Targeted Nanozymes-enabled Treatment of Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVDs) pose a significant threat to human health due to their 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 in recent years, Nanotechnology offers new perspectives and means for treating cardiovascular diseases. Especially, nanozyme-based targeted therapeutic drugs can specifically address the biological processes in areas affected by cardiovascular diseases, enabling precise treatment. Compared to traditional medicines, targeted nanozymes offer advantages such as high efficiency, specificity, controllability, and fewer side effects, leading to significant progress in treating cardiovascular diseases. This paper first introduces the design strategies for active targeting with nanozymes and the related mechanisms for treating cardiovascular diseases. It then outlines recent applications of targeted nanozymes in three typical cardiovascular diseases: ischemic stroke, atherosclerosis, and myocardial infarction. Finally, it discusses the challenges in applying targeted nanozymes and the prospects for future development.

1 Introduction

Cardiovascular diseases (CVDs) include coronary heart disease, stroke, atherosclerosis, and myocardial infarction, which are characterized by circulatory disorders[1]. Several modifiable factors, such as metabolic risk factors and lifestyle behaviors, can lead to CVDs. These include hypertension, diabetes, hyperlipidemia, obesity, smoking, physical inactivity, unhealthy diets, mental stress, and anxiety[2]. In 2019, approximately 17.9 million people lost their lives to CVDs, which accounts for 32% of global deaths, making it one of the primary causes of death worldwide as

reported by the World Health Organization. Estimates suggest that by 2030, more than 24 million people will die due to complications related to CVDs[3]. The pathophysiological mechanisms of CVDs include chronic inflammation, oxidative stress overload, and hypoxia[4], which supports that targeted anti-inflammatory therapy[5], oxidative stress reduction, and hypoxia improvement are important therapeutic targets to reduce the risk of CVDs. However, traditional treatment methods, such as antioxidants, anti-inflammatory drugs, and natural antioxidant enzymes, hinder their clinical application due to low bioavailability, poor stability, and potential side effects. This necessitates innovation and alternative approaches. In recent years, the rapid development of nanomedicine has significantly contributed to innovations in biomedical technology. Among these advances, nanozymes have garnered significant attention for their excellent anti-inflammatory, antioxidant[6], and reactive oxygen species (ROS)-scavenging capabilities[7], positioning them as promising candidate drugs for treating cardiovascular diseases. Nanozymes are nanomaterials with a size range of 1-100 nm, they exhibit activity similar to natural enzymes and possess the properties of nanomaterials. In 2007, Yan et al discovered that Fe_3O_4 has HRP-like properties[8], confirming that inorganic materials have enzymatic properties and promoting the rapid development of the field of nanozyme. Following the kinetics of enzymatic reactions, they can trigger the conversion of substrates into products under specific conditions. Nanozymes with a single enzyme activity can catalyze only one substrate reaction, while those with two or more multi-enzyme activities can catalyze different substrates, triggering cascade reactions[9]. Most nanozymes have similar redox properties to natural enzymes, e.g., catalase-like (CAT), superoxide dismutase-like (SOD), glutathione peroxidase-like (GPx), peroxidase-like (POD), glucose oxidase-like (GOx), and oxidative enzyme-like (OXD)[10]. Based on different types of nanomaterials, nanozymes can be categorized into metal nanoparticles, metal oxide nanoparticles, carbon-based nanomaterials, and metal-organic frameworks (MOFs), among others. Apart from applications in biosensing[11], imaging[12], and biochemical analysis (electrochemical detection), nanozymes also exhibit significant potential in disease diagnosis and treatment. This includes areas such as anti-inflammatory[13], anti-tumor[14–17], antibacterial[18–20], and virus detection [21,22], etc. In particular, nanozymes designed with active targeting capabilities offer a compelling approach to cardiovascular disease treatment. Their ability to precisely identify and accumulate at pathological sites, along with lower side effects, helps overcome the inherent limitations of traditional drugs, showcasing a promising future in this field.

