Nanomaterials and exercise interventions: A synergistic approach for atherosclerosis therapy (Review)

QUANQUAN ZHOU[1], GE-LIN ZHANG[2], WEITONG SUN[3], JIAYI CAI[4] and LI-HUA YU[3]

[1]College of Physical Education, Shandong Sport University, Jinan, Shandong 250000, P.R. China; [2]College of Physical Education, Changsha University of Science and Technology, Changsha, Hunan 410000, P.R. China; [3]College of Physical Education, Yanshan University, Qinhuangdao, Hebei 066000, P.R. China; [4]School of Economics and Management, The University of Sydney, Sydney NSW 2006, Australia

Received August 27, 2025; Accepted November 12, 2025

DOI: 10.3892/ijmm.2025.5715

Abstract. Atherosclerosis constitutes the fundamental pathological basis for cardiovascular diseases, with its pathogenesis intricately associated with dysfunctions in vascular endothelial and smooth muscle cells. Nanomaterials have emerged as a promising research focus within the biomedical field, attributed to their distinctive physicochemical properties. The present review explores the potential of nanomaterials, in conjunction with exercise interventions, to synergistically enhance vascular cell function, thereby presenting innovative therapeutic strategies against atherosclerosis. The present review systematically evaluates the various types of nanomaterials, elucidates their mechanisms of action, examines the synergistic effects of exercise interventions and discusses the challenges encountered in clinical translation, along with prospective directions for future research in this dynamic field.

Contents

Correspondence to: Dr Li-Hua Yu, College of Physical Education, Yanshan University, 438 West Section of Hebei Street, Haigang, Qinhuangdao, Hebei 066000, P.R. China
E-mail: yulihua7890@126.com

Key words: nanomaterials, vascular cell function, exercise intervention, atherosclerosis, synergistic therapy

1. Introduction

Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction, lipid accumulation and plaque formation within arterial walls, notably contributing to cardiovascular morbidity and mortality on a global scale (1). According to the 2024 Heart Disease and Stroke Statistics Update of American Heart Association, cardiovascular diseases, for which atherosclerosis is the underlying pathology in most cases, remain the leading cause of death globally (2). Traditional therapeutic approaches, such as the use of statins, have proven effective in reducing cholesterol levels and decreasing the incidence of cardiovascular events (3). However, these treatments are frequently associated with adverse effects and may not be suitable for all patients. Consequently, there is an urgent demand for alternative therapeutic strategies that can effectively manage atherosclerosis while minimizing side effects. Recent advancements in nanotechnology have highlighted the potential of nanomaterials to carry out a pivotal role in the treatment and prevention of atherosclerosis (4). Nanomaterials exhibit unique properties, including high surface area, modifiability and targeted delivery capabilities, rendering them particularly advantageous for drug delivery and the modulation of cellular functions. Furthermore, exercise has been shown to improve vascular function through various mechanisms, including enhanced endothelial nitric oxide (NO) production and reduced oxidative stress (5,6). Combining the therapeutic potential of nanomaterials with the beneficial effects of exercise presents a novel approach to enhance vascular health and combat atherosclerosis.

Previous research suggests that nanomaterials can modulate the inflammatory response in vascular cells, thereby mitigating the progression of atherosclerosis (7-9). Certain nanoparticles, for example, have been shown to suppress the expression of pro-inflammatory cytokines and facilitate the resolution of inflammation in endothelial cells (ECs) (9,10). Nanomaterials can potentially halt or reverse atherosclerosis by targeting inflammatory pathways (11). Combining these with exercise, which releases factors such as NO to improve endothelial function (12), may enhance their therapeutic effects (13). Exercise could also increase the delivery and effectiveness of nanomaterial treatments in the vascular system.

Previous research has highlighted the importance of understanding the interactions between nanomaterials and the vascular microenvironment (14,15). The distinctive properties of nanomaterials considerably affect their behavior within biological systems, encompassing aspects such as biocompatibility, biodistribution and pharmacokinetics (16). Consequently, an in-depth examination of these interactions is imperative for optimizing the design of nanomaterials specifically engineered for vascular applications.

The present review explores how combining nanomaterials with physical exercise can impact atherosclerosis. It examines numerous studies on using nanomaterials to improve endothelial function, reduce inflammation and aid lipid clearance in atherosclerotic lesions. Additionally, it examines how exercise enhances the effectiveness of nanomaterial therapies and the biological mechanisms involved. Ultimately, integrating nanomaterials with physical exercise presents a promising strategy for improved vascular health and reduced cardiovascular disease burden. Future research should focus on understanding these synergistic effects and exploring clinical applications for managing atherosclerosis.

2. The role of nanomaterials in regulating vascular cell function

Protective effects of nanomaterials on vascular ECs. Nanomaterials have emerged as promising agents for the protection of vascular ECs by reducing oxidative stress and inflammation, and enhance the release of NO (17,18). For example, gold nanoparticles have been demonstrated to activate the nuclear factor erythroid 2-related factor 2 signaling pathway (19), which reduces reactive oxygen species (ROS) production. This activation markedly reduces oxidative stress in ECs, preserving their function and integrity (19). Moreover, silica nanoparticles carrying anti-inflammatory drugs effectively inhibit the NF-κB pathway, reducing endothelial inflammation (20). This is key as chronic inflammation carries out a key role in endothelial dysfunction and the advancement of atherosclerosis (20). Additionally, carbon-based nanomaterials can mimic endothelial nitric oxide synthase (eNOS) activity, promoting the release of NO, which is key for vasodilation (21). This increase in NO improves vascular tone and contributes to the protective effects on ECs, highlighting their potential as treatments for vascular diseases.

Protective effects of nanomaterials on vascular smooth muscle cells (VSMCs). Nanomaterials carry out a key role in influencing VSMC phenotypes by inhibiting pathological proliferation and maintaining a contractile phenotype (22). Polymer-based nanoparticles are used to deliver miR-145, which regulates the transcription factor Krüppel-like factor (KLF) 4, key for VSMC phenotype modulation (23). By modulating the expression of KLF4, these nanoparticles effectively inhibit the pathological VSMCs proliferation, a key characteristic of atherosclerosis (24,25). Furthermore, magnetic nanoparticles activate the RhoA/ROCK pathway, thereby promoting the maintenance of a contractile phenotype in VSMCs. This mechanical activation is essential for preventing the phenotypic transition from a contractile to a synthetic state, a process frequently associated with vascular remodeling and the development of atherosclerotic plaques (26). Additionally, nanofibrous scaffolds provide mechanical cues that influence the remodeling of the extracellular matrix, consequently affecting collagen secretion and the overall vascular architecture (27).

Optimization strategies for nanomaterial targeted delivery systems. Optimization of nanomaterial-based targeted delivery systems is essential for improving their therapeutic efficacy in vascular applications. Surface modification techniques, such as polyethylene glycol-ylation, have been utilized to extend the circulation time of nanoparticles within the bloodstream (28), thereby enhancing their bioavailability and reducing premature clearance by the immune system. Moreover, the incorporation of targeting ligands, such as RGD peptides, can substantially increase the specificity of these nanomaterials for diseased vascular sites, facilitating more effective treatment of conditions such as atherosclerosis (29). Stimuli-responsive systems such as pH-sensitive nanocarriers allow localized drug release in the acidic environments of atherosclerotic plaques, increasing drug efficacy and reducing side effects (30). Combining therapies, such as photothermal treatment with drug delivery, enables precise control over treatment timing and location, optimizing outcomes in vascular diseases (31). These strategies enhance the role of nanomaterials in vascular health therapy.

3. Mechanisms of exercise interventions in improving vascular function

The mechanical and biological effects of shear stress on vascular cells. Exercise applies mechanical forces to the vascular endothelium, mainly through blood flow-induced shear stress, which activates signaling pathways key for endothelial function (32). This includes the activation of eNOS, leading to increased NO production, essential for vascular relaxation and homeostasis (33). Shear stress also boosts KLF2 expression, protecting ECs by regulating inflammation and vascular tone (34). Additionally, exercise-induced blood flow influences the cell cycle of vascular wall cells, promoting their proliferation and migration, key for vascular remodeling and repair (35). Shear stress activates mechanotransduction pathways, such as the integrin-FAK-Akt signaling cascade, which are important for ECs to adapt to mechanical stimuli and preserve vascular integrity (36,37).

Exercise-mediated metabolic reprogramming. Physical exercise triggers metabolic changes in various tissues, including the vascular system, by activating AMPK and Peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), which increase mitochondrial function and biogenesis (38,39). This enhances energy production and oxidative capacity in ECs, improving vascular function. Exercise also facilitates lipid metabolism by delivering liver X receptor agonists through nanocarriers, regulating cholesterol and inflammation in vascular tissues (40,41). Increased autophagic flux, supported by exercise and mTOR-inhibiting nanomedicines (42), helps degrade damaged organelles and proteins (43,44), enhancing cellular health and vascular healing.

Systemic regulation of the vascular microenvironment by exercise. Physical exercise triggers changes in the vascular microenvironment, affecting circulating factors that improve vascular function (45). A key element is irisin, a myokine released during exercise, which increases vascular permeability and aids drug delivery, especially in nanomedicine. Moreover, exercise also redistributes immune cells, notably stabilizing atherosclerotic plaques through the activation of Ly6C^low monocytes (46). This alteration in immune cell dynamics carries out a key role in promoting vascular health and stability. Additionally, exercise-regulated sympathetic nervous system activity can enhance the distribution and effectiveness of therapeutic agents, including nanomedicines, in targeted vascular tissues (47). These adaptations underscore the role of exercise in improving vascular health and function.

4. Nanomaterials and exercise synergistically combat atherosclerosis: Experimental evidence

Synergistic effects in preclinical research models. Preclinical studies using animal models, especially the alipoprotein $E^{-/-}$ ($apoE^{-/-}$) mouse model relevant to atherosclerosis, have shown that combining exercise with nanomaterials such as poly-lactide-co-glycolic acid (PLGA) nanoparticles markedly reduces plaque area by ~42% compared with using either alone (48,49). This suggests that nanocarriers can enhance the benefits of exercise by improving drug delivery in vascular tissues. Additionally, research with porcine coronary artery models indicates that injectable hydrogels combined with exercise improve vascular remodeling, showing that exercise can increase the effectiveness of nanomaterials (13). Additionally, research employing 3D vascular chips has provided valuable insights into the dynamic responses of nanofibers under conditions that simulate exercise, highlighting the key role of mechanical forces in influencing the interaction between nanomaterials and vascular cells (50). These findings collectively indicate that the integration of exercise with nanomaterial therapies can lead to enhanced vascular health and reduced atherosclerotic burden. However, despite the promising nature of the preclinical evidence discussed, the clinical translational potential of the combined nanomaterial and exercise therapies remains unverified. Currently, there is a notable lack of relevant clinical studies involving humans. Advancing this field necessitates the execution of rigorously designed clinical trials to clarify the biodistribution, safety and potential synergistic effects of nanomaterials in conjunction with exercise within patient populations.

