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Reactive Oxygen Species Scavenging Nanomedicine for the Treatment of Ischemic Heart Disease

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Ischemic heart disease (IHD) is the leading cause of disability and mortality worldwide. Reactive oxygen species (ROS) have been shown to play key roles in the progression of diabetes, hypertension, and hypercholesterolemia, which are independent risk factors that lead to atherosclerosis and the development of IHD. Engineered biomaterial-based nanomedicines are under extensive investigation and exploration, serving as smart and multifunctional nanocarriers for synergistic therapeutic effect. Capitalizing on cell/molecule-targeting drug delivery, nanomedicines present enhanced specificity and safety with favorable pharmacokinetics and pharmacodynamics. Herein, the roles of ROS in both IHD and its risk factors are discussed, highlighting cardiovascular medications that have antioxidant properties, and summarizing the advantages, properties, and recent achievements of nanomedicines that have ROS scavenging capacity for the treatment of diabetes, hypertension, hypercholesterolemia, atherosclerosis, ischemia/reperfusion, and myocardial infarction. Finally, the current challenges of nanomedicines for ROS-scavenging treatment of IHD and possible future directions are discussed from a clinical perspective.

1. Introduction

Ischemic heart disease (IHD) is a leading cause of death and disability worldwide. In 2017, IHD affected around 126 million people globally (1655 per 100 000), which was estimated to be 1.72% of the world's population.[1] Reactive oxygen species (ROS) have been shown to play key roles in the progression of various pathological conditions, such as diabetes, hypertension, and hypercholesterolemia, that lead to IHD. However, physiological concentrations of ROS generated during cellular metabolism are essential for cell development, survival, and signaling, and play a significant role as second messengers within cells. Although ROS regulates normal cellular functions, including gene transcription, signal transduction, and homeostasis,[2] excessive ROS overwhelms the cellular antioxidant capacity,

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resulting in cardiovascular disorders, including endothelial dysfunction, atherosclerosis, ischemia/reperfusion (I/R) injury, etc.

Nanomedicine, making use of the combination between engineered biomaterials and advanced nanotechnologies, serving as a complement of conventional drugs, is developing fast over the recent years. Nanomedicine can be designed to present unique properties and functions based on the pathogenesis and pathophysiological requirements of different diseases. The adjustable size, variable charge, high surface-to-volume ratio, and other physicochemical characteristics make it possible to encapsulate various newly developed or commercial drugs, leading to the optimization of drug pharmacokinetic and pharmacodynamic profiles.[3] Meanwhile, nanomedicine can be modified or decorated with multifunctional linkers, ligands, or coatings, which endow them with the advantages of prolonged blood circulation, targeted delivery, and controlled release, thereby inducing the precise treatment and enhanced therapeutic effect.[4] A wide range of nanomaterials from inorganic to organic, from protein to polymer, have been reported to be used for nanocarrier fabrication based on their physiological properties.[5] Nanocarriers such as liposome, noisome, dendrimer, micelle, mesoporous silica, carbon nanotube, metal–organic frameworks, and metal–phenolic networks have been shown to exhibit different specialties, providing a wealth of options for the design and synthesis of nanomedicines.[6]

This review aims at giving a detailed description of the roles and pathogenic mechanisms of ROS in IHD and its risk factors, thereby providing potential therapeutic targets, instructing the design and development of nanomedicine. In this review, the basic knowledge, generation mechanisms, and physiological functions of ROS are first introduced. Then, the roles of ROS in IHD, the medications exhibiting antioxidant properties, and the recent progress in nanomedicines serving as ROS scavengers for the treatment of IHD are discussed in detail. Finally, the review will put forward the current challenges of nanomedicines and possible future directions from a clinical perspective (**Figure 1**).

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2. Biology of ROS

ROS are a number of highly reactive molecules and free radicals derived from molecular oxygen metabolism.[7] These include free radicals, such as superoxide anion (O_2^-), hydroxyl radical (OH·), alkoxyl radical (RO·), peroxyl radical (ROO·), and non-radicals, such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), ozone (O_3), and hypochlorous acid (HOCl).[7] The free radical superoxide (O_2^-), a proximal ROS, leads to the formation of $ONOO^-$, OH·, and H_2O_2.

The major ROS-producing systems are reduced nicotinamide dinucleotide phosphate (NADPH) oxidase (NOX)[8] and the electron transport chain in the mitochondria.[9] Others include xanthine oxidase (XO),[10] uncoupled nitric oxide synthase (NOS),[11] peroxisomes,[12] lipoxygenases,[13] cyclooxygenases,[14] myeloperoxidase,[15] and monoamine oxidases.[16]

The NOX family comprises of NOX1-5, DUOX1, and DUOX2 isoforms.[17] NOX1, 2, 3, and 5 mainly produce O_2^-, while NOX4, DUOX1, and DUOX2 generate mainly H_2O_2. All NOX isoforms share both conserved structural properties and functions.[17] All NOX isoforms have 6–7 transmembrane domains, a flavin adenine dinucleotide (FAD), and NADPH-binding cytosolic domains.[17,18] NOX generates O_2^- by a complex reaction once NADPH binds to the cytosolic COOH terminus. Initially, the electrons from NADPH are used to reduce FAD to FADH. FADH is then used to reduce O_2 on the other side of the membrane.[19] NOX4 generates H_2O_2 as a function of oxygen concentration through rapid response to pO_2 changes. The binding of one oxygen molecule will be reduced by the heme and generate H_2O_2 in the end.[20] DUOX1 and DUOX2 are also called thyroid oxidase 1 and thyroid oxidase 2, respectively, and originally identified in the thyroid gland to provide H_2O_2 for the thyroid peroxidase-mediated oxidation of iodide (I^-) during thyroid hormone biosynthesis.[21] They are located at the apical pole of epithelial cells where they produce H_2O_2 and entertain oxidation processes through peroxidases like the oxidation of iodide in the thyroid gland[21] or host defense in the lung epithelium.[22]

Native NOX proteins are activated by activators such as cytokines,[23] growth factors,[24] physical forces,[25] hypoxia,[26] and G-protein-coupled receptor agonists,[27] and pathophysiological conditions, such as hypertension,[28] hypercholesterolemia,[29] and diabetes mellitus,[30] can activate NOX, resulting in an enhanced production of ROS.

3. Physiological Roles of ROS in Vascular Homeostasis

ROS are generated by oxidant enzymes located in different subcellular organelles. Physiological concentrations of ROS are important signaling molecules that maintain vascular homeostasis. Almost all the cells in the vascular wall, including endothelial cells (ECs), smooth muscle cells (SMCs), adventitial cells, and intimal myeloid cells, possess the ability to generate ROS. Generally, both ROS production and elimination are dependent on enzymic and nonenzymic pathways.

Enzymic sources of ROS are closely related to redox signaling in the vascular system. NOX, XO, and uncoupled NOS

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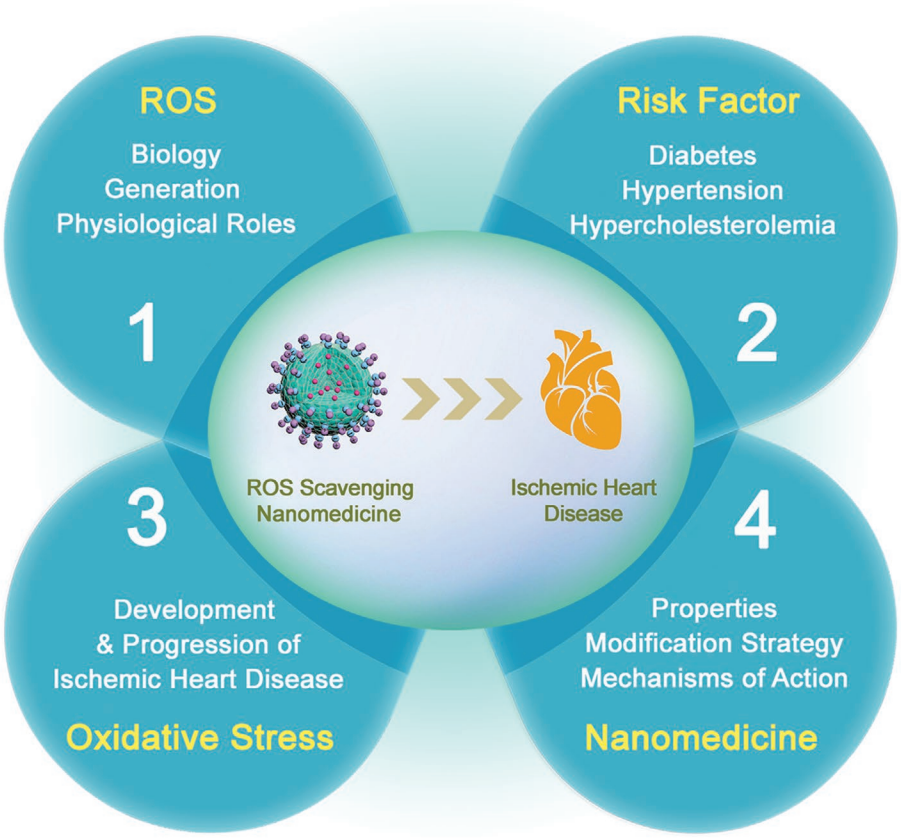

Figure 1. This review focuses on introducing the following several parts: 1) introduction of ROS and their roles in different cells and diseases; 2) risk factors involved in IHD and the relationship between ROS and these risk factors; 3) the role of the risk factors in the development and progression of IHD; 4) introduction of nanomedicine properties, modification strategies, and mechanisms of reaction for the treatment of IHD.

are the most important sources of vascular ROS. NOX is the major source of ROS production in the vascular system under various conditions. ECs, SMCs, and intimal myeloid cells express NOX1, NOX2, NOX4, and NOX5, while adventitial cells mainly express NOX2 and NOX4.[31] Thus, the main ROS generated by NOX in vascular cells is H_2O_2 and O_2^-. XO uses oxygen and purine through hypoxanthine and xanthine oxidation to produce O_2^- and H_2O_2.[32] Uncoupled NOS refers to the function of endothelial NOS (eNOS) which is changed to produce O_2^- instead of NO under pathological conditions.[33] Deficiency of eNOS cofactor tetrahydrobiopterin (BH4), depletion of eNOS substrate L-arginine, accumulation of methylarginines, and S-glutathionylation of eNOS, are the major causes for eNOS uncoupling.[34]

Mitochondrial respiratory electron transport chain (ETC) is another important source of ROS. Usually, the superoxide anion generated in the mitochondrial matrix can be converted by the manganese-dependent superoxide dismutase (MnSOD, also known as SOD2) into H_2O_2, and then further detoxified by glutathione peroxidase (GPX) and thioredoxin enzymes into H_2O. O_2^- diffuses into the cytoplasm and is transformed by copper-zinc-dependent SOD (CuZnSOD, also known as SOD1) into H_2O_2.[35]

3.1. Generation and Roles of ROS in ECs

The major sources of ROS in ECs are the NOX. Although ECs express NOX1, NOX2, NOX4, and NOX5 isoforms, NOX2 and NOX4 are the main isoforms.[36] NOX2 and NOX4, which interact with p22phox, contribute equally to endothelial ROS production under basal condition.[36] ROS may be directly involved in EC migration, proliferation, and tubular formation, as H_2O_2 has been shown to induce EC proliferation and migration.[37] ROS increases vascular endothelial growth factor expression in vitro and in vivo[38] and its signaling and induces angiogenesis.[39] NOX2 in ECs plays an important role in vascular redox signaling.[40]

Increased endothelial ROS is a consequence of vascular disease pathogenesis and is sufficient to independently drive disease pathogenesis. Exposure to excessive O_2^- and H_2O_2 induces apoptosis of ECs, which leads to EC loss.[41] Increased intracellular ROS causes another type of programmed EC death, anoikis, as a result of detachment of ECs from extracellular matrix. This process is probably associated with increased mitochondria-derived ROS, which can be inhibited by *N*-acetylcysteine (NAC) and diphenylene iodonium, an inhibitor of NOX.[42] EC apoptosis, stimulated by oxidized LDL, angiotensin II (Ang II), high glucose, and TNF-α, is

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inhibited by superoxide dismutase (SOD), catalase, NAC, and antioxidant vitamins.[41]

Specific endothelial overexpression of NOX2 is sufficient to increase vascular ROS, activate downstream signaling pathways, and potentiate hemodynamic response to Ang II.[40] Furthermore, Ang II-induced ROS in ECs causes aortic dissection in a transgenic mouse model with ECs specifically overexpressing NOX2.[43] ROS induces expression of vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1), which promote adhesion of inflammatory cells.[44] Increased expression of adhesion molecules on ECs leads to monocyte adhesion and ultimately atherosclerotic lesion formation. Antioxidants, such as pyrrolidine dithiocarbamate (PDTC) and NAC,[45] can suppress VCAM-1 and ICAM-1 expression and reduce adhesion of inflammatory cells.

3.2. Generation and Roles of ROS in SMCs

SMCs express NOX1, NOX2, NOX4, and NOX5. NOX1 and NOX4 are mainly expressed in the SMCs of large arteries, NOX2 is mainly expressed in the SMCs of resistant and coronary arteries, while NOX5 is mainly expressed in the SMCs of human aorta.[46] NOX isoforms have different roles in SMCs.[19,47] NOX1 localizes to the plasma membrane, caveolae, and endosomes and has a role in SMC function.[48] NOX4 localizes to focal adhesions, the endoplasmic reticulum, and mitochondria and maintains SMCs in a quiescent contractile state.[49]

ROS promotes SMC differentiation from stem cells and modulates phenotypic switch between differentiated and quiescent phenotype and proliferative phenotype.[46c] H_2O_2 produced by NOX4 activates SMC-specific transcription factors, including serum response factor and myocardin, to induce mouse ESCs into SMCs.[50] Enforced NOX4 expression maintains differentiation and functional features of mESCs-derived SMCs.[50] In addition, enforced Pla2g7 expression increases ROS generation and enhances SMC differentiation, which can be inhibited by free radical scavenger and flavoprotein inhibitor of NOX.[51]

ROS regulates vascular tone through modulating SMC contraction. The effects of ROS on SMC contractions are dependent on the chemical nature of ROS and/or activation of various protein kinases.[52] O_2^- directly scavenges NO produced by ECs to exert vasoconstrictor effect through activation of specific kinases including Src kinases, Rho kinases, and ERKs.[52] H_2O_2 increases calponin and myocardin expression through inducing miR-145 expression in SMCs.[53]

3.3. Generation and Roles of ROS in Myeloid Cells

ROS has a significant role in macrophage differentiation and function. NOX are primary sources of ROS in macrophages. NOX1- and NOX2-generated ROS are critical for the differentiation of mouse monocytes to M2-type macrophages.[54] NOX1 and NOX2 are critical for the activation of the MAPKs, JNK, and ERK during M2 macrophage polarization.[54] Furthermore, inhibition of O_2^- specifically blocks the differentiation of M2 macrophages.[55] NOX4 has been shown to promote polarization of M2 macrophages as deficiency of NOX4 reduces M2 macrophage through reduction in STAT6 activation and increase in NFκB activity.[56]

Human monocytes and macrophages express functionally active NOX5.[57] A NOX5-p22phox complex drives monocyte-dendritic cell (Mo-DC) differentiation.[58] NOX5 expression is strongly increased during Mo-DC differentiation. NOX5 is localized at the outer membrane of the mitochondria and interacts with p22phox in Mo-DC. NOX5 controls Mo-DC differentiation by regulating the JAK/STAT/MAPK and NFκB pathways.[58]

ROS generated in macrophages has antimicrobial function.[59] ROS produced by macrophages inactivates phagocytosed bacteria by the oxidative burst generated by NOX2, which is a major source of extracellular ROS produced by macrophages in response to bacterial or viral infection.[59,60] In addition to NOX2, ROS from mitochondria is another major source for phagosomal ROS during bacterial or viral infection.[61] A few studies showed that NOX in macrophage has a direct impact on the progression of atherosclerosis. NOX5 has been implied in the progression of atherosclerosis as macrophages exposed to IFNγ or oxidized LDL increase in NOX5 protein expression and elevation in intracellular Ca^{2+} concentration and NOX is present in $CD68^+$ Mac-rich area within human carotid artery atherosclerotic plaques.[57]

4. Risk Factors in the Development and Progression of IHD

The prevalence of hypertension, hypercholesterolemia, and diabetes are 32%, 39%, and 9.3% of adults, respectively, worldwide.[62] They are independent and most common risk factors that can increase the oxidative stress and have been considered and evidenced as deleterious factors for the development of IHD.

4.1. Diabetes

4.1.1. Introduction of Diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by carbohydrate intolerance and resultant chronic hyperglycemia. It is a major cause of vascular complications (both microvascular and macrovascular). Patients with diabetes have a two to fourfold risk of cardiovascular diseases (CVDs) compared with patients without diabetes.

Type 2 diabetes mellitus (T2DM) is a result of 2 hallmark mechanisms: i) beta cell dysfunction and ii) insulin resistance. They lead to hyperglycemia which increases ROS, affects nuclear DNA and activates poly(ADP-ribose) polymerase (PARP), and then modifies and inhibits glyceraldehyde 3-phosphate dehydrogenase (GAPDH). These may lead to the activation of 4 crucial pathways which are responsible for the microvascular and macrovascular complications[63] (**Figure 2**). The 4 pathways are:

i) Increased flux through the polyol pathway which lowers glutathione (GSH), a critical intracellular antioxidant.

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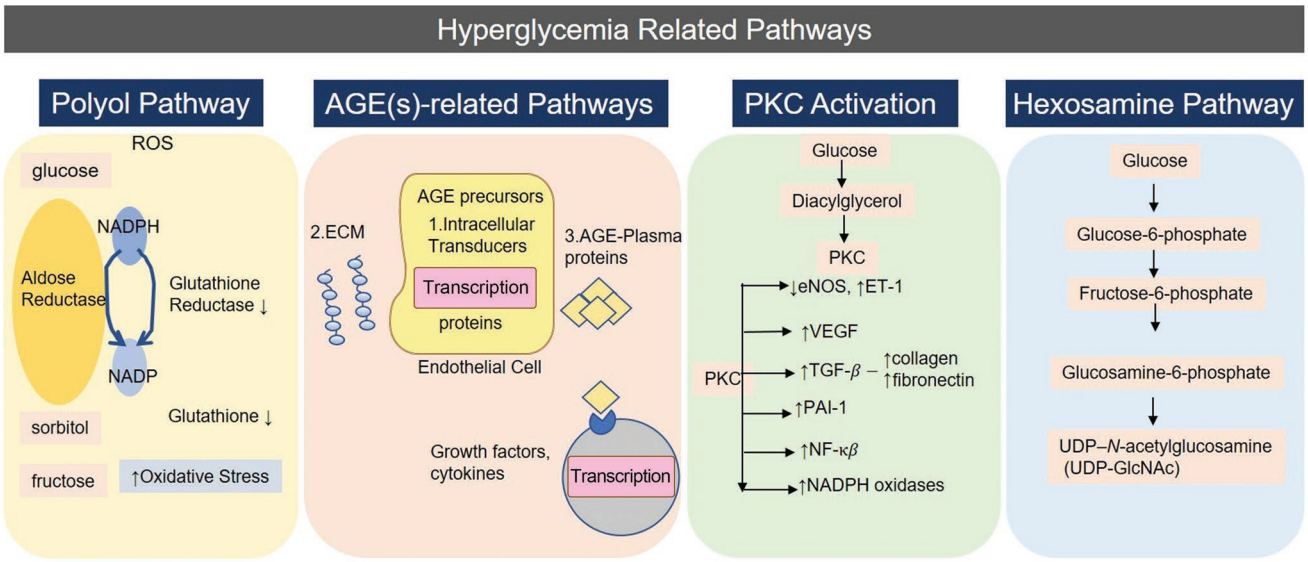

Figure 2. The four hyperglycemia related pathways: 1) polyol pathway with increased flux through the polyol pathway which lowers glutathione a crucial antioxidative enzyme thus resulting in increased oxidative stress; 2) AGE(s) related pathways with modification of intracellular proteins, extracellular matrix molecules, and circulating proteins; 3) protein kinase C activation with downstream endothelial activation; and 4) hexosamine pathway which contributes to modification of EC proteins.

ii) Intracellular formation of advanced glycation end products (AGE) precursors which subsequently leads to 3 effects:
   - Modification of intracellular proteins including those involved in the regulation of gene transcription
   - Modification of extracellular matrix molecules, which alters matrix-cell signaling
   - Modification of circulating proteins such as albumin in the blood which can attach to receptors for AGE, leading to downstream signaling of inflammation and endothelium activation responsible for vascular pathologies.

iii) Activation of PKC pathway, which has a variety of effects on gene expression that are crucial contributors towards vascular dysfunction and thrombosis.

iv) Increased hexosamine pathway activity which contributes towards modification of EC protein leading to activation of endothelial inflammation and thrombotic pathways.

4.1.2. The Role of ROS in Diabetes

In diabetes, the signaling oxidative pathways are up-regulated which may lead to ROS generation. The generated ROS can further induce the augmentation of beta cell dysfunction and insulin resistance.[64] Followings are 3 processes in which hyperglycemia affects ROS signaling pathways:

1) Nonenzymatic glycosylation reaction (Maillard Reaction) involving various proteins occurs with long-term hyperglycemia in various tissues and organs. The reaction results in production of Schiff base, Amadori products as intermediary metabolites, and advanced glycosylation end products (AGEs) as final product along with ROS.[63]
2) Mitochondrial electron transport chain mechanism is activated in patients with diabetes with increased ROS production.[65]
3) Membrane-bound NOX is known to be stimulated in patients with T2DM most likely through AGEs, insulin (high levels are seen in individuals with T2DM), and Ang II (also known to be upregulated in long-standing diabetes mellitus).[64]

The upregulation of the signaling oxidative pathways results in further augmentation of beta cell dysfunction and insulin resistance thus leading to a continuous feed forward fuel loop mechanism (**Figure 3**):

1) Perpetuated beta cell dysfunction by ROS: The increased ROS in the pancreas leads to activation of the JNK pathway which induces nucleo-cytoplasmic translocation of pancreatic and duodenal homeobox-1 (PDX-1) with reduced activity and suppression of insulin production.[64]
2) Perpetuated insulin sensitivity by ROS: The increase in free fatty acid, inflammatory mediators, and oxidative stress (increase in ROS) leads to endoplasmic reticulum stress in the liver and upregulation of 2 pathways, the JNK pathway, and the IkappaB kinase β (IKK) pathway. The upregulation of these 2 pathways leads to upregulation of signaling mechanisms contributing towards increase in insulin resistance.[66]

Activated downstream pathways of endothelial activation, inflammation, vascular SMCs infiltration, and thrombosis lead to atherosclerosis in diabetes (**Figure 4**). The steps involved in the process include:

1) Increased ROS
   - Disrupts the glycocalyx (which covers the luminal surface of the ECs and is an important determinant of vascular rheology and permeability).[67]
   - Inactivates eNOS which results in less formation of nitric oxide. Increased stimulation of membrane-bound NADPH leads to formation of more ROS.

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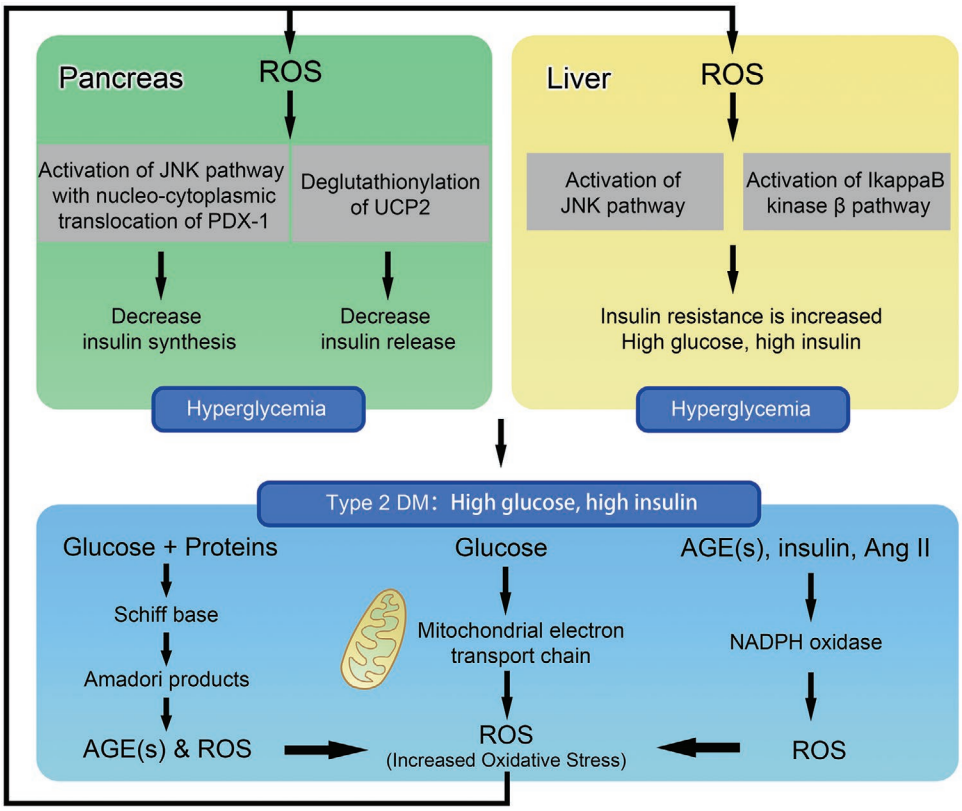

Figure 3. Illustration showing the feed forward fuel mechanism of the oxidative stress signaling mechanism in T2DM. The high glucose leads to increased formation of ROS which in turn leads to beta cell dysfunction and insulin resistance contributing further to high glucose thus leading into a continuous feed forward fuel mechanism.

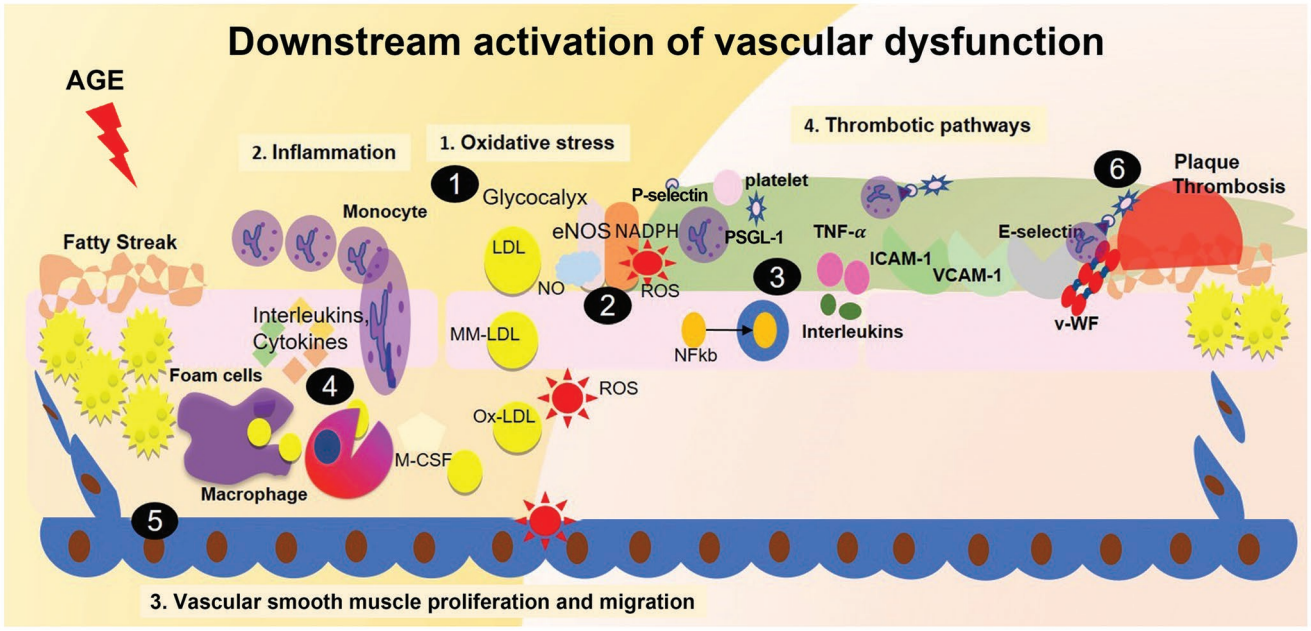

Figure 4. Illustration showing the mechanisms that activate downstream pathways of endothelial activation, inflammation, vascular SMC infiltration, and thrombosis leading to atherosclerosis.

