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Review Article

Advances in cardiovascular gene therapy: a systematic review of nanoparticle-based delivery strategies for atherosclerosis

Mahan Khani[1*], Kianoush Shahryari[2*], Samira Masoumi[3*], Maryam Alipour[4*], Zahra Mirzaye[5], Maryam Fathollahzadeh[6], Fatemeh Atefat[7], Behnaz Bastami[8], Mahsa Rostami Ghezeljeh[9], Hanie Khalili[6], Nikoo Navidighaziani[10], Hossein Zare[4], Vajihe Kooshamoghadam[11], Sepehr Ramezanipour[12], Ghazaleh Elahabadi[13], Samaneh Dodge[14], Faizeh Parvandi[15], Tina Fattahi[16], Amirhosein Ghafouri-Asbagh[17], Farbod Khosravi[18], Mahsa Asadi Anar[18]

[1]Tehran University of Medical Sciences, Tehran, Iran; [2]Shahid Beheshti University of Medical Science, Tehran, Iran; [3]Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran; [4]School of Medicine, Kerman University of Medical Sciences, Kerman, Iran; [5]Medical Student at Kerman University of Medical Sciences, Kerman, Iran; [6]Student Research Committee, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [7]School of Medicine, Shiraz University of Medical Science, Shiraz, Iran; [8]Kish International Campus, University of Tehran, Kish Island, Iran; [9]Kerman University of Medical Sciences, Kerman, Iran; [10]Student Research Committee, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran; [11]Yazd Cardiovascular Research Center, Non-Communicable Diseases Research Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [12]Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran; [13]Department of Clinical Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran; [14]School of Pharmacy, Shahid Beheshti University of Medical Science, Tehran, Iran; [15]Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; [16]Islamic Azad University of Medical Sciences, Tehran, Iran; [17]Research Center for Chronic Inflammatory Diseases, Tehran University of Medical Sciences, Tehran, Iran; [18]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [*]Equal contributors.

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Abstract: Background: Atherosclerosis (AS), the primary cause of cardiovascular morbidity and mortality, involves chronic vascular inflammation and plaque formation. While conventional therapies target systemic risk factors, their limited plaque-specific effects and adverse profiles have driven the exploration of targeted delivery systems. Nanoparticle-mediated delivery of nucleic acid therapies offers a promising strategy to modulate inflammation and promote plaque regression at the molecular level. This study aimed to systematically evaluate recent preclinical evidence on the effectiveness of functionalized nanoparticles for delivering nucleic acid-based therapies to atherosclerotic plaques. Methods: This systematic review, conducted in accordance with the PRISMA 2020 guidelines, evaluated preclinical studies published between 2018 and 2024 that utilized nanoparticles to deliver siRNA, miRNA inhibitors, or antisense oligonucleotides (ASOs) to atherosclerotic plaques. Data extraction included nanoparticle type, targeting ligands, size, loading efficiency, administration route, and therapeutic outcomes. Comparative figures were generated, including a bar chart of plaque reduction efficacy by nanoparticle type and a qualitative heatmap mapping functionalization strategies to molecular targets. Results: Fifteen animal studies met the inclusion criteria. Nanoparticles varied in size (5-190 nm), composition (cyclodextrin, gold, polymeric, lipid-based), and targeting mechanisms (e.g., VCAM1, CD36, integrin ligands). High efficacy was reported for functionalized carriers targeting macrophages or inflammatory pathways, with plaque reductions up to 65.8%. Visual analyses highlighted cyclodextrin-integrin and rHDL-based systems as top-performing strategies, while a heatmap revealed preferred pairings of delivery ligands with nucleic acid targets. Conclusion: Functionalized nanoparticles demonstrate robust preclinical efficacy for delivering nucleic acids to atherosclerotic plaques. These findings support their potential for targeted, multimodal therapy in cardiovascular disease, warranting further clinical investigation into scalable, biocompatible delivery platforms.

Keywords: Atherosclerosis, nanoparticles, drug delivery systems, nanomedicine, nucleic acid therapies, plaques, targeted therapy, macrophage targeting, inflammation, gene silencing

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Introduction

Atherosclerosis (AS) is a progressive inflammatory disease of the arterial wall and the principal pathological driver of cardiovascular morbidity and mortality worldwide [1, 2]. Despite advances in risk factor modification and pharmacotherapy, residual cardiovascular risk remains high, particularly in patients with established plaques or recurrent events [3].

Current pharmacological approaches, including statins, antiplatelet agents, and anti-inflammatory drugs, primarily exert systemic effects and are limited in their capacity to directly modulate plaque biology. Even with optimized medical therapy, the reversal of advanced lesions remains elusive, and procedural interventions, such as stenting or bypass grafting, are constrained by the risks of restenosis, thrombosis, and a limited impact on systemic inflammation [4].

Nanoparticle-mediated delivery systems have emerged as a promising strategy to overcome these limitations by enabling targeted delivery of therapeutic agents to diseased vascular sites. In particular, the use of functionalized nanoparticles for the delivery of nucleic acid therapeutics, such as small interfering RNAs (siRNAs), microRNA (miRNA) inhibitors, and antisense oligonucleotides (ASOs), offers a molecularly precise approach to modulate key pathogenic pathways within plaques, including macrophage activation, lipid metabolism, and cytokine signaling [5, 6].

The clinical utility of such platforms lies in their capacity to enhance therapeutic payload stability, prolong circulation time, improve cellular uptake through receptor-mediated mechanisms, and minimize off-target toxicity. Moreover, recent advances in ligand engineering and nanocarrier architecture have enabled selective targeting of inflammatory endothelium and lesional macrophages, key drivers of plaque instability.

This systematic review synthesizes evidence from recent preclinical studies investigating nucleic acid-loaded nanoparticles in animal models of atherosclerosis. By comparing delivery strategies, therapeutic efficacy, and targeting mechanisms, we aim to delineate design principles that can guide the development of clinically translatable nano therapies for cardiovascular disease.

Method

The current study is a systematic review that adheres to the principles outlined in the PRISMA checklist [7]. The study protocol has been registered within the Open Science Framework (OSF). (DOI 10.17605/OSF.IO/R65P7).

Search strategy

Our keywords included Atherosclerosis, Nanoparticles, Nanotechnology, Nanomaterials, Therapeutics, Plaques, Targeted therapy, Targeted strategy, Drug delivery systems, Drug delivery, Drug carrier, and Nanomedicine Atherosclerosis treatment. Database Studies that met our inclusion criteria were included in our work from 2018 to 2024 (**Table 1**). The references, including articles and relevant studies, have been checked manually.

Eligibility criteria

Our inclusion criteria were to use articles that are original studies. Additionally, all our studies underwent the refereeing process. Both human and animal studies were reviewed in our work. Additionally, studies presenting biomarker imaging cases were accepted and utilized.

Also, regarding the exclusion criteria, articles not in English were excluded. Review articles and book chapters were removed. Additionally, they were removed if the study was a letter to the editor or a poster presentation. Case reports and case series were also deleted. Also, those articles that did not examine the imaging of biological markets were excluded from our work.

Data extraction

We used Ryan's Intelligent Tool for systematic reviews to screen studies. Moreover, three reviewers (HZ, ZM, and MA) screened these studies. A fourth reviewer resolved disagreements (MAA). We extracted the studies based on the written data variables presented in **Table 2**.

