Review Article

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An updated overview of nanoparticle-induced cardiovascular toxicity

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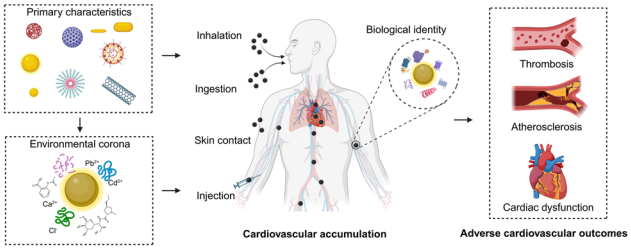
Abstract: The cardiovascular system is pivotal in the systemic distribution and toxicity of nanoparticles (NPs) upon their entry into circulation. Therefore, it is crucial to extensively investigate the adverse cardiovascular effects of NPs. This review presents the advancements in understanding the cardiovascular distribution of NPs and their potential adverse effects, particularly in humans. We first discussed the uptake and distribution of NPs in cardiovascular tissues and cells, which result in adverse outcomes such as hemolysis, blood coagulation dysfunction, vascular endothelial damage, and cardiac pathological damage and function impairment. Additionally, we discuss the current understanding of the mechanisms underlying NP-induced cardiovascular toxicity, including oxidative stress, inflammation, mitochondrial damage, and autophagy. Moreover, we systematically reviewed the factors influencing NPs circulation, retention, clearance, and toxicity within the cardiovascular system, which include the primary physicochemical properties of NPs, modifications of NPs with biological molecules, physiological and pathological conditions of the body, and their interaction with other environmental chemicals. Finally, we proposed the challenges associated with NP cardiovascular toxicity, with the aim of providing insights into the interactions between NPs and cardiovascular components and offering valuable perspectives for the development of safer NP-based therapies and biomedical applications.



Graphical abstract

Keywords: nanotoxicology, cardiovascular system, nano-bio interactions

1 Introduction

Nanotechnology, defined as the manipulation of matter on an atomic or molecular scale, has revolutionized numerous fields [1–4]. However, the rapid advancement and widespread application of nanotechnology inevitably lead to environmental release and human exposure to nanoparticles (NPs) [5]. Whether encountered environmentally, occupationally, or medically, NPs can interact uniquely with biological systems due to their extremely small size and high surface area-to-volume ratio, raising significant concerns about their health impact [6–8].

Humans may be exposed to NPs through various ways, including skin contact, inhalation, and ingestion [5,9]. After crossing primary biological barriers such as the skin, the air–blood barrier, and the intestinal barrier, NPs initially enter the cardiovascular system before being transported and accumulated in vital organs [10,11]. For biomedical applications, NPs are designed to have a long-circulating effect to facilitate drug delivery [12,13]. NP-based drug delivery systems have shown great potential in overcoming the limitations of free drugs and offering multiple therapeutic effects in treating several diseases through improving bioavailability, targeting ability, efficacy, and safety [14–16]. However, nanomedicines still face challenges that limit their clinical translation due to insufficient information on the mechanisms influencing blood circulation, biodistribution, and fate, as

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well as the biocompatibility of nanomedicines [7,17]. Consequently, the cardiovascular system is at the forefront of nano bio-distribution, making the potential adverse effects of NPs on the cardiovascular system, a critical area of concern that requires extensive attention. Mounting evidence has shown that NPs can damage the cardiovascular system through interactions with various blood cells [18,19], vascular endothelial cells (ECs) [20,21], and myocardial cells [22,23]. Recently, potential adverse effects of NPs on the cardiovascular system, particularly focusing on specific types of NPs [24–26], or special cells and animal models [27,28], have been reviewed extensively. However, a comprehensive review providing a complete and up-to-date overview of the cardiovascular distribution and toxicity of NPs is still lacking.

Using "'cardiovascular toxicity' AND 'nanoparticles'" as search terms, we screened and analyzed the 1,569 and 2,540 research papers obtained in the Web of Science and Google Scholar databases. The top five concepts of the obtained papers include biomaterials, pharmacology, toxicology, biochemistry and molecular biophysics, and transport and circulation. Based on the literature on the reported adverse cardiovascular effects of NPs, we comprehensively reviewed recent advancements in the distribution of NPs within the cardiovascular system, their potential adverse effects, and the underlying mechanisms governing NP interactions with cardiovascular tissues, particularly in humans. Additionally, detailed scrutiny was conducted on the factors influencing NPs circulation, retention, clearance, and toxicity within the cardiovascular system. We also addressed the challenges associated with NP-induced cardiovascular toxicity, aiming to illuminate NP interactions with cardiovascular components and provide valuable perspectives for the development of safer NP-based therapies and biomedical applications.

2 Distribution of NPs in cardiovascular system

The reticuloendothelial system generally exhibits higher NP accumulation compared to the heart [29]. Nonetheless, the cardiovascular system is recognized as a major site for NP distribution [24]. Accumulation of various types of NPs in the heart has been documented across different animals, irrespective of exposure route-whether through inhalation or ingestion. Polymer NPs, including nanoplastics [30,31], metal NPs [32,33], carbon-based NPs [34,35], and other inorganic NPs [36,37], all exhibited heart accumulation. Experimental evidence directly confirms the presence of NPs in myocardial cells of Wistar rats orally exposed to polystyrene microplastics (PS, *diameter* = 0.5 μm) at doses of 5 or 50 mg/L for 90 days [38]. Although NP uptake by cardiomyocytes has been observed in various cell lines *in vitro*, such as primary cardiomyocytes from Wistar rats [39,40], cardiomyocyte-derived HL-1 cells [41], human cardiomyocytes (AC16) [42], and H9c2 rat cardiomyoblasts [39,43], detailed studies on the mechanism of NP-cardiomyocyte interactions remain limited. For example, it was found that the titanate nanotubes (TiONts) were taken up by neonatal rat cardiomyocytes through two distinct pathways, which include endocytosis, specifically the macropinocytosis (in the case of nanohybrids larger than 500 nm) and diffusion through the membrane, while the spherical TiO_2 was considered to be exclusively taken up through endocytosis, indicating that the shape and probably their specific surface have a predominant impact in the internalization step [40]. Consistently, macropinocytosis was found to be involved in the cellular uptake of hydroxyapatite (HAp) by cardiomyocyte-derived HL-1 cells [41]. In contrast, $CsPbBr_3$ NPs were taken up by human cardiomyocytes AC16 *via* macropinocytosis and phagocytosis, followed by vesicle delivery into lysosomes [42]. However, the atrial natriuretic peptide-modified, heart-targeted porous silicon NPs were internalized by primary cardiomyocytes partly *via* the guanylate cyclase-A receptor expressed at the cell membrane [39].

