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REVIEW

Emerging Approaches for the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease: The Application of Nanomedicines

Te Shi[1,*], Haiyan Yue[1,*], Wen Wang[2,*], Yu Gao[1], Sheng Xu[1], Jie Gao[3], Chuan Yin[4]

[1]Department of Gastroenterology, Naval Medical Center, Naval Medical University, Shanghai, 200050, People's Republic of China; [2]Department of Marine Biomedicine and Polar Medicine, Naval Medical Center, Naval Medical University, Shanghai, 200433, People's Republic of China; [3]Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, People's Republic of China; [4]Department of Gastroenterology, Shanghai Changzheng Hospital, Naval Medical University, Shanghai, 200003, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chuan Yin, Department of Gastroenterology, Shanghai Changzheng Hospital, Naval Medical University, Shanghai, 200003, People's Republic of China, Email ilse1225@163.com; Jie Gao, Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, People's Republic of China, Email gaojiehighclea@smmu.edu.cn

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 25% of the global population, with limited pharmacological treatment options. While lifestyle modification remains foundational, nanomedicine offers promising strategies to overcome drug delivery challenges, including poor solubility, low bioavailability, and off-target effects. This review systematically examines nanomedicine design strategies across four therapeutic domains: (1) lipid metabolism regulation, (2) anti-inflammatory and antioxidant therapy, (3) insulin sensitization, and (4) gene regulation. We critically analyze hepatic cell-specific targeting approaches, evaluate the biological effects of nanomedicines beyond drug delivery, and discuss the strengths and limitations of current preclinical evidence. Key challenges for clinical translation are examined, including long-term biosafety, animal model relevance, and the gap between preclinical promise and clinical reality. While recent FDA approvals of semaglutide and resmetirom for MASH with fibrosis represent significant progress, nanomedicine may address unmet needs through combination therapies, cell-specific targeting, and theranostic approaches. By integrating emerging trends in intelligent nanomedicine design, this review provides a roadmap for advancing nanomedicines from bench to bedside for MASLD treatment.

Keywords: metabolic dysfunction-associated steatotic liver disease, nanomedicines, drug delivery, targeted therapy

Introduction

Nonalcoholic fatty liver disease (NAFLD), a metabolic liver condition associated with overnutrition and insulin resistance,[1,2] is characterized by a disease spectrum that progresses from steatosis to steatohepatitis (NASH), fibrosis, and cirrhosis.[3] In 2020, international experts redefined the condition as metabolic dysfunction-associated fatty liver disease (MAFLD) to reflect its strong metabolic basis.[4,5] This terminology was further refined in 2023 through a multisociety consensus led by the American Association for the Study of Liver Diseases (AASLD),[3] which introduced metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) to enhance clinical recognition.[6] Throughout this review, the terms MASLD and MASH are consistently employed as the standard nomenclature. MASLD progression to MASH affects approximately 25% of the global population and occurs in 12%–14% of cases,[7] with regional variations exemplified by a 32.7% prevalence reported in Shanghai, China.[8] Importantly, approximately 20% of MASH patients develop advanced cirrhosis,[9] and this condition has emerged as a leading etiology of hepatocellular carcinoma (HCC).[10–12] Without intervention, MASLD is projected to become the primary indication for liver transplantation, with MASH-related mortality estimated to increase by 178% by 2030,[13] posing substantial challenges to healthcare systems worldwide.[14]

