

Targeted nanozyme-enabled treatment of cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) pose a significant threat to human health due to the high mortality and morbidity rates. Traditional drugs often have limited efficacy due to inherent constraints, such as low bioavailability and notable side effects. As a highly regarded therapeutic strategy, nanotechnology offers new perspectives and means for treating CVDs. Nanozyme-based targeted therapeutic drugs specifically address the biological processes in areas affected by CVDs, thereby achieving precise treatment. Compared to traditional drugs, targeted nanozymes offer advantages, such as high efficiency, specificity, controllability, and fewer side effects, showing great efficacy in treating CVDs. This paper first explores the design strategies and mechanisms of nanozyme-based targeted therapy, then introduces its application in key CVDs, such as ischemic stroke, myocardial infarction, and coronary heart disease. Finally, the paper discusses the challenges of introducing targeted nanozymes into clinical applications and the future development prospects in the treatment of CVDs.

Keywords: active targeting, nanozymes, cardiovascular diseases

1. INTRODUCTION

Cardiovascular diseases (CVDs) include coronary heart disease, stroke, and myocardial infarction, which are characterized by circulatory disorders [1]. Several modifiable factors, such as metabolic risk factors and lifestyle behaviors, may trigger CVDs. These modifiable factors include hypertension, diabetes, hyperlipidemia, obesity, cigarette smoking, physical inactivity, unhealthy diets, mental stress, and anxiety [2]. In 2019, approximately 17.9 million people lost their lives due to CVDs, accounting for 32% of global deaths, thus making CVDs a primary cause of global deaths, as reported by the World Health Organization. Estimates suggest that by 2030 greater than 24 million people will die due to complications related to CVDs [3]. The pathophysiologic mechanisms underlying CVDs include chronic inflammation, oxidative stress overload, hypoxia, metabolic dysregulation, genetic factors, endothelial dysfunction, hemodynamic changes, and neurohormonal activation [4], which supports the notion that targeted anti-inflammatory therapy

[5], oxidative stress reduction, and hypoxia improvement are important therapeutic strategies to reduce the risk of CVDs. However, traditional treatment methods, such as antioxidants, anti-inflammatory drugs, antihypertensive drugs, lipid-lowering medications, and anticoagulants, hinder clinical application due to low bioavailability, poor stability, and potential side effects. There is an urgent need to develop safe and effective therapeutic drugs for CVDs to benefit patients with CVDs.

In recent years the rapid development of nanomedicine has significantly contributed to innovations in biomedical technology. Among these advances, nanozymes have garnered wide attention for their excellent anti-inflammatory, antioxidant [6], and reactive oxygen species (ROS)-scavenging capabilities [7]. Nanozymes are nanomaterials with a size range of 1–100 nm. Nanozymes exhibit activity similar to natural enzymes and possess the properties of nanomaterials [8]. In 2007 Yan et al. [9] first discovered that Fe₃O₄ has horseradish peroxidase (HRP)-like properties, confirming that inorganic materials have enzymatic properties

Mini Review

and promoting the rapid development of nanozyme technology.

Compared to natural enzymes, nanozymes have better physicochemical stability and durability for harsh environments, lower cost, and easier preparation and regulation. Moreover, nanozymes with a single enzyme activity catalyze only one substrate reaction, while nanozymes with two or more multi-enzyme activities catalyze different substrates, triggering cascade reactions [10]. Nanozymes enable the design of multi-enzyme systems capable of catalyzing cascade reactions, unlike natural enzymes. These properties make nanozymes a promising candidate for the treatment of CVDs. Many nanozymes have similar redox properties to natural enzymes, including catalase-like (CAT), superoxide dismutase-like (SOD), glutathione peroxidase-like (GPx), peroxidase-like (POD), glucose oxidase-like (GOx), and oxidative enzyme-like (OXD) [11]. Based on different types of nanomaterials, nanozymes can be categorized into metal nanoparticles, metal oxide nanoparticles, carbon-based nanomaterials, and metal-organic frameworks (MOFs). Nanozymes with active targeting capabilities offer a promising therapeutic approach for treating cardiovascular diseases (CVDs), addressing key limitations of traditional drug treatments. By selectively accumulating at pathologic sites and minimizing side effects, these nanozymes enable precise intervention in disease areas. For example, Liu et al. [12] developed a new

Fe-Cur@TA nanozyme that can reduce immune cell infiltration, promote macrophage M2 polarization, inhibit secretion of validating factors, and block the inflammatory free radical cycle. Liu et al. [12] also reported that Fe-Cur@TA nanozymes have a high affinity for cardiac tissues of animal models, suggesting the potential for Fe-Cur@TA application in CVDs. In addition, Liao et al. [13] developed ceria nanozymes that target cellular mitochondria. These nanozymes are selectively enriched in the mitochondria, alleviate cellular oxidative stress, improve mitochondrial dysfunction, and have shown good therapeutic effects in ischemic stroke [13]. In summary, nanozymes with targeting capabilities accurately locate pathologic sites, selectively accumulate in affected areas, and reduce off-target effects, making nanozymes with targeting capabilities an innovative, forward-looking solution for CVD therapy.

In the past few years many advances have been made in the treatment of CVDs with nanozymes but there are many incomplete reports. Although some reviews have attempted to summarize the existing research progress, a more comprehensive summary is still needed in the treatment of CVDs with nanozymes. Therefore, this paper comprehensively introduces the mechanism underlying nanozymes in the treatment of CVDs, the current targeted therapy strategies, and the application of nanozymes in related diseases to provide strong support for the development of cardiovascular nanotechnology (Figure 1).