Besides the interaction with myocardial cells, NPs entering circulation can interact directly with various types of blood cells. For instance, it was demonstrated that the interaction between silver NPs (Ag NPs) and fish red blood cells (RBCs) was regulated by the size of Ag NPs, with more particles of middle size (50 nm) being adsorbed to the cell surface and internalized by RBCs, compared with smaller (15 nm) or larger (100 nm) ones [18]. In another investigation, gold nanorods (Au NRs), coated with hexadecyltrimethylammonium bromide but not poly (sodium-*p*-styrenesulfonate) were internalized by mouse RBCs, leading to induced hemolysis [44]. Circulating NPs have also been observed to be actively internalized into human granulocytes and monocytes, with the specific endocytic mechanism yet to be fully elucidated [45]. In addition to the physicochemical properties of NPs, the interaction of NPs with immune cells in human blood is significantly influenced by the adsorption of various plasma components in a person-specific manner, contributing to the complexity of nano-blood cell interaction [46]. Although specific plasma proteins such as hemoglobin [46] and coagulation factor XII [47] are known to play crucial roles in NP-induced hematological responses, further investigation is required to understand how biological molecules modulate NP characteristics and subsequently regulate their hematological behaviors.

Furthermore, the vascular endothelium, a monolayer of ECs, is in direct contact with circulating NPs, and ECs have demonstrated the capacity to uptake NPs [48]. Four distinct pathways of endocytosis, including caveolin-mediated, clathrin-mediated, phagocytosis, and micropinocytosis, are well-recognized for their involvement in NP uptake of ECs [49]. Although the endothelial cellular uptake of NPs depends mainly on the characteristics of the NPs, it showed a negative correlation with the flow rate of the bloodstream [50,51]. However, the uptake of rod-like NPs is less affected by increased flow rate compared to spherical NPs [51]. Additionally, shear stress is an important factor contributing to mechanical damage of ECs induced by rod-like NPs, but not by the spherical NPs.

As has been shown above, the cardiovascular system is highly complex with multiple functional cells and various biological molecules. To date, research studies have revealed interactions between NPs and different cell types within the cardiovascular system, highlighting the crucial role of biomolecules in the behaviors and distribution of NPs (Figure 1). Given the critical and multifaceted role of the cardiovascular system in the distribution and toxicity of NPs, further study should focus on elucidating the detailed molecular mechanisms underlying these interactions. Specifically, studies should target cardiomyocytes, blood cells, and vascular ECs, aiming to understand the endocytic pathways and the role of specific receptors and plasma proteins in mediating NP uptake and effects.

3 Toxicity of NPs to the cardiovascular system and the underlying mechanism

3.1 Effect on blood components

Whole blood comprises essential components such as RBCs, white blood cells, platelets, and plasma, which are responsible for transporting oxygen and nutrients to tissues (RBCs), defending against external xenobiotic agents (white blood cells), and promoting blood clots formation in wounds (platelets). Plasma, on the other hand, creates a balanced acid–base environment and osmotic pressure, enabling the circulation of blood cells and critical proteins throughout the body. The toxicity of NPs to the cardiovascular system is initiated through their interaction with the diverse blood components.

In male BALB/c mice, administration of PS NPs *via* caudal vein injection led to coagulation dysfunction. This was evidenced by decreased prothrombin time and activated partial thromboplastin time, along with the increased plasma fibrinogen and elevated levels of tissue factor (TF), protease-activated receptor-1, and fibrinogen in the aortic arch [52]. The activation of the Janus kinase 1/signal transducers and activators of transcription-3/TF pathway was proposed as the main molecular mechanism underlying the nanoplastic-induced coagulation dysfunctions and prethrombotic state.

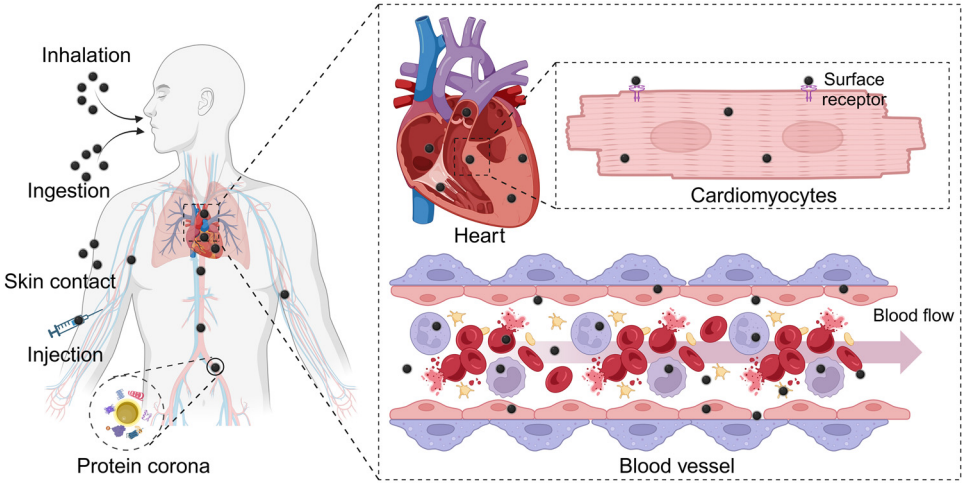

Figure 1: Routes of exposure, distribution of NPs, and interactions between NPs and different cell types within the cardiovascular system.

