microenvironment homeostasis through reinforcing tight junctions (eg, ZO-1) and rebalancing gut microbiota to mitigate bacterial/toxin translocation. (**E**) Therapeutic outcomes, including reduced cytokine levels, recovery of cardiac function, neuronal protection, improved colon length, and microbiota remodeling. (**F**) Intelligent responsiveness, in which nanozymes are activated or switched by pathological cues (low pH, high ROS) and/or external stimuli (light and ultrasound). (**G**) Multi-layered targeting and predictive inverse design: passive accumulation via the enhanced permeability and retention (EPR) effect, active targeting via surface ligands, and data-driven ML/AI screening to optimize nanozyme structures according to disease demands (eg, antioxidant capacity and stability). (**H**) Representative design case of a drug-loaded, surface-coated nanozyme (eg, CS/PEG coating and celastrol payload) to improve stability and therapeutic efficacy.

Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; POD, peroxidase; GPx, glutathione peroxidase; NF-κB, nuclear factor kappa B; ZO-1, zonula occludens-1; EPR, enhanced permeability and retention; CS, chitosan; PEG, polyethylene glycol.

blue-based multifunctional nanozyme (PBNZ@PP-Man) designed to simultaneously target and neutralize the diverse pro-inflammatory factors defining the plaque microenvironment.[138] This concept of multi-target intervention has been further refined by systems such as BSA@PB/Cur and PCZ@PB NCs, which go beyond simple ROS scavenging to actively suppress key cytokines like TNF-α and IL-1β, thereby inhibiting the formation of foam cells that constitute the plaque core.[139,140]

However, is suppressing inflammation sufficient to halt disease progression? Growing evidence suggests that senescent cells within the vessel wall interact with ROS to further exacerbate the pathology, highlighting the need for therapies that also address cellular aging. Recognizing the compromised antioxidant defense systems in these senescent cells, Wei Hui's group designed a cascade nanozyme (MSe1) that mimics SOD and glutathione peroxidase. By clearing excess ROS, MSe1 effectively inhibits endothelial senescence, slowing the trajectory of plaque development.[141] Taking this dual-targeting approach a step further, Chen et al synthesized a mesoporous palladium–boron–phosphorus ternary nanozyme. This system does not just scavenge ROS; by co-loading hydrogen (to reduce inflammation) and 4,4′-dimethoxychalcone (to target senescence), it orchestrates a comprehensive repair process—eliminating macrophage inflammation while simultaneously activating autophagy in endothelial cells to clear senescent components.[142]

Ultimately, these advances frame atherosclerosis as a multi-faceted target where nanozymes can integrate antioxidation, anti-inflammation, and cholesterol regulation into a single platform.[143,144] As the field moves forward, the focus is shifting from simple efficacy to precision; future designs will likely prioritize enhanced safety through ultrasound-controlled release or biomimetic encapsulation, potentially integrating immunomodulatory functions to reshape the vascular immune landscape entirely.[145] (Figure 3A)

Myocardial Ischemia-Reperfusion Injury (MIRI)

Reperfusion therapy following myocardial infarction presents a clinical paradox: while essential for restoring blood supply, it frequently triggers severe cellular dysfunction driven by a sudden surge in ROS and uncontrolled