Table 1. Curated search strategies for each chosen database

Database	Search Syntax	Result
PubMed	((((((((((((((((((((((((((((((((((((“nanoparticle strategies”[Title/Abstract]) OR (Nanoparticle[Title/Abstract])) OR (“Nanocrystalline Materials”[Title/Abstract])) OR (“Material, Nanocrystalline”[Title/Abstract])) OR (“Materials, Nanocrystalline”[Title/Abstract])) OR (“Nanocrystalline Material”[Title/Abstract])) OR (Nanocrystals[Title/Abstract])) OR (Nanocrystal[Title/Abstract])) OR (“Nanoparticles”[Mesh])) OR (“Calcifying Nanoparticles”[Title/Abstract])) OR (“Calcifying Nanoparticles”[Mesh])) OR (Dendrimers[Title/Abstract])) OR (“Dendrimers”[Mesh])) OR (“Metal Nanoparticles”[Title/Abstract])) OR (“Metal Nanoparticles”[Mesh])) OR (“Magnetic Iron Oxide Nanoparticles”[Title/Abstract])) OR (“Magnetic Iron Oxide Nanoparticles”[Mesh])) OR (Nanoshells[Title/Abstract])) OR (“Nanoshells”[Mesh])) OR (“Multifunctional Nanoparticles”[Title/Abstract])) OR (“Multifunctional Nanoparticles”[Mesh])) OR (Nanocapsules[Title/Abstract])) OR (“Nanocapsules”[Mesh])) OR (Nanoconjugates[Title/Abstract])) OR (“Nanoconjugates”[Mesh])) OR (Nanodiamonds[Title/Abstract])) OR (“Nanodiamonds”[Mesh])) OR (Nanogels[Title/Abstract])) OR (“Nanogels”[Mesh])) OR (Nanospheres[Title/Abstract])) OR (“Nanospheres”[Mesh])) OR (Fullerenes[Title/Abstract])) OR (“Fullerenes”[Mesh])) OR (“Quantum Dots”[Title/Abstract])) OR (“Quantum Dots”[Mesh])) OR (Nanoparticles[Title/Abstract]) AND ((((((((((((((((((((“nucleic acid therapy”[Title/Abstract]) OR (“Nucleic Acids”[Title/Abstract])) OR (“Acids, Nucleic”[Title/Abstract])) OR (“Nucleic Acid”[Title/Abstract])) OR (“Acid, Nucleic”[Title/Abstract])) OR (“Nucleic Acids”[Mesh])) OR (“Cell-Free Nucleic Acids”[Title/Abstract])) OR (“Cell-Free Nucleic Acids”[Mesh])) OR (“Circulating MicroRNA”[Title/Abstract])) OR (“Circulating MicroRNA”[Mesh])) OR (“Circulating Tumor DNA”[Title/Abstract])) OR (“Circulating Tumor DNA”[Mesh])) OR (DNA[Title/Abstract])) OR (“DNA”[Mesh])) OR (“Immobilized Nucleic Acids”[Title/Abstract])) OR (“Immobilized Nucleic Acids”[Mesh])) OR (“Nucleic Acid Heteroduplexes”[Title/Abstract])) OR (“Nucleic Acid Heteroduplexes”[Mesh])) OR (“Nucleic Acid Probes”[Title/Abstract])) OR (“Nucleic Acid Probes”[Mesh])) OR (RNA[Title/Abstract])) OR (“RNA”[Mesh]) AND ((((((((((((((((“Plaque, Atherosclerotic”[Title/Abstract]) OR (“Atherosclerotic Plaques”[Title/Abstract])) OR (“Atherosclerotic Plaque”[Title/Abstract])) OR (“Fatty Streak, Arterial”[Title/Abstract])) OR (“Arterial Fatty Streak” [Title/Abstract])) OR (“Arterial Fatty Streaks”[Title/Abstract])) OR (“Streak, Arterial Fatty” [Title/Abstract])) OR (Fibroatheroma[Title/Abstract])) OR (Fibroatheromas[Title/Abstract])) OR (“Fibroatheromatous Plaques”[Title/Abstract])) OR (“Fibroatheromatous Plaque”[Title/Abstract])) OR (“Plaque, Fibroatheromatous”[Title/Abstract])) OR (Atheroma[Title/Abstract])) OR (Atheromas[Title/Abstract])) OR (“Atheromatous Plaques”[Title/Abstract])) OR (“Atheromatous Plaque”[Title/Abstract])) OR (“Plaque, Atheromatous”[Title/Abstract])) OR (“Plaque, Atherosclerotic”[Mesh])	42
WOS	((((((((((((TS=(“nucleic acid therapy”)) OR TS=(“Nucleic Acids”)) OR TS=(“Acids, Nucleic”)) OR TS=(“Nucleic Acid”)) OR TS=(“Acid, Nucleic”)) OR TS=(“Cell-Free Nucleic Acids”)) OR TS=(“Circulating MicroRNA”)) OR TS=(“Circulating Tumor DNA”)) OR TS=(DNA)) OR TS=(“Immobilized Nucleic Acids”)) OR TS=(“Nucleic Acid Probes”)) OR TS=(RNA)) OR TS=(“Nucleic Acid Heteroduplexes”) AND ((((((((((((((((((((TS=(“nanoparticle strategies”)) OR TS=(Nanoparticle)) OR TS=(“Nanocrystalline Materials”)) OR TS=(“Material, Nanocrystalline”)) OR TS=(“Materials, Nanocrystalline”)) OR TS=(“Nanocrystalline Material”)) OR TS=(Nanocrystals)) OR TS=(Nanocrystal)) OR TS=(“Calcifying Nanoparticles”)) OR TS=(Dendrimers)) OR TS=(“Metal Nanoparticles”)) OR TS=(“Magnetic Iron Oxide Nanoparticles”)) OR TS=(Nanoshells)) OR TS=(“Multifunctional Nanoparticles”)) OR TS=(Nanocapsules)) OR TS=(Nanoconjugates)) OR TS=(Nanodiamonds)) OR TS=(Nanogels)) OR TS=(Nanospheres)) OR TS=(Fullerenes)) OR TS=(Nanoparticles)) OR TS=(“Quantum Dots”) AND ((((((((((((((((TS=(“Plaque, Atherosclerotic”)) OR TS=(“Atherosclerotic Plaques”)) OR TS=(“Atherosclerotic Plaque”)) OR TS=(“Fatty Streak, Arterial”)) OR TS=(“Arterial Fatty Streak”)) OR TS=(“Arterial Fatty Streaks”)) OR TS=(“Streak, Arterial Fatty”)) OR TS=(Fibroatheroma)) OR TS=(Fibroatheromas)) OR TS=(“Fibroatheromatous Plaques”)) OR TS=(“Fibroatheromatous Plaque”)) OR TS=(“Plaque, Fibroatheromatous”)) OR TS=(Atheroma)) OR TS=(Atheromas)) OR TS=(“Atheromatous Plaques”)) OR TS=(“Plaque, Atheromatous”)) OR TS=(“Atheromatous Plaque”)	45

Scopus	(TITLE-ABS-KEY("nucleic acid therapy") OR TITLE-ABS-KEY("Nucleic Acids") OR TITLE-ABS-KEY("Acids, Nucleic") OR TITLE-ABS-KEY("Nucleic Acid") OR TITLE-ABS-KEY("Acid, Nucleic") OR TITLE-ABS-KEY("Cell-Free Nucleic Acids") OR TITLE-ABS-KEY("Circulating MicroRNA") OR TITLE-ABS-KEY("Circulating Tumor DNA") OR TITLE-ABS-KEY(DNA) OR TITLE-ABS-KEY("Immobilized Nucleic Acids") OR TITLE-ABS-KEY("Nucleic Acid Probes") OR TITLE-ABS-KEY(RNA) OR TITLE-ABS-KEY("Nucleic Acid Heteroduplexes")) AND (TITLE-ABS-KEY("nanoparticle strategies") OR TITLE-ABS-KEY(Nanoparticle) OR TITLE-ABS-KEY("Nanocrystalline Materials") OR TITLE-ABS-KEY("Material, Nanocrystalline") OR TITLE-ABS-KEY("Materials, Nanocrystalline") OR TITLE-ABS-KEY("Nanocrystalline Material") OR TITLE-ABS-KEY(Nanocrystals) OR TITLE-ABS-KEY(Nanocrystal) OR TITLE-ABS-KEY("Calcifying Nanoparticles") OR TITLE-ABS-KEY(Dendrimers) OR TITLE-ABS-KEY("Metal Nanoparticles") OR TITLE-ABS-KEY("Magnetic Iron Oxide Nanoparticles") OR TITLE-ABS-KEY("Multifunctional Nanoparticles") OR TITLE-ABS-KEY(Nanoshells) OR TITLE-ABS-KEY(Nanocapsules) OR TITLE-ABS-KEY(Nanoconjugates) OR TITLE-ABS-KEY(Nanodiamonds) OR TITLE-ABS-KEY(Nanogels) OR TITLE-ABS-KEY(Nanospheres) OR TITLE-ABS-KEY(Fullerenes) OR TITLE-ABS-KEY(Nanoparticles) OR TITLE-ABS-KEY("Quantum Dots")) AND (TITLE-ABS-KEY("Plaque, Atherosclerotic") OR TITLE-ABS-KEY("Atherosclerotic Plaques") OR TITLE-ABS-KEY("Atherosclerotic Plaque") OR TITLE-ABS-KEY("Fatty Streak, Arterial") OR TITLE-ABS-KEY("Arterial Fatty Streak") OR TITLE-ABS-KEY("Arterial Fatty Streaks") OR TITLE-ABS-KEY("Streak, Arterial Fatty") OR TITLE-ABS-KEY(Fibroatheroma) OR TITLE-ABS-KEY(Fibroatheromas) OR TITLE-ABS-KEY("Fibroatheromatous Plaques") OR TITLE-ABS-KEY("Fibroatheromatous Plaque") OR TITLE-ABS-KEY("Plaque, Fibroatheromatous") OR TITLE-ABS-KEY(Atheroma) OR TITLE-ABS-KEY(Atheromas) OR TITLE-ABS-KEY("Atheromatous Plaques") OR TITLE-ABS-KEY("Plaque, Atheromatous") OR TITLE-ABS-KEY("Atheromatous Plaque"))	124

Table 2. Summary characteristics of included studies

Author	Year	Country	Animal model	N animal	Therapeutic agent	Type of nanoparticle	Size/ charge	Mechanism/route of delivery	Injected dose	Loading capacity and loading efficiency (LC&LE)	Key findings
Chenwen Li [13]	2020	China	ApoE-deficient mice (ApoE-/-)	12-20	anti-miR33	cyclodextrin-derived pH-responsive and integrin-targeting nanoparticles	Size: 147.5 ± 2.1 nm Charge: 9.9 ± 0.1 mV	• pH-Responsive Nanoparticles • Intravenous Injection • Integrin-Targeting (Targeting Ligands) • Endolysosomal Escape • Enhanced Cellular Uptake by using of cationic materials and specific ligands	Low dose: 0.5 mg/kg High dose: 2 mg/kg two injections at the first week, followed by weekly injections for 2 months	LE: 88.1 ± 2.2%	• MicroRNA-33 Targeting: The study highlights the potential of microRNA-33 (miR-33) as a therapeutic target for atherosclerosis due to its role in regulating cholesterol efflux and immune responses. • Nanoparticle Design: The researchers developed pH-responsive nanoparticles that can deliver antisense oligonucleotides against miR-33 (anti-miR33) specifically to atherosclerotic plaques. • The nanotherapies promoted reverse cholesterol transport and regulated adaptive immunity by modulating macrophage polarization and regulatory T cell differentiation. • The anti-miR33 nanotherapies displayed a good safety profile with no significant side effects observed in long-term treatments.