This paper reviews the mechanisms of nanozymes in treating cardiovascular diseases, the design strategies for active targeting, and the in vivo applications and efficacy of nanozymes in ischemic stroke, atherosclerosis, and myocardial infarction. Additionally, we discuss the challenges that targeted nanozymes may face in the future when it comes to the treatment of cardiovascular diseases. (Figure 1)

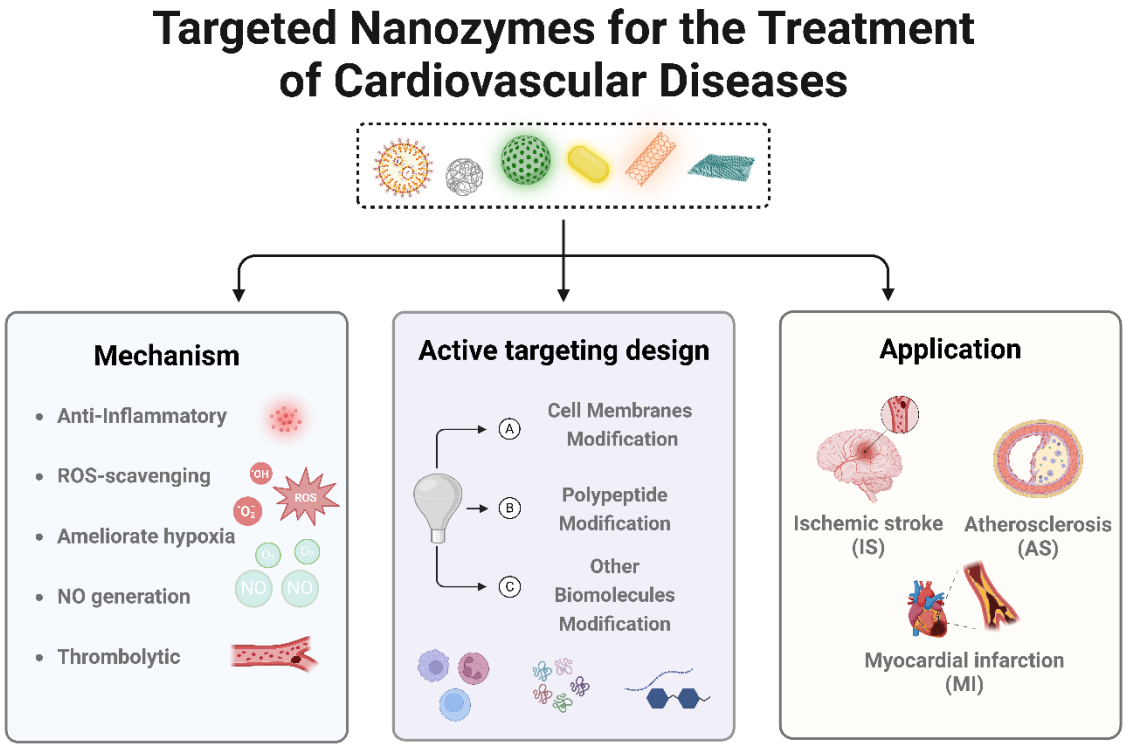

Figure 1. Summary of this review: the mechanisms by which nanozymes treat cardiovascular diseases, the design strategies for active targeting, and their applications in three typical cardiovascular diseases.

2 Mechanisms of Nanozymes for CVDs

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

Table 1. Mechanisms of nanozymes 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	[26]
	Cu-TCPP-Mn	MI	SOD, CAT	MI and myocardial I/R injury animal models	ROS scavenging and inflammation inhibition	[27]
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	[32]
	PBzyme	IS	SOD, CAT	I/R model, OGD/R induced cell damage model	Antioxidant and anti-inflammatory responses and antiapoptosis	[33]
	$CeVO_4$	Hypoxia-ischemia (HI) brain damage	SOD	Rice-Vannucci HI model in P7 mice	Suppressed oxidative stress and up-regulated Nrf2 expression	[34]
Ameliorate Hypoxia	YC-1@[RBC-PL] NVs	IS	Catalyzing the decomposition of H_2O_2	SD middle cerebral artery occlusion (MCAO) model	Generating oxygen and inhibiting HIF-1α activation	[37]
NO Generation	CeO_2 NPs	AS	NOS	ApoE knockout mice	Escalating endogenous nitric oxide levels	[41]
	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	[42]
Thrombolytic	HMPB-rtPA@PM	Thrombotic diseases	•O_2−, •OH, H_2O_2 scavenging ability	Carotid artery thrombosis model, black tail model	Inhibit platelet aggregation and regulate the inflammatory microenvironment by scavenging ROS	[44]
	PLTV-IO-MB PENPs	Vascular blockages	-	$FeCl_3$ method induced thrombus animal model	Site-specific mechanical-photothrombolysis	[45]