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Table 1. Antidiabetic drugs with antioxidant properties.

Metformin	1) Reduces NOX and mitochondria-mediated ROS production and DNA damage[74] 2) Increases gene expression of glutathione peroxidase 1 (GPX1), sirtuin 3 (SIRT3), SOD, CAT, and GSH[75] 3) Reduces oxidative stress markers such as malondialdehyde (MDA), AGE, AOPP, and Ox-LDL[75b,76]
Sodium-glucose cotransporter-2 inhibitors	
Dapagliflozin	1) Reduces H_2O_2, MDA, and 8-iso-prostaglandin F2α (8-iso-PGF2α)[77] 2) Reduces cytosolic and mitochondrial ROS production[78] 3) Increases SOD1, SOD2, and catalase expression[77b]
Empagliflozin	1) Improves endothelial function and reduces oxidative stress[79] 2) Increases myocardial levels of Sirt3 and SOD2[80]
Ipragliflozin	1) Reduces oxidative stress and inflammation[81]
Glucagon-like peptide-1	
Liraglutide	1) Activates AMPK/Sirt1 pathway to inhibit oxidative stress and apoptosis[72] 2) Reduces eNOS uncoupling and increases NO bioavailability[82] 3) Reduces TNF-α induced oxidative stress and inflammation[83] 4) Inactivates NOX2[84] 5) Activates NRF2[85]
Exenatide	1) Reduces 8-iso-prostaglandin F2α and malondialdehyde levels[86] 2) Reduces ROS and MDA and NOX expression[87] 3) Increases the expression and activities of SOD and GSH-Px[87] 4) Increases expression of NAD(P)H dehydrogenase [quinone] 1 (NQO-1), glutathione S-transferase PI, HO-1[88]
Dipeptidyl peptidase-4	
Linagliptin	1) Inhibits the AGE induced ROS[89]
Teneligliptin	1) Induces expression of HO-1 and NAD(P)H dehydrogenase quinone-1[90] 2) Downregulates $P22^{phox}$[90]

- Causes vascular SMCs change in phenotype, increased proliferation, and migration to form foam cells and fatty plaques.[68]
- Activates platelets with higher propensity to form platelet monocyte aggregates, increased adhesion, and participation in thrombotic pathways.
- Promotes the initiation of coagulation by targeting the TF–fVII complex as well as tissue factor protein inhibitor (TFPI).
- Activates protein C (APC), enhances the conversion of fibrinogen to thrombin and enhances PAI-1 activity and propagates formation of a thrombus.

2) Results in downstream cytonuclear translocation of NFkB and activation and increased expression of endothelial surface markers ICAM-1, VCAM-1, E-selectin which further facilitates inflammation cell recruitment
3) Increased oxidation of LDL and activation of inflammation leads to ingestion by macrophages and monocytes and formation of foam cells and through release of cytokines and growth factors further propagation of inflammation.
4) Thrombus formation involves the adhesion, activation, and aggregation of platelets as well as activation of the coagulation cascade which is mainly triggered by tissue factor binding to activated factor VII with downstream activation of coagulation pathway and fibrin formation.[69]

4.1.3. Antidiabetic Drugs with Antioxidant Properties

Diabetes pharmacotherapy is known to reduce oxidative stress (**Table 1**). Metformin, a biguanide, has been used as a first-line medication for diabetes for decades now. It is known to reduce oxidative stress through increasing the antioxidant defense mechanisms and reducing oxidative stress. It increases the antioxidant stress through SOD1, GSH/Gpx1, SIRT1, thioredoxin, and PON1. It reduces oxidative stress through inhibition of AMPK and PKC-NOX pathways and reduces endothelial inflammation and leukocyte–endothelial interactions through inhibition of AMPK pathways and RAGE-LOX 1 pathways.[70] Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which have shown cardiovascular benefits regardless of presence of diabetes, are also known to reduce oxidative stress and suppress damage mediated by advanced glycation end-products.[71] Glucagon-like peptide-1 (GLP-1) analogs, another class of medications known to have cardioprotective effects, are also known to have beneficial effects on cardiac steatosis, DAG-PKC-NAD(P)H pathway, oxidative stress, and apoptosis via activation of AMPK-Sirt1 pathway, independent of a glucose-lowering effect.[72] Although dipeptidyl peptidase-4 (DPP4) inhibitors have not demonstrated significant cardioprotective effects in cardiovascular outcome trials, it is known to reduce oxidative stress.[73]

4.2. Hypertension

4.2.1. Introduction of Hypertension

Hypertension is one of the leading risk factors for IHD.[91] Hypertension doubles the risk of CVD and accelerates the development of atherosclerosis. Hypertension contributes to atherosclerosis through several mechanisms (**Figure 5**):

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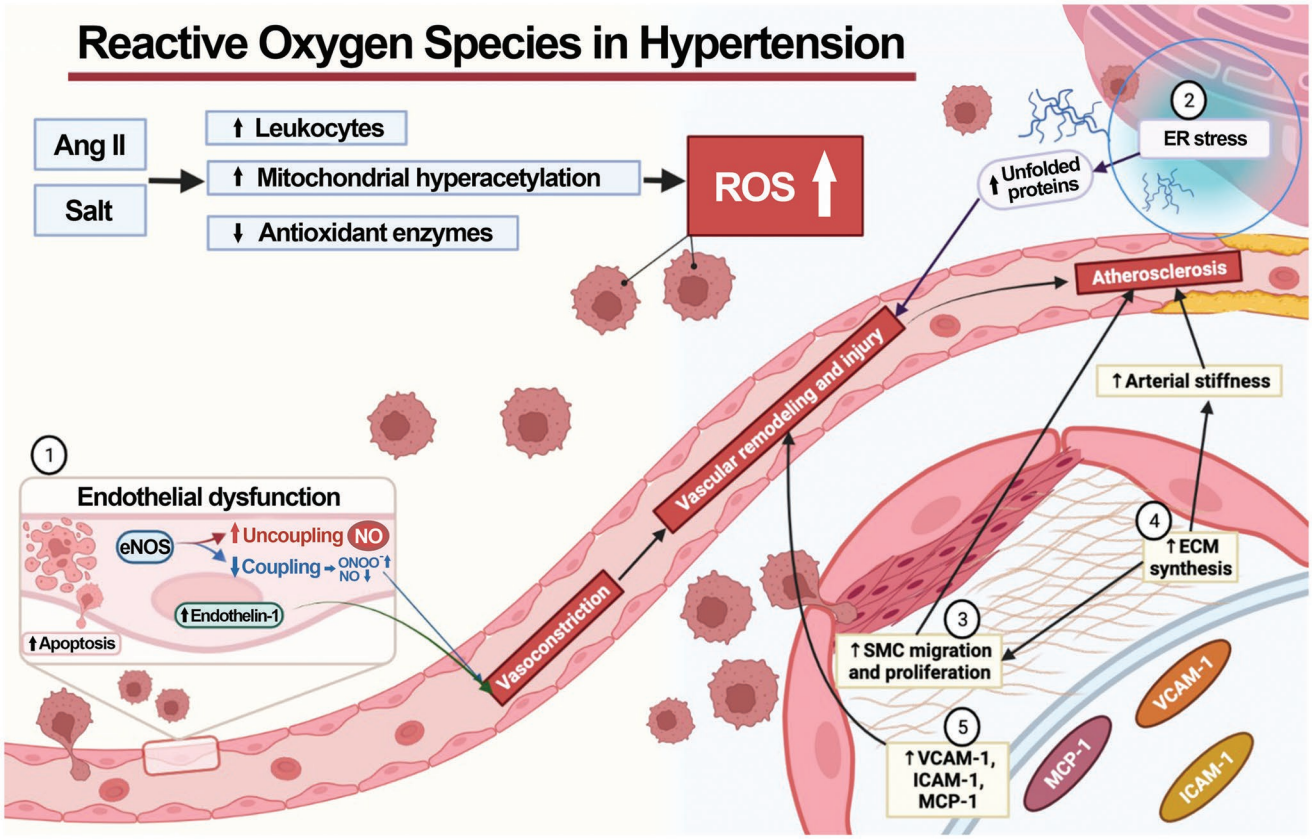

Figure 5. Illustration showing the pathways through which Ang II or high salt leads to atherosclerosis and increased ROS production in hypertension. The increased ROS production in hypertension leads to endothelial dysfunction, increased ER stress, SMC migration and proliferation, ECM synthesis, and expression of adhesion molecules and MCP-1, all of which contribute to the development of atherosclerosis.

i) Arterial stiffness: Hypertension promotes extracellular matrix (ECM) synthesis resulting in vascular thickness and structural stiffening.[92] By increasing the load of the stiff components within the arterial wall and reorganizing the spatial distribution of VSMC and ECM, it increases arterial stiffness.[93]
ii) Oxidative stress and NO bioavailability: Ang II increases ROS production through NOX and XO leading to oxidative stress and endothelial dysfunction within arterial walls.[94] Hypertensive factors, such as Ang II and salt, may activate the innate immune system which leads to ROS production.[95] ROS promotes vasoconstriction and vascular remodeling to increase systemic vascular resistance.[96] ROS destruct NO and leads to deficiency of NO bioavailability and endothelial dysfunction. Impaired NO bioactivity is associated with arterial stiffness and high blood pressure.[97]
iii) Immune and inflammation: Accumulating evidences suggest a link between arterial hypertension and immune system (both innate and adaptive) and inflammation.[95a,98,99] Monocytes/macrophages and neutrophils have been shown to increase in Ang II-induced hypertension or in spontaneously hypertensive rats.[100] Adaptive immune cells, including $CD4^+$, $CD8^+$, natural killer, regulatory T cells, and B cells have been linked to hypertension. A mouse strain lacking T and B cells showed blunted blood pressure increase after Ang II infusion.[101]

4.2.2. The Role of ROS in Hypertension

Hypertension is associated with increased ROS production. The increased ROS production either results from NOX activated by hypertensive factors, such as Ang II and salt or impaired degradation by antioxidant enzymes:

1) Ang II induces O_2^- production through NOX1 and NOX2.[102] O_2^- can be degraded by reaction with NO three times faster than by SOD, leading to loss of NO and generation of $ONOO^-$, which in turn has been shown to uncouple the eNOS.[35] The reduced NO bioavailability leads to impaired endothelium-dependent relaxation.
2) High salt induces high blood pressure and enhances ROS production. High salt in mice with reduced renal mass enhances O_2^- and H_2O_2 generation in arteries and induces maximal contractions in response to Ang II. This is dependent on O_2^- and H_2O_2 produced by NOX2 and NOX4, respectively.[103] In rats fed with high fructose/salt diet exhibited a salt-dependent hypertension accompanied by increased ROS and decreased renal SOD activity.[104]
3) Ang II inhibits mitochondrial deacetylase SIRT3 activity which leads to mitochondrial hyperacetylation. This results in SOD2 inactivation and oxidative stress.[105]
4) Hypertension downregulates endogenous antioxidant enzymes, such as SOD1, SOD2, and catalase, in vessels or

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kidneys of animals received Ang II infusion or genetically hypertensive mice.[106]

5) Hypertension causes eNOS uncoupled to generate vasoinjurious O_2^-.[107]
6) ROS are generated during the unfolded protein response primarily through NOX4 activation in hypertension.[108]

The increased ROS cause EC apoptosis and dysfunction, SMC proliferation and migration, vessel inflammation, and vascular remodeling, vessel matrix alteration leading to atherosclerosis (Figure 5). The steps involved in the process include:

1) Oxidative Stress promotes EC apoptosis.[109] Apoptotic ECs can release several types of membrane-bound extracellular vesicles through which contribute to intercellular communication during the development of atherosclerosis.[110]
2) Endothelial dysfunction:[111] ROS uncouples the eNOS-catalyzed reduction of O_2 from the oxidation of L-arginine. This results in the superoxide which directly react with NO to produce $ONOO^-$.[112] This causes eNOS to become a ROS-producing enzyme, thus accelerating the atherosclerotic process.
3) Oxidative stress (H_2O_2 and O_2^-) has been indicated to promote SMC proliferation and migration which contributes to the initiation and early progression of atherosclerosis.[113] Enhanced H_2O_2 is correlated with increased protein content, proliferation, and migration of SMCs.[114] O_2^- mediates plasminogen urokinase-induced SMC proliferation.[46c]
4) Increased ROS leads to vascular inflammation through activation of Ca^{2+} signal, tyrosine kinases, or mitogen-activated protein kinases (MAPK) by non-genomic action and increases expression of MCP-1, VCAM-1, ICAM-1, and atherogenic genes by genomic action via activating NF-κB.[115] An inflamed vessel recruits inflammatory cells, such as monocytes to promote atherosclerosis
5) Pathological changes in ROS levels lead to excess ECM production which disrupts vessel ECM homeostasis.[116] This affects inflammatory response, the proliferation, and migration of vascular SMCs, neointimal formation, and vascular fibrosis seen in atherosclerosis s.[116]
6) Oxidative stress can directly trigger unfolded protein response through oxidation of endoplasmic reticulum stress signaling molecules. Activated unfolded protein response causes protein accumulation and misfolding which lead to apoptosis, phenotypic switching, dedifferentiation, and transdifferentiation. All of these contribute to vascular remodeling and injury.[106]

4.2.3. Anti-Hypertensive Drugs with Antioxidant Properties

A variety of anti-hypertensive drugs possess antioxidant properties (**Table 2**). Ang II not only stimulates NOX to produce s H_2O_2 and O_2^-, but also increases the production of mitochondrial ROS.[117] Thus, the inhibition of Ang II production and activity helps reduce ROS production in hypertension. In addition, drugs of calcium channel blockers and beta-blockers also have shown antioxidant effects.

Angiotensin-converting enzyme (ACE) inhibitors have been shown to have antioxidant effect. Experimental studies suggest that Enalapril and Captopril enhance GSH-dependent antioxidant defenses in mouse tissues[118] and exert an antioxidant effect against the electrolysis-induced ROS in the rabbit aortic rings.[119] Captopril can protect H_2O_2-induced endothelial dysfunction through the AKT/mTOR pathway[120] and suppress NOX expression in dog coronary arteries or HUVECs.[121] Both Quinaprilat and Enalaprilat can decrease oxidative stress in HUVECs induced by propofol.[122] Clinically, hypertensive patients treated with 10 mg Lisinopril orally per day for three months had serum markers of oxidative stress (MDA, TAS, and GSH) significantly reduced and systolic and diastolic BP lowered.[123] Compared with a calcium channel blocker, an ACE inhibitor seems to be more effective to protect against DNA oxidative damage in hypertensive patients with different stages of chronic kidney disease.[124]

Angiotensin II receptor blockers (ARB) can reduce ROS production which is independent of its effect on the blood pressure.[125] Irbesartan (10 μg mL^{-1}) reduces ROS production induced by Ang II in primary human Tenon's fibroblasts.[126] Olmesartan and valsartan reduce ROS, such as 8-epi-prostaglandin F2α (8-epi-PGF2α) and 8-hydroxydeoxyguanosine (OHdG), in urine of hypertensive DN patients after a 16-week treatment.[125] Azilsartan, but not candesartan, improves eNOS activity and reduces NOX2 and NOX4 expression in aortic rings of KKAy diabetic mice.[127] Valsartan (160 mg daily) has a profound and rapid ROS reduction effect as ROS generated by polymorphonuclear cells and mononuclear cells fell are significantly reduced after 7 days of treatment.[128]

Drugs of calcium channel blockers (CCB) have antioxidant effects as calcium signaling pathway interacts with ROS. Increased levels of Ca^{2+} activate ROS-generating enzymes and formation of free radicals while CCBs may directly scavenge ROS or preserve SOD activity.[129] Amlodipine is able to increase the NO bioavailability, firstly via enhanced NO formation and secondly by prolonging the half-life of NO through antioxidative properties.[130] Benidipine suppresses lysophosphatidylcholine induced endothelial dysfunction in human aortic ECs through inhibition of ROS production, which is independent of its inhibition of L-type voltage-gated calcium channels.[131] Lacidipine reduces about two-thirds of the ox-LDL induced ROS production in HUVECs.[129a] Lercanidipine reduces intracellular ROS through inactivating Ras-ERK1/2 signaling.[132]

Beta blockers have antioxidant properties in addition to blocking the effects of adrenaline. Carvedilol inhibits O_2^- release from human neutrophils[133] and scavenges free radicals.[134] Nebivolol inhibits O_2^- formation by vascular NOX in Ang II or ethanol-treated rats,[135] suppresses vascular NOS uncoupling in hyperlipidemic rabbits,[136] prevents vascular NOX activation, stimulates NO production,[137] and reduces NO degradation.[138] A combined intervention of BH4 and Nebivolol more effectively increased NO generation and the expression level of myocardial eNOS mRNA, eNOS expression of dimers, phospholamban, SERCA2a, and cGMP in spontaneously hypertensive rats.[139] Clinically, Metoprolol, Bisoprolol, and Carvedilol have shown antioxidant property in addition to blocking the effects of adrenaline to improve heart function in patients with heart failure.[140]

Aliskiren, a renin inhibitor, has been shown to increase activities of AKT and eNOS leading to improve NO bioavailability, reduced O_2^-, and nitrotyrosine content and NOX activity

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Table 2. Anti-hypertensive drugs with antioxidant properties.

ACE inhibitors	
Enalapril	1) Enhances GSH[118] 2) Scavenges ROS[119]
Captopril	1) Enhances GSH[118] 2) Protects EC from H_2O_2 through AKT/mTOR pathway[120] 3) Suppresses NOX expression[121] 4) Scavenges ROS[119]
Quinaprilat	1) Decreases H_2O_2 and MDA induced by propofol[122]
Enalaprilat	1) Decreases H_2O_2 induced by propofol[122] 2) Increases SOD activity and reduces the thiobarbituric acid reactive substances level[144]
Lisinopril	1) Reduces Superoxide and hydroxyl radical in diabetic myocardium[145] 2) Reduces serum markers of oxidative stress[146]
Perindopril	1) Increases eNOS expression and activity[147] 2) Increases NO[147]
Angiotensin II receptor blockers	
Irbesartan	1) Reduces superoxide and p22phox[126,148] 2) Increases NO bioavailability[148] 3) Increases GSH and SOD activity[149]
Olmesartan	1) Reduces as 8-epi-prostaglandin F2α (8-epi-PGF2α) and 8-hydroxydeoxyguanosine (OHdG)[125] 2) Reduces ROS production[150] 3) Enhances NO release[151]
Azilsartan	1) Improves eNOS activity and reduces NOX2 and NOX4 expression[127] 2) Restores uncoupled eNOS[127] 3) Inhibits NOX2 and NOX4[127]
Valsartan	1) Reduces 8-epi-PGF2α and OHdG[125] 2) Reduces ROS generated by polymorphonuclear cells and mononuclear cells[128,152] 3) Promotes NO synthesis[153]
Calcium channel blockers	
Amlodipine	1) Enhances NO formation and increases NO bioavailability[130] 2) Promotes the unclamping of eNOS from caveolin to potentiate NO production[154] 3) Reduces O_2^- and $ONOO^-$ production[155]
Benidipine	1) Inhibits ROS production[131] 2) Decreases oxidative stress in polymorphonuclear cells[156]
Lacidipine	1) Reduces the ox-LDL induced ROS[129a] 2) Reduces ROS[157]
Nifedipine	1) Prevents high glucose-induced ROS generation and increases basal eNOS activity[158] 2) Indirectly Upregulates SOD expression[159]
Lercanidipine	1) Reduces intracellular ROS[132]
Beta-blockers	
Carvedilol	1) Inhibits O_2^- release from neutrophils[133] 2) Scavenges free radicals[133] 3) Increases SOD1, and GPx-1 expression[160] 4) Increases NO synthesis[161]
Nebivolol	1) Inhibits O_2^- produced by NOX2 induced by Ang II[135b] 2) Suppresses vascular NOS uncoupling[136] 3) Prevents vascular NOX activation[137] 4) Stimulates endothelial NO production[137] 5) Reduces NO degradation[138]
Renin inhibitor	
Aliskiren	1) Improved NO bioavailability[141] 2) Increases the activity of eNOS and AKT and BH_4 levels[141] 3) Reduces $gp91^{phox}$ protein expression[141]

in aorta of hyperlipidemic rabbits.[141] However, a more recent study suggested that aliskiren alone is insufficient to prevent hypertension-induced vascular oxidative stress and endothelial dysfunction in a rat model of two-kidney, one-clip (2K1C)

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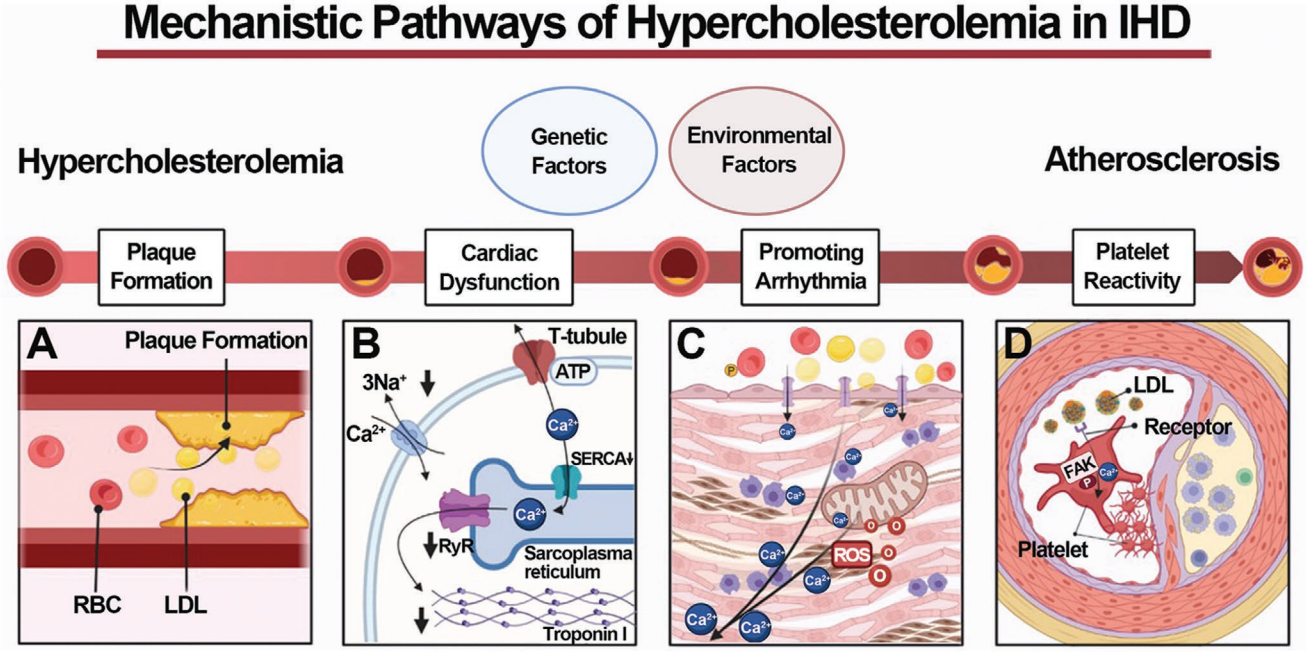

Figure 6. Mechanistic pathways through which hypercholesterolemia contributes to IHD: A) Damaging the endothelium allows LDL-cholesterol to accumulate in the artery wall and attracts inflammatory cells to internalize the LDL-cholesterol, which directly contributes to plaque formation; B) Decreasing ion channel protein expression and troponin I, increasing cardiac fibrosis, and inhibiting cardiac autophagy, through which cause cardiac dysfunction; C) Lipid accumulation in myocardium results in abnormal Ca^{2+} current and expression of gap junction protein. Mitochondrial oxidative stress induces Ca^{2+} leak. Increased expression and activation of CaMKII increases arrhythmia risk; D) Binding of LDL to its receptors on platelets induces FAK phosphorylation and Ca^{2+} increase. This signal transduction increases platelet reactivity to mediate plaque rupture and atherothrombosis.

hypertension.[142] The difference may be explained by different animal models used.

