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REVIEW

Recent Advances in Nanozymes for the Treatment of Atherosclerosis

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Abstract: Atherosclerosis (AS) is a complex, multifactorial cardiovascular disease characterized by lipid accumulation, chronic inflammation, oxidative stress, and endothelial dysfunction. Conventional therapies, including lipid-lowering and anti-inflammatory agents, offer limited efficacy due to inadequate lesion targeting, low bioavailability, and systemic side effects. Nanozymes, which engineered nanomaterials with intrinsic enzyme-mimetic catalytic activities have recently emerged as a transformative therapeutic strategy capable of simultaneously modulating oxidative stress, inflammation, and lipid metabolism. This review comprehensively summarizes recent advances in nanozyme-based interventions for AS, focusing on representative systems such as Prussian blue, cerium oxide, selenium-based, and multifunctional composite nanozymes. We critically discuss their design principles, catalytic mechanisms, lesion-targeting strategies, and therapeutic outcomes in preclinical models. Additionally, we highlight key translational challenges, including biosafety concerns, pharmacokinetic limitations, and manufacturing standardization, which currently impede clinical application. By integrating catalytic activity with targeted delivery and microenvironment-responsive functionalities, nanozymes offer a promising paradigm for precision therapy in AS. Future research should prioritize enhancing biocompatibility, optimizing therapeutic specificity, and establishing scalable, reproducible fabrication methods to facilitate clinical translation. This review aims to provide a systematic framework and insightful guidance for advancing nanozyme-based therapeutics toward clinical application in cardiovascular disease management.

Keywords: atherosclerosis, nanozymes, drug delivery, nanomedicine

Introduction

AS is a chronic inflammatory vascular disorder characterized by progressive lipid accumulation, endothelial dysfunction, and inflammatory responses within arterial walls.[1] It serves as the common pathological underpinning of numerous cardiovascular and cerebrovascular diseases, including coronary artery disease, stroke, and peripheral artery disease, which collectively pose substantial threats to global health.[2–4] According to the World Health Organization's Global Health Estimates and data from the Institute for Health Metrics and Evaluation's Global Burden of Disease study, cardiovascular diseases accounted for approximately 19.91 million deaths worldwide in 2021, constituting roughly 33% of total global mortality[5]. Traditional pharmacological strategies, primarily focused on oral lipid-lowering (eg, statins) and anti-inflammatory medications, remain first-line treatments for managing AS.[6–8] However, these therapies exhibit significant limitations, including low bioavailability, delayed therapeutic onset, poor specificity, and notable systemic toxicity.[9–11]

Nanomedicine has emerged as a transformative approach to address the inherent limitations of conventional pharmacotherapy.[12–15] By leveraging nanotechnology, nano drug delivery systems significantly enhance drug solubility, prolong systemic circulation time, optimize biodistribution, and mitigate adverse effects.[16–18] Despite these advantages, traditional nanocarriers face substantial biological barriers, particularly their rapid recognition and clearance by the

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mononuclear phagocyte system, which hampers efficient drug delivery to targeted atherosclerotic lesions.[19–21] With the interdisciplinary integration and rapid evolution of materials science, nanotechnology, and biomedical engineering, nanozyme-based therapeutics have recently surfaced as a novel paradigm, offering remarkable potential in disease diagnostics and therapeutics. Nanozymes, defined as engineered nanoparticles possessing intrinsic enzyme-mimetic catalytic activities, exhibit unique physicochemical properties and biological functions.[22–27] Typically characterized by dimensions less than 100 nanometers, nanozymes may be composed of organic materials, inorganic materials, or hybrid composites, each tailored for distinct catalytic functions.[28–30] Due to their nanoscale effects, nanozymes efficiently evade rapid systemic clearance, thereby achieving enhanced bioavailability and prolonged circulation. Furthermore, their high surface-to-volume ratios enable extensive surface functionalization with diverse ligands, significantly enhancing targeted delivery capability and therapeutic precision. Nanozyme-based therapeutics have shown exceptional efficacy, particularly in oncology, demonstrating robust catalytic performance, excellent stability, and biocompatibility.[31–33] These distinctive advantages have stimulated significant research interest toward exploring their application potential in cardiovascular diseases, including AS. Nanozyme delivery systems offer multifaceted therapeutic benefits through solubilization of hydrophobic drugs, extension of drug half-life, enhancement of lesion-specific targeting, and attenuation of systemic toxicities, presenting vast potential in cardiovascular clinical translation.[34–38]

In this review, we critically analyze recent advances in nanozyme-based targeted therapeutic systems for the management of AS. Initially, we elucidate the complex pathophysiological mechanisms underpinning AS progression, detailing oxidative stress-induced reactive oxygen species (ROS) generation, endothelial dysfunction, inflammation, and plaque instability. Subsequently, we outline conventional therapeutic interventions, highlighting their inherent limitations and unmet clinical needs. We place particular emphasis on nanozyme-driven approaches designed to specifically counteract ROS accumulation and plaque development. The discussion encompasses various nanozyme formulations, including Prussian blue nanozymes, cerium oxide nanozymes, carbon quantum dots nanozymes, and multifunctional composite nanozymes, elucidating their respective design rationales, catalytic mechanisms, and therapeutic efficacies as demonstrated in preclinical and emerging clinical studies. By systematically synthesizing the current state of knowledge and identifying existing gaps, we underscore the significant therapeutic advantages offered by nanozyme-based targeted drug delivery platforms in AS treatment. Additionally, innovative combinatorial strategies integrating multiple nanozymes modalities and precision targeting methods are proposed as promising avenues for advancing therapeutic outcomes. Ultimately, our objective is to provide comprehensive insights and practical guidance to researchers and clinicians aiming to harness nanotechnology-driven innovations to substantially improve diagnostic accuracy, therapeutic efficacy, and overall patient prognosis in AS (Figure 1).

Mechanisms of AS

AS is a chronic and complex vascular disorder characterized by gradual lesion progression that remains clinically silent during early stages. Its etiology involves intricate interactions among various factors, including dyslipidemia, local hemodynamic disturbances, autoimmune responses, environmental influences, and genetic predispositions.[39–41] Importantly, endothelial dysfunction and lipid accumulation within arterial walls serve as primary initiating events.

Multiple pathogenic stimuli including immunological triggers, pathogenic microorganisms, oxidative stress, and hemodynamic shear stress that induce endothelial cell activation and subsequent damage. Activated endothelial cells express elevated levels of adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and P-selectin, alongside chemokines, facilitating monocyte recruitment and transmigration into the arterial intima. Monocytes internalize oxidized low-density lipoprotein (oxLDL) particles within the intima, differentiating into macrophages.[42–44] These macrophages perpetuate inflammatory cascades that exacerbate lesion development by releasing pro-inflammatory cytokines, chemokines, and ROS. The progression of AS can generally be described in three major stages: initiation, progression, and complication (Figure 2).

Initiation

The arterial wall typically consists of three structural layers: the adventitia, media, and intima. Early atherosclerotic lesions form primarily within the intimal layer.[45] Initial events involve the infiltration and retention of LDL particles within the

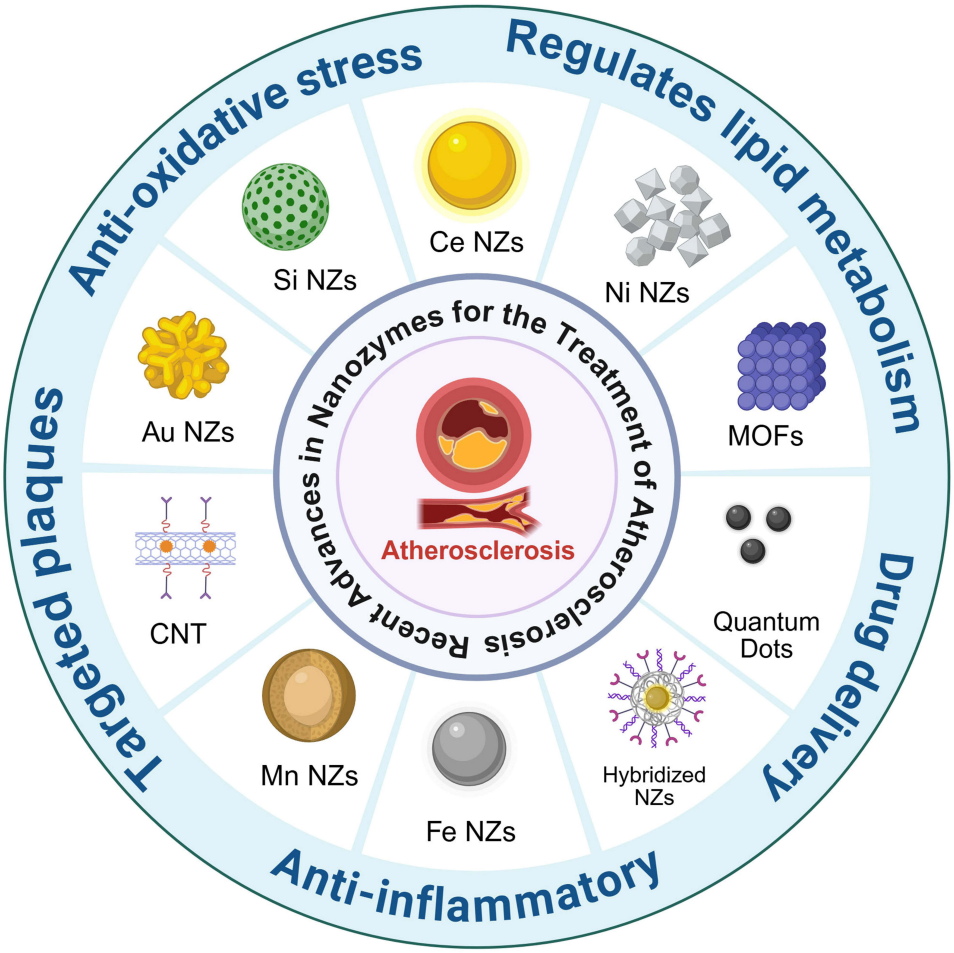

Figure 1 Schematic representation of different nanozymes for the treatment of atherosclerosis by exerting anti-inflammatory, anti-inflammatory, plaque targeting, modulation of lipid metabolism and drug delivery.

arterial intima, where they undergo oxidative modifications to become oxLDL, a highly pro-inflammatory and immunogenic substance. OxLDL triggers local inflammatory reactions, endothelial dysfunction, and promotes the expression of adhesion molecules and inflammatory mediators.[46–48] Activated endothelial cells subsequently upregulate adhesion molecules and chemokines, promoting monocyte adhesion and infiltration.[49] Once inside the intima, monocytes differentiate into macrophages, which actively internalize oxLDL via scavenger receptors, thus forming foam cells. Foam cell formation is a critical event in early lesion development, contributing to the formation of fatty streaks.[50] Concurrently, T lymphocytes infiltrate the intima and modulate local immune responses. CD4+ T helper 1 cells predominate within lesions, secreting pro-inflammatory cytokines such as interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α). IFN-γ notably amplifies macrophage activation and inflammation, suppresses collagen synthesis by smooth muscle cells (SMCs), and accelerates extracellular matrix degradation, compromising plaque stability. TNF-α and IL-2 similarly enhance local inflammation and disturb lipid metabolism, intensifying the progression of lesions.[51] Additionally, endothelial cells and SMCs actively participate in inflammatory processes by producing cytokines such as IL-1, IL-6, IL-8, and chemokines like monocyte chemotactic protein-1. These mediators amplify inflammatory responses and enhance monocyte recruitment, foam cell formation, and lesion progression. Platelets also play a crucial role by releasing chemokines and growth factors, further driving vascular inflammation and cellular proliferation within the plaque.[52]

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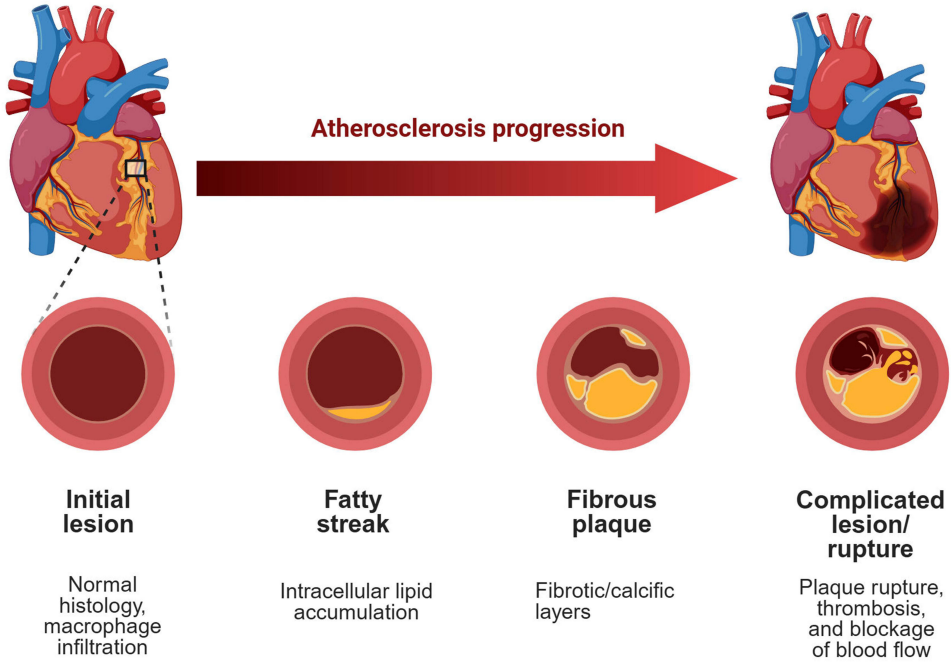

Figure 2 Schematic representation of the pathogenesis of atherosclerosis and plaque formation.