Targeted Nanozymes for the Treatment of Cardiovascular Diseases

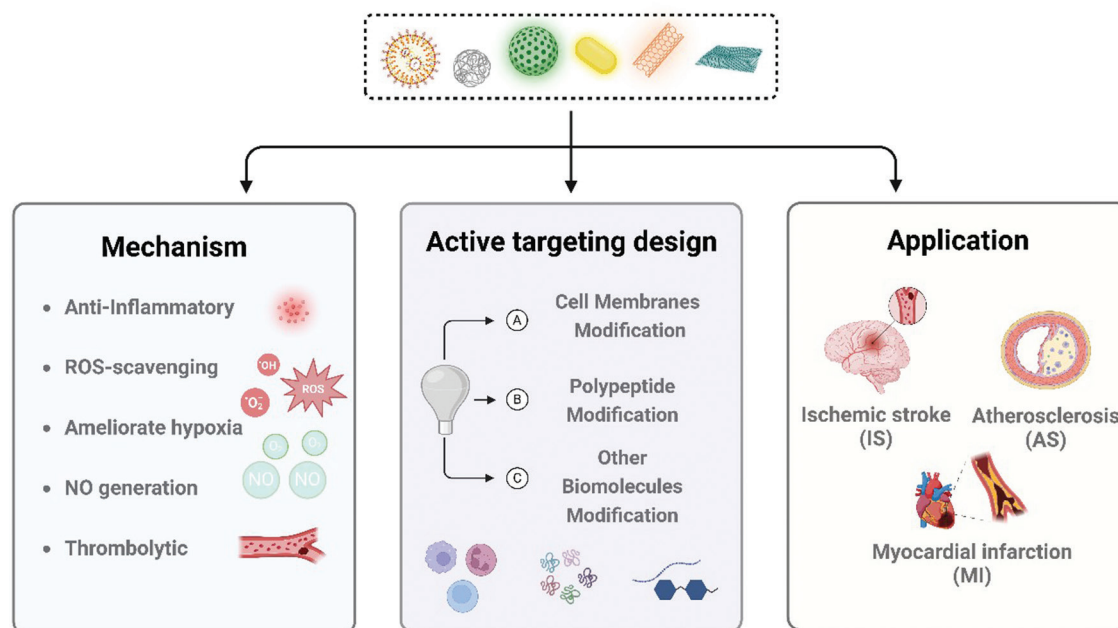


Figure 1 | Summary of this review: the mechanisms by which nanozymes treat CVDs, the design strategies for active targeting, and application.

2. MECHANISMS UNDERLYING NANOZYMES FOR CVDs

CVDs encompass a diverse range of conditions with varying etiologies, pathogenesis, and clinical manifestations, yet CVDs all share common pathologic processes, such as inflammation and oxidative stress. This section will discuss several typical mechanisms by which nanozymes contribute to the treatment of CVDs (Table 1).

2.1 Anti-inflammatory

Inflammation is a protective response of the immune system to damage-inducing factors and is the most common pathogenic process in the human body, which can be severely harmful when dysregulated. Inflammation is the foundation for the development and progression of CVDs; relieving inflammation can reduce the risk of CVDs [15, 24]. In recent years some nanozymes have demonstrated intrinsic anti-inflammatory properties that modulate the expression of pro- and anti-inflammatory molecules. These nanozymes target inflammatory sensors or macrophages to diagnose, treat, monitor, and balance inflammatory immune homeostasis [25]. For example, Zhang et al. [14] developed an injectable multifunctional hydrogel [ALG-(ZIF-8)] comprised of a zinc-based nanozyme (ZIF-8). The hydrogel exhibits SOD and CAT-like activities, facilitating a significant shift in macrophages towards the M2 phenotype [14]. This shift effectively mitigates inflammatory responses, promotes angiogenesis in the infarcted region, reduces ROS, and disrupts the ROS-driven inflammatory cascade. Moreover, Xiang et al. [15] developed an integrated bimetallic nanozyme derived from MOF (Cu-TCPP-Mn). This nanozyme mimics the cascade activities of SOD and CAT to eliminate ROS. In a mouse model of MI and a rat model of I/R injury, the bimetallic MOF nanozyme demonstrated excellent ROS scavenging and anti-inflammatory performance during the early inflammatory stage of cardiac injury. Thus, the favorable anti-inflammatory activity of nanozymes can be used to inhibit the inflammatory response in a variety of CVDs and this anti-inflammatory activity is more highly targeted than that of conventional anti-inflammatory drugs.

2.2 ROS-scavenging

Excessive intracellular accumulation of ROS is an important cause of oxidative stress-induced damage, inflammatory cascade, and iron death [26]. ROS act as signaling molecules in cells, which activates cellular signaling cascades, induces apoptosis, and affects gene expression [27]. There is normally a balance between the production and elimination of ROS in the body. However, when ROS production increases or the body's ability to clear ROS decreases, excessive ROS accumulate, leading to oxidative stress. This oxidative stress triggers inflammatory responses, DNA damage, cellular senescence, and programmed cell death, which are significant in the development of CVDs [9]. In normal cells, several natural