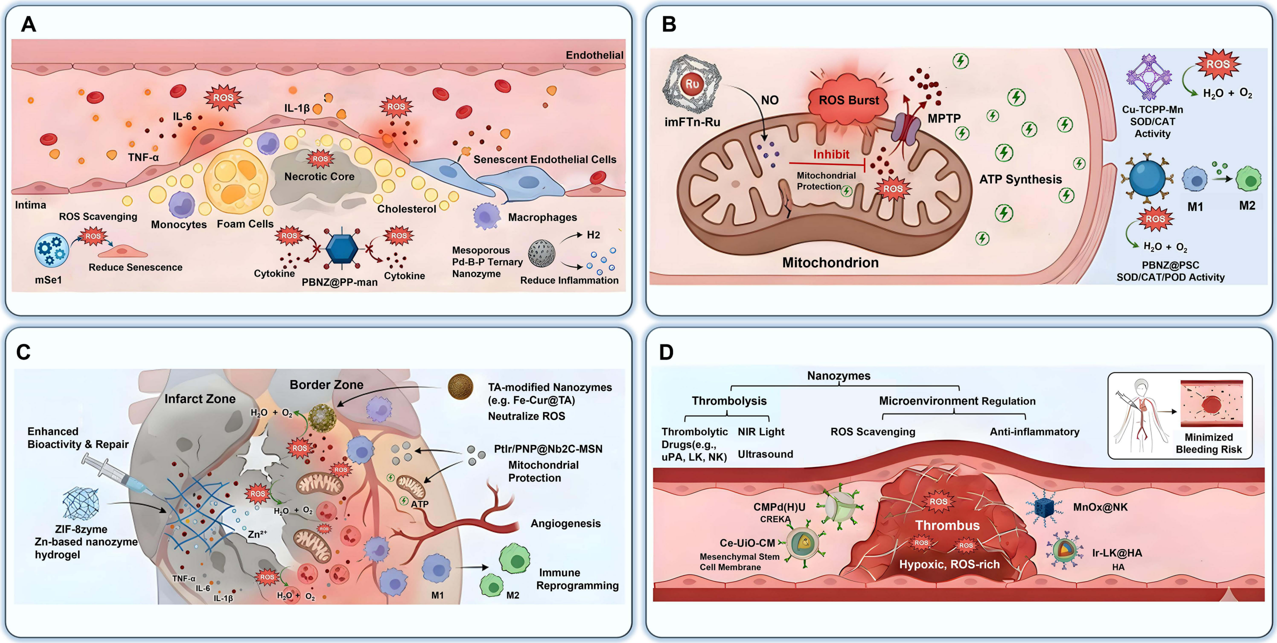


Figure 3 Multifunctional nanozyme strategies in cardiovascular diseases. (**A**) Nanozymes mitigate atherosclerosis by scavenging ROS, suppressing pro-inflammatory cytokines, regulating cholesterol-associated plaque progression, and alleviating vascular cell senescence within the atherosclerotic microenvironment. (**B**) In myocardial ischemia–reperfusion injury, nanozymes attenuate ROS bursts and inflammatory cascades, protect mitochondria (eg, limiting MPTP opening), preserve ATP synthesis, and modulate macrophage polarization to promote tissue repair. (**C**) Following myocardial infarction, nanozymes neutralize ROS, enhance angiogenesis, and reprogram the immune microenvironment (M1-to-M2 shift), thereby reducing adverse ventricular remodeling. M1 and M2 denote pro-inflammatory (classically activated) and anti-inflammatory/pro-repair (alternatively activated) macrophage phenotypes, respectively. (**D**) Stimuli-responsive, thrombus-targeted nanozyme platforms integrate on-demand thrombolytic drug release with catalytic ROS regulation and anti-inflammatory activity, improving thrombolysis while minimizing systemic bleeding risk.
Abbreviations: MPTP, mitochondrial permeability transition pore; ATP, adenosine triphosphate.

inflammation.[146–149] Consequently, the therapeutic goal has shifted toward biomimetic designs that can manage this “oxidative burst” while protecting cellular organelles.

Given that mitochondria act as the epicenter of this crisis—where dysfunction triggers massive ROS production and cell death—preserving mitochondrial integrity is paramount. Zhang et al tackled this by engineering imFTn-Ru, a mitochondria-targeted nanozyme with NO-generating capacity. By localizing action to the organelle, this agent significantly reduced mitochondrial ROS and inhibited the opening of the mitochondrial permeability transition pore (MPTP), offering a targeted defense that preserved membrane potential in vivo.[150] While mitochondrial protection addresses the source of injury, mitigating the broader tissue damage requires robust, synergistic catalysis. To this end, Xiang et al developed a MOF-based bimetallic nanozyme (Cu-TCPP-Mn) that mimics both SOD and CAT activities, ensuring rapid, high-capacity ROS elimination.[151]

Yet, effective treatment extends beyond immediate ROS scavenging to long-term immune modulation. Gu et al demonstrated this with PBNz@PSC, a Prussian blue nanozyme that leverages the enhanced permeability and retention (EPR) effect to accumulate in damaged tissue. Its innovation lies not just in its enzymatic activity, but in its ability to repolarize macrophages from a pro-inflammatory M1 state to a reparative M2 phenotype, achieving outcomes superior to conventional treatments like sulfotanshinone IIA sodium.[134] These findings suggest that the future of MIRI treatment lies in nanozymes that serve as multifunctional guardians—simultaneously managing oxidative stress, inflammation, and energy metabolism. (Figure 3B)