Progression and Complications

As atherosclerotic lesions mature, SMCs, migrating from the media or proliferating in situ, actively synthesize ECM proteins including collagen, elastin, and proteoglycans resulting in intimal thickening and plaque stabilization in early phases.[53] However, macrophages within plaques secrete matrix metalloproteinases (MMPs), enzymes that degrade collagen fibers critical to fibrous cap integrity. Continuous ECM degradation by MMPs weakens the fibrous cap, increasing susceptibility to plaque rupture. Moreover, within advanced lesions, apoptosis and necrosis of macrophages and SMCs result in the accumulation of necrotic debris and the formation of lipid-rich necrotic cores.[54] Impaired efferocytosis, the clearance of apoptotic cells, further exacerbates inflammation and lesion instability. Although lesions typically expand outward initially, compensatory arterial remodeling eventually becomes insufficient, leading to inward plaque growth and significant luminal narrowing. Advanced atherosclerotic plaques may eventually cause critical obstruction of the arterial lumen, severely impairing blood flow, especially under conditions of increased myocardial oxygen demand.[55] This impairment clinically manifests as angina, transient ischemic attacks, or claudication. Compromised plaque integrity significantly heightens the risk of plaque rupture or erosion, exposing thrombogenic material (eg, tissue factor) from the necrotic core to circulating blood, precipitating acute thrombotic events.[56–58] Such thrombotic events can rapidly lead to vascular occlusion, triggering acute myocardial infarction, ischemic stroke, or sudden death. Non-occlusive thrombi also contribute substantially to lesion growth through the release of growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor, and fibroblast growth factor, promoting further SMC migration, proliferation, and ECM synthesis. These processes collectively culminate in advanced, complicated lesions characterized by extensive calcification, fibrosis, and heightened susceptibility to catastrophic cardiovascular complications.[59]

Traditional Diagnosis and Treatment of AS

AS is a chronic, progressive vascular disease characterized by the silent and gradual accumulation of lipid-rich plaques within arterial walls, often remaining asymptomatic for decades[60]. Clinical manifestations typically arise when significant arterial narrowing or thrombotic occlusion occurs, resulting in compromised blood flow and an increased risk of life-

threatening complications such as myocardial infarction, ischemic stroke, and peripheral arterial disease.[61] Hence, early and precise diagnosis is crucial for effective management and prevention of severe cardiovascular events.

Diagnostic Techniques

Definitive diagnosis of AS commonly relies on advanced imaging techniques aimed at accurately identifying and characterizing atherosclerotic plaques in terms of their location, severity, composition, and vulnerability. Widely used non-invasive imaging modalities include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).[62–64] Ultrasound imaging, particularly carotid ultrasound, serves as a routine screening method due to its simplicity, safety, and cost-effectiveness in detecting intimal-media thickness and plaques.[65–67] However, ultrasound imaging provides limited resolution and insufficient detail regarding plaque composition. Computed tomography angiography (CTA), another non-invasive modality, effectively visualizes arterial calcifications, luminal narrowing, and plaque burden, and is commonly employed for coronary artery assessment. Nevertheless, CTA exposes patients to ionizing radiation and contrast media, potentially causing nephrotoxicity in susceptible individuals. MRI offers superior soft tissue contrast without ionizing radiation exposure and allows detailed characterization of plaque composition, including lipid-rich cores, fibrous caps, calcifications, and intraplaque hemorrhage.[68–70] However, MRI is limited by higher costs, longer scan times, lower accessibility, and dependence on advanced image analysis. PET, utilizing radiotracers such as 18F-fluorodeoxyglucose (18F-FDG), provides functional imaging by detecting inflammation and metabolic activity within plaques, offering valuable insights into plaque vulnerability. PET's main limitations include high costs, limited spatial resolution, and radiation exposure. Invasive imaging techniques such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and intravascular fluorescence imaging (IFI) offer exceptional spatial resolution and plaque characterization, thus being predominantly used during interventional procedures to guide treatment decisions. IVUS precisely assesses plaque morphology and vessel remodeling, OCT provides unparalleled detail on fibrous cap thickness and microstructural integrity, and IFI offers molecular-level imaging, further informing the assessment of plaque vulnerability.[71–73] Despite their advantages, these invasive methods are limited by their invasiveness, procedural risks, and high costs. Development and optimization of advanced contrast agents and imaging protocols continue to be vital areas of research aimed at improving diagnostic accuracy, safety, and patient outcomes. Newer molecular imaging probes targeting specific inflammatory markers and plaque components are currently under investigation, holding promise for earlier and more accurate detection of vulnerable plaques. The main therapeutic agents are summarized in Table 1.

Pharmacological Treatments

Pharmacotherapy remains the cornerstone of AS management, particularly during early, asymptomatic stages. Key pharmacological approaches target lipid metabolism, platelet aggregation, thrombosis, and inflammation. Lipid-lowering therapy primarily involves statins, which inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoAR), thereby reducing low-density lipoprotein cholesterol (LDL-C) levels, stabilizing plaques, and reducing cardiovascular events.[74–76] Despite widespread usage, statin intolerance and insufficient efficacy in specific populations, such as patients with familial hypercholesterolemia, necessitate alternative lipid-lowering therapies, including PCSK9 inhibitors (eg, evolocumab, alirocumab), cholesterol absorption inhibitors (eg, ezetimibe), and novel RNA-based therapies. Antiplatelet agents, including aspirin and P2Y12 receptor inhibitors (eg, clopidogrel, ticagrelor), effectively reduce thrombotic risks associated with plaque rupture.[77–79] Recently, combinations such as rivaroxaban (a factor Xa inhibitor) with aspirin have demonstrated improved cardiovascular outcomes, though associated with increased bleeding risk. Anti-inflammatory strategies targeting inflammatory pathways implicated in atherogenesis have emerged prominently.[80,81] Monoclonal antibodies like canakinumab (IL-1β inhibitor) demonstrated substantial efficacy by attenuating systemic inflammation and reducing cardiovascular event rates.[82–84] Colchicine, traditionally used for gout, has shown promising cardiovascular benefits by reducing inflammation-mediated events. In contrast, non-steroidal anti-inflammatory drugs (NSAIDs) exhibit mixed cardiovascular outcomes and are generally avoided for long-term AS management. Mainstream clinical therapeutic agents for AS are organized in Table 1.

Table 1 Mainstream Clinical Therapeutic Agents for AS

Type	Drug	Mechanism	Limitation
Statins	Atorvastatin, Rosuvastatin	Inhibits hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, reduces cholesterol synthesis, and lowers low-density lipoprotein (LDL), LDL-C levels; it also has anti-inflammatory, vascular endothelial function and other multifunctional effects	Some patients may experience muscle toxicity and elevated liver enzymes; limited efficacy in severe dyslipidemia such as familial hypercholesterolemia
Antiplatelet	Aspirin, clopidogrel, tigrilol	Aspirin inhibits platelet aggregation by reducing thromboxane A2 synthesis through inhibition of cyclooxygenase (COX), while clopidogrel and tegretol block platelet activation signaling through inhibition of the P2Y12 receptor.	Aspirin may cause adverse reactions such as gastrointestinal bleeding; clopidogrel resistance is present in some patients; tegretol may cause side effects such as dyspnea
Angiotensin-converting enzyme inhibitor (ACEI)/ Angiotensin II receptor antagonist (ARB)	Enalapril, Chlorosartan	ACEI inhibits angiotensin-converting enzyme and reduces angiotensin II production, lowering blood pressure and improving vascular remodeling; ARB exerts a similar effect by blocking the binding of angiotensin II to its receptors.	ACEIs may cause adverse effects such as dry cough and low blood pressure; ARBs have relatively few side effects but may be more expensive
Beta-blocker	Metoprolol, Bisoprolol	Blocking β receptor, slowing down heart rate, decreasing myocardial contractility, and reducing myocardial oxygen consumption; meanwhile, it has certain antihypertensive and antiarrhythmic effects.	May cause bradycardia, fatigue, bronchospasm and other adverse effects; long-term use and sudden discontinuation may cause rebound phenomenon
Calcium channel blockers	Nifedipine, Amlodipine	Blocking calcium ion inward flow, relaxing vascular smooth muscle, lowering blood pressure; also inhibits myocardial contractility, reducing myocardial oxygen consumption	May cause headache, facial flushing, ankle edema and other adverse reactions; some short-acting formulations may cause large fluctuations in blood pressure

Interventional and Surgical Treatments

Advanced symptomatic AS frequently necessitates invasive procedures to restore arterial patency and alleviate ischemia. Percutaneous coronary interventions (PCI), involving balloon angioplasty followed by stenting with either bare-metal stents or drug-eluting stents, remain standard approaches.[85–87] DES specifically release anti-proliferative medications, significantly reducing restenosis rates. However, procedural complications, such as restenosis and stent thrombosis, remain clinical challenges. Surgical interventions, particularly coronary artery bypass grafting, are indicated in extensive coronary artery disease or when PCI is not feasible, significantly improving prognosis and survival rates.[88–90] Peripheral arterial disease may also require interventions such as endarterectomy or bypass surgery to restore limb perfusion. Despite significant advances in diagnosis and treatment, current methods still face limitations in early plaque detection, accurate risk stratification, and personalized therapeutic interventions. Emerging technologies, including precision medicine approaches, advanced molecular imaging techniques, targeted drug delivery systems, and novel pharmacological agents, hold potential to overcome existing limitations, enhance therapeutic efficacy, and ultimately improve patient outcomes.[91,92]

Nanozyme-Based Therapeutic Strategies

Given the complexity of AS pathogenesis, diverse nanozyme systems have been engineered to target different pathological mechanisms such as oxidative stress, inflammation, and lipid accumulation. Each nanozyme type, Prussian blue, cerium oxide, selenium-based, and multifunctional composites—exhibits unique structural and catalytic characteristics. In this section, we not only summarize representative studies but also provide comparative insights to guide future

nanozyme design and selection for AS therapy. Nanozymes are a class of engineered nanomaterials that exhibit intrinsic enzyme-like catalytic activities, enabling them to modulate multiple pathological pathways central to AS progression. Unlike conventional single-target therapies, nanozymes offer a multifunctional platform capable of simultaneously addressing oxidative stress, chronic inflammation, cellular senescence, and lipid accumulation. A key mechanism by which nanozymes exert therapeutic effects is the scavenging of excessive ROS through superoxide dismutase (SOD)-, catalase (CAT)-, or glutathione peroxidase (GPx)-like activities, thereby protecting vascular endothelial cells and smooth muscle cells from oxidative injury. In addition, many nanozymes inhibit pro-inflammatory signaling cascades such as the NF-κB pathway, reducing the expression of cytokines like TNF-α and IL-6 and attenuating macrophage-driven inflammation. Some nanozyme platforms have been shown to suppress endothelial cell senescence and promote autophagy, counteracting the senescence-associated secretory phenotype that exacerbates plaque development. Moreover, nanozymes can enhance cholesterol efflux from foam cells by upregulating transporters such as ABCA1 and ABCG1, thereby reducing lipid accumulation within lesions. Surface modification with targeting ligands or incorporation of stimuli-responsive elements allows nanozymes to achieve lesion-specific delivery and controlled release in response to pathological microenvironments. Collectively, these mechanisms position nanozymes as a highly versatile and promising therapeutic modality for the comprehensive management of AS.