Other anti-hypertensive drugs possessing antioxidant property include vasoactive intestinal peptide and lercanidipine. Vasoactive intestinal peptide reduces formyl-peptide-induced ROS production by targeting a MAPK-$p47^{phox}$ phosphorylation pathway in monocytes.[143]

4.3. Hypercholesterolemia

4.3.1. Introduction of Hypercholesterolemia

Hypercholesterolemia, especially increased low density lipoprotein (LDL) cholesterol, is a risk factor for the development of atherosclerosis and IHD. The cause of hypercholesterolemia can be genetic, environmental, or both. Environmental causes include high-fat diets, lack of exercise, and air pollutants.[162] The amount of ingested fat and total calories are the most important dietary factors to induce obesity and hypercholesterolemia.[163] About one in every six adults in the U.S. population has hyperlipidemia.[164] People with hypercholesterolemia are twice as likely to develop IHD as those with cholesterol levels in the normal range.[164]

Hypercholesterolemia has direct effects on the heart through several mechanisms (**Figure 6**):

i) Direct contribution to plaque formation: High cholesterol damages the endothelium to allow LDL cholesterol to accumulate in the artery wall and attracts inflammatory cells to internalize LDL-cholesterol. The accumulated cholesterol and inflammatory cells form atherosclerosis in the arterial wall.[165]

ii) Promoting cardiac dysfunction: hypercholesterolemia results in:
- Decreased expression of Ca^{2+}-ATPase (SERCA), ryanodine receptors (RyR), and Na^+/Ca^{2+} exchangers;[166]
- Increased cardiac interstitial fibrosis and the loss of troponin I due to increased systemic oxidative stress and proinflammation by increased serum triglyceride and free fatty acids (FFAs);[167]
- Inhibited cardiac autophagy through increasing p62 and reducing LC3 expression and increased apoptosis by increasing cleaved caspase-3 expression level through the mTOR pathway.[168]
- Promoting LV arrhythmia: Long-term hypercholesterolemia causes lipid accumulation in myocardium which results in:
- Abnormal Ca^{2+} current and expression of gap junction protein and prolonged action potential duration (APD) and QTc interval to promote arrhythmia;[169]
- Mitochondrial oxidative stress which induces intracellular calcium leak and LV arrhythmia;[170]

iii) Increased expression and activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which leads to increased sensitivity to arrhythmia-induced electrical remodeling, prolonged action potential duration, downregulated cardiac ion channels including Cav1.2 and Kv4.2/Kv4.3, and decreased conduction velocity.[171]

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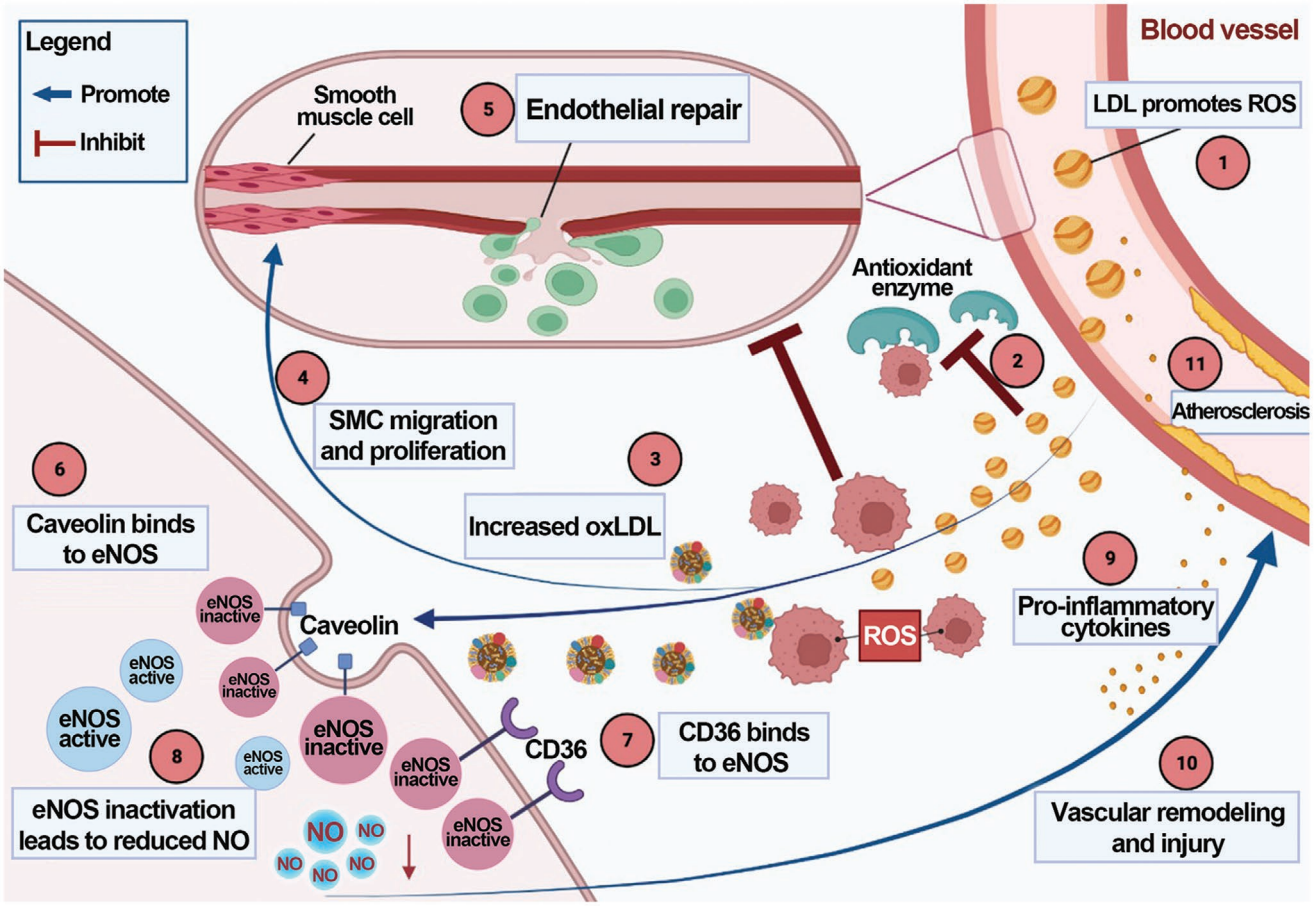

Figure 7. Illustration showing the pathways through which hypercholesterolemia leads to increased ROS production. Hypercholesterolemia either directly increases ROS production or through inhibits antioxidant enzyme activity. Increased ROS limits endothelial, directly inactivates eNOS, increases oxLDL to either indirectly inhibit eNOS activity or promote SMC migration and proliferation. In addition, hypercholesterolemia promotes proinflammatory cytokines production. All of these contribute to the development of atherosclerosis in hypercholesterolemia.

iv) Increased platelet reactivity: platelets are shown to be highly active and are more prone to be activated and aggregated in hypercholesterolemia.[172] Binding of LDL to LDL receptors on platelets induces focal adhesion kinase (FAK) phosphorylation, which induces intracellular Ca^{2+} increase. This signal transduction results in increased platelet reactivity,[173] which is associated with an enhanced platelet thrombus formation on an injured artery[174] and is the key mediator of plaque rupture and atherothrombosis.[175]

4.3.2. The Role of ROS in Hypercholesterolemia

Hypercholesterolemia is associated with both the generation of biologically active oxLDL and enhanced oxidant stress. Hypercholesterolemia affects ROS through below several mechanisms (**Figure 7**):

1) Increases ROS production through increased NOX4 activity,[176] activation of angiotensin II type-1 receptor,[177] affecting the cellular lipid components included in rafts, resulting in modification of cellular reactions that produce ROS.[29]
2) Hypercholesterolemia decreases expression of antioxidant enzyme, such as GPx, CAT, and SOD.[178]

The increased ROS and oxLDL which cause less NO bioavailability, endothelial dysfunction, and activation of inflammation through which contributes to atherosclerosis (Figure 4):[179]

1) Hypercholesterolemia and ROS limit endothelial healing after injuries which are the main stimulus for development of the atherosclerotic plaque.[180]
2) Increased ROS causes eNOS inactivation and reduced NO production through:
   i) Enhanced caveolin binding to eNOS.[179]
   ii) Increased oxLDL enhances binding of CD36 to eNOS on ECs.[181]
3) ROS increases oxLDL to stimulate SMC migration and proliferation through up-regulation of osteopontin.[182]
4) Hypercholesterolemia and ROS regulate various types of kinases and transcription factors, such as NFκB, to activate proinflammatory genes leading to atherosclerosis.[183]
5) Ox-LDL stimulates platelet activation to express proinflammatory cytokines, such as adhesion molecules and thrombogenic tissue factor, which play crucial roles in proatherogenic mechanisms.[184]

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Table 3. Anti-hypercholesterolemia drugs with antioxidant properties.

Statin	
Atorvastatin	1) Up-regulates adiponectin expression through which downregulates NOX2 subunits, $Gp91^{phox}$[187] 2) Activates AKT to increase eNOS, SIRT1, and catalase expression[185c,194] 3) Increases eNOS activity and NO production[185c] 4) Reduces expression of NOX, p22phox, and NOX1[185c] 5) Reduces ROS production[185c]
Fluvastatin	1) Increases the expression eNOS, guanosine triphosphate cyclohydrolase (GTPCH), and intracellular BH4.[188a] 2) Increases NO production[185c]
Pravastatin	1) Activates AKT to increase eNOS, SIRT1, and CAT expression[185c,194] 2) Inhibits endothelial senescence induced by H_2O_2[194] 3) Increases NO production[185c]
Simvastatin	1) Activates NRF2 through the PI3K/Akt pathway[190] 2) Reduces ROS through inhibiting NOX/p38 MAPK pathway[191] 3) Increases NO production[185c] 4) Activates AKT to increase eNOS expression[185c,194] 5) Induces HO-1[195] 6) Inhibits NOX1 and NOX2[185c]
Pitavastatin	1) Activates AKT to increase eNOS, SIRT1, and CAT expression[185c,194] 2) Reduces O_2^- production[196]

4.3.3. Anti-Hypercholesterolemia Drugs with Antioxidant Properties

Since hypercholesterolemia enhances ROS production, some anti-hyperlipidemic drugs with antioxidant property have been investigated and reported (**Table 3**). Statins are the most common drugs for the treatment of hypercholesterolemia. In addition to decreasing cholesterol synthesis through inhibition of HMG-CoA reductase, statins improve NO product, endothelial function, and angiogenesis, interfere with the synthesis of isoprenoid intermediates to exert their antioxidant effect.[185]

Statins can reduce concentration of the circulating soluble NOX2-derived peptide and inhibit NOX2 in platelets,[186] up-regulate adiponectin expression through which downregulates NOX2 subunits, Gp91phox,[187] increase eNOS expression and activity,[185c,188] induce antioxidant enzyme expression (catalase, SOD, and HO-1) and increase their activities (catalase, SOD, GSH, and paraoxonase 1),[189] and lower ROS product by activating nuclear factor-erythroid 2-related factor 2 (NRF2) through the PI3K/Akt pathway[190] or inhibiting NOX/p38 MAPK pathway.[191]

Sericin, a natural macromolecular protein derived from silkworm *Antheraea assamensis*, not only lowers the serum total cholesterol level, but also has antioxidant property by reducing the thiobarbituric acid reactive substances level and increasing the endogenous antioxidant in hearts.[192] Febuxostat, an inhibitor of XO, not only significantly lowered LDL, but also has a potent anti-inflammatory and antioxidant activity by decreasing serum levels of lipid peroxidation index, proinflammatory cytokines, and enhancing antioxidant enzyme activity in rabbits with high fat diet.[193]

5. Introduction of IHD

IHD is a condition in which coronary arteries get narrowed due to the formation of plaque (atherosclerosis), accompanied by the reduced blood and oxygen supply to the heart muscle, which can ultimately induce heart attack. It is the most common heart disease and can also be called coronary heart disease or coronary artery disease. Four types from mild to severe, stable angina, unstable angina, MI, and sudden cardiac death are included in IHD. Despite the introduction of percutaneous coronary intervention (PCI) has markedly reduced the mortality caused by MI since 1977, MI remains the leading cause of death worldwide. Revascularization by PCI restores blood supply to the ischemic myocardium and therefore salvages the heart muscle to a large extent. Paradoxically, PCI treatment often leads to unexpected muscle damage accompanied with myocardial stunning or lethal arrhythmias, a phenomenon coined as myocardial ischemia-reperfusion injury (I/R injury).[197] Emerging evidence indicates that myocardial I/R injury is predominantly attributable to the massive production of ROS upon restoration of blood flow to the ischemic myocardium.[198]

5.1. Source of ROS in I/R

In MI, the main ROS species include O_2^-, H_2O_2, OH^-, $\cdot OH$, and HClO. The reactive nitrogen species (RNS), NO, and peroxynitrite ($ONOO^-$), generated by eNOS and iNOS under pathological conditions, are sometimes also included as ROS.[199] Upon myocardial ischemia, overall myocardial redox is enhanced as a result of an increase in antioxidant activity and neglectable changes in ROS production.[199] However, large quantities of ROS are generated from the ubisemiquinone site of the mitochondrial electron transport chain in cardiomyocytes during ischemia before reperfusion.[200] Upon restoration of blood blow to the ischemic myocardium following revascularization, paradoxically, massive ROS are produced by the stressed mitochondria,[201] activated membrane NOX,[202] cytosolic XO,[198,203] as well as the uncoupled NOS.[198] In addition, calcium overload in cardiomyocytes during ischemia can activate XO to produce ROS.[203] Iron can be released during I/R and cause production of ROS via Fenton reaction, an iron-catalyzed chemical reaction that forms O_2^-, hydroxyl radical $OH\cdot$ from H_2O_2.[204]

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ROS are produced by several cell types during myocardial I/R injury. The most obvious ROS source during myocardial reperfusion is cardiomyocytes which produce ROS by altered mitochondrial electron transport chain.[198] Restoration of blood flow to the previously ischemic myocardium is accompanied with rapid infiltration of inflammatory cells including neutrophils and monocytes. Using NOX, the activated neutrophils and macrophages can burst with a large amount of ROS, resulting in significant myocardial I/R injury.[205] Detailed analysis in a mouse model of I/R injury demonstrates that isoforms NOX1 and NOX2 contribute to detrimental ROS production during myocardial reperfusion.[205a] ROS produced by isoform NOX4 does not affect myocardial infarct size during I/R injury but exacerbates post-MI left ventricular remodeling and dysfunction via polarizing macrophages towards proinflammatory phenotype.[205a] Interestingly, recent studies indicate that the cytoplasmic domain of tissue factor, which arguments ROS production in monocytes/macrophages, enhances macrophage iNOS expression and polarize macrophages towards proinflammatory phenotype, resulting in post-MI adverse left ventricular remodeling.[206] Apart from infiltrating inflammatory cells, ECs may also employ NOX to generate ROS under I/R injury.[207] eNOS plays a critical role in the regulation of vascular function by producing NO. However, eNOS may be uncoupled under ischemia due to the lack of its substrate amino acid L-arginine or the cofactor BH4, resulting in the production of superoxide instead of NO.[208] This superoxide may recruit activated neutrophils to the disturbed endothelium and the neutrophil-endothelium adherence can stimulate activation of xanthine oxidase, another ROS generator primarily expressed in ECs, to further produce O_2^-.[209]

5.2. The Role of ROS in MI

The pathological roles of ROS in MI are well established.[210] In brief, ROS either directly cause lipid peroxidation, oxidation of DNA and proteins through which induce cell death, or participate in inflammatory signaling. In cell signaling, ROS can activate NF-κB[211] which induces expression of several inflammatory cytokines and chemokines, including TNF-α, IL-1, and IL-6.[212] In addition, NOX4-associated ROS oxidation activates NLRP3 inflammasome and its downstream inflammatory pathways.[213]

Interestingly, exposure to low dose of ROS prior to reperfusion seems to elicit cardioprotective effects against myocardial I/R injury, which may account for the clinically used remote preconditioning.[214] The molecular mechanisms underneath this adaptive pretreatment may be due to: 1) upregulation of several endogenous antioxidant enzymes, including CAT, GSH-Px, glutathione reductase, glutathione transferase, NADPH-quinone oxidoreductase 1, and HO-1, via activation of NRF2,[215] and 2) the prevention of eNOS uncoupling and subsequent massive production of ROS.[216]

5.3. ROS Scavengers in MI

Given the detrimental effects of oxidative stress in MI, elimination of ROS by enhancing antioxidant activity has been proposed as a therapeutic strategy to reduce myocardial I/R injury.[210b,217]

5.3.1. Endogenous Antioxidants

Endogenous antioxidants, consisting of enzymatic and non-enzymatic antioxidants, form primary defense mechanisms to eliminate ROS in MI. Enzymatic antioxidants include GPX, SOD, and catalase, and non-enzymatic antioxidants include uric acid, lipoic acid, bilirubin, GSH, and melatonin.[218] Genetic overexpression of GPX and SOD have been shown to alleviate oxidative stress and protect the heart from myocardial I/R injury.[219] Overexpression of 5-oxoprolinase (OPLAH), a protein that hydrolyzes ATP, reduces 5-oxoproline level and oxidative stress, resulting in cardiac protection in MI.[220] Level of 5-methoxytryptophan (5-MTP), a 5-methoxyindole metabolite of L-tryptophan, decreases in the heart following MI. Administration of 5-MTP has been reported to prevent cardiac injury after MI by promoting mitochondrial stabilization and controlling redox imbalance.[221] In addition, intravenous administration of the paracrine growth factor neuregulin-1 alleviates oxidative stress by inhibiting NOX4 in myocardial I/R injury.[222] These recent findings suggest that there are some proteins such as OPLAH, 5-MTP, and Neuregulin-1 may behave as endogenous antioxidants under pathological conditions and they may be considered new therapeutic targets for the treatment of MI.

5.3.2. Medications with Antioxidant Property

A variety of drugs used for treatment of IHD have shown antioxidant properties (**Table 4**). Metformin, a drug commonly used for the treatment of type II diabetes has been shown to reduce incidence of MI and all-cause mortality in type II diabetes patients.[223] Metformin protects against myocardial I/R injury via AMPK-dependent suppression of NOX4.[224] XO inhibitors (XOI), classified as purine-like (allopurinol and oxypurinol) and non-purine (febuxostat and topiroxostat) XOI, present antioxidant properties by reducing the production of ROS derived from purine metabolism.[225] Pentaerythritol tetranitrate (PETN) has been shown to be a promising therapeutic option in the treatment of IHD through inducing HO-1 expression, increasing NO bioactivity, and preventing mitochondrial O_2^- generation and NOX4 upregulation.[226]

Several antithrombotic drugs also possess antioxidant properties. Aspirin has been shown to inhibit ROS production through downregulation of NOX4 and iNOS in HUVECs exposed to oxi-LDL.[227] Aspirin attenuated endogenous levels of ROS and upregulated SOD, catalase, glutathione-S-transferases -4 and -10 in the nematode *Caenorhabditis elegans*.[228] Aspirin eugenol ester (AEE) is another compound with anti-inflammatory and antioxidant stress pharmacological activity. It reduces the induction of MDA and promotes catalase, SOD, and GPx activities in paraquat-induced lung injury in rats.[229] Although it seems that aspirin possesses anti-ROS property, there is no direct evidence that aspirin can inhibit ROS production in I/R injury after MI, especially in patients.

Heparin inhibits ROS generated by polymorphonuclear (PMN) and mononuclear (MNC) leucocytes in normal subjects.[230] Enoxaparin, a low molecular weight heparin, has been shown to not only partially reverse doxorubicin-induced cardiotoxicity through suppression of oxidative stress (decreasing

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Table 4. IHD medications with antioxidant properties.

Metformin	1) Suppresses NOX4 via AMPK[224]
XOI	1) Reduces ROS production[225]
Aspirin	1) Inhibits ROS production by downregulating NOX4 and iNOS[227] 2) Upregulates expression of endogenous antioxidant enzymes[228]
Aspirin eugenol ester (AEE)	1) Reduces MDA[229] 2) Enhance enzymatic activity of catalase, SOD, and GPx[229]
Heparin/Enoxaparin	1) Inhibits ROS generation by leukocytes[230] 2) Decreases MDA and increases total antioxidant capacity[231]
Hirudin	1) Restores SOD activity[234] 2) Reduces ROS and MDA generation through NRF2 activation[234]

MDA and increased total antioxidant capacity), but also reduced inflammation (TNF-α and IL-1β) and apoptosis (caspase-3) in a cardiotoxicity rat model.[231] On the contrary, Bredthauer et al., did not find reduction of ROS production in polymorphonuclear neutrophils isolated from healthy volunteers.[232] This difference could be due to the pathophysiology condition in the rat study.[231] Hirudin inhibited Ang II-induced ROS generation, LDH activity, and MDA content, and increased SOD activity through inhibiting ERK1/2 in myocardial fibroblasts.[233] Hirudin has cardioprotective effect through restoring SOD, reducing ROS and MDA through the activation of NRF2 in rat model of MI.[234]

5.3.3. Nutraceuticals with Antioxidant Property

In addition to pharmacotherapy, nutraceuticals, such as vitamins A, B, C, D, and E, lutein, zeaxanthin, zinc, lipoic acid, *N*-acetyl cysteine, Omega, resveratrol, trimethylglycine, and garlic oil, etc., can help reduce oxidative stress and achieve myocardial protection in MI.[218,235]

Multivitamins are thought to reduce oxidative stress and inflammation.[236] Benfotiamine (Vitamin B1 derivative), a NOX inhibitor, could improve antioxidant profile and ameliorate cardiac injury in isoproterenol-induced MI.[237] In addition, Benfotiamine has been shown to be effective as an antioxidant and has been studied more in relationship to microvascular complications in diabetes.[238] However, the outcomes of using vitamins as exogenous antioxidants for the treatment of MI in clinic have been inconsistent over the past few decades.[239] Clinical trials on small clinical cohorts reported the treatment efficacy of combined treatment with antioxidant vitamins A, C, and E and beta-carotene in patients with recent acute MI.[239a] On the contrary, a meta-analysis of 50 randomized controlled trials with 294478 participants failed to confirm the cardioprotective effects of vitamin and antioxidant supplements.[239b] In the same meta-analysis, the authors also reported that the beneficial effects of vitamin B and E were only claimed in randomized controlled trials in which the trial supplements were supplied by the pharmaceutical industry.[239b] This finding raises a concern over other industry-supported antioxidant studies, such as a study claiming that Omega 3 protects the heart from myocardial I/R injury by reinforcing the antioxidant defense system.[240] A multi-target antioxidant strategy shall be practiced to achieve synergistic cardio-protection effects.[241]

N-Acetylcysteine, an antioxidant thiol-containing compound, has been widely used in clinical trials for the treatment of MI either alone[242] or in combination with other drugs[243] and showed protection of myocardial I/R injury. A recent small clinical trial on 112 randomized STEMI patients undergoing PCI intervention reported that early use of high-dose intravenous NAC in combination with low-dose intravenous nitroglycerin reduced infarct size in patients.[244] In addition, some studies demonstrated that post-MI treatment with NAC also attenuated heart failure progression in both animal models[245] and human patients.[246] Apart from patients undergoing PCI, NAC has also been tested in patients undergoing cardiac surgery in numerous clinical trials, unfortunately, two recent meta-analysis studies failed to confirm any improvement in clinical outcomes as reported in some trials.[247] While the reasons accounting for the inconsistency in clinical outcomes among trials are complex, apparently large multicentered randomized clinical trials on NAC in MI patients undergoing PCI or cardiac surgery are still needed to validate the therapeutic efficacy of NAC in limiting I/R injury and post MI cardiac dysfunction.

Neferine (Nef), a bisbenzylisoquinoline alkaloid isolated from green seed embryos of Nelumbo nucifera Gaertn has glycocalyx-protective effect through suppressing the production of mitochondrial ROS and decreasing oxidative damage.[248] Green tea extract (GTE) rich in epigallocatechin-3-gallate (EGCG) has antioxidation and iron chelation properties.[249] GTE effectively decreased plasma MDA and iron accumulation and MDA production in both the pancreas and liver in the mice overloaded with iron via a 3,5,5-trimethylhexanoyl-ferrocene supplemented (Fe) diet.[249]

Resveratrol found in various natural food products, is a type of natural phenol and has antioxidant and anti-inflammatory properties.[250] Resveratrol was found to be able to effectively scavenge $\cdot OH$, O_2^-, and metal-induced radicals and exhibited protective effects against lipid peroxidation in cell membranes and DNA damage caused by ROS.[251] Resveratrol enhanced mitochondrial ROS scavenge, attenuated oxidative injury, upregulated GSH-Px, and SOD2 expression in HUVECs through AMPK-PGC-1α-ERRα-Sirt3 signaling pathway.[252]

6. Nanomedicine for the Treatment of IHD and Risk Factors

Nanomedicine, with specific features such as prolonged drug circulation time and reduced side effects, is developing fast in

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this century.[3a,6c,253] Based on the pathophysiological changes of various types of diseases, different multifunctional nanomaterials can be used to realize the customization of drug carriers and contribute to the prevention and treatment of diseases.[6b,254] ROS are vital risk factors of diabetes, hypertension, and hypercholesterolemia. Therapeutic strategies targeting ROS during the development and progression of IHD have greatly improved the treatment outcomes.[255]

6.1. Nanomedicines for the Treatment of Diabetes, Hypertension, and Hypercholesterolemia

Nanomaterials such as liposome, polymer, and nanocrystal-based nanocarriers are the most commonly used FDA-approved nanotechnology-based drug delivery platforms for the treatment of diabetes, hypertension, and hypercholesterolemia.[256]

6.1.1. Nanomedicine for the Treatment of Diabetes

Three most significant contributions of nanotechnology to diabetes are:

i) The development of novel nano-sensors for the accurate and sensitive blood glucose measurement;[257]
ii) Glucose-responsive insulin delivery system which facilitates self-regulated delivery of insulin for a better glycemic control;[258]
iii) The development of nanomaterials for anti-diabetes or anti-diabetic drug delivery.[259]

Glucose is detectable in different body fluids such as interstitial fluid, saliva, sweat, and serum. Using glucose oxidase (GOD) as the recognition molecule to bind with glucose, a zinc oxide nanorod-based field-effect transistor has been reported to measure glucose concentration in interstitial fluid with relatively low sensitivity (1.6 mA mM^{-1} cm^{-2}).[260] Carbon nanotubes entrapping the enzymes in a chitosan matrix have been shown to have good sensitivity in detecting glucose in saliva, however, it has a very narrow detection range.[261] More recently, a glucose biosensor by combing nanotechnology to increase the electroactive area and third-generation sensor technology, a device with wide detection range (0.02–30 mM) has been developed.[262] Using extremely sensitive metal oxide nano-sensors, the continuous glucose monitoring from sweat is feasible through electronically induced reversible and localized pH change.[257b] A nanostructured polyaniline (PANI)/GOD on double-sided, screen-printed, flexible electrodes doped with Prussian blue has been successfully applied in continuous glucose monitoring in serum.[263]

Due to the drawbacks of conventional injectable insulin, nanomaterials carrying insulin for oral and pulmonary delivery have been developed.[264] In addition, anti-diabetic drugs, such as phytocompounds,[265] Metformin,[266] Dapagliflozin,[267] Empagliflozin,[268] Liraglutide,[269] Exenatide,[270] and Linagliptin[271] have been reported to use alginate,[272] chitosan,[272a,273] poly(lactic-*co*-glycolic acid) (PLGA),[274] dextran,[258,275] poly(alkyl cyanoacrylates) (PACA), lipid,[276] poly(lactic acid) (PLA),[277] micelle,[278] Niosome,[279] etc., as delivery systems. More strikingly, zinc oxide nanoparticle (ZnONP) itself has shown anti-diabetic effect.[280] ZnONPs decline the blood glucose levels (39.79%) to a similar level by insulin (48.60%). A poly(L-lysine) cationic polymer incorporating insulin delivery complexes system has been shown to respond to glucose.[281] These complexes are able to release insulin triggered by glucose in mice with type 1 diabetes (T1D). A microneedle-array patch containing pH-sensitive insulin-loaded nanoparticles together with GOD and CAT-loaded pH-insensitive nanoparticles has been constructed for transcutaneous insulin delivery.[282] The microneedles effectively reduced high blood glucose level for a prolonged period in mice with T1D. By modulating the degree of modification of acid-degradable or acetylated-dextran polymer, glucose-responsive nanoparticles made from dextran with a rapid and extended-release profile was developed.[258] A single subcutaneous injection of these nanoparticles provided 16 h of glycemic control in T1D mice. Although animal studies showed that nanoparticle-based anti-diabetic drug delivery can achieve glycemic control, efforts are needed to develop biocompatible, biodegradable, and hypoimmunological nanoparticles with prolonged responsive period (up to 1 week) for human subjects.

6.1.2. Nanomedicine for the Treatment of Hypertension

The most significant contributions of nanotechnology to hypertension are to develop nanomaterials for antihypertensive drug delivery. Various anti-hypertensive drugs with antioxidant properties, such as aliskiren,[283] felodipine,[284] amlodipine,[285] nifedipine,[286] lercanidipine,[287] and vasoactive intestinal peptide,[288] have been encapsulated into nanoparticles for antihypertensive drug delivery. Nanomaterials such as liposome,[287,288] PLGA,[284,285] chitosan, PLA,[283] and poly(ε-caprolactone (PCL)[286] have shown efficient and controlled delivery of these drugs for a better control of blood pressure in animal model of hypertension.[256] The major advantage of using nanomedicine is its ability to manage BP fluctuations by maintaining high and prolonged plasma drug concentrations with lower drug dosage. For instance, a poly(acrylic acid)-modified MoS_2 nanoparticle (PAA-MoS_2 NP)-based transdermal-drug delivery system (TDDS) was developed by He and co-authors.[289] In this study, the three-dimensional flower-like MoS_2 NPs were first synthesized, followed by the decoration of poly(acrylic acid). Then, the atenolol (ATE), a β1-adrenergic receptor-blocking agent used to treat hypertension, was loaded in the MoS_2 NPs through adsorption, leading to the formation of the final nanomedicine PAA-MoS_2 NPs. PAA serving as a biocompatible and hydrophilic polymer was used to control the hydrophilic and hydrophobic balance and stability of the nanomedicine. MoS_2 NPs can respond to near infrared NIR laser irradiation with excellent photothermal conversion performance, thereby leading to the controlled release of ATE and the promotion of the ATE permeation through the skin. Benefiting from various advantages of TDDS such as good patient compliance, reduced side effects, evitable first-pass effect, and prolonged action duration, this colloidally stable nanomedicine exhibits the drug-release percentage by 44.72 ± 1.04% and the enhanced skin penetration by a factor of 1.85.

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Other examples, such as liposome,[287–288] PLGA,[284–285] chitosan, PLA,[283] cyclodextrin,[290] and poly(ε-caprolactone) (PCL)[286] for efficient and controlled delivery of aliskiren,[283] felodipine,[284] amlodipine,[285] nifedipine,[286] vasoactive intestinal peptide,[287,288] captopril,[290] or lercanidipine,[287,288] have been shown to significantly improve drug adsorption and bioavailability and marked reduction in blood pressure. Overall, anti-hypertension nanocarriers protect the encapsulated drugs from rapid clearance in circulation and prolong the systemic availability of drugs at the desired concentration, which eventually regulates the BP.