Myocardial Infarction

Myocardial infarction (MI) initiates a devastating cascade of ischemic necrosis and oxidative stress that, if unchecked, leads to permanent scarring and ventricular remodeling.[152,153] While early revascularization is the standard of care, the rapid neutralization of ROS remains a critical, yet often unmet, need for preserving remaining cardiac function. Nanozymes have shown exceptional promise here, particularly when designed to mimic the body’s intrinsic defense mechanisms. For example, Wang et al utilized ultra-small (<5 nm) PtIr bimetallic nanozymes to maintain mitochondrial structure under oxidative duress. Their data from rat MI models revealed that converting excess ROS into harmless byproducts significantly enhanced cardiomyocyte viability and microvascular density compared to traditional controls.[135] Similarly, PNP@Nb2C-MSN nanozymes have been shown to facilitate angiogenesis within the infarcted zone, highlighting the regenerative potential of these materials.[154]

But can we ensure these potent agents reach the heart in sufficient quantities? To overcome the challenge of cardiac targeting, recent strategies have exploited the high affinity of tannic acid (TA) for heart tissue. Liu et al developed Fe-Cur @TA nanozymes, achieving a ten-fold increase in cardiac retention. This precise accumulation allowed for a disruption of the oxidative stress–inflammation cycle, reducing immune cell infiltration and promoting beneficial M2 macrophage polarization.[155] Gu et al further validated this targeting strategy with a TA-modified MnO_2 nanozyme, confirming that localized delivery effectively inhibits post-MI fibrosis.[156]

Looking beyond simple targeting, the latest generation of nanozymes aims to actively reprogram the immune microenvironment. Chen et al’s ZIF-8zyme exemplifies this, functioning as a dual antioxidant and anti-inflammatory agent that shifts macrophage phenotype to support tissue repair.[157] Taking this concept into tissue engineering, Zhong et al integrated catalytic activity into a structural scaffold, creating an injectable Zn-based nanozyme hydrogel (ZIF-8–ALG). This hydrogel performs a dual function: it acts as a physical barrier to block ROS-driven inflammatory cascades and, by gradually releasing zinc ions into the nutrient-deprived infarct zone, synergistically enhances bioactivity and angiogenesis.[62](Figure 3C)

Thrombosis and Antithrombotic Strategies

Thrombosis represents a critical emergency where the obstruction of cardiac vessels can rapidly escalate to acute MI. The current cornerstone of treatment—thrombolytic injection—is fraught with limitations, primarily a narrow therapeutic window and the significant risk of systemic bleeding.[158–161] The field is thus seeking a solution that offers the potency of traditional drugs with the precision of targeted delivery. Nanozymes have emerged as ideal candidates for this, acting as “smart carriers” that integrate thrombolysis with microenvironmental modulation.

One innovative approach to reducing systemic toxicity involves stimuli-responsive activation. CMPd(H)U, a multifunctional nanozyme, utilizes a fibrin-recognizing ligand (CREKA) to home in on thrombotic sites. Once localized, near-infrared irradiation triggers the release of urokinase for on-demand thrombolysis. Crucially, this system also generates hydrogen to scavenge ROS, thereby suppressing neuronal pyroptosis and mitigating reperfusion injury—a benefit traditional thrombolytics cannot offer.[160] Taking a different structural approach, Ir-LK@HA encapsulates lumbrokinase within a hyaluronic acid shell. This design extends the drug's biological half-life and ensures release only within the thrombus microenvironment, while the iridium core provides real-time CT imaging capabilities to monitor treatment progress.[162]

Furthermore, mimicking biological membranes has proven effective for evasion and targeting. A cerium-based MOF nanozyme (Ce-UiO-66), cloaked in mesenchymal stem cell membranes, utilizes ultrasound triggering to generate O_2 via catalase-like activity, achieving efficient clot dissolution in rat models.[66] Such strategies highlight a paradigm shift: rather than relying solely on chemical lysis, nanozymes like the nattokinase-loaded MnOx platform facilitate a multipronged attack—scavenging ROS while locally releasing lytic agents.[163] By combining targeted drug delivery with intrinsic enzyme-mimetic activities, these integrated strategies are poised to rewrite the standards of thrombolytic therapy, offering high efficacy with substantially reduced bleeding risks. (Figure 3D)

Targeted Strategies for Nanozymes in Cardiovascular Diseases

In cardiovascular disease treatment, traditional drugs are often limited by off-target toxicity and inadequate site-specific accumulation. Targeted delivery has therefore emerged as the central strategy for nanozymes, enabling precise localization of catalytic activity at lesion sites and transforming their intrinsic "enzymatic power" into genuine "therapeutic power."