Molecular mechanisms of synergistic action. Exercise and nanomaterials work together at the molecular level to combat atherosclerosis through several mechanisms (51). A key mechanism is epigenetic regulation, where exercise boosts the demethylation effects of histone deacetylase inhibitors delivered by nanocarriers, enhancing their therapeutic impact on vascular health (52,53). Additionally, exercise-induced exosomes and exosome-like nanoparticles interact to strengthen cellular signaling pathways vital for cardiovascular disease prevention and treatment (54). Furthermore, the timing of exercise can affect the efficacy of pH-sensitive nanomedicines, indicating that exercise-related biological rhythms can influence nanomaterial therapy outcomes (55). These molecular insights underscore the complex interplay between exercise and nanotechnology in the treatment of atherosclerosis, emphasizing the need for a tailored approach that considers both physical activity and nanomaterial properties.

Validation of synergistic effects using advanced imaging techniques. Advanced imaging technologies, such as cutting-edge imaging technologies, have markedly validated the combined effects of exercise and nanomaterials. PET/MRI has been key in tracking nanoparticle distribution during exercise, offering insights into treatment dynamics by visualizing their accumulation in atherosclerotic lesions (56). Furthermore, super-resolution microscopy has precisely observed nanomedicine deposition on plaque fibrous caps after exercise, suggesting enhanced targeted delivery (57). Additionally, Raman spectroscopy effectively monitors biochemical changes in plaques post-exercise and nanomaterial treatment (58,59). Collectively, these advanced imaging techniques not only validate the synergistic effects observed in preclinical models but also pave the way for future clinical applications, highlighting the potential of integrating exercise with nanomedicine to mitigate atherosclerosis.

5. Nanomedicine: Innovation in drug delivery strategies

Numerous therapeutic drugs can slow atherosclerosis by enhancing SMC function. Several therapeutic agents include short hairpin RNA, small interfering (si)RNAs, natural extracts and chemicals (60-63). However, the application of these therapeutic agents for the treatment of metabolic disorders is unfortunately limited by pharmacological issues, including drug instability, rapid degradation and poor specificity (64).

Nanomedicine has attracted widespread attention due to its advantage in drug delivery (65). As theragnostic agents with high molecular specificity, nanoparticles have been shown to serve as drug delivery carriers to facilitate the diagnosis and treatment of diseases. Due to their dimensions <100 nm (ASTM International, 2006), the advantages of nanoparticles include i) efficient delivery of drug insoluble or poorly soluble in water, ii) targeted drug delivery in a tissue/cell type -specific pattern, iii) controlled absorption and sustained drug release, iv) delivery of drugs to intracellular sites of action or to the soma, v) high binding ability and capture efficiency due to a relatively high surface to volume ratio, vi) delivery of two or more drugs for combination therapy due to the nano-sizes, vii) visualization of drug sites by combining therapeutic agents with imaging modalities; viii) protect the therapeutic agents and increase their stability, viiii) immune-evading and tumor-targeting capabilities and x) great biocompatibility and high drug loading efficiency *in vivo* drug efficacy (66-70). Nanomedicine has incomparable advantages over ordinary drugs. It has high solubility, can greatly enhance the absorption and bioavailability of oral drugs, can make the drug pass through the blood-brain barrier to act on the central nervous system, can penetrate the epidermis to enhance the absorption of the preparation and can also enhance the drug targeting. Therefore, nanoparticles have a wide application in the field of biomedicine due to their aforementioned medical characteristics.

Despite its advantages, nanomedicine has several drawbacks, such as toxicity, genotoxicity and carcinogenicity. Given their small size, nanoparticles can circulate in the body and accumulate in tissues, posing health risks. Metal nanoparticles such as titanium dioxide, gold, silver and platinum can harm human health. For example, 21 nm titanium dioxide nanoparticles can cause neuroinflammation, brain and spleen injury, heart damage, and lung toxicity (71,72). Gold nanoparticles have been found in urine and blood 3 months after exposure (73), and platinum nanoparticles accumulate in the liver and spleen, causing liver and kidney toxicity (74). To date, the advantages of using nanoparticles over traditional medical strategies seem to outweigh their disadvantages. Nanoparticles in medicine must be designed carefully and validated through a series of experiments to ensure their safety.

6. Application of nanomedicine for therapeutics of atherosclerosis

Nanomedicine, using nanomaterials such as nanoparticles, is rapidly advancing in treating atherosclerosis (Fig. 1). Nanotechnology markedly impacts healthcare, including targeted nanotherapeutics (75), medical imaging (76), diagnostics (77), vaccines (78) and regenerative medicine. Previous studies show nanoparticles can slow vascular disease by targeting vascular cells (79-110) (Table I). Due to its importance, several reviews cover the role of nanomedicine in treating diseases such as cancer, atherosclerosis and diabetes (77,111,112). Therefore, it is important to increase awareness of the benefits of pharmaceutical nanotechnology and existing treatments for atherosclerosis (Fig. 1).

Nanomedicine improved atherosclerosis by targeting SMCs. Imbalanced SMC proliferation can cause pathological angiogenesis, leading to plaque growth and rupture in coronary arteries, potentially resulting in cardiovascular mortality. Accurate ultrasound detection of nanoparticles on atherosclerotic plaque neovascularization can aid in early diagnosis of unstable plaques. Super-paramagnetic iron oxide particles (SPIONs) conjugated with annexin A5 are more effective than non-targeted SPIONs in identifying atherosclerotic lesions in rabbits (113). Additionally, synthetic high density lipoprotein nanoparticles with Apo A1 (APOA1) and triphenyl phosphonium cations can detect mitochondrial membrane potential collapse and apoptotic cells (114). The mTOR pathway is involved in VSMC and pulmonary arterial SMCs (PASMCs) proliferation in pulmonary arterial hypertension (115,116), and administration of mTOR siRNA nanomedicines can markedly inhibit PASMC proliferation after hypoxia (115). Nanoparticles notably attenuate oxidized low-density lipoprotein-induced SMC proliferation and thrombosis through downregulating the expression of scavenger receptor and key proinflammatory markers, implying the promise of nanomedicine for next-generation cardiovascular therapeutics (117). Therefore, nanomedicines carrying drugs may be promising therapeutics for diseases associated with the proliferation of SMCs (Fig. 2).

Nanomedicine offers an effective approach to treating atherosclerosis by improving SMC dysfunction and inhibiting cell proliferation (118). In early atherosclerosis, SMCs increase adhesion molecules and pro-inflammatory cytokines. A nano-delivery system, including 17-βE loaded nano-emulsions, notably reduced the expression of these molecules (119), highlighting its therapeutic potential. Additionally, miR-146a-5p nanomedicines, which target inflammation via the NF-κB pathway, reduced neointimal hyperplasia in rat arteries post-revascularization (120). Thus, nanomedicines can effectively deliver drugs to injury sites, showing promise against neointimal hyperplasia.

Nanomedicine improved atherosclerosis by targeting ECs. Atherosclerosis is a chronic disease marked by lipid deposition and inflammation in arterial walls (121), leading to plaque growth and potential rupture, which can cause myocardial infarction (MI). The severity of the disease is influenced by plaque size and composition, affecting stability. Unstable plaques may rupture under altered blood flow, blocking capillaries and causing cardiovascular events such as MI, stroke and peripheral artery disease (122). Endothelial injury exacerbates atherosclerosis by promoting platelet aggregation, coagulation and SMC proliferation (123), making the endothelium vital in plaque development, stability and rupture.

Previous studies indicate that nanoparticles can deliver drugs to ECs for diagnosing or treating atherosclerotic diseases (79-110,124,125) (Table I; Fig. 2). Ultrasound imaging of plaque neovascularization can improve early detection of unstable plaques. VEGFR-2 targeting antibody nano-microbubbles are more effective than blank ones in detecting plaques in rats (126). IL-10, an inflammation regulator, suppresses pro-inflammatory responses in atherosclerosis by inhibiting NF-κB activation (127). Branched poly (β-amino ester) nanoparticles with IL-10 plasmid DNA can slow atherosclerosis progression (128). The nanoparticle-VHPKQHRGGSGC peptide drug delivery system targets ECs, enhancing the anti-inflammatory effects of IL-10 on atherosclerotic plaques (128). Triptolide could inhibit inflammatory responses and angiogenesis in ECs (129), which might improve the symptoms and delay the progression of atherosclerosis. APRPG (Ala-Pro-Arg-Pro-Gly) peptide-modified nanoliposomes, a novel sustained-release drug delivery system targeting ECs, enhances inhibitory effects of triptolide on laser-induced neovascularization (130). Nanomedicine not only inhibits angiogenesis but also enhances endothelial function to treat atherosclerosis. In primary ECs, amorphous selenium quantum dots improved endothelium-dependent relaxation and accelerated wound healing, reducing atherosclerotic plaque in aortic arteries (131). Encapsulating cherry extract from *Prunus avium L.* in nanoparticles protected HUVECs from oxidative stress and decreased ROS production (132). Molybdenum disulfide nanoparticles (MoS2 NPs) show promise as a multifunctional therapeutic, reversing hydrogen peroxide-induced endothelial senescence by enhancing autophagy (133). Additionally, mRNA-p5RHH nanoparticles can be assembled into nuclease-resistant nanoparticles (134). Cyclin-dependent kinase inhibitor $p27^{Kip1}$ nanoparticles target endothelial denudation areas, promoting vessel reendothelialization and reducing neointima formation after injury (135). Mesoporous silica nanoparticles with CD9 antibodies deliver rosuvastatin to senescent ECs and macrophages, slowing atherosclerosis progression in $apoE^{-/-}$ mice (136). These EC-targeted nanotherapies are promising for atherosclerosis