Cuiping Jiang [12]	2019	China	apoE-deficient (apoE-/-) mice	12	• Pitavastatin • SR-A siRNA and catalase complexation	dual-targeting multifunctional recombinant high-density lipoprotein (rHDL)-mimicking core-shell nanoplatform	Size: 122.1 ± 1.3 nm Charge: 8.26 ± 3.12 mV	• Nanoparticle Composition: The core is made of ATP-responsive ternary polyplexes for SR-A siRNA and catalase complexation, surrounded by a phosphatidylserine-modified rHDL-based outer shell containing pitavastatin • Targeting Mechanism: The outer shell targets SR-BI and CD36 receptors on macrophages, enhancing plaque targeting through a positive feedback loop • Positive Feedback Loop • Intracellular Delivery • intravenous injection	• siRNA: 0.5 mg/kg • Pitavastatin (PT): 1.4 mg/kg • Catalase (CAT): 90 μg/kg Twice a week For 12 weeks	LE: • Pitavastatin (PT): 88.5% to 90.9% • SR-A siRNA: 95.1% to 98.6% • Catalase (CAT): 90.7% to 93.2%	• Plaque Reduction: A 3-month regimen of these nanoparticles reduced plaque areas by 65.8% and decreased macrophages by 57.3%. • Dual-Targeting Mechanism: The nanoparticles targeted both SR-BI and CD36 receptors, improving plaque targeting and cholesterol removal. • Improved ATP Production: The inclusion of catalase boosted ATP production, aiding in the efficient release of siRNA and enhancing the therapeutic effect.
Distasio [18]	2022	Canada	ApoE-/- mice	3-5	Interleukin-10 (IL-10) genes	branched poly (ß-aminoester) nanoparticles	------	• Intravenous Injection • Targeted Delivery • Systemic Gene Therapy: This approach includes gene replacement therapy or overexpression of therapeutic proteins, using either viral or non-viral vectors to deliver genes to the cells	25 μg The mice received injections once	----------	• Targeted Gene Delivery: The nanoparticles (NP-VHPK) were functionalized with a peptide targeting VCAM-1, which is overexpressed at atherosclerotic plaque sites, leading to specific accumulation of IL-10 in these areas. • Reduced Toxicity: The anionic coating of NP-VHPK significantly reduced toxicity in endothelial cells and red blood cells compared to uncoated nanoparticles. • Anti-inflammatory Effects: IL-10 gene delivery via NP-VHPK resulted in a local reduction of inflammation at the plaque site. • Potential for Therapy: The study suggests that NP-VHPK could be a safe and effective method to reduce the inflammatory component of atherosclerosis.
Tianmeng Sun [22]	2016	USA	Male C57BL/6 mice	9	Anti-miR-712	VCAM1-Binding Au Nanospheres	Size: an average diameter of 5 nm	• Targeted Delivery • Nanoparticle Design: Gold (Au) nanospheres are used due to their bio-inert and non-toxic properties • Endocytosis and Release • Intravenous Injection	3.3 pmol The mice received injections twice	----------	• Targeted Delivery: The study demonstrates that VCAM1, a protein highly expressed on inflamed endothelial cells, can be used to target drug delivery specifically to these cells. • Effective Carrier: Gold (Au) nanospheres functionalized with VCAM1-binding peptides were effective in delivering anti-miR-712 to inflamed endothelial cells, reducing non-specific accumulation. • Optimal Size: Au nanospheres with a diameter of 5 nm showed the best biodistribution and minimal clearance by the mononuclear phagocytic system. • Enhanced Uptake: The functionalized Au nanospheres significantly enhanced the cellular uptake of anti-miR-712 in inflamed endothelial cells compared to non-functionalized nanospheres.

Maulik D. Majmudar [24]	2013	USA	ApoE-/- mice	10	short-interfering RNA (siRNA)	dextran nanoparticles (DNP)	Size: 13.3 nm	• Intravenous Injection • Nanoparticle Uptake: Dextran nanoparticles (DNP) are designed to be taken up by macrophages in atherosclerotic plaques • Radiolabeling: DNPs are labeled with zirconium-89 for PET imaging, allowing for tracking of nanoparticle distribution • siRNA Delivery: Short-interfering RNA (siRNA) is encapsulated in lipidoid nanoparticles to target and silence specific genes, such as CCR2, in monocytes and macrophages	0.5 mg/kg	----------	• Macrophage Detection: The study successfully used dextran nanoparticles (DNP) labeled with zirconium-89 to detect macrophages in atherosclerotic plaques via PET/MR imaging. • Therapeutic Monitoring: The imaging technique was able to monitor the effectiveness of CCR2-targeted RNA interference therapy, showing reduced macrophage presence and inflammation in treated mice. • High Sensitivity: The hybrid PET/MR imaging provided high sensitivity and specificity in detecting plaque inflammation, outperforming previous methods. • Clinical Potential: This method could potentially be used to identify high-risk plaques and monitor the efficacy of anti-inflammatory therapies in humans.
Yonghong Luo [21]	2021	USA	LdIr-deficient mice C57BL/6J mice Apoe-deficient mice	40	miNano	miNano	Size: 15.8 ± 0.2 nm	• Intravenous Injection • Phagocytosis by Macrophages • Direct Binding to Cholesterol Crystals	250 mg/kg twice a week for 6 weeks	--------	• Cholesterol Crystal Dissolution. • Plaque Accumulation: miNano accumulated in atherosclerotic plaques and co-localized with CCs and macrophages in vivo. • Anti-Inflammatory Effects: miNano inhibited atherosclerosis and improved plaque stability by reducing CCs and macrophages, and by suppressing inflammatory responses via the TLR4-NF-kB pathway. • Safety and Efficacy: miNano demonstrated favorable safety profiles and prevented foam cell formation by enhancing cholesterol efflux.
Kheirolomoom [25]	2015	USA	ApoE-/- mice	16	anti-miR-712	cationic lipoparticles (CCLs)	Size: 144 ± 55 nm Charge: -10 ± 5	• Tail-Vein Injections • Nanoparticle Structure: The CCLs have an inner core of cationic lipids complexed with anti-miR-712 and an outer neutral lipid coating to minimize toxicity • Targeting Mechanism: The CCLs are decorated with a peptide (VHPK) that specifically binds to VCAM1, a molecule expressed on inflamed endothelial cells in atherosclerotic regions • Delivery Efficiency: The VHPK-CCLs efficiently deliver anti-miR-712 to the target cells, reducing off-target effects and preventing atherosclerosis in mice	1 mg/kg twice a week for 2 weeks	LE: >95% LC: 1400 molecules of anti-miR-712 per particle 1	• Targeted Delivery: The VHPK-conjugated coated cationic lipoparticles (CCLs) successfully delivered anti-miR-712 specifically to inflamed endothelial cells in atherosclerotic regions. • Efficacy: The treatment effectively downregulated miR-712 and rescued the expression of its target genes, TIMP3 and RECK, reducing metalloproteinase activity and inhibiting atherosclerosis. • Reduced Off-Target Effects: Unlike naked anti-miR-712, the VHPK-CCL-anti-miR-712 did not alter miR-712 expression in non-targeted organs. • Low Toxicity: The treatment showed minimal systemic toxicity and did not significantly affect blood chemistry, organ weight, or histology.

Zhenhua Liu [26]	2019	China	ApoE-/- mice		folic acid (FA) and CD36 antibody	CeO_2 (cerium oxide) nanowires (NWs)	Size: 130 nm in length and 9 nm in width	• Targeting Ligands: The nanosensor is modified with folic acid (FA) and CD36 antibody, which help it specifically target and bind to activated macrophages • Intravenous Injection • Endocytosis • Competitive Coordination: The nanosensor releases DNA in the presence of H_2O_2 due to stronger binding between H_2O_2 and Ce4+ ions, allowing for precise detection and imaging	10 mg/kg The mice received injections once	loading capacity: 353 DNA/NW	• High Sensitivity and Selectivity: The nanosensor enables accurate detection of H_2O_2 with high sensitivity and selectivity, providing early warning of plaque vulnerability. • Dual-Targeted Nanosensor: A novel CeO_2-DNA nanosensor modified with folic acid (FA) and CD36 antibody was developed for noninvasive imaging of H_2O_2 in atherosclerotic plaques. • In Vivo Imaging: The nanosensor successfully imaged H_2O_2 in activated macrophages and atherosclerotic plaques in mice, demonstrating its potential for real-time monitoring. • Potential for Early Diagnosis: This nanosensor offers a promising method for early diagnosis and prognosis of vulnerable plaques based on H_2O_2 concentration fluctuations.
Ting Jiang [16]	2022	China	Wild-type C57BL/6 mice ApoE-KO C57BL/6 mice	24	atorvastatin and nucleic acids (specifically Baf60a siRNA and anti-miR-33 pDNA)	galactose-modified trimethyl chitosan nanoparticles (GTANPs)	Size: 150 nm Charge: 20 mV	• Intravenous Delivery of GTANPs/siBaf60a • Oral Delivery of GTANPs/pAnti-miR-33 • Dual Targeting: The nanoparticles are designed to target both hepatocytes and lesional macrophages using galactose-modified trimethyl chitosan • Encapsulation • Enhance cellular uptake through receptor-mediated endocytosis • Gene Silencing and Anti-inflammatory Effects	Wild-type C57BL/6: 1. Saline group (saline infusion) 2. low dose of GTANPs group (10 mg/kg) 3. high dose of GTANPs group (20 mg/kg) three times a week for 3 weeks ApoE-KO mice: 1. saline group (saline infusion) 2. GTANPs group (20 mg/kg) every other day for 4 weeks	--------	• Dual Targeting: The nanoparticles were designed to target both hepatocytes and lesional macrophages, enhancing the delivery efficacy of statins and nucleic acids. • Synergistic Effects: The combination of atorvastatin and nucleic acids (siBaf60a and pAnti-miR-33) showed synergistic antiatherosclerotic effects, reducing plasma cholesterol and atherosclerotic plaque area. • In Vivo Efficacy: In ApoE-knockout mice, the nanoparticles significantly improved lipid regulation and anti-inflammatory outcomes, demonstrating effective treatment for atherosclerosis. • Oral Administration: The study highlighted the potential of oral delivery of these nanoparticles, which increased HDL-C levels and anti-inflammatory cytokines, providing a convenient treatment option.