Molecular Recognition via Ligand and Peptide Functionalization

Active targeting through surface modification with bioactive ligands represents a foundational approach to enhancing specificity. Peptide functionalization, in particular, has demonstrated robust efficacy in directing nanozymes to specific tissues.[164,165] For instance, the incorporation of cardiac-targeting peptides into CeO_2/Au-pep nanozymes allows for the selective delivery of therapeutic miRNA to ischemic myocardium, effectively mitigating ischemia-reperfusion injury (I/RI).[166] Similarly, the modification of nanoplatforms with peptides such as S2P (targeting macrophages) or Transferrin (targeting the blood-brain barrier) facilitates the precise interception of inflammatory pathways in atherosclerosis and ischemic stroke, respectively.[167,168]

Beyond peptides, ligand-receptor interactions are widely exploited. Hyaluronic acid (HA) and mannose have been utilized to target CD44 and mannose receptors, which are overexpressed on activated macrophages within atherosclerotic plaques.[138,169,170] These interactions ensure that nanozymes not only accumulate at the lesion site but are also internalized by the target effector cells, significantly enhancing anti-inflammatory and antioxidative efficacy.

Biomimetic Engineering: Cell Membrane Camouflage

Leveraging the intrinsic chemotactic capabilities of inflammatory cells offers a sophisticated "Trojan horse" strategy. During CVD progression, inflammatory mediators drive the migration of neutrophils and monocytes to lesion sites. By coating nanozymes with neutrophil-like or macrophage cell membranes, researchers have created biomimetic platforms that inherit this migratory behavior.[137] For example, neutrophil-membrane-coated Prussian blue nanozymes (MPBzyme@NCM) can selectively bind to inflamed cerebral microvascular endothelial cells, facilitating active delivery to ischemic brain regions.[171] This biomimetic approach effectively bridges the gap between synthetic catalysis and biological navigation.

Organelle-Specific Targeting

Beyond cellular-level precision, organelle-specific targeting has also been explored. The imFTn-Ru nanocatalyst, developed by researchers at Nankai University, integrates three modules: an ischemia-injured cardiomyocyte-targeting unit, a lysosome-escaping unit, and a mitochondria-targeting unit. This multi-level design enabled precise mitochondrial delivery, preserving mitochondrial function and mitigating ischemia–reperfusion injury.[150]

Microenvironment-Responsive

Pathological tissues are characterized by unique chemical hallmarks, such as acidosis and elevated ROS. Advanced nanozymes, such as ultra-small PtIr nanostructures, are engineered to activate specifically within these ROS-rich environments, acting as SOD and catalase mimics to reshape the inflammatory landscape.[135]

Synergistic and Hierarchical Designs

The most advanced systems currently employ combinatorial strategies. By integrating passive targeting (via the Enhanced Permeability and Retention effect) with active ligand binding, therapeutic outcomes are maximized. Recent innovations include dual-functionalized nanozymes modified with both cardiac-homing peptides and mitochondrial-targeting moieties (eg, TPP), enabling a hierarchical delivery process that treats both the tissue and the subcellular organelle.[172] Furthermore, mannose-modified Metal-Organic Frameworks (MOFs) have been designed to degrade specifically within the acidic microenvironment of infarcted tissue, releasing therapeutics like quercetin locally while minimizing systemic side effects.[173]

Clinical Prospects and Challenges of Nanozymes in Cardiovascular Disease Management

Barriers to Clinical Translation

While preclinical data compel us to view nanozymes as potent agents against oxidative stress and inflammation in CVDs, a significant chasm persists between laboratory synthesis and bedside application.[174] The transition from defining these entities as mere "catalytic nanomaterials" to validating them as "clinical therapeutics" requires us to look beyond their intrinsic chemical potential and confront the physiological realities that stifle their efficacy. The field currently faces a complex matrix of impediments, ranging from the loss of catalytic fidelity in vivo to the formidable barriers of cardiac delivery, safety, and scalability.