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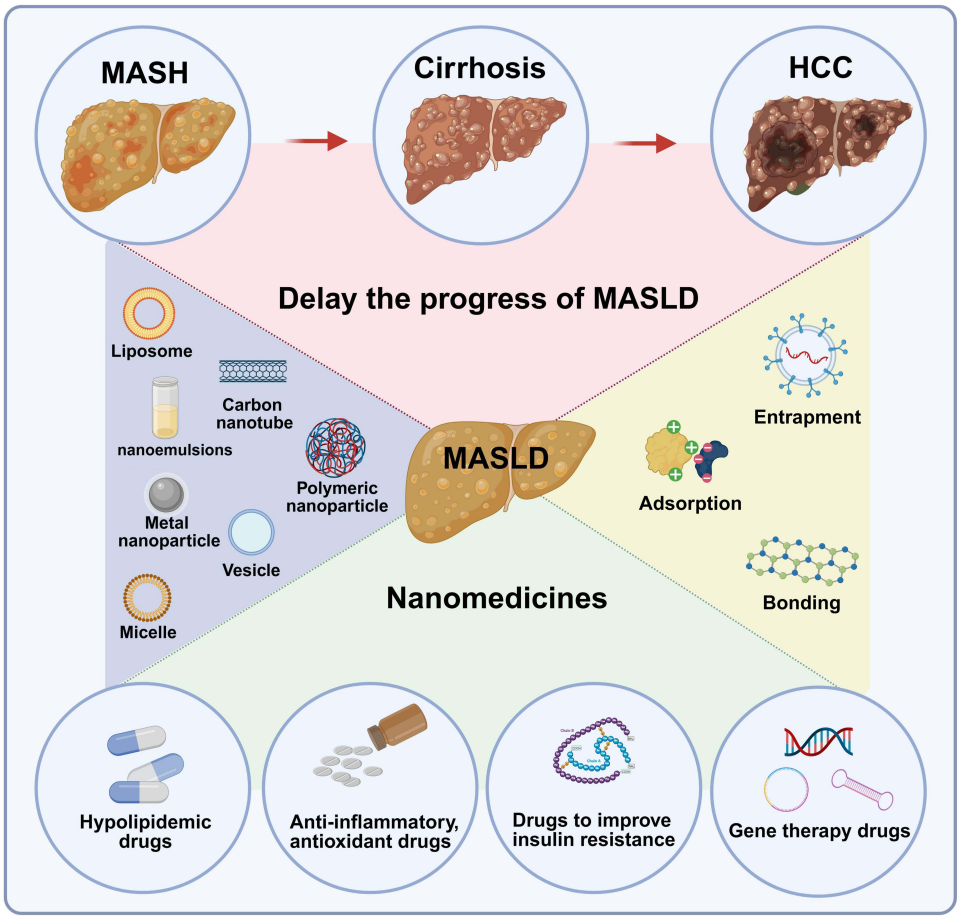
Graphical Abstract



The increasing recognition of MASLD severity has intensified the focus on its clinical management. While lifestyle modification remains foundational,[15] the recent U.S. Food and Drug Administration (FDA) approvals of semaglutide and resmetirom for MASH with significant fibrosis marked a paradigm shift, offering the first targeted pharmacologic options.[16,17] Despite this progress, the clinical management of MASLD still relies heavily on conventional agents such as hepatoprotectants, insulin sensitizers, and lipid-lowering agents, which are hampered by poor aqueous solubility, low oral bioavailability, and suboptimal efficacy.[18–21] These limitations necessitate the development of advanced cell-specific drug delivery technologies to overcome the barriers associated with current therapeutics.[18,22]

Nanomedicines represent a transformative strategy for managing MASLD, employing advanced delivery systems such as nanoparticles, polymeric micelles, liposomes, and nanogels to achieve precise hepatic targeting.[23] As shown in Table 1, these carriers encapsulate drugs by embedding, adsorption, or conjugation, enhancing their solubility, shielding against degradation, and improving their bioavailability.[24–26] By leveraging size-dependent targeting and surface functionalization, nanomedicines facilitate controlled release, prolong circulation time, promote accumulation at disease sites, and reduce off-target effects—collectively addressing the core limitations of conventional MASLD therapies.[27–29] The development of precision platforms, including dendrimers and engineered liposomes, focuses on optimizing nanomedicine size, morphology, and physicochemical properties to tailor in vivo biodistribution and therapeutic efficacy.[30,31] Nanomedicine achieves liver-targeted delivery primarily through two mechanisms. Passive targeting utilizes the size of nanoparticles (typically 100–200 nm), allowing them to be captured by Kupffer cells in the liver sinusoids or trapped within the hepatic sinusoids.[32,33] Active targeting involves modifying the surface of nanomedicines with liver

Table 1 Comparison of Conventional vs Advanced Delivery for Solubility and Efficacy

Drug/Agent	Limitation (Conventional)	Enhanced System	Bioavailability/Efficacy Improvement	Ref.
Silymarin	Poor solubility,<1% bioavailability	Chitosan-LPNs, phytosomes, nanosuspensions	6–14x higher bioavailability, improved liver protection	[40–43]
Atorvastatin	Poor solubility, 12% bioavailability	Nanostructured lipid carriers	2–3.6x higher bioavailability, better lipid control	[44]
Insulin	Poor oral absorption	Lipid nanoparticles, OLNs, SLNs	Up to 28% relative bioavailability, effective glucose lowering	[45–47]
Luteolin, Thymoquinone	Poor solubility, low efficacy	SNEDDS, nanoemulsions	3–4x higher bioavailability, enhanced hepatoprotection	[48, 49]

Abbreviations: LPNs, lipid–polymer hybrid nanoparticles; OLNs, organic lipid nanoparticles; SLNs, solid lipid nanoparticles; SNEDDS, self-nanoemulsifying drug delivery system.