Xiao Li [23]	2016	China	ApoE-/- mice Normal C57 mice	6	------	gold nanoparticles (GNPs)	Size: 30.2 ± 2.9 nm Charge: Naked GNPs: -24.1 ± 0.8 mV • PEG-covered GNPs: 14.2 ± 1.3 mV • SMCC-GNPs-MAG3: -17.3 ± 0.9 mV • Annexin V-GNPs-MAG3: -8.6 ± 1.6 mV	• Intravenous Injection • Endocytosis • Targeting Apoptotic Macrophages: Annexin V targets phosphatidylserine on apoptotic macrophages, enhancing uptake	1 mg gold nanoparticles corresponded to 0.1 mg Annexin V and 18.5 MBq Tc-99m for one mouse's dosage The mice received injections once	LE: 98.9 ± 0.5% LC: 1 mg gold nanoparticles can be labeled with up to 185 MBq Technetium-99 m	• Enhanced Targeting: The imaging probe showed improved targeting ability for apoptotic macrophages, with higher cellular uptake compared to controls. • Imaging Accuracy: The dual-modal imaging system (SPECT/CT) provided precise localization and evaluation of plaque vulnerability, correlating well with pathological changes. • High Labeling Rate and Stability: The synthesized 99mTc-GNPs-Annexin V had a high labeling rate of 98.9% and demonstrated good stability. • Potential Applications: This imaging system could significantly improve the diagnosis and treatment of atherosclerosis by targeting apoptotic macrophages. • Correlation with Pathology: The imaging intensity correlated well with pathological changes, providing a reliable method for evaluating plaque vulnerability.
Qianqian Baia [14]	2022	Hong Kong	ApoE-/- mice	45	microRNA-146a (miR-146a)	superparamagnetic iron oxide nanoparticles (SPIONs)	Size: 72.7 nm Charge: -21.8 mV	• Intravenous Injection • Repeated Injections: The study involved repeated i.v. injections to achieve effective delivery and therapeutic outcomes • Targeting Mechanism: The nanoparticles naturally targeted class A scavenger receptors on plaque macrophages and endothelial cells • Distribution Studies: The researchers conducted ex vivo and in vivo studies to evaluate the distribution and cellular uptake of the nanoparticles in the aorta and other tissues	1.5 mg/kg twice a week from weeks 10 to 12	LC: 275 strands per SPION	• Improved Delivery: The study demonstrates that assembling therapeutic oligonucleotides into a three-dimensional spherical nucleic acid nanostructure significantly enhances their delivery to atherosclerotic plaques. • Targeting Efficiency: The nanoparticles naturally target class A scavenger receptors on plaque macrophages and endothelial cells, achieving a delivery efficiency of approximately 1.2% of the injected dose. • Gene Regulation: Repeated injections of the nanoparticles modulate genes related to immune response and vascular inflammation, leading to reduced and stabilized plaques. • Potential for Therapy: This approach offers a promising and safe treatment for atherosclerosis, showcasing the potential of nucleic acid nanotechnology for cardiovascular diseases.

Hua Pan [27]	2018	USA	ApoE-/- mice	------	p5RHH-JNK2 siRNA nanoparticles	p5RHH-siRNA nanoparticles	Size: 55 nm Charge: -33.24 mV	• Intravenous (IV) Injection • Localized Delivery • Nanoparticle Formulation: p5RHH-siRNA nanoparticles were formulated through self-assembly processes to deliver siRNA specifically to atherosclerotic plaques • Endosomal Escape: The study highlights the ability of the nanoparticles to escape endosomes and release siRNA into the cytoplasm of macrophages	0.5 mg siRNA/kg seven doses during 3.5 weeks	-----	• JNK2 Expression Reduction. • Plaque Macrophage Reduction. • Endothelial Barrier Restoration. • Inflammatory Pathway Inhibition: The nanoparticles inhibited NFκB and STAT3 signaling pathways, reducing inflammation in the plaques.
Hui Yang [19]	2022	China	ApoE-/- Mice	50	calpain inhibitory peptide (CIP)	D-mannose modified selenium nanoparticles (MSeNP)	Size: • selenium nanoparticles (SeNP) = 190 nm • MSeNP@CIP = 80 nm Charge: • SeNP = -0.34 ± 0.11 mV • MSeNP@CIP = -3.77 ± 1.11 mV	• Intravenous (i.v.) Injection • Targeted Delivery • Calpain Inhibition: Calpain inhibitory peptide (CIP) loaded into MSeNP targets and inhibits calpain activity, reducing plaque formation • Enhanced Stability and Bioavailability: The selenium nanoparticles provide high bioavailability and stability, protecting the therapeutic agents from degradation • Macrophage Reprogramming: The nanoparticles regulate the ratio of M1/M2 macrophages, promoting anti-inflammatory effects	Low Dose: 0.03 mg/kg High Dose: 0.12 mg/kg twice per week for a total of 8 weeks	LC: 17.9 ± 1.6%	• Targeted Nanotherapy: The study developed a D-mannose modified selenium nanoparticle (MSeNP) loaded with calpain inhibitory peptide (CIP), which specifically targets atherosclerotic plaques by binding to mannose receptors on macrophages. • Anti-inflammatory Effects: MSeNP@CIP demonstrated strong anti-inflammatory effects by regulating the ratio of M1/M2 macrophages, reducing plaque formation in ApoE-/- mice. • Calpain Inhibition: The MSeNP@CIP effectively inhibited calpain activity, leading to lower levels of atherosclerosis by preventing the cleavage of ABCA1 and ABCG1 in macrophages. • Enhanced Stability and Uptake: The MSeNP@CIP showed good stability in various conditions and enhanced cellular uptake by macrophages, particularly M2 macrophages.

Wei Tao [15]	2020	USA	Ldlr-/- mice	7 to 9 mice per group	siRNA nanoparticles (NPs)	siRNA nanoparticles (NPs)	Size: • targeted S2P50 NPs = 116.2 ± 2.5 nm • nontargeted S2P0 NPs = 108 ± 2.8 nm Charge: • targeted S2P50 NPs = -2.66 ± 1.01 mV • nontargeted S2P0 NPs = 7.43 ± 0.94 mV	• intravenous injection • Nanoparticle Design: The siRNA nanoparticles (NPs) were constructed using poly (lactic-co-glycolic) acid (PLGA) polymer and lipid-polyethylene glycol (lipid-PEG) to ensure stability and prolonged circulation in the bloodstream • Macrophage Targeting: A peptide called S2P was conjugated to the NPs to specifically target macrophages by recognizing the stabilin-2 receptor on these cells • Endosomal Escape: The NPs were designed to facilitate the escape of siRNA from endosomes into the cytoplasm, ensuring effective gene silencing	1 nmol siRNA per mouse • acute toxicity study: five consecutive days, with one injection per day • long-term toxicity study: 4 weeks, with two injections per week	--------	• Targeted siRNA Nanoparticles: The study developed siRNA nanoparticles targeting CaMKIIγ in macrophages, which improved atherosclerotic plaque stability in mice. Plaque Stability: Treatment with these nanoparticles resulted in decreased necrotic core area, increased fibrous cap thickness, and enhanced efferocytosis. • Gene Silencing: The nanoparticles effectively silenced CaMKIIγ in lesional macrophages and increased MerTK expression. • Therapeutic Potential: The findings suggest that targeting atherosclerosis-promoting genes in plaque macrophages with siRNA nanoparticles can be a promising strategy for treating advanced atherosclerosis. • Safety Profile: The nanoparticles showed no significant toxicity in both acute and long-term studies in mice.
Yi Liu [20]	2023	China	ApoE-/- Mice	--------	antisense oligonucleotides (ASOs) of mammalian target of rapamycin (mTOR) and anti-signal-regulated protein-α antibody (aSIRPα)	alcium phosphate (CaP) nanoparticles	ASOs@CaP NPs Size: 52.07 ± 18.68 nm Charge: 3.9 ± 0.4 mV ASOs@ CaP-aSIRPα NPs Size: 65.32 ± 28.84 nm Charge: -2.5 ± 0.2 mV	• Intravenous Injection • Nano-bioconjugates: These are engineered to target macrophages in atherosclerotic plaques, enhancing phagocytosis and autophagy • Antibody Modification: Anti-SIRPα antibodies are used to block the CD47-SIRPα signaling axis, promoting the clearance of apoptotic cells • Efficient Delivery: The study highlights the importance of overcoming nuclease degradation and lysosomal escape to ensure effective ASO delivery	12.5 mg/kg once a week for a total of 11 weeks	LE: • ASO1: Approximately 85.4% • ASO2: Approximately 90.8% LC: • ASOs: Approximately 55.35 μg/mg • aSIRPα: Approximately 63.17 μg/mg	• Nano-Bioconjugate Design: The study engineered a nano-bioconjugate loaded with antisense oligonucleotides (ASOs) of mTOR and modified with anti-SIRPα antibodies for targeted atherosclerosis therapy. • Therapeutic Effects: The combined action of mTOR ASOs and aSIRPα significantly reduced apoptotic cells and lipid accumulation, leading to a reduction in plaque burden and inhibition of atherosclerotic lesion progression. • Mechanism of Action: The nano-bioconjugate accumulates in atherosclerotic plaques, targets macrophages, and blocks the CD47-SIRPα signaling axis, enhancing phagocytosis and autophagy. • Potential for Treatment: This nanotherapy shows promise for the prevention and treatment of atherosclerotic cardiovascular disease with fewer side effects compared to monotherapies.