The most immediate scientific hurdle lies in preserving catalytic efficiency and specificity within the complex physiological environment.[175,176] Unlike the controlled conditions of a reaction flask, the biological milieu is replete with interfering proteins and fluctuating ionic strengths that can rapidly foul active sites. Consequently, we see an urgent need for bioinspired designs that impose enzyme-like structural and electronic constraints on catalytic centers. For example, by engineering single-atom or dual-atom nanozymes with well-defined coordination environments, researchers can fine-tune adsorption energetics at the atomic level, offering a route to enhance catalytic efficiency far beyond that of conventional defect-driven surfaces.[177–180] To further insulate these active centers, constructing confined microenvironments—such as porous frameworks or protein-mimetic shells—can regulate mass transport and shield against nonspecific protein adsorption.[181] But physical protection alone is insufficient; true clinical viability demands "dynamic adaptability." By incorporating stimulus-responsive motifs that emulate natural enzyme gating, such as ROS- or pH-triggered masking, we can engineer systems that remain silent in healthy tissue yet become hyper-active within the lesion, thereby maximizing precision while minimizing off-target redox perturbation.[22,182]

Even if catalytic competence is preserved, delivering these agents to the ischemic myocardium presents a challenge far greater than that encountered in oncology. While the Enhanced Permeability and Retention (EPR) effect is a cornerstone of tumor targeting, vascular permeability in inflamed myocardium is notoriously transient and heterogeneous. The heart's high perfusion rates and substantial shear forces create a "wash-out" effect, resulting in minimal residence time for circulating nanoparticles and leading to predominant sequestration by the Reticuloendothelial System (RES).[183,184] This creates a difficult engineering paradox: large functionalized particles may enhance specific recognition but fail to penetrate the dense extracellular matrix and fibrotic tissues, whereas ultra-small particles risk rapid renal clearance before achieving a therapeutic dose.

This delivery challenge precipitates a critical, often overlooked safety question: What is the long-term metabolic fate of these catalytically active materials? Unlike inert drug carriers, nanozymes are designed to continuously modulate redox reactions. If these potent catalysts accumulate off-target—particularly in the liver, kidneys, or healthy myocardium—they risk disrupting essential redox homeostasis. The heart is uniquely vulnerable to such perturbations, where interference with mitochondrial electron transport chains or calcium signaling could precipitate arrhythmias or contractile dysfunction—subtle risks that short-term animal models frequently fail to capture.[185] Furthermore, the non-biodegradable nature of many high-performance inorganic nanozymes complicates regulatory approval, as their long-term tissue retention and biotransformation pathways remain largely unmapped.[186]

Ultimately, even scientifically perfect candidates face the industrial bottleneck of manufacturing scalability.[187] The catalytic prowess of nanozymes is intrinsically linked to microscopic parameters such as particle size, crystal plane exposure, and dopant ratios—features that are hypersensitive to synthesis conditions like temperature and precursor purity. This sensitivity often results in significant batch-to-batch variations that are unacceptable for clinical use.[188] Without unified standards for evaluating activity under physiological conditions, or stringent Quality Control (QC) metrics for active site density, satisfying Good Manufacturing Practice (GMP) requirements remains an elusive goal.[189]

Future Perspectives and Strategic Directions

How do we navigate these physiological and industrial minefields to propel nanozymes from academic concepts to viable cardiovascular therapies? The answer lies in shifting our research paradigm from empirical material screening to rational, mechanism-driven design.

To address the precision-toxicity trade-off, the next generation of nanozymes must evolve from "always-on" catalysts to "smart" systems that activate exclusively within the pathological microenvironment.[22,182,190] By exploiting disease-specific cues—such as the acidic pH of ischemic tissue, elevated ROS levels, or the overexpression of Matrix Metalloproteinases (MMPs)—we can design nanozymes with "masked" activities that are unveiled only at the target site.[125] For instance, pH-responsive polymer shells can shield the active core in the bloodstream and dissociate only within the acidic ischemic myocardium, an "on-demand" strategy essential for limiting systemic off-target disturbances.[191,192]

Furthermore, given that CVD pathology is a multifaceted cascade involving oxidative stress, inflammation, apoptosis, and fibrosis, relying on a single mode of action is increasingly viewed as insufficient. We envision nanozymes evolving into versatile, multimodal platforms that synergize with other therapeutic modalities. Integrating nanozyme-based ROS scavenging with drug delivery, gene editing, or gas therapy offers a comprehensive treatment strategy capable of simultaneously addressing early-stage inflammation and late-stage ventricular remodeling.[193]