cell-specific ligands (such as galactose or asialoglycoprotein) to enable active recognition and binding to receptors on hepatocyte surfaces (eg., ASGPR).[34,35] Furthermore, the carriers can be designed to respond to the liver microenvironment (eg., pH and enzymes), achieving intelligent controlled release of drugs at the disease site.[36,37] The concept of intelligent, microenvironment-responsive systems is exemplified by innovations in cancer therapy and wound healing, where stimuli-responsive hydrogels and nanovesicles demonstrate precise spatiotemporal control over drug release.[38,39] This significantly enhances drug accumulation in the liver, improves therapeutic efficacy, and reduces systemic toxicity. Despite progress, the current literature lacks a systematic integration of nanomedicine classifications, surface engineering strategies, and mechanism-based insights across diverse treatment paradigms. This review therefore aims to critically synthesize recent advances, delineate translational prospects and challenges, and facilitate the rational development of targeted therapies for MASLD.

This review distinguishes itself from the literature through two key contributions. First, we provide the first systematic synthesis linking nanomedicine design strategies to the specific pathological processes of MASLD, moving beyond general discussions of liver-targeted nanomedicines. Second, we propose an analytical framework that categorizes nanomedicines according to their mechanistic targets—lipid metabolism modulation, inflammation resolution, insulin sensitivity restoration, and gene regulatory interventions—thereby establishing a pathophysiology-guided classification system. Additionally, we critically analyze the barriers hindering clinical translation, illustrated with concrete examples from recent trials, and outline potential breakthrough pathways for advancing MASLD nanomedicine toward clinical application.

Hepatic Cell-Specific Targeting Strategies

The liver represents a structurally and functionally complex organ comprising multiple cell types with distinct physiological roles in MASLD pathogenesis.[6] Understanding the cellular distribution patterns of nanomedicines within the liver microenvironment is essential for designing effective targeted therapies that can overcome the limitations of conventional drug delivery approaches.[35,40] This section systematically examines how nanoparticles interact with different liver cell populations and describes the strategies employed to achieve precise cell-specific drug delivery (Figure 1).

Cellular Distribution of Nanomedicines in the Liver

The liver comprises approximately 60% parenchymal cells (primarily hepatocytes) and 40% nonparenchymal cells, including Kupffer cells (liver-resident macrophages), liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells (HSCs).[41] Each cell type plays distinct roles in MASLD progression and exhibits unique nanoparticle uptake characteristics that must be considered when designing targeted delivery systems.

Hepatocytes, the primary parenchymal cells responsible for lipid metabolism, glucose homeostasis, and protein synthesis,[1] express the asialoglycoprotein receptor (ASGPR) at high density (approximately 500,000 receptors per cell), rendering them attractive targets for use with galactose- or N-acetylgalactosamine (GalNAc)-modified