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. Although inflammation is usually beneficial, it can be seriously harmful when dysregulated. Inflammation is the foundation for the development and progression of CVDs, and regulating inflammation can reduce the risk of cardiovascular disease [23,24]. In recent years, Some nanozymes have demonstrated intrinsic anti-inflammatory properties that modulate the expression of both pro-inflammatory and anti-inflammatory molecules. These nanozymes target inflammatory sensors or macrophages to diagnose, treat, monitor, and balance inflammatory immune homeostasis[25]. For example, Zhang and coworkers[26] 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. This shift effectively mitigates inflammatory responses, promotes angiogenesis in the infarcted region, reduces ROS, and disrupts the ROS-driven inflammatory cascade. Xiang *et al*.[27] have developed an integrated bimetallic nanozyme Cu-TCPP-Mn derived from a MOF. This nanozyme, exhibiting SOD and CAT mimic activities, this capability facilitates synergistic scavenging of ROS and safeguarding of cardiac tissues against damage induced by oxidative stress and inflammation. It also showed long-term cardiac protection ability by remodeling ventricular structure, reducing scarring, promoting angiomyogenesis, and finally improving cardiac function.

2.2 ROS-Scavenging

ROS, including superoxide anion (·O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical (·OH), and so on[28]. ROS act as signaling molecules in cells, activating cellular signaling cascades, inducing apoptosis, and affecting gene expression[29]. Normally, there is a balance between the production and elimination of ROS in the body. However, when ROS production increases or the body's ability

to clear them decreases, excessive ROS accumulate, leading to oxidative stress. This oxidative stress can trigger inflammatory responses, DNA damage, cellular senescence, and programmed cell death, which are significant in the development of cardiovascular diseases[30]. In normal cells, several natural antioxidant enzymes, such as SOD, CAT, GPx, and GSH, work together to remove excess ROS and maintain redox homeostasis [31]. 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 cardiovascular diseases. In recent research, the single platinum (Pt) atom nanozyme (PtsaN-C) demonstrates 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[32]. Prussian blue enzyme (PBzyme) with CAT-like and SOD-like nanozyme activities was designed by Liu and coworkers[33]to study ischemic stroke. This unique substance can efficiently eliminate 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 neurological function following ischemic stroke. Jiang *et al*.[34]reported cerium vanadate ($CeVO_4$) nanozyme with SOD-like enzyme activity, which 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.

2.3 Ameliorate Hypoxia

The narrowing of coronary arteries or plaque rupture can lead to blood flow obstruction, resulting in inadequate perfusion and local hypoxia in the ischemic area. This triggers irregular ATP (adenosine triphosphate) synthesis, increased generation of ROS, and heart dysfunction, serving as a crucial driving force in the development of cardiovascular diseases[35]. 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 cardiovascular diseases[36]. In recent years, nanozymes have been found to function to improve the hypoxic microenvironment and achieve pro-angiogenesis by regulating the expression of HIF (hypoxia-inducible factor), VEGF (vascular endothelial growth factor), and EGFR (endothelial growth factor) signaling. For instance, Liu *et al*.[37]developed hybrid membrane nanovesicles (YC-1@[RBC-PL] NVs) by wrapping red blood cell (RBC) and platelet (PL) membranes with the hypoxia-inducible factor-1α (HIF-1α) inhibitor YC-1. YC-1 @ [RBC-PL] NVs promote functional recovery of the neurovascular unit (NVU). This is achieved through several mechanisms: PL-mediated angiogenesis, red blood cell-derived peroxidase catalysis of hydrogen peroxide for oxygen supply, YC-1-mediated inhibition of HIF-1α activity, and neuroprotection.