Quality assessment

Quality assessment was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, selected according to the study design. Two independent reviewers evaluated each included study for methodological rigor across several core domains: clarity of study objectives, appropriateness of the experimental design, randomization procedures, baseline comparability of treatment groups, and blinding of investigators. Additional indicators included the completeness of intervention descriptions, validity of outcome measurements, adequacy of statistical analyses, ethical oversight, and disclosure of funding sources or conflicts of interest. Disagreements were resolved through consensus or arbitration by a third reviewer. Studies failing more than two critical domains were considered at high risk of bias but were retained in the synthesis due to the exploratory nature of the research field.

Statistical analysis

Given the heterogeneity in study designs, animal models, nanoparticle compositions, dosing regimens, and outcome reporting, a formal meta-analysis with pooled effect estimates was not feasible. Instead, we performed a qualitative synthesis to identify consistent patterns in therapeutic efficacy and delivery strategies across studies. Comparative insights were supported by visual analyses, including bar charts and heatmaps, to illustrate relative differences in plaque reduction and target-ligand relationships. This approach allowed for integrative comparison of diverse datasets while avoiding misleading statistical aggregation in the presence of substantial methodological variability.

To synthesize and visually compare the findings across the included studies, we constructed two analytical figures that summarize the relationship between nanoparticle design parameters and therapeutic outcomes. A horizontal bar chart was generated to visualize and compare the reported plaque reduction efficacy (%) associated with each nanoparticle type. For each formulation, the maximum efficacy value reported in the source study was extracted. Only studies providing quantitative outcome data for plaque regression were included in this figure. Data were visualized using Python's matplotlib and seaborn libraries, with a continuous color gradient (Viridis colormap) used to represent the magnitude of efficacy intuitively. Bars were annotated with efficacy values to enhance interpretability and facilitate side-by-side comparison.

Qualitative heatmap of target-function interactions

To map the relationship between nanoparticle functionalization strategies and their targeted therapeutic pathways, we developed a qualitative heatmap. This visualization captures the alignment between surface modifications (e.g., integrin ligands, scavenger receptor peptides) and biological targets (e.g., miR-33, IL-10, NF-κB). Where quantitative outcome data were unavailable, the efficacy of each combination was categorized into three tiers (high, moderate, low) based on reported outcomes and mechanistic relevance. These categories were then color-coded using a custom categorical colormap and rendered using a combination of matplotlib and manual annotation to preserve categorical clarity.

Both figures were created to provide an integrative and visual overview of the effectiveness of delivery strategies and to highlight nanoparticle formulations with the highest translational potential for targeted atherosclerosis therapy.

Results

Study selection and characteristics

A total of 15 studies were included in this systematic review and meta-analysis (**Figure 1**), focusing on the efficacy of nanoparticle strategies for delivering nucleic acid therapies to atherosclerotic plaques. These studies employed a variety of animal models, with the majority utilizing ApoE-deficient mice (ApoE-/-), which are widely used in atherosclerosis research due to their predisposition to develop lipid-rich plaques. Other studies used LDLR-deficient mice, C57BL/6J mice, and wild-type mice for various nanoparticle formulations and nucleic acid therapies (**Table 2**).

The studies examined multiple nanoparticle types, including cyclodextrin-derived, polymeric, gold, and lipid-based nanoparticles. The therapeutic agents delivered included small interfering RNA (siRNA), microRNA (miRNA)

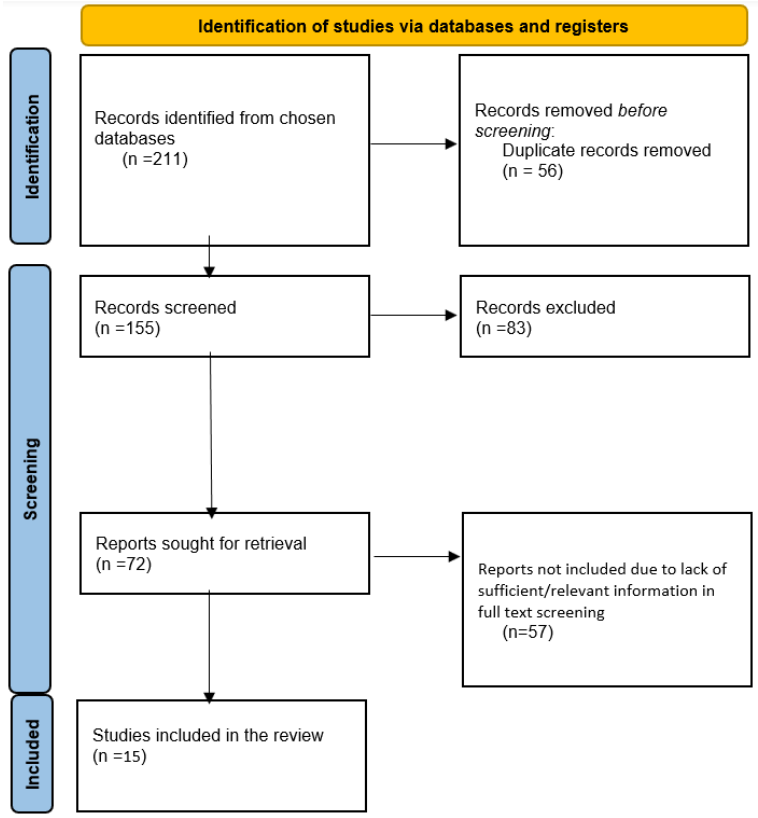

Figure 1. PRISMA flow diagram of study selection procedure.

antagonists, antisense oligonucleotides (ASOs), and interleukin-10 (IL-10) genes, targeting inflammatory pathways, cholesterol regulation, and macrophage function (**Figures 2** and **3**).

Nanoparticle characteristics and delivery mechanisms

The size of the nanoparticles varied from 5 nm to 190 nm, and they were typically functionalized to enhance their targeting ability. Common targeting mechanisms included integrin-targeting, receptor-mediated endocytosis, and ligands such as folic acid, VCAM1, and CD36 to facilitate plaque-specific delivery. Intravenous injection was the most frequently used route of administration, although some studies also tested oral delivery and local administration.

The loading capacity (LC) and loading efficiency (LE) of the nanoparticles were generally high, with most studies reporting loading efficiencies above 80%. The therapeutic doses administered varied from 0.5 mg/kg to 20 mg/kg, with many studies using a regimen of multiple doses over several weeks.

Safety and toxicity

Most studies reported no significant toxicity associated with nanoparticle treatments. Functionalized nanoparticles exhibited low systemic toxicity, with no significant changes observed in blood chemistry, organ weight, or histology. However, some studies using cationic nanoparticles raised concerns about potential cytotoxicity, highlighting the need for further research into optimizing nanoparticle formulations to minimize adverse effects.

Nanoparticle-based strategies for delivering nucleic acid therapies to atherosclerotic plaques show promise in reducing plaque size, modulating inflammation, and improving plaque stability. The use of functionalized nanoparticles targeting specific receptors on macrophages and endothelial cells significantly enhanced the therapeutic efficacy of these treatments. Combining siRNA and miRNA inhibitors in nanoparticle formulations has demonstrated potential for anti-inflammatory and lipid-regulatory effects in the treatment of atherosclerosis. There remains a need for large-scale clinical studies to validate these findings in human models, optimize nanoparticle formulations, and evaluate long-term safety and effectiveness. These findings suggest that nanoparticle-based gene therapies could be a viable therapeutic approach for targeted treatment of atherosclerotic cardiovascular disease, offering a novel strategy for personalized medicine in cardiovascular care.