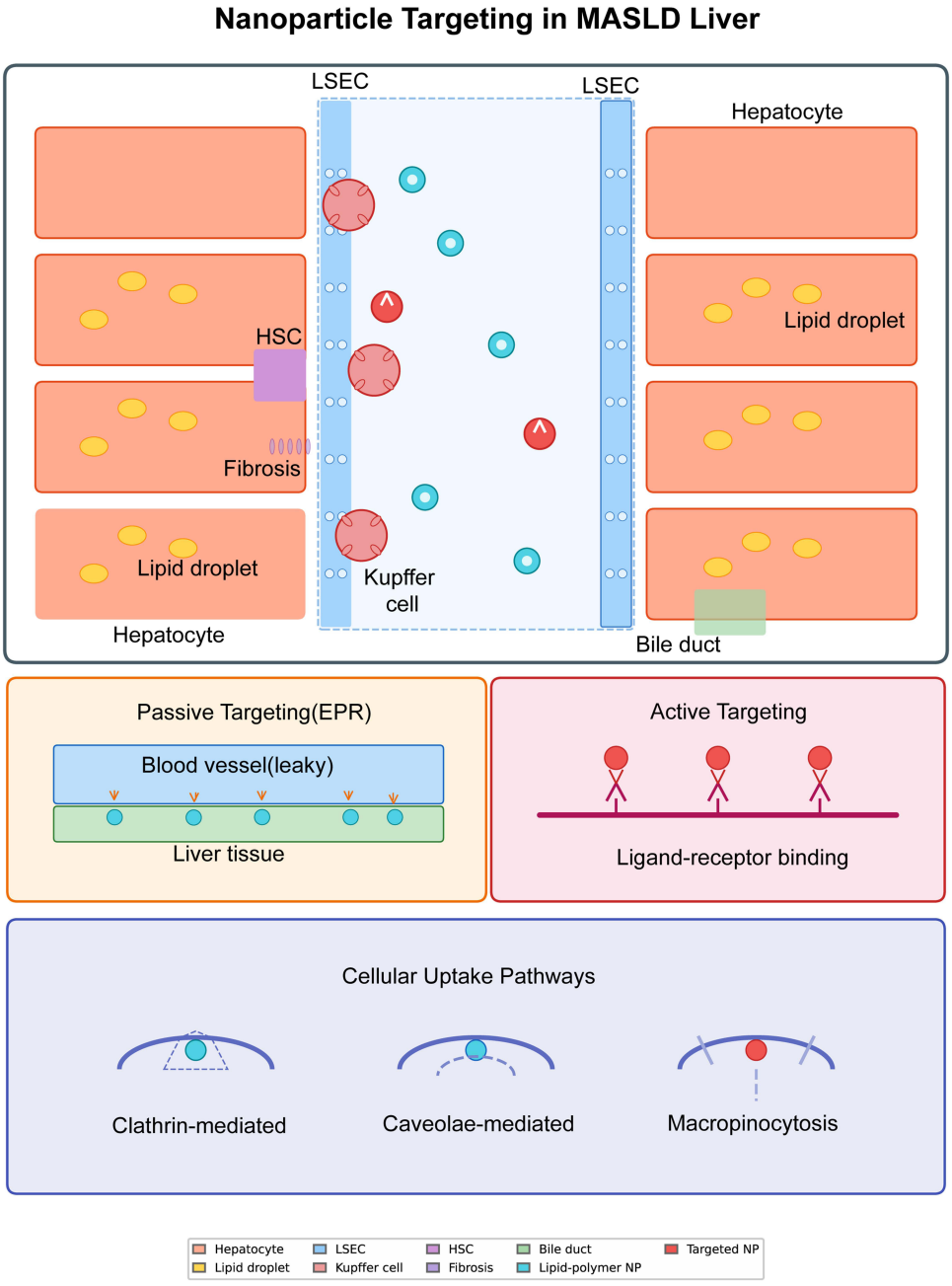


Figure 1 Schematic illustration of nanoparticle distribution in the MASLD liver microenvironment. Created with Adobe Illustrator.

nanoparticles.[42] ASGPR is a C-type lectin that specifically recognizes terminal galactose or GalNAc residues and undergoes rapid endocytosis and recycling (approximately every 15 minutes), thereby facilitating efficient intracellular drug delivery.[43]

Kupffer cells constitute 15–20% of liver cells and serve as the primary phagocytic defense mechanism.[44,45] These liver-resident macrophages express high levels of mannose receptors (CD206), scavenger receptors, and complement receptors, enabling them to efficiently recognize and internalize circulating nanoparticles.[46] Studies have demonstrated that Kupffer cells are the predominant cell type responsible for nanoparticle sequestration in the liver, with up to 98% of Kupffer cells internalizing administered nanoparticles within 24 hours.[32]

Hepatic stellate cells represent 5–8% of liver cells and constitute the primary fibrogenic cells in advanced MASLD.[47] Quiescent HSCs store approximately 80% of the body's vitamin A as retinyl palmitate in lipid droplets and express

retinol-binding protein (RBP) receptors. Upon activation during fibrosis progression, HSCs upregulate the expression of various receptors, including CD44, platelet-derived growth factor receptors, and integrins, thereby providing multiple targeting opportunities for antifibrotic nanotherapeutics.[48] Liver sinusoidal endothelial cells form the fenestrated lining of hepatic sinusoids with pore sizes ranging from 50–350 nm.[49] LSECs express hyaluronic acid receptors (HARE/Stabilin-2) and mannose receptors (CD206), enabling them to participate in nanoparticle clearance and targeting.[50] The fenestrated structure of LSECs allows nanoparticles smaller than the pore size to pass through into the space of Disse, where they can access hepatocytes and HSCs.[51] The hierarchical uptake of nanoparticles in the liver follows a distinct pattern: Kupffer cells>LSECs>HSCs>hepatocytes.[32,52] This distribution pattern highlights the challenges associated with achieving hepatocyte-specific delivery because of efficient phagocytic clearance by Kupffer cells, necessitating the development of sophisticated targeting strategies to overcome this biological barrier.[53]

Passive Targeting Mechanisms

Passive targeting exploits the natural anatomical and physiological characteristics of the liver to achieve nanoparticle accumulation without specific ligand–receptor interactions. The enhanced permeability and retention (EPR) effect, first described by Maeda et al, represents a fundamental mechanism through which passive nanoparticles target hepatic tissues.