6.1.3. Nanomedicine for the Treatment of Hypercholesterolemia

Hypercholesterolemia is regarded as one of the strongest risk factors for the progression of IHD. The most significant contributions of nanotechnology to hypercholesterolemia are to develop nanotechnology-based approaches for the treatment of hypercholesterolemia.[291] A variety of nanomaterials, such as PLGA,[292] chitosan,[293] cationic lipids,[294] and liposomes[295] have been used as carriers of Atorvastatin,[292a] Lovastatin,[294a] Simvastatin,[292b,294b] Pitavastatin,[296] Kudingcha,[293a] or proprotein convertase subtilisin/kexin 9 (PCSK9)[295] to lower cholesterol level.[291a] More uniquely, negatively charged nanoliposomes are able to prevent dyslipidemia in rabbits fed with a high-cholesterol diet.[297] These nanoparticulate formulations are ideal carriers to improve the bioavailability, prolong the drug release, and minimize the dose-dependent adverse effect. A representative nanomedicine combining both antioxidant and lipid-lowering activity was developed by Casals and co-workers.[298] In this study, the 5 nm CeO_2 nanozymes were encapsulated into a mesoporous silica shell. CeO_2 nanoparticles serving as nanozymes by mimicking the functions of various endogenous antioxidant enzymes (such as SOD, catalase, and peroxidase) have been widely reported to participate in various cross-reactions related to ROS and inflammation.[299] Moreover, CeO_2 nanoparticles can directly affect the cell metabolism of fatty acids, leading to the amelioration of hyperlipidemia.[300] The application of the biocompatible and safe mesoporous silica ($mSiO_2$) shell aims to maximize the nanomedicine stability in physiological microenvironment, maintain the ROS-scavenging capacity of CeO_2 nanozymes, and minimize the nanomedicine non-hepatic biodistribution. This nanomedicine exhibited a particle size of 53.8 ± 8.7 nm, and the CeO_2 core was 5.3 ± 0.8 nm. After five weeks of drug administration, this nanomedicine successfully reduced hyperlipidemia which was evidenced by the decreased level of the circulating triglyceride, palmitic acid, and LDL-cholesterol. An ezetimibe chitosan nanoparticle exhibiting enhanced antihyperlipidemic activity was developed and optimized by Ahmed and co-workers.[301] Ezetimibe is a medication used for the treatment of hypercholesterolemia, which can also combine with statin for a synergistic therapeutic effect. Ezetimibe works by inhibiting the intestinal absorption of cholesterol, thereby lowing the circulating cholesterol level. In this study, the natural cationic linear heteropolysaccharide chitosan exhibiting good biodegradability, bioadhesion, non-allergenicity, and non-toxicity was applied to encapsulate the anti-hypercholesterolemia drug ezetimibe for oral administration. Compared with the commercial anti-hypercholesterolemia drug choletimibe, this nanomedicine showed better therapeutic effect. The decreased lipid profile was showed by the following percent variations. Serum total cholesterol: 29.62%; triglycerides: 33.17%; LDL-C: 51.78%; VLDL-C: 33.19%; atherogenic index: 43.16%; total lipids: 29.07%.

6.2. Nanomedicine for the Treatment of IHD

IHD is a common dangerous component of CVDs with high morbidity and mortality including stable angina, unstable angina, MI, and sudden cardiac death. Due to the development of atherosclerosis, blood flow in coronary artery is partially obstructed, leading to the lack of blood supply of heart muscle cells. Therefore, heart muscle cells may be damaged or killed resulting from the oxygen limitation. Plaque formation in lining of coronary artery mediates the progress and outcome of pathology in atherosclerosis, during which the transformation of macrophages into foam cells and the accumulation of fatty lipids, calcium, and cellular derris within lesion site occurred. Besides dyslipidemia, pathogenesis such as inflammation, oxidation, and thrombosis participate fundamentally in atherogenesis and ischemic events.[302] In this section, several aspects of nanomedicines for IHD treatment are summarized, including: 1) representative IHD treatment strategies, 2) EC determinants for targeted delivery of nanomedicine, 3) modification of nanomedicine for enhanced therapeutic effect, and 4) nanomedicine geometries affect the therapeutic ability.

6.2.1. Representative IHD Treatment Strategies

Researches focusing on the exploration of therapeutic effect of various nanomedicine on endothelium and cardiomyocyte are abundant and diverse. Targeting antioxidants, anti-inflammatory, and antithrombotic nanomedicine agents to ECs yielded very promising results in preclinical studies.

1) Antioxidant Nanomedicine.

SOD and Catalase: Oxidative stress has been considered and evidenced as deleterious factor for the development of IHD. Nanomedicines aiming at endothelia ROS detoxification can be achieved by involving antioxidants such as SOD and catalase protein conjugates. SOD, a metal-containing enzyme, converts superoxide into H_2O_2. Catalase, a tetrameric enzyme, decomposes H_2O_2 into H_2O and O_2. The application of SOD and catalase for antioxidant interventions could alleviate various pathological mechanisms. However, their therapeutic performance as free drug without modification has been largely restricted by fast elimination, easy inactivity, and inadequate delivery to target sites in vivo. Therefore, diverse modifications including conjugating with PEG or other functional ligands, encapsulation into nanocarriers such as liposomes and ferritin cages, have been widely explored. Some of these enzyme derivatives or enzyme nanomedicines showed significantly enhanced catalytic effect. For example, SOD after lecithinization showed affinity to various types of cells including endothelium, and

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Table 5. Representative nanomedicine for the treatment of ROS in vascular disease.

Disease	Structure of Nanomedicine	Carrier/ Nanomaterial	Cargo	Materials for Decoration	Application and Therapeutic effect	Properties	Ref.
Atherosclerosis	Sim@PMPB NC	Porous manganese-substituted Prussian blue nanocubes	Simvastatin	–	ROS scavenging, inflammation mitigation, foam cell formation inhibition	Mn-based MRI imaging	[308]
Atherosclerosis	AMC	Polymeric micelle, PEG–PPS	Andrographolide	–	Anti-inflammation and oxidative stress	ROS-responsive	[316]
Myocardial ischemia-reperfusion injury	MCTD-NPs	PLGA	Resveratrol	Ischemic myocardium targeted peptide, SS-31	Eliminate mitochondrial ROS, reduce infarct size in MI/RI	pH-Responsive, ischemic myocardium targeting, mitochondria targeting	[313]
Myocardial infarction	MSC-GO	Graphene oxide flakes	Extracellular matrix protein	–	Improve the engraftment and therapeutic efficacy of mesenchymal stem cell for cardiac tissue repair	Prolong the survive time of mesenchymal stem cell	[317]
Atherosclerosis	MM-AT-NPs	Oxidation-sensitive chitosan oligosaccharide	Atorvastatin	Macrophage membrane	Combination of pharmacotherapy and inflammatory cytokines sequestration, the macrophage membrane sequesters proinflammatory cytokines to suppress local inflammation	ROS-responsive, macrophage membrane does not help avoid the clearance of nanoparticles	[315]
Myocardial infarction	PEG@luminol-Ce6	PEG amphiphilic copolymers	–	Ce6, luminol	Diagnostic and therapeutic targeting of tissue that is undergoing I/R injury	ROS-responsive, fluorescence imaging	[318]
Myocardial I/R injury	PVAX, HPOX	Hydroxybenzyl alcohol, vanillyl alcohol	–	Peroxalate ester linkages	Improvement in cardiac output and fraction shortening, decrease INF-α, MCP-1 mRNA level	H_2O_2-responsive	[319]
Myocardial I/R injury	PEG-*b*-PPS-Rg3	PEG, PPS	Ginsenoside Rg3	–	Improve the cardiac function and reduce the infarct size	ROS-responsive	[320]
Myocardial ischemia	BN–PEG–NLC	Lipids	Baicalin	PEG-SA	Antioxidant effect and free radical scavenging activity	–	[321]
Myocardial infarction	MMP-Sch B SLNs	Lipids	Schisandrin B	PEG, matrix metalloproteinase-sensitive peptide	Heart-targeted drug delivery, enhance drug penetration, reduce infarction size	Matrix metalloproteinase-sensitive	[322]
Myocardial I/R injury	Exenatide/ PLL–PEG–PLL	PLL–PEG–PLL	Exenatide	–	Reduce the myocardial damage, promote the myocardial function	–	[323]
Coronary heart disease	$[Cu(ox)(bib)]_n$	Cu(II) coordination polymer	–	–	Promote the cardiac function, antioxidative effect	–	[324]

exhibited protective effects in MI, tumor, and other pathological conditions.[303] SOD and catalase conjugating to specific antibodies (such as anti-PECAM antibody) may lead to an improved EC targeting ability.[304] In addition, loading SOD or catalase in different functional nanocarriers may also endow the drug-loaded nanomedicine with different properties.[305] Nanocarriers such as liposomes, magnetic nanoparticles, ferritin cages, and polymeric nanoparticles have been investigated for vascular delivery of antioxidants.[306] For instance, Muzykantov and co-workers reported a PEG–liposome-based nanomedicine in which a SOD/catalase mimetic drug (EUK-134) was loaded.[307] For targeting endothelium, the antibody to PECAM-1 was further coated on liposome carriers. The modified nanomedicine can bind to ECs, inhibit the occurrence of cytokine-induced inflammation, and significantly alleviate the excessive ROS-related pathological conditions.

Antioxidative Drugs: Nanomedicine and nanotechnology integrating antioxidative therapy against atherosclerosis for IHD treatment may be a good choice. Many drugs such as simvastatin, resveratrol, and atorvastatin have been reported for the treatment of ROS in vascular diseases (**Table 5**). For example, a nanomedicine consisting of a biomimetic Prussian blue analog, porous manganese-substituted Prussian blue nanocubes (PMPB-NC), and a clinical antioxidative drug simvastatin was designed to

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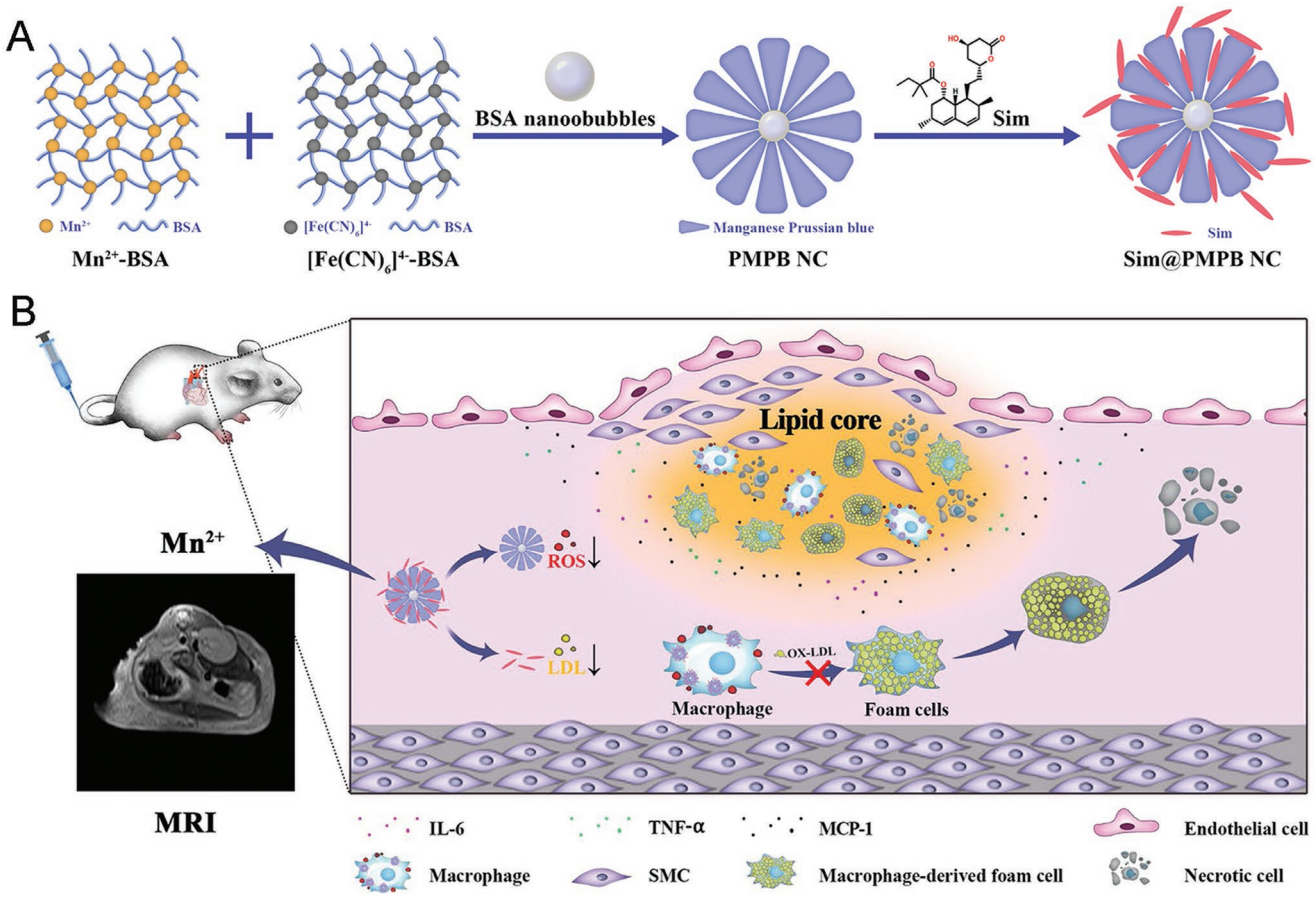

Figure 8. A) The fabrication process of Sim@PMPB NC. B) Schematic illustration of how the SiM@PMBP NC achieved the relief of atherosclerosis. A,B) Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0).[308] Copyright 2021, The Authors, published by Springer Nature.

scavenge ROS and mitigate local inflammation (**Figure 8**A).[308] The PMPB-NC served as both enzyme-like catalyst for ROS scavenging and carrier of simvastatin. The combination of PMPB-NC and simvastatin potentiated the therapeutic outcomes: the reduced ROS level, the secretion of proinflammatory cytokines, the accumulation of collagen, the thickness of fibrous cap, and the birth of foam cells, consequently leading to the depletion of plaques and relief of atherosclerosis (Figure 8B). The excessive ROS generation resulted from the I/R injury after MI can greatly increase the mortality of patients.[309] Efficient distribution of antioxidant drugs such as resveratrol and Ginsenoside Rg3 to ischemic cardiomyocytes may reduce the cardiovascular injury after reperfusion and provide a good prognosis.[310] Mitochondria is the main source of cellular ROS which may subsequently induce oxidative stress and cell apoptosis.[311] In addition, excessive mitochondrial ROS can also cause mitochondrial dysfunction, which may further increase ROS production.[312] To achieve the targeted drug delivery and eliminate cardiac-generated ROS, a dual-shell polymeric nanoplatform consisting of ischemic myocardium targeting peptide STSMLKA, mitochondria targeting ligand SS-31, and ROS scavenger resveratrol was developed by Zhou's group (**Figure 9**A).[313] Due to the existence of the ischemic myocardium targeting peptide STSMLKA, this nanoparticle exhibited enhanced accumulation ability in the ischemic myocardium. Then, the positively charged SS-31 helped the escape of the nanoparticles from being endocytosed by lysosomes and led to the nanoparticle accumulation in mitochondria. Finally, the resveratrol was released and showed great ROS elimination efficacy (Figure 9B). Compared with free drugs, the nanoparticles exhibited excellent ischemia cardiomyocyte targeted resveratrol delivery, leading to the reduction of the infarct size, inhibition of the apoptosis of cardiomyocytes, and the protection of the cardiac function. By taking advantage of the elevated ROS level in ischemic cardiovascular tissues, several ROS-responsive nanoplatforms were developed to control the specific payload release and to monitor the damaged tissues in real time.[314] To specifically deliver drugs to the local inflammation areas of atherosclerosis where ROS are overproduced, a biomimetic nanoparticle formula derived from the macrophage membrane was reported by Wang's group.[315] Based on the unique property of reduced reticuloendothelial system clearance and enhanced drug delivery ability, a macrophage membrane was applied to coat a ROS-responsive nanoparticle in which atorvastatin was included for atherosclerosis treatment (Figure 9C). The biomimetic nanoparticles not only improved the targeted drug delivery to the lesion site but also scavenged the proinflammatory factors, which play key roles in atherosclerosis formation, around the lesion microenvironment due to the existence of the macrophage membrane.

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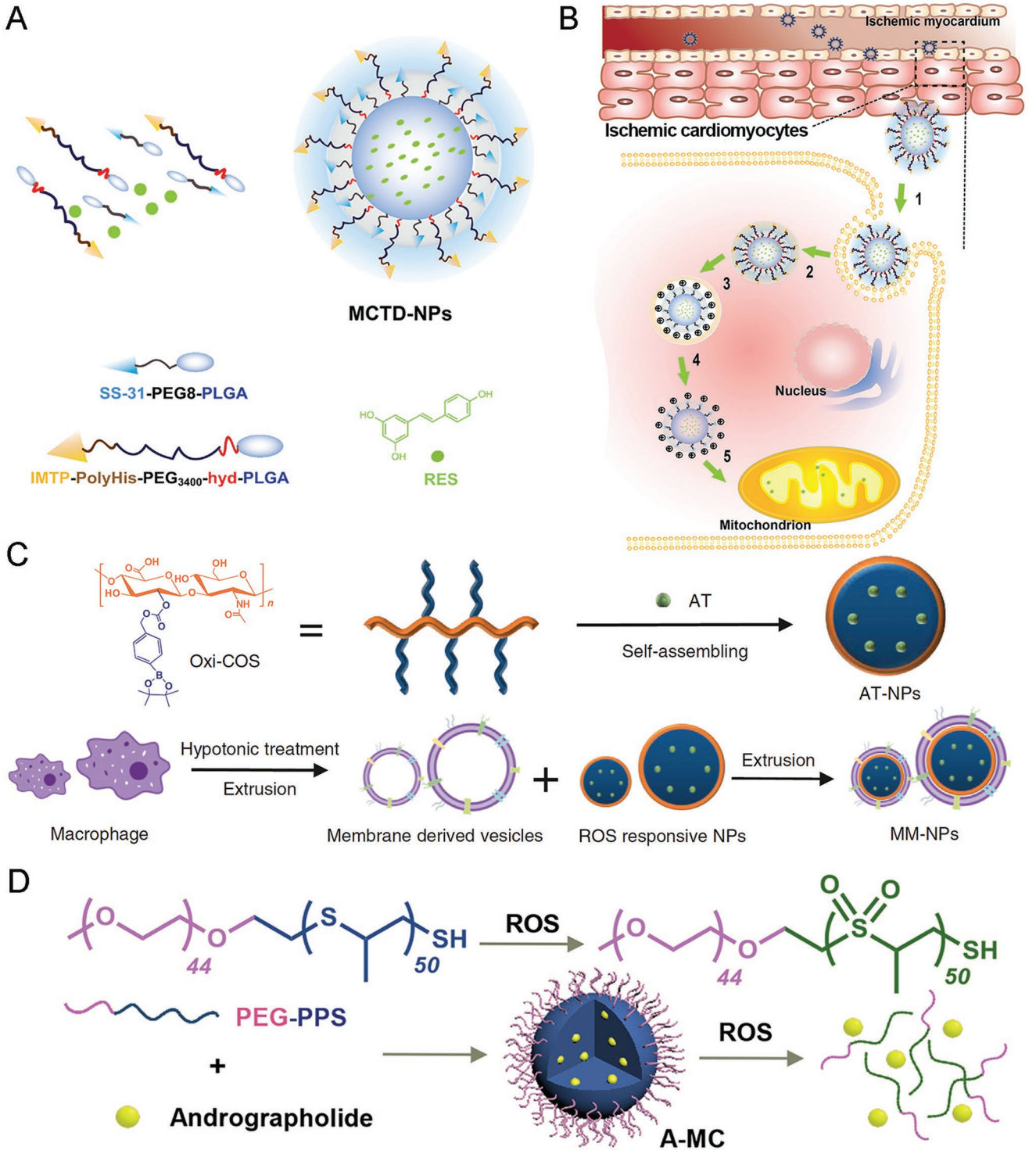

Figure 9. A) The contents of the MCTD-NPs nanomedicine. B) Schematic illustration of the nanomedicine intracellular functions. 1) Ischemic myocardium targeting. 2) Endocytosis. 3) pH response in lysosome. 4) Lysosomal escape. 5) Mitochondrial targeting. A,B) Reproduced with permission.[313] Copyright 2019, Elsevier. C) The fabrication process of the MM-NPs nanomedicine. Reproduced with permission.[315] Copyright 2020, Springer Nature. D) The fabrication and rupture processes of the ROS-responsive nanomedicine. Reproduced with permission.[325] Copyright 2018, Elsevier.

When the biomimetic nanoparticles accumulated at the targeted tissues, atorvastatin could be released in response to the pathologically overproduced ROS, thereby leading to a satisfying treatment effect.

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ROS-Responsive Polymers: A smart drug delivery system focusing on ROS depletion in the pathogenesis of atherosclerosis was reported by Wu and co-workers.[316] In this study, a ROS-consuming block copolymer poly(ethylene glycol) and poly(propylene sulfide) (PEG–PPS) loaded with andrographolide was developed (Figure 9D). Because of the presence of the PPS, this copolymer can not only consume ROS to produce sulfoxides or sulfones, but also cause quick rupture of the micelle to release the encapsulated andrographolide. Andrographolide is a labdane diterpenoid with excellent anti-inflammation ability. Therefore, the andrographolide-loaded PEG–PPS exhibited a combinational antioxidant effect, alleviating oxidative stress and achieving a great therapeutic effect against atherosclerosis.

Treatments using nanomedicine can help define the mechanisms of pathology. For instance, in order to analyze the function of different enzymes, anti-PECAM/catalase conjugate and anti-PECAM/SOD conjugate were prepared and used for the treatment of mice with lung injury or hypertension. For lung injury protection test, only anti-PECAM/catalase conjugate exhibited positive therapeutic effect. Alveolar edema was reduced and arterial oxygen decline was attenuated. These results help define the key role of H_2O_2 in tissue damage. For anti-hypertension test, only anti-PECAM/SOD conjugate can prevent the tetrahydrobiopterin oxidation and normalize the vessel vasoreactivity. These results affirm the vasoconstriction effects of superoxide. Moreover, because catalase can negate the effect of SOD, the vasodilation effect of H_2O_2 was then unveiled.[304,326] Furthermore, researches have evidenced that NOX is the major source of ROS in ECs resulting from the elevated pathological mediators in vascular disease conditions.[327] Under the stimulation of various inflammatory cytokines, NOX fluxes superoxide anion into the ensuing endosomes of ECs. Surplus endosomal superoxide may further induce proinflammation activation. Therefore, some efforts have been made to test the corresponding pathological pathway. A PLVAP antibody-decorated and SOD-loaded nanomedicine was designed.[328] Because of the existence of PLVAP ligand, this nanomedicine realized targeted delivery of SOD to caveolae-derived endosome, leading to the inhibition of pulmonary inflammation and some proinflammatory cytokines. These results indicate that targeting SOD nanomedicine to these vesicles offers very specific and potent antioxidant effects.

2) Anti-Inflammatory Nanomedicine.

In addition to antioxidants, the approach targeting anti-inflammatory nanomedicine agents to ECs yielded promising results. For instance, dexamethasone as a classical long-lasting glucocorticoid for anti-inflammation action can inhibit the inflammatory cascade efficiently, reducing the expression of both proinflammatory cytokines (such as IL-1, IL-6, and TNF-α) and CAM (such as ICAM-1).[329] However, there is no natural affinity of dexamethasone to endothelium. Only a small fraction of dose can act at target sites, which may lead to various side effects such as hypertension, osteoporosis, and hyperglycemia when used for the treatment of vascular diseases. To solve this problem, a dexamethasone nanomedicine decorated with the endothelium targeting antibody was designed by Eckmann and co-workers.[330] Lysozyme dextran nanogel (NG) was chosen to be the nanocarrier with rapid cargo uptake and release ability and low cytotoxicity. The antibody of ICAM-1 was further conjugated on the NG in which the dexamethasone was loaded. As a result, the assembled nanomedicine Ab–NG–dexamethasone can specifically accumulate in lesion site and minimize the inflammatory response. Similarly, the liposome-based nanomedicine loaded with dexamethasone could also alleviate the inflammation of lung, kidney, skin, eye, and arthritis with reduced side effects.[331] TM with direct and indirect anti-inflammation effect has also been reported to be involved in endothelial treatment. Compared with free soluble TM, fusing scFv antibody which can bind to PECAM on endothelium with TM (scFv/TM) can greatly improve the therapeutic effect of TM due to the newly added targeting ability.[332] Surprisingly, another scFv/TM targeting ICAM achieved better therapeutic effect, which may result from the coinstantaneous existence of ICAM and its adjacent TM receptor (EPCR).[333] Moreover, a co-targeting formulation for both TM (scFv/TM) and PECAM (scFv/PECAM) epitopes achieved the maximal effect.[334] This collaborative enhancement of the juxtapositional endothelial determinations induced a fivefold increase of the downstream proteins and a 40% decrease of the inflammatory markers. Other endothelial determinations such as VCAM was reported to enhance the targeting ability of liposome in which the anti-inflammatory drug prostaglandin, PGE2, was loaded for the treatment of atherosclerosis. This nanomedicine reversed the atherosclerotic lesions and prolonged the overall survival time.[335]

3) Antithrombotic Nanomedicine.

The natural antithrombotic mechanisms of ECs in pathological conditions are usually downregulated.[336] Therefore, pathologically altered vessels tend to thrombosis, which may contribute to IHD. In this scenario, recombinant antithrombotic protein was considered a good choice to solve this problem by anchoring them on the endothelial surface. Representative antithrombotic proteins including TM and plasminogen activating agents (tPA/uPA) have been explored and tested.[337] In the beginning, researchers tried to link the anticoagulants to endothelial determinant E-selectin antibody.[338] However, the anchored protein can be easily endocytosed from the vascular lumen. Subsequently, antibodies to PECAM and ICAM which cannot be endocytosed by ECs were used for this kind of conjugation.[339] This strategy helped dissolve the thrombus clots successfully. Furthermore, recombinant single-chain antigen-binding fragments (scFv) were reported to conjugate with uPA.[340] This newly fused nanomedicine (scFv/uPA) could accumulate in pulmonary lumen for several hours and induce the lysis of emboli in a mouse model. The antithrombotic protein TM suffers from suppression in many vascular pathologies.[341] A replacement therapy using the PECAM-targeted nanomedicine scFv/TM was reported.[342] This nanomedicine could bind on the endothelial surface because of the existence of PECAM EC determination, and attenuate the process of thrombosis and tissue damage, with limited side effect. These designs help open a new field in which on-demand endothelium-targeted thromboprophylaxis can be realized.[343]

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4) Other Therapeutic Strategies.

Cellular cardiomyoplasty using progenitor or stem cell-derived cells is regarded as promising therapeutics for the treatment of IHD and heart failure.[344] However, it is facing the challenge of poor survival due to the overproduced ROS at the infarcted region after the cardiovascular reperfusion.[345] A high level of ROS has been shown to prevent the mesenchymal stem cells from adhering to the heart tissue extracellular matrices and to induce the mesenchymal stem cell anoikis.[345] To address this issue, a graphene oxide flake modified with extracellular matrix proteins was developed for cell transplantation.[317] The flake significantly decreased ROS-mediated cell death and enhanced paracrine secretion of mesenchymal stem cells to promote cardiac tissue repair and function restoration after I/R. This study demonstrates that preventing the implanted cells from being attacked by ROS in myocardium after I/R can effectively ameliorate the engraftment and therapeutic efficacy.

6.2.2. EC Determinants for Targeted Delivery of Nanomedicine

There are various EC adhesion molecules expressed in the sites of vascular pathology.[346] They are natural and attractive class of cell determinants for targeted nanomedicine delivery to the endothelium in vasculature of interest. Based on the properties and functions of different EC determinants, corresponding ligands can be designed and decorated on nanomedicine to realize the recognition and active targeting of nanomedicine to ECs.[347] Following we list some representative EC determinants with their properties. 1) ACE.[348] A luminal transmembrane endothelial glycoprotein, enriched in lung capillaries, regulate blood pressure, convert Ang I into Ang II. 2) Thrombomodulin (TM).[349] A luminal transmembrane endothelial glycoprotein, convert thrombin into antithrombotic and anti-inflammatory enzyme. 3) ICAM-1 and platelet-EC adhesion molecule 1 (PECAM-1).[350] Stable and inducible adhesion molecules, offer flexibility for drug endocytosis. 4) VCAM-1 and selectins.[351] Inducible cell adhesion molecule, absent on vascular lumen when healthy, exposed when ECs are activated pathologically. 5) Caveolae.[352] Flask-shaped invaginations, exist in plasmalemma, related to the intracellular trafficking and signaling of ECs, types include amino peptidase P (APP) and Plasmalemma Vesicle Associated Protein (PLVAP). 6) APN and integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_5\beta_1$.[353] Angiogenesis and tumor-related determinants, expressed on vasculature that undergoes angiogenesis in various tumors. A wide range of CAM (such as PECAM, VCAM-1, PLVAP, and ICAM)-decorated nanomedicines loaded with various antioxidant including SOD for endothelia-targeted treatment have been reported and summarized.[354]

6.2.3. Modification of Nanomedicine for Enhanced Therapeutic Effect

Active targeting is a typical method for nanomedicine to achieve precise drug delivery. Ligand molecules offering affinity to vascular cells such as antibodies and their derivatives have been explored and reported to conjugate to nanomedicine to enhance the targeting ability. Representative ligands include peptides, aptamers, hormones, nucleic acids, nutrients, single-chain antigen-binding fragments, etc.[343,352,355] Through these modifications, nanomedicine can bind to multiple endothelia cell determinants or epitopes via versatile mechanisms, realizing the recognition between nanomedicine and the targeted endothelia cells.