Traditional pharmacological interventions for AS, administered orally or intravenously, often exhibit limitations such as poor solubility, rapid clearance, short half-life, insufficient targeting capability, and notable systemic toxicity.[93–96] These shortcomings significantly restrict their clinical efficacy and overall therapeutic potential. Consequently, the development of advanced therapeutic approaches that enhance treatment effectiveness and minimize adverse side effects has emerged as a critical research area in cardiovascular medicine.

In recent years, advancements in nanotechnology have facilitated the emergence of Nanozymes, engineered nanoparticles exhibiting intrinsic enzyme-like catalytic activities.[97–100] These nanozyme systems have demonstrated significant promise in various biomedical fields, including oncology, inflammation therapy, and cardiovascular diseases, owing to their unique physicochemical properties, multifunctional capabilities, and biocompatibility.[101–103] Nanozymes possess several notable advantages for AS management. Firstly, their nanoscale size allows for efficient drug loading or encapsulation of diverse therapeutic agents, such as small molecule drugs, nucleic acids, peptides, proteins, and diagnostic imaging probes. By encapsulating and delivering drugs specifically to the diseased vascular sites, nanozymes substantially enhance therapeutic efficacy while reducing systemic toxicity.[104] Moreover, stable encapsulation within nanozymes shields therapeutic molecules from enzymatic degradation and premature clearance in the circulation, thereby significantly prolonging their circulation time and bioavailability. Secondly, nanozymes exhibit inherent catalytic activity, enabling them to directly modulate pathological biochemical reactions characteristic of AS, such as oxidative stress and inflammation. For instance, certain nanozymes mimic natural antioxidant enzymes like SOD, CAT, or GPx, efficiently neutralizing ROS and thereby attenuating oxidative damage, inflammation, and endothelial dysfunction. The ability of nanozymes to decompose specific ROS such as hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), and hydroxyl radicals (•OH) is central to their therapeutic effect in atherosclerosis. For instance, catalase-like activity decomposes H_2O_2 into water and oxygen, thereby reducing oxidative injury to endothelial cells and preventing the activation of pro-inflammatory transcription factors such as NF-κB. SOD-like activity converts O_2^- into H_2O_2, which is further detoxified, thereby protecting mitochondria and vascular smooth muscle cells from oxidative damage. Additionally, some nanozymes inhibit lipid peroxidation by scavenging •OH and peroxyl radicals, thereby reducing the formation of oxidized LDL (ox-LDL), a critical driver of foam cell formation and plaque growth. By modulating these ROS-dependent processes, nanozymes not only attenuate chronic vascular inflammation but also enhance plaque stability and reduce necrotic core formation. Furthermore, nanozymes can be functionalized with targeting ligands such as antibodies, peptides, or aptamers, which facilitate their selective accumulation at atherosclerotic lesion sites via active targeting strategies.[105] This targeted delivery significantly enhances the therapeutic concentration of the loaded agents specifically within plaques, minimizing off-target effects and systemic toxicity. Additionally, stimuli-responsive nanozymes that respond to local pathological cues (eg, acidic pH, oxidative stress, enzyme overexpression) have been developed, allowing controlled and triggered drug release precisely at lesion sites, further improving therapeutic outcomes. Preclinical studies have demonstrated promising results of various nanozyme systems in the treatment of AS. Notable

examples include cerium oxide nanoparticles exhibiting ROS-scavenging activity, Prussian blue nanoparticles capable of mimicking peroxidase activity, and carbon quantum dots with multifunctional antioxidant and anti-inflammatory properties.[106] These systems have shown substantial efficacy in reducing plaque size, stabilizing vulnerable plaques, and improving endothelial function in animal models of AS. The advantages and representatives of the main nanozymes are summarized in Table 2.

Despite their significant therapeutic potential, nanozymatic therapies still face critical challenges and barriers to clinical translation.[107] Key issues include ensuring optimal safety profiles, enhancing biocompatibility and biodegradability, achieving precise control of catalytic activity, and validating long-term therapeutic efficacy through rigorous preclinical and clinical evaluations. In conclusion, nanozymatic therapy represents a transformative advancement in AS treatment, combining efficient drug delivery, intrinsic catalytic therapeutic effects, and precise targeting capabilities.[108] Ongoing research focused on optimizing these multifunctional nanozyme systems and addressing translational challenges holds great promise for revolutionizing the clinical management and prognosis of patients with AS and associated cardiovascular diseases.

Prussian Blue Nanozyme

Prussian Blue (PB), originally discovered in 1704 by German chemist Johann Diesbach, is one of the earliest synthesized inorganic compounds.[109–111] Chemically known as ferric ferrocyanide ($Fe_4[Fe(CN)_6]_3$), PB exhibits a distinctive porous cubic crystal structure characterized by pore diameters ranging from approximately 5 to 20 nm. This structural attribute endows PB with an exceptionally high specific surface area, robust chemical stability, and minimal risk of cyanide ion release under physiological conditions, establishing a solid foundation for its biocompatibility and biosafety. PB's unique molecular framework facilitates multiple advantageous properties crucial for biomedical applications. At the core of its functionality is the Fe^{2+}/Fe^{3+} valence transition, which imparts intrinsic enzyme-mimicking catalytic activities, such as peroxidase (POD), CAT, and SOD. These activities allow PB to efficiently neutralize ROS including H_2O_2 and O_2^-, thereby suppressing ROS-induced oxidative stress and mitigating iron-catalyzed Fenton reactions responsible for lipid peroxidation and ferroptosis—critical pathological events in AS. The nanoscale nature of PB nanoparticles (10–100 nm) significantly enhances their functional versatility. The nanoparticle surface, enriched with functional groups such as hydroxyl and carboxyl groups, facilitates various surface modifications to improve systemic circulation and lesion targeting capabilities. Polyethylene glycol (PEG) coatings are commonly employed to extend blood circulation time, while targeting ligands such as RGD peptides or antibody fragments can be conjugated to enhance lesion specificity. Furthermore, PB's porous structure allows effective encapsulation and controlled release of various therapeutic agents, including small molecules, siRNAs, peptides, and proteins, thus establishing a multifunctional platform for combined therapeutic and diagnostic purposes. PB nanozymes have shown exceptional therapeutic potential through multiple

Table 2 Table of Different Nanozymes and Their Advantages

Nanozyme Type	Representative Materials	Catalytic Activity	Key Therapeutic Advantages
Prussian Blue Nanozyme	Prussian blue nanoparticles ($Fe_4[Fe(CN)_6]_3$)	Peroxidase-like, catalase-like, SOD-like	Efficient ROS scavenging; anti-inflammatory; promotes M2 macrophage polarization; enhances plaque stability
Cerium Oxide Nanozyme	CeO_2 nanoparticles	SOD-like, catalase-like	Self-regenerative antioxidant; reduces oxidative stress; targets inflammatory macrophages; improves endothelial function
Selenium-Based Nanozyme	Selenium-doped MOFs; selenium nanoparticles	GPx-like; dual SOD/GPx-like (cascade)	Dual ROS elimination; anti-senescent; inhibits foam cell formation; reduces inflammatory cytokines; stabilizes plaques
Composite Nanozyme	Pd-B-P alloy nanozyme; Se-doped Cu formate nanozyme	Multi-enzyme mimicry; combined ROS/inflammation	Synergistic ROS scavenging; anti-inflammatory; anti-senescent; anti-foam cell; enhances fibrous cap integrity
Carbon-based Nanozyme	Carbon quantum dots; graphene oxide	Peroxidase-like, oxidase-like	Biocompatible; multifunctional antioxidant; potential for imaging-guided therapy

intervention mechanisms in AS. Notably, PB-mediated ROS scavenging significantly reduces oxidative stress-induced endothelial dysfunction, monocyte adhesion, and subsequent inflammatory cascades. PB also attenuates inflammatory signaling pathways, particularly the NF-κB pathway, effectively decreasing the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and curbing inflammatory infiltration. Additionally, PB promotes anti-inflammatory M2 macrophage polarization and enhances the efflux of cholesterol via ATP-binding cassette transporters ABCA1 and ABCG1, substantially reducing lipid accumulation within plaques and stabilizing atherosclerotic lesions.

He et al[112] developed a sophisticated multifunctional PB-based nanozyme, termed PBNZ@PP-Man, which seamlessly integrates intrinsic enzyme-mimetic catalytic activities with targeted drug delivery and immunomodulatory functions. The PB nanozyme core exhibited potent CAT- and SOD-like activities, enabling efficient ROS scavenging. To enhance targeting specificity, the nanozyme surface was functionalized with dual ligands: P-selectin-binding peptides (PP) and mannose (Man). The PP moiety selectively targeted activated endothelial cells overexpressing P-selectin, thereby inhibiting monocyte adhesion and transmigration into the vascular intima, while mannose facilitated macrophage-specific uptake, promoting efferocytosis and clearance of apoptotic cells. In vitro experiments demonstrated significant reductions in monocyte adhesion, intracellular ROS levels, and pro-inflammatory cytokine production. In vivo studies using ApoE$^{-/-}$ mice further confirmed the therapeutic potential, showing marked plaque regression (27.9% reduction in aortic arch lesion area), enhanced fibrous cap stability with a 2.6-fold increase in collagen deposition, reduced macrophage infiltration by 46%, and a 77% decrease in matrix metalloproteinase-9 (MMP-9) expression. Pharmacokinetic analysis revealed that PEGylation prolonged the systemic circulation half-life of PBNZ@PP-Man to 8.43 hours, enabling greater plaque accumulation and superior therapeutic efficacy compared to non-targeted nanozyme formulations (Figure 3).

In another innovative approach, Xu et al[113] designed a bovine serum albumin (BSA)-encapsulated Prussian Blue-curcumin nanozyme (BSA@PB/Cur). This formulation uniquely integrated PB's antioxidant enzymatic properties, curcumin's potent anti-inflammatory effects, and photothermal therapy capabilities activated by near-infrared (NIR) irradiation to disrupt the vicious inflammatory feedback loop within atherosclerotic plaques. BSA encapsulation significantly improved physiological stability and reduced nonspecific interactions. Under NIR irradiation, BSA@PB/Cur generated localized heat, promoting lipid efflux from macrophage-derived foam cells by upregulating cholesterol efflux transporters ABCA1 and ABCG1. Curcumin's potent anti-inflammatory action inhibited NF-κB signaling, resulting in decreased production of inflammatory mediators (TNF-α, IL-1β). In vitro results demonstrated substantial ROS scavenging, reduced lipid deposition, and enhanced cholesterol efflux. Additionally, photothermal activation synergistically enhanced therapeutic outcomes by facilitating intracellular lipid removal. Collectively, this study demonstrated that BSA@PB/Cur significantly ameliorated multiple pathological aspects of AS simultaneously, highlighting its potential for multifunctional therapeutic applications.