The size of nanoparticles critically affects their hepatic distribution and cellular uptake profiles. The optimal size range for passive liver targeting is generally considered to be 50–200 nm.[54] Particles smaller than 10 nm are rapidly cleared by renal filtration, whereas those larger than 500 nm are predominantly sequestered by Kupffer cells.[54] Liver sinusoidal fenestrations (50–200 nm) act as size-selective filters, allowing smaller nanoparticles to pass through the space of Disse while retaining larger particles within the sinusoidal lumen.[55] Systematic studies have demonstrated that compared with smaller particles, nanoparticles in the 40–100 nm range exhibit longer circulation times and improved hepatic accumulation.[54] However, smaller particles (<50 nm) showed enhanced tissue penetration capabilities. For liver targeting specifically, nanoparticles in the 50–150 nm range appear to achieve an optimal balance between circulation time and hepatocyte accessibility.[56]

Compared with charged particles, neutral and zwitterionic nanoparticles generally exhibit prolonged circulation times and reduced Kupffer cell uptake. The formation of a protein corona upon contact with blood proteins significantly influences nanoparticle biodistribution and targeting efficiency.[57] PEGylation creates a hydrophilic stealth layer that reduces opsonization and reticuloendothelial system (RES) clearance, thereby extending the circulation half-life and increasing the probability of target cells being reached.[58] Intravenously administered nanoparticles naturally accumulate in the liver because of their high blood flow (approximately 25% of cardiac output) and the abundance of phagocytic cells.[52] This passive hepatic targeting can be advantageous for MASLD therapy but presents challenges in achieving cell-specific delivery. Strategies to modulate passive targeting include adjusting the particle size to favor hepatocyte access through sinusoidal fenestrations or engineering surface properties to minimize Kupffer cell recognition.[34]

Active Targeting Strategies

Active targeting employs specific ligand–receptor interactions to direct nanoparticles to desired cell populations, potentially overcoming the limitations of passive distribution and achieving enhanced therapeutic efficacy.

ASGPR represents the most extensively validated target for hepatocyte-specific delivery, with approximately 500,000 receptors per cell.[59] Multivalent GalNAc conjugates exhibit nanomolar-to-picomolar binding affinities for ASGPR, enabling highly efficient hepatocyte targeting. The clinical success of GalNAc-siRNA drugs—including Onpattro (patisiran), Givlaari (givosiran), Leqvio (inclisiran), and Amvuttra (vutrisiran)—demonstrates the translational potential of this approach.[54,60] Recent technological advances include Silence Therapeutics' serinol-based GalNAc conjugates, Arrowhead's TRiM™ platform, and Sirnaomics' GalAhead™ technology using miniaturized hairpin RNAi triggers.[61] As of 2024, five GalNAc-siRNA drugs have received FDA approval, with more than 30 candidates in clinical development for hepatic indications.[54] For MASH specifically, ARO-HSD (Phase II), ALN-HSD (Phase II), and LY3849891, which target PNPLA3 (Phase I), are under active investigation.[60]

Table 2 Comparison of Hepatic Cell-Specific Targeting Strategies

Cell Type	Receptor Target	Ligand	Optimal Size	Representative Studies	Ref.
Hepatocytes	ASGPR (500,000 receptors/cell)	Galactose, GalNAc	50–150 nm	Onpattro, Givlaari, Leqvio, Amvuttra; ARO-HSD (Phase II), ALN-HSD (Phase II), LY3849891 (Phase I)	[64, 69, 70]
Kupffer cells	CD206 (mannose receptor)	Mannose	>500 nm (passive); ManC-LNPs (active)	ManC-LNPs with 8–10 fold CD206+ enrichment	[56, 60]
Hepatic stellate cells	RBP receptor; CD44	Retinol (vitamin A); Hyaluronic acid	Not specified	BMS-986263/ND-L02-s0201 (NCT02227459); Retinol-modified nanoparticles; Dual fibronectin/ CD44 nanoparticles	[71–73]
Liver sinusoidal endothelial cells	HARE/Stabilin-2; CD206	Hyaluronic acid; Mannose	50–350 nm (fenestrations)	HA micelles for CD44+ targeting; ManC-LNPs	[74, 75]

Mannose receptors (CD206) are highly expressed on Kupffer cells (70–80%) and LSECs, making them attractive targets for nonparenchymal liver cell delivery.[50] Mannose-conjugated cholesterol-containing lipid nanoparticles (ManC-LNPs) are enriched 8–10-fold in CD206+ cells, with linker chemistry significantly influencing targeting efficiency.[50] Recent studies have demonstrated that shorter PEG lipids (C10/C12) enhance mannose–CD206 interactions through faster PEG shedding.