A ferritin-based nanomedicine for targeted delivery of therapeutic enzymatic SOD to sub-cellular compartment endosomes was designed and reported by Muzykantov's group.[354b] This study aimed to deliver the SOD to endothelial caveolae-derived endosomes, in which superoxide accumulated. To target the small entry aperture of caveolae, caveolaer PLVAP antibodies were decorated on the SOD-loaded nanomedicine. This nanomedicine showed efficient cellular internalization, followed by the transportation of SOD to sub-cellular endosomes, therefore, leading to an enhanced ROS scavenging effect.

In order to realize the targeted endothelial delivery of antioxidant enzymes, magnetically responsive nanomedicine was developed.[356] After precipitation of calcium oleate in the magnetite-based ferrofluid, the magnetic carrier formed, followed by the loading of model antioxidant enzymes SOD and catalase. Under the guidance of high gradient magnetic field, the magnetic nanomedicine realized the targeted delivery of therapeutic enzymes to ECs. Moreover, the magnetic carrier can protect the enzymes form proteolysis and early leakage in plasma.

Prolong the action time of drug through nanomedicine modification. SOD is a classical and primary internal antioxidant, playing a key role in controlling endogenous oxidative stress. However, endogenous SOD activity decreased over time within the lesion site, leading to the massive accumulation of ROS and the loss of redox balance, which can subsequently induce secondary oxidative damage. Exogenous SOD has been investigated to scavenge ROS in vivo. Unluckily, the half-life of native SOD is extremely short (4–8 min), and its concentration in the lesion site is inadequate due to the lack of targeted affinity. To solve this problem, a SOD-loaded nanomedicine was designed by Sonia and co-workers.[357] Two ligands polybutadiene (PBD) and poly(propylene oxide) (PPO) were first decorated on poly(ethylene glycol) (PEG) polymer respectively. Then, the newly synthesized copolymers PEG–PBD and PEG–PPO–PEG were used to fabricate the porous polymersomes, followed by the loading of SOD within the aqueous interior. Interestingly, these porous polymersomes are permeable to molecules less than 5 kDa. Molecules bigger than 10 kDa cannot penetrate the porous polymersomes. In this context, the porous polymersomes are permeable for ROS but not proteases, providing binding and uptake of the nanomedicine into endosomal-lysosomal vesicles, where the ROS-degrading enzymes exert their function, for a prolonged time due to the protection of SOD against proteases. Similarly, another antioxidant catalase decorated with PEG was synthesized by Muzykantov's group.[358] The resultant PEG–catalase was further encapsulated by a PEG–PLA polymer carrier (PNC). After such modification, this catalase-loaded nanomedicine exhibited excellent protease degradation resistance ability. This researcher also used another copolymer PEG–PLGA to encapsulate catalase and peroxide.[359] Subsequently,

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targeting endothelia cells ligands anti-PECAM/SA and IgG/SA were decorated on the copolymer. This nanomedicine successfully protected the loaded catalase from external proteolysis and exerted remarkable enzymatic activity. Decoration of the endothelia targeting ligands helped actively delivery of the encapsulated catalase to ECs.

6.2.4. Nanomedicine Geometries Affect the Therapeutic Ability

In addition to modification and decoration, the geometries of nanomedicine also affect its therapeutic ability. Nanomedicine geometry is related to the circulation, tissue penetration, interactions within cells, and pharmacokinetics.[360] Geometry parameters such as size, shape, and plasticity can easily modulate the function of nanomedicine. Ultrasmall nanomedicine less than 10 nm can easily undergo rapid renal clearance with reduced circulation time.[361] Typically, spherical nanomedicine within tens of nanometers can be administrated via vascular, muscular, or dermal injection. Nanomedicine with a size of 100–200 nm usually avoids the entrapment of liver disse space and splenic sinusoid, leading to a prolonged blood circulation time and high blood concentration.[362] While nanomedicines larger than a few hundred nanometers require airway or vascular injection.[363] Meanwhile, large size nanomedicines exhibit reduced opportunity to access to targets due to the enhanced blood dragging force.[307,364]

Nanomedicine shape is another important geometry parameter. Compared with nanomedicines with spherical shape, elongated nanomedicines possess enhanced specificity to endothelia cells.[365] For example, Mitragotri and co-workers evidenced that rod-shaped nanomedicine exhibited high specific accumulation at the target using a microfluidic system in vitro, compared with the spherical counterparts. They concluded the potential mechanism: high avidity and specificity result from the balance between polyvalent interactions (increase binding) and the shear-related detachment/entropic loss (decrease binding).[366] Similarly, a long and flexible polymeric filomicelles nanomedicine was designed and reported by Muzykantov and co-workers.[367] The filomicelles were decorated with antibodies used for endothelial surface molecule recognition for targeted delivery. After modification, the nanomedicine exhibited high specificity to EC with prolonged circulation time and strong structural integrity and dynamic flexibility. In addition to the filamentous nanomedicine, a disk-shaped nanomedicine targeting endothelia ICAM-1 was reported to own long half-life in circulation and high specificity to vascular beds.[365] Generally, nanomedicine with unusual shapes such as discoid, ellipsoid, and filamentous show longer circulation compared to spherical counterparts, except for the worm-like filomicelles with an extreme elongation.[354d]

For lipid or polymeric nanomedicines with changeable shape and size, their plasticity has an obvious impact on therapeutic effect. In general, nanomedicine with good plasticity is relative to prolonged blood circulation.[363a] Immune cells such as phagocytic cells and macrophages prefer to uptake rigid nanomedicines rather than soft ones.[363a,368] However, this phenomenon also occurred in ECs.[368b,369] This may greatly impede the endocytosis of endothelia-targeted nanomedicine. Therefore, rational and smart shape design could endow nanomedicine with better therapeutic performance.

7. Challenges and Future Directions of Nanomedicines for the Treatment of IHD

IHD is one of the leading causes of disability among the large percentage of the world population. It imposes a great burden on every country and its people. Despite the humongous sociomedical impact and wide spread, nanomedicine targeting IHD received relatively modest investments compared to oncological, immunological, or infectious diseases. Apart from the financial constraints, the following scientific concerns should also be considered.

1) Tolerance.[306] Compared with oncological or other conditions, patients with CVDs have much lower tolerance of side effects. Adverse drug reactions may greatly affect the heart physiological conditions, leading to the dysfunction or even strike of heart.
2) Side effects.[370] Sometimes, due to the unintended functions of the decorated ligands or targeting molecules on the nanomedicine, effects which are not beneficial or even benign can be obtained.[343] Potential organs/tissues that can interact with drug delivery systems include liver, spleen, kidneys, lungs, thymus, bone marrow, blood, central nervous system, etc. Therefore, the benefit/risk ratio must be discreetly evaluated when designing or preparing a nanomedicine.[306]
3) Disease prevention. Compared with oncology, immunology, or infectious diseases, the tertiary prevention of CVDs exerts better effects. Risk factors such as diabetes, hypertension, hypercholesterolemia can be controlled by regular medications (Tables 1–3).
4) Immunogenicity.[371] Cellular host defense to protect the body from external and internal invasion can recognize and regard the engineered sub-micron nanomedicine as a threat, and react accordingly. The complement system/resident intravascular leukocytes in innate immunity, and cellular/humoral immunity response in adaptive immunity can be activated by nanomedicines, leading to the impediment of their therapeutic ability.
5) The route of administration.[372] Currently designed nanomedicines are mostly used through intravascular infusion. Therefore, the need for repetitive injections in ambulatory and perennial home care limits the practicality of nanomedicine.

The above limitations and challenges are representative impediments of the nanomedicine therapeutic action. These considerations also illustrate the paramount importance of the safety requirements in cardiovascular nanomedicine, which need to be balanced before designing a nanomedicine.

Although substantial progress has been made in nanomedicine to improve the solubility, release, and absorption rate of poorly soluble drugs, there are still several issues that need to be solved before it can be fully translated into clinic.

1) Synergy. Currently, most clinical studies about ROS and hypertension, diabetes, and hypercholesterolemia are limited to

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biomarkers of systemic oxidative stress. Despite being closely correlated to these pathological conditions, no ROS modulator or carried by nanoparticles as a sole therapy has been successfully translated from bench to bedside to date, indicating these pathological conditions are probably the causes of increased ROS. Thus, combing medications or nutraceuticals using nanocarriers which are targeting different antioxidant pathways may give rise to additive or synergistic protective effects to achieve better cardio-protection.

2) Delivery mode. Currently, most nanoparticles are given through periphery circulation and are expected to home at injury site. This potentially reduces therapeutic efficacy as only a small portion of nanoparticles exert function. Also, the function of ROS is "double-edged sword" and is involved in both physiological and pathological conditions. Strategies on how to improve tissue or organ-specific homing of nanoparticles are needed.
3) Biosafety. Nanoparticles are made of either biological samples or metal and synthetic biomaterials. The former includes cells-derived cell membrane and nanovesicle. The source of cells shall be pathogen-free and ethic-free. The latter may be toxic to specific tissues or cells. Although nanoparticles have been shown to be safe in rodent studies, systematic studies to address biosafety of nanoparticles have not been performed in clinically relevant large animal models.
4) Translation. Most applications of nanomedicines are tested in rodents. Although therapeutic efficacies are evident in various disease models, limited studies were performed in clinically relevant large animal disease models for biosafety and efficacy assessment.
5) Quality control. Most nanoparticles are home-made which may cause big variations from different labs. Good manufacturing practice shall be applied to ensure nanomedicine products to be consistently produced with quality standards.
6) Large-scale manufacturing. Industrial scale-up of nanomedicine is required to be clinically relevant. Although nanomedicine preparations in the laboratory are well documented, there is limited information on the scale-up technologies of nanomedicines. Detailed experimental protocols on a large-scale nanomedicine production are urgently needed.

This review focuses on introducing the ROS scavenging nanomedicine for the treatment of IHD. Moreover, ROS play key roles in many other pathologies such as acute lung injury,[373] hyperoxia,[374] Parkinson's disease,[375] ischemia,[376] brain transient ischemia,[377] radiation injury,[305,378] inflammation,[305,379] thrombosis,[380] and cancer.[381] Therefore, this review should be a stepstone for the development and exploration of ROS scavenging nanomedicine to improve the therapeutic outcomes of not only CVDs, but also respiratory, neurological, oncological, inflammatory, and other pathological conditions.

8. Conclusions

The rapid development of nanotechnology as a therapeutic tool will have a great impact on the treatment of IHD such as diabetes, hypertension, hypercholesterolemia, and atherosclerosis. This may change the concept and the way in which we treat patients. Although the potential benefits from nanomedicine are high, a number of issues as detailed in this review shall be solved before nanomedicines can be fully translated into clinic. Appropriate guidelines and policies to assess its risk and treatment effects shall be established to warrant it unique role in the treatment of IHD.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] M. A. Khan, M. J. Hashim, H. Mustafa, M. Y. Baniyas, S. Al Suwaidi, R. AlKatheeri, F. M. K. Alblooshi, M. Almatrooshi, M. E. H. Alzaabi, R. S. Al Darmaki, S. Lootah, *Cureus* **2020**, *12*, e9349.
[2] L. Milkovic, A. Cipak Gasparovic, M. Cindric, P. A. Mouthuy, N. Zarkovic, *Cells* **2019**, *8*, 793.
[3] a) M. Qiu, A. Singh, D. Wang, J. L. Qu, M. Swihart, H. Zhang, P. N. Prasad, *Nano Today* **2019**, *25*, 135; b) M. E. Lobatto, V. Fuster, Z. A. Fayad, W. J. M. Mulder, *Nat. Rev. Drug Discovery* **2011**, *10*, 835; c) E. K. H. Chow, D. Ho, *Sci. Transl. Med.* **2013**, *5*, 216rv4.
[4] a) J. Majumder, O. Taratula, T. Minko, *Adv. Drug Delivery Rev.* **2019**, *144*, 57; b) S. Su, P. M. Kang, *Pharmaceutics* **2020**, *12*, 837.
[5] W. Sang, Z. Zhang, Y. Dai, X. Chen, *Chem. Soc. Rev.* **2019**, *48*, 3771.
[6] a) C. K. W. Chan, L. Zhang, C. K. Cheng, H. R. Yang, Y. Huang, X. Y. Tian, C. H. J. Choi, *Small* **2018**, *14*, 1702793; b) Z. Zhang, W. Sang, L. S. Xie, Y. L. Dai, *Coord. Chem. Rev.* **2019**, *399*, 213022; c) Z. Zhang, L. Xie, Y. Ju, Y. Dai, *Small* **2021**, *17*, e2100314.

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[7] R. Li, Z. Jia, M. A. Trush, *React. Oxygen Species* **2016**, *1*, 9.
[8] J. D. Lambeth, A. S. Neish, *Annu. Rev. Pathol.: Mech. Dis.* **2014**, *9*, 119.
[9] M. P. Murphy, *Biochem. J.* **2009**, *417*, 1.
[10] J. George, A. Struthers, *Ther. Clin. Risk Manage.* **2009**, *5*, 799.
[11] J. L. Zweier, C. A. Chen, L. J. Druhan, *Antioxid. Redox Signaling* **2011**, *14*, 1769.
[12] C. Lismont, M. Nordgren, P. P. Van Veldhoven, M. Fransen, *Front. Cell Dev. Biol.* **2015**, *3*, 35.
[13] S. Y. Kim, T. B. Kim, K. A. Moon, T. J. Kim, D. Shin, Y. S. Cho, H. B. Moon, K. Y. Lee, *Exp. Mol. Med.* **2008**, *40*, 461.
[14] W. L. Smith, D. L. DeWitt, R. M. Garavito, *Annu. Rev. Biochem.* **2000**, *69*, 145.
[15] T. Nakazato, M. Sagawa, K. Yamato, M. Xian, T. Yamamoto, M. Suematsu, Y. Ikeda, M. Kizaki, *Clin. Cancer Res.* **2007**, *13*, 5436.
[16] D. Maggiorani, N. Manzella, D. E. Edmondson, A. Mattevi, A. Parini, C. Binda, J. Mialet-Perez, *Oxid. Med. Cell. Longevity* **2017**, *2017*, 3017947.
[17] a) K. Bedard, K. H. Krause, *Physiol. Rev.* **2007**, *87*, 245; b) F. Magnani, S. Nenci, E. Millana Fananas, M. Ceccon, E. Romero, M. W. Fraaije, A. Mattevi, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 6764.
[18] D. I. Brown, K. K. Griendling, *Free Radicals Biol. Med.* **2009**, *47*, 1239.
[19] B. Lassegue, A. San Martin, K. K. Griendling, *Circ. Res.* **2012**, *110*, 1364.
[20] Y. Nisimoto, B. A. Diebold, D. Cosentino-Gomes, J. D. Lambeth, *Biochemistry* **2014**, *53*, 5111.
[21] A. Yoshihara, T. Hara, A. Kawashima, T. Akama, K. Tanigawa, H. Wu, M. Sue, Y. Ishido, N. Hiroi, N. Ishii, G. Yoshino, K. Suzuki, *Thyroid* **2012**, *22*, 1054.
[22] X. De Deken, B. Corvilain, J. E. Dumont, F. Miot, *Antioxid. Redox Signaling* **2014**, *20*, 2776.
[23] a) M. M. Behrens, S. S. Ali, L. L. Dugan, *J. Neurosci.* **2008**, *28*, 13957; b) J. R. Weaver, T. R. Holman, Y. Imai, A. Jadhav, V. Kenyon, D. J. Maloney, J. L. Nadler, G. Rai, A. Simeonov, D. A. Taylor-Fishwick, *Mol. Cell. Endocrinol.* **2012**, *358*, 88; c) M. M. Murillo, I. Carmona-Cuenca, G. Del Castillo, C. Ortiz, C. Roncero, A. Sanchez, M. Fernandez, I. Fabregat, *Biochem. J.* **2007**, *405*, 251.
[24] a) H. J. Kim, C. H. Kim, J. H. Ryu, J. H. Joo, S. N. Lee, M. J. Kim, J. G. Lee, Y. S. Bae, J. H. Yoon, *Free Radicals Biol. Med.* **2011**, *50*, 1039; b) M. S. Weng, J. H. Chang, W. Y. Hung, Y. C. Yang, M. H. Chien, *J. Exp. Clin. Cancer Res.* **2018**, *37*, 61; c) Y. M. Kim, S. J. Kim, R. Tatsunami, H. Yamamura, T. Fukai, M. Ushio-Fukai, *Am. J. Physiol. Cell Physiol.* **2017**, *312*, C749.
[25] a) J. Hwang, M. H. Ing, A. Salazar, B. Lassegue, K. Griendling, M. Navab, A. Sevanian, T. K. Hsiai, *Circ. Res.* **2003**, *93*, 1225; b) X. Liang, Z. Wang, M. Gao, S. Wu, J. Zhang, Q. Liu, Y. Yu, J. Wang, W. Liu, *BMC Ophthalmol.* **2019**, *19*, 79.
[26] R. Rathore, Y. M. Zheng, C. F. Niu, Q. H. Liu, A. Korde, Y. S. Ho, Y. X. Wang, *Free Radicals Biol. Med.* **2008**, *45*, 1223.
[27] A. Petry, A. Gorlach, *Antioxid. Redox Signaling* **2019**, *30*, 74.
[28] M. Santillo, A. Colantuoni, P. Mondola, B. Guida, S. Damiano, *Front. Physiol.* **2015**, *6*, 194.
[29] E. Amiya, *World J. Cardiol.* **2016**, *8*, 689.
[30] S. P. Gray, E. Di Marco, J. Okabe, C. Szyndralewiez, F. Heitz, A. C. Montezano, J. B. de Haan, C. Koulis, A. El-Osta, K. L. Andrews, J. P. Chin-Dusting, R. M. Touyz, K. Wingler, M. E. Cooper, H. H. Schmidt, K. A. Jandeleit-Dahm, *Circulation* **2013**, *127*, 1888.
[31] D. Burtenshaw, M. Kitching, E. M. Redmond, I. L. Megson, P. A. Cahill, *Front. Cardiovasc. Med.* **2019**, *6*, 89.
[32] R. Harrison, *Drug Metab. Rev.* **2004**, *36*, 363.
[33] H. Li, S. Horke, U. Forstermann, *Atherosclerosis* **2014**, *237*, 208.
[34] a) N. J. Alp, S. Mussa, J. Khoo, S. Cai, T. Guzik, A. Jefferson, N. Goh, K. A. Rockett, K. M. Channon, *J. Clin. Invest.* **2003**, *112*, 725; b) K. Venardos, W. Z. Zhang, C. Lang, D. M. Kaye, *Int. J. Biochem. Cell Biol.* **2009**, *41*, 2522; c) V. Vasilev, J. Matrozova, A. Elenkova, S. Vandeva, G. Kirilov, S. Zacharieva, *Exp. Clin. Endocrinol. Diabetes* **2013**, *121*, 551; d) C. A. Chen, T. Y. Wang, S. Varadharaj, L. A. Reyes, C. Hemann, M. A. Talukder, Y. R. Chen, L. J. Druhan, J. L. Zweier, *Nature* **2010**, *468*, 1115.
[35] Y. Wang, R. Branicky, A. Noe, S. Hekimi, *J. Cell Biol.* **2018**, *217*, 1915.
[36] A. Petry, T. Djordjevic, M. Weitnauer, T. Kietzmann, J. Hess, A. Gorlach, *Antioxid. Redox Signaling* **2006**, *8*, 1473.
[37] N. Maulik, D. K. Das, *Free Radicals Biol. Med.* **2002**, *33*, 1047.
[38] M. Kuroki, E. E. Voest, S. Amano, L. V. Beerepoot, S. Takashima, M. Tolentino, R. Y. Kim, R. M. Rohan, K. A. Colby, K. T. Yeo, A. P. Adamis, *J. Clin. Invest.* **1996**, *98*, 1667.
[39] M. Ushio-Fukai, Y. Tang, T. Fukai, S. I. Dikalov, Y. Ma, M. Fujimoto, M. T. Quinn, P. J. Pagano, C. Johnson, R. W. Alexander, *Circ. Res.* **2002**, *91*, 1160.
[40] J. K. Bendall, R. Rinze, D. Adlam, A. L. Tatham, J. de Bono, N. Wilson, E. Volpi, K. M. Channon, *Circ. Res.* **2007**, *100*, 1016.
[41] S. Dimmeler, A. M. Zeiher, *Regul. Pept.* **2000**, *90*, 19.
[42] A. E. Li, H. Ito, RoviraII, K. S. Kim, K. Takeda, Z. Y. Yu, V. J. Ferrans, T. Finkel, *Circ. Res.* **1999**, *85*, 304.
[43] L. M. Fan, G. Douglas, J. K. Bendall, E. McNeill, M. J. Crabtree, A. B. Hale, A. Mai, J. M. Li, M. A. McAteer, J. E. Schneider, R. P. Choudhury, K. M. Channon, *Circulation* **2014**, *129*, 2661.
[44] a) C. C. Lin, C. C. Yang, C. Y. Wang, H. C. Tseng, C. S. Pan, L. D. Hsiao, C. M. Yang, *Front. Pharmacol.* **2015**, *6*, 310; b) H. Sellak, E. Franzini, J. Hakim, C. Pasquier, *Blood* **1994**, *83*, 2669.
[45] a) N. Marui, M. K. Offermann, R. Swerlick, C. Kunsch, C. A. Rosen, M. Ahmad, R. W. Alexander, R. M. Medford, *J. Clin. Invest.* **1993**, *92*, 1866; b) C. Weber, W. Erl, A. Pietsch, M. Strobel, H. W. Ziegler-Heitbrock, P. C. Weber, *Arterioscler. Thromb.* **1994**, *14*, 1665.
[46] a) S. A. Gupte, P. M. Kaminski, S. George, L. Kouznestova, S. C. Olson, R. Mathew, T. H. Hintze, M. S. Wolin, *Am. J. Physiol.: Heart Circ. Physiol.* **2009**, *296*, H1048; b) R. M. Touyz, X. Chen, F. Tabet, G. Yao, G. He, M. T. Quinn, P. J. Pagano, E. L. Schiffrin, *Circ. Res.* **2002**, *90*, 1205; c) A. Badran, S. A. Nasser, J. Mesmar, A. F. El-Yazbi, A. Bitto, M. M. Fardoun, E. Baydoun, A. H. Eid, *Int. J. Mol. Sci.* **2020**, *21*, 8764.
[47] L. L. Hilenski, R. E. Clempus, M. T. Quinn, J. D. Lambeth, K. K. Griendling, *Arterioscler., Thromb., Vasc. Biol.* **2004**, *24*, 677.
[48] W. Yin, E. O. Voit, *BMC Syst. Biol.* **2013**, *7*, 20.
[49] R. E. Clempus, D. Sorescu, A. E. Dikalova, L. Pounkova, P. Jo, G. P. Sorescu, H. H. Schmidt, B. Lassegue, K. K. Griendling, *Arterioscler., Thromb., Vasc. Biol.* **2007**, *27*, 42.
[50] Q. Xiao, Z. Luo, A. E. Pepe, A. Margariti, L. Zeng, Q. Xu, *Am. J. Physiol. Cell Physiol.* **2009**, *296*, C711.
[51] Q. Xiao, A. E. Pepe, G. Wang, Z. Luo, L. Zhang, L. Zeng, Z. Zhang, Y. Hu, S. Ye, Q. Xu, *Arterioscler., Thromb., Vasc. Biol.* **2012**, *32*, 730.
[52] Q. Chen, Q. Wang, J. Zhu, Q. Xiao, L. Zhang, *Br. J. Pharmacol.* **2018**, *175*, 1279.
[53] S. Chettimada, H. Ata, D. K. Rawat, S. Gulati, A. G. Kahn, J. G. Edwards, S. A. Gupte, *Am. J. Physiol.: Heart Circ. Physiol.* **2014**, *306*, H214.
[54] Q. Xu, S. Choksi, J. Qu, J. Jang, M. Choe, B. Banfi, J. F. Engelhardt, Z. G. Liu, *J. Biol. Chem.* **2016**, *291*, 20030.
[55] Y. Zhang, S. Choksi, K. Chen, Y. Pobezinskaya, I. Linnoila, Z. G. Liu, *Cell Res.* **2013**, *23*, 898.
[56] V. Helfinger, K. Palfi, A. Weigert, K. Schroder, *Oxid. Med. Cell. Longevity* **2019**, *2019*, 3264858.
[57] A. Manea, S. A. Manea, A. M. Gan, A. Constantin, I. M. Fenyo, M. Raicu, H. Muresian, M. Simionescu, *Biochem. Biophys. Res. Commun.* **2015**, *461*, 172.