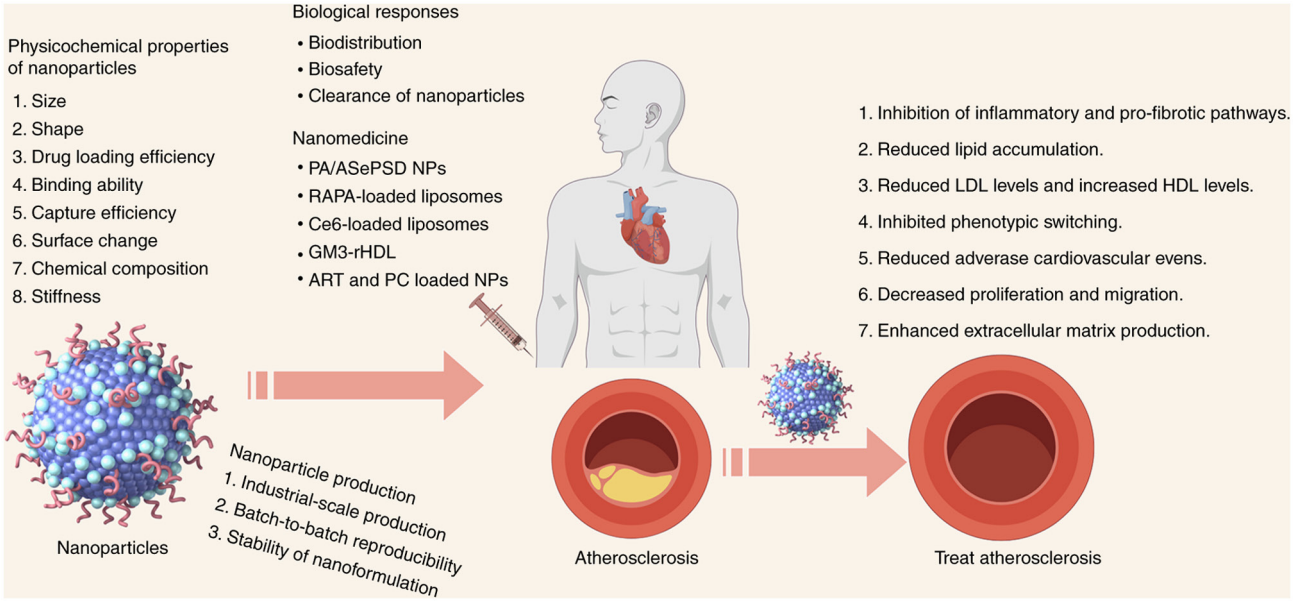

Figure 1. Application of nanomedicine for therapeutics of atherosclerosis. Schematic representation of nanoparticles functionalized with specific physicochemical properties, including size, surface charge, functional groups, shape, stiffness and chemical composition, is provided. The biological responses to these nanoparticles encompass biodistribution, biosafety and clearance. In the field of nanomedicine, examples include RAPA-loaded liposomes, Ce6-loaded liposomes, PAIASePSD nanoparticles, GM3-rHDL and nanoparticles loaded with ART and PC. These nanomedicines are produced through industrial-scale production processes, ensuring batch-to-batch reproducibility and stability of the nanoformulations. When nanomaterials are administered intravenously, they can exert various beneficial effects, such as the inhibition of inflammatory and pro-fibrotic pathways, reduction of lipid accumulation, decrease in LDL levels, increase in HDL levels, reduction of drug toxicity, mitigation of adverse cardiovascular events and improvement of endothelial cell and smooth muscle cell function. The efficacy of targeted delivery of dual or multiple therapeutics across different anti-atherogenic pathways is key for synergistic anti-atherosclerosis therapies. ART, artemisinin; Ce6, Chlorin e6; GM3-rHDL, GM3-functionalized reconstituted high-density lipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PA/ASePSD NPs, polylactide/alpha-lactalbumin selective pH-sensitive delivery nanoparticles; PC, procyanidins. RAPA, rapamycin.

and other cardiovascular diseases. For instance, silica-coated magnetic iron oxide nanoparticles can label endothelial progenitor cells (EPCs) from male rats, forming magnetized EPCs (137). Transplanting these EPCs improves cardiac function, reduces infarction size and decreases myocardial cell apoptosis, enhancing myocardial infarction treatment (138).

Invasive therapy technology, such as NO-producing vascular stents, offers a novel therapeutic strategy for treating arterial stenosis. A study by Yang *et al* (139) demonstrated that stents functionalized with 3,3-diselenodipropionic acid and S-nitrosothiols implanted into vessels via nanomaterials can produce NO, promote EC growth, reduce platelet activation and VSMC activity (Fig. 2). This nanocoating technique creates an endothelium-like environment, presenting a novel treatment strategy for cardiovascular diseases.

Nanomedicine improved atherosclerosis by targeting macrophages. Atherosclerosis is an inflammatory disease of the artery walls involving immune cells such as macrophages, which are key in its progression (77,140). Targeting macrophage-related processes offers potential for diagnostics and therapies. Early in atherogenesis, arterial ECs recruit macrophages via chemokine-receptor interactions and adhesion molecules such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 (141). This recruitment system is redundant, allowing for the inhibition of plaque formation by targeting multiple adhesion molecules (141). Additionally, vascular macrophages contribute to atherosclerosis through the expression of the olfactory receptor Olfr2 and related signaling molecules (142). Aberrant activation and polarization of arterial macrophages affect apoptosis and efferocytosis, associate with lipid accumulation and the inflammatory response in macrophages to the development of atherosclerotic lesions (143). Indeed, suppression of macrophages reduced atherosclerosis in mice (144), emphasizing the importance of detecting subclinical disease in humans for monocyte-directed treatment.

Nanotechnology could enhance atherosclerosis treatment by developing new diagnostic and therapeutic methods to lower cardiovascular disease risk. Gao *et al* (145) introduced a biomimetic drug delivery system using ROS-responsive nanoparticles coated with macrophage membranes, which block proinflammatory cytokines to reduce inflammation. This approach, along with pharmacotherapy, increases atherosclerosis treatment efficacy, indicating that macrophage membrane-coated systems are well-suited for inflammatory diseases (145). Rapamycin-loaded nanoparticles using activated macrophage membrane proteins have shown promise by inhibiting macrophage proliferation and reducing inflammation and plaque changes (146). Long-term use of PLGA nanoparticles enhances lysosomal degradation, reduces macrophage apoptosis, necrotic core formation and cytotoxic protein aggregates, while increasing fibrous cap formation (147), suggesting they can alleviate macrophage lysosomal dysfunction in atherosclerosis. RNA interference (RNAi) with nanoparticles effectively inhibited key adhesion molecules, reducing macrophage recruitment to atherosclerotic lesions (141). Thus, nanomedicine can improve atherosclerosis by targeting macrophages (Fig. 2). However, nanoparticles can also worsen vascular disease; for example, inhaled

Table I. Examples of nanotherapies for the targeted therapy CVDs.

Nanoparticles loaded drug	CVDs	Mechanism of action	Administration route	Model of use/animal	(Refs.)
HA conjugated ATV NPs	Atherosclerosis	Inhibition of inflammation	Intravenous injection	Macrophages, apoE$^{-/-}$ mice	(81)
RAPA-loaded liposomes	Atherosclerosis	Attenuation of arteriosclerosis	Intravenous injection	Endothelial cells, LDLR$^{-/-}$ mice or apoE$^{-/-}$ mice	(82,110)
NPs loaded with LFP	Atherosclerosis	Anti-atherosclerosis	Intravenous injection	*In vitro*, apoE$^{-/-}$ mice	(83)
Gliclazide-loaded nanoghosts	Atherosclerosis	Attenuation of arteriosclerosis	Intravenous injection	Monocytes, rabbits	(84)
Pioglitazone loaded Polymer-NPs	Atherosclerosis	Inhibition of inflammation	-	THP-1 cells	(85)
Ce6 loaded liposome	Atherosclerosis	Inhibition of migration and cholesterol efflux in foam cells	Intravenous injection	HCAEC, MOVAS, apoE$^{-/-}$ mice	(86)
MM@MTX NPs	Atherosclerosis	Attenuation of arteriosclerosis	Tail vein injection	apoE$^{-/-}$ mice	(87)
Rapa@UiO-66-NH-FAM-IL-1Ra	Atherosclerosis	Anti-atherosclerosis treatment	Tail vein injection	Macrophage, apoE$^{-/-}$ mice	(88)
Hyaluronic acid-guided cerasome NPs	Atherosclerosis	Treatment of atherosclerosis	Intravenous injection	CD44-positive cells, apoE$^{-/-}$ mice	(89)
PA/ASePSD NPs	Atherosclerosis	Anti-inflammation and regulation of lipid metabolism	Intravenous injection	RAW 264.7, apoE$^{-/-}$ mice	(90)
PPARδ-agonist-loaded NPs	Atherosclerosis	Attenuation of arteriosclerosis	Intravenous injection	VSMC, apoE$^{-/-}$ mice	(91)
ZIF-8 NPs loaded with LP	Atherosclerosis	Therapy of atherosclerosis	Intravenous injection	apoE$^{-/-}$ mice	(92)
Necrosulfonamide-loaded porous NPs	Atherosclerosis	Suppress inflammatory responses	-	Macrophages	(93)
ART and PC loaded NPs	Atherosclerosis	Attenuation of arteriosclerosis	Intravenous injection	Macrophage, apoE$^{-/-}$ mice	(94)
Cyclodextrin-loaded NPs	Atherosclerosis	Treatment of atherosclerosis	Tail vein injection	Macrophage, apoE$^{-/-}$ mice	(95)
pH-sensitive hyaluronic acid NPs	Atherosclerosis	Therapy of atherosclerosis	Tail vein injection	Macrophages, SMCs, apoE$^{-/-}$ mice	(96)
HA-functionalized mesoporous silica NPs loading simvastatin	Atherosclerosis	Therapy of atherosclerosis	Tail vein injection	Macrophages, HUVECs	(97)

Table I. Continued.

Nanoparticles loaded drug	CVDs	Mechanism of action	Administration route	Model of use/animal	(Refs.)
Self-oxygenation mesoporous MnO2 NPs	Atherosclerosis	Therapy of atherosclerosis	Intravenous injection	Macrophage, apoE$^{-/-}$mice	(98)
Bevacizumab encapsulation into PLGA NPs	Atherosclerosis	Therapy of atherosclerosis	-	Endothelial cells, macrophages	(99)
Nano-enabled biotinylated anti-LDL	CVDs	Reduction in LDL levels, and an increase in HDL levels	Jugular vein	Large White pigs	(100)
Everolimus-Loaded rHDL	Atherosclerosis	Therapy of atherosclerosis	Inject flow (Vinj) of 0.2 ml/min	Macrophages, apoE$^{-/-}$ mice	(101)
GM3-rHDL	Atherosclerosis	Inhibition of foam cel l formation	Single administration	Macrophages, apoE$^{-/-}$ mice	(102)
Administration of rHDL to deliver miRNA	Atherosclerosis	Increasing cholesterol efflux	Sequential administration	Triple-cell 2D-atheroma model	(103)
Netrin-1 antibody-functionalized NPs loaded metformin	AAAs	Reduced the aneurysm diameter	Tail vein injection	VSMCs, THP-1, apoE$^{-/-}$ mice	(104)
Galactose-modified nanoparticles for delivery of microRNAs	AAAs	Reduced the production of related proinflammatory cytokines	Tail vein injection	BMDMs, apoE$^{-/-}$ mice, patients with AAA	(105)
PGG-NPs	AAAs	Suppressed inflammatory cytokines and increased anti-inflammatory cytokines	Intravenous injections	Pathogen-free C57BL/6 male mice	(106)
Statin-loaded NPs	AAAs	Prevented AAAs expansion	Intravenous injections	Rat models	(107)
ROS-responsive NPs	AAAs	Inhibited calcification and attenuated ROS stress and apoptosis	Intravenous injections	AAA rats	(108)
EDTA- and PGG-loaded NPs	AAAs	Reduction of MMP activity, elastin degradation and calcification	Tail vein injection	Calcium chloride-injury rats	(109)

ATV, Atorvastatin; HA, Hyaluronan; NPs, Nanoparticle; RAPA, Rapamycin; LFP, lipid-specific AIEgen; Ce6, Chlorin e6; HCAEC, human coronary artery endothelial cells; MOVAS, mouse aortic vascular smooth muscle cells; MM@MTX NPs, MTX nanoparticles (MTX NPs) camouflaged with macrophage membranes; ZIF-8, zeolitic imidazolate framework-8; LP, losartan potassium; ART, Artemisinin; PC, Procyanidins; HA, hyaluronic acid; rHDL, reconstituted high-density lipoprotein; GM3-rHDL, Ganglioside GM3-functionalized reconstituted high-density lipoprotein; AAAs, Abdominal aortic aneurysms; BMDMs, bone marrow-derived macrophages; PGG-NPs, pentagalloyl glucose-loaded nanoparticles; PGG, pentagalloyl glucose; MMP, matrix metalloproteinase.