Despite promising advances, several challenges remain to be addressed for the clinical translation of PB nanozymes. Firstly, detailed mechanistic studies are necessary to fully elucidate their in vivo catalytic kinetics, biodistribution, and metabolic pathways. Secondly, standardized manufacturing protocols to ensure consistent nanoparticle size, enzyme activity, and batch-to-batch reproducibility are critical. Moreover, long-term biosafety profiles and potential immunogenicity of repeated PB administrations require extensive evaluation. Future research should also explore personalized approaches integrating precise biomarkers and real-time monitoring to optimize treatment efficacy and safety. In conclusion, Prussian Blue nanozymes represent a versatile and powerful platform capable of addressing multiple pathological facets of AS simultaneously. Their multifunctional properties combining catalytic antioxidation, inflammation modulation, targeted drug delivery, and diagnostic capabilities hold significant promise for enhancing the effectiveness of AS treatments. The continuous exploration of innovative designs and deeper understanding of PB nanozymes will undoubtedly facilitate their successful clinical translation, transforming AS therapy from symptomatic management toward genuine etiological reversal. In comparison with other nanozymes, Prussian blue nanozymes are notable for their structural porosity, multi-enzyme mimicking capacity, and excellent biocompatibility. However, their ROS scavenging ability is relatively non-specific, and they may be less effective in targeting senescence or cholesterol efflux compared to selenium- or cerium-based platforms. The surface modification flexibility of PB nanozymes allows for efficient combination with targeting ligands, but their stability and catalytic regeneration potential are still inferior to cerium oxide nanozymes.

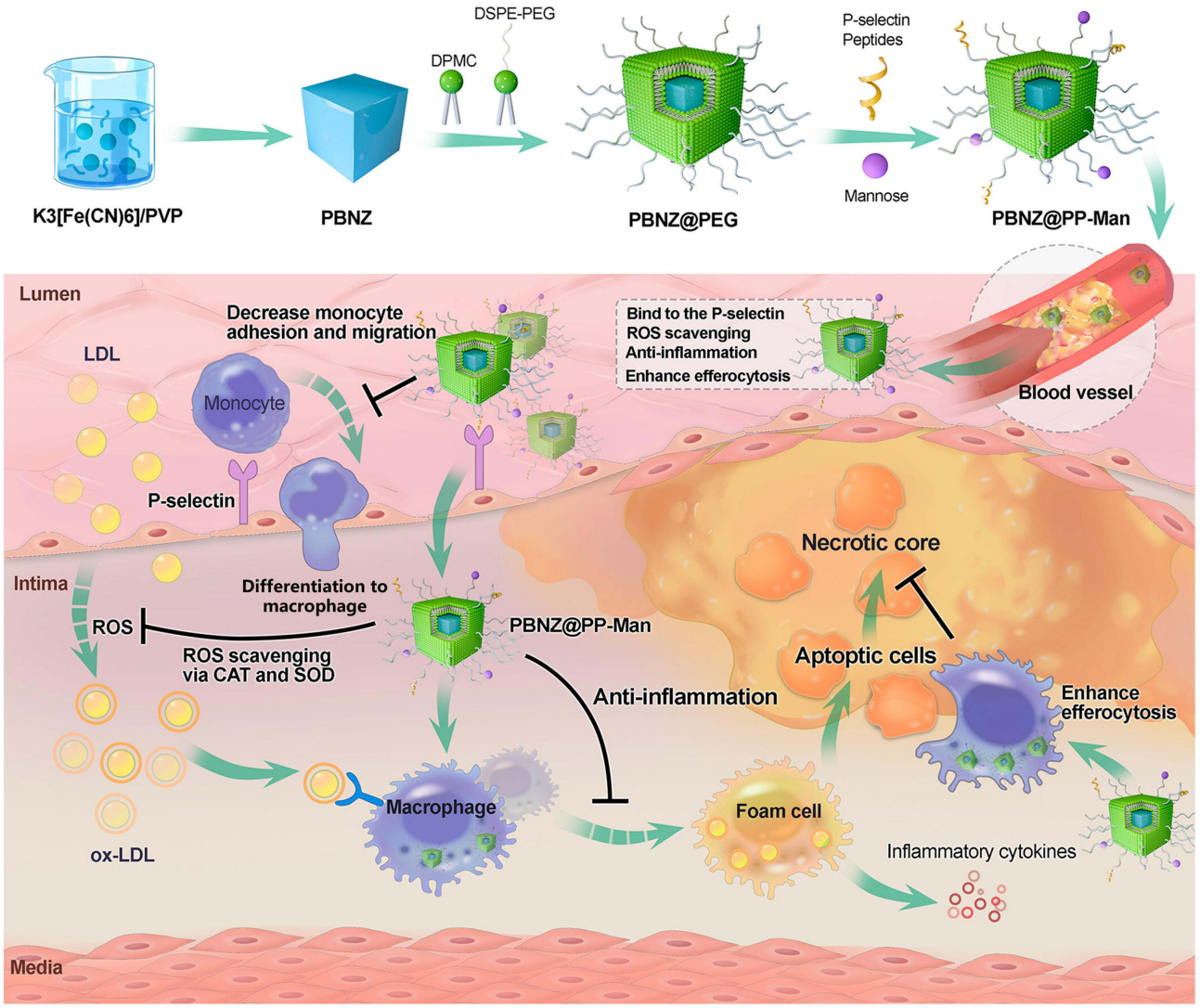

Figure 3 A schematic illustration shows the engineering of PBNZ@PP-Man and its use as a multifunctional therapy for improving the proinflammatory plaque environment and reducing atherosclerosis. PBNZ@PP-Man targets the inflamed endothelium of atherosclerotic plaques through P - selectin binding. It mitigates atherosclerosis mainly by inhibiting monocyte infiltration, scavenging ROS with CAT- and SOD - like activities, and enhancing efferocytosis. Reproduced from He H, Han Q, Wang S, et al. Design of a multifunctional nanozyme for resolving the proinflammatory plaque microenvironment and attenuating atherosclerosis. ACS nano. 2023;17(15):14555–14571. Copyright © 2023 American Chemical Society.[112]

Cerium Oxide Nanozyme

Cerium oxide (CeO_2) is a rare-earth metal oxide known for its unique redox properties, which stem from the facile transition between Ce^{3+} and Ce^{4+} oxidation states.[114–117] This redox cycling endows cerium oxide nanoparticles (CeO_2 NPs) with potent enzyme-mimicking capabilities, especially SOD- and CAT-like activities, enabling them to scavenge a wide spectrum of ROS. In recent years, CeO_2 nanozymes have garnered increasing attention as multifunctional nanotherapeutics, owing to their excellent biocompatibility, regenerative antioxidant activity, and potential for surface modification.[118–120] These features make CeO_2 NPs particularly attractive in the treatment of chronic inflammatory diseases such as AS, where oxidative stress and inflammation play central roles in disease progression.

AS is a chronic cardiovascular disease characterized by excessive ROS and sustained inflammation within the vascular wall. Conventional treatments often exhibit limited efficacy due to inadequate targeting and reliance on single-mechanism interventions. Addressing these limitations, recent research has highlighted the use of cerium oxide nanozymes, leveraging their intrinsic enzyme-like activities for multifunctional and targeted therapeutic strategies. Fu et al[121] developed an innovative multifunctional cerium oxide nanozyme system based on small molecule-assisted

assembly, designed to achieve synergistic therapeutic effects in AS treatment. Specifically, Zoledronic acid (ZOL), possessing imidazole and bisphosphonic acid functional groups, facilitated the self-assembly of cerium ions to form cerium oxide-zoledronic acid nanozymes (CZ NCs). These nanozymes combine the intrinsic SOD and CAT mimetic activities of traditional cerium oxide nanozymes with metal-organic framework (MOF)-like properties, enabling efficient loading of therapeutic agents such as Probucol, an antioxidant drug. The resulting nanocomposite, CZ@PB NCs, was further encapsulated with platelet membranes to construct a biomimetic nanoplatform (PCZ@PB NCs). This advanced biomimetic system retained multi-enzymatic activities while achieving enhanced targeting through passive vascular penetration and active adhesion mediated by platelet membrane affinity towards inflammation sites in AS plaques. Morphological characterization revealed uniform spherical CZ NCs with an average diameter of approximately 10 nm, increasing to approximately 25 nm after loading with PB. Platelet membrane modification imparted a more negative surface potential (−18.86 mV), significantly enhancing colloidal stability. Functional assays demonstrated exceptional ROS scavenging capacity, with PCZ@PB NCs achieving over 80% catalytic scavenging efficiency for both H_2O_2 and O_2^-. In lipopolysaccharide (LPS)-activated macrophages, PCZ@PB NCs markedly reduced intracellular ROS levels by 60%, downregulated pro-inflammatory factors such as TNF-α and MMP-9 expression by 45% and 50% respectively, and promoted cholesterol efflux via upregulation of ABCA1 and ABCG1, resulting in a 40% decrease in lipid accumulation within foam cells. In vivo experiments conducted in ApoE$^{-/-}$ mice demonstrated significant therapeutic efficacy. PCZ@PB NCs showed 2.5-fold higher aortic enrichment compared to unmodified counterparts 12 hours post intravenous administration. After treatment, the total plaque area in the aorta was significantly reduced by approximately 60%, and macrophage infiltration ($CD68^+$ cells) in plaques was decreased by 35%. Expression of plaque-stabilizing collagen fibers increased by 20%, and detrimental MMP-9 levels decreased by 55%. Importantly, PCZ@PB NCs displayed excellent biocompatibility, with minimal hepatic and renal toxicity and a hemolysis rate below 5% (Figure 4).

Wang et al[122] further expanded the therapeutic potential of cerium oxide nanozymes by developing a hyaluronic acid (HA)-modified cerium oxide nanoparticle (HA-CeO_2 NPs) platform. Hyaluronic acid, a naturally occurring polysaccharide, exhibits a strong binding affinity for CD44 receptors, which are highly expressed on inflammatory macrophages residing within atherosclerotic plaques. By leveraging this biological interaction, the modification with HA not only enabled targeted delivery of the nanozyme to diseased vascular tissues but also enhanced its colloidal stability and biocompatibility. Utilizing a green synthesis method, the authors successfully fabricated spherical HA-CeO_2 NPs with an average diameter of approximately 25 nm and a stable negative zeta potential of −21.78 mV, both of which contribute to prolonged circulation and reduced nonspecific aggregation in vivo. Comparative experiments revealed that HA-CeO_2 NPs exhibited significantly superior ROS scavenging activity compared to dextran- or poly(aspartic acid)-modified CeO_2 NPs, achieving an impressive 85% inhibition of superoxide anions at a concentration of 0.8 mM. This enhanced antioxidant capacity was attributed to a higher Ce^{3+}/Ce^{4+} ratio, as confirmed by X-ray photoelectron spectroscopy, which facilitates more efficient redox cycling. In vitro cellular uptake studies further demonstrated that HA-CeO_2 NPs were internalized by activated RAW 264.7 macrophages via CD44-mediated endocytosis with 40% greater efficiency than dextran-modified counterparts, confirming the targeting advantage conferred by HA functionalization. Functionally, treatment with HA-CeO_2 NPs led to a 60% reduction in ox-LDL uptake by macrophages and a significant decrease in foam cell formation, which are critical steps in atherogenesis. Additionally, HA-CeO_2 NPs effectively reduced intracellular ROS levels by 55% in hydrogen peroxide-stimulated vascular smooth muscle cells (MOVAS) and macrophages, resulting in a 30% improvement in cell viability compared to conventional antioxidant therapies such as probucol. In vivo fluorescence imaging performed in ApoE$^{-/-}$ mice demonstrated that HA-CeO_2 NPs achieved threefold higher accumulation within aortic plaques relative to free fluorescent dyes or other polymer-modified CeO_2 nanozymes, while exhibiting minimal off-target deposition in hepatic and splenic tissues. After 11 weeks of repeated systemic administration, the HA-CeO_2 NP treatment group showed a substantial 65% reduction in aortic plaque area, a 40% reduction in inflammatory cell infiltration within plaques, and a 25% decrease in serum LDL cholesterol levels. Importantly, no significant hepatic or renal toxicity was observed, as evidenced by normal histopathological examination and unaltered liver and kidney function biomarkers. Collectively, these findings underscore the potential of HA-CeO_2 NPs as a multifunctional, biocompatible, and targeted nanozyme platform capable of simultaneously mitigating oxidative stress, suppressing inflammation, and reducing lipid accumulation, thereby providing a promising therapeutic strategy for the treatment of atherosclerosis (Figure 5).