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[58] V. Marzaioli, M. Hurtado-Nedelec, C. Pintard, A. Tlili, J. C. Marie, R. C. Monteiro, M. A. Gougerot-Pocidalo, P. M. Dang, J. El-Benna, *Blood* **2017**, *130*, 1734.
[59] M. Herb, M. Schramm, *Antioxidants* **2021**, *10*, 313.
[60] E. E. To, R. Vlahos, R. Luong, M. L. Halls, P. C. Reading, P. T. King, C. Chan, G. R. Drummond, C. G. Sobey, B. R. S. Broughton, M. R. Starkey, R. van der Sluis, S. R. Lewin, S. Bozinovski, L. A. J. O'Neill, T. Quach, C. J. H. Porter, D. A. Brooks, J. J. O'Leary, S. Selemidis, *Nat. Commun.* **2017**, *8*, 69.
[61] a) A. P. West, I. E. Brodsky, C. Rahner, D. K. Woo, H. Erdjument-Bromage, P. Tempst, M. C. Walsh, Y. Choi, G. S. Shadel, S. Ghosh, *Nature* **2011**, *472*, 476; b) E. E. To, J. R. Erlich, F. Liong, R. Luong, S. Liong, F. Esaq, O. Oseghale, D. Anthony, J. McQualter, S. Bozinovski, R. Vlahos, J. J. O'Leary, D. A. Brooks, S. Selemidis, *Antioxid. Redox Signaling* **2020**, *32*, 929.
[62] a) N. C. D. R. F. Collaboration, *Lancet* **2021**, *398*, 957; b) A. Pirillo, M. Casula, E. Olmastroni, G. D. Norata, A. L. Catapano, *Nat. Rev. Cardiol.* **2021**, *18*, 689; c) P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A. A. Motala, K. Ogurtsova, J. E. Shaw, D. Bright, R. Williams, I. D. F. D. A. Committee, *Diabetes Res. Clin. Pract.* **2019**, *157*, 107843.
[63] M. Brownlee, *Diabetes* **2005**, *54*, 1615.
[64] H. Kaneto, N. Katakami, M. Matsuhisa, T. A. Matsuoka, *Mediators Inflammation* **2010**, *2010*, 453892.
[65] F. Scialo, D. J. Fernandez-Ayala, A. Sanz, *Front. Physiol.* **2017**, *8*, 428.
[66] S. J. Forrester, D. S. Kikuchi, M. S. Hernandes, Q. Xu, K. K. Griendling, *Circ. Res.* **2018**, *122*, 877.
[67] F. E. Lennon, P. A. Singleton, *Am. J. Cardiovasc. Dis.* **2011**, *1*, 200.
[68] M. Yang, J. Fang, Q. Liu, Y. Wang, Z. Zhang, *Biochem. Biophys. Res. Commun.* **2017**, *494*, 526.
[69] P. R. Kvietys, D. N. Granger, *Free Radicals Biol. Med.* **2012**, *52*, 556.
[70] T. Salvatore, P. C. Pafundi, R. Galiero, L. Rinaldi, A. Caturano, E. Vetrano, C. Aprea, G. Albanese, A. Di Martino, C. Ricozzi, S. Imbriani, F. C. Sasso, *Biomedicines* **2020**, *9*, 3.
[71] M. R. Cowie, M. Fisher, *Nat. Rev. Cardiol.* **2020**, *17*, 761.
[72] T. Inoue, T. Inoguchi, N. Sonoda, H. Hendarto, H. Makimura, S. Sasaki, H. Yokomizo, Y. Fujimura, D. Miura, R. Takayanagi, *Atherosclerosis* **2015**, *240*, 250.
[73] H. Liu, L. Guo, J. Xing, P. Li, H. Sang, X. Hu, Y. Du, L. Zhao, R. Song, H. Gu, *Eur. J. Pharmacol.* **2020**, *875*, 173037.
[74] a) C. Algire, O. Moiseeva, X. Deschenes-Simard, L. Amrein, L. Petruccelli, E. Birman, B. Viollet, G. Ferbeyre, M. N. Pollak, *Cancer Prev. Res.* **2012**, *5*, 536; b) H. S. Shin, J. Ko, D. A. Kim, E. S. Ryu, H. M. Ryu, S. H. Park, Y. L. Kim, E. S. Oh, D. H. Kang, *Sci. Rep.* **2017**, *7*, 5690.
[75] a) N. Diaz-Morales, S. Rovira-Llopis, C. Banuls, S. Lopez-Domenech, I. Escribano-Lopez, S. Veses, A. Jover, M. Rocha, A. Hernandez-Mijares, V. M. Victor, *Antioxid. Redox Signaling* **2017**, *27*, 1439; b) B. Chukwunonso Obi, T. Chinwuba Okoye, V. E. Okpashi, C. Nonye Igwe, E. Olisah Alumanah, *J. Diabetes Res.* **2016**, *2016*, 1635361.
[76] A. Esteghamati, P. H. Monnavar, M. Nakhjavani, S. P. Naraghi, R. Safari, H. Mirmiranpour, *Ann. Clin. Diabetes Endocrinol.* **2018**, *1*, 1007.
[77] a) F. F. Li, G. Gao, Q. Li, H. H. Zhu, X. F. Su, J. D. Wu, L. Ye, J. H. Ma, *J. Diabetes Res.* **2016**, *2016*, 5347262; b) S. J. Shin, S. Chung, S. J. Kim, E. M. Lee, Y. H. Yoo, J. W. Kim, Y. B. Ahn, E. S. Kim, S. D. Moon, M. J. Kim, S. H. Ko, *PLoS One* **2016**, *11*, e0165703.
[78] N. Zaibi, P. Li, S. Z. Xu, *PLoS One* **2021**, *16*, e0247234.
[79] S. Steven, M. Oelze, A. Hanf, S. Kroller-Schon, F. Kashani, S. Roohani, P. Welschof, M. Kopp, U. Godtel-Armbrust, N. Xia, H. Li, E. Schulz, K. J. Lackner, L. Wojnowski, S. P. Bottari, P. Wenzel, E. Mayoux, T. Munzel, A. Daiber, *Redox Biol.* **2017**, *13*, 370.
[80] H. Oshima, T. Miki, A. Kuno, M. Mizuno, T. Sato, M. Tanno, T. Yano, K. Nakata, Y. Kimura, K. Abe, W. Ohwada, T. Miura, *J. Pharmacol. Exp. Ther.* **2019**, *368*, 524.
[81] A. Tahara, E. Kurosaki, M. Yokono, D. Yamajuku, R. Kihara, Y. Hayashizaki, T. Takasu, M. Imamura, Q. Li, H. Tomiyama, Y. Kobayashi, A. Noda, M. Sasamata, M. Shibasaki, *J. Pharm. Pharmacol.* **2014**, *66*, 975.
[82] J. Helmstadter, K. Frenis, K. Filippou, A. Grill, M. Dib, S. Kalinovic, F. Pawelke, K. Kus, S. Kroller-Schon, M. Oelze, S. Chlopicki, D. Schuppan, P. Wenzel, W. Ruf, D. J. Drucker, T. Munzel, A. Daiber, S. Steven, *Arterioscler., Thromb., Vasc. Biol.* **2020**, *40*, 145.
[83] A. Shiraki, J. Oyama, H. Komoda, M. Asaka, A. Komatsu, M. Sakuma, K. Kodama, Y. Sakamoto, N. Kotooka, T. Hirase, K. Node, *Atherosclerosis* **2012**, *221*, 375.
[84] M. Ding, Q. H. Fang, Y. T. Cui, Q. L. Shen, Q. Liu, P. H. Wang, D. M. Yu, C. J. Li, *J. Diabetes Its Complications* **2019**, *33*, 267.
[85] C. G. Zhu, Y. Luo, H. Wang, J. Y. Li, J. Yang, Y. X. Liu, H. Q. Qu, B. L. Wang, M. Zhu, *Horm. Metab. Res.* **2020**, *52*, 532.
[86] X. Wang, Z. Li, X. Huang, F. Li, J. Liu, Z. Li, D. Bai, *Acta Cir. Bras.* **2019**, *34*, e20190010000001.
[87] L. Buldak, K. Labuzek, R. J. Buldak, G. Machnik, A. Boldys, B. Okopien, *Naunyn Schmiedebergs Arch. Pharmacol.* **2015**, *388*, 905.
[88] P. Dandona, H. Ghanim, S. Abuaysheh, K. Green, S. Dhindsa, A. Makdissi, M. Batra, N. D. Kuhadiya, A. Chaudhuri, *J. Clin. Endocrinol. Metab.* **2018**, *103*, 1180.
[89] Y. Ishibashi, T. Matsui, S. Maeda, Y. Higashimoto, S. Yamagishi, *Cardiovasc. Diabetol.* **2013**, *12*, 125.
[90] G. Pujadas, V. De Nigris, F. Prattichizzo, L. La Sala, R. Testa, A. Ceriello, *Endocrine* **2017**, *56*, 509.
[91] J. Rivera, C. G. Sobey, A. K. Walduck, G. R. Drummond, *Redox Rep.* **2010**, *15*, 50.
[92] E. Hopps, R. Lo Presti, G. Caimi, *Kidney Blood Pressure Res.* **2017**, *42*, 347.
[93] P. Lacolley, V. Regnault, P. Segers, S. Laurent, *Physiol. Rev.* **2017**, *97*, 1555.
[94] a) A. C. Montezano, M. Dulak-Lis, S. Tsiropoulou, A. Harvey, A. M. Briones, R. M. Touyz, *Can. J. Cardiol.* **2015**, *31*, 631; b) A. Nguyen Dinh Cat, A. C. Montezano, D. Burger, R. M. Touyz, *Antioxid. Redox Signaling* **2013**, *19*, 1110.
[95] a) R. Jung, J. Wild, J. Ringen, S. Karbach, P. Wenzel, *Am. J. Hypertens.* **2021**, *34*, 143; b) U. O. Wenzel, H. Ehmke, M. Bode, *Cell Tissue Res.* **2021**, *385*, 393.
[96] M. C. Staiculescu, C. Foote, G. A. Meininger, L. A. Martinez-Lemus, *Int. J. Mol. Sci.* **2014**, *15*, 23792.
[97] K. Kakabadze, I. Megreladze, N. Khvichia, N. Mitagvaria, N. Kipiani, M. Dumbadze, T. Sanikidze, *Cardiol. Res.* **2021**, *12*, 16.
[98] A. E. Norlander, M. S. Madhur, D. G. Harrison, *J. Exp. Med.* **2018**, *215*, 21.
[99] G. R. Drummond, A. Vinh, T. J. Guzik, C. G. Sobey, *Nat. Rev. Immunol.* **2019**, *19*, 517.
[100] a) R. Zhang, H. Inagawa, K. Kazumura, H. Tsuchiya, T. Miwa, N. Morishita, S. Uchibori, J. Hanashiro, T. Masaki, H. Kobara, G. I. Soma, *Anticancer Res.* **2018**, *38*, 4289; b) U. Wenzel, J. E. Turner, C. Krebs, C. Kurts, D. G. Harrison, H. Ehmke, *J. Am. Soc. Nephrol.* **2016**, *27*, 677; c) U. O. Wenzel, M. Bode, C. Kurts, H. Ehmke, *Br. J. Pharmacol.* **2019**, *176*, 1853.
[101] a) T. J. Guzik, N. E. Hoch, K. A. Brown, L. A. McCann, A. Rahman, S. Dikalov, J. Goronzy, C. Weyand, D. G. Harrison, *J. Exp. Med.* **2007**, *204*, 2449; b) M. S. Madhur, A. Kirabo, T. J. Guzik, D. G. Harrison, *Hypertension* **2020**, *75*, 930.
[102] a) A. Dikalova, R. Clempus, B. Lassegue, G. Cheng, J. McCoy, S. Dikalov, A. San Martin, A. Lyle, D. S. Weber, D. Weiss,

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W. R. Taylor, H. H. Schmidt, G. K. Owens, J. D. Lambeth, K. K. Griendling, *Circulation* **2005**, *112*, 2668; b) K. Matsuno, H. Yamada, K. Iwata, D. Jin, M. Katsuyama, M. Matsuki, S. Takai, K. Yamanishi, M. Miyazaki, H. Matsubara, C. Yabe-Nishimura, *Circulation* **2005**, *112*, 2677.
[103] L. Li, E. Y. Lai, Z. Luo, G. Solis, M. Mendonca, K. K. Griendling, A. Wellstein, W. J. Welch, C. S. Wilcox, *Hypertension* **2018**, *72*, 1208.
[104] W. C. Dornas, L. M. Cardoso, M. Silva, N. L. Machado, D. A. Chianca Jr., A. C. Alzamora, W. G. Lima, V. Lagente, M. E. Silva, *Sci. Rep.* **2017**, *7*, 46051.
[105] S. I. Dikalov, A. E. Dikalova, *Antioxid. Redox Signaling* **2019**, *31*, 710.
[106] K. K. Griendling, L. L. Camargo, F. J. Rios, R. Alves-Lopes, A. C. Montezano, R. M. Touyz, *Circ. Res.* **2021**, *128*, 993.
[107] A. Daiber, N. Xia, S. Steven, M. Oelze, A. Hanf, S. Kroller-Schon, T. Munzel, H. Li, *Int. J. Mol. Sci.* **2019**, *20*, 187.
[108] C. X. Santos, L. Y. Tanaka, J. Wosniak, F. R. Laurindo, *Antioxid. Redox Signaling* **2009**, *11*, 2409.
[109] N. Kobayashi, F. A. DeLano, G. W. Schmid-Schonbein, *Arterioscler., Thromb., Vasc. Biol.* **2005**, *25*, 2114.
[110] S. Paone, A. A. Baxter, M. D. Hulett, I. K. H. Poon, *Cell. Mol. Life Sci.* **2019**, *76*, 1093.
[111] B. R. Silva, L. Pernomian, L. M. Bendhack, *Front. Physiol.* **2012**, *3*, 441.
[112] T. Munzel, A. Daiber, V. Ullrich, A. Mulsch, *Arterioscler., Thromb., Vasc. Biol.* **2005**, *25*, 1551.
[113] A. C. Doran, N. Meller, C. A. McNamara, *Arterioscler., Thromb., Vasc. Biol.* **2008**, *28*, 812.
[114] H. J. Sung, S. G. Eskin, Y. Sakurai, A. Yee, N. Kataoka, L. V. McIntire, *Ann. Biomed. Eng.* **2005**, *33*, 1546.
[115] M. Mittal, M. R. Siddiqui, K. Tran, S. P. Reddy, A. B. Malik, *Antioxid. Redox Signaling* **2014**, *20*, 1126.
[116] R. Mohindra, D. K. Agrawal, F. G. Thankam, *J. Cardiovasc. Transl. Res.* **2021**, *14*, 647.
[117] a) S. I. Dikalov, R. R. Nazarewicz, *Antioxid. Redox Signaling* **2013**, *19*, 1085; b) M. Birk, E. Baum, J. K. Zadeh, C. Manicam, N. Pfeiffer, A. Patzak, J. Helmstadter, S. Steven, M. Kuntic, A. Daiber, A. Gericke, *Antioxidants* **2021**, *10*, 1238.
[118] E. M. de Cavanagh, F. Inserra, L. Ferder, C. G. Fraga, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2000**, *278*, R572.
[119] J. H. Kim, H. Kim, Y. H. Kim, W. S. Chung, J. K. Suh, S. J. Kim, *Korean J. Thorac. Cardiovasc. Surg.* **2013**, *46*, 14.
[120] X. Shi, Y. Guan, S. Jiang, T. Li, B. Sun, H. Cheng, *Arch. Med. Sci.* **2019**, *15*, 152.
[121] T. Li, R. Zhou, Y. Yao, Q. Yang, C. Zhou, W. Wu, Q. Li, Z. You, X. Zhao, L. Yang, C. Li, D. Zhu, Y. Qiu, M. Luo, Z. Tan, H. Li, Y. Chen, G. Gong, Y. Feng, K. Dian, J. Liu, *Antioxid. Redox Signaling* **2014**, *21*, 2095.
[122] M. Wojewodzka-Zelezniakowicz, A. Gromotowicz-Poplawska, W. Kisiel, E. Konarzewska, J. Szemraj, J. R. Ladny, E. Chabielska, *J. Renin-Angio-Aldo. Syst.* **2017**, *18*, 1470320316687197.
[123] Z. A. A. I. H. Mahmood, *Pharmacia* **2021**, *68*, 705.
[124] Y. Dincer, N. Sekercioglu, M. Pekpak, K. N. Gunes, T. Akcay, *Renal Failure* **2008**, *30*, 1006.
[125] S. Ogawa, H. Kobori, N. Ohashi, M. Urushihara, A. Nishiyama, T. Mori, T. Ishizuka, K. Nako, S. Ito, *Biomarker Insights* **2009**, *4*, 97.
[126] D. Kim, U. Pattamatta, E. Kelly, P. R. Healey, N. Carnt, H. Zoellner, A. J. R. White, *Transl. Vis. Sci. Technol.* **2018**, *7*, 20.
[127] S. Matsumoto, M. Shimabukuro, D. Fukuda, T. Soeki, K. Yamakawa, H. Masuzaki, M. Sata, *Cardiovasc. Diabetol.* **2014**, *13*, 30.
[128] P. Dandona, V. Kumar, A. Aljada, H. Ghanim, T. Syed, D. Hofmayer, P. Mohanty, D. Tripathy, R. Garg, *J. Clin. Endocrinol. Metab.* **2003**, *88*, 4496.
[129] a) J. Zou, Y. Li, H. Q. Fan, J. G. Wang, *BMC Res. Notes* **2012**, *5*, 168; b) T. Godfraind, *Philos. Trans. R. Soc., B* **2005**, *360*, 2259.
[130] R. Berkels, D. Taubert, H. Bartels, T. Breitenbach, W. Klaus, R. Roesen, *Pharmacology* **2004**, *70*, 39.
[131] M. Matsubara, K. Hasegawa, *Atherosclerosis* **2005**, *178*, 57.
[132] J. R. Wu, S. F. Liou, S. W. Lin, C. Y. Chai, Z. K. Dai, J. C. Liang, I. J. Chen, J. L. Yeh, *Pharmacol. Res.* **2009**, *59*, 48.
[133] T. L. Yue, P. J. McKenna, R. R. Ruffolo Jr., G. Feuerstein, *Eur. J. Pharmacol.* **1992**, *214*, 277.
[134] T. L. Yue, H. Y. Cheng, P. G. Lysko, P. J. McKenna, R. Feuerstein, J. L. Gu, K. A. Lysko, L. L. Davis, G. Feuerstein, *J. Pharmacol. Exp. Ther.* **1992**, *263*, 92.
[135] a) G. T. do Vale, C. B. P. da Silva, A. H. Sousa, N. A. Gonzaga, J. M. Parente, K. M. Araujo, M. M. Castro, C. R. Tirapelli, *Cardiovasc. Toxicol.* **2021**, *21*, 224; b) M. Oelze, A. Daiber, R. P. Brandes, M. Hortmann, P. Wenzel, U. Hink, E. Schulz, H. Mollnau, A. von Sandersleben, A. L. Kleschyov, A. Mulsch, H. Li, U. Forstermann, T. Munzel, *Hypertension* **2006**, *48*, 677.
[136] H. Mollnau, E. Schulz, A. Daiber, S. Baldus, M. Oelze, M. August, M. Wendt, U. Walter, C. Geiger, R. Agrawal, A. L. Kleschyov, T. Meinertz, T. Munzel, *Arterioscler., Thromb., Vasc. Biol.* **2003**, *23*, 615.
[137] S. A. Sorrentino, C. Doerries, C. Manes, T. Speer, C. Dessy, I. Lobysheva, W. Mohmand, R. Akbar, F. Bahlmann, C. Besler, A. Schaefer, D. Hilfiker-Kleiner, T. F. Luscher, J. L. Balligand, H. Drexler, U. Landmesser, *J. Am. Coll. Cardiol.* **2011**, *57*, 601.
[138] A. Coats, S. Jain, *J. Hum. Hypertens.* **2017**, *31*, 376.
[139] X. Guan, X. Guan, C. Lu, B. Shang, Y. Zhao, Y. Meng, Z. Zhang, *BMC Pharmacol. Toxicol.* **2020**, *21*, 84.
[140] K. Nakamura, M. Murakami, D. Miura, K. Yunoki, K. Enko, M. Tanaka, Y. Saito, N. Nishii, T. Miyoshi, M. Yoshida, H. Oe, N. Toh, S. Nagase, K. Kohno, H. Morita, H. Matsubara, K. F. Kusano, T. Ohe, H. Ito, *Pharmaceuticals* **2011**, *4*, 1088.
[141] T. Imanishi, H. Tsujioka, H. Ikejima, A. Kuroi, S. Takarada, H. Kitabata, T. Tanimoto, Y. Muragaki, S. Mochizuki, M. Goto, K. Yoshida, T. Akasaka, *Hypertension* **2008**, *52*, 563.
[142] A. Martins-Oliveira, D. A. Guimaraes, C. S. Ceron, E. Rizzi, D. M. M. Oliveira, C. R. Tirapelli, D. E. Casarini, F. B. Fernandes, L. C. Pinheiro, J. E. Tanus-Santos, *Eur. J. Pharmacol.* **2018**, *821*, 97.
[143] P. Chedid, T. Boussetta, P. M. C. Dang, S. A. Belambri, V. Marzaioli, M. Fasseau, F. Walker, A. Couvineau, J. El-Benna, J. C. Marie, *Mucosal Immunol.* **2017**, *10*, 332.
[144] G. Chandran, K. N. Sirajudeen, N. S. Yusoff, M. Swamy, M. S. Samarendra, *Oxid. Med. Cell. Longevity* **2014**, *2014*, 608512.
[145] F. Fiordaliso, I. Cuccovillo, R. Bianchi, A. Bai, M. Doni, M. Salio, N. De Angelis, P. Ghezzi, R. Latini, S. Masson, *Life Sci.* **2006**, *79*, 121.
[146] I. H. M. Zeina, A. Althanoon, *Pharmacia* **2021**, *68*, 7.
[147] L. Comini, T. Bachetti, A. Cargnoni, D. Bastianon, G. L. Gitti, C. Ceconi, R. Ferrari, *Pharmacol. Res.* **2007**, *56*, 42.
[148] M. J. Brosnan, C. A. Hamilton, D. Graham, C. A. Lygate, E. Jardine, A. F. Dominiczak, *J. Hypertens.* **2002**, *20*, 281.
[149] X. Zhao, D. Yang, W. Xu, W. Xu, Z. Guo, *JCPSP-J. Coll. Physicians Surg.* **2019**, *29*, 422.
[150] H. Ichikawa, I. Narita, M. Narita, T. Tanno, Y. Yokono, Y. Kimura, M. Tanaka, T. Osanai, K. Okumura, H. Tomita, *Int. Heart J.* **2018**, *59*, 1445.
[151] R. P. Mason, R. F. Jacob, R. Kubant, A. Jacoby, F. Louka, J. J. Corbalan, T. Malinski, *Br. J. Clin. Pharmacol.* **2012**, *74*, 141.
[152] K. Yasunari, K. Maeda, T. Watanabe, M. Nakamura, J. Yoshikawa, A. Asada, *J. Am. Coll. Cardiol.* **2004**, *43*, 2116.
[153] Y. Zhao, L. Wang, S. He, X. Wang, W. Shi, *Bosnian J. Basic Med. Sci.* **2017**, *17*, 132.
[154] S. Batova, J. DeWever, T. Godfraind, J. L. Balligand, C. Dessy, O. Feron, *Cardiovasc. Res.* **2006**, *71*, 478.
[155] M. S. Zhou, E. A. Jaimes, L. Raij, *Am. J. Hypertens.* **2004**, *17*, 167.
[156] K. Yasunari, K. Maeda, M. Nakamura, T. Watanabe, J. Yoshikawa, *Hypertens. Res.* **2005**, *28*, 107.

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[157] X. Liu, Z. Huang, Y. Zhang, X. Shui, F. Liu, Z. Wu, S. Xu, *Front. Cardiovasc. Med.* **2021**, *8*, 692540.
[158] T. Hayashi, T. Yamaguchi, Y. Sakakibara, K. Taguchi, M. Maeda, M. Kuzuya, Y. Hattori, *PLoS One* **2014**, *9*, e88391.
[159] K. Fukuo, J. Yang, O. Yasuda, M. Mogi, T. Suhara, N. Sato, T. Suzuki, S. Morimoto, T. Ogihara, *Circulation* **2002**, *106*, 356.
[160] R. F. Araujo Junior, V. B. Garcia, R. F. Leitao, G. A. Brito, C. Miguel Ede, P. M. Guedes, A. A. de Araujo, *PLoS One* **2016**, *11*, e0148868.
[161] K. Kurosaki, U. Ikeda, Y. Maeda, K. Shimada, *J. Mol. Cell. Cardiol.* **2000**, *32*, 333.
[162] a) C. J. Patel, M. R. Cullen, J. P. Ioannidis, A. J. Butte, *Int. J. Epidemiol.* **2012**, *41*, 828; b) Y. Wang, D. Xu, *Lipids Health Dis.* **2017**, *16*, 132.
[163] J. Lopez-Miranda, C. Williams, D. Lairon, *Br. J. Nutr.* **2007**, *98*, 458.
[164] S. S. Virani, A. Alonso, H. J. Aparicio, E. J. Benjamin, M. S. Bittencourt, C. W. Callaway, A. P. Carson, A. M. Chamberlain, S. Cheng, F. N. Delling, M. S. V. Elkind, K. R. Evenson, J. F. Ferguson, D. K. Gupta, S. S. Khan, B. M. Kissela, K. L. Knutson, C. D. Lee, T. T. Lewis, J. Liu, M. S. Loop, P. L. Lutsey, J. Ma, J. Mackey, S. S. Martin, D. B. Matchar, M. E. Mussolino, S. D. Navaneethan, A. M. Perak, G. A. Roth, et al., *Circulation* **2021**, *143*, e254.
[165] a) K. J. Moore, F. J. Sheedy, E. A. Fisher, *Nat. Rev. Immunol.* **2013**, *13*, 709; b) X. H. Yu, D. W. Zhang, X. L. Zheng, C. K. Tang, *Prog. Lipid Res.* **2019**, *73*, 65.
[166] T. Y. Luo, M. J. Su, Y. F. Yang, Y. B. Liu, H. C. Liang, C. C. Wu, Y. T. Lee, *J. Biomed. Sci.* **2004**, *11*, 829.
[167] a) Q. Han, S. C. Yeung, M. S. M. Ip, J. C. W. Mak, *Lipids Health Dis.* **2018**, *17*, 255; b) S. Watanabe, S. Kumazaki, K. Kusunoki, T. Inoue, Y. Maeda, S. Usui, R. Shinohata, T. Ohtsuki, S. Hirohata, S. Kusachi, K. Kitamori, M. Mori, Y. Yamori, H. Oka, *J. Atheroscler. Thromb.* **2018**, *25*, 439.
[168] a) H. C. Hsu, C. Y. Chen, B. C. Lee, M. F. Chen, *Eur. J. Nutr.* **2016**, *55*, 2245; b) Z. Giricz, G. Koncsos, T. Rajtik, Z. V. Varga, T. Baranyai, C. Csonka, A. Szobi, A. Adameova, R. A. Gottlieb, P. Ferdinandy, *Lipids Health Dis.* **2017**, *16*, 60; c) H. P. Glazer, R. M. Osipov, R. T. Clements, F. W. Sellke, C. Bianchi, *Cell Cycle* **2009**, *8*, 1738.
[169] A. S. Aromolaran, M. Boutjdir, *Front. Physiol.* **2017**, *8*, 431.
[170] L. C. Joseph, P. Subramanyam, C. Radlicz, C. M. Trent, V. Iyer, H. M. Colecraft, J. P. Morrow, *Heart Rhythm* **2016**, *13*, 1699.
[171] P. Zhong, D. Quan, Y. Huang, H. Huang, *J. Cardiovasc. Pharmacol.* **2017**, *70*, 245.
[172] a) D. Siegel-Axel, K. Daub, P. Seizer, S. Lindemann, M. Gawaz, *Cardiovasc. Res.* **2008**, *78*, 8; b) N. Wang, A. R. Tall, *Blood* **2016**, *127*, 1949.
[173] I. A. Relou, C. M. Hackeng, J. W. Akkerman, E. Malle, *Cell. Mol. Life Sci.* **2003**, *60*, 961.
[174] L. Lacoste, J. Y. Lam, J. Hung, G. Letchacovski, C. B. Solymoss, D. Waters, *Circulation* **1995**, *92*, 3172.
[175] L. Wang, C. Tang, *Int. J. Mol. Sci.* **2020**, *21*, 9760.
[176] Z. V. Varga, K. Kupai, G. Szucs, R. Gaspar, J. Paloczi, N. Farago, A. Zvara, L. G. Puskas, Z. Razga, L. Tiszlavicz, P. Bencsik, A. Gorbe, C. Csonka, P. Ferdinandy, T. Csont, *J. Mol. Cell. Cardiol.* **2013**, *62*, 111.
[177] T. Petnehazy, K. Y. Stokes, J. M. Russell, D. N. Granger, *Hypertension* **2005**, *45*, 209.
[178] a) T. Suanarunsawat, W. D. Ayutthaya, T. Songsak, S. Thirawarapan, S. Poungshompoo, *Oxid. Med. Cell. Longevity* **2011**, *2011*, 962025; b) M. H. A. H. I. Alfarisi, Z. B. H. Mohamed, A. H. Hamdan, C. A. Che Mohamad, *Int. Food Res. J.* **2020**, *27*, 8; c) S. Rivera-Mancia, A. S. Jimenez-Osorio, O. N. Medina-Campos, E. Colin-Ramirez, M. Vallejo, A. Alcantara-Gaspar, R. Cartas-Rosado, J. Vargas-Barron, J. Pedraza-Chaverri, *Int. J. Environ. Res. Public Health* **2018**, *15*, 2687.
[179] I. Lobysheva, G. Rath, B. Sekkali, C. Bouzin, O. Feron, B. Gallez, C. Dessy, J. L. Balligand, *Arterioscler., Thromb., Vasc. Biol.* **2011**, *31*, 2098.
[180] R. Altman, *Thromb. J.* **2003**, *1*, 4.
[181] A. Blair, P. W. Shaul, I. S. Yuhanna, P. A. Conrad, E. J. Smart, *J. Biol. Chem.* **1999**, *274*, 32512.
[182] J. Liu, Y. Ren, L. Kang, L. Zhang, *Int. J. Mol. Med.* **2014**, *33*, 1341.
[183] F. A. Yazan Ranneh, Abdah Md Akim, Hasiah Abd. Hamid, Huzwah Khazaai, A. Fadel, *Appl. Biol. Chem.* **2017**, *60*, 12.
[184] K. Stellos, R. Sauter, M. Fahrleitner, J. Grimm, D. Stakos, F. Emschermann, V. Panagiota, S. Gnerlich, A. Perk, T. Schonberger, B. Bigalke, H. F. Langer, M. Gawaz, *Arterioscler., Thromb., Vasc. Biol.* **2012**, *32*, 2017.
[185] a) J. Bouitbir, A. L. Charles, A. Echaniz-Laguna, M. Kindo, F. Daussin, J. Auwerx, F. Piquard, B. Geny, J. Zoll, *Eur. Heart J.* **2012**, *33*, 1397; b) S. Costa, M. Reina-Couto, A. Albino-Teixeira, T. Sousa, *Rev. Port. Cardiol.* **2016**, *35*, 41; c) A. M. Gorabi, N. Kiaie, S. Hajighasemi, M. Banach, P. E. Penson, T. Jamialahmadi, A. Sahebkar, *J. Clin. Med.* **2019**, *8*, 2051.
[186] P. Pignatelli, R. Carnevale, D. Pastori, R. Cangemi, L. Napoleone, S. Bartimoccia, C. Nocella, S. Basili, F. Violi, *Circulation* **2012**, *126*, 92.
[187] R. Carnevale, P. Pignatelli, S. Di Santo, S. Bartimoccia, V. Sanguigni, L. Napoleone, G. Tanzilli, S. Basili, F. Violi, *Atherosclerosis* **2010**, *213*, 225.
[188] a) C. Aoki, A. Nakano, S. Tanaka, K. Yanagi, S. Ohta, T. Jojima, K. Kasai, H. Takekawa, K. Hirata, Y. Hattori, *Int. J. Cardiol.* **2012**, *156*, 55; b) M. Margaritis, K. M. Channon, C. Antoniades, *Antioxid. Redox Signaling* **2014**, *20*, 1198; c) I. Kosmidou, J. P. Moore, M. Weber, C. D. Searles, *Arterioscler., Thromb., Vasc. Biol.* **2007**, *27*, 2642; d) C. Mineo, P. W. Shaul, *Adv. Exp. Med. Biol.* **2012**, *729*, 51.
[189] a) A. K. Kanugula, P. N. Gollavilli, S. B. Vasamsetti, S. Karnewar, R. Gopoju, R. Ummanni, S. Kotamraju, *FEBS J.* **2014**, *281*, 3719; b) N. Grosser, K. Erdmann, A. Hemmerle, G. Berndt, U. Hinkelmann, G. Smith, H. Schroder, *Biochem. Biophys. Res. Commun.* **2004**, *325*, 871; c) A. Nagila, T. Permpongpaiboon, S. Tantrarongroj, P. Porapakkham, K. Chinwattana, S. Deakin, S. Porntadavity, *Pharmacol. Rep.* **2009**, *61*, 892.
[190] D. Chartoumpekis, P. G. Ziros, A. Psyrogiannis, V. Kyriazopoulou, A. G. Papavassiliou, I. G. Habeos, *Biochem. Biophys. Res. Commun.* **2010**, *396*, 463.
[191] H. Tong, X. Zhang, X. Meng, L. Lu, D. Mai, S. Qu, *Front. Mol. Neurosci.* **2018**, *11*, 165.
[192] M. Deori, D. Devi, S. Kumari, A. Hazarika, H. Kalita, R. Sarma, R. Devi, *Front. Pharmacol.* **2016**, *7*, 319.
[193] M. M. Heikal, A. A. Shaaban, W. F. Elkashef, T. M. Ibrahim, *Can. J. Physiol. Pharmacol.* **2019**, *97*, 611.
[194] H. Ota, M. Eto, M. R. Kano, T. Kahyo, M. Setou, S. Ogawa, K. Iijima, M. Akishita, Y. Ouchi, *Arterioscler., Thromb., Vasc. Biol.* **2010**, *30*, 2205.
[195] T. S. Lee, C. C. Chang, Y. Zhu, J. Y. Shyy, *Circulation* **2004**, *110*, 1296.
[196] S. Inamoto, T. Yoshioka, C. Yamashita, M. Miyamura, T. Mori, A. Ukimura, C. Matsumoto, Y. Matsumura, Y. Kitaura, T. Hayashi, *Hypertens. Res.* **2010**, *33*, 579.
[197] a) M. H. Huang, K. K. Poh, H. C. Tan, F. G. Welt, C. Y. Lui, *Int. J. Cardiol.* **2016**, *214*, 374; b) M. H. Huang, P. H. Loh, H. C. Tan, K. K. Poh, *Singapore Med. J.* **2019**, *60*, 608.
[198] D. N. Granger, P. R. Kvietys, *Redox Biol.* **2015**, *6*, 524.
[199] D. Moris, M. Spartalis, E. Spartalis, G. S. Karachaliou, G. I. Karaolanis, G. Tsourouflis, D. I. Tsilimigras, E. Tzatzaki, S. Theocharis, *Ann. Transl. Med.* **2017**, *5*, 326.
[200] L. B. Becker, T. L. vanden Hoek, Z. H. Shao, C. Q. Li, P. T. Schumacker, *Am. J. Physiol.* **1999**, *277*, H2240.
[201] M. G. Perrelli, P. Pagliaro, C. Penna, *World J. Cardiol.* **2011**, *3*, 186.