Underpinning these functional advances must be a return to biomimetic principles. Future designs should move beyond static structures to create dynamic, adaptive systems that mimic the metal centers of metalloenzymes or utilize soft interfaces capable of conformational changes.[177,179,180] Finally, to accelerate the discovery of such complex materials, the field must embrace data-driven approaches over traditional "trial-and-error" optimization. By leveraging machine learning to predict structure-activity relationships and utilizing "Heart-on-a-Chip" technologies for high-throughput physiological screening, we can rigorously filter candidates before proceeding to costly animal studies.[194–197] Through this convergence of rigorous materials science and artificial intelligence, nanozymes hold the potential to revolutionize cardiovascular disease management.

Conclusion

As the inflammatory mechanisms underlying CVDs continue to be elucidated, the shortcomings of conventional anti-inflammatory therapies—most notably limited targeting precision and constrained regulatory breadth—have become increasingly apparent, highlighting the need for therapeutic platforms that are both effective and controllable. In this context, nanozyme-based strategies have attracted growing attention because their tunable catalytic reactivity and engineering flexibility enable multi-pronged and sustained modulation of pathological inflammation. By scavenging reactive oxygen species, reshaping immune responses, interrupting inflammatory signaling cascades, and protecting cardiomyocytes, nanozymes are increasingly recognized as a promising direction at the interface of materials science and cardiovascular immunology. Notably, through antioxidant enzyme–mimicking activities, responsiveness to inflammatory microenvironments, and regulation of immune-cell behaviors, nanozymes have already demonstrated encouraging therapeutic benefits across diverse CVD models.

Despite these advances, translating nanozyme-enabled therapies from experimental validation to clinical practice will require systematic solutions to several key challenges, including further improvement of catalytic efficiency, reliable targeted delivery, comprehensive biosafety evaluation, and scalable, reproducible manufacturing. Looking ahead, closer integration of materials engineering, biomedicine, imaging technologies, and systems biology is expected to accelerate the development of multifunctional nanozyme platforms featuring intelligent sensing, adaptive feedback regulation, and precise lesion targeting. Such progress may establish new therapeutic paradigms and technological foundations for managing refractory CVDs. Overall, nanozymes represent not only a practical means to mitigate oxidative stress and restore inflammatory balance, but also a versatile materials basis for constructing mechanism-guided precision treatment systems. Their translational potential in cardiovascular medicine merits sustained and in-depth investigation, with the prospect of reshaping future strategies for cardiovascular therapy.

Abbreviations

ROS, reactive oxygen species; CVD, Cardiovascular disease; CVDs, cardiovascular diseases; NSAIDs, nonsteroidal anti-inflammatory drugs; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; RA, rheumatoid arthritis; POD, peroxidase; CS, chitosan; PEG, polyethylene glycol; AS, Atherosclerosis; MIRI, Myocardial ischemia–reperfusion injury; MPTP, mitochondrial permeability transition pore; MMP, membrane potential; MOF, metal–organic framework; MI, Myocardial infarction; TA, tannic acid; NK, Nattokinase; LK, lumbrokinase; HA, hyaluronic acid; CHP, cardiac-homing peptide; TPP, triphenylphosphine; RES, reticuloendothelial system; O_2-, superoxide anions; OH, hydroxyl radicals; H_2O_2, hydrogen peroxide; Au, gold; Ag, silver; Pt, platinum; Pd, palladium; CQAs, Quality Attributes; QC, Quality Control; GMP, Good Manufacturing Practice; MMPs, Matrix Metalloproteinases; IBD, inflammatory bowel disease.

Acknowledgments

The authors acknowledge the financial support from the National Natural Science Foundation of China (32201141) (awarded to Chang Liu), the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai (PWZxq2022-08) (awarded to Xinghui Liu), the Shanghai Pudong New Area Science and Technology Development Fund public institution livelihood research project (PKJ2024-Y27) (awarded to Chang Liu), the Pudong New Area Health System's Health Talent Youth Training Program (2025PDWSYCQN-07)(awarded to Chang Liu.)

Disclosure

The authors report no conflicts of interest in this work.

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