Similarly, pulmonary exposure to Ag NPs triggered prothrombotic events and alterations in plasma coagulation markers, including fibrinogen and plasminogen activator inhibitor-1, in BALB/c mice [53]. Consistently, activation of various hematologic parameters in human blood was observed after exposure to Ag NPs (12 nm, 30 mg/L). These included hemolysis of RBCs, α-granule secretion in platelets, approximately 4-fold increase of CD11b expression on granulocytes, elevated coagulation markers such as thrombin–antithrombin-III complex (about 1.6-fold increase), kallikrein-like and FXIIa-like activities, and activation of complement cascade [54]. In contrast, commercially available carboxylated PS NPs (hydrodynamic diameters of 49 nm in water) exhibited minimal hemolytic potential to RBCs but upregulated the expression of P-selection, a marker of platelets activation, and promoted platelet–monocyte aggregation at a concentration of 300 mg/L [55]. Furthermore, NPs such as graphene oxide NPs [56] and poly(n-butylcyano-acrylate) NPs were found to elicit an inflammatory reaction in blood [57]. When RBCs, mononuclear cells, and platelets were isolated and used to investigate the direct interaction between NPs and specific blood cell types. The RBCs displayed morphological changes [58,59] and hemolysis response [19,60] upon exposure to various types of NPs. The hemolytic activity of NPs is primarily attributed to oxidative stress and direct interactions with cell membranes [18,61,62]. Human peripheral blood lymphocytes exposed to NPs exhibited inflammatory response [63], G0/G1 cell cycle arrest [64], apoptosis [65], and DNA damage [66], dependent on the NPs' chemical composition, particle size, and surface modifications. Similar effects were also observed in lymphocytes from rodents [67] and cell lines such as the THP-1 human leukemia monocytic cell [68] and RAW 264.7 mouse monocyte/macrophage-like cell [56]. The toxicity of NPs to lymphocytes can be partly attributed to intracellular reactive oxygen species (ROS) imbalance [69] and dysfunction of mitochondria and lysosomes [70]. Additionally, various studies have shown that NPs affect platelets function through either procoagulant or anticoagulant activities, which were dictated by their physicochemical characteristics, like particle size and surface area [71,72]. Understanding NP–platelet interactions is crucial not only for developing safe nanomedicines to mitigate adverse biological effects but also for creating targeted therapeutics for critical clinical scenarios.

It is well-known that NPs entering the circulatory system can interact with proteins circulating in the blood, thereby altering their primary properties, biological behaviors, and toxicity [73–75]. However, much less is known regarding the pathological outcomes of NP-altered plasma protein components on individuals. A recent work reported that a primary lipid-based corona formed on the surface of silica (SiO_2) NPs following their entry into the alveoli of mice after intranasal instillation, which enhanced the adsorption of apolipoprotein A-I (Apo A-I) in the blood [76]. Although protein adsorption reduced the cellular uptake and cytotoxicity of SiO_2 NPs, the rapid elimination of the NPs decreased the Apo A-I level in the blood, resulting in atherosclerotic lesions, indicating the correlation between plasma protein adsorption and cardiovascular damage induced by NPs exposure. In contrast, polyvinylpyrrolidone-stabilized gold NP (Au NP) coatings could inhibit blood protein adsorption, indicating the potential use in blood-contact medical applications [77].

3.2 Damage to vascular structures

The vascular endothelium, comprising ECs, constitutes the inner layer of blood vessels and plays a pivotal role in regulating vascular functions such as blood flow, blood pressure, and angiogenesis [78]. ECs secrete various biologically active mediators, including nitric oxide (NO) and arachidonic acid derivatives, which contribute to vascular homeostasis [79]. The endothelial layer forms a non-thrombogenic and non-adhesive surface that maintains blood fluidity and acts as a selectively permeable barrier for molecules [80]. The interaction between NPs and ECs occurs as NPs pass through biological barriers *via* non-injected routes, circulate in the bloodstream, and undergo clearance from the blood. So far, NP-induced damage to the vascular structure has been confirmed *in vitro* [81], *ex vivo* [82], and *in vivo* [83]. Its exposure triggers endothelial leakiness and impairs angiogenesis by disrupting cytoskeleton organization, reducing the expression of cellular adhesion molecules, and inducing apoptosis in ECs [84–86]. Furthermore, NPs cause endothelial nitric oxide synthases (NOS) system disorder [87], oxidative stress [88], and endoplasmic reticulum (ER) stress [89], promoting vascular endothelial dysfunction. It is worth noting that non-coding RNAs also play key roles in NP-induced toxicity. For example, a cluster of RNA transcripts involved in the phagosome, gap junction, TNF, and chemokine signaling pathways is dysregulated in EA.hy926 human ECs after exposure to PM2.5 [90]. miR-451a negatively regulates the interleukin-6 receptor (IL6R)/STAT/TF signaling pathway, which accelerates SiO_2 NP-induced vascular endothelial dysfunction and prethrombotic state [91]. Additionally, autophagy perturbation is crucial in NP-induced EC dysfunction. For instance, various classical autophagy signaling pathways, generally mediated by ROS or NO/NOS system disorder, such as phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (mTOR) [92], mitogen-activated protein kinases (MAPK)/B-cell leukemia/

lymphoma 2 (Bcl-2) [93], and vascular endothelial growth factor receptor 2 (VEGFR2)/MAPK/extracellular signal-regulated kinase 1/2 (Erk1/2)/mTOR pathways [84], are involved in SiO_2 NP-induced endothelial dysfunction. Similarly, ROS-mediated mitochondria-lysosome damage [94,95] and NO/NOS system disorder-mediated autophagy [87] are responsible for Ag NP- and magnetic ferroferric oxide NP (Fe_3O_4 NP)-induced EC dysfunction, respectively. Recently, it was found that SiO_2 NPs (50 nm) induced cardiovascular toxicity in primary human umbilical vein endothelial cells (HUVECs) by triggering nuclear receptor coactivator 4 (NCOA4)-mediated autophagy, leading to ferroptosis [96]. Interestingly, NPs may also induce ROS- and endocytosis-independent endothelial leakiness. For example, anionic PS and poly(methyl methacrylate) NPs induced endothelial leakiness by disrupting vascular endothelial cadherin junctions in ECs, independent of ROS production, autophagy, and apoptosis [82].

3.3 Injury to the heart

The heart is a muscular organ that pumps blood throughout the body. According to a 2022 Statistical Update, heart failure impacts approximately 64 million people worldwide [97]. The incidence and mortality of heart failure are strongly associated with environmental pollution [98–100]. Studies have shown that exposure to NPs triggers cardiac dysfunction in rodents. For example, multi-walled carbon nanotubes exposed *via* oropharyngeal aspiration (4 mg/kg body weight) exacerbate myocardial ischemia–reperfusion (I/R) injury by activating mast cell and the IL-33/IL-1-like receptor ST2 axis [101]. In an *ex vivo* heart model, amorphous SiO_2 NPs disturbed cardiac function by increasing mitochondrial permeability [102]. In a mouse embryo model, zinc oxide NPs (ZnO NPs) increased the risk of heart tube malformation during early cardiogenesis by inducing apoptosis, programmed necrosis, and ferroptosis-mediated precardiac cell death [103].