antioxidant enzymes, such as SOD, CAT, GPx, and GSH, work together to remove excess ROS and maintain redox homeostasis [28]. However, in diseased cells these natural enzymes may be insufficient or dysfunctional, resulting in ROS accumulation. Nanozymes, which mimic natural enzyme activity, can help scavenge excess ROS and mitigate oxidative stress-induced damage in CVDs. The single platinum (Pt) atom nanozyme (PtsaN-C) has recently been shown to have exceptional ROS-scavenging performance, outperforming Pt cluster-based centers by offering better synergistic effects and enhanced metal electron properties. PtsaN-C effectively counteracts ROS, restores cellular homeostasis, and prevents the progression of apoptosis following I/R injury [16]. Prussian blue enzyme (PBzyme) with CAT- and SOD-like nanozyme activities was designed by Liu et al. [17] to study ischemic stroke. This unique substance efficiently eliminates ROS from the body, thereby preventing the activation of macrophages and reducing the release of inflammatory factors in the brain. Moreover, PBzyme fosters the polarization of microglial cells to the M2 type, inhibits neuronal apoptosis, and contributes to the recovery of neurologic function following ischemic stroke. Jiang et al. [18] reported that cerium vanadate (CeVO_4) nanozyme with SOD-like enzyme activity can be used to achieve non-invasive treatment of hypoxia-ischemia (HI) brain injury in neonatal mice by targeting the mitochondria of cerebral neurons. The CeVO_4 nanozyme restored HI-induced oxidative stress by activating the Nrf2 antioxidant pathway. In conclusion, nanozymes exhibit great therapeutic potential and application prospects for a variety of ROS-mediated CVD-related diseases.

2.3 Ameliorate hypoxia

Coronary artery narrowing or plaque rupture can lead to blood flow obstruction, resulting in inadequate perfusion and local hypoxia in the ischemic area, which triggers irregular adenosine triphosphate (ATP) synthesis, increased generation of ROS, and heart dysfunction and serves as a crucial driving force in the development of CVDs [29]. Promoting angiogenesis, vascular remodeling, and establishing collateral circulation in tissues can alleviate hypoxia and prevent apoptosis and necrosis. Therefore, oxygen regulation could be a crucial therapeutic target for mitigating CVDs [30]. In recent years nanozymes have been shown to improve the hypoxic microenvironment and achieve pro-angiogenesis by regulating hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF) expression and endothelial growth factor (EGFR) signaling. Liu et al. [19] developed hybrid membrane nanovesicles (YC-1@[RBC-PL] NVs) by wrapping red blood cell (RBC) and platelet (PL) membranes with an HIF-1 α inhibitor (YC-1). YC-1@[RBC-PL] NVs promote functional recovery of the neurovascular unit (NVU) [19]. This is achieved through the following mechanisms: PL-mediated angiogenesis; RBC-derived peroxidase catalysis of hydrogen peroxide for oxygen supply; YC-1-mediated inhibition of HIF-1 α activity; and neuroprotection.

Mini Review

Table 1 | Nanozymes mechanisms for CVDs.

Therapeutic mechanisms	Nanozymes	Type of diseases	Activities	Symptom or model	Strategies of therapies	Reference
Anti-Inflammatory	ALG-(ZIF-8)	MI	SOD, CAT	SD rat MI model	Eliminating surplus ROS in the infarcted region and interrupting ROS-driven inflammatory cascades	[14]
	Cu-TCPP-Mn	MI	SOD, CAT	MI and myocardial I/R injury animal models	ROS scavenging and inflammation inhibition	[15]
ROS-Scavenging	PtsaN-C	Myocardial I/R injury	SOD, CAT, POD, GPx	Myocardial I/R injury mice model, OGD/R induced cell damage model	ROS clearance, maintenance of calcium and redox homeostasis, and suppression of MAPK/Jnk signaling pathway	[16]
	PBzyme	IS	SOD, CAT	I/R model, OGD/R induced cell damage model	Antioxidant and anti-inflammatory responses and anti-apoptosis	[17]
	CeVO ₄	Hypoxia-ischemia (HI) brain damage	SOD	Rice-Vannucci HI model in P7 mice	Suppressed oxidative stress and up-regulated Nrf2 expression	[18]
Ameliorate Hypoxia	YC-1@[RBC-PL] NVs	IS	Catalyzing the decomposition of H ₂ O ₂	SD middle cerebral artery occlusion (MCAO) model	Generating oxygen and inhibiting HIF-1 α activation	[19]
NO Generation	CeO ₂ NPs	AS	NOS	ApoE knockout mice	Escalating endogenous nitric oxide levels	[20]
	L-arg-loaded selenium-coated gold nanocage (AASP)	Myocardial I/R injury	Total nitric oxide synthase (TNOS)	Myocardial I/R injury in rats, OGD/R-induced cell damage model	Scavenged ROS and produced NO to maintain mitochondrial function	[21]
Thrombolytic	HMPB-rtPA@PM	Thrombotic diseases	$\cdot\text{O}_2^-$, $\cdot\text{OH}$, H ₂ O ₂ scavenging ability	Carotid artery thrombosis model, black tail model	Inhibit platelet aggregation and regulate the inflammatory microenvironment by scavenging ROS	[22]
	PLTV-IO-MB PENPs	Vascular blockages	-	FeCl ₃ method-induced thrombus animal model	Site-specific mechanical-photothrombolysis	[23]