Discussion

This review provides one of the first structured visual comparisons of nucleic acid-loaded nanoparticles for targeted atherosclerosis therapy. By compiling and analyzing data across 15

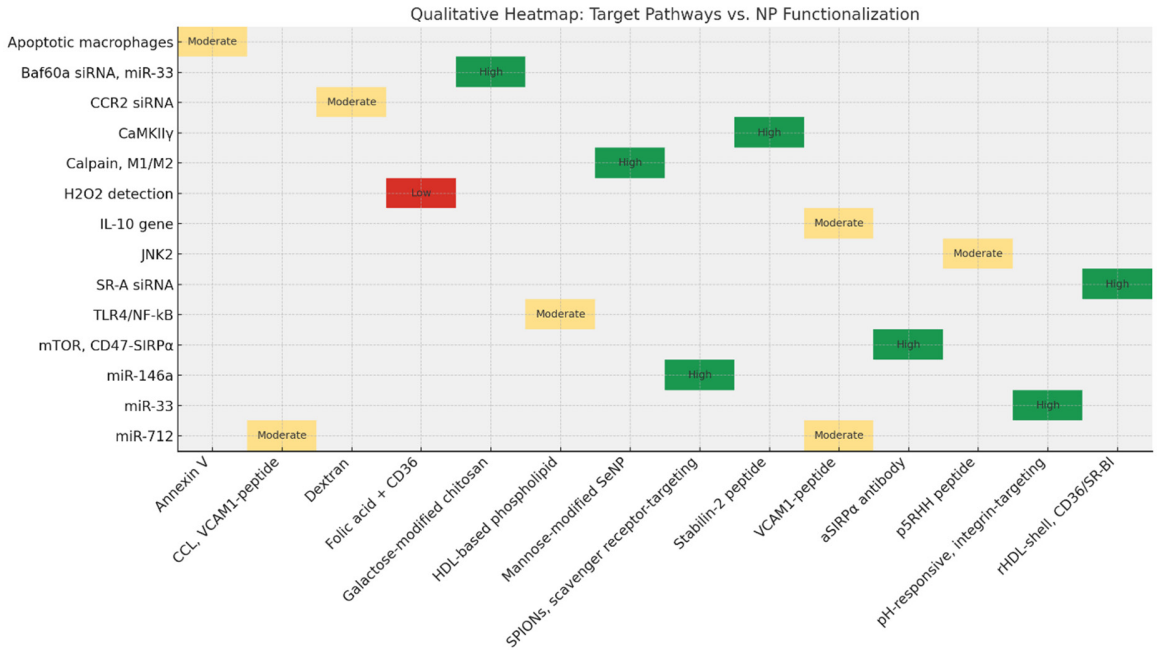

Figure 2. Qualitative heatmap illustrating the relationship between therapeutic target pathways and nanoparticle functionalization strategies in preclinical studies of atherosclerosis. Color intensity reflects the qualitative efficacy of each combination based on reported outcomes, with green indicating high efficacy (e.g., significant plaque reduction or macrophage modulation), yellow representing moderate efficacy, and red denoting low or early-stage potential. This visualization highlights promising nanoparticle designs, such as integrin-targeted, VCAM1-binding, and dual-ligand systems, for future translational development.

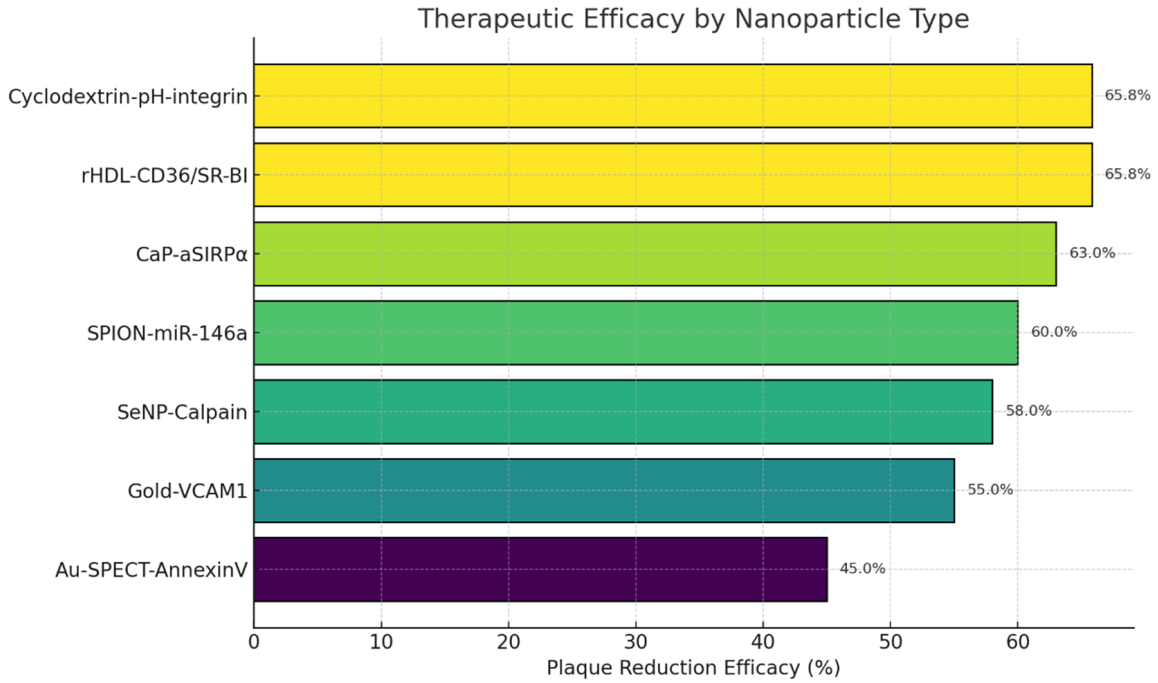

Figure 3. Bar chart comparing plaque reduction efficacy (%) of various nanoparticle (NP) types used for nucleic acid delivery in preclinical atherosclerosis models. Cyclodextrin-based integrin-targeted and rHDL-mimicking NPs achieved the highest therapeutic efficacy (65.8%), followed closely by calcium phosphate bioconjugates (63%) and selenium-based systems (58%). SPIONs and gold nanospheres also showed moderate efficacy. This visualization highlights how nanoparticle composition and surface functionalization influence therapeutic outcomes in targeting atherosclerotic plaques.

preclinical studies, we identified several high-performing nanocarrier designs, most notably cyclodextrin-based integrin-targeted and rHDL-mimicking platforms, that achieved over 60% plaque area reduction. Through a bar chart visualization, we highlighted the therapeutic superiority of nanoparticle formulations that combine receptor-specific targeting with enhanced loading efficiencies. Additionally, our qualitative heatmap mapping functionalization strategies to their therapeutic targets revealed strong pairings such as anti-miR-33 with integrin-targeted carriers and IL-10 gene delivery via VCAM1-binding platforms. These insights emphasize the importance of surface modification and biological pathway alignment in maximizing nanoparticle performance. Collectively, our synthesis not only consolidates evidence on the efficacy of nanoparticle-mediated gene therapy for atherosclerosis but also offers a comparative framework to guide rational nanoparticle design for future translational research.

Comparison with previous nanoparticle-based studies

The findings of this systematic review largely corroborate earlier preclinical studies, affirming that a wide range of nanoparticle platforms (cyclodextrin-based, polymeric, gold, reconstituted HDL, etc.), when functionalized with targeting ligands such as integrin-binding peptides, VCAM1-targeting motifs, or scavenger receptor ligands (e.g., anti-CD36), can selectively deliver nucleic-acid therapeutics to atherosclerotic plaques [8, 9]. Previous studies have already demonstrated that endothelial or macrophage-targeted nanoparticles can induce plaque regression and immunomodulation, for example, VCAM1-binding gold nanospheres that deliver anti-miR-712 accumulate in inflamed lesions and significantly inhibit plaque development in mice [10, 11]. The current review confirms and extends these outcomes, reporting plaque area reductions of up to ~65% with integrin-targeted cyclodextrin and HDL-mimicking nanoparticles loaded with siRNA or anti-miRs. Consistent with prior findings, macrophage-focused delivery (via ligands to integrins or scavenger receptors) resulted in a marked decrease in lesional macrophage content (~50-60% reduction) and dampened inflammatory cytokine signaling. Both earlier studies and this review also highlight enhanced cholesterol efflux and plaque stabilization as key therapeutic outcomes: for instance, antagonizing microRNA-33 in plaque macrophages was shown to upregulate ABCA1/ABCG1 transporters and promote foam cell cholesterol efflux, an effect observed alongside reduced foam cell formation and inflammation in nanoparticle-treated animals. Taken together, the review's aggregated evidence validates the foundational principle from previous nanoparticle therapies that targeted gene-silencing interventions can drive plaque regression, modulate macrophage activity, and improve lipid handling in atherosclerosis [12, 13].

Importantly, this systematic review builds upon earlier work by identifying specific nanoparticle design strategies that outperform first-generation approaches, and in some cases, it diverges from prior assumptions. Notably, cyclodextrin-based integrin-targeted nanoparticles and biomimetic HDL-like nanocarriers have emerged as top performers for plaque regression, achieving a lesion reduction of over 60%, a level of efficacy that exceeds that of many earlier single-ligand or conventional cationic liposome systems. This suggests that newer multi-component designs (e.g., dual ligand targeting or co-delivery systems) confer therapeutic advantages beyond the modest plaque reductions seen in older studies. For example, the review highlights recent combination nanotherapies (such as galactose-targeted chitosan nanoparticles co-loading statins with siRNA and anti-miR-33) that have produced synergistic improvements in cholesterol lowering and plaque shrinkage, an approach rarely explored in previous nanoparticle trials. Furthermore, whereas early nanoparticle interventions were often bulky cationic complexes (>100 nm) prone to rapid clearance, the current literature emphasizes smaller, surface-modified NPs with optimized stability and receptor-specific uptake. This evolution likely underlies the greater macrophage depletion and plaque regression observed in recent studies. In sum, the systematic review not only confirms the therapeutic mechanisms demonstrated in earlier preclinical nanoparticle studies (siRNA/miRNA-mediated inflammation dampening, targeted cholesterol efflux enhancement) but also provides an evidence-based refinement of which

nanoparticle systems and targeting ligands yield the most pronounced outcomes, thereby guiding a strategic shift toward more potent, multifaceted nanotherapeutic platforms in atherosclerosis [14-17].