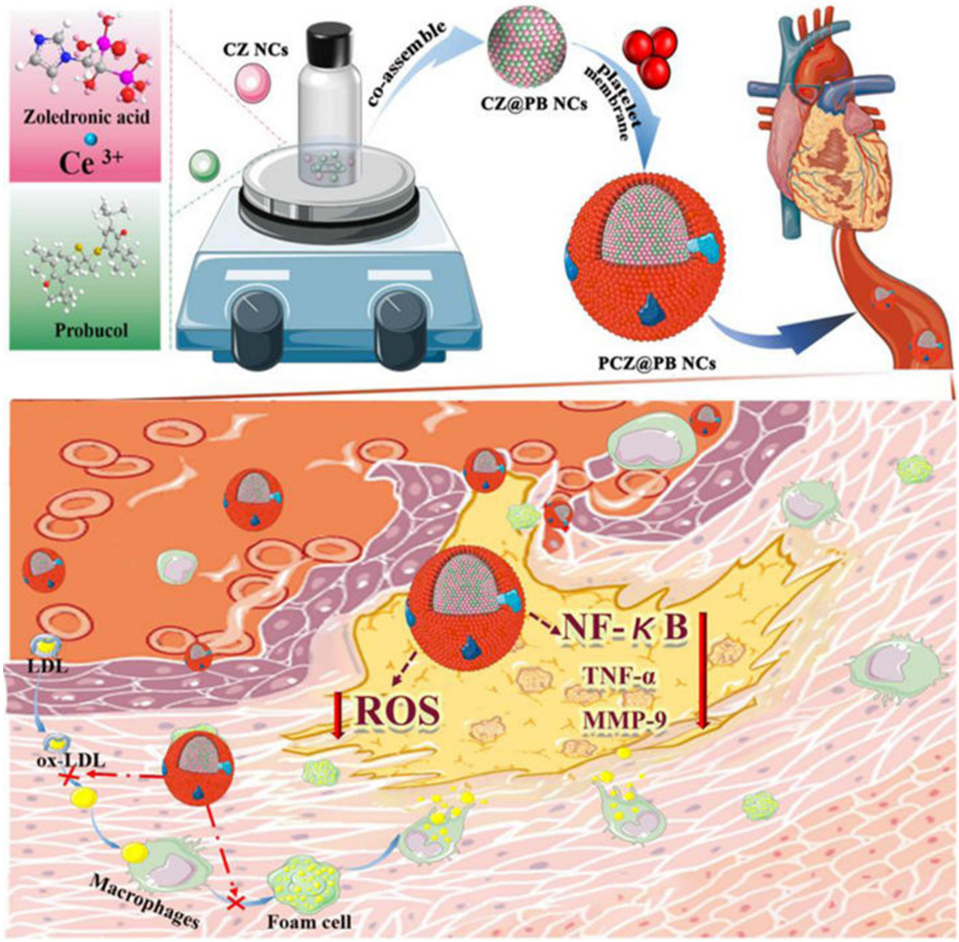

Figure 4 The biomimetic probucol-loaded nanozyme is fabricated by assembling zoledronic acid, cerium ions, and probucol, then encapsulating the assembly within platelet membranes. Once administered, the PCZ@PB NCs accumulate at atherosclerotic plaques. This occurs via passive accumulation and active targeting of inflamed sites. As a result, they effectively reduce OX-LDL production, inhibit inflammatory cytokines, and eliminate excess ROS. Reproduced from Fu X, Yu X, Jiang J, et al. Small molecule-assisted assembly of multifunctional ceria nanozymes for synergistic treatment of atherosclerosis. Nat Commun. 2022;13(1):6528. Creative Commons Attribution 4.0 International License[121] Springer 2022.

These pioneering studies illustrate the transformative potential of cerium oxide nanozymes in AS therapy by integrating robust antioxidant activity, precise inflammation-targeting strategies, and advanced drug delivery capabilities. Nevertheless, several critical challenges remain for their clinical translation. These include the need for systematic evaluation of long-term safety, biodistribution, and biodegradation; scalable synthesis methods that ensure consistent physicochemical properties; and strategies for integrating real-time imaging and disease monitoring. In addition, the dynamic redox cycling of cerium ions within the nanozyme matrix provides both an advantage and a limitation. While the switchable Ce^{3+}/Ce^{4+} states confer self-regenerating antioxidant capacity, excessive accumulation in tissues or chronic exposure may lead to unforeseen oxidative stress or immunomodulatory effects that require careful investigation. Moreover, optimizing the surface chemistry to balance stability, targeting specificity, and catalytic reactivity is essential for enhancing therapeutic performance. Looking forward, interdisciplinary integration—combining nanomaterial engineering, systems biology, and translational medicine—will be vital for the continued development of cerium oxide nanozyme-based therapies. With ongoing advances in single-cell profiling, organ-on-chip models, and AI-assisted design, the next generation of CeO_2 nanozymes may provide not only therapeutic efficacy but also diagnostic insight and personalized treatment strategies. As such, cerium oxide nanozymes hold great promise in advancing AS therapy from generalized symptomatic relief toward mechanism-based precision intervention.

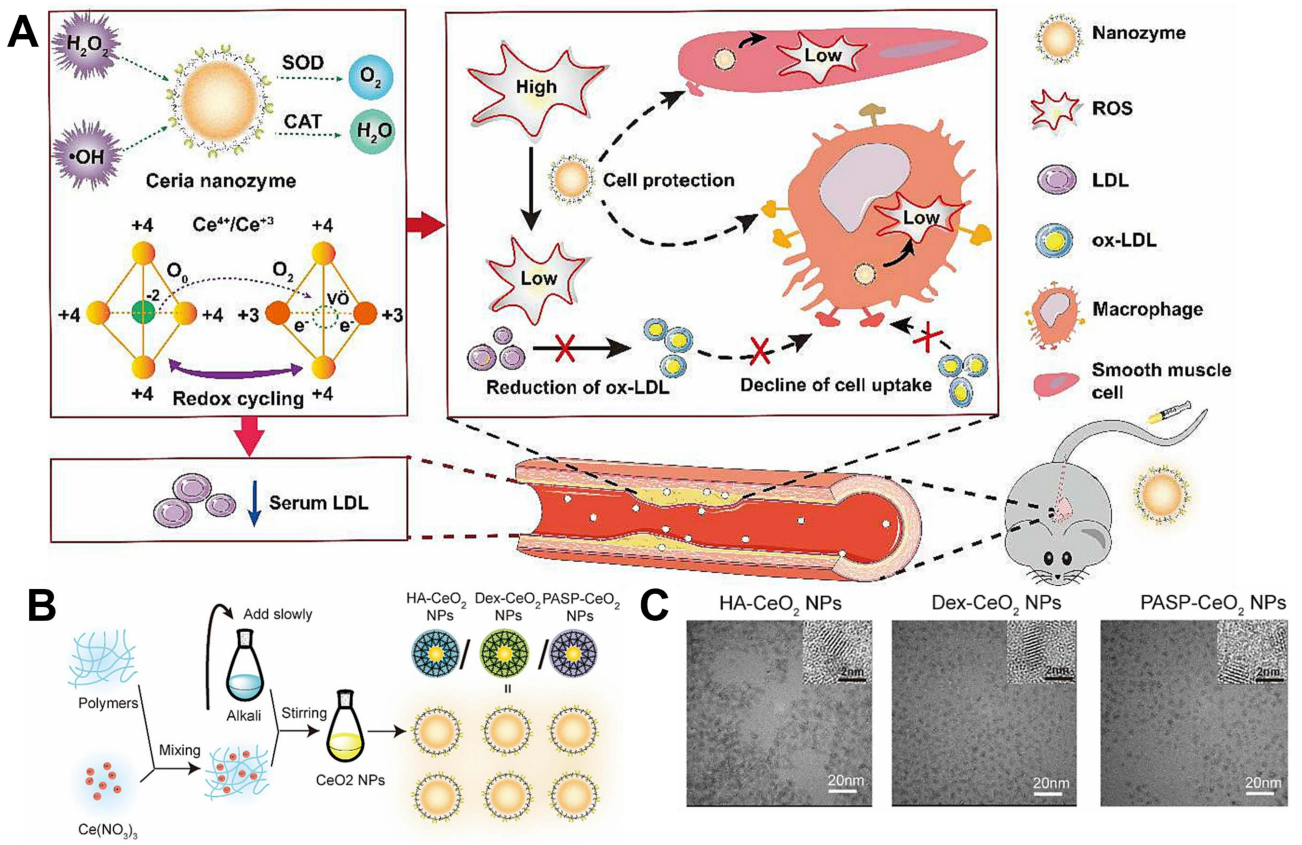

Figure 5 (**A**) Schematic representation of surface-bound hyaluronic acid to generate cerium nanozyme and enhance the mitigating effect of atherosclerosis. (**B**) Schematic representation of cerium oxide nanoparticles synthesized by different schemes and (**C**) transmission electron microscopy images bar: 20 nm. Reproduced from Wang S, Zhang J, Li W, et al. Hyaluronic acid-guided assembly of ceria nanozymes as plaque-targeting ROS scavengers for anti-atherosclerotic therapy. Carbohydr Polym. 2022;296:119940. Copyright © 2022. Published by Elsevier Ltd.[122]

Selenium-Based Nanozyme

Selenium is a biologically essential trace element known for its pivotal role in redox homeostasis and immune regulation.[123–125] In the human body, selenium is a critical cofactor for various antioxidant enzymes, most notably glutathione peroxidases (GPxs) and thioredoxin reductases, which serve as major defenders against ROS and oxidative damage. Recent advances in nanotechnology have enabled the engineering of selenium into nanozymes with GPx-like activity, combining the inherent catalytic capacity of selenium with the design versatility and stability of nanomaterials. These selenium-based nanozymes offer regenerative antioxidant capacity, tunable physicochemical properties, and enhanced biocompatibility, making them attractive candidates for treating ROS-driven diseases, including AS.

AS is not only driven by dyslipidemia and inflammation but also fundamentally associated with oxidative stress and cellular senescence, particularly of vascular endothelial cells. Senescent endothelial cells exhibit reduced regenerative capacity and antioxidant enzyme expression while producing excessive levels of inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α). This senescence-associated secretory phenotype (SASP) contributes to vascular dysfunction, enhances ox-LDL formation, and promotes foam cell accumulation, thereby accelerating atherosclerotic plaque growth and instability. A growing body of evidence indicates that deficiencies in endogenous antioxidant enzymes such as SOD and GPx exacerbate this pathogenic cascade. However, natural enzymes are limited in clinical application due to poor physicochemical stability, short circulation half-life, and high production costs. In this context, nanozymes which synthetic nanomaterials with enzyme-like catalytic activity that offer promising therapeutic alternatives due to their tunable activity, long-term stability, and potential for multifunctional integration. Liu et al[126] addressed these challenges by designing a selenium-doped MOF-based cascade nanozyme, termed MSe1, which mimics the dual enzymatic functions of SOD and GPx. Constructed from MIL-53 (Fe)-NO_2 as a MOF scaffold and doped with Se