In addition to mammalian models, the zebrafish (*Danio rerio*) model is a viable alternative for the cardiovascular toxicity study of hazardous chemicals [104]. A recent study proposed that zebrafish embryos can be utilized to predict the circulation times of NPs in mice and to facilitate the quantification of NP–cell interactions [105]. Potential adverse cardiac effects of various NPs, including neodymium oxide (Nd_2O_3) NPs [106], copper NPs [107], Au NRs [108], and carbon NPs [109], have been identified in zebrafish embryos. The primary adverse outcomes include pericardial edema, cardiac arrhythmia, and reductions in cardiac parameters such as stroke volume, ejection fraction, and cardiac output [86,107,110,111]. Interestingly, raising the environmental temperature from 27 to 30°C increased lethality but reduced cardiovascular toxicity of PS NPs by enhancing the myocardial contractility of larvae [111].

Recently, some non-animal models, including 3D cell co-cultures, organoids, and organ-on-a-chip technologies, have been developed for evaluating the health risks of environmental toxicants [27,112]. For high-throughput determination of the cardiotoxicity of NPs, a heart-on-a-chip model based on neonatal rat ventricular myocytes was constructed using a mussel-inspired 3D fiber scaffold [113]. Using this platform, researchers found that TiO_2 and Ag NPs impaired the contractile function of cardiac tissues by causing structural damage. In another study, a heart-on-a-chip platform was developed by seeding ECs and iPSC-derived cardiomyocytes onto a 3D perfusable and vascularized microfluidic system to evaluate the toxicity of air pollution-related NPs including CuO and SiO_2 NPs [114]. Results showed that CuO NPs are highly toxic to cardiac tissue, causing ROS-mediated electrical and contractile dysfunction through penetrating, which further disrupted cardiac troponin T and led to the release of cardiac injury biomarkers like B-type natriuretic peptide, N-terminated pro-hormone BNP, and Troponin I. In contrast, SiO_2 NPs primarily induced the secretion of pro-inflammatory cytokines and modulated the intracellular Ca^{2+} handling.

In addition to the cardiotoxicity induced by NPs, some studies have demonstrated that certain NPs may have protective effects against cardiotoxicity. For instance, curcumin NPs protected male Wistar albino rats from doxorubicin- and cisplatin-induced cardiotoxicity by preventing the chemical-induced oxidative stress and restoring the altered levels and activities of various cardiac parameters [115,116]. Similarly, zero-valent iron NPs functionalized with the biocompatible polymer sodium carboxymethylcellulose significantly protected male BALB/c mice from cecal ligation and puncture-induced septic myocardial injury. This protection was primarily achieved through attenuation of inflammation, inhibition of oxidative stress and apoptosis, improvement of mitochondrial function, regulation of ER stress, and activation of the AMP-activated protein kinase (AMPK) pathway [117]. These findings highlight the complexity of nano-heart interaction, underscoring the need for a more comprehensive and in-depth exploration of NP-disturbed cardiac function.

On the whole, NPs can interact with blood components and various cells within the cardiovascular system, causing toxicity at multiple levels. The induction of cellular stress and inflammation is a common mechanism underlying NP-induced cardiovascular toxicity, although the specific signaling pathways involved can vary significantly. Under real exposure conditions, NP-induced alterations in blood components, damage to vascular structures, and injury to the heart collectively contribute to adverse cardiovascular

outcomes, such as arrhythmia, atherosclerosis, myocardial infarction, and other cardiovascular diseases (Figure 2).

4 Critical factors affecting the cardiovascular toxicity of NPs

4.1 Primary physicochemical characteristics of NPs

It is well recognized that the physicochemical properties are key determinants of NP-induced toxicity [118,119]. Composition, particle size, shape, and surface functionalization are the four fundamental characteristics of NPs. This section discusses how these factors affect the cardiovascular toxicity of NPs and how to minimize the NP toxicity based on these four properties. Additionally, the distinct contribution of free metal ions released from metal-based particles is included (Figure 3a).

4.1.1 Composition

A pilot study comparing the differential toxicity of noble metal NPs indicated that Ag NPs are the most toxic, while Au NPs are non-toxic. Both Ag NPs and Au NPs exhibit similar uptake and accumulation in zebrafish embryos, which is higher than platinum (Pt) NPs [120]. Under identical exposure conditions, Ag NPs induce hatching delays, decreased heart rate, impaired touch response, axis curvatures, pericardial effusion, abnormal cardiac morphology, circulatory defects, and eye malformation. Pt NPs, on the other hand, cause hatching delays, decreased heart rate, impaired touch response, and axis curvatures. Furthermore, distinct toxicity to cardiovascular cells is observed among various metal-based NPs including ZnO, Ag, TiO_2, Fe_2O_3, Fe_3O_4, MgO, and Y_2O_3 NPs, as summarized previously [121]. For cross-comparison of results from different studies, most types of NPs exhibited procoagulant activity on platelets [122–125], whereas Ag NPs have been reported to have an anticoagulant effect in several studies [126,127]. Collectively, these studies suggest that composition is crucial in determining the cardiovascular toxicity of NPs.

4.1.2 Particle size

Several studies have shown that smaller NPs tend to be more toxic to the cardiovascular system than larger ones. For instance, 20 nm Fe_3O_4 NPs exhibit a greater capability to reduce lesion plaque stability and accelerate the progression of atherosclerosis compared to 200 nm Fe_3O_4 NPs in male C57BL/6J background apolipoprotein E-deficient ($ApoE^{-/-}$) mice, with the polarization of M1 macrophages associated with the unstable plaques [128]. Similarly, for SiO_2 NPs in the size range of 30–600 nm, smaller NPs show higher cardiovascular toxicity in male Wistar rats, and the endothelial NO/NOS system