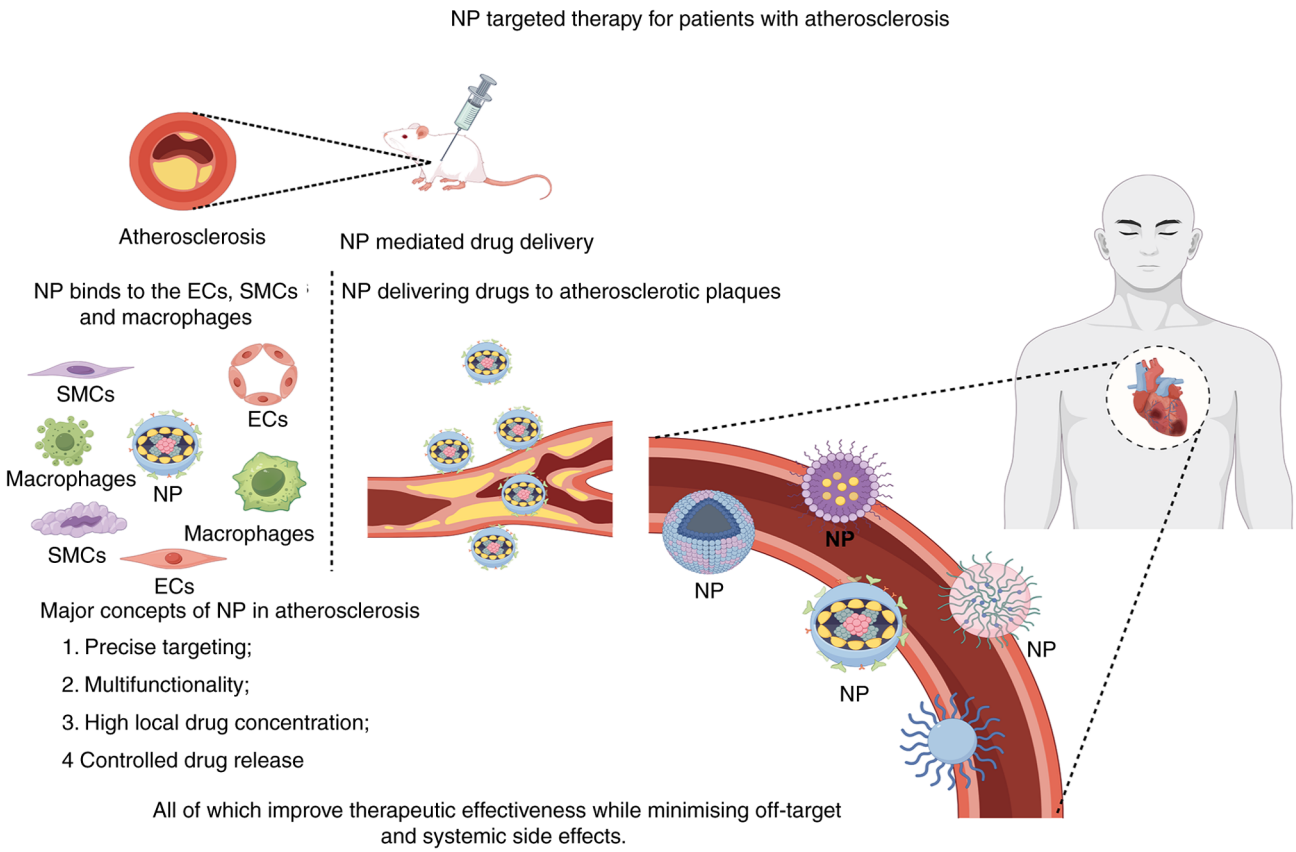

Figure 2. NP targeting atherosclerotic plaques in mouse and human models. NP have the capability to bind to ECs, SMCs and macrophages, facilitating NP-mediated drug delivery to atherosclerotic plaques within blood vessels in both murine and human models. Key concepts of NP application in atherosclerosis include precise targeting, multifunctionality, high local drug concentration and controlled drug release. These attributes collectively enhance therapeutic efficacy while minimizing off-target and systemic side effects. ECs, endothelial cells; NP, nanoparticles; SMCs, smooth muscle cells.

silica nanoparticles can exacerbate lesions and increase pro-inflammatory M1 macrophages (148).

7. Conclusions and future perspectives

Exercise-induced acute and adaptive physiological changes may notably improve the *in vivo* microenvironment for nano-drugs, thereby enhancing their efficacy (149). This synergistic effect can be attributed to several mechanistic pathways: i) Hemodynamics and vascular permeability: Exercise increases cardiac output and tissue blood flow, potentially facilitating the delivery and accumulation of nanoparticles in target tissues such as the heart or skeletal muscle, ii) metabolic and immune reprogramming: Exercise-induced metabolic alterations, such as reduced insulin resistance and immunomodulation, including an increase in anti-inflammatory M2 macrophages, may enhance the susceptibility of target cells to therapeutic agents such as nucleic acids and small molecules, while also mitigating inflammatory responses that could degrade nanoparticles, iii) cellular uptake: The upregulation of specific cell surface receptors, such as certain integrins, during exercise, when aligned with the targeting ligands on nanoparticles, could markedly enhance cellular internalization. Consequently, exercise should not be viewed merely as an adjuvant therapy but rather as a 'bio-enhancer' that actively modulates the host environment to optimize pharmacokinetics.

Despite promising advancements in preclinical research and the application of nanomaterials, challenges remain that could hinder progress. A primary challenge lies in the ethical implications associated with ongoing clinical trials, especially with fast-evolving science and issues such as COVID-19 (150). Ensuring the relevance and value of clinical trials as new information emerges is key for maintaining public trust and scientific integrity. Furthermore, the integration of nanomaterials into clinical practice presents notable obstacles, including concerns regarding toxicity, immunogenicity and regulatory approval processes (151). However, these challenges also present opportunities for innovation and interdisciplinary collaboration. By fostering partnerships among researchers, clinicians and regulatory bodies, the field can develop robust frameworks that address these issues while advancing scientific knowledge and improving patient outcomes. Future research should focus on overcoming these barriers to fully harness the potential of emerging technologies in personalized medicine and preclinical research.

Nanoparticles have several advantages over traditional therapeutic agents, including the ability to target specific tissues or cells, controlled drug release and reduced toxicity. Nonetheless, there are important limitations and challenges in cardiovascular nanomedicine that should be noted (79-110,152,153) (Table I). Future advancements in nanoparticle-based therapies for the diagnosis and treatment of arteriosclerosis are anticipated, with ongoing development and refinement in this

field (4,7,77). These nanoparticles have the potential to inhibit pro-atherogenic processes in macrophages, VSMCs and ECs, thereby enhancing the resolution of inflammation and stabilizing plaques. Furthermore, this work addresses the enduring challenge of translating nanomaterials into clinical applications by summarizing current obstacles and suggesting avenues for innovation and enhancement in nanomaterial design. This may involve the creation of novel and more efficacious therapeutic agents, the development of improved targeting strategies to ensure precise delivery of nanoparticles to plaque sites, and the integration of nanoparticle-based therapies with other treatment modalities, such as surgical interventions or stenting.

The utilization of nanoparticles coated with natural membranes derived from cells or extracellular vesicles for targeted drug delivery to the skin has been explored (154). Recent advancements in imaging techniques have enabled scientists to observe and comprehend the interactions of nanoparticles with biological systems at an ultrastructural level (155). Techniques such as cryo-electron microscopy, super-resolution microscopy and advanced spectroscopy are pivotal for elucidating the safety, biodistribution, and fundamental mechanisms of action of nanomedicines. Interfacial self-assembly nanoarrays pertain to spontaneously organized nanostructures at interfaces, which depend on the intrinsic properties of the materials involved, including surface energy, molecular structure and interactions (156). Moreover, plasmonic alloys have been shown to enhance metabolic fingerprints, facilitating the rapid diagnosis and classification of MI (157). This advancement holds the potential to reduce the duration of emergency department visits and improve MI treatment outcomes. Thus, nanomedicine is transforming from a simple 'drug deliveryman' to a 'comprehensive medical platform' that can intelligently interact with life systems, analyze diseases at the molecular level, and achieve precise diagnosis and efficient treatment integration.

It is imperative to critically evaluate the heterogeneous findings on nanomaterials. Some studies highlight their benefits, while other studies raise concerns about their biocompatibility and long-term implications (158,159). A balanced approach is needed to weigh positive results against potential risks, guiding the development of standardized clinical protocols. Future research should prioritize elucidating the mechanisms that govern the interactions between nanomaterials and cardiovascular cells, alongside optimizing nanomaterial design for improved efficacy and safety. There is an urgent need for rigorously designed clinical trials to evaluate the long-term impacts of nanomaterials in the treatment of atherosclerosis. Additionally, interdisciplinary collaborations among materials scientists, biologists and clinicians will be key to advancing this field.

The present review highlights the considerable potential of the nano-platform for applications such as tumor-targeted therapy; however, there are considerable challenges associated with its clinical translation, particularly in relation to long-term *in vivo* safety and biodistribution. Due to their material composition and size, the nanoparticles are likely to undergo sequestration and clearance predominantly in the liver and spleen. The potential risks of long-term toxicity, immunogenicity and off-target accumulation necessitate comprehensive evaluation in future studies, particularly through systematic long-term animal experiments. Addressing these safety concerns is essential for the advancement of this platform toward clinical application and will constitute a primary focus of forthcoming research.

The present review posits a key perspective: Nanomaterials and exercise should not be viewed as independent interventions but rather as synergistic agents that converge on common molecular pathways, thereby offering a transformative approach to cardiovascular therapy. This integration propels the field forward in two notable ways. Firstly, on a mechanistic level, it introduces a novel concept of 'bidirectional regulation', for example, in the context of inflammatory pathways, exercise promotes an anti-inflammatory state by modulating myokines such as IL-6, which increases IL-10 and decreases TNF-α levels (160). Concurrently, nanomaterials can be engineered to deliver anti-inflammatory agents (161), such as siRNA targeting TNF-α, directly to gut microbiota for ulcerative colitis therapy (162). This dual approach effectively remodels the inflammatory microenvironment through both 'systemic modulation' and 'localized precision strike' strategies. Secondly, at a translational level, it introduces an innovative paradigm of 'preconditioning combined with therapy'. Exercise acts as a safe and cost-effective systemic 'preconditioning' strategy that optimizes the overall physiological environment by enhancing vascular function and reducing oxidative stress (163). This creates a less favorable environment for the subsequent administration of nanotherapeutics. This integrated approach not only has the potential to enhance the efficacy of monotherapies but also addresses the multi-pathway dysregulation characteristic of complex diseases, representing a key direction for the future integration of precision medicine and lifestyle interventions.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