Retinol-binding protein (RBP) receptors are upregulated on activated hepatic stellate cells, providing a selective targeting opportunity. Vitamin A-coupled liposomes and retinol-modified nanoparticles have demonstrated selective HSC uptake and antifibrotic efficacy in preclinical models.[62,63] A phase 1b/2 trial (NCT02227459) evaluating vitamin A-coupled lipid nanoparticles containing an HSP47-targeting siRNA (BMS-986263) revealed a promising reduction in the expression of fibrotic markers.[64,65]

CD44 is overexpressed on activated HSCs during fibrosis progression. Hyaluronic acid-modified nanoparticles exploit this receptor for selective HSC targeting, with the hydrophilic HA coating simultaneously evading macrophage recognition.[66,67] Recent advances include dual fibronectin/CD44-targeted nanoparticles that disrupt Golgi apparatus function and inhibit hedgehog signaling in activated HSCs.[68]

A comparison of the major hepatic cell-specific targeting strategies is presented in Table 2. Despite the promise of active targeting, its clinical application in MASLD therapy faces substantial hurdles. Even high-affinity ASGPR ligands achieve only a 2-fold increase in hepatocyte uptake compared with that of nontargeted nanoparticles, as the majority are sequestered by Kupffer cells and liver sinusoidal endothelial cells, making true cell-specific delivery extremely challenging. Moreover, disease progression significantly alters receptor expression profiles and the hepatic microenvironment; fibrosis-induced portal hypertension and microcirculatory changes impair nanoparticle accessibility to target cells, necessitating stage-adapted targeting strategies. Clinical translation is further complicated by patient heterogeneity, which demands personalized approaches—hepatocyte-targeted lipid-lowering therapy for simple steatosis, Kupffer cell-directed anti-inflammatory treatment for inflammatory MASH, and hepatic stellate cell-targeted antifibrotic intervention for fibrotic MASH. Ligand incorporation adds manufacturing complexity and batch-to-batch consistency challenges, but long-term safety data concerning cumulative toxicity, immunogenicity, and off-target effects remain limited. Future efforts should focus on multiligand cooperative targeting to improve cell selectivity, develop intelligent nanomedicines responsive to MASLD-specific pathological cues (altered pH, elevated ROS, and enzyme dysregulation), and integrate theranostic capabilities for real-time treatment monitoring. Addressing the critical bottlenecks of targeting efficiency, scalable production, and long-term safety is essential for advancing cell-specific nanomedicines from the bench to the bedside.

Application of Nanomedicines for Drug Therapy in MASLD

Nanomedicines in Lipid-Lowering Drug Therapy for MASLD

Hypolipidemic agents, primarily statins and fibrates, constitute cornerstone therapies for managing dyslipidemia. Statins competitively inhibit HMG-CoA reductase to reduce cholesterol synthesis,[76] demonstrating the potential to attenuate hepatic steatosis, inflammation, and fibrogenesis.[69] Fibrates activate PPARα receptors, enhancing mitochondrial β-

oxidation while reducing hepatic enzymes and triglycerides.[70] However, their therapeutic efficacy in MASLD remains inconclusive, potentially because of their low bioavailability and hepatotoxicity. Emerging evidence supports the use of nanomedicine-mediated strategies to improve the encapsulation efficiency and drug payload, thereby increasing therapeutic bioavailability.