2.4 NO generation

Nitric oxide (NO), which is widely distributed in various tissues throughout the body, primarily induces vasodilation through the cyclic guanosine monophosphate (cGMP) pathway. NO also diffuses into the bloodstream, inhibiting platelet aggregation and adhesion [31]. Therefore, NO dilates blood vessels, increases blood flow, reduces vascular resistance, and alleviates cardiac load, thereby lowering blood pressure and preventing CVDs. The lack of NO may lead to vasoconstriction, hypertension, atherosclerosis, and other cardiovascular system disorders [32]. Therefore, supplementation of endogenous NO improves vasodilation and reduces inflammation, ultimately lowering the risk of CVDs [33]. Sun et al. [20] were the first to show that CeO₂ nanoparticles (NPs) possess nitric oxide synthase (NOS)-like activity. These NPs successfully increased NO secretion in endothelial cells and macrophages by catalyzing the production of NO or its derivatives from L-arginine (L-Arg). The NOS-like activity and reactive endogenous NO of CeO₂ NPs promote lipid redistribution, stabilize endothelial NOS (eNOS) expression, and inhibit inducible NOS (iNOS), which leads to a reduction in vascular plaque accumulation. A recent study showed that an L-arg-loaded selenium-coated gold nanocage with myocardial targeting properties (AASP) maintains mitochondrial function by scavenging ROS and generating NO, thereby inhibiting cardiomyocyte apoptosis *in vitro*. Additionally, AASP reduces myocardial infarction/reperfusion injury (MI/RI) in rats by sustaining mitochondrial function and regulating NO signaling and effectively improves cardiac function *in vivo* by inhibiting cardiomyocyte apoptosis and fibrosis [21].

2.5 Thrombolytic

Thrombosis is a significant pathologic process in CVDs [34]. Therefore, thrombolysis and antiplatelet aggregation are now essential therapeutic strategies to improve CVDs. A platelet membrane (PM)-functionalized hollow mesoporous Prussian blue nanomedicine (HMPB-rtPA@PM) developed by Zhang et al. [22], was loaded with two FDA-approved drugs, Prussian blue (PB) and alteplase (rtPA). The HMPB-rtPA@PM has excellent antioxidant enzyme activity and scavenges ROS, inhibits platelet aggregation, and demonstrates strong thrombus-targeting capability, rapid fibrinolysis, and modulation of the inflammatory microenvironment in ROS-mediated thrombosis, which could lead to effective thrombolytic therapy. Similarly, Zheng et al. [23] utilized cold atmospheric plasma (CAP), human platelet vesicles (PLTVs), and methylene blue (MB) to generate self-assembled plasma nanopropellers (PLTV-IO-MB PENPs). The synthesized PLTV-IO-MB PENPs target thrombotic clots. Magnetic resonance imaging (MRI) and fluorescence imaging showed that a specific PLTV-IO-MB PENP accumulation can be visualized at the thrombotic site, allowing for the precise localization of the thrombotic lesion. The remaining PLTV-IO-MB PENPs are guided to deep

thrombotic clots using static magnets and the PLTV-IO-MB PENPs possess near infrared (NIR) irradiation-induced photodynamic therapy (PDT) and photothermal therapy (PTT) properties for remote photothrombolysis. The multimodal magnet therapy and phototherapy strategy effectively achieves site-specific mechanical photo thrombolysis and prevents thrombus recurrence.

3. ACTIVE TARGETING DESIGN OF NANOZYMES FOR CVDs

Nanozymes can be modified with specific targeting molecules, such as antibodies, nucleic acids, peptides, cell membranes, or other molecules capable of recognizing disease markers, to achieve precise localization and treatment of cardiovascular lesions [35]. The active targeting functionality of these molecules allows nanozymes to remain in the affected area and improve the lesions. This section will introduce three active targeting design strategies for nanozymes (Table 2).

3.1 Cell membrane modification

Nanozymes show potential in utilizing the inflammatory microenvironment of CVDs to perform targeted and specific therapies. The chemotactic effect of inflammatory cells, i.e., the induction of inflammatory cells, such as neutrophils, monocytes, and lymphocytes, by inflammatory mediators and chemokines drive the inflammatory cells to migrate from the blood or other tissues to the inflammatory lesions of CVDs. In the early stages of atherosclerosis, endothelial cells attract monocytes to the arterial wall through chemokine receptor interactions and the expression of cell adhesion molecules [42]. Therefore, modifying the inflammatory cell membrane on nanozymes can precisely deliver nanozymes to the inflammatory lesions of CVDs to achieve accurate targeting of the inflammatory microenvironment in cardiovascular lesion areas. Feng et al. [36] have developed a non-invasive treatment for ischemic stroke by creating a targeted delivery system based on nanozymes. This system employs a coating of neutrophil-like cell membranes (NCMs) on mesoporous Prussian blue nanozymes (MPBzyme@NCM), which provides a mechanism for selective binding to inflamed cerebral microvascular endothelial cells (Figure 2a). This targeted approach facilitates the active delivery of MPBzyme@NCM to areas of the brain affected by ischemia. Hu et al. [37] loaded tetrapodal PdH nanozymes with ROS-scavenging, anti-inflammatory, and autophagy-activating activities onto macrophages. The macrophages can be used to target these nanozymes to arterial plaques for the treatment of atherosclerosis. This multifunctional nanozyme effectively reduces ROS levels and inhibits inflammation-related pathologic processes in plaque areas [38].

3.2 Polypeptide modification

Peptides coupled to a nanozyme can be targeted as ligands to the corresponding receptors at the lesion site,

Mini Review

Table 2 | Active targeting design of nanozymes for CVDs.