QZ, GLZ, WS and LHY conceived the structure of the manuscript; QZ and LY drafted the initial manuscript; QZ, GZ, WS, JC and LHY revised and edited the manuscript. All authors contributed to the preparation of this manuscript. All the authors approved the final manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ and Han M: Inflammation and atherosclerosis: Signaling pathways and therapeutic intervention. Signal Transduct Target Ther 7: 131, 2022.
2. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, *et al*: 2024 Heart disease and stroke statistics: A report of us and global data from the American Heart Association. Circulation 149: e347-e913, 2024.
3. Oveisgharan S, Yu L, Barnes LL, Agrawal S, Schneider JA, Bennett DA and Buchman AS: Association of statins with cerebral atherosclerosis and incident parkinsonism in older adults. Neurology 98: e1976-e1984, 2022.
4. Cheng J, Huang H, Chen Y and Wu R: Nanomedicine for diagnosis and treatment of atherosclerosis. Adv Sci (Weinh) 10: e2304294, 2023.
5. Powers SK, Deminice R, Ozdemir M, Yoshihara T, Bomkamp MP and Hyatt H: Exercise-induced oxidative stress: Friend or foe? J Sport Health Sci 9: 415-425, 2020.
6. Arazi H, Eghbali E and Suzuki K: Creatine supplementation, physical exercise and oxidative stress markers: A review of the mechanisms and effectiveness. Nutrients 13: 869, 2021.
7. Chen J, Zhang X, Millican R, Sherwood J, Martin S, Jo H, Yoon YS, Brott BC and Jun HW: Recent advances in nanomaterials for therapy and diagnosis for atherosclerosis. Adv Drug Deliv Rev 170: 142-199, 2021.
8. He Z, Chen W, Hu K, Luo Y, Zeng W, He X, Li T, Ouyang J, Li Y, Xie L, *et al*: Resolvin D1 delivery to lesional macrophages using antioxidative black phosphorus nanosheets for atherosclerosis treatment. Nat Nanotechnol 19: 1386-1398, 2024.
9. Tang J, Li T, Xiong X, Yang Q, Su Z, Zheng M and Chen Q: Colchicine delivered by a novel nanoparticle platform alleviates atherosclerosis by targeted inhibition of NF-κB/NLRP3 pathways in inflammatory endothelial cells. J Nanobiotechnology 21: 460, 2023.
10. Zhou L, Tang S, Li F, Wu Y, Li S, Cui L, Luo J, Yang L, Ren Z, Zhang J, *et al*: Ceria nanoparticles prophylactic used for renal ischemia-reperfusion injury treatment by attenuating oxidative stress and inflammatory response. Biomaterials 287: 121686, 2022.
11. Gao M, Tang M, Ho W, Teng Y, Chen Q, Bu L, Xu X and Zhang XQ: Modulating plaque inflammation via targeted mRNA nanoparticles for the treatment of atherosclerosis. ACS Nano 17: 17721-17739, 2023.
12. Qi Y, Wang S, Luo Y, Huang W, Chen L, Zhang Y, Liang X, Tang J, Zhang Y, Zhang L, *et al*: Exercise-induced Nitric oxide contributes to spatial memory and hippocampal capillaries in rats. Int J Sports Med 41: 951-961, 2020.
13. Lima MR, Moreira BJ, Bertuzzi R and Lima-Silva AE: Could nanotechnology improve exercise performance? Evidence from animal studies. Braz J Med Biol Res 57: e13360, 2024.
14. Wang-Bishop L, Kimmel BR, Ngwa VM, Madden MZ, Baljon JJ, Florian DC, Hanna A, Pastora LE, Sheehy TL, Kwiatkowski AJ, *et al*: STING-activating nanoparticles normalize the vascular-immune interface to potentiate cancer immunotherapy. Sci Immunol 8: eadd1153, 2023.
15. Li C, Zhao Z, Luo Y, Ning T, Liu P, Chen Q, Chu Y, Guo Q, Zhang Y, Zhou W, *et al*: Macrophage-disguised manganese dioxide nanoparticles for neuroprotection by reducing oxidative stress and modulating inflammatory microenvironment in acute ischemic stroke. Adv Sci (Weinh) 8: e2101526, 2021.
16. Zhang X, Donskyi IS, Tang W, Deng S, Liu D, Zhang S, Zhao Q and Xing B: Biological effects of black phosphorus nanomaterials on mammalian cells and animals. Angew Chem Int Ed Engl 62: e202213336, 2023.
17. Luo L, Zhang H, Zhang S, Luo C, Kan X, Lv J, Zhao P, Tian Z and Li C: Extracellular vesicle-derived silk fibroin nanoparticles loaded with MFGE8 accelerate skin ulcer healing by targeting the vascular endothelial cells. J Nanobiotechnology 21: 455, 2023.
18. Germande O, Baudrimont M, Beaufils F, Freund-Michel V, Ducret T, Quignard JF, Errera MH, Lacomme S, Gontier E, Mornet S, *et al*: NiONPs-induced alteration in calcium signaling and mitochondrial function in pulmonary artery endothelial cells involves oxidative stress and TRPV4 channels disruption. Nanotoxicology 16: 29-51, 2022.
19. Serra MF, Cotias AC, Pimentel AS, Arantes ACS, Pires ALA, Lanzetti M, Hickmann JM, Barreto E, Carvalho VF, Silva PMRE, *et al*: Gold nanoparticles inhibit steroid-insensitive asthma in mice preserving histone deacetylase 2 and NRF2 pathways. Antioxidants (Basel) 11: 1659, 2022.
20. Arnst J, Jing Z, Cohen C, Ha SW, Viggeswarapu M and Beck GR: Bioactive silica nanoparticles target autophagy, NF-κB, and MAPK pathways to inhibit osteoclastogenesis. Biomaterials 301: 122238, 2023.
21. Kabirian F, Baatsen P, Smet M, Shavandi A, Mela P and Heying R: Carbon nanotubes as a nitric oxide nano-reservoir improved the controlled release profile in 3D printed biodegradable vascular grafts. Sci Rep 13: 4662, 2023.
22. Keyoumu Y, Huo Q, Cheng L, Ma H, Zhang M, Ma Y and Ma X: The detailed biological investigations about combined effects of novel polyphenolic and photo-plasmonic nanoparticles loaded graphene nanosheets on coronary endothelial cells and isolated rat aortic rings. J Photochem Photobiol B 202: 111666, 2019.
23. Kang K, Sun C, Li H, Liu X, Deng J, Chen S, Zeng L, Chen J, Liu X, Kuang J, *et al*: N6-methyladenosine-driven miR-143/145-KLF4 circuit orchestrates the phenotypic switch of pulmonary artery smooth muscle cells. Cell Mol Life Sci 81: 256, 2024.
24. Park C, Baek KI and Jo H: Saving KLF2/4 from γ-protocadherin to reduce vascular inflammation and atherosclerosis. Nat Cardiovasc Res 3: 1021-1023, 2024.
25. Wang Y, Zhang K, Li T, Maruf A, Qin X, Luo L, Zhong Y, Qiu J, McGinty S, Pontrelli G, *et al*: Macrophage membrane functionalized biomimetic nanoparticles for targeted anti-atherosclerosis applications. Theranostics 11: 164-180, 2021.
26. Yang W, Lu C, Chu F, Bu K, Ma H, Wang Q, Jiao Z, Wang S, Yang X, Gao Y, *et al*: Fluoride-induced hypertension by regulating RhoA/ROCK pathway and phenotypic transformation of vascular smooth muscle cells: In vitro and in vivo evidence. Ecotoxicol Environ Saf 281: 116681, 2024.
27. Hao D, Swindell HS, Ramasubramanian L, Liu R, Lam KS, Farmer DL and Wang A: Extracellular matrix mimicking nanofibrous scaffolds modified with mesenchymal stem cell-derived extracellular vesicles for improved vascularization. Front Bioeng Biotechnol 8: 633, 2020.
28. Hatakeyama H, Akita H and Harashima H: A multifunctional envelope type nano device (MEND) for gene delivery to tumours based on the EPR effect: A strategy for overcoming the PEG dilemma. Adv Drug Deliv Rev 63: 152-160, 2010.
29. Kitagawa T, Kosuge H, Uchida M, Iida Y, Dalman RL, Douglas T and McConnell MV: RGD targeting of human ferritin iron oxide nanoparticles enhances in vivo MRI of vascular inflammation and angiogenesis in experimental carotid disease and abdominal aortic aneurysm. J Magn Reson Imaging 45: 1144-1153, 2017.
30. Liu S, Zhao Y, Shen M, Hao Y, Wu X, Yao Y, Li Y and Yang Q: Hyaluronic acid targeted and pH-responsive multifunctional nanoparticles for chemo-photothermal synergistic therapy of atherosclerosis. J Mater Chem B 10: 562-570, 2022.
31. Li S, Li F, Wang Y, Li W, Wu J, Hu X, Tang T and Liu X: Multiple delivery strategies of nanocarriers for myocardial ischemia-reperfusion injury: Current strategies and future prospective. Drug Deliv 31: 2298514, 2024.
32. Walsh D, Kostyunina DS, Blake A, Boylan J and McLoughlin P: Shear stress-induced restoration of pulmonary microvascular endothelial barrier function following ischemia reperfusion injury requires VEGFR2 signaling. Am J Physiol Lung Cell Mol Physiol 328: L389-L404, 2025.
33. Martelli A, Abate F, Roggia M, Benedetti G, Caradonna E, Calderone V, Tenore GC, Cosconati S, Novellino E and Stornaiuolo M: Trimethylamine N-Oxide (TMAO) acts as inhibitor of endothelial nitric oxide synthase (eNOS) and Hampers NO production and acetylcholine-mediated vasorelaxation in rat aortas. Antioxidants (Basel) 14: 517, 2025.
34. Min L, Zhong F, Gu L, Lee K and He JC: Krüppel-like factor 2 is an endoprotective transcription factor in diabetic kidney disease. Am J Physiol Cell Physiol 327: C477-C486, 2024.
35. Yang Q, Chen S, Wang X, Yang X, Chen L, Huang T, Zheng Y, Zheng X, Wu X, Sun Y and Wu J: Exercise mitigates endothelial pyroptosis and atherosclerosis by downregulating NEAT1 through N6-methyladenosine modifications. Arterioscler Thromb Vasc Biol 43: 910-926, 2023.
36. Tanaka K, Chen M, Prendergast A, Zhuang Z, Nasiri A, Joshi D, Hintzen J, Chung M, Kumar A, Mani A, *et al*: Latrophilin-2 mediates fluid shear stress mechanotransduction at endothelial junctions. EMBO J 43: 3175-3191, 2024.