2.4 NO Generation

Nitric oxide (NO), widely distributed in various tissues throughout the body, primarily induces vasodilation through the cyclic guanosine monophosphate (cGMP) pathway. It can also diffuse into the bloodstream, inhibiting platelet aggregation and adhesion[38]. 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 nitric oxide may lead to vasoconstriction, hypertension, atherosclerosis, and other cardiovascular system disorders[39]. Therefore, supplementation of endogenous NO can improve vasodilation and reduce inflammation,

ultimately lowering the risk of CVDs[40]. Sun *et al*. [41] were the first to reveal that CeO_2 nanoparticles (NPs) possess nitric oxide synthase (NOS)-like activity. These nanoparticles successfully increased nitric oxide (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 CeO_2 NPs promoted lipid redistribution, stabilized endothelial NOS (eNOS) expression, and inhibited inducible NOS (iNOS). Consequently, this led 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, effectively improving in vivo cardiac function by inhibiting cardiomyocyte apoptosis and fibrosis[42].

2.5 Thrombolytic

Thrombosis is a significant pathological process in cardiovascular diseases[43]. Therefore, thrombolysis and antiplatelet aggregation are now essential therapeutic strategies to improve cardiovascular diseases. A platelet membrane (PM)-functionalized hollow mesoporous Prussian blue nanomedicine (HMPB-rtPA@PM), developed by Zhang[44] and his colleagues, is loaded with two FDA-approved drugs, Prussian blue (PB) and alteplase (rtPA). The HMPB-rtPA@PM has excellent antioxidant enzyme activity, can scavenge ROS, inhibit 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*.[45] utilized cold atmospheric plasma (CAP), human platelet vesicles (PLTV), and methylene blue (MB) to generate self-assembled plasma nanopropellers (PLTV-IO-MB PENPs). The synthesized PLTV-IO-MB PENPs can target thrombotic clots. 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 they possess NIR irradiation-induced PDT and PTT properties for remote photothrombolysis. The multimodal magnet therapy and phototherapy strategy effectively achieve site-specific mechanical photo thrombolysis and prevent 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[46]. 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).

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	[48]
	Macrophage loading	TN-PdH@Ms	ABTS+• and H_2O_2, • O2−, •OH scavenging ability, CAT, SOD	AS	ApoE−/− Mice	Antioxidation, anti-inflammatory, and autophagy activation	[49]
Polypeptide Modification	P-selectin binding peptides (PP) and mannose (Man) molecules	PBNZ@PP-Man	CAT, SOD	AS	ApoE−/− Mice	ROS scavenging properties andtheenhancement of macrophage efferocytosis	[50]
	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	[51]
Other Biomolecules Modification	Tannic acid (TA)	TA-Ce NCs	•OH elimination capacity and total antioxidant activity, SOD, CAT	Ischemic heartdisease (IHD)	The murine I/R model, H_2O_2 and OGD/R induced cell damage model	Cardiac accumulation and intracellular ROS scavenging	[52]
	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	[53]

3.1 Cell Membranes 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, can drive them to migrate from the blood or other tissues to the inflammatory lesions of cardiovascular diseases. In the early stages of atherosclerosis, for example, endothelial cells attract monocytes to the arterial wall through chemokine receptor interactions and the expression of cell adhesion molecules [47]. Therefore, modifying the membrane of inflammatory cells, on nanozymes can precisely deliver them to the inflammatory lesions of cardiovascular diseases, achieving accurate targeting of the inflammatory microenvironment in cardiovascular lesion areas. Feng and his coworkers[48] 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 (NCM) on mesoporous Prussian blue nanozymes (MPBzyme@NCM), providing a mechanism for selective binding to inflamed cerebral microvascular endothelial cells (Fig 2a). This targeted approach facilitates the active delivery of MPBzyme@NCM to areas of the brain affected by ischemia. Hu *et al*.[49] 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 can effectively reduce ROS levels and inhibit inflammation-related pathological processes in plaque areas.