An Egyptian study engineered atorvastatin calcium (AC)-loaded β-cyclodextrin (β-CD) nanospheres (AC-NSs) to increase their solubility and oral bioavailability for fatty liver therapy.[77] Pharmacokinetic analysis revealed a 2.13-fold improvement in oral bioavailability versus the AC suspension in a rat model. AC-NS notably reduced total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels and increased high-density lipoprotein cholesterol (HDL-C) levels while ameliorating hepatic steatosis, highlighting the therapeutic potential of nanoenabled statin delivery systems. Nanoliposomes, composed of phospholipid bilayers with hydrophilic heads oriented toward aqueous media and hydrophobic tails forming spherical nanoparticles,[71] are optimized for encapsulating hydrophobic agents within the phospholipid matrix, rendering them ideal carriers for poorly water-soluble therapeutics.[71] In the study by Cao et al,[72] fenofibrate (FNB) was encapsulated in phospholipid-based nanoliposomes, resulting in an enhanced drug payload and controlled in vitro release kinetics. In MCD diet-induced MASLD mice, the administration of 20 mg/kg/day of FNB-Nanolipo (initiated concomitantly with MCD feeding for 7 days) or 40 mg/kg/day (initiated 7 days post-MCD feeding for 7 days) elevated plasma FNB levels by 11.8-fold or 57.3-fold (both $P<0.05$), respectively, with concomitant reductions in hepatic lipid content of 54.7% or 35.5% (both $P<0.05$), demonstrating dose-dependent therapeutic efficacy in MASLD prevention and intervention.[72] In subsequent research by Cao et al,[73] polyurethane (PU) was engineered as a nanomedicine for FNB. Drug-loaded FNB-PU nanoparticles were fabricated via eco-friendly aqueous-phase synthesis, with FNB encapsulation achieved through ultrasonication. Compared with native FNB, the FNB-PU nanoparticles presented superior drug loading capacity and sustained release kinetics, increased oral FNB absorption, increased cellular uptake, and significantly attenuated hepatic lipid accumulation. To address the targeting potential and stimuli-responsive delivery of nanoparticles, Du et al[74] developed a ROS-responsive system based on a vitamin E-derived peroxyester and DSPE-PEG conjugate to increase the efficacy of FNB against MASLD. The encapsulation efficiency of the FNB-loaded nanoparticles (FNB-NPs) was 97.25±0.6%, the drug loading capacity was 29.67±0.1%, and the hydrodynamic diameter was 197.0±0.2 nm in vitro. According to the results of the pharmacodynamic evaluations, compared with native FNB, the FNB-NPs demonstrated superior efficacy, significantly attenuating hepatic lipid deposition in MASLD mice through enhanced hepatic drug release and upregulation of PPARα expression.[74] Additionally, the FNB-NPs effectively alleviated MASLD-associated oxidative stress. Recent studies further revealed that enhancing heme oxygenase-1 (HO-1) expression in adipocytes reduces lipid accumulation in obese mice by promoting the browning of white adipose tissue (WAT) to energy-dissipating brown adipose tissue (BAT), a process termed brown adipogenesis.[75,78] Y Won et al[79] engineered nanoparticles loaded with HO-1 inducers by functionalizing poly(lactic acid)-hydroxyglycolic acid (PLGA) nanoparticles with a prohibitin-binding peptide (PBP, CKGGRAKDC), enabling specific targeting of white adipocytes and macrophages in adipose tissue. Furthermore, Hong J et al[80] demonstrated that PBP-conjugated HO-1 inducer-loaded nanoparticles (PBP-NPs) selectively targeted steatotic livers, suppressed hormone overexpression and inhibited the hepatic uptake of circulatory lipids in MASH mice (Figure 2). PBP-NPs attenuated hepatic steatosis, inflammation, and fibrogenesis through multiple mechanisms: facilitating white-to-brown adipocyte conversion to increase thermogenesis, downregulating lipid transporter overexpression to reduce hepatic lipid deposition, modulating macrophage polarization to suppress proinflammatory responses, and significantly lowering circulatory lipids and cytokines in obese adipose tissue.

Lipid-based and polymeric carriers effectively address the solubility and bioavailability challenges of hypolipidemic agents. Peptide-modified nanoparticles have potential in drug delivery because of their prolonged circulation half-life, enhanced cellular internalization, and improved targeting specificity. These nanopharmaceuticals not only augment therapeutic efficacy and safety profiles but also broaden the horizons of drug design, facilitating the translation of preclinical breakthroughs into clinical applications.

However, improved pharmacokinetics (PK) do not equate to therapeutic superiority in MASLD. The limited efficacy of conventional statins and fibrates stems not only from low bioavailability or hepatotoxicity but also primarily from a lack of liver-specific targeting. While nanomedicines can enhance PK parameters, such gains alone are insufficient to reverse