37. Russell-Puleri S, Dela Paz NG, Adams D, Chattopadhyay M, Cancel L, Ebong E, Orr AW, Frangos JA and Tarbell JM: Fluid shear stress induces upregulation of COX-2 and PGI2 release in endothelial cells via a pathway involving PECAM-1, PI3K, FAK, and p38. Am J Physiol Heart Circ Physiol 312: H485-H500, 2017.
38. Palabiyik AA and Palabiyik E: Pharmacological approaches to enhance mitochondrial biogenesis: Focus on PGC-1A, AMPK, and SIRT1 in cellular health. Mol Biol Rep 52: 270, 2025.
39. Zhu C, Zhang Z, Zhu Y, Du Y, Han C, Zhao Q, Li Q, Hou J, Zhang J, He W and Qin Y: Study on the role of Dihuang Yinzi in regulating the AMPK/SIRT1/PGC-1α pathway to promote mitochondrial biogenesis and improve Alzheimer's disease. J Ethnopharmacol 337: 118859, 2025.
40. Pinto PR, Rocco DDFM, Okuda LS, Machado-Lima A, Castilho G, da Silva KS, Gomes DJ, Pinto Rde S, Iborra RT, Ferreira Gda S, *et al*: Aerobic exercise training enhances the in vivo cholesterol trafficking from macrophages to the liver independently of changes in the expression of genes involved in lipid flux in macrophages and aorta. Lipids Health Dis 14: 109, 2015.
41. da Silva Pereira JA, de Souza GP, Virgilio-da-Silva JV, Prodonoff JS, de Castro G, Pimentel LF, Mousovich-Neto F, Davanzo GG, Aguiar CF, Breda CNS, *et al*: LXR regulation of adipose tissue inflammation during obesity is associated with dysregulated macrophage function. Obesity (Silver Spring) 33: 78-90, 2025.
42. Chiang CF, Wang ZZ, Hsu YH, Miaw SC and Lin WL: Exercise improves the outcome of anticancer treatment with ultrasound-hyperthermia-enhanced nanochemotherapy and autophagy inhibitor. PLoS One 18: e0288380, 2023.
43. Zhao Y, Ying X, Pang X, Lin Y, Shen J, Zhao Y, Shen W, Yang Y, Hong Z, Wu W, *et al*: Exercise-induced Sesn2 mediates autophagic flux to alleviate neural damage after ischemic stroke in mice. Exp Neurol 386: 115174, 2025.
44. Zhao Y, Hong Z, Lin Y, Shen W, Yang Y, Zuo Z and Hu X: Exercise pretreatment alleviates neuroinflammation and oxidative stress by TFEB-mediated autophagic flux in mice with ischemic stroke. Exp Neurol 364: 114380, 2023.
45. Tarumi T, Tomoto T, Sugawara J and Zhang R: Aerobic exercise training for the aging brain: Effective dosing and vascular mechanism. Exerc Sport Sci Rev 53: 31-40, 2025.
46. Herbin O, Regelmann AG, Ramkhelawon B, Weinstein EG, Moore KJ and Alexandropoulos K: Monocyte adhesion and plaque recruitment during atherosclerosis development is regulated by the adapter protein Chat-H/SHEP1. Arterioscler Thromb Vasc Biol 36: 1791-1801, 2016.
47. Raine LB, McDonald K, Shigeta TT, Hsieh SS, Hunt J, Chiarlitti NA, Lim M, Gebhardt K, Collins N, De Lisio M, *et al*: Sympathetic nervous system and exercise affects cognition in youth (SNEACY): Study protocol for a randomized crossover trial. Trials 22: 154, 2021.
48. Dash R, Yadav M, Biswal J, Chandra A, Goel VK, Sharma T, Prusty SK and Mohapatra S: Modeling of chitosan modified PLGA atorvastatin-curcumin conjugate (AT-CU) nanoparticles, overcoming the barriers associated with PLGA: An approach for better management of atherosclerosis. Int J Pharm 640: 123009, 2023.
49. Janssen SLJE, van Everdingen WM, Saalmink WBJ, Lamers SK, Vroemen WHM, Denessen EJS, Berge K, Bekers O, Hopman MTE, Brink M, *et al*: Relationship between exercise-induced cardiac troponin elevations and occult coronary atherosclerosis in Middle-aged athletes. J Am Coll Cardiol 85: 2370-2382, 2025.
50. Yan Q, Yan X, Yang X, Li S and Song J: The use of PET/MRI in radiotherapy. Insights Imaging 15: 63, 2024.
51. Ficker ES, Maranhão RC, Chacra APM, Neves VC, Negrão CE, Martins VC and Vinagre CG: Exercise training accelerates the removal from plasma of LDL-like nanoemulsion in moderately hypercholesterolemic subjects. Atherosclerosis 212: 230-236, 2010.
52. Shanmugam G, Rakshit S and Sarkar K: HDAC inhibitors: Targets for tumor therapy, immune modulation and lung diseases. Transl Oncol 16: 101312, 2022.
53. Kitahara M, Inoue T, Mani H, Takamatsu Y, Ikegami R, Tohyama H and Maejima H: Exercise and pharmacological inhibition of histone deacetylase improves cognitive function accompanied by an increase of gene expressions crucial for neuronal plasticity in the hippocampus. Neurosci Lett 749: 135749, 2021.
54. Lai Z, Liang J, Zhang J, Mao Y, Zheng X, Shen X, Lin W and Xu G: Exosomes as a delivery tool of exercise-induced beneficial factors for the prevention and treatment of cardiovascular disease: A systematic review and meta-analysis. Front Physiol 14: 1190095, 2023.
55. Sharma AK, Kumar A, Sahu M, Sharma G, Datusalia AK and Rajput SK: Exercise preconditioning and low dose copper nanoparticles exhibits cardioprotection through targeting GSK-3β phosphorylation in ischemia/reperfusion induced myocardial infarction. Microvasc Res 120: 59-66, 2018.
56. Watkins LE, Goyal A, Gatti AA and Kogan F: Imaging of joint response to exercise with MRI and PET. Skeletal Radiol 52: 2159-2183, 2023.
57. Coelho S, Baek J, Walsh J, Gooding JJ and Gaus K: 3D active stabilization for single-molecule imaging. Nat Protoc 16: 497-515, 2021.
58. Karageorgou MA, Bouziotis P, Stiliaris E and Stamopoulos D: Radiolabeled iron oxide nanoparticles as dual modality contrast agents in SPECT/MRI and PET/MRI. Nanomaterials (Basel) 13: 503, 2023.
59. Bouziotis P, Psimadas D, Tsotakos T, Stamopoulos D and Tsoukalas C: Radiolabeled iron oxide nanoparticles as dual-modality SPECT/MRI and PET/MRI agents. Curr Top Med Chem 12: 2694-2702, 2012.
60. Zhang X, Xie K, Zhou H, Wu Y, Li C, Liu Y, Liu Z, Xu Q, Liu S, Xiao D and Tao Y: Role of non-coding RNAs and RNA modifiers in cancer therapy resistance. Mol Cancer 19: 47, 2020.
61. Wang HN, Xiang JZ, Qi Z and Du M: Plant extracts in prevention of obesity. Crit Rev Food Sci Nutr 62: 2221-2234, 2022.
62. Raguram A, Banskota S and Liu DR: Therapeutic in vivo delivery of gene editing agents. Cell 185: 2806-2827, 2022.
63. Marini I, Uzun G, Jamal K and Bakchoul T: Treatment of drug-induced immune thrombocytopenias. Haematologica 107: 1264-1277, 2022.
64. Peñaherrera-Pazmiño AB, Criollo M and Gonzalez-Pastor R: Phytochemical nanoencapsulation and microfluidics drive gene and tumor microenvironment modulation. Front Pharmacol 16: 1694752, 2025.
65. Takedatsu H, Mitsuyama K and Torimura T: Nanomedicine and drug delivery strategies for treatment of inflammatory bowel disease. World J Gastroenterol 21: 11343-11352, 2015.
66. Cordeiro RA, Santo D, Farinha D, Serra A, Faneca H and Coelho JFJ: High transfection efficiency promoted by tailor-made cationic tri-block copolymer-based nanoparticles. Acta Biomater 47: 113-123, 2017.
67. Li Z, Li G, Xu J, Li C, Han S, Zhang C, Wu P, Lin Y, Wang C, Zhang J, *et al*: Hydrogel transformed from nanoparticles for prevention of tissue injury and treatment of inflammatory diseases. Adv Mater 34: e2109178, 2022.
68. Sun R, Wang X, Nie Y, Hu A, Liu H, Zhang K, Zhang L, Wu Q, Li K, Liu C, *et al*: Targeted trapping of endogenous endothelial progenitor cells for myocardial ischemic injury repair through neutrophil-mediated SPIO nanoparticle-conjugated CD34 antibody delivery and imaging. Acta Biomater 146: 421-433, 2022.
69. Wang Y, Malcolm DW and Benoit DSW: Controlled and sustained delivery of siRNA/NPs from hydrogels expedites bone fracture healing. Biomaterials 139: 127-138, 2017.
70. Jing L, Qu H, Wu D, Zhu C, Yang Y, Jin X, Zheng J, Shi X, Yan X and Wang Y: Platelet-camouflaged nanococktail: Simultaneous inhibition of drug-resistant tumor growth and metastasis via a cancer cells and tumor vasculature dual-targeting strategy. Theranostics 8: 2683-2695, 2018.
71. Hou J, Wang L, Wang C, Zhang S, Liu H, Li S and Wang X: Toxicity and mechanisms of action of titanium dioxide nanoparticles in living organisms. J Environ Sci (China) 75: 40-53, 2019.
72. Haghighat F, Kim Y, Sourinejad I, Yu IJ and Johari SA: Titanium dioxide nanoparticles affect the toxicity of silver nanoparticles in common carp (Cyprinus carpio). Chemosphere 262: 127805, 2021.
73. Miller MR, Raftis JB, Langrish JP, McLean SG, Samutrtai P, Connell SP, Wilson S, Vesey AT, Fokkens PHB, Boere AJF, *et al*: Inhaled nanoparticles accumulate at sites of vascular disease. ACS Nano 11: 4542-4552, 2017.
74. Czubacka E and Czerczak S: Are platinum nanoparticles safe to human health? Med Pr 70: 487-495, 2019.
75. Sun D, Chen J, Wang Y, Ji H, Peng R, Jin L and Wu W: Advances in refunctionalization of erythrocyte-based nanomedicine for enhancing cancer-targeted drug delivery. Theranostics 9: 6885-6900, 2019.