ions at an optimized 1:1 molar ratio, MSe1 was engineered to achieve sequential ROS scavenging in a physiological environment. The dual enzyme mimicry allowed efficient elimination of both superoxide anions and hydrogen peroxide. Additionally, MSe1 was designed with a negative surface charge (zeta potential ~ −25 mV), promoting preferential accumulation in inflamed endothelial tissues via passive targeting mechanisms. In vitro enzyme activity assays demonstrated MSe1's potent catalytic efficiency: at a concentration of 0.8 mg/mL, MSe1 scavenged 87% of O_2^-, outperforming undoped MOFs (72%) and Se nanoparticles alone (65%). Hydrogen peroxide decomposition reached 79% within 10 minutes, representing a 30% enhancement over GPx-mimicking Se-only nanostructures. In a hydrogen peroxide-induced senescence model using human umbilical vein endothelial cells (HUVECs), MSe1 treatment (20 μg/mL) reduced senescence-associated β-galactosidase (SA-β-gal) positivity to 18% ± 3%, significantly lower than that in the model group (35% ± 4%) and superior to monofunctional nanozymes (28% ± 3%). Furthermore, immunofluorescence staining showed a 62% reduction in γ-H2AX that a marker of DNA double-strand breaks and a 55% reduction in the senescence marker p16, indicating effective attenuation of oxidative stress-induced cellular senescence. In a macrophage model stimulated with ox-LDL, pretreatment with MSe1 led to a 58% reduction in DiI-ox-LDL fluorescence intensity, indicating suppression of ox-LDL uptake. Oil Red O staining confirmed a 42% reduction in intracellular lipid deposition, with foam cell formation decreasing from 45% to 26%. These results suggest that MSe1 not only protects endothelial cells from senescence but also effectively inhibits foam cell development by macrophages, disrupting key events in early plaque formation. In vivo studies in $ApoE^{-/-}$ mice fed a high-fat diet for 12 weeks followed by intravenous administration of MSe1 (8 mg/kg, three times weekly) for 8 weeks yielded compelling results. Oil Red O staining showed that the percentage of aortic plaque area in the MSe1-treated group was 10.75% ± 2.93%, a dramatic reduction compared to saline (32.16% ± 3.08%), Se-mono (28.20% ± 4.50%), and unmodified MOF (27.03% ± 4.02%) groups. Masson staining of the aortic root revealed a 42% increase in collagen fiber content, a 35% increase in fibrous cap thickness, and a 48% reduction in MMP-9 expression, indicating significant plaque stabilization. Immunohistochemical analyses further confirmed a 52% reduction in $CD68^+$ macrophage infiltration within plaques and a decrease in IL-6 and TNF-α expression by 45% and 51%, respectively. Dihydroethidium staining revealed a 63% reduction in superoxide levels, highlighting MSe1's potent antioxidant capacity. In vascular endothelium, immunofluorescence analysis demonstrated that the expression of senescence markers p16 and γ-H2AX decreased by 57% and 59%, respectively, indicating that MSe1 effectively suppressed vascular cell senescence. Biosafety assessments showed no significant differences in liver and kidney function indicators (ALT, AST, BUN) or blood parameters between the MSe1-treated and control groups. Histological examination of major organs (liver, spleen, kidney) via H&E staining showed no signs of inflammation, necrosis, or nanoparticle accumulation. Inductively coupled plasma-optical emission spectrometry (ICP-OES) revealed that Fe and Se were predominantly distributed in the liver and spleen but were largely cleared 85% within 72 hours, indicating a low risk of long-term toxicity. Overall, MSe1 represents a next-generation cascade nanozyme capable of integrating multi-enzyme mimetic activities with anti-inflammatory, anti-senescent, and anti-foam cell functionalities. By targeting both oxidative stress and cellular senescence that two central drivers of atherosclerotic progression MSe1 offers a promising paradigm for a comprehensive, mechanism-oriented treatment strategy (Figure 6).

Moving forward, several opportunities and challenges merit attention in the advancement of Se-based nanozyme therapy. First, integrating active targeting ligands, such as peptides or antibodies, could further improve lesion specificity and minimize off-target effects. Second, incorporating diagnostic imaging agents or ROS-responsive fluorophores may enable real-time monitoring of therapeutic efficacy and disease progression. Third, long-term safety evaluations and pharmacokinetics in large animal models are critical to ensure clinical viability. Furthermore, combination therapies with lipid-lowering agents or immunomodulators may yield synergistic benefits in plaque regression and stabilization. In summary, selenium-based nanozymes offer a rational and multifaceted strategy for tackling AS at the molecular and cellular levels. The integration of Se's inherent redox capabilities with modern nanotechnology presents a versatile platform to combat endothelial dysfunction, oxidative stress, foam cell formation, and inflammation in one system. With further optimization and translational research, Se nanozymes hold the potential to redefine the therapeutic landscape of AS and related cardiovascular disorders.

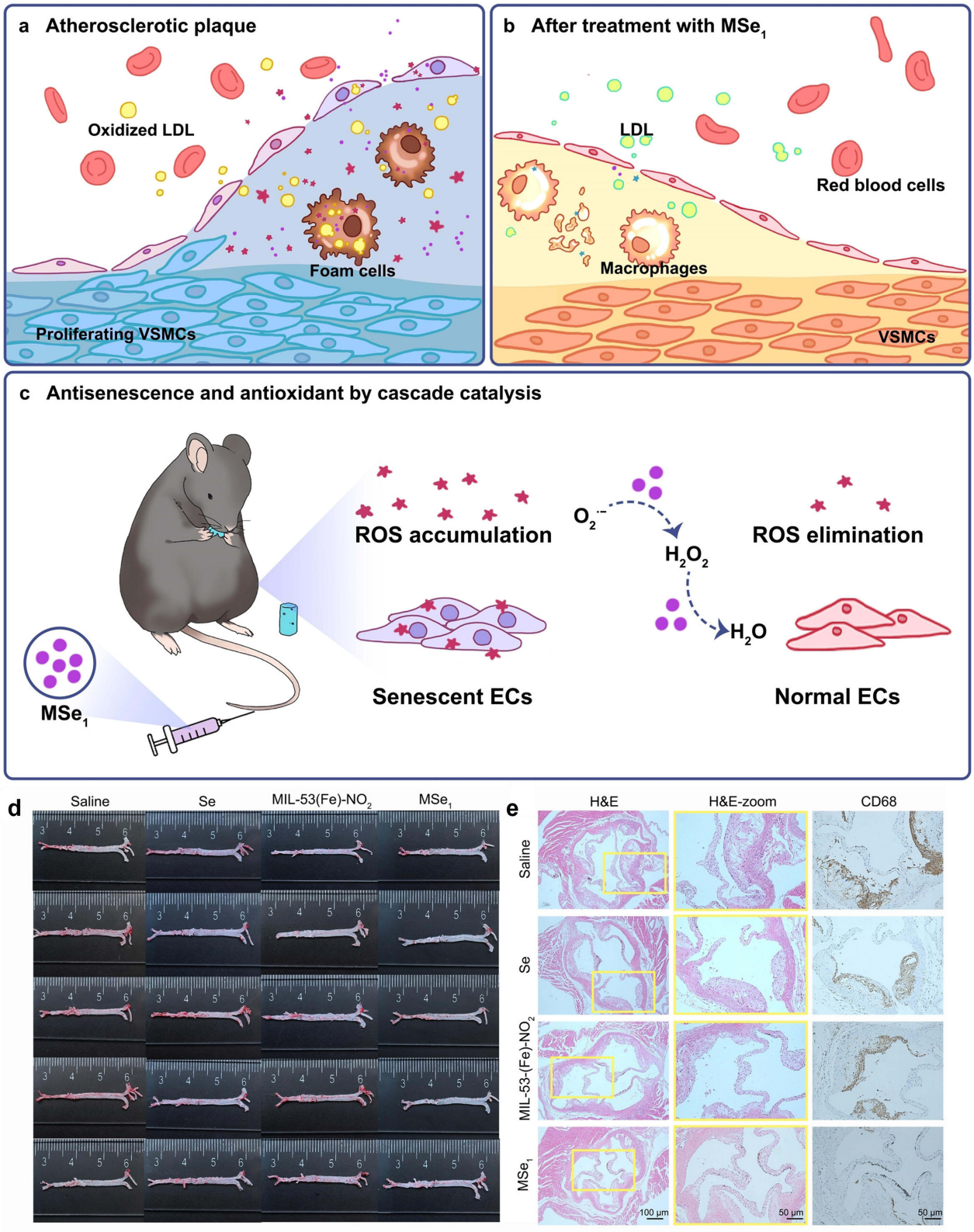

Figure 6 (**a**) The microenvironment of atherosclerotic plaques is depicted schematically, featuring senescent endothelial cells (ECs), proliferating vascular smooth muscle cells (VSMCs), foam cells, and a substantial quantity of ROS. (**b**) The application of MSe1 cascade nanozyme has proven effective in significantly alleviating atherosclerosis. (**c**) Through leveraging the anti-aging and antioxidant properties of multi-enzyme cascade antioxidant nanozyme, atherosclerosis can be efficiently treated. (**d**) Images of whole aorta frontal ORO staining are presented, showcasing the aorta of ApoE$^{-/-}$ mice after treatment with saline and various nanozymes. (**e**) Shows representative and magnified images of aortic root sections stained with H&E and CD68 antibodies. The scale bars measure 100 μm for H&E staining, while for the magnified H&E and CD68 staining, the scale bars are 50 μm. Reproduced from Liu W, Zhang Y, Wei G, et al. Integrated cascade nanozymes with antisenescence activities for atherosclerosis therapy. Angew Chem Int Ed Engl. 2023;62(33): e202304465. © 2023 Wiley-VCH GmbH.[126]

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Combination of Nanozymes

As the understanding of AS advances, it has become increasingly clear that this disease involves a convergence of multiple pathological processes including oxidative stress, endothelial senescence, chronic inflammation, and lipid metabolic disorders. Conventional mono-functional therapies targeting a single aspect of disease pathology are often insufficient to achieve comprehensive disease control. In this context, combination nanozyme systems have emerged as a promising strategy to achieve synergistic therapeutic outcomes by simultaneously addressing multiple targets within the complex atherosclerotic microenvironment. These systems integrate two or more catalytic domains or functional components into a unified nanostructure, enabling concurrent ROS elimination, anti-inflammatory regulation, cellular senescence suppression, and lipid metabolism modulation. Unlike traditional treatments or even single-function nanozymes, composite nanozymes exhibit enhanced catalytic efficiency, dynamic biological responsiveness, and the potential for precisely coordinated therapeutic intervention. Their modular design also allows for the incorporation of targeting ligands, therapeutic payloads, and responsive release mechanisms, further augmenting their clinical value.

The development of AS is closely related to vascular endothelial cell senescence, excessive accumulation of ROS and macrophage-driven inflammatory responses. As endothelial cells age, their antioxidant defenses weaken, promoting DNA damage and the secretion of inflammatory cytokines. Simultaneously, macrophage uptake of oxidized low-density lipoprotein leads to foam cell formation and plaque expansion. Conventional therapies struggle to address these diverse mechanisms simultaneously, underscoring the urgent need for multifunctional nanotherapeutics. Dai et al introduced a ternary mesoporous nanozyme known as D@MPdH nanoparticles, combining anti-aging and anti-inflammatory activities.[127] The platform is based on a palladium-boron-phosphorus alloy synthesized via a soft-templating method, forming a mesoporous scaffold capable of loading molecular hydrogen and the autophagy-activating compound 4,4′-dimethoxychalcone. This system mimics superoxide dismutase and catalase activity to eliminate ROS, while the hydrogen molecule functions as a gaseous anti-inflammatory agent. Dimethoxychalcone activates autophagy, facilitating the degradation of damaged cellular components and mitigating endothelial cell senescence. The result is a powerful antioxidant, anti-inflammatory, and anti-aging therapeutic platform (Figure 7).

Huang et al developed a selenium-doped copper formate nanozyme (Cuf-Se) that combines the antioxidant properties of selenium with the catalytic activity of copper to achieve dual superoxide dismutase and glutathione peroxidase mimicry.[128] The nanozyme exhibited high stability, biocompatibility, and the ability to reduce senescence and foam cell formation in both cellular and animal models. The introduction of selenium enhanced the catalytic performance while also contributing to DNA protection and improved endothelial function. In another approach, Ding et al designed a high-entropy alloy-based nanozyme with chiral selectivity and an amorphous atomic structure. The nanozyme, containing platinum, palladium, copper, and iron atoms, displayed powerful enzyme-mimicking activity and was specifically engineered to accumulate in senescent cells due to surface chirality. By combining senolytic and senomorphic functions, this system was able to selectively eliminate senescent cells and inhibit senescence-associated secretory phenotype signaling, thereby mitigating inflammation and promoting fibrous cap remodeling. Mechanistic investigations of these multifunctional nanozymes have revealed extensive biological reprogramming capabilities. For example, transcriptomic profiling of tissues treated with D@MPdH nanoparticles demonstrated simultaneous modulation of more than fifteen signaling pathways related to inflammation, senescence, and cholesterol metabolism. Such broad-spectrum effects cannot be replicated by single-agent systems and represent a major advance in the treatment of AS. From a clinical translation standpoint, these combination nanozymes provide a number of practical advantages. They reduce reliance on polypharmacy, improve lesion-specific accumulation, and offer synergistic efficacy at lower dosages, thereby decreasing systemic toxicity. However, their complexity introduces new challenges including synthesis reproducibility, potential interactions among active components, and the need for in-depth pharmacokinetic and toxicological evaluation (Figure 8).