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[202] S. Matsushima, H. Tsutsui, J. Sadoshima, *Trends Cardiovasc. Med.* **2014**, *24*, 202.
[203] L. C. Hool, *Heart, Lung Circ.* **2009**, *18*, 3.
[204] S. Pucheu, C. Coudray, N. Tresallet, A. Favier, J. de Leiris, *Cardiovasc. Drugs Ther.* **1993**, *7*, 701.
[205] a) V. Braunersreuther, F. Montecucco, M. Asrih, G. Pelli, K. Galan, M. Frias, F. Burger, A. L. Quindere, C. Montessuit, K. H. Krause, F. Mach, V. Jaquet, *J. Mol. Cell. Cardiol.* **2013**, *64*, 99; b) L. Yu, G. Yang, X. Zhang, P. Wang, X. Weng, Y. Yang, Z. Li, M. Fang, Y. Xu, A. Sun, J. Ge, *Circulation* **2018**, *138*, 2820.
[206] a) M. A. Cunningham, P. Romas, P. Hutchinson, S. R. Holdsworth, P. G. Tipping, *Blood* **1999**, *94*, 3413; b) S. Y. Chong, O. Zharkova, S. Yatim, X. Wang, X. C. Lim, C. Huang, C. Y. Tan, J. Jiang, L. Ye, M. S. Tan, V. Angeli, H. H. Versteeg, M. Dewerchin, P. Carmeliet, C. S. P. Lam, M. Y. Chan, D. P. V. de Kleijn, J. W. Wang, *Theranostics* **2021**, *11*, 9243.
[207] S. P. Loukogeorgakis, M. J. van den Berg, R. Sofat, D. Nitsch, M. Charakida, B. Haiyee, E. de Groot, R. J. MacAllister, T. W. Kuijpers, J. E. Deanfield, *Circulation* **2010**, *121*, 2310.
[208] L. Xie, M. A. Talukder, J. Sun, S. Varadharaj, J. L. Zweier, *J. Mol. Cell. Cardiol.* **2015**, *86*, 14.
[209] a) D. N. Granger, *Am. J. Physiol.* **1988**, *255*, H1269; b) B. E. Lee, A. H. Toledo, R. Anaya-Prado, R. R. Roach, L. H. Toledo-Pereyra, *J. Invest. Med.* **2009**, *57*, 902.
[210] a) D. J. Grieve, J. A. Byrne, A. C. Cave, A. M. Shah, *Heart, Lung Circ.* **2004**, *13*, 132; b) A. van der Pol, W. H. van Gilst, A. A. Voors, P. van der Meer, *Eur. J. Heart Failure* **2019**, *21*, 425; c) M. Hori, K. Nishida, *Cardiovasc. Res.* **2009**, *81*, 457.
[211] K. Lingappan, *Curr. Opin. Toxicol.* **2018**, *7*, 81.
[212] T. Liu, L. Zhang, D. Joo, S. C. Sun, *Signal Transduction Targeted Ther.* **2017**, *2*, 17023.
[213] J. S. Moon, K. Nakahira, K. P. Chung, G. M. DeNicola, M. J. Koo, M. A. Pabon, K. T. Rooney, J. H. Yoon, S. W. Ryter, H. Stout-Delgado, A. M. Choi, *Nat. Med.* **2016**, *22*, 1002.
[214] M. M. Galagudza, D. L. Sonin, T. D. Vlasov, D. I. Kurapeev, E. V. Shlyakhto, *Int. J. Exp. Pathol.* **2016**, *97*, 66.
[215] H. Zhu, Z. Jia, B. R. Misra, L. Zhang, Z. Cao, M. Yamamoto, M. A. Trush, H. P. Misra, Y. Li, *Cardiovasc. Toxicol.* **2008**, *8*, 71.
[216] M. N. S. Santana, D. S. Souza, R. Miguel-Dos-Santos, T. K. Rabelo, C. M. L. Vasconcelos, J. M. Navia-Pelaez, I. C. G. Jesus, J. A. D. Silva-Neto, S. Lauton-Santos, L. Capettini, S. Guatimosim, R. G. Rogers, M. Santos, V. J. Santana-Filho, T. R. R. Mesquita, *J. Mol. Cell. Cardiol.* **2018**, *125*, 61.
[217] J. Gonzalez-Montero, R. Brito, A. I. Gajardo, R. Rodrigo, *World J. Cardiol.* **2018**, *10*, 74.
[218] K. Neha, M. R. Haider, A. Pathak, M. S. Yar, *Eur. J. Med. Chem.* **2019**, *178*, 687.
[219] a) T. Shiomi, H. Tsutsui, H. Matsusaka, K. Murakami, S. Hayashidani, M. Ikeuchi, J. Wen, T. Kubota, H. Utsumi, A. Takeshita, *Circulation* **2004**, *109*, 544; b) P. Wang, H. Chen, H. Qin, S. Sankarapandi, M. W. Becher, P. C. Wong, J. L. Zweier, *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 4556.
[220] A. van der Pol, A. Gil, H. H. W. Sillje, J. Tromp, E. S. Ovchinnikova, I. Vreeswijk-Baudoin, M. Hoes, I. J. Domian, B. van de Sluis, J. M. van Deursen, A. A. Voors, D. J. van Veldhuisen, W. H. van Gilst, E. Berezikov, P. van der Harst, R. A. de Boer, R. Bischoff, P. van der Meer, *Sci. Transl. Med.* **2017**, *9*, eaam8574.
[221] W. T. Hsu, Y. H. Tseng, H. Y. Jui, C. C. Kuo, K. K. Wu, C. M. Lee, *J. Mol. Cell. Cardiol.* **2021**, *158*, 101.
[222] F. Wang, H. Wang, X. Liu, H. Yu, X. Huang, W. Huang, G. Wang, *J. Cell. Mol. Med.* **2021**, *25*, 1783.
[223] Y. W. Wang, S. J. He, X. Feng, J. Cheng, Y. T. Luo, L. Tian, Q. Huang, *Drug Des., Dev. Ther.* **2017**, *11*, 2421.
[224] Y. Shi, S. A. Hou, *Mol. Med. Rep.* **2021**, *24*, 712.
[225] M. Bredemeier, L. M. Lopes, M. A. Eisenreich, S. Hickmann, G. K. Bongiorno, R. d'Avila, A. L. B. Morsch, F. da Silva Stein, G. G. D. Campos, *BMC Cardiovasc. Disord.* **2018**, *18*, 24.
[226] D. Fraccarollo, P. Galuppo, J. Neuser, J. Bauersachs, J. D. Widder, *Hypertension* **2015**, *66*, 978.
[227] B. Chen, J. Zhao, S. Zhang, W. Wu, R. Qi, *J. Cardiovasc. Pharmacol.* **2012**, *59*, 405.
[228] S. Ayyadevara, P. Bharill, A. Dandapat, C. Hu, M. Khaidakov, S. Mitra, R. J. Shmookler Reis, J. L. Mehta, *Antioxid. Redox Signaling* **2013**, *18*, 481.
[229] Z. D. Zhang, Y. J. Yang, X. W. Liu, Z. Qin, S. H. Li, J. Y. Li, *Toxicology* **2021**, *453*, 152721.
[230] P. Dandona, T. Qutob, W. Hamouda, F. Bakri, A. Aljada, Y. Kumbkarni, *Thromb. Res.* **1999**, *96*, 437.
[231] R. A. Shaker, S. H. Abboud, H. C. Assad, N. Hadi, *BMC Pharmacol. Toxicol.* **2018**, *19*, 3.
[232] A. Bredthauer, M. Kopfmueller, M. Gruber, S. M. Pfaehler, K. Lehle, W. Petermichl, T. Seyfried, D. Bitzinger, A. Redel, *Cardiovasc. Ther.* **2020**, *2020*, 9783630.
[233] C. Yu, W. Wang, X. Jin, *Med. Sci. Monit.* **2018**, *24*, 6264.
[234] H. Zhang, H. Chen, J. Li, Y. Bian, Y. Song, Z. Li, F. He, S. Liu, Y. Tsai, *Int. J. Biol. Macromol.* **2020**, *162*, 425.
[235] a) C. Shi, P. Wang, S. Airen, C. Brown, Z. Liu, J. H. Townsend, J. Wang, H. Jiang, *Eye Vis.* **2020**, *7*, 33; b) S. M. B. Asdaq, A. S. Alamri, W. F. Alsanie, M. Alhomrani, *Molecules* **2021**, *26*, 5137.
[236] J. B. Blumberg, B. B. Frei, V. L. Fulgoni, C. M. Weaver, S. H. Zeisel, *Nutrients* **2017**, *9*, 849.
[237] L. A. Ahmed, O. F. Hassan, O. Galal, D. F. Mansour, A. El-Khatib, *PLoS One* **2020**, *15*, e0232413.
[238] O. A. Stirban, H. Zeller-Stefan, J. Schumacher, W. Gaus, D. Ziegler, T. Schuerholz, R. Pop-Busui, *J. Diabetes Its Complications* **2020**, *34*, 107757.
[239] a) R. B. Singh, M. A. Niaz, S. S. Rastogi, S. Rastogi, *Am. J. Cardiol.* **1996**, *77*, 232; b) S. K. Myung, W. Ju, B. Cho, S. W. Oh, S. M. Park, B. K. Koo, B. J. Park, Korean Meta-Analysis (KORMA) Study Group, *BMJ [Br. Med. J.]* **2013**, *346*, f10.
[240] R. L. Castillo, C. Arias, J. G. Farias, *Cell Biochem. Funct.* **2014**, *32*, 274.
[241] R. Rodrigo, J. Gonzalez-Montero, C. G. Sotomayor, *Biomedicines* **2021**, *9*, 620.
[242] J. Sochman, J. Vrbska, B. Musilova, M. Rocek, *Clin. Cardiol.* **1996**, *19*, 94.
[243] M. A. Arstall, J. Yang, I. Stafford, W. H. Betts, J. D. Horowitz, *Circulation* **1995**, *92*, 2855.
[244] S. Pasupathy, R. Tavella, S. Grover, B. Raman, N. E. K. Procter, Y. T. Du, G. Mahadavan, I. Stafford, T. Heresztyn, A. Holmes, C. Zeitz, M. Arstall, J. Selvanayagam, J. D. Horowitz, J. F. Beltrame, *Circulation* **2017**, *136*, 894.
[245] a) T. E. Lehnen, M. V. Santos, A. Lima, A. L. Maia, S. M. Wajner, *Endocrinology* **2017**, *158*, 1502; b) C. R. M. Costa, F. A. C. Seara, M. S. Peixoto, I. P. Ramos, R. A. Q. Barbosa, A. B. Carvalho, R. S. Fortunato, A. L. B. Silveira, E. L. Olivares, *Mol. Biol. Rep.* **2020**, *47*, 8645; c) C. Adamy, P. Mulder, L. Khouzami, N. Andrieu-Abadie, N. Defer, G. Candiani, C. Pavoine, P. Caramelle, R. Souktani, P. Le Corvoisier, M. Perier, M. Kirsch, T. Damy, A. Berdeaux, T. Levade, C. Thuillez, L. Hittinger, F. Pecker, *J. Mol. Cell. Cardiol.* **2007**, *43*, 344.
[246] a) D. Yesilbursa, A. Serdar, T. Senturk, Z. Serdar, S. Sag, J. Cordan, *Heart Vessels* **2006**, *21*, 33; b) A. H. Talasaz, H. Khalili, F. Fahimi, Y. Jenab, M. A. Broumand, M. Salarifar, F. Darabi, *Am. J. Cardiovasc. Drugs* **2014**, *14*, 51.
[247] a) G. Wang, D. Bainbridge, J. Martin, D. Cheng, *J. Cardiothorac. Vasc. Anesth.* **2011**, *25*, 268; b) J. E. G. Pereira, R. El Dib, L. G. Braz, J. Escudero, J. Hayes, B. C. Johnston, *PLoS One* **2019**, *14*, e0213862.

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[248] X. Y. Liu, H. X. Xu, J. K. Li, D. Zhang, X. H. Ma, L. N. Huang, J. H. Lu, X. Z. Wang, *Front. Physiol.* **2018**, *9*, 102.
[249] P. Koonyosying, S. Kongkarnka, C. Uthaipibull, S. Svasti, S. Fucharoen, S. Srichairatanakool, *Biomed. Pharmacother.* **2018**, *108*, 1694.
[250] R. Gal, L. Deres, K. Toth, R. Halmosi, T. Habon, *Int. J. Mol. Sci.* **2021**, *22*, 10152.
[251] a) V. L. Truong, M. Jun, W. S. Jeong, *BioFactors* **2018**, *44*, 36; b) G. Luo, Z. Li, Y. Wang, H. Wang, Z. Zhang, W. Chen, Y. Zhang, Y. Xiao, C. Li, Y. Guo, P. Sheng, *Inflammation* **2016**, *39*, 775.
[252] X. Zhou, M. Chen, X. Zeng, J. Yang, H. Deng, L. Yi, M. T. Mi, *Cell Death Dis.* **2014**, *5*, e1576.
[253] a) Z. Zhang, B. Li, L. Xie, W. Sang, H. Tian, J. Li, G. Wang, Y. Dai, *ACS Nano* **2021**, *15*, 16934; b) Z. Zhang, W. Sang, L. Xie, W. Li, B. Li, J. Li, H. Tian, Z. Yuan, Q. Zhao, Y. Dai, *Angew. Chem., Int. Ed.* **2021**, *60*, 1967; c) Y. Liu, J. Q. Wang, Q. Q. Xiong, D. Hornburg, W. Tao, O. C. Farokhzad, *Acc. Chem. Res.* **2021**, *54*, 291; d) Q. Zhou, C. Y. Dong, W. F. Fan, H. P. Jiang, J. J. Xiang, N. S. Qiu, Y. Piao, T. Xie, Y. W. Luo, Z. C. Li, F. S. Liu, Y. Q. Shen, *Biomaterials* **2020**, *240*, 119902; e) S. P. Varahachalam, B. Lahooti, M. Chamaneh, S. Bagchi, T. Chhibber, K. Morris, J. F. Bolanos, N. Y. Kim, A. Kaushik, *Int. J. Nanomed.* **2021**, *16*, 539.
[254] a) P. Gao, Y. Y. Chen, W. Pan, N. Li, Z. Liu, B. Tang, *Angew. Chem., Int. Ed.* **2021**, *60*, 16763; b) W. Shi, Y. C. Ching, C. H. Chuah, *Int. J. Biol. Macromol.* **2021**, *170*, 751; c) Z. Mirza, S. Karim, *Semin. Cancer Biol.* **2021**, *69*, 226.
[255] a) C. Ramamurthy, M. Padma, I. D. M. Samadanam, R. Mareeswaran, A. Suyavaran, M. S. Kumar, K. Premkumar, C. Thirunavukkarasu, *Colloids Surf., B* **2013**, *102*, 808; b) X. L. Yang, C. J. Li, Y. P. Wan, P. Smith, G. W. Shang, Q. J. Cui, *Int. J. Nanomed.* **2014**, *9*, 4023; c) L. Y. He, Y. M. Su, L. H. Jiang, S. K. Shi, *J. Rare Earths* **2015**, *33*, 791; d) K. Sugamura, J. F. Keaney, *Free Radicals Biol. Med.* **2011**, *51*, 978; e) D. Matuz-Mares, H. Riveros-Rosas, M. M. Vilchis-Landeros, H. Vazquez-Meza, *Antioxidants* **2021**, *10*, 1220.
[256] I. S. Fancher, I. Rubinstein, I. Levitan, *Hypertension* **2019**, *73*, 250.
[257] a) R. M. DiSanto, V. Subramanian, Z. Gu, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* **2015**, *7*, 548; b) X. Strakosas, J. Selberg, P. Pansodtee, N. Yonas, P. Manapongpun, M. Teodorescu, M. Rolandi, *Sci. Rep.* **2019**, *9*, 10844.
[258] L. R. Volpatti, M. A. Matranga, A. B. Cortinas, D. Delcassian, K. B. Daniel, R. Langer, D. G. Anderson, *ACS Nano* **2020**, *14*, 488.
[259] a) Y. Li, T. Cui, X. Kong, X. Yi, D. Kong, J. Zhang, C. Liu, M. Gong, *FASEB J.* **2018**, *32*, 2992; b) F. Araujo, N. Shrestha, M. J. Gomes, B. Herranz-Blanco, D. Liu, J. J. Hirvonen, P. L. Granja, H. A. Santos, B. Sarmento, *Nanoscale* **2016**, *8*, 10706.
[260] X. L. Zong, R. Zhu, *Sens. Actuators, B* **2018**, *255*, 2448.
[261] J. Liu, S. Sun, H. Shang, J. Lai, L. Zhang, *Electroanalysis* **2016**, *28*, 2016.
[262] P. Bollella, L. Gorton, R. Ludwig, R. Antiochia, *Sensors* **2017**, *17*, 1912.
[263] Y. Cai, B. Liang, S. Chen, Q. Zhu, T. Tu, K. Wu, Q. Cao, L. Fang, X. Liang, X. Ye, *Biosens. Bioelectron.* **2020**, *165*, 112408.
[264] G. Sharma, A. R. Sharma, J. S. Nam, G. P. Doss, S. S. Lee, C. Chakraborty, *J. Nanobiotechnol.* **2015**, *13*, 74.
[265] X. Nie, Z. Chen, L. Pang, L. Wang, H. Jiang, Y. Chen, Z. Zhang, C. Fu, B. Ren, J. Zhang, *Int. J. Nanomed.* **2020**, *15*, 10215.
[266] a) S. K. Chinnaiyan, D. Karthikeyan, V. R. Gadela, *Pharm. Nanotechnol.* **2018**, *6*, 253; b) S. Kumar, G. Bhanjana, R. K. Verma, D. Dhingra, N. Dilbaghi, K. H. Kim, *J. Pharm. Pharmacol.* **2017**, *69*, 143.
[267] a) A. Angelopoulou, E. Voulgari, A. Kolokithas-Ntoukas, A. Bakandritsos, K. Avgoustakis, *AAPS PharmSciTech* **2018**, *19*, 621; b) A. Zafar, *J. Oleo Sci.* **2020**, *69*, 1389.
[268] T. Khan, S. Khan, M. Akhtar, J. Ali, A. K. Najmi, *Neurochem. Int.* **2021**, *150*, 105158.
[269] Y. Shi, M. Yin, Y. Song, T. Wang, S. Guo, X. Zhang, K. Sun, Y. Li, *J. Biomater. Appl.* **2021**, *35*, 754.
[270] a) X. Bao, K. Qian, P. Yao, *J. Nanobiotechnol.* **2020**, *18*, 67; b) H. Guo, X. Yan, H. Tang, X. Zhang, *Curr. Drug Delivery* **2021**, *19*, 32.
[271] P. Shah, K. Chavda, B. Vyas, S. Patel, *Drug Delivery Transl. Res.* **2021**, *11*, 1166.
[272] a) S. Maity, P. Mukhopadhyay, P. P. Kundu, A. S. Chakraborti, *Carbohydr. Polym.* **2017**, *170*, 124; b) P. Mukhopadhyay, S. Maity, S. Mandal, A. S. Chakraborti, A. K. Prajapati, P. P. Kundu, *Carbohydr. Polym.* **2018**, *182*, 42.
[273] a) N. K. Al-Nemrawi, S. S. M. Alsharif, K. H. Alzoubi, R. Q. Alkhatib, *Pharm. Dev. Technol.* **2019**, *24*, 967; b) F. C. Barbosa, M. C. D. Silva, H. N. D. Silva, D. Albuquerque, A. A. R. Gomes, S. M. L. Silva, M. V. L. Fook, *Polymers* **2020**, *12*, 2499; c) R. Panwar, N. Raghuwanshi, A. K. Srivastava, A. K. Sharma, V. Pruthi, *Mater. Sci. Eng., C* **2018**, *92*, 381.
[274] a) C. Kozuka, C. Shimizu-Okabe, C. Takayama, K. Nakano, H. Morinaga, A. Kinjo, K. Fukuda, A. Kamei, A. Yasuoka, T. Kondo, K. Abe, K. Egashira, H. Masuzaki, *Drug Delivery* **2017**, *24*, 558; b) S. Malathi, P. Nandhakumar, V. Pandiyan, T. J. Webster, S. Balasubramanian, *Int. J. Nanomed.* **2015**, *10*, 2207; c) J. Z. Wu, G. R. Williams, H. Y. Li, D. X. Wang, S. D. Li, L. M. Zhu, *Drug Delivery* **2017**, *24*, 1513.
[275] K. C. Lee, W. J. Chen, Y. C. Chen, *Nanomedicine* **2017**, *12*, 1823.
[276] a) M. J. Ansari, M. K. Anwer, S. Jamil, R. Al-Shdefat, B. E. Ali, M. M. Ahmad, M. N. Ansari, *Drug Delivery* **2016**, *23*, 1972; b) E. Muntoni, E. Marini, N. Ahmadi, P. Milla, C. Ghe, A. Bargoni, M. T. Capucchio, E. Biasibetti, L. Battaglia, *Acta Diabetol.* **2019**, *56*, 1283.
[277] M. E. El-Naggar, F. Al-Joufi, M. Anwar, M. F. Attia, M. A. El-Bana, *Colloids Surf., B* **2019**, *177*, 389.
[278] a) J. Zhang, J. Zhou, T. Zhang, Z. Niu, J. Wang, J. Guo, Z. Li, Z. Zhang, *ACS Appl. Mater. Interfaces* **2019**, *11*, 12904; b) J. Singh, P. Mittal, G. Vasant Bonde, G. Ajmal, B. Mishra, *Artif. Cells, Nanomed., Biotechnol.* **2018**, *46*, S546.
[279] M. S. Alam, A. Ahad, L. Abidin, M. Aqil, S. R. Mir, M. Mujeeb, *Biomed. Pharmacother.* **2018**, *97*, 1514.
[280] S. A. Siddiqui, M. M. Or Rashid, M. G. Uddin, F. N. Robel, M. S. Hossain, M. A. Haque, M. Jakaria, *Biosci. Rep.* **2020**, *40*, BSR20193972.
[281] J. Wang, Z. Wang, G. Chen, Y. Wang, T. Ci, H. Li, X. Liu, D. Zhou, A. R. Kahkoska, Z. Zhou, H. Meng, J. B. Buse, Z. Gu, *ACS Nano* **2021**, *15*, 4294.
[282] S. Yao, Y. Wang, J. Chi, Y. Yu, Y. Zhao, Y. Luo, Y. Wang, *Adv. Sci.* **2021**, *9*, 2103449.
[283] I. Antal, M. Kubovcikova, V. Závišová, M. Koneracká, O. Pechanova, A. Barta, M. Cebová, V. Antal, P. Diko, M. Zduriencikova, M. Pudlak, P. Kopčanský, *J. Magn. Magn. Mater.* **2015**, *380*, 280.
[284] U. Shah, G. Joshi, K. Sawant, *Mater. Sci. Eng., C* **2014**, *35*, 153.
[285] A. Arora, N. Shafiq, S. Jain, G. K. Khuller, S. Sharma, S. Malhotra, *PLoS One* **2015**, *10*, e0128208.
[286] Y. I. Kim, L. Fluckiger, M. Hoffman, I. Lartaud-Idjouadiene, J. Atkinson, P. Maincent, *Br. J. Pharmacol.* **1997**, *120*, 399.
[287] P. B. Deshpande, A. K. Gurram, A. Deshpande, G. V. Shavi, P. Musmade, K. Arumugam, R. K. Averineni, S. Mutalik, M. S. Reddy, N. Udupa, *Life Sci.* **2016**, *162*, 125.
[288] I. Rubinstein, H. Ikezaki, H. Onyuksel, *Int. J. Pharm.* **2006**, *316*, 144.
[289] K. Zhang, Y. L. Zhuang, J. W. Li, X. C. Liu, S. H. He, *Int. J. Nanomed.* **2020**, *15*, 5517.
[290] B. de Azevedo Mde, L. Tasic, J. Fattori, F. H. Rodrigues, F. C. Cantos, L. P. Ribeiro, V. de Paula, D. Ianzer, R. A. Santos, *Int. J. Nanomed.* **2011**, *6*, 1005.