76. Li P, Wang D, Hu J and Yang X: The role of imaging in targeted delivery of nanomedicine for cancer therapy. Adv Drug Deliv Rev 189: 114447, 2022.
77. Chen W, Schilperoort M, Cao Y, Shi J, Tabas I and Tao W: Macrophage-targeted nanomedicine for the diagnosis and treatment of atherosclerosis. Nat Rev Cardiol 19: 228-249, 2022.
78. Patra S, Singh M, Wasnik K, Pareek D, Gupta PS, Mukherjee S and Paik P: Polymeric nanoparticle based diagnosis and nanomedicine for treatment and development of vaccines for cerebral malaria: A review on recent advancement. ACS Appl Bio Mater 4: 7342-7365, 2021.
79. Choi KA, Kim JH, Ryu K and Kaushik N: Current nanomedicine for targeted vascular disease treatment: Trends and perspectives. Int J Mol Sci 23: 12397, 2022.
80. Aili T, Zong JB, Zhou YF, Liu YX, Yang XL, Hu B and Wu JH: Recent advances of self-assembled nanoparticles in the diagnosis and treatment of atherosclerosis. Theranostics 14: 7505-7533, 2024.
81. Hossaini Nasr S, Rashidijahanabad Z, Ramadan S, Kauffman N, Parameswaran N, Zinn KR, Qian C, Arora R, Agnew D and Huang X: Effective atherosclerotic plaque inflammation inhibition with targeted drug delivery by hyaluronan conjugated atorvastatin nanoparticles. Nanoscale 12: 9541-9556, 2020.
82. Liu X, Lin C, Zhong W, Yuan Z, Yan P and Guan S: Effective attenuation of arteriosclerosis following lymphatic-targeted delivery of hyaluronic acid-decorated rapamycin liposomes. Int J Nanomedicine 18: 4403-4419, 2023.
83. Xu H, She P, Ma B, Zhao Z, Li G and Wang Y: ROS responsive nanoparticles loaded with lipid-specific AIEgen for atherosclerosis-targeted diagnosis and bifunctional therapy. Biomaterials 288: 121734, 2022.
84. Karami Z, Mehrzad J, Akrami M and Hosseinkhani S: Anti-inflammation-based treatment of atherosclerosis using Gliclazide-loaded biomimetic nanoghosts. Sci Rep 13: 13880, 2023.
85. Groner J, Tognazzi M, Walter M, Fleischmann D, Mietzner R, Ziegler CE, Goepferich AM and Breunig M: Encapsulation of pioglitazone into Polymer-nanoparticles for potential treatment of atherosclerotic diseases. ACS Appl Bio Mater 6: 2111-2121, 2023.
86. Zou L, Zhang Y, Cheraga N, Abodunrin OD, Qu KY, Qiao L, Ma YQ, Chen LJ and Huang NP: Chlorin e6 (Ce6)-loaded plaque-specific liposome with enhanced photodynamic therapy effect for atherosclerosis treatment. Talanta 265: 124772, 2023.
87. Zhu L, Li H, Li J, Zhong Y, Wu S, Yan M, Ni S, Zhang K, Wang G, Qu K, *et al*: Biomimetic nanoparticles to enhance the reverse cholesterol transport for selectively inhibiting development into foam cell in atherosclerosis. J Nanobiotechnology 21: 307, 2023.
88. Xu Z, Wu Z, Huang S, Ye K, Jiang Y, Liu J, Liu J, Lu X and Li B: A metal-organic framework-based immunomodulatory nanoplatform for anti-atherosclerosis treatment. J Control Release 354: 615-625, 2023.
89. Ma Q, Wu S, Yang L, Wei Y, He C, Wang W, Zhao Y, Wang Z, Yang S, Shi D, *et al*: Hyaluronic Acid-guided cerasome nano-agents for simultaneous imaging and treatment of advanced atherosclerosis. Adv Sci (Weinh) 10: e2202416, 2022.
90. Xu H, She P, Zhao Z, Ma B, Li G and Wang Y: Duplex responsive nanoplatform with cascade targeting for atherosclerosis photoacoustic diagnosis and multichannel combination therapy. Adv Mater 35: e2300439, 2023.
91. Huang X, Zhang Y, Zhang W, Qin C, Zhu Y, Fang Y, Wang Y, Tang C and Cao F: Osteopontin-targeted and PPARδ-agonist-loaded nanoparticles efficiently reduce atherosclerosis in apolipoprotein $E^{-/-}$ mice. ACS Omega 7: 28767-28778, 2022.
92. Sheng J, Zu Z, Zhang Y, Zhu H, Qi J, Zheng T, Tian Y and Zhang L: Targeted therapy of atherosclerosis by zeolitic imidazolate framework-8 nanoparticles loaded with losartan potassium via simultaneous lipid-scavenging and anti-inflammation. J Mater Chem B 10: 5925-5937, 2022.
93. Boersma B, Möller K, Wehl L, Puddinu V, Huard A, Fauteux-Daniel S, Bourquin C, Palmer G and Bein T: Inhibition of IL-1β release from macrophages targeted with necrosulfonamide-loaded porous nanoparticles. J Control Release 351: 989-1002, 2022.
94. Zhou H, You P, Liu H, Fan J, Tong C, Yang A, Jiang Y and Liu B: Artemisinin and Procyanidins loaded multifunctional nanocomplexes alleviate atherosclerosis via simultaneously modulating lipid influx and cholesterol efflux. J Control Release 341: 828-843, 2021.
95. Mehta S, Bongcaron V, Nguyen TK, Jirwanka Y, Maluenda A, Walsh APG, Palasubramaniam J, Hulett MD, Srivastava R, Bobik A, *et al*: An Ultrasound-responsive theranostic Cyclodextrin-loaded nanoparticle for multimodal imaging and therapy for atherosclerosis. Small 18: e2200967, 2022.
96. Cheraga N, Ye Z, Xu MJ, Zou L, Sun NC, Hang Y, Shan CJ, Yang ZZ, Chen LJ and Huang NP: Targeted therapy of atherosclerosis by pH-sensitive hyaluronic acid nanoparticles co-delivering all-trans retinal and rapamycin. Nanoscale 14: 8709-8726, 2022.
97. Song K, Tang Z, Song Z, Meng S, Yang X, Guo H, Zhu Y and Wang X: Hyaluronic Acid-functionalized mesoporous silica nanoparticles loading simvastatin for targeted therapy of atherosclerosis. Pharmaceutics 14: 1265, 2022.
98. Sun W, Xu Y, Yao Y, Yue J, Wu Z, Li H, Shen G, Liao Y, Wang H and Zhou W: Self-oxygenation mesoporous MnO_2 nanoparticles with ultra-high drug loading capacity for targeted arteriosclerosis therapy. J Nanobiotechnology 20: 88, 2022.
99. De Negri Atanasio G, Ferrari PF, Baião A, Perego P, Sarmento B, Palombo D and Campardelli R: Bevacizumab encapsulation into PLGA nanoparticles functionalized with immunouteroglobin-1 as an innovative delivery system for atherosclerosis. Int J Biol Macromol 221: 1618-1630, 2022.
100. du Toit LC, Hulisani Demana P and Essop Choonara Y: A nano-enabled biotinylated anti-LDL theranostic system to modulate systemic LDL cholesterol. Int J Pharm 628: 122258, 2022.
101. Deuringer B, Härdtner C, Krebs K, Thomann R, Holzer M, Hilgendorf I and Süss R: Everolimus-loaded reconstituted high-density lipoprotein prepared by a novel dual centrifugation approach for Anti-atherosclerotic therapy. Int J Nanomedicine 17: 5081-5097, 2022.
102. Wei B, Li Y, Ao M, Shao W, Wang K, Rong T, Zhou Y and Chen Y: Ganglioside GM3-functionalized reconstituted high-density lipoprotein (GM3-rHDL) as a novel nanocarrier enhances antiatherosclerotic efficacy of statins in $apoE^{-/-}$ C57BL/6 mice. Pharmaceutics 14: 2534, 2022.
103. Jebari-Benslaiman S, Uribe KB, Benito-Vicente A, Galicia-Garcia U, Larrea-Sebal A, Santin I, Alloza I, Vandenbroeck K, Ostolaza H and Martín C: Boosting cholesterol efflux from foam cells by sequential administration of rHDL to deliver MicroRNA and to remove cholesterol in a triple-cell 2D atherosclerosis model. Small 18: e2105915, 2022.
104. Zhang Z, Zhuang J, Sun D, Ding Q, Zheng H, Li H, Zhang X, Du Y, Ma T and Meng Q: Netrin-1 monoclonal antibody-functionalized nanoparticle loaded with metformin prevents the progression of abdominal aortic aneurysms. Int J Nanomedicine 18: 627-639, 2023.
105. Chen X, Wu Y, Li R, Li C, Xu L, Qiao W and Dong N: Galactose-modified nanoparticles for delivery of microRNA to mitigate the progress of abdominal aortic aneurysms via regulating macrophage polarization. Nanomedicine 44: 102564, 2022.
106. Dhital S, Rice CD and Vyavahare NR: Reversal of elastase-induced abdominal aortic aneurysm following the delivery of nanoparticle-based pentagalloyl glucose (PGG) is associated with reduced inflammatory and immune markers. Eur J Pharmacol 910: 174487, 2021.
107. Fukuhara N, Honda Y, Ukita N, Matsui M, Miura Y and Hoshina K: Efficient suppression of abdominal aortic aneurysm expansion in rats through systemic administration of statin-loaded nanomedicine. Int J Mol Sci 21: 8702, 2020.
108. Cheng J, Zhang R, Li C, Tao H, Dou Y, Wang Y, Hu H and Zhang J: A Targeting nanotherapy for abdominal aortic aneurysms. J Am Coll Cardiol 72: 2591-2605, 2018.
109. Nosoudi N, Chowdhury A, Siclari S, Karamched S, Parasaram V, Parrish J, Gerard P and Vyavahare N: Reversal of vascular calcification and aneurysms in a rat model using dual targeted therapy with EDTA- and PGG-loaded nanoparticles. Theranostics 6: 1975-1987, 2016.
110. Boada C, Zinger A, Tsao C, Zhao P, Martinez JO, Hartman K, Naoi T, Sukhoveshin R, Sushnitha M, Molinaro R, *et al*: Rapamycin-loaded biomimetic nanoparticles reverse vascular inflammation. Circ Res 126: 25-37, 2019.
111. Bhatia SN, Chen X, Dobrovolskaia MA and Lammers T: Cancer nanomedicine. Nat Rev Cancer 22: 550-556, 2022.
112. Luo XM, Yan C and Feng YM: Nanomedicine for the treatment of diabetes-associated cardiovascular diseases and fibrosis. Adv Drug Deliv Rev 172: 234-248, 2021.