In summary, combination nanozyme platforms represent a cutting-edge direction in the development of nanotherapeutics for AS. By unifying multiple catalytic and regulatory functions within a single construct, these systems are uniquely positioned to disrupt the multifactorial progression of AS. Future research should aim to refine their design, improve their biosafety, and explore their integration with imaging and diagnostic technologies. The rational design of multifunctional nanozymes, informed by systems biology and supported by advanced material engineering, holds transformative potential for precision cardiovascular therapy.

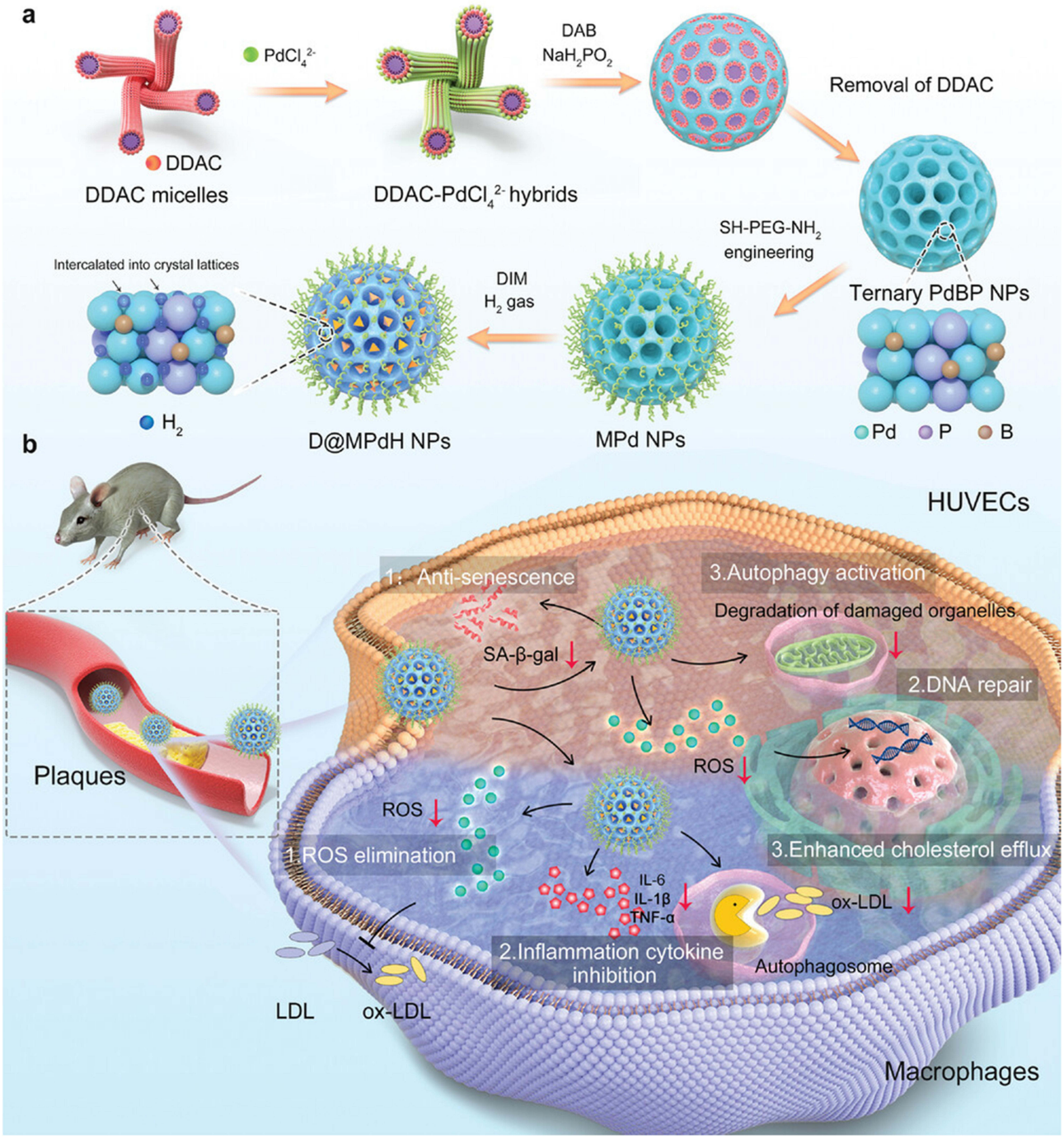

Figure 7 Schematic representation of the synthetic methodology for D@MPdH NPs, along with the anti-atherogenic treatment facilitated by these newly developed D@MPdH NPs. (**a**) A diagram outlining the synthetic steps for D@MPdH NPs is presented. This encompasses the synthesis of ternary PdBP NPs, the process of PEGylation, and the subsequent loading of hydrogen gas (H_2) and 3,3′-diindolylmethane (DIM) to yield the D@MPdH NPs. (**b**) A schematic depiction of the therapeutic mechanism of D@MPdH NPs is shown. It involves the prevention of senescence in HUVECs and the exertion of anti-oxidative and anti-inflammatory effects within macrophages. Reproduced from Dai C, Hu R, Cao S, et al. Mesoporous Ternary Nanozymes with Anti-Senescence and Anti-Inflammation Activities for Atherosclerosis Management. Adv Funct Mater. 2024;34(22):2313646. © 2024 Wiley-VCH GmbH.[127]

Clinical Translational Challenges and Limitations

Nanozymes have emerged as promising agents for the treatment of AS due to their ability to mimic the catalytic activity of natural enzymes and modulate multiple pathological processes such as oxidative stress, chronic inflammation, and vascular cell senescence. By integrating ROS scavenging, anti-inflammatory modulation, and cellular protective functions into a single nanoplatform, nanozymes have demonstrated robust preclinical efficacy in a variety of in vitro and

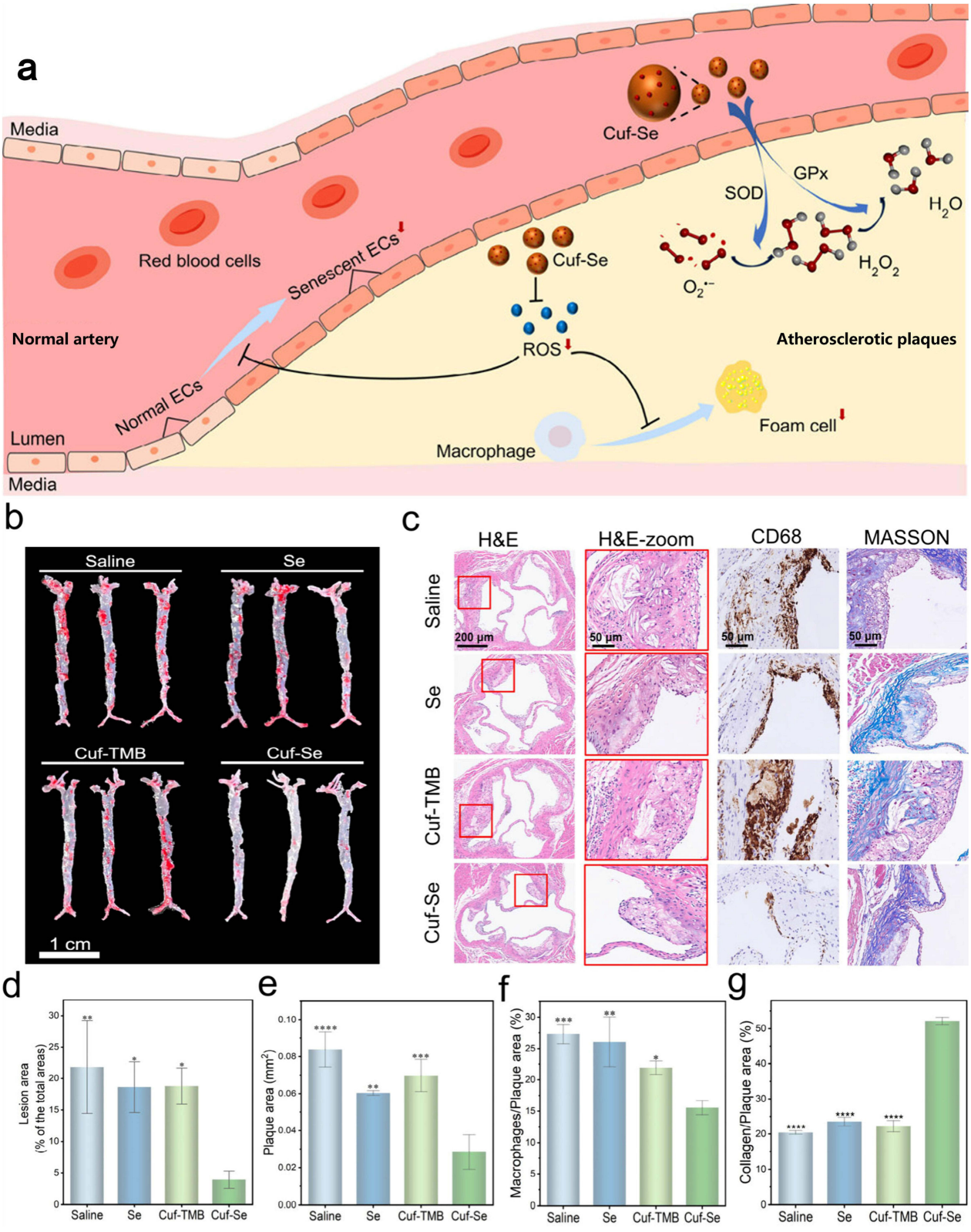

Figure 8 (**a**) Schematic diagram of atherosclerosis treatment using Cuf-Se nanozymes to decompose H_2O_2, inhibit ROS, and prevent foam cell formation. (**b**) Visual depictions of entire aortas following ORO staining. (**c**) Representative images of sections from the aortic root that have been stained with H&E, an antibody targeting CD68, and Masson's trichrome stain. The scale bar for the H&E staining is 200 micrometers, whereas the scale bars for the magnified H&E view, CD68 staining, and Masson's staining are all 50 micrometers. Quantitative assessment of: (**d**) the area of lesions within the aortas, (**e**) the areas occupied by plaques, (**f**) the numbers of macrophages, and (**g**) the content of collagen. The data are presented in the form of mean ±SD, with a sample size of n = 3. *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 vs Cuf-Se group. Reproduced from Huang X, Zhou Y, Guo Y, et al. Selenium-doped copper formate nanozymes with antisenescence and oxidative stress reduction for atherosclerosis treatment. Nano Lett. 2025;25:2662–2669. Copyright © 2025 American Chemical Society.[128]

in vivo models. Despite these encouraging findings, their clinical translation remains hindered by a number of fundamental challenges, including concerns over biosafety, insufficient targeting accuracy, pharmacokinetic limitations, lack of standardized evaluation criteria, and production scalability constraints.[129–131] This section systematically examines the current translational bottlenecks associated with nanozyme-based therapies for AS and proposes key areas for future research and technological development.