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[291] a) N. Gupta, N. Sharma, S. K. Mathur, R. Chandra, S. Nimesh, *Artif. Cells, Nanomed., Biotechnol.* **2018**, *46*, 188; b) K. Sharma, K. Kumar, N. Mishra, *Drug Delivery* **2016**, *23*, 694.

[292] a) Z. Li, W. Tao, D. Zhang, C. Wu, B. Song, S. Wang, T. Wang, M. Hu, X. Liu, Y. Wang, Y. Sun, J. Sun, *Asian J. Pharm. Sci.* **2017**, *12*, 285; b) A. Soni, P. Dandagi, A. Gadad, V. Mastiholimath, *Asian J. Pharm.* **2011**, *5*, 57.

[293] a) H. Zhang, X. Zou, Q. Huang, X. Zhong, Z. Huang, *Cell. Physiol. Biochem.* **2018**, *45*, 2257; b) H. L. Zhang, Y. Tao, J. Guo, Y. M. Hu, Z. Q. Su, *Int. Immunopharmacol.* **2011**, *11*, 457; c) Y. Tao, H. Zhang, B. Gao, J. Guo, Y. Hu, Z. Su, *J. Nanomater.* **2011**, *2011*, 814606.

[294] a) B. Sarangi, K. Mishra, G. P. Mohanta, P. K. Manna, *Eur. Polym. J.* **2020**, *122*, 109366; b) H. B. Abo-Zalam, E. S. El-Denshary, R. M. Abdelsalam, I. A. Khalil, M. M. Khattab, M. A. Hamzawy, *Biomed. Pharmacother.* **2021**, *139*, 111494.

[295] a) A. A. Momtazi-Borojeni, M. R. Jaafari, M. Afshar, M. Banach, A. Sahebkar, *Arch. Med. Sci.* **2021**, *17*, 1365; b) A. A. Momtazi-Borojeni, M. R. Jaafari, A. Badiee, M. Banach, A. Sahebkar, *BMC Med.* **2019**, *17*, 223.

[296] S. Katsuki, T. Matoba, S. Nakashiro, K. Sato, J. Koga, K. Nakano, Y. Nakano, S. Egusa, K. Sunagawa, K. Egashira, *Circulation* **2014**, *129*, 896.

[297] A. A. Momtazi, E. Abdollahi, m. r. Jaafari, M. Banach, G. Watts, A. Sahebkar, *Curr. Vasc. Pharmacol.* **2021**, *19*, 69.

[298] M. Parra-Robert, M. L. Zeng, Y. Shu, G. Fernandez-Varo, M. Perramon, D. Desai, J. H. Chen, D. D. Guo, X. Zhang, M. Morales-Ruiz, J. M. Rosenholm, W. Jimenez, V. Puntes, E. Casals, G. Casals, *Nanoscale* **2021**, *13*, 8452.

[299] E. Casals, M. L. Zeng, M. Parra-Robert, G. Fernandez-Varo, M. Morales-Ruiz, W. Jimenez, V. Puntes, G. Casals, *Small* **2020**, *16*, 1907322.

[300] M. Parra-Robert, E. Casals, N. Massana, M. L. Zeng, M. Perramon, G. Fernandez-Varo, M. Morales-Ruiz, V. Puntes, W. Jimenez, G. Casals, *Biomolecules* **2019**, *9*, 425.

[301] M. H. Shukr, S. Ismail, S. M. Ahmed, *J. Drug Delivery Sci. Technol.* **2019**, *49*, 383.

[302] P. Libby, *Nature* **2021**, *592*, 524.

[303] T. Ishihara, K. I. Tanaka, Y. Tasaka, T. Namba, J. Suzuki, T. Ishihara, S. Okamoto, T. Hibi, M. Takenaga, R. Igarashi, K. Sato, Y. Mizushima, T. Mizushima, *J. Pharmacol. Exp. Ther.* **2009**, *328*, 152.

[304] V. V. Shuvaev, M. Christofidou-Solomidou, F. Bhora, K. Laude, H. Cai, S. Dikalov, E. Arguiri, C. C. Solomides, S. M. Albelda, D. G. Harrison, V. R. Muzykantov, *J. Pharmacol. Exp. Ther.* **2009**, *331*, 404.

[305] E. Hood, E. Simone, P. Wattamwar, T. Dziubla, V. Muzykantov, *Nanomedicine* **2011**, *6*, 1257.

[306] J. Nong, P. M. Glassman, V. R. Muzykantov, *Adv. Drug Delivery Rev.* **2022**, *184*, 114180.

[307] M. D. Howard, C. F. Greineder, E. D. Hood, V. R. Muzykantov, *J. Controlled Release* **2014**, *177*, 34.

[308] Y. Zhang, Y. F. Yin, W. Zhang, H. Y. Li, T. X. Wang, H. H. Yin, L. P. Sun, C. X. Su, K. Zhang, H. X. Xu, *J. Nanobiotechnol.* **2021**, *19*, 161.

[309] a) M. Shilo, H. Oved, L. Wertheim, I. Gal, N. Noor, O. Green, E. S. Baruch, D. Shabat, A. Shapira, T. Dvir, *Adv. Sci.* **2021**, *8*, 2102919; b) T. J. Zhao, W. Wu, L. H. Sui, Q. Huang, Y. Y. Nan, J. H. Liu, K. L. Ai, *Bioact. Mater.* **2022**, *7*, 47; c) Y. H. Cheng, S. J. Cheng, H. H. Chen, W. C. Hsu, *Colloids Surf., B* **2022**, *209*, 112150; d) Y. Watanabe, T. Nakamura, M. Uematsu, D. Fujioka, D. Inomata, Y. Saito, T. Horikoshi, T. Yoshizaki, T. Kobayashi, K. Nakamura, K. Kugiyama, *Free Radicals Biol. Med.* **2021**, *176*, 241.

[310] a) L. Li, Y. Wang, R. Guo, S. Li, J. Y. Ni, S. Gao, X. M. Gao, J. Y. Mao, Y. Zhu, P. L. Wu, H. J. Wang, D. L. Kong, H. Zhang, M. F. Zhu, G. W. Fan, *J. Controlled Release* **2020**, *317*, 259; b) W. Y. Chen, D. L. Li, *Front. Chem.* **2020**, *8*, 732.

[311] a) D. A. Brown, H. N. Sabbah, S. R. Shaikh, *Pharmacol. Ther.* **2013**, *140*, 258; b) R. R. Bartz, H. B. Suliman, C. A. Piantadosi, *Front. Physiol.* **2015**, *6*, 291.

[312] a) F. Bagheri, V. Khori, A. M. Alizadeh, S. Khalighfard, S. Khodayari, H. Khodayari, *Life Sci.* **2016**, *165*, 43; b) D. B. Zorov, M. Juhaszova, S. J. Sollott, *Physiol. Rev.* **2014**, *94*, 909.

[313] Y. Cheng, D. Z. Liu, C. X. Zhang, H. Cui, M. Liu, B. L. Zhang, Q. B. Mei, Z. F. Lu, S. Y. Zhou, *Nanomed. Nanotechnol. Biol. Med.* **2019**, *16*, 236.

[314] a) B. X. Ma, H. Xu, Y. A. Wang, L. Yang, W. H. Zhuang, G. C. Li, Y. B. Wang, *ACS Appl. Mater. Interfaces* **2021**, *13*, 35410; b) A. Maruf, Y. Wang, L. Luo, Y. Zhong, D. Nurhidayah, B. Y. Liu, D. Tang, M. A. Rouf, H. J. Zhang, Y. X. Yin, W. Wu, G. X. Wang, *Part. Part. Syst. Charact.* **2020**, *37*, 2000021; c) M. L. Shen, H. L. Li, S. Y. Yao, X. D. Wu, S. Liu, Q. B. Yang, Y. J. Zhang, J. S. Du, S. L. Qi, Y. P. Li, *Mater. Sci. Eng., C* **2021**, *126*, 112164.

[315] C. Gao, Q. X. Huang, C. H. Liu, C. H. T. Kwong, L. D. Yue, J. B. Wan, S. M. Y. Lee, R. B. Wang, *Nat. Commun.* **2020**, *11*, 2622.

[316] T. Wu, X. Y. Chen, Y. Wang, H. Xiao, Y. Peng, L. T. Lin, W. H. Xia, M. Long, J. Tao, X. T. Shuai, *Nanomed. Nanotechnol. Biol. Med.* **2018**, *14*, 2215.

[317] J. Park, B. Kim, J. Han, J. Oh, S. Park, S. Ryu, S. Jung, J. Y. Shin, B. S. Lee, B. H. Hong, D. Choi, B. S. Kim, *ACS Nano* **2015**, *9*, 4987.

[318] M. Ziegler, X. Xu, M. L. Yap, H. Hu, J. Zhang, K. Peter, *Adv. Ther.* **2019**, *2*, 1800133.

[319] S. Bae, M. Park, C. Kang, S. Dilmen, T. H. Kang, D. G. Kang, Q. Ke, S. U. Lee, D. Lee, P. M. Kang, *J. Am. Heart Assoc.* **2016**, *5*, e003697.

[320] L. Li, Y. Wang, R. Guo, S. Li, J. Ni, S. Gao, X. Gao, J. Mao, Y. Zhu, P. Wu, H. Wang, D. Kong, H. Zhang, M. Zhu, G. Fan, *J. Controlled Release* **2020**, *317*, 259.

[321] S. W. Zhang, J. Wang, J. Pan, *Drug Delivery* **2016**, *23*, 3696.

[322] M. F. Shao, W. F. Yang, G. Y. Han, *Int. J. Nanomed.* **2017**, *12*, 7121.

[323] Y. Zhang, P. Qian, H. Zhou, R. L. Shen, B. Hu, Y. J. Shen, X. F. Zhang, X. H. Shen, G. T. Xu, L. M. Jin, *Kidney Blood Pressure Res.* **2018**, *43*, 1273.

[324] X. Z. Li, B. Y. Li, X. W. Jin, F. Q. Dong, H. Y. Li, *J. Coord. Chem.* **2020**, *73*, 297.

[325] T. Wu, X. Chen, Y. Wang, H. Xiao, Y. Peng, L. Lin, W. Xia, M. Long, J. Tao, X. Shuai, *Nanomedicine* **2018**, *14*, 2215.

[326] a) J. Y. Han, V. V. Shuvaev, V. R. Muzykantov, *J. Pharmacol. Exp. Ther.* **2011**, *338*, 82; b) V. V. Shuvaev, J. Y. Han, S. Tliba, E. Arguiri, M. Christofidou-Solomidou, S. H. Ramirez, H. Dykstra, Y. Persidsky, D. N. Atochin, P. L. Huang, V. R. Muzykantov, *PLoS One* **2013**, *8*, e77002.

[327] E. D. Hood, C. F. Greineder, C. Dodia, J. Y. Han, C. Mesaros, V. V. Shuvaev, I. A. Blair, A. B. Fisher, V. R. Muzykantov, *J. Controlled Release* **2012**, *163*, 161.

[328] V. V. Shuvaev, R. Y. Kiseleva, E. Arguiri, C. H. Villa, S. Muro, M. Christofidou-Solomidou, R. V. Stan, V. R. Muzykantov, *J. Controlled Release* **2018**, *272*, 1.

[329] D. Rocksén, B. Lilliehöök, R. Larsson, T. Johansson, A. Bucht, *Clin. Exp. Immunol.* **2000**, *122*, 249.

[330] M. C. C. Ferrer, V. V. Shuvaev, B. J. Zern, R. J. Composto, V. R. Muzykantov, D. M. Eckmann, *PLoS One* **2014**, *9*, e102329.

[331] a) M. A. Hegeman, P. M. Cobelens, J. Kamps, M. P. Hennus, N. J. Jansen, M. J. Schultz, A. J. van Vught, G. Molema, C. J. Heijnen, *Br. J. Pharmacol.* **2011**, *163*, 1048; b) S. A. Asgeirsdóttir, P. J. Zwiers, H. W. Morselt, H. E. Moorlag, H. I. Bakker, P. Heeringa, J. W. Kok, C. G. Kallenberg, G. Molema, J. A. Kamps, *Am. J. Physiol. Renal. Physiol.* **2008**, *294*, F554; c) N. Hashida, N. Ohguro, N. Yamazaki, Y. Arakawa, E. Oiki, H. Mashimo, N. Kurokawa, Y. Tano, *Exp. Eye Res.* **2008**, *86*, 138; d) M. Everts, G. A. Koning, R. J. Kok, S. A. Asgeirsdóttir, D. Vestweber,

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D. K. Meijer, G. Storm, G. Molema, *Pharm. Res.* **2003**, *20*, 64; e) G. A. Koning, R. M. Schiffelers, M. H. Wauben, R. J. Kok, E. Mastrobattista, G. Molema, T. L. ten Hagen, G. Storm, *Arthritis Rheum.* **2006**, *54*, 1198.

[332] B.-S. Ding, N. Hong, J.-C. Murciano, K. Ganguly, C. Gottstein, M. Christofidou-Solomidou, S. M. Albelda, A. B. Fisher, D. B. Cines, V. R. Muzykantov, *Blood* **2008**, *111*, 1999.

[333] C. F. Greineder, A. M. Chacko, S. Zaytsev, B. J. Zern, R. Carnemolla, E. D. Hood, J. Han, B. S. Ding, C. T. Esmon, V. R. Muzykantov, *PLoS One* **2013**, *8*, e80110.

[334] C. F. Greineder, J. B. Brenza, R. Carnemolla, S. Zaitsev, E. D. Hood, D. C. Pan, B. S. Ding, C. T. Esmon, A. M. Chacko, V. R. Muzykantov, *FASEB J.* **2015**, *29*, 3483.

[335] P. I. Homem de Bittencourt, D. J. Lagranha, A. Maslinkiewicz, S. M. Senna, A. M. V. Tavares, L. P. Baldissera, D. R. Janner, J. S. Peralta, P. M. Bock, L. L. P. Gutierrez, G. Scola, T. G. Heck, M. S. Krause, L. A. Cruz, D. S. P. Abdalla, C. J. Lagranha, T. Lima, R. Curi, *Atherosclerosis* **2007**, *193*, 245.

[336] C. T. Esmon, *J. Thromb. Haemostasis* **2003**, *1*, 1343.

[337] D. A. Dichek, J. Anderson, A. B. Kelly, S. R. Hanson, L. A. Harker, *Circulation* **1996**, *93*, 301.

[338] J. M. Kiely, M. I. Cybulsky, F. W. Luscinskas, M. A. Gimbrone Jr., *Arterioscler., Thromb., Vasc. Biol.* **1995**, *15*, 1211.

[339] a) J.-C. Murciano, S. Muro, L. Koniaris, M. Christofidou-Solomidou, D. W. Harshaw, S. M. Albelda, D. N. Granger, D. B. Cines, V. R. Muzykantov, *Blood* **2003**, *101*, 3977; b) C. F. Greineder, I. H. Johnston, C. H. Villa, K. Gollomp, C. T. Esmon, D. B. Cines, M. Poncz, V. R. Muzykantov, *Blood Adv.* **2017**, *1*, 1452.

[340] B.-S. Ding, C. Gottstein, A. Grunow, A. Kuo, K. Ganguly, S. M. Albelda, D. B. Cines, V. R. Muzykantov, *Blood* **2005**, *106*, 4191.

[341] C. T. Esmon, *Semin. Thromb. Hemostasis* **2006**, *32*, 49.

[342] B. S. Ding, N. Hong, M. Christofidou-Solomidou, C. Gottstein, S. M. Albelda, D. B. Cines, A. B. Fisher, V. R. Muzykantov, *Am. J. Respir. Crit. Care Med.* **2009**, *180*, 247.

[343] V. V. Shuvaev, J. S. Brenner, V. R. Muzykantov, *J. Controlled Release* **2015**, *219*, 576.

[344] a) Z. Tao, S. Loo, L. Su, S. Tan, G. Tee, S. U. Gan, J. Zhang, X. Chen, L. Ye, *Cardiovasc. Res.* **2021**, *117*, 1578; b) K. K. Poh, P. S. S. Lee, A. H. Djohan, M. J. Galupo, G. G. Songco, T. C. Yeo, H. C. Tan, A. M. Richards, L. Ye, *Cells* **2020**, *9*, 949; c) S. H. Tan, S. J. Loo, Y. Gao, Z. H. Tao, L. P. Su, C. X. Wang, S. L. Zhang, Y. H. Mu, Y. H. Cui, D. Abdurrachim, W. H. Wang, J. Lalic, K. C. Lim, J. Bu, R. S. Tan, T. H. Lee, J. Zhang, L. Ye, *Theranostics* **2021**, *11*, 7879; d) L. Ye, Y. H. Chang, Q. Xiong, P. Zhang, L. Zhang, P. Somasundaram, M. Lepley, C. Swingen, L. Su, J. S. Wendel, J. Guo, A. Jang, D. Rosenbush, L. Greder, J. R. Dutton, J. Zhang, T. J. Kamp, D. S. Kaufman, Y. Ge, J. Zhang, *Cell Stem Cell* **2014**, *15*, 750; e) J. S. Wendel, L. Ye, R. Tao, J. Zhang, J. Zhang, T. J. Kamp, R. T. Tranquillo, *Stem Cells Transl. Med.* **2015**, *4*, 1324; f) J. S. Wendel, L. Ye, P. Zhang, R. T. Tranquillo, J. J. Zhang, *Tissue Eng., Part A* **2014**, *20*, 1325.

[345] H. Song, M. J. Cha, B. W. Song, I. K. Kim, W. Chang, S. Lim, E. J. Choi, O. Ham, S. Y. Lee, N. Chung, Y. Jang, K. C. Hwang, *Stem Cells* **2010**, *28*, 555.

[346] a) S. Muro, V. R. Muzykantov, *Curr. Pharm. Des.* **2005**, *11*, 2383; b) C. Garnacho, S. M. Albelda, V. R. Muzykantov, S. Muro, *J. Controlled Release* **2008**, *130*, 226.

[347] a) V. V. Shuvaev, S. Tliba, J. Pick, E. Arguiri, M. Christofidou-Solomidou, S. M. Albelda, V. R. Muzykantov, *J. Controlled Release* **2011**, *149*, 236; b) J. W. Myerson, B. Braender, O. McPherson, P. M. Glassman, R. Y. Kiseleva, V. V. Shuvaev, O. Marcos-Contreras, M. E. Grady, H. S. Lee, C. F. Greineder, R. V. Stan, R. J. Composto, D. M. Eckmann, V. R. Muzykantov, *Adv. Mater.* **2018**, *30*, 1802373.

[348] B. Beneteauburnat, B. Baudin, *Crit. Rev. Clin. Lab. Sci.* **1991**, *28*, 337.

[349] S. Perkowski, J. Sun, S. Singhal, J. Santiago, G. D. Leikauf, S. M. Albelda, *Am. J. Respir. Cell Mol. Biol.* **2003**, *28*, 682.

[350] a) R. Kiseleva, C. F. Greineder, C. H. Villa, E. D. Hood, V. V. Shuvaev, J. Sun, A. M. Chacko, V. Abraham, H. M. DeLisser, V. R. Muzykantov, *PLoS One* **2017**, *12*, e0169537; b) C. F. Greineder, A. M. Chacko, S. Zaytsev, B. J. Zern, R. Carnemolla, E. D. Hood, J. Y. Han, B. S. Ding, C. T. Esmon, V. R. Muzykantov, *PLoS One* **2013**, *8*, e80110; c) S. Muro, X. M. Cui, C. Gajewski, J. C. Murciano, V. R. Muzykantov, M. Koval, *Am. J. Physiol.: Cell Physiol.* **2003**, *285*, C1339.

[351] a) M. Everts, R. J. Kok, S. A. Asgeirsdóttir, B. N. Melgert, T. J. Moolenaar, G. A. Koning, M. J. van Luyn, D. K. Meijer, G. Molema, *J. Immunol.* **2002**, *168*, 883; b) S. Kessner, A. Krause, U. Rothe, G. Bendas, *Biochim. Biophys. Acta* **2001**, *1514*, 177.

[352] D. P. McIntosh, X. Y. Tan, P. Oh, J. E. Schnitzer, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 1996.

[353] a) T. Miki, Y. Takegami, K. Okawa, T. Muraguchi, M. Noda, C. Takahashi, *J. Biol. Chem.* **2007**, *282*, 12341; b) D. S. Harburger, D. A. Calderwood, *J. Cell Sci.* **2009**, *122*, 159; c) R. O. Hynes, *Cell* **2002**, *110*, 673.

[354] a) V. V. Shuvaev, S. Tliba, M. Nakada, S. M. Albelda, V. R. Muzykantov, *J. Pharmacol. Exp. Ther.* **2007**, *323*, 450; b) V. V. Shuvaev, M. Khoshnejad, K. W. Pulsipher, R. Y. Kiseleva, E. Arguiri, J. C. Cheung-Lau, K. M. LeFort, M. Christofidou-Solomidou, R. V. Stan, I. J. Dmochowski, V. R. Muzykantov, *Biomaterials* **2018**, *185*, 348; c) V. V. Shuvaev, J. Y. Han, K. J. Yu, S. H. Huang, B. J. Hawkins, M. Madesh, M. Nakada, V. R. Muzykantov, *FASEB J.* **2011**, *25*, 348; d) V. V. Shuvaev, S. Muro, E. Arguiri, M. Khoshnejad, S. Tliba, M. Christofidou-Solomidou, V. R. Muzykantov, *J. Controlled Release* **2016**, *234*, 115.

[355] a) R. Pasqualini, D. M. McDonald, W. Arap, *Nat. Immunol.* **2001**, *2*, 567; b) P. N. Reynolds, S. A. Nicklin, L. Kaliberova, B. G. Boatman, W. E. Grizzle, I. V. Balyasnikova, A. H. Baker, S. M. Danilov, D. T. Curiel, *Nat. Biotechnol.* **2001**, *19*, 838.

[356] M. Chorny, E. Hood, R. J. Levy, V. R. Muzykantov, *J. Controlled Release* **2010**, *146*, 144.

[357] S. Kartha, L. S. Yan, C. L. Weisshaar, M. E. Ita, V. V. Shuvaev, V. R. Muzykantov, A. Tsourkas, B. A. Winkelstein, Z. L. Cheng, *Adv. Healthcare Mater.* **2017**, *6*, 1700500.

[358] E. A. Simone, T. D. Dziubla, E. Arguiri, V. Vardon, V. V. Shuvaev, M. Christofidou-Solomidou, V. R. Muzykantov, *Pharm. Res.* **2009**, *26*, 250.

[359] T. D. Dziubla, V. V. Shuvaev, N. K. Hong, B. J. Hawkins, M. Madesh, H. Takano, E. Simone, M. T. Nakada, A. Fisher, S. M. Albelda, V. R. Muzykantov, *Biomaterials* **2008**, *29*, 215.

[360] a) D. Ma, S. Tian, J. Baryza, J. C. Luft, J. M. DeSimone, *Mol. Pharmaceutics* **2015**, *12*, 3518; b) J. W. Myerson, A. C. Anselmo, Y. Liu, S. Mitragotri, D. M. Eckmann, V. R. Muzykantov, *Adv. Drug Delivery Rev.* **2016**, *99*, 97.

[361] H. S. Choi, W. Liu, P. Misra, E. Tanaka, J. P. Zimmer, B. Itty, M. G. Bawendi, J. V. Frangioni, *Nat. Biotechnol.* **2009**, *25*, 1165.

[362] R. A. Petros, J. M. DeSimone, *Nat. Rev. Drug Discovery* **2010**, *9*, 615.

[363] a) A. C. Anselmo, M. Zhang, S. Kumar, D. R. Vogus, S. Menegatti, M. E. Helgeson, S. Mitragotri, *ACS Nano* **2015**, *9*, 3169; b) N. S. Oltra, P. Nair, D. E. Discher, *Annu. Rev. Chem. Biomol. Eng.* **2014**, *5*, 281.

[364] a) V. V. Shuvaev, M. A. Ilies, E. Simone, S. Zaitsev, Y. Kim, S. Cai, A. Mahmud, T. Dziubla, S. Muro, D. E. Discher, V. R. Muzykantov, *ACS Nano* **2011**, *5*, 6991; b) A. C. Anselmo, S. Mitragotri, *J. Controlled Release* **2014**, *190*, 531.

[365] S. Muro, C. Garnacho, J. A. Champion, J. Leferovich, C. Gajewski, E. H. Schuchman, S. Mitragotri, V. R. Muzykantov, *Mol. Ther.* **2008**, *16*, 1450.

[366] P. Kolhar, C. Anselmo Aaron, V. Gupta, K. Pant, B. Prabhakarpandian, E. Ruoslahti, S. Mitragotri, *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 10753.

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[367] V. V. Shuvaev, M. A. Ilies, E. Simone, S. Zaitsev, Y. Kim, S. S. Cai, A. Mahmud, T. Dziubla, S. Muro, D. E. Discher, V. R. Muzykantov, *ACS Nano* **2011**, *5*, 6991.
[368] a) J. Key, A. L. Palange, F. Gentile, S. Aryal, C. Stigliano, D. Di Mascolo, E. De Rosa, M. Cho, Y. Lee, J. Singh, P. Decuzzi, *ACS Nano* **2015**, *9*, 11628; b) A. C. Anselmo, S. Mitragotri, *Adv. Drug Delivery Rev.* **2017**, *108*, 51.
[369] J. Sun, L. Zhang, J. Wang, Q. Feng, D. Liu, Q. Yin, D. Xu, Y. Wei, B. Ding, X. Shi, X. Jiang, *Adv. Mater.* **2015**, *27*, 1402.
[370] M. Howard, B. J. Zern, A. C. Anselmo, V. V. Shuvaev, S. Mitragotri, V. Muzykantov, *ACS Nano* **2014**, *8*, 4100.
[371] H. Parhiz, M. Khoshnejad, J. W. Myerson, E. Hood, P. N. Patel, J. S. Brenner, V. R. Muzykantov, *Adv. Drug Delivery Rev.* **2018**, *130*, 90.
[372] P. M. Glassman, J. W. Myerson, L. T. Ferguson, R. Y. Kiseleva, V. V. Shuvaev, J. S. Brenner, V. R. Muzykantov, *Adv. Drug Delivery Rev.* **2020**, *157*, 96.
[373] J. Han, V. V. Shuvaev, V. R. Muzykantov, *Ther. Delivery* **2012**, *3*, 263.
[374] B. A. Freeman, S. L. Young, J. D. Crapo, *J. Biol. Chem.* **1983**, *258*, 12534.
[375] E. V. Batrakova, S. Li, A. D. Reynolds, R. L. Mosley, T. K. Bronich, A. V. Kabanov, H. E. Gendelman, *Bioconjugate Chem.* **2007**, *18*, 1498.
[376] V. V. Shuvaev, V. R. Muzykantov, *J. Controlled Release* **2011**, *153*, 56.
[377] M. K. Reddy, V. Labhasetwar, *FASEB J.* **2009**, *23*, 1384.
[378] M. Christofidou-Solomidou, V. R. Muzykantov, *Treat. Respir. Med.* **2006**, *5*, 47.
[379] X. Yi, M. C. Zimmerman, R. Yang, J. Tong, S. Vinogradov, A. V. Kabanov, *Free Radicals Biol. Med.* **2010**, *49*, 548.
[380] R. Carnemolla, V. V. Shuvaev, V. R. Muzykantov, *Semin. Thromb. Hemostasis* **2010**, *36*, 332.
[381] a) V. Aggarwal, H. S. Tuli, A. Varol, F. Thakral, M. B. Yerer, K. Sak, M. Varol, A. Jain, A. Khan, G. Sethi, *Biomolecules* **2019**, *9*, 735; b) U. S. Srinivas, B. W. Q. Tan, B. A. Vellayappan, A. D. Jeyasekharan, *Redox Biol.* **2019**, *25*, 101084.

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