Active targeting design	Nanozymes	Activities	Type of diseases	Symptom or model	Strategies of therapies	Reference
Cell Membranes Modification	Neutrophil membrane	MPBzyme@NCM	CAT, SOD	IS	A mouse model of transient middle cerebral artery occlusion (tMCAO)	Microglia polarization toward M2, reduced recruitment of neutrophils, decreased apoptosis of neurons, and proliferation of neural stem cells, neuronal precursors, and neurons [36]
Polypeptide Modification	Macrophage loading	TN-PdH@Ms	ABTS ^{•+} and H ₂ O ₂ , •O ₂ ⁻ , •OH	AS	ApoE ^{-/-} Mice	Antioxidation, anti-inflammatory, and autophagy activation [37]
	P-selectin binding peptides (PP) and mannose (Man) molecules	PBNZ@PP-Man	CAT, SOD	AS	ApoE ^{-/-} Mice	ROS scavenging properties and the enhancement of macrophage efferocytosis [39]
	Transferrin (Tf)	Eda-MnO ₂ @Tf (EMT)	SOD, CAT	IS	Rats with MCAO	Eliminate ROS, reducing the levels of inflammatory factors in the lesion area [40]
Other Biomolecules Modification	Tannic acid (TA)	TA-Ce NCS	•OH elimination capacity and total antioxidant	Ischemic heart disease (IHD)	The murine I/R model, H ₂ O ₂ and OGD/R induced cell damage model	Cardiac accumulation and intracellular ROS scavenging [41]
	Mannan	Que@MOF/Man	ABTS ^{•+} , DPPH [•] , •O ₂ ⁻ , •OH and nitric oxide radical (•NO) scavenging ability	MI	MI injury model in rats	Mitigate oxidative stress and regulate inflammation response for cardiac repair [43]

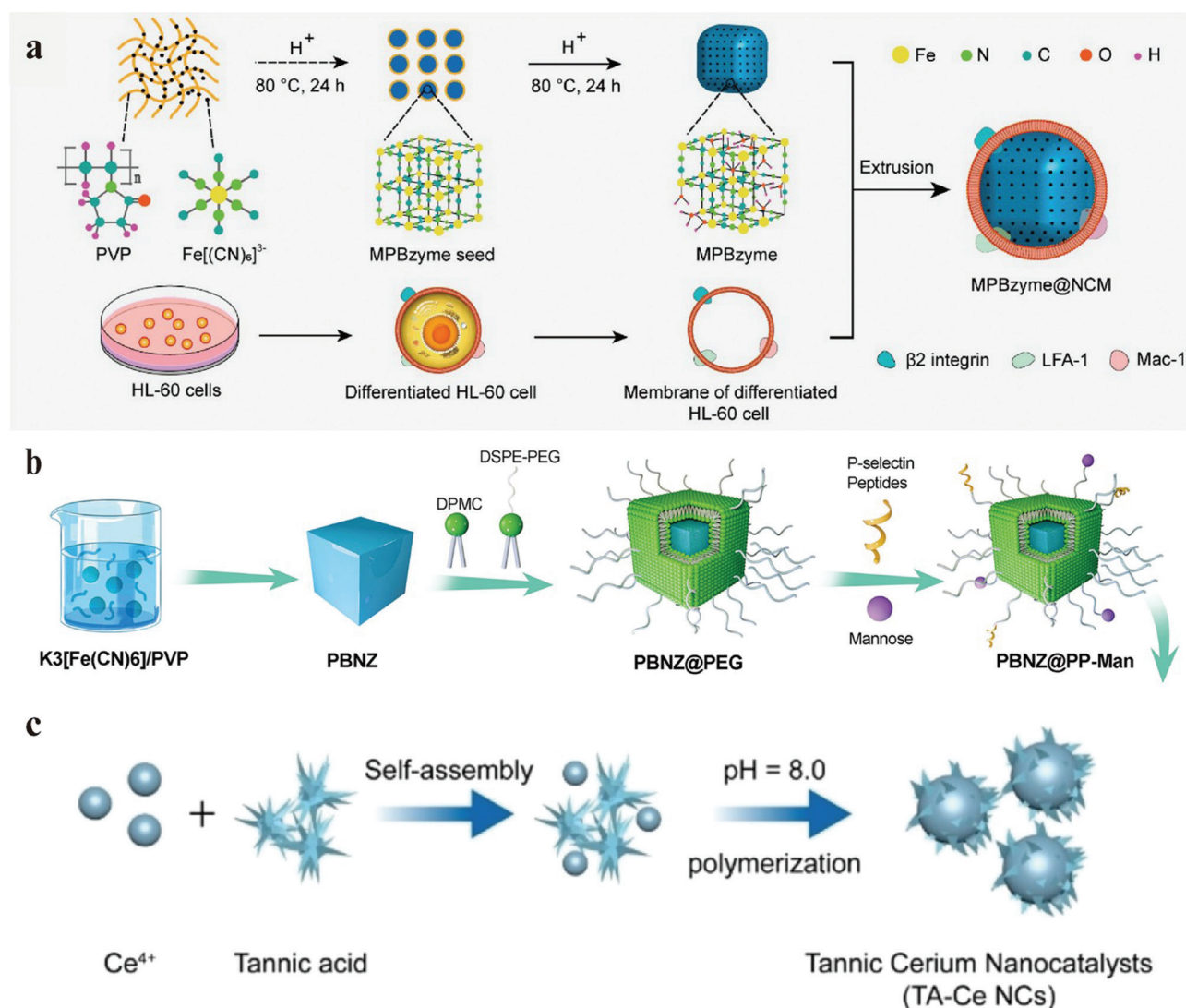


Figure 2 | Active targeting design of nanozymes for CVDs.