A primary concern in the clinical translation of nanozymes lies in their biosafety, particularly regarding long-term toxicity, organ accumulation, and immunogenicity.[132–134] A primary concern in the clinical application of nanozymes is biosafety, particularly regarding long-term toxicity, organ accumulation, and immunogenicity. Many nanozymes are composed of metal elements such as cerium, iron, manganese, gold, or palladium, which, although essential to their catalytic activity, raise concerns about potential chronic toxicity. Upon systemic administration, these inorganic components may accumulate in clearance organs such as the liver, spleen, and kidneys. Long-term retention of metal-based nanozymes could disrupt normal organ function, provoke inflammatory responses, or interfere with cellular homeostasis. Therefore, thorough toxicokinetic profiling including extended monitoring of blood biochemistry, histopathology, and organ-specific metal burden is essential. In addition to the core material, surface ligands and coatings used to improve stability, circulation time, or targeting may elicit innate or adaptive immune responses. These reactions range from mild cytokine release to severe complement activation-related pseudoallergy, especially in the context of repeated or high-dose exposure. Surface charge also plays a critical role: positively charged nanozymes can enhance cellular uptake through electrostatic interactions but may simultaneously disrupt cell membranes and increase cytotoxicity; negatively charged or neutral particles often show better biocompatibility but reduced internalization efficiency. Size and morphology further influence in vivo behavior. Smaller nanozymes (<20–30 nm) may penetrate tissues more effectively and be excreted via renal pathways, but are also more prone to nonspecific distribution and rapid clearance. Larger or irregularly shaped particles may persist longer in circulation but risk aggregation or entrapment in the reticuloendothelial system, potentially leading to organ stress or dysfunction. Moreover, the degradation behavior of nanozymes remains incompletely understood—some may persist in biological tissues for weeks or months, highlighting the need for long-term elimination and metabolism studies. Current safety assessments are often limited to short-term rodent models, which cannot fully capture chronic toxicity, immunogenic memory, or interspecies pharmacokinetics. Thus, future preclinical evaluation should incorporate long-term studies in large animal models, include dose-escalation and recovery phases, and employ advanced tr[135] acking techniques to monitor biodistribution, accumulation, and clearance in real time. In conclusion, while nanozymes hold strong therapeutic promise, their biosafety profile must be rigorously characterized through multidimensional studies before clinical translation can be realized. This includes a comprehensive evaluation of not only acute toxicity, but also sub-chronic and chronic effects, immunocompatibility, and long-term metabolic fate.

While nanozymes have shown robust therapeutic effects in short-term preclinical studies—such as reduced plaque burden, enhanced fibrous cap thickness, and decreased macrophage infiltration—data on their long-term efficacy remain limited. Most published work is restricted to animal studies of 4–8 weeks in ApoE$^{-/-}$ or LDLR$^{-/-}$ mice. Only a few studies have extended treatment to 12 weeks or beyond, showing improved collagen content and reduced necrotic core areas, which are surrogate indicators of plaque stability. However, such studies rarely assess recurrence risk or the prevention of cardiovascular endpoints such as myocardial infarction, stroke, or mortality. To validate the durable benefits of nanozyme therapy, future studies should include long-term treatment windows and post-treatment monitoring phases. Imaging-based assessments (eg, serial PET-CT or MRI) and quantification of dynamic biomarkers would be particularly useful. Moreover, advanced animal models that more closely replicate human plaque evolution, rupture, and thrombotic sequelae are needed to establish translational relevance. Currently, no nanozyme-based platform has entered clinical trials for atherosclerosis, although iron oxide and cerium oxide nanomaterials have reached Phase I/II trials in oncology or imaging applications. These precedents provide encouraging safety baselines, but dedicated cardiovascular trials are essential to demonstrate sustained plaque modulation and long-term prevention of adverse cardiovascular events.

The issue of precise targeting remains a persistent obstacle. Although surface modifications using ligands, peptides, or antibodies can endow nanozymes with preferential affinity for atherosclerotic lesions, the complexity of the in vivo vascular microenvironment often undermines targeting efficiency. In particular, the heterogeneous cellular composition and dynamic molecular milieu within atherosclerotic plaques pose significant challenges for

specific delivery. Competing interactions with circulating proteins and non-target cells may further hinder nanozyme accumulation at the lesion site. Moreover, many nanozymes exhibit rapid clearance from systemic circulation due to opsonization and uptake by the mononuclear phagocyte system. For example, unmodified nanozymes often have short blood half-lives, limiting their ability to achieve therapeutic concentrations at target tissues. The metabolism and excretion pathways of most nanozymes remain poorly characterized, adding uncertainty to their pharmacological profile and long-term safety.

Another important limitation is the lack of standardized criteria for assessing nanozyme efficacy in AS. Studies often employ disparate methodologies to measure therapeutic outcomes, such as plaque area reduction, inflammatory cytokine levels, oxidative stress markers, or cellular viability indices.[136–138] The variability in experimental design, endpoint selection, and measurement techniques hampers the ability to perform cross-study comparisons or meta-analyses, impeding objective evaluation of therapeutic efficacy. Additionally, long-term outcomes remain insufficiently studied. While many investigations report short-term improvements in plaque burden and inflammatory status, few address durability of effect or the potential for disease relapse following treatment cessation.[139–142] From a manufacturing standpoint, the scale-up of nanozyme production poses significant technical and economic challenges. Most nanozymes are synthesized using complex procedures that require strict control over reaction parameters such as pH, temperature, and reagent concentrations. Small deviations during production can result in batch-to-batch variability in particle size, enzyme-like activity, and structural integrity. For example, the preparation of metal-organic framework-derived nanozymes or mesoporous ternary alloy nanozymes such as palladium-boron-phosphorus composites often involves delicate templating techniques and multistep purification, which are difficult to replicate consistently at industrial scale. Additionally, methods involving metal ion doping, such as selenium incorporation into MOFs, demand precise stoichiometric and spatial control to ensure catalytic uniformity. Without reliable scale-up protocols, clinical-grade nanozymes remain difficult to produce cost-effectively and reproducibly.

Quality control and regulatory standardization represent further barriers to clinical application. Current protocols for characterizing nanozyme parameters such as particle size distribution, surface charge, enzyme-mimicking activity, and storage stability are highly inconsistent across laboratories. For instance, dynamic light scattering and transmission electron microscopy may yield divergent particle size estimates depending on sample preparation and instrumental settings. There are no universally accepted impurity thresholds or assay conditions for measuring enzyme activity, which is highly sensitive to variables such as substrate concentration, pH, and temperature. Stability testing is also inadequately defined, with limited data available on how nanozyme activity and structure evolve under different storage and transport conditions. The absence of harmonized analytical frameworks impedes regulatory review and complicates integration into clinical workflows.

In conclusion, while nanozymes hold significant promise for the treatment of AS, their clinical translation is contingent upon overcoming a spectrum of biosafety, targeting, pharmacokinetic, manufacturing, and standardization challenges. Future research should prioritize the development of biocompatible and biodegradable nanozyme platforms with tunable activity, enhanced targeting precision, and well-defined pharmacological behavior. Parallel efforts must focus on establishing robust manufacturing protocols and regulatory benchmarks to ensure quality control and facilitate approval pathways. With concerted interdisciplinary collaboration among materials scientists, pharmacologists, and clinicians, nanozymes may yet fulfill their potential as transformative agents in the management of cardiovascular disease.

Conclusion and Future Perspectives

AS remains a leading cause of morbidity and mortality worldwide, with oxidative stress, chronic inflammation, and vascular cell senescence forming the core pathological triad that drives disease progression. While conventional pharmacological treatments provide symptomatic relief, they are often constrained by limited targeting capability and their focus on single biological pathways. The emergence of nanozymes, which are nanomaterials exhibiting enzyme-like catalytic properties, offers a transformative approach by enabling simultaneous intervention across multiple disease mechanisms. This review has comprehensively summarized recent advances in nanozyme-based strategies for AS treatment, highlighting representative platforms including Prussian blue, cerium oxide, selenium-derived nanozymes, and multifunctional composite systems. These nanozymes are capable of mimicking natural antioxidant enzymes such as

superoxide dismutase, catalase, and glutathione peroxidase, effectively reducing ROS and attenuating oxidative injury. In parallel, many nanozyme platforms have demonstrated additional benefits in suppressing inflammatory signaling, promoting cholesterol efflux, reducing cellular senescence, and enhancing plaque stability. Especially notable are multifunctional nanozyme constructs that integrate catalytic activity with controlled drug release, biomolecular targeting, and microenvironment-responsive behavior, thereby allowing precise and coordinated remodeling of atherosclerotic lesions.

Despite the encouraging progress, the clinical translation of nanozymes remains challenged by several critical factors. These include biosafety concerns related to long-term exposure and organ accumulation, suboptimal pharmacokinetics, limited targeting specificity under physiological conditions, and a lack of unified standards for evaluating therapeutic efficacy and manufacturing consistency[135]. Furthermore, the underlying mechanisms of action for some nanozyme systems remain insufficiently understood, and there is a need for long-term studies addressing durability of effect, systemic clearance, and recurrence risk post-treatment. To overcome these limitations, future research must prioritize the development of nanozyme platforms that exhibit high catalytic stability, precise biological targeting, and degradability under physiological conditions. New fabrication techniques such as microfluidics-based assembly and supramolecular self-organization may provide better control over size, shape, and functional integration, enhancing reproducibility and scalability for clinical application. The incorporation of responsive motifs that react to the biochemical milieu of plaques, for example, pH, oxidative stress levels, or enzyme activity can enable site-specific activation, thereby improving efficacy and reducing off-target effects. Moreover, emerging technologies offer new opportunities to accelerate innovation in this field. Artificial intelligence-driven materials discovery can assist in predicting structure-function relationships and optimizing catalytic performance. Machine learning algorithms can analyze large datasets from preclinical studies to refine nanozyme design and anticipate safety profiles. Single-cell transcriptomics and spatial proteomics may uncover precise molecular signatures of atherosclerotic plaques, guiding the customization of nanozyme therapies for specific lesion phenotypes. Additionally, integrating nanozymes with real-time monitoring tools such as wearable biosensors and smart imaging probes can enable longitudinal assessment of therapeutic outcomes and dynamic disease progression. In conclusion, nanozymes represent a highly promising class of therapeutic agents with the potential to reshape the landscape of AS management. Their capacity to concurrently modulate oxidative damage, inflammation, lipid metabolism, and cellular senescence aligns well with the multifactorial nature of cardiovascular pathology. Continued interdisciplinary efforts to address current translational barriers supported by innovations in materials science, biotechnology, and data analytics will be crucial for unlocking the full clinical potential of nanozyme-based precision medicine.

To further advance clinical translation, several key challenges must be addressed. Improving targeting specificity requires the rational design of ligand-functionalized nanozymes that selectively recognize plaque components such as inflamed endothelium, macrophages, or oxidized lipids. In addition, engineering stimuli-responsive systems that release therapeutic payloads in response to plaque microenvironment cues such as low pH, elevated ROS, or enzyme activity can enhance lesion-selective delivery while minimizing systemic exposure. Regarding biosafety, the development of nanozymes based on biodegradable materials or renal-clearable constructs can reduce long-term accumulation risks. Surface modification strategies that neutralize surface charge or mask immunogenic motifs may further minimize immune activation. Looking forward, nanozyme research for AS can benefit from integration with real-time imaging, wearable biosensors, and AI-assisted catalyst optimization. Omics-based characterization of plaque heterogeneity may also enable the design of personalized nanozyme therapies targeting specific molecular signatures of atherosclerosis. These innovations hold great promise for translating nanozyme-based precision medicine into effective, safe, and individualized interventions for cardiovascular disease. Future advances in nanozyme development for atherosclerosis will depend on the ability to integrate catalytic function with intelligent design and clinical applicability. One critical direction is the creation of biodegradable, renal-clearable nanozymes to mitigate long-term organ retention. Another key area is the engineering of stimuli-responsive platforms that activate catalytic activity in disease-specific microenvironments. Additionally, combining diagnostic and therapeutic capabilities into a single nanozyme (ie, theranostic agents) would enable real-time monitoring of treatment efficacy and dynamic plaque responses. The use of AI-assisted design and high-throughput screening can further optimize catalytic efficiency, target specificity, and safety profiles. Finally, translating these findings into clinical practice will require long-term animal studies and regulatory engagement to design first-in-human trials, ideally starting with nanozyme systems already validated in other therapeutic areas.

Data Sharing Statement

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