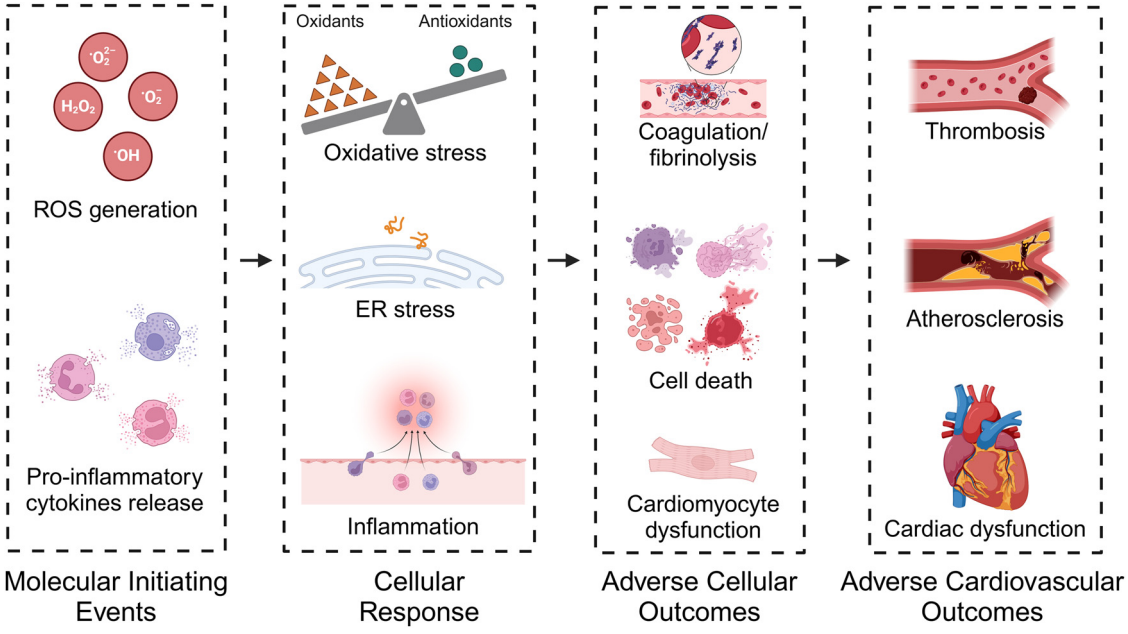

Figure 2: Key mechanism involved in NP-induced adverse cardiovascular effects.

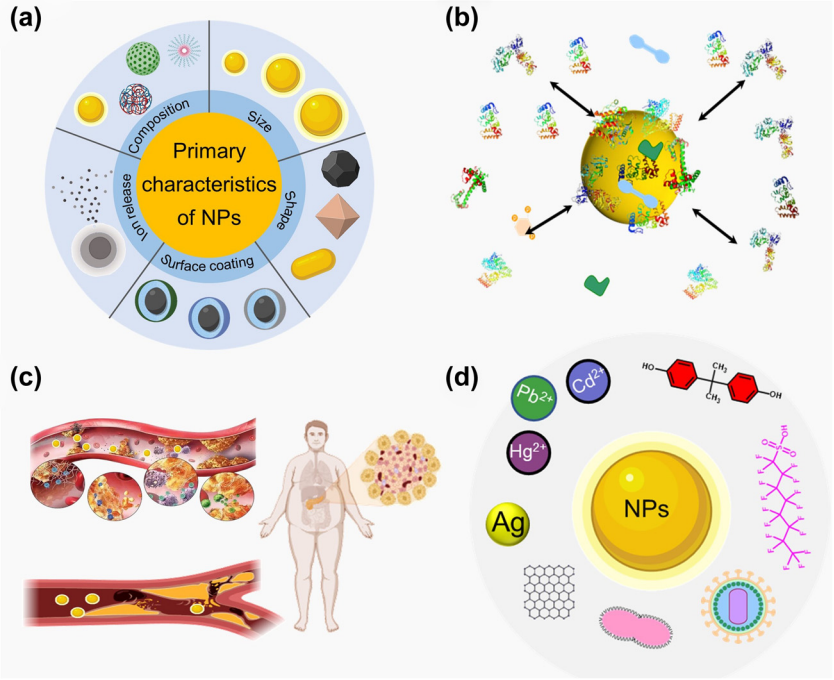

Figure 3: Critical factors affecting the cardiovascular toxicity of NPs. (a) The primary physicochemical characteristics of NPs. (b) Formation of biomolecular corona on the surface of NPs. (c) Different physiological and pathological conditions of the body. (d) Combined exposure to environmental chemicals.

disorder was considered one of the mechanisms involved in SiO_2 NP-induced endothelial dysfunction [83]. However, this tendency is not always consistent. A study comparing the cardiovascular toxicity of Ag NPs of varying sizes with capping agents found that 20 nm Ag NPs induced greater cardiac I/R injury in male Sprague–Dawley rats than the 110 nm NPs 1 day following intratracheal instillation, independent of the capping agent [129]. However, the greatest injury occurred in rats exposed to 110 nm polyvinylprryolidone-capped Ag NPs 7 days after intratracheal instillation. Particle size showed minimal effect on NP-triggered toxicity to vascular ECs for ZnO NPs of 20 and 90 nm [130], and nitrodopamide–poly(ethylene glycol)-grafted iron oxide NPs of 3.3, 6.7, and 8.0 nm [131]. While Au NPs (50 nm) showed the highest surface adsorption and internalization by fish RBCs compared to smaller (15 nm) or larger (100 nm) ones [18], Au NPs in the size range of 10–30 nm were considered effective in inducing endothelial leakiness [132]. Hence, there might be a cut-off size for NPs to induce cardiovascular toxicity, which may depend on the properties of NPs and the adverse outcomes measured.

4.1.3 Shape

Shape regulates the cardiovascular fate and toxicity of NPs, particularly during the interaction with ECs in the cardiovascular system. More spherical and rod-like Au NPs are taken up by HUVECs than hollow NPs and core/shell silica@gold nanocrystals with the same coating [133]. Rod-like NPs generally interact more with vascular ECs than spherical NPs under both static and flow conditions. For example, elongated rod-shaped PS NPs demonstrate greater binding ability with cerebral microvasculature cells than the PS spheres [134]. The uptake and elimination of rod-like SiO_2 NPs are faster than those of spherical NPs, although their peak accumulations in HUVECs are comparable [51]. Interestingly, larger rod- and disk-shaped PEG NPs show higher uptake than smaller ones, which is opposite to the size effect observed for spherical particles under flow conditions [135]. Utilizing this shape-induced enhancement of endothelial targeting, a pilot study confirmed the possibility of applying antibody-coated rod-shaped PS structures for targeting lung and brain endothelium [136].