a. Mesoporous Prussian blue nanozyme (MPBzyme) coated with the neutrophil-like cell membrane (NCM). Reprinted with permission [36]. Copyright 2021, American Chemical Society. b. Nanozyme (PBNZ@PP-Man) modified with PP and Man molecules. Reprinted with permission [39]. Copyright 2023, American Chemical Society. c. Tannic acid-assembled tetravalent cerium nanozyme (TA-Ce) (Reprinted with permission [41]. Copyright 2023, Wiley-VCH.

positioning the nanozyme to the lesion tissue and functioning. Using atherosclerosis as an example, one can design peptides targeting inflammatory endothelial cell markers (E-selectin, VCAM-1, and PECAM-1), inflammatory cells (CD36, CCR2, CCR5, ApoA-I, and ApoE), and thrombus biomarkers (GPIIb/IIIa, P-selectin, AV β 3, and FXIIIa) to achieve active targeting of nanozymes. A multifunctional nanozyme (PBNZ@PP-Man), which was designed by He et al. [39], incorporates Prussian blue, p-selectin-binding peptide (PP), and mannose (Man) molecules (Figure 2b). PP specifically targets P-selectin on activated endothelial cells covering plaques, while Man interacts with mannose receptors on macrophages

[39]. Together, these interactions mediate the active accumulation of PBNZ@PP-Man within atherosclerotic plaques, effectively inhibiting monocyte recruitment and the onset of plaque inflammation. Similarly, Zhao et al. [40] have designed a targeted transferrin (Tf)-based manganese dioxide nanozyme (MnO_2 @Tf, MT) using a mild biomimetic mineralization method. This technique successfully loaded edaravone (Eda), a clinical neuroprotective agent, onto MT to construct the Eda- MnO_2 @Tf (EMT) nanoplatform [40]. Transferrin receptor 1 (TfR) is highly expressed in the blood-brain barrier (BBB). Therefore, the Tf peptide in the EMT nanoplatform rapidly penetrates the BBB via endocytosis to

Mini Review

reach the lesion area, effectively targeting the site of brain ischemia. The inherent hydroxyl radical scavenging ability and capabilities of the Tf peptide in the EMT nanoplatfrom are similar to superoxide dismutase and catalase prompt clearing of free radicals at the lesion site, alleviating oxidative stress-induced inflammatory damage to the BBB.

3.3 Other biomolecule modifications

Nanozymes can also be modified with other biomolecules, such as sugars, hyaluronic acid, and folic acid, without affecting the biological activity. These biomolecules can impart targeting specificity to NPs, enhancing biocompatibility while reducing toxicity. Wang et al. [41] designed a tannic acid-assembled tetravalent cerium (TA-Ce) nanozyme with cardiac cell targeting and antioxidant capabilities and applied the TA-Ce nanozyme to the treatment of ischemia/reperfusion injury (Figure 2c). This article introduces a mannan-based nano-drug (Que@MOF/Man) that was designed to target inflamed infarcted hearts and deliver the antioxidant and anti-inflammatory agent, quercetin (Que) [43]. Man is a yeast polysaccharide containing d-mannose residues that are recognized by Man receptors on macrophages. This recognition promotes inflammation-specific accumulation and targeted intracellular uptake of Que@MOF/Man in macrophages.

4. TARGETED NANOZYMES IN THE TREATMENT OF CVDs

Following the discussion on the therapeutic mechanisms and targeting design strategies of nanozymes, this section introduces nanozyme application in key CVDs in recent years (Table 3).

4.1 Targeted nanozymes for ischemic stroke

Ischemic stroke (IS) is a condition that occurs when brain tissue damage occurs due to insufficient blood supply to the brain. IS is usually caused by thrombosis or arterial stenosis and is the second leading cause of death worldwide, as well as a significant cause of disability [50]. Many studies have shown that nanozymes, as a new type of antioxidant, reduce intracellular ROS levels following brain injury, mitigating oxidative stress-induced damage to the central nervous system [44]. Consequently, nanozyme-based targeted therapeutic agents are widely used in research on IS. Wang et al. [45] designed a novel peptide-templated manganese dioxide (PNzyme/MnO₂) nanozyme. This multifunctional nanozyme possesses capabilities, including fibrinogen binding, thrombolysis, clotting enzyme cleavage, and blood-brain barrier penetration. The PNzyme/MnO₂ nanozyme achieves precise localization in thrombotic ischemic regions through multistage targeting and cascade processes. Simultaneously, the PNzyme/MnO₂ nanozyme combines the thrombolytic activity of functional peptides with the ROS-scavenging ability of nanozymes, effectively

Table 3 | Targeted nanozymes in the treatment of CVDs.