3.2 Polypeptide Modification

Peptides coupled to nanozyme can be targeted as ligands to the corresponding receptors at the lesion site, positioning the nanozyme to the lesion tissue and thus functioning. Using atherosclerosis as an example, one can design peptides targeting inflammatory endothelial cell markers such as E-selectin, VCAM-1, PECAM-1, inflammatory cells CD36, CCR2, CCR5, APoA-I, APOE, and thrombus biomarkers GPIIb/IIIa, P-selectin, AVβ3, FXIIIa, to achieve active targeting of nanozymes. A multifunctional nanozyme named PBNZ@PP-Man, designed by He and coworkers[50], incorporates

Prussian blue, p-selectin-binding peptide (PP), and mannose (Man) molecules. (Fig 2b) PP specifically targets P-selectin on activated endothelial cells covering plaques, while Man interacts with mannose receptors on macrophages. 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*. [51]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) nano platform. Transferrin receptor 1 (TfR) is highly expressed in the blood-brain barrier. Therefore, the Tf peptide in the EMT nano-platform rapidly penetrates the blood-brain barrier via endocytosis to reach the lesion area, effectively targeting the site of brain ischemia. Its inherent hydroxyl radical scavenging ability and capabilities similar to superoxide dismutase and catalase promptly clear free radicals at the lesion site, alleviating oxidative stress-induced inflammatory damage to the blood-brain barrier.

3.3 Other Biomolecules Modification

Nanozymes can also be modified with other biomolecules such as sugars, hyaluronic acid, folic acid, etc., without affecting their biological activity. These biomolecules can impart targeting specificity to nanoparticles, enhancing their biocompatibility while reducing toxicity. For instance, Wang *et al*. [52] designed a tannic acid-assembled tetravalent cerium nanozyme (TA-Ce) with cardiac cell targeting and antioxidant capabilities and applied it to the treatment of ischemia/reperfusion injury (Fig 2c). This article[53] introduces a mannan-based nano-drug, Que@MOF/Man, designed to target inflamed infarcted hearts and deliver the antioxidant and anti-inflammatory agent quercetin (Que). Mannan (Man) is a yeast polysaccharide containing d-mannose residues that mannose receptors on macrophages can recognize. This recognition promotes inflammation-specific accumulation and targeted intracellular uptake of Que@MOF/Man in macrophages.