4.1.4 Surface coating

Modifying the NP surface can easily alter their physicochemical properties, including electronegativity, hydrophobicity, and even targeting specific proteins. Consequently, surface functionalization has become a popular strategy for designing and synthesizing NPs. Surface chemistry is critical for NP-

induced toxicity in the cardiovascular system. For example, in H9c2 cells, cerium oxide NPs showed surface-charge-dependent cell localization and cytotoxicity. Positively charged NPs were the most toxic, although neutral NPs had the highest cellular internalization [137]. While PEG-modified Au nanorods exhibited negligible toxicity to both vascular endothelial and smooth muscle cells because of the lower cellular uptake, rod-like Au NPs coated with polyelectrolyte could be internalized by vascular endothelium, causing cytotoxicity and impairing the relaxation function of aortic rings [138]. In another study comparing the differential adverse effects of SiO_2 NPs with various functionalization-amino (NH_2-SiO_2), polyethyleneimine (PEI-SiO_2), succinic acid (SUCC-SiO_2), and PEG functionalization (PEG-SiO_2). PEI-SiO_2 had the most disruptive effect on blood circulation due to its efficient penetration into the zebrafish embryo, followed by SUCC-SiO_2 and PEG-SiO_2, depending on surface-functionalization-controlled penetrance of biological membranes [139]. Drug coating (*e.g.*, antibodies, RNA) can also impact the toxicity of NPs by altering their surface charge, size, or biocompatibility of NPs, which may, in turn, affect their toxicity to the cardiovascular system. For instance, a noncationic NP coated with a shell of microRNA-146a oligonucleotides, which regulate the NF-κB pathway, can specifically target class A scavenger receptors on plaque macrophages and ECs, offering potential benefits for cardiovascular disease [140]. NPs conjugated with antibodies have been considered as an effective tool for targeted therapy of cardiovascular diseases [14]. However, it has been found recently that antibody-targeted NPs prepared by conjugation chemistries activated the complement cascade of plasma proteins, leading to large changes in the biodistribution of NPs and multiple toxicities, which included a 50% drop in platelet count [141].

4.1.5 Ion release

Metal-based NPs release metal ions into the solution, potentially contributing to cardiovascular toxicity following NP exposure. In a recent study, Ag NPs were found to induce oxidative stress, DNA damage, and apoptosis in the heart and trigger prothrombotic events and alterations in coagulation markers in BALB/c mice [53]. Variations in effects were observed between the particles and Ag^+. Specifically, Ag^+ increased thrombogenicity and oxidative stress marker without causing DNA damage or apoptosis in the heart, unlike Ag NPs. Some studies attribute observed toxic effects solely to either particles or metal ions. For instance, selenium NPs, but not sodium selenite, were reported to increase mortality, pericardial edema, and cardiac arrhythmia in zebrafish (*D. rerio*) embryos in a dose-dependent manner [110]. Conversely, Zn^{2+} not ZnO NPs, contributed to cytotoxicity in H9c2 cells, evidenced by morphological damage, decreased intracellular expression of cardiac protein (troponin I and atrial natriuretic peptide), alterations in mitochondrial membrane potential, and cell death [23]. In a word, distinguishing particle effects from those of the released ions heavily relies on the advancing analytical methods for *in situ* characterization of the NP state, necessitating future research efforts.

4.2 Secondary modification by biological molecules

Although NPs with varied physicochemical properties are used to evaluate their adverse effects on cells or animals, they are not what the cells exactly "see." Upon entering the complex physiological environments, NPs adsorb a variety of biomolecules to form biomolecule corona, such as protein corona, which gives the NPs a new identity that determines the nano-bio interactions [142,143]. As a result, secondary modification by biological molecules is crucial in cardiovascular nanotoxicity (Figure 3b).

The formation of protein corona generally reduces the cardiovascular toxicity of NPs. For instance, the pre-formation of a serum protein corona around citrate-capped Au NRs eliminated nanorod-induced hemolysis and morphology change in mouse RBCs, reduced the uptake of nanorods by phagocytic U937 monocytes, and mitigated complement activation induced by citrate-capped Au NRs [144]. The protein corona also mitigated the cytotoxicity and inflammatory response induced by NPs in various types of cardiovascular cells, such as HUVECs [145,146], THP-1 [147,148], and RAW264.7 cells [149,150], by preventing direct interaction of NPs with cell membranes, aggregation and/or degradation of NPs, reducing cellular uptake of NPs, and subsequently decreasing ROS production [143]. In BALB/c mice, the specific adsorption of blood coagulation factor XII prevented the abnormal activation of the coagulation cascade induced by amorphous silica NPs with diameters of 70 nm [151]. In contrast, some studies have suggested that protein adsorption enhances the cardiovascular toxicity of NPs. On the one hand, an inflammatory response was promoted in various circulation-related cells like neutrophils [152], HUVECs [153], THP-1 [154,155], and RAW264.7 cells [153], with the induction of oxidative stress, unfolded protein response, and activation of inflammatory signaling pathways. On the other hand, the enhancement of the NP-activated complement system was confirmed both *in vivo* [156] and *in vitro* [157]. This disagreement is understandable due to the extremely complex protein components in blood, which can regulate the

properties and bio-effects of NPs in diverse and person-specific manner [46,158].

In addition to governing whole-body circulation, the cardiovascular system serves as a crucial conduit linking various internal organs while biological barriers demarcate them. Limited research has indicated that the protein corona formed on NPs governs barrier crossing, tissue targeting, and NP accumulation [159,160]. Conversely, barrier crossing has been observed to alter the components of the protein corona [161]. Nevertheless, the intricate interplay between barrier crossing and protein corona structure remains insufficiently understood.

4.3 Physiological and pathological conditions of the body

The biological functions of the body vary under different physiological and pathological conditions, leading to distinct responses to environmental contaminant exposures. Consequently, the health risks of environmental contaminants, including NPs, to susceptible population groups particularly vulnerable to pollutants or other environmental hazards [162], have been evaluated recently [163]. For example, in atherosclerosis-prone ApoE$^{-/-}$ mice, exposure to NPs such as nickel NPs [164] and single-walled carbon nanotubes (SWCNTs) [165] resulted in increased plaque formation and accelerated atherosclerosis progression. Inhalation of Zr-doped CeO_2 NPs for 4 weeks *via* nose-only exposure (4 mg/m^3 NP for 3 h/day, 5 days/week, and recovery for 4 weeks post the final exposure) triggered lung inflammation in ApoE$^{-/-}$ mice exclusively, without altering the size of atherosclerotic plaques [166]. In perfused hearts isolated from spontaneously diabetic Wistar rats or hypertensive rats, Ag NPs induce sustained vasoconstriction and enhanced cardiac contractility, with or without impacting the NO/NOS system functionality (Figure 4). Both diabetes and hypertension conditions heightened the cardiotoxic effects of Ag NPs [167,168]. A similar accelerated cardiovascular response was observed in a spontaneously hypertensive rat model, demonstrating that SWCNTs induced endothelial dysfunction in the pulmonary circulation and peripheral vascular thrombosis [169]. These results suggest that individuals with preexisting cardiovascular diseases are more vulnerable to NP exposures (Figure 3c).