Type of diseases	Nanozymes	Activities	Targeting design	Symptom or model	Strategies of therapies	Reference
Ischemic stroke (IS)	Pnzyme/MnO ₂	SOD, CAT	Polypeptides modified	Mice and rat IS models	Thrombolytic, oxygen species scavenging, neuroprotective actions	[45]
	D@HPB@SPM NPs	CAT, POD	Sialic acid (SA) and platelet membrane modified	Rat models of tMCAO	Scavenging ROS, degrading neutrophil extracellular traps (NETs)	[51]
	TPP@/(CeO ₂ +ROF)	·O ₂ ⁻ , ·OH and ABTS ⁺ radical scavenging ability	Triphenyl-phosphine-based modifications	MCAO model in SD rat	Attenuates oxidative damage and apoptosis	[13]
Atherosclerosis (AS)	PCZ@PB NCs	CAT, SOD	Platelet membrane modified	Apo E-/- mice model of AS	ROS-scavenging, anti-inflammatory	[47]
	37pA-PtLNP, 37pALNP/6877002	·O ₂ ⁻ , ·OH and H ₂ O ₂ scavenging ability	Macrophage modified	AS in Apo E-/- mice	Reducing the expression of proinflammatory cytokines and chemokines	[48]
	HA-CeO ₂ NPs	SOD	Hyaluronic acid modified	AS in Apo E-/- mice	Scavenge ROS to reduce the formation of ox-LDL	[52]
Myocardial infarction (MI)	ZIF-8zyme	SOD, CAT, GPx	FA-PEG modified	RAW264.7 cells, HUVEC cells	Anti-oxidative and anti-inflammatory ability, reprogramming M1 macrophages polarization	[53]
	Fe-Cur@TA	SOD, CAT	Tannic acid (TA) modified	A mouse model of MI, a beagle dog model of MI	Free radicals scavenging and anti-inflammatory properties	[12]

clearing ROS in apoptotic cells and exerting a neuroprotective effect. The PNzyme/MnO₂ nanozyme promotes the polarization of microglial cells from M1 (pro-inflammatory) to M2 (anti-inflammatory), inhibits the secretion of pro-inflammatory cytokines, reduces T cell and neutrophil recruitment, and suppresses inflammation and immune reactions induced by ischemia-reperfusion. The PNzyme/MnO₂ nanozyme provides the most effective protection against IS through combined targeting, thrombolytic, ROS-clearance, and anti-inflammatory capabilities.

D@HPB@SPM NPs are composed of a sialic acid (SA)-modified PM shell and a hollow Prussian blue NP core loaded with deoxyribonuclease I (DNase I) [51]. SA has a unique binding affinity for L-selectin, which is abundantly expressed on circulating neutrophils. This allows D@HPB@SPM NPs to target neutrophils and “hitch a ride” across the BBB into damaged brain parenchyma. Once inside, the neutrophils are activated and release D@HPB@SPM NPs through the formation of neutrophil extracellular traps (NETs). Finally, DNase I breaks down the DNA framework of the NETs, hastening NET destruction. D@HPB@SPM NPs reduce neutrophil-induced brain damage by degrading NETs in a “bridge-burning” manner and alleviate oxidative stress by effectively scavenging ROS. The D@HPB@SPM NPs were systematically validated in a transient middle cerebral artery occlusion (tMCAO) rat model, demonstrating D@HPB@SPM NP accumulation in ischemic brain regions and their therapeutic efficacy.

A cerium oxide nanozyme-based nanoplatfrom [TPP@CeO₂+ROF] was designed and synthesized by Liao et al. [13]. In this system, DSPE encapsulates CeNZs to enhance bioavailability, while triphenylphosphine-based modification allows the nanosystem to precisely target mitochondria. The fourth-generation PDE4 inhibitor, roflumilast, is loaded for neuroprotection. TPP@CeO₂+ROF effectively mediates mitochondrial damage, alleviates oxidative stress and apoptosis, and reduces brain infarct volume and BBB injury.

4.2 Targeted nanozymes for atherosclerosis

The primary cause of atherosclerosis (AS) is the prolonged deposition of high cholesterol and fats, forming plaques on the inner walls of arteries. As these plaques gradually enlarge, the plaques obstruct arteries, restrict blood flow, and ultimately result in complications, such as heart disease and IS. Increased ROS generation, lipid peroxidation, and inflammation are prevalent throughout the entire disease process [46]. Fu et al. [47] used zoledronic acid (ZOL) molecules containing imidazole and bis phosphonic acid groups to aid in the assembly of cerium ions to prepare functionalized cerium-zirconium nanocomposites (CZ NCs) and finally constructed nanoplatfroms encapsulated with PMs (PCZ@PB NCs). PCZ@PB NCs clear excessive cellular ROS, downregulate pro-inflammatory factor expression, and cooperatively inhibit the formation of foam cells with drugs. These

findings suggest the potential of biomimetic PCZ@PB NCs for treating AS. In another study, Yang et al. [48] successfully developed a plaque-targeting nanosystem (37pA-PtLNP and 37pA-LNP/6877002). As an ROS scavenger, 37pA-PtLNP is enriched in macrophages to alleviate intracellular oxidative stress. In addition, the combined administration of 37pA-PtLNP with 37pA-LNP/6877002 inhibits macrophage M1 polarization, reduces proinflammatory factors, and significantly degrades plaque in ApoE^{-/-} mice with AS by reducing oxidative stress and modulating the inflammatory response [48]. Hyaluronic acid (HA)-guided cerium dioxide (HA-CeO₂) NPs were designed by Wang et al. [52] as innovative reactive oxygen scavengers to target atherosclerotic plaques. The high expression of the HA receptor, CD44, in AS-associated macrophages allows HA-based cerium dioxide NPs to be efficiently absorbed through CD44-mediated endocytosis. This design enables the NPs to actively target plaque-associated macrophages, remove excessive ROS, protect macrophages from ROS-induced damage, and effectively inhibit endocytosis of oxidized low-density lipoprotein (ox-LDL) by activated macrophages. Overall, although AS is not a specific CVD, AS has been shown to be one of the major causes of multiple CVDs, so anti-AS has an important role in the treatment of CVDs. This section details the outstanding performance of nanozymes in anti-AS, which provides more safe and feasible options for anti-AS treatment.