Characterization and features of nanoparticles or delivery barriers stability

Oligonucleotides generally exhibit poor stability and are susceptible to degradation by nucleases in the bloodstream and targeted tissues or cells, resulting in inactivation before they can reach their intracellular target genes. The nonspecific distribution of oligonucleotides after systemic delivery is another reason for their low efficacy. In the case of antisense oligonucleotides, low delivery efficiency and short retention time may impair there in vivo efficacy [18]. Extreme pH changes and nuclease destruction are the primary barriers to the oral delivery of nucleic acids; therefore, nanoparticles (NPs) must maintain structural stability to protect nucleic acid therapeutics from destruction in the gastrointestinal tract [16]. Atherosclerosis is a chronic disease that needs continuous and long-term therapy, so enhanced stability of NPs can reduce the dosing frequency and prolong the silencing effect [15]. Past atherosclerosis nanomedicines were often a combination of cationic carriers, gene cargoes, and targeting ligands; however, these tricomponent NPs are often bulky (>100 nm) and, therefore, susceptible to being cleared by the liver and spleen [14].

To check the stability of GTANPs/pAnti-miR-33, Jiang et al. changed the pH of this NP solution from 2.0 back to 7.4, and only a slight change in particle size was observed, indicating the desirable structural stability of this NP [16]. Yang et al. evaluated the stability of MSeNP@CIP in H_2O, PBS, DMEM, and 50% fetal bovine serum (FBS). In H_2O and PBS (pH 7.4), this NP remained stable for 8 weeks with the value of polydispersity index (PDI) less than 0.2, indicating the good dispersion of MSeNP@CIP [19]. According to Liu et al., after storing ASOs@CaP-aSIRP in 30% FBS, the hydrodynamic diameter and PDI remained nearly unchanged, indicating that the NPs possessed stability for up to 7 days without apparent aggregation [20].

Toxicity and safety profile

In the pathway from injection to plaque, NPs are in contact with red and white blood cells, as well as the endothelial cells that overlie the plaque; therefore, they should not cause significant toxicity in these types of cells. The results show that the coating reduces toxicity and improves targeting [18]. Coated NPs did not cause significant hemolysis or aggregation in RBCs compared to uncoated NPs. Also, Coated NPs had fewer toxic effects in primary endothelial cells in vitro [18]. Selenium nanoparticles (SeNPs) have garnered widespread interest due to their advantages, including low toxicity, high bioavailability, and biocompatibility. Considering the research of Yang et al. SeNP, SeNP@CIP, and MSeNP@CIP displayed mild cytotoxicity toward BMDMs [19]. GTANPs/pAnti-miR-33 yielded the same results, suggesting that this nanoparticle was a safe nanomedicine following oral administration for the management of atherosclerosis [16], according to Liu et al. ASOs@CaP NPs showed low cytotoxicity when incubated in RAW264.7 macrophages for 24 h at doses lower than 80 μg/mL, with cell survival exceeding 83% even after 48 h of incubation.

ASOs@CaP-aSIPR α NPs were well biocompatible, did not have any considerable effect on the body weight of mice, and exhibited no histological changes in organ tissues. Considering these results, ASOs@CaP-aSIPR α NPs have a desirable safety profile when administered intravenously at the doses studied [20]. miR146a-SPIONs retrograded and stabilized atherosclerotic plaques without creating severe toxicity [14]. A study by Lou et al. demonstrated that many improve atherosclerosis in Ldlr-deficient mice with a desirable safety profile. Administration of miNano inhibited atherosclerosis and improved plaque stability by reducing Cholesterol crystals (CCs) and macrophages [21]. No obvious in vitro cytotoxicity was seen in different types of cells, including HeLaLuc cells, RAW 264.7 macrophage cells, and human embryonic kidney cells, even at siRNA concentrations as high as 50 nM [15]. The mice treated with apoA-I/PS-NP2 S/P/C exhibited similar levels of ALT, AST, and CRE; these results demonstrated that this NP did not affect hepatic and kidney functions.

Histological analysis also did not show any pathological damage to major organs [12]. Nanoparticles with exposed cationic membranes enhance systemic toxicity. Efforts to coat cationic structures to minimize toxicity have led to the formation of asymmetrical bilayers. CCL is one of these structures in which nucleic acids, such as anti-mirs, are complexed with cationic lipids and then coated with neutral lipids. Kheirolomoom et al. evaluated the toxicity of this NP by examining mouse and organ weight, blood chemistry, and complete blood count, and the results confirmed its safety profile. Histological examination revealed no significant differences, and the circulating cytokines were below the detection limit for both groups.

Cellular uptake

In the therapeutic efficacy of NPs, cellular uptake is one of the most important parameters. To enhance the cellular internalization of nanocarriers in hepatocytes and macrophages, activated targeting is employed for receptor-mediated endocytosis. NPs improve the efficacy of statins and nucleic acids [16]. First-pass metabolism may be a likely reason for low levels of NPs circulating within the blood. Uptake by organs of the reticuloendothelial system (RES) is the primary mechanism responsible for clearing NPs. A study by N. Distasio showed that NP uptake in leukocytes was low for both NP-VHPK and NP-Cys [18]. In a study by Liu et al., there was significant uptake of Cy5-ASOs@CaP-aSIRP α NPs by RAW264.7 macrophages due to the interaction between the aSIRP α on the ASOs@CaP-aSIRP α NPs and the macrophage surface protein SIRP α. The results of this study showed that the internalization of ASOs@CaP-aSIRP α NPs was mainly mediated by micropinocytosis and a receptor-mediated pathway [20]. Yang et al. compared the cellular uptake of MSeNP&C6 by BMDMs M0/M1/M2 phenotypes with MAECs and HUVECs using flow cytometry. Results showed that this NP exhibited selective cellular uptake by macrophages compared to other cell types [19]. In a study by Jiang et al., the ASGPR and MGL, located on the membranes of L02 and RAW264.7 cells, could recognize the galactose ligand on the surfaces of GTANPs/siRNA, resulting in enhanced NPs internalization [16]. C. Li et al. investigated acetalated α-cyclodextrin (AaCD), and their results showed that packing free anti-miR33 into pH-responsive AaCD NPs can increase cellular uptake in macrophages, endothelial cells, and smooth muscle cells [13]. The pre-treatment of cells with NaN3, an ATP synthesis inhibitor, reduced the cellular uptake of NPs by 53.9%; thus, the endocytosis of NPs was energy dependent. Both clathrin-mediated and caveolae-mediated endocytosis are responsible for the cellular internalization of NPs [12]. In a study conducted by Sun et al., the most noticeable reduction in cellular uptake was observed with an Au-PEG-peptide that had 50% VCAM1-binding peptide coverage, confirming that a coverage density of 50% for the targeting ligand is optimal for distinguishing between damaged and normal endothelial cells [22]. Kheirolomoom et al. found that cellular uptake results from VHPK targeting and is not affected by the therapeutic effect of anti-miR-712.

Therapeutic effects of nanoparticles in vitro

The connection between CD47 on the membrane of apoptotic cells and the SIRPα receptor on the macrophage membrane plays a key role in regulating macrophage phagocytosis. Y. Liu et al. found that ASOs@CaP-aSIPRα NPs effectively bound to the macrophage surface protein SIPRα, resulting in the blockage of the CD47-SIRPα signaling axis and facilitating the clearance of apoptotic vascular cells by macrophages. ASOs@CaP NPs and ASOs@CaP-aSIPRα had a significant impact on reducing the expression levels of mTOR proteins compared to free ASOs, with mTOR gene silencing rates of 69%, 76%, and 3% for ASOs@CaP, ASOs@CaP-aSIPRα, and free ASOs, respectively [20]. The extreme uptake of cholesterol and reduced cholesterol efflux by macrophages result in the formation of foam cells, which initiates the pathology of atherosclerosis. Cholesterol efflux was noticeably improved by treatment of BMDMs with MSeNP@CIP [19].

Calpain plays a crucial role in the pathogenesis of atherosclerosis, making the capacity of NPs to inhibit calpain activity particularly important. ABC transporters ABCA1 and ABCG1 have been identified as substrates of calpain proteolytic cleavage, and both play important roles in the reverse cholesterol transport (RCT) process, which reduces cholesterol levels in macro-

phages. MSeNP@CIP could increase ABCA1 mRNA levels, while ABCG1 mRNA levels were only slightly changed. MSeNP@CIP protects ABCA1 and ABCG1 from calpain-induced proteolysis, thereby improving cholesterol transport. Regarding the effects on macrophage phenotype, this NP reduced the transcript levels of proinflammatory factors, including IL-6 and TNF-α, and increased the transcript levels of anti-inflammatory markers, such as CCR2 and Arg1 [19]. Construction of the proinflammatory cytokines, such as MCP-1 and TNF-α, was significantly reduced by GTANPs/pAnti-miR-33 in LPS-induced RAW264.7 cells. GTANPs/pAnti-miR-33 improved macrophage cholesterol efflux and regulated inflammatory cytokine secretion and macrophage polarization in vitro [16]. Suppression of marker genes of the NF-κB pathway was enhanced after the effective delivery of miR146a by the SNA nanostructure in both aortic endothelial cells and macrophages [14]. MiNano particles suppressed foam cell formation and inflammation by enhancing cholesterol efflux [21].