NPs also exhibit increased toxicity to the cardiovascular system in other susceptible populations. For instance, carbon black [170], carbon nanotubes [171], and TiO_2 NPs [172] impaired the coagulatory functions of mice with pulmonary inflammation, likely due to enhanced permeability in the pulmonary vessel. RBCs isolated from cancer patients were more sensitive to the procoagulant effects of Ag NPs [173]. In a study comparing the differential toxicity of SiO_2 NPs in male Sprague–Dawley rats at ages 3 weeks, 8 weeks, and 20 months – representing young, adult, and old age groups – myocardial ischemic damage, atrioventricular blockages, and increased fibrinogen concentration and blood viscosity were observed exclusively in old age rats [174].

4.4 Combination with other environmental chemicals

In general, NPs do not exist independently but are combined with other organic or inorganic chemicals in the natural environment. It is well-known that the surface properties and biological performance of NPs can be modified by co-existing environmental chemicals [175]. However, the combined effect of NPs and other environmental chemicals is often overlooked [176]. Understanding these interactions is crucial for assessing the real-world risks associated with NP exposure in environments where multiple chemicals coexist. It underscores the importance of evaluating not only individual NP toxicity but also considering their interactions with other environmental stressors for comprehensive cardiovascular risk assessment and mitigation strategies (Figure 3d).

To date, various studies have shown that NPs and their bound chemicals can independently induce oxidative stress and inflammation in cardiovascular tissues. Co-exposure may exacerbate these effects through synergistic interactions, intensifying cellular damage and impairing cardiovascular function. For example, co-exposure with methylmercury further aggravates SiO_2 NP-induced bradycardia, vascular endothelial damage, and neutrophil-mediated inflammation in zebrafish (*D. rerio*) embryos. Oxidative stress and genes including *stxbp1a*, *celf4*, *ahr1b*, and *bai2* are associated with co-exposure-induced cardiovascular toxicity, and cardiac muscle contraction is targeted by *dre-miR-7147*, *dre-miR-26a*, and *dre-miR-375* [177,178]. In another study, combined exposure to SiO_2 NPs and $CdCl_2$ caused more severe cardiovascular damage, indicated by altered heart morphology, reduced heart rate, and damaged vascular ECs through oxidative stress, cellular apoptosis, and inflammation [179]. In male Sprague–Dawley rats, co-administration of SiO_2 NPs with lead acetate or methylmercury also led to additive or synergistic cardiovascular toxicity, evidenced by endothelial damage, hypercoagulation,

myocardial interstitial edema, and ultrastructural changes such as myofibril disorder, myocardial gap expansion, and mitochondrial damage [180,181]. Similar findings were observed when NPs were co-exposed with 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153), a typical organic environmental contaminant, exhibiting increased stroke volume and potentiated brain damage in C57BL/6 mice subjected to I/R [182].

Despite the enhanced cardiotoxicity of NPs and environmental contaminants, antagonistic effects have also been reported. A recent study showed that PS NPs could