113. van Tilborg GAF, Vucic E, Strijkers GJ, Cormode DP, Mani V, Skajaa T, Reutelingsperger CP, Fayad ZA, Mulder WJ and Nicolay K: Annexin A5-functionalized bimodal nanoparticles for MRI and fluorescence imaging of atherosclerotic plaques. Bioconjug Chem 21: 1794-1803, 2010.
114. Marrache S and Dhar S: Biodegradable synthetic high-density lipoprotein nanoparticles for atherosclerosis. Proc Natl Acad Sci USA 110: 9445-9450, 2013.
115. Zhang H, Gong Y, Wang Z, Jiang L, Chen R, Fan X, Zhu H, Han L, Li X, Xiao J and Kong X: Apelin inhibits the proliferation and migration of rat PASMCs via the activation of PI3K/Akt/mTOR signal and the inhibition of autophagy under hypoxia. J Cell Mol Med 18: 542-553, 2014.
116. Zheng H, Zhai W, Zhong C, Hong Q, Li H, Rui B, Zhu X, Que D, Feng L, Yu B, *et al*: Nkx2-3 induces autophagy inhibiting proliferation and migration of vascular smooth muscle cells via AMPK/mTOR signaling pathway. J Cell Physiol 236: 7342-7355, 2021.
117. Chan JW, Lewis DR, Petersen LK, Moghe PV and Uhrich KE: Amphiphilic macromolecule nanoassemblies suppress smooth muscle cell proliferation and platelet adhesion. Biomaterials 84: 219-229, 2016.
118. Anghelache M, Voicu G, Deleanu M, Turtoi M, Safciuc F, Anton R, Boteanu D, Fenyo IM, Manduteanu I, Simionescu M and Calin M: Biomimetic nanocarriers of Pro-resolving lipid mediators for resolution of inflammation in atherosclerosis. Adv Healthc Mater 13: e2302238, 2024.
119. Deshpande D, Kethireddy S, Janero DR and Amiji MM: Therapeutic efficacy of an ω-3-fatty acid-containing 17-β estradiol Nano-delivery system against experimental atherosclerosis. PLoS One 11: e0147337, 2016.
120. Sano M, Akagi D, Naito M, Hoshina K, Miyata K, Kataoka K and Ishihara S: Systemic single administration of anti-inflammatory microRNA 146a-5p loaded in polymeric nanomedicines with active targetability attenuates neointimal hyperplasia by controlling inflammation in injured arteries in a rat model. FASEB J 36: e22486, 2022.
121. Basatemur GL, Jørgensen HF, Clarke MCH, Bennett MR and Mallat Z: Vascular smooth muscle cells in atherosclerosis. Nat Rev Cardiol 16: 727-744, 2019.
122. Bentzon JF, Otsuka F, Virmani R and Falk E: Mechanisms of plaque formation and rupture. Circ Res 114: 1852-1866, 2014.
123. Halcox JPJ, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, Nour KR and Quyyumi AA: Prognostic value of coronary vascular endothelial dysfunction. Circulation 106: 653-658, 2002.
124. Hou L, Zhang M, Liu L, Zhong Q, Xie M and Zhao G: Therapeutic applications of nanomedicine in metabolic diseases by targeting the endothelium. QJM 116: 493-501, 2022.
125. Deng Y, Deng X, Li Y, Tian J, Wu M, Tang J, Liang X, Yang X, He X, Liu Y, *et al*: Size-adjustable nanoparticles co-target macrophages and endothelial cells for enhanced atherosclerosis therapy. Colloids Surf B Biointerfaces 255: 114952, 2025.
126. Wang Y, Feng Y, Yang X, Wang W and Wang Y: Diagnosis of atherosclerotic plaques using vascular endothelial growth factor receptor-2 targeting antibody Nano-microbubble as ultrasound contrast agent. Comput Math Methods Med 2022: 6524592, 2022.
127. Bu T, Li Z, Hou Y, Sun W, Zhang R, Zhao L, Wei M, Yang G and Yuan L: Exosome-mediated delivery of inflammation-responsive mRNA for controlled atherosclerosis treatment. Theranostics 11: 9988-10000, 2021.
128. Distasio N, Dierick F, Ebrahimian T, Tabrizian M and Lehoux S: Design and development of branched Poly(β-aminoester) nanoparticles for Interleukin-10 gene delivery in a mouse model of atherosclerosis. Acta Biomater 143: 356-371, 2022.
129. Song C, Wang Y, Cui L, Yan F and Shen S: Triptolide attenuates lipopolysaccharide-induced inflammatory responses in human endothelial cells: Involvement of NF-κB pathway. BMC Complement Altern Med 19: 198, 2019.
130. Lai K, Li Y, Gong Y, Li L, Huang C, Xu F, Zhong X and Jin C: Triptolide-nanoliposome-APRPG, a novel sustained-release drug delivery system targeting vascular endothelial cells, enhances the inhibitory effects of triptolide on laser-induced choroidal neovascularization. Biomed Pharmacother 131: 110737, 2020.
131. Zhu ML, Wang G, Wang H, Guo YM, Song P, Xu J, Li P, Wang S and Yang L: Amorphous nano-selenium quantum dots improve endothelial dysfunction in rats and prevent atherosclerosis in mice through Na/H exchanger 1 inhibition. Vascul Pharmacol 115: 26-32, 2019.
132. Beconcini D, Fabiano A, Zambito Y, Berni R, Santoni T, Piras AM and Di Stefano R: Chitosan-based nanoparticles containing cherry Extract from *Prunus avium* L. to improve the resistance of endothelial cells to oxidative stress. Nutrients 10: 1598, 2018.
133. Ke S, Lai Y, Zhou T, Li L, Wang Y, Ren L and Ye S: Molybdenum disulfide nanoparticles resist oxidative Stress-mediated impairment of autophagic flux and mitigate endothelial cell senescence and angiogenic dysfunctions. ACS Biomater Sci Eng 4: 663-674, 2018.
134. Yan H, Hu Y, Lyu Y, Akk A, Hirbe AC, Wickline SA, Pan H, Roberson EDO and Pham CTN: Augmented expression of superoxide dismutase 2 mitigates progression and rupture of experimental abdominal aortic aneurysm. Theranostics 15: 4016-4032, 2025.
135. Lockhart JH, VanWye J, Banerjee R, Wickline SA, Pan H and Totary-Jain H: Self-assembled miRNA-switch nanoparticles target denuded regions and prevent restenosis. Mol Ther 29: 1744-1757, 2021.
136. Pham LM, Kim EC, Ou W, Phung CD, Nguyen TT, Pham TT, Poudel K, Gautam M, Nguyen HT, Jeong JH, *et al*: Targeting and clearance of senescent foamy macrophages and senescent endothelial cells by antibody-functionalized mesoporous silica nanoparticles for alleviating aorta atherosclerosis. Biomaterials 269: 120677, 2021.
137. Zhang BF, Jiang H, Chen J, Hu Q, Yang S and Liu XP: Silica-coated magnetic nanoparticles labeled endothelial progenitor cells alleviate ischemic myocardial injury and improve long-term cardiac function with magnetic field guidance in rats with myocardial infarction. J Cell Physiol 234: 18544-18559, 2019.
138. Yu B, Li H, Zhang Z, Chen P, Wang L, Fan X, Ning X, Pan Y, Zhou F, Hu X, *et al*: Extracellular vesicles engineering by silicates-activated endothelial progenitor cells for myocardial infarction treatment in male mice. Nat Commun 14: 2094, 2023.
139. Yang Z, Yang Y, Xiong K, Li X, Qi P, Tu Q, Jing F, Weng Y, Wang J and Huang N: Nitric oxide producing coating mimicking endothelium function for multifunctional vascular stents. Biomaterials 63: 80-92, 2015.
140. Huang SF, Zhao G, Peng XF and Ye WC: The pathogenic role of long Non-coding RNA H19 in atherosclerosis the miR-146a-5p/ANGPTL4 pathway. Front Cardiovasc Med 8: 770163, 2021.
141. Sager HB, Dutta P, Dahlman JE, Hulsmans M, Courties G, Sun Y, Heidt T, Vinegoni C, Borodovsky A, Fitzgerald K, *et al*: RNAi targeting multiple cell adhesion molecules reduces immune cell recruitment and vascular inflammation after myocardial infarction. Sci Transl Med 8: 342ra380, 2016.
142. Orecchioni M, Kobiyama K, Winkels H, Ghosheh Y, McArdle S, Mikulski Z, Kiosses WB, Fan Z, Wen L, Jung Y, *et al*: Olfactory receptor 2 in vascular macrophages drives atherosclerosis by NLRP3-dependent IL-1 production. Science 375: 214-221, 2022.
143. Seneviratne AN, Edsfeldt A, Cole JE, Kassiteridi C, Swart M, Park I, Green P, Khoyratty T, Saliba D, Goddard ME, *et al*: Interferon regulatory factor 5 controls necrotic core formation in atherosclerotic lesions by impairing efferocytosis. Circulation 136: 1140-1154, 2017.
144. Stoneman V, Braganza D, Figg N, Mercer J, Lang R, Goddard M and Bennett M: Monocyte/macrophage suppression in CD11b diphtheria toxin receptor transgenic mice differentially affects atherogenesis and established plaques. Circ Res 100: 884-893, 2007.
145. Gao C, Huang Q, Liu C, Kwong CHT, Yue L, Wan JB, Lee SMY and Wang R: Treatment of atherosclerosis by macrophage-biomimetic nanoparticles via targeted pharmacotherapy and sequestration of proinflammatory cytokines. Nat Commun 11: 2622, 2020.
146. Boada C, Zinger A, Tsao C, Zhao P, Martinez JO, Hartman K, Naoi T, Sukhoveshin R, Sushnitha M, Molinaro R, *et al*: Rapamycin-loaded biomimetic nanoparticles reverse vascular inflammation. Circ Res 126: 25-37, 2020.
147. Zhang X, Misra SK, Moitra P, Zhang X, Jeong SJ, Stitham J, Rodriguez-Velez A, Park A, Yeh YS, Gillanders WE, *et al*: Use of acidic nanoparticles to rescue macrophage lysosomal dysfunction in atherosclerosis. Autophagy 19: 886-903, 2023.
148. Stachyra K, Wiśniewska A, Kiepura A, Kuś K, Rolski F, Czepiel K, Chmura Ł, Majka G, Surmiak M, Polaczek J, *et al*: Inhaled silica nanoparticles exacerbate atherosclerosis through skewing macrophage polarization towards M1 phenotype. Ecotoxicol Environ Saf 230: 113112, 2021.

149. Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, Aubertin-Leheudre M, Bernabei R, Cadore EL, Cesari M, *et al*: International exercise recommendations in older adults (ICFSR): Expert elines. J Nutr Health Aging 25: 824-853, 2021.
150. Bierer BE, Zarin DA and Gelinas L: Deprioritization of ongoing clinical trials. Ethics Hum Res 45: 27-33, 2023.
151. Wang J, Ding Y, Chong K, Cui M, Cao Z, Tang C, Tian Z, Hu Y, Zhao Y and Jiang S: Recent advances in lipid nanoparticles and their safety concerns for mRNA delivery. Vaccines (Basel) 12: 1148, 2024.
152. Jiang Y, Zhou Y, Li Z and Guo L: Nanomedicine in cardiovascular and cerebrovascular diseases: Targeted nanozyme therapies and their clinical potential and current challenges. J Nanobiotechnology 23: 543, 2025.
153. Wang J, Zhao W, Zhang Z, Liu X, Xie T, Wang L, Xue Y and Zhang Y: A Journey of challenges and victories: A bibliometric worldview of nanomedicine since the 21st Century. Adv Mater 36: e2308915, 2024.
154. Macário-Soares A, Sousa-Oliveira I, Correia M, Pires PC, Sharma A, Kumar Jha N, Zare EN, Veiga F, Gowda BHJ, Borzacchiello A, *et al*: Cell membrane and extracellular vesicle membrane-coated nanoparticles: An envisaged approach for the management of skin conditions. View 5: 20240043, 2024.
155. Ghosh A, Gupta A, Jena S, Kirti A, Choudhury A, Saha U, Sinha A, Kumari S, Kujawska M, Kaushik A and Verma SK: Advances in posterity of visualization in paradigm of nano-level ultra-structures for nano-bio interaction studies. View 6: 20240042, 2025.
156. Li Y, Liang D, Wang R, Yang S, Liu W, Sang Q, Pu J, Wang Y and Qian K: Interfacial Self-assembly nanostructures: Constructions and applications. Small 20: e2405318, 2024.
157. Zhang Z, Li Y, Wang R, Yang S, Li P, Zhao K, Gu Y, Meng K, Li J, Pu J, *et al*: Plasmonic alloys enhance metabolic fingerprints for rapid diagnosis and classification of myocardial infarction. Nano Today 62: 102702, 2025.
158. Nel AE, Mädler L, Velegol D, Xia T, Hoek EM, Somasundaran P, Klaessig F, Castranova V and Thompson M: Understanding biophysicochemical interactions at the nano-bio interface. Nat Mater 8: 543-557, 2009.
159. Zhang Q, Zhang J, Song J, Liu Y, Ren X and Zhao Y: Protein-based nanomedicine for therapeutic benefits of cancer. ACS Nano 15: 8001-8038, 2021.
160. Luo B, Xiang D, Ji X, Chen X, Li R, Zhang S, Meng Y, Nieman DC and Chen P: The anti-inflammatory effects of exercise on autoimmune diseases: A 20-year systematic review. J Sport Health Sci 13: 353-367, 2024.
161. Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, Liu C, Barnes S, Grizzle W, Miller D and Zhang HG: A novel nanoparticle drug delivery system: The anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Mol Ther 18: 1606-1614, 2010.
162. Cui C, Du M, Zhao Y, Tang J, Liu M, Min G, Chen R, Zhang Q, Sun Z and Weng H: Functional Ginger-derived extracellular vesicles-coated ZIF-8 containing TNF-α siRNA for ulcerative colitis therapy by modulating gut microbiota. ACS Appl Mater Interfaces 16: 53460-53473, 2024.
163. Wang E, Rossman MJ, Groot HJ, Garten RS, Jarrett CL, Helgerud J, Hoff J and Richardson RS: Leg vascular function with advancing age in men: The impact of physical activity and endurance exercise training. J Appl Physiol (1985) 139: 473-481, 2025.