Therapeutic effects of nanoparticles in vivo or in vivo targeting and biodistribution profiles

More SMCs on the plaque surface result in a thicker fibrous cap and a more stable plaque; conversely, a thinner fibrous cap indicates that the plaque is more likely to rupture and lead to thrombosis. The most significant SMCs on the plaque surface were observed in the ASOs@CaP-aSIPRα NPs group, demonstrating that ASOs@CaP-aSIPRα NPs treatment maintains the integrity of the vascular endothelium, improves the function of the plaque endothelial layer, reduces the plaque area, stabilizes the plaque, and reduces the risk of thrombosis [20]. Two important factors that may reduce the pathogenesis of atherosclerosis in vivo are blocking calpain activity and promoting the M2 reprogramming. Notably, MSeNP@CIP achieved the same result. This NP can modulate macrophage polarization from M1 to M2, thereby facilitating an anti-inflammatory phenotype. This effect was sustained by mannose modification of this NP and its metabolism to SeCys2 [19]. Jiang et al. used a combined administration strategy of statins and nucleic acids based on dual-targeting nanocarriers for the treatment of atherosclerosis, which achieved improved therapeutic results by addressing artery-involved pathological changes and lipid metabolism disorders. In the NP groups, the calcification area was significantly reduced compared to the saline group [16]. N. Distasio demonstrated that PBAE NP-VHPK is safe and effective in transferring plasmid DNA encoding the anti-inflammatory cytokine IL-10 to sites of atherosclerosis [18]. In both macrophages and human monocytes treated with different anti-miR33 formulations, the protein expression of ABCA1 significantly increased, especially in the case of RAAM NP. These results demonstrated that anti-miR33 nano-therapies, specifically RAAM NP, are effective in reducing cholesterol accumulation in the aorta and liver by enhancing the reverse cholesterol transport pathway. Anti-miR33 monotherapies can change macrophage activation from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype. Additional evidence has demonstrated the protective role of adaptive regulatory T (Treg) cell immunity in preventing lesion formation. Findings demonstrated that anti-miR33 nano therapy can promote the differentiation of Treg cells [13]. The size of the necrotic core plays a key role in plaque vulnerability and rupture, which is noticeably reduced after treatment with miR-146a-SPIONs. The results of this study demonstrated that a full systemic treatment of these NPs lowered proinflammatory cytokines in the aorta [14]. Lou et al. developed an HDL-based phospholipid nanoparticle, miNano. This NP possesses various capabilities, including direct binding to CCs, CC-dissolving ability, enhancement of cholesterol efflux, accumulation in atherosclerotic plaques, prevention of foam cell formation, suppression of inflammatory responses in macrophages, and stabilization of atherosclerotic plaques. With this wide range of abilities, miNano is a promising approach to treat atherosclerosis [21]. C. Jiang et al. developed a NP, which showed that a 3-month regimen of this NP reduced plaque areas by 65.8% and decreased macrophages by 57.3% [12]. A combination of VCAM1-binding peptide and Au nanosphere provides an efficient strategy for the selective delivery of anti-atherosclerotic miRNAs or other drugs to inhibit the formation of atherosclerotic plaques [22]. X. Li et al. synthesized Annexin V-modified hybrid gold nanoparticles, and this imaging system (gold nanoparticle-based SPECT/CT imaging probe) could successfully localize and diagnose vulnerable atherosclerotic plaques by

targeting apoptotic macrophages [23]. The study done by M.D.Majmudar outlined the use of qRT-PCR to measure gene expression changes in aortic extracts, finding that silencing the CCR2 gene decreased inflammation-related gene expression. It also demonstrated the potential of using nanoparticle-assisted PET/MR imaging to detect inflammatory cells in atherosclerotic plaques in mice. The imaging mainly detected monocytes/macrophages, indicating limited specificity. However, targeting monocyte recruitment with RNAi technology reduced inflammation and the macrophage imaging signal, suggesting this method could help identify unstable plaques and assess treatments in clinical settings [24].

Limitations

While this review synthesizes the most recent advances in nanoparticle-based nucleic acid delivery for atherosclerosis, several limitations warrant consideration. First, the included studies were limited to English-language and open-access publications, which may have led to selection bias and the exclusion of potentially relevant findings in non-indexed or gray literature. Second, the heterogeneity across studies, in nanoparticle composition, targeting strategies, animal models, dosing regimens, and outcome reporting, precluded meta-analytic pooling and limited direct comparative analyses. Although our visualizations partially mitigate this by revealing qualitative trends, standardized reporting frameworks for nanotherapeutic studies are urgently needed to enable rigorous cross-study synthesis.

Moreover, most studies relied on small animal models, such as ApoE-/- or LDLR-/- mice, which differ significantly from human atherosclerotic pathophysiology in terms of lesion complexity, immune response, and risk of plaque rupture. Translational applicability remains limited without validation in large animal models or humanized systems. Furthermore, the dominance of intravenous administration across studies overlooks alternative routes (e.g., oral, transendothelial) that may offer improved clinical feasibility and patient compliance. Long-term safety data, particularly regarding immune clearance, off-target effects, and biodistribution, remain insufficiently characterized in the preclinical literature.

Despite these limitations, our structured synthesis and comparative analyses provide critical insight into which nanoparticle design parameters, such as functional ligand selection, payload stability, and targeting specificity, most strongly associate with therapeutic efficacy. These findings lay the groundwork for rational design principles that can inform next-generation clinical nano therapies for cardiovascular disease.

Clinical translation and regulatory considerations

While the preclinical efficacy of functionalized nanoparticles in targeted atherosclerosis therapy is compelling, several barriers must be addressed before human application is feasible. Translational challenges include the need to replicate targeting specificity and therapeutic effects in the complex pathophysiology of human atherosclerosis, where plaque composition, immune responses, and vascular microenvironments differ substantially from murine models. Large-scale manufacturing under Good Manufacturing Practice (GMP) conditions presents additional challenges, particularly for multifunctional or ligand-modified nanoparticles that require precise physicochemical consistency. Regulatory pathways for nanomedicines remain stringent, with safety evaluations requiring comprehensive biodistribution, immunogenicity, and long-term toxicity data in large animal models before clinical trials. Furthermore, the integration of nucleic acid-based nanotherapies into existing cardiovascular treatment algorithms will require demonstration of additive benefit over current standard-of-care therapies in well-powered, randomized controlled trials. Addressing these translational and regulatory challenges will be critical to advancing nanoparticle-mediated gene therapies from preclinical promise to clinical reality.

Conclusion

This systematic review underscores the promising role of functionalized nanoparticles as precision delivery vehicles for nucleic acid-based therapies targeting atherosclerosis. Across 15 preclinical studies, we identified a consistent pattern of therapeutic success associated with nanoparticles engineered for targeted delivery to macrophages, inflammato-

ry signaling pathways, and regulators of lipid metabolism. Notably, platforms incorporating integrin-binding ligands, scavenger receptor targets, or dual-functional cores achieved significant plaque regression and immune modulation, with efficacy rates as high as 65.8%.

Our comparative analyses, via bar charts and heatmaps, demonstrate that both nanoparticle architecture and biological target selection critically influence treatment outcomes. These findings provide a strategic framework to guide the rational design of next-generation nano therapies, highlighting the importance of size, surface functionalization, and loading efficiency in optimizing therapeutic performance.

Despite the translational promise, significant challenges remain, including inter-study heterogeneity, reliance on murine models, and limited safety data. Addressing these gaps will require standardized reporting guidelines, expansion into large-animal or humanized models, and long-term evaluation of nanoparticle biocompatibility.

In sum, targeted nanoparticle delivery of nucleic acids represents a frontier in the molecular treatment of atherosclerosis. As the field moves toward clinical translation, this review offers critical insights to accelerate the development of scalable, safe, and mechanistically precise nano therapies for cardiovascular disease.

Disclosure of conflict of interest

None.

Abbreviations

AS, Atherosclerosis; CVD, cardiovascular disease; EC, Endothelial Cell; LDL, Low-Density Lipoprotein; oxLDL, Oxidized Low-Density Lipoprotein; ROS, Reactive Oxygen Species; IL, Interleukin; VSMC, Vascular Smooth Muscle Cell; VCAM1, Vascular Cell Adhesion Molecule 1; CD36, Cluster of Differentiation 36; siRNA, Small Interfering RNA; miRNA, MicroRNA; ASO, Antisense Oligonucleotide; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; STAT3, Signal Transducer and Activator of Transcription 3; SR-A, Scavenger Receptor Class A; SR-BI, Scavenger Receptor Class B Type I; HDL, High-Density Lipoprotein; rHDL, Recombinant High-Density Lipoprotein; NP, Nanoparticle; SPION, Superparamagnetic Iron Oxide Nanoparticle; LE, Loading Efficiency; LC, Loading Capacity; PET, Positron Emission Tomography; MR, Magnetic Resonance; SPECT, Single Photon Emission Computed Tomography; PDI, Polydispersity Index; ATP, Adenosine Triphosphate; mTOR, Mammalian Target of Rapamycin; CCR2, C-C Motif Chemokine Receptor 2; SIRPα, Signal Regulatory Protein Alpha; ASOs@CaP, Antisense Oligonucleotides Loaded on Calcium Phosphate Nanoparticles; CCL, Coated Cationic Lipoparticle; AaCD, Acetalated Alpha-Cyclodextrin; NaN3, Sodium Azide; FBS, Fetal Bovine Serum; ABCA1/ABCG1, ATP Binding Cassette Transporters A1 and G1; RCT, Reverse Cholesterol Transport; Treg, Regulatory T Cell; MAG3, Mercaptoacetyltriglycine; Tc-99m, Technetium-99m; PLGA, Poly(lactic-co-glycolic acid); PEG, Polyethylene Glycol.

Address correspondence to: Mahsa Asadi Anar, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ORCID: 0000-0002-5772-2472; E-mail: Mahsa.boz@gmail.com

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