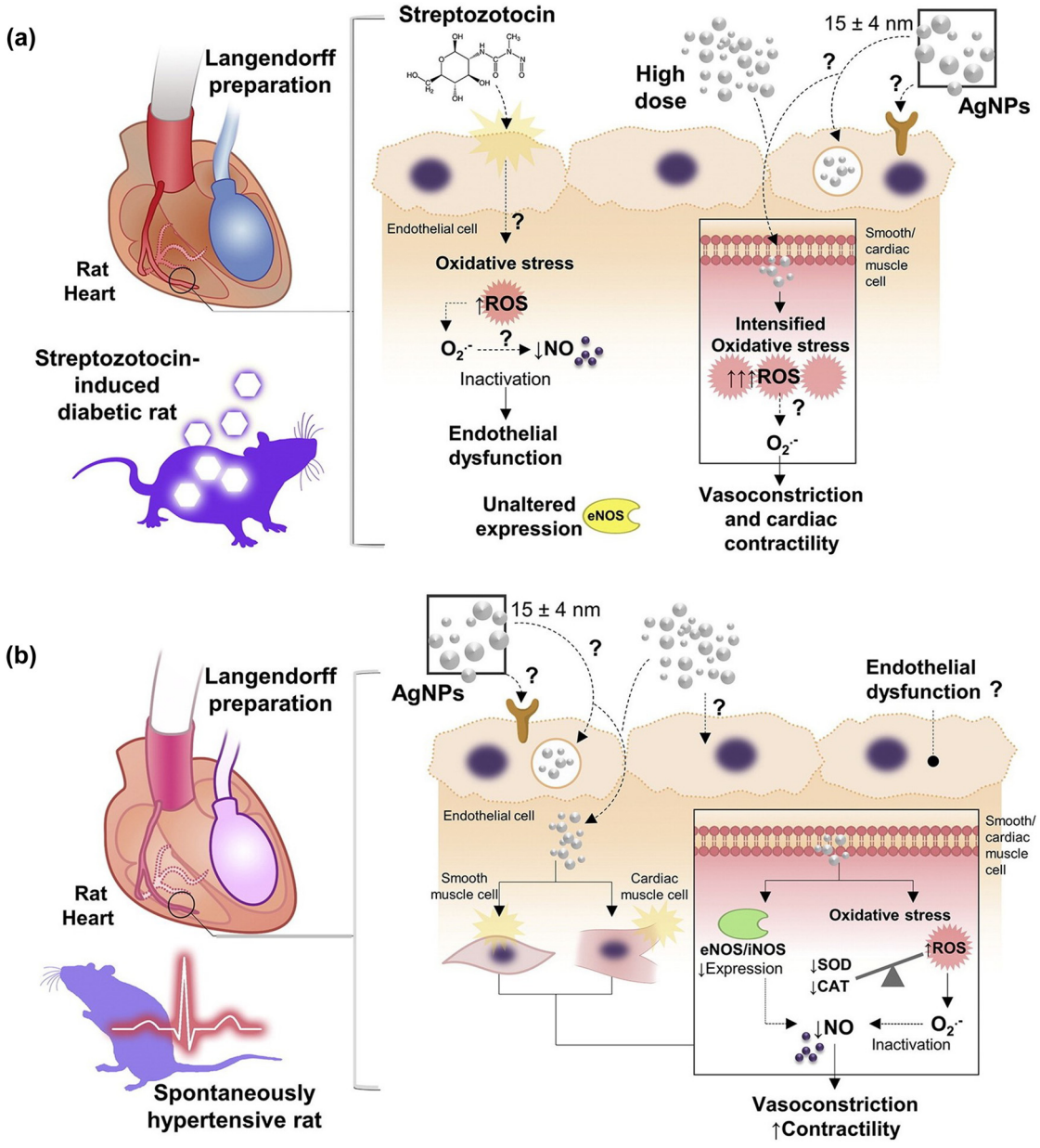

Figure 4: Diabetes and hypertension intensified cardiotoxicity because of Ag NPs administration in isolated perfused hearts. (a) Ag NP cardiac effects in diabetes were evaluated using perfused hearts from streptozotocin (STZ)-induced diabetic rats using the Langendorff preparation. STZ-induced diabetic rats showed low basal levels of NO. Ag NPs promoted persistent vasoconstriction, increased cardiac contractility, ROS release, and catalase (CAT) expression. Furthermore, Ag NPs did not alter NO production nor endothelial NO-synthase (eNOS) expression. Reprinted from Ramirez-Lee *et al.* [167]. Copyright © 2017 Elsevier Inc. (b) Ag NP cardiac effects in hypertension were evaluated using perfused hearts from spontaneously hypertensive rats according to the Langendorff preparation. Ag NPs promoted persistent vasoconstriction and increased cardiac contractility. Furthermore, Ag NPs reduced NO generation by reducing endothelial/inducible NO-synthase expressions. Ag NPs increased ROS release and reduced antioxidant enzyme expression such as CAT and superoxide anion dismutase (SOD). Reprinted from Ramirez-Lee *et al.* [168]. Copyright © 2017 Elsevier Inc.

adsorb the polycyclic aromatic hydrocarbons (PAHs) from the exposure medium, decreasing the bioavailability and bioaccumulation of PAHs, and consequently diminishing PAH-induced cardiovascular toxicity in developing zebrafish [183]. Taken together, the complex interactions between NPs and other environmental chemicals require more comprehensive investigation in future research. Specifically, the effects of co-existing natural organic matter and inorganic ligands, beyond conventional contaminants, on NP-induced cardiovascular toxicity should be carefully evaluated.

5 Gaps and insight

Besides the extensive toxicity/safety evaluation of NPs in relation to human health and environmental safety, so far, whether therapeutic NPs will provide more benefits or pose greater toxicity is a critical issue in the field of nanomedicine. On the one hand, therapeutic NPs can improve the efficacy and bioavailability of free drugs and minimize systemic side effects, which might result in better therapy outcomes. However, concerns remain regarding the toxicity of the NPs themselves and their interaction with the body. For example, some NPs may accumulate in certain organs (like the liver or spleen) over time leading to adverse effects. Furthermore, the drug release profile from NPs may not always be as predictable or controllable as expected, which could result in off-target effects. As mentioned above, the properties of the NPs, such as size, surface charge, and material composition, influence their biocompatibility, toxicity, and other nano-bio interactions. Therefore, specific design strategies can be employed to increase the efficacy/toxicity ratio of NPs. For instance, surface modification is the most commonly used strategy for minimizing NP toxicity. Functionalizing NPs with biocompatible polymers (*e.g.*, PEGylation) or preparation biomimetic NPs with natural molecules (*e.g.*, albumin, chitosan, cell membrane, and extracellular vesicles) can evade the immune system, extend the circulation time, and increase therapeutic efficacy.

Despite these research advances, several specific gaps in current knowledge warrant immediate attention, such as the influence on cardiac electrophysiology, especially their effects on arrhythmogenic potential and conduction system. Understanding and evaluating how NP can affect cardiac electrical activity, cardiac conduction system (*e.g.*, atrioventricular node and Purkinje fibers) and impulse propagation is crucial for assessing potential cardiovascular toxicity. Another special gap is the NP-bio interactions with pre-existing cardiovascular conditions. Studying how NPs interact with cardiovascular tissues already compromised by diseases (*e.g.*, hypertension and atherosclerosis) is vital. Such studies can determine whether NPs exacerbate existing conditions or induce novel pathophysiological responses.

Moreover, knowledge gaps regarding the fate and adverse impacts of NPs on the human cardiovascular system remain to be elucidated, primarily due to limited direct evidence on the health risks of NPs exposure in humans. Addressing these gaps requires interdisciplinary research efforts integrating nanotechnology, cardiovascular biology, toxicology, and clinical medicine. Robust preclinical models, advanced imaging techniques, and biomarker assessments are essential tools to advance our understanding of NP cardiovascular distribution and toxicity, ultimately facilitating safer clinical translation of NP-based therapies and diagnostics.

6 Conclusion

The increased applications of nanotechnology have led to innovations in various fields; however, serious concerns are rapidly arising regarding NP-induced potential toxicity to public health. NPs entering the circulation can interact with various components of the cardiovascular system at multiple levels, leading to cardiovascular toxicity. Both the synthetic identity including composition, size, shape, surface coating, Ion release, and biological identity (after absorption with biological molecules) of NPs, as well as the exposure dose and time affect the NP-induced cardiovascular toxicity. However, it is worth noting that the real-world NP exposure scenarios differ significantly from controlled laboratory conditions. In the real world, organisms are exposed to a complex mixture of NPs, which can interact differently with biological systems compared to simplified NPs used in controlled experiments; Low-dose and chronic exposure would contribute to the potential accumulation of NPs in tissues and organs over time. Moreover, the combined effects of NPs and other environmental pollutants or stressors (*e.g.*, heavy metals and organic pollutants) on human health are often overlooked. On the other hand, specific design strategies can be employed to mitigate adverse biological effects while preserving the intended therapeutic and diagnostic benefits of NPs. For instance, modulating surface charge and hydrophilicity can influence NP biodistribution and cellular uptake, potentially minimizing toxicity by reducing off-target interactions and enhancing biocompatibility. Optimizing NP size and shape, and choosing biocompatible core materials are also crucial to avoid harmful effects. Collectively, these strategies advance

the development of safer and more effective nanomedicines and diagnostic tools, contributing to improved outcomes in biomedical applications.

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