4.3 Targeted nanozymes for myocardial infarction

MI is a condition that occurs when the coronary arteries are blocked, causing a lack of oxygen to heart muscle. The lack of oxygen can lead to heart muscle cell death and activate the immune response, resulting in inflammation and the release of ROS, which can cause severe damage to the heart [49]. Chen et al. [53] used folate polymethylene ethylene glycol (FA-PEG) to synthesize an *in situ* zeolite imidazole acid frame nanozyme (ZIF-8 zyme) that has antioxidant and anti-inflammatory properties. Because the folic acid receptor (FR) is widely expressed on many immune cell membranes and mediates selective phagocytosis, ZIF-8 zyme specifically targets M1 macrophages, which facilitates M1 macrophage polarization to the M2 phenotype, reducing proinflammatory cytokine secretion. As a result, cardiomyocyte survival is significantly promoted under a highly inflammatory state. This finding shows the great potential of treating high inflammation-related acute myocardial infarction (AMI). Similarly, Liu et al. [12] have developed a novel type of nanozyme (Fe-Cur@TA) that combines Fe³⁺ with the anti-inflammatory drug, curcumin (Cur), and further modifies Cur with tannic acid (TA). These Fe-Cur@TA nanozymes exhibit excellent free radical scavenging and anti-inflammatory properties, which reduce immune cell infiltration, promote macrophage polarization towards the M2-like phenotype, inhibit inflammatory cytokine secretion, and block inflammatory free-radical circulation [12]. Moreover, the Fe-Cur@

Mini Review

TA nanozyme has a high affinity for cardiac tissues, which improves cardiac retention and uptake capacity. In mouse and preclinical beagle MI models, the Fe-Cur@TA nanozyme has been shown to preserve cardiac function and reduce scar size, suggesting the potential clinically translational value in CVDs.

5. CONCLUSIONS AND PROSPECTS

CVDs remain a major threat to human health due to the high incidence and mortality rates. Traditional treatment methods are often limited by low bioavailability and significant side effects. Recent advances in nanotechnology, particularly the development of nanozymes, offer a promising alternative for treating CVDs. Nanozymes, with enzyme-like activities and nanomaterial properties, show great potential in targeting key pathologic processes, such as inflammation, oxidative stress, and hypoxia, which are central to the progression of CVDs. In recent years, several studies reported that nanozymes have unique advantages and great prospects in the treatment of CVDs. This paper summarized the active targeting design strategies and therapeutic mechanisms of nanozymes in the treatment of CVDs.

In the previous section we detailed the important role of antioxidant nanozymes in CVDs. Nanozymes can mimic natural antioxidant enzymes, such as SOD and CAT. Several SOD-mimicking nanozymes have been developed based on cerium, manganese, and iron. These nanozymes can undergo reversible redox changes as natural enzymes. Interestingly, under hypoxic conditions, some SOD-mimicking nanozymes can completely replace or even outperform the activity of natural enzymes. These properties help regulate immune responses and promote tissue repair. It is worth noting that H_2O_2 is an important material basis for cells to exert redox reactions, and *in vivo* H_2O_2 is regulated by at least two enzymes (CAT and GPx) in which CAT removes H_2O_2 during oxidative stress and GPx regulates redox signaling in cells. Therefore, current research is trying to develop multifunctional nanozymes with CAT and GPx activities and many CAT nanozymes are being explored as potential therapeutic approaches for CVDs.

ROS and oxidative stress also have a critical role in CVDs. Eliminating ROS and reducing oxidative stress in cardiovascular tissues have been shown to be an effective therapeutic strategy for many CVDs. Nanozymes with active targeting capabilities can precisely localize at disease sites, then scavenge ROS at specific disease sites to exert cardioprotective effects. The mouse models of targeted nanozymes in IS, AS, and MI have demonstrated multifunctionality and effectiveness. For example, targeted nanozymes have been shown to reduce infarct size, promote angiogenesis, and improve cardiac function after MI. Similarly, targeted nanozymes have a crucial role in alleviating ischemic damage in stroke models and reducing plaque formation in AS.

ROS-scavenging nanozymes combined with other therapeutic agents may also enhance therapeutic efficacy and minimize side effects. This is a feasible and promising option for the treatment of CVDs.

Targeted nanozymes have made significant progress in the treatment of CVDs. Compared to traditional therapies, targeted nanozymes offer higher specificity, greater efficiency, and fewer side effects. Despite these promising findings, several challenges remain in the clinical translation of nanozyme-based therapies: 1) long-term stability of nanozymes *in vivo*; 2) biocompatibility and toxicity of nanozymes; 3) precise targeting of nanozymes to diseased tissues and distribution metabolism of nanozymes *in vivo* are needed to be improved and assessed; 4) differences in physicochemical properties due to batch effects; and 5) extensive clinical trials are needed to validate the safety and efficacy of nanozyme-based therapies.

To respond to these challenges and promote the clinical application of nanozymes, more efforts are needed in the construction of rational nanozymes designs strategies, scientific standards of nanozymes preparation, and appropriate modifications of nanozymes to maximize the selectivity of nanozymes to specific tissues and organs as well as the long-term stability of the nanozymes *in vivo*. In addition, the development of multifunctional nanozymes combined with natural enzymes or existing drugs for the treatment of CVDs can also be considered. Due to the complex pathogenesis of CVDs, it is important to understand the mechanism underlying the disease and target functions to develop better and more specific nanozymes. In conclusion, we firmly believe that with the efforts of researchers worldwide, the above problems will be solved and nanozymes will be widely used in future clinical applications.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Mini Review

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