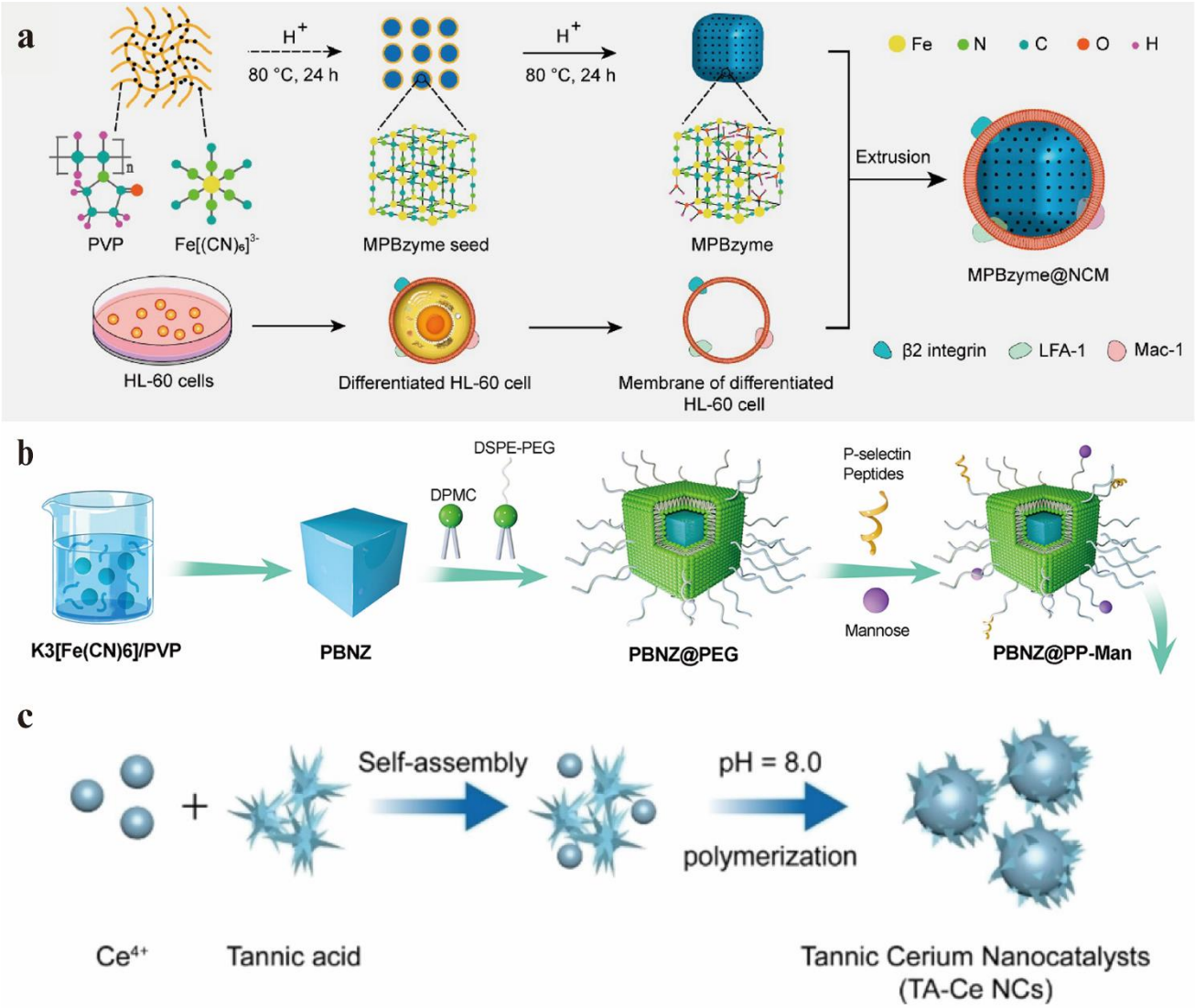

Fig. 2. Active targeting design of nanozymes for CVDs. a. Mesoporous Prussian Blue nanozyme (MPBzyme) coated with the neutrophil-like cell membrane (NCM). Reprinted with permission [48]. Copyright 2021, American Chemical Society. b. Nanozyme (PBNZ@PP-Man) modified with PP and Man molecules. Reprinted with permission [50]. Copyright 2023, American Chemical Society. c. Tannic acid-assembled tetravalent cerium nanozyme (TA-Ce) (Reprinted with permission [52]. Copyright 2023, Wiley-VCH.

4 Targeted Nanozymes in the Treatment of CVDs

Following the discussion on the therapeutic mechanisms and targeting design strategies of nanozymes, this section presents examples of nanozymes employed in the targeted treatment of three typical CVDs in recent years (Table 3).

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	[56]
	D@HPB@SPM NPs	CAT, POD	Sialic acid (SA) and platelet membrane modified	Rat models of tMCAO	Scavenging ROS,degrading neutrophil extracellular traps (NETs)	[57]
	TPP@(CeO2+ROF)	•O_2−, •OH and ABTS+• radical scavenging ability	Triphenyl-phosphine-based modifications	MCAO model in SD rat	Attenuates oxidative damage and apoptosis	[58]
Atherosclerosis (AS)	PCZ@PB NCs	CAT, SOD	Platelet membrane modified	Apo E−/− mice model of AS	ROS-scavenging, anti-inflammatory	[60]
	37pA – PtLNP, 37pALNP/6877002	•O_2−, •OH and H_2O_2 scavenging ability	Macrophage modified	AS in Apo E−/− mice	Reducing the expression of proinflammatory cytokines and chemokines	[61]
	HA-CeO_2 NPs	SOD	Hyaluronic acid modified	AS in Apo E−/− mice	Scavenge ROS to reduce the formation of ox-LDL	[62]
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	[64]
	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	[65]

4.1 Targeted Nanozymes for Ischemic Stroke

Ischemic stroke (IS) is a condition that occurs when brain tissue damage happens due to insufficient blood supply to the brain. It 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[54]. Many studies have shown that nanozymes, as a new type of antioxidant, can reduce intracellular ROS levels following brain injury, mitigating oxidative stress-induced damage to the central nervous system[55]. Consequently, nanozyme-based targeted therapeutic agents are widely used in research on ischemic stroke. For instance, the group of Wang[56] designed a novel peptide-templated manganese dioxide nanozyme (PNzyme/MnO_2). This multifunctional nanozyme possesses capabilities such as fibrinogen binding, thrombolysis, clotting enzyme cleavage, and blood-brain barrier penetration. It achieves precise localization in thrombotic ischemic regions through multistage targeting and cascade processes. Simultaneously, it combines the thrombolytic activity of functional peptides with the ROS-scavenging ability of nanozymes, effectively clearing ROS in apoptotic cells and exerting a neuroprotective effect. It promotes the polarization of microglial cells from M1 (pro-inflammatory) to M2 (anti-inflammatory), inhibits the secretion of pro-inflammatory cytokines, reduces the recruitment of T cells and neutrophils, and suppresses inflammation and immune reactions induced by ischemia-reperfusion. PNzyme/MnO_2 provides the most effective protection against ischemic stroke through its combined targeting, thrombolytic, ROS-clearance, and anti-inflammatory capabilities.

D@HPB@SPM NPs[57] are composed of a sialic acid (SA)-modified platelet membrane shell and a hollow Prussian blue nanoparticle core loaded with Deoxyribonuclease I (DNase I). 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 blood-brain barrier 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 their 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 their accumulation in ischemic brain regions and their therapeutic efficacy.

A cerium oxide nanozyme-based nanoplatform, TPP@(CeO_2+ROF)[58], was designed and synthesized by Liao and coworkers. In this system, DSPE encapsulates CeNZs to enhance their bioavailability, while triphenylphosphine-based modification allows the nanosystem to target mitochondria precisely. The fourth-generation PDE4 inhibitor, roflumilast, is loaded for neuroprotection. TPP@(CeO_2+ROF) can effectively mediate mitochondrial damage, alleviate oxidative stress and apoptosis, and reduce brain infarct volume and blood-brain barrier 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, they obstruct arteries, restricting blood flow, and ultimately resulting in complications such as heart disease and ischemic stroke. Increased ROS generation, lipid peroxidation, and inflammation are prevalent throughout the entire disease process[59]. Fu et al.[60] used zoledronic acid molecules (ZOL) 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 nanoplatforms encapsulated with platelet membranes (PCZ@PB NCs). PCZ@PB NCs clear excessive cellular ROS, downregulate the expression of pro-inflammatory factors and cooperatively inhibit the formation of foam cells with drugs. These findings suggest the potential of biomimetic PCZ@PB NCs for treating atherosclerosis. In another study, Yang et al. [61]designed and fabricated macrophage-targeting Pt lipid nanoparticles, modified with 37pA, denoted as 37pA-PtLNP for the targeted delivery of a TRAF6 inhibitor and Pt-NPs. 37pA-PtLNP serves as a ROS scavenger, accumulating in bone marrow-derived macrophages, alleviating intracellular oxidative stress, and modulating the plaque microenvironment. Furthermore, the introduction of the TRAF6 inhibitor 6877002 loaded into macrophage-targeting lipid nanoparticles (37pA-LNP/6877002) can inhibit the activation of the classical inflammatory NF-kB pathway induced by CD40. Co-administration of 37pA-PtLNP and 37pA-LNP/6877002 significantly regresses plaques by reducing oxidative stress and inhibiting the release of pro-inflammatory cytokines, thereby modulating the inflammatory immune response. Hyaluronic acid (HA)-guided cerium dioxide nanoparticles (HA-CeO_2 NPs) were designed by Wang et al.[62] as innovative reactive oxygen scavengers to target atherosclerotic plaques. The high expression of the HA receptor CD44 in atherosclerosis-associated macrophages allows HA-based cerium dioxide nanoparticles to be efficiently absorbed through CD44-mediated endocytosis. This design enables the nanoparticles to actively target plaque-associated macrophages, remove excess ROS, protect macrophages from ROS-induced damage, and effectively inhibit the endocytosis of oxidized low-density lipoprotein (ox-LDL) by activated macrophages.

4.3 Targeted Nanozymes for Myocardial Infarction

Myocardial infarction (MI) is a condition that occurs when the coronary artery is blocked, causing a lack of oxygen to the heart muscle. This lack of oxygen can lead to the death of heart muscle cells and activate the immune response, causing inflammation and the release of ROS, which can cause severe damage to the heart[63]. The group of Chen[64] used folate polymethylene ethylene glycol (FA-PEG) to synthesize the in situ zeolite imidazole acid frame nanozyme (ZIF-8 zyme) that has antioxidant and anti-inflammatory properties. Since the folic acid receptor (folate receptor, FR) is widely expressed on many immune cell membranes and mediates selective phagocytosis, ZIF-8 zyme can specifically target M1 macrophages. This helps in the polarization of M1 macrophages to M2 phenotype, reducing proinflammatory cytokine secretion. As a result, it significantly promotes the

survival of cardiomyocytes under a highly inflammatory state. This shows the great potential of treating high inflammation-related acute myocardial infarction (AMI). Similarly, Liu et al. [65] have developed a novel type of nanozymes called Fe-Cur@TA, which combines Fe^{3+} with the anti-inflammatory drug curcumin (Cur) and further modifies it with tannic acid (TA). These Fe-Cur@TA nanozymes exhibit excellent free radical scavenging and anti-inflammatory properties, which can reduce immune cell infiltration, promote macrophage polarization towards M2-like phenotype, inhibit inflammatory cytokine secretion, and block inflammatory free-radical circulation. Moreover, the Fe-Cur@TA nanozyme has a high affinity for cardiac tissues, which improves their cardiac retention and uptake capacity. In mouse and preclinical Beagle MI models, Fe-Cur@TA nanozyme has been shown to preserve cardiac function and reduce scar size, suggesting their potential clinically translational value in cardiovascular diseases.

5 Limitations

The development of nanozymes for the treatment of cardiovascular diseases (CVDs) shows great promise, but several limitations need to be addressed before these therapies can be widely adopted in clinical practice. First and foremost, the potential toxicity of the nanomaterials used in nanozymes needs to be thoroughly investigated to ensure they do not cause adverse immune responses or other harmful effects. Additionally, while nanozymes can be designed with targeting capabilities, achieving precise and efficient targeting of diseased tissues remains challenging. Non-specific accumulation of nanozymes in healthy tissues can reduce their therapeutic efficacy and increase the risk of side effects. Therefore, enhancing the specificity of nanozyme targeting is crucial for maximizing therapeutic benefits and minimizing harm. Furthermore, a comprehensive understanding of the in vivo behavior of nanozymes, including their distribution, metabolism, and clearance, is necessary. Pharmacokinetic studies are fundamental for determining the optimal dosage and administration routes for nanozyme therapies.

6 Conclusions and Prospects

Cardiovascular diseases remain a major threat to human health due to their 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 cardiovascular diseases. Nanozymes, with their enzyme-like activities and nanomaterial properties, show great potential in targeting key pathological processes such as inflammation, oxidative stress, and hypoxia, which are central to the progression of cardiovascular diseases.

This paper summarizes the active targeting design strategies and therapeutic mechanisms of nanozymes in treating cardiovascular diseases. Nanozymes can mimic natural antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), effectively eliminating reactive oxygen species (ROS) and reducing oxidative stress in cardiovascular tissues. Their anti-inflammatory properties help regulate immune responses and promote tissue repair. Additionally, nanozymes with active targeting capabilities can precisely localize at disease sites, enhancing therapeutic efficacy while minimizing side effects. The application of targeted nanozymes in ischemic stroke, atherosclerosis, and myocardial infarction has demonstrated their multifunctionality and effectiveness. For example, targeted nanozymes have been shown to reduce infarct size, promote angiogenesis, and improve cardiac function after myocardial infarction. Similarly, they play a crucial role in alleviating ischemic damage in stroke models and reducing plaque formation in atherosclerosis. Despite these promising findings, there are still challenges in the clinical translation

of nanozyme-based targeted therapies, including the long-term stability, biocompatibility, and potential toxicity of nanozymes. Future research should focus on optimizing nanozyme formulations, improving targeting efficiency, and conducting extensive in vivo studies to better understand their interactions with biological systems.

In conclusion, targeted nanozymes have made significant progress in the treatment of cardiovascular diseases. Compared to traditional therapies, they offer higher specificity, greater efficiency, and fewer side effects. Continued research and development in this field hold great potential for transforming cardiovascular disease treatment and improving patient outcomes.

7 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 a potential conflict of interest.

8 Author Contributions

Writing original draft, literature review and analysis, and editing, L.L. and J.L.; table making, graphic designing, reviewing, and editing, X.W., X.H., C.Z. and Q.P.; formal analysis, funding acquisition, and editing, W.Y. and Z.Q. All authors read and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

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