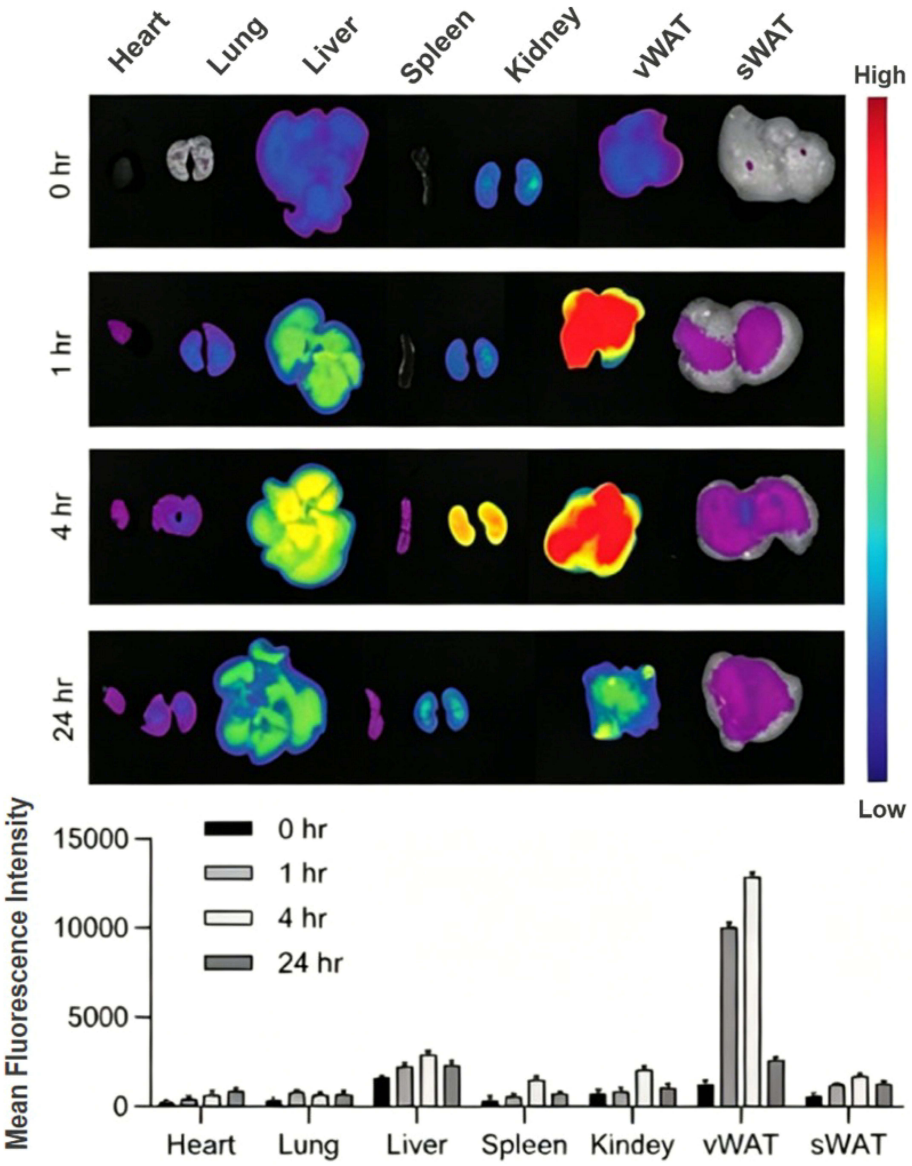


Figure 2 Schematic illustration of fatty liver/adipose tissue dual-targeting PBP-NPs containing HO-1 inducers for the treatment of obesity, obesity-induced T2DM, and nonalcoholic steatohepatitis. Reprinted with permission from Wiley-VCH GmbH. Hong J, Kim YH. Fatty Liver/Adipose Tissue Dual-Targeting Nanoparticles with Heme Oxygenase-1 Inducer for Amelioration of Obesity, Obesity-Induced Type 2 Diabetes, and Steatohepatitis. *Advanced Science*. 2022;9(33). Creative Commons.[80]

established steatohepatitis or fibrosis. True therapeutic advantage should be defined by disease-modifying endpoints (eg., MASH resolution, fibrosis regression), not by surrogate PK metrics. Encouragingly, active-targeting and stimuli-responsive systems offer added benefits—such as selective hepatic accumulation, macrophage modulation, and white-to-brown adipocyte conversion—beyond mere PK enhancement. Future nanomedicine strategies must rigorously dissect whether efficacy arises from the improved PK of old drugs or from distinct mechanisms of action. Otherwise, the inherent limitations of conventional agents in addressing the multifactorial pathogenesis of MASLD may be masked.

Applications of Nanomedicines in Anti-Inflammatory and Antioxidant Drug Therapy for MASLD

The pathogenesis of MASLD involves a complex interplay of multiple factors characterized by dysregulation of the metabolic–immune–inflammatory network across multiple organs.[81,82] Oxidative stress and inflammation are intrinsically interconnected in this process: de novo lipogenesis activation and mitochondrial dysfunction trigger substantial reactive

oxygen species (ROS) accumulation,[83,84] which not only directly damages hepatocytes but also activates inflammatory signaling and hepatic stellate cells, thereby linking metabolic disturbances to hepatic inflammation and fibrosis progression.[85,86] Given this pathological interplay, many hepatoprotective agents (eg., silymarin and curcumin) possess dual antioxidant and anti-inflammatory activities, representing key therapeutics for MASLD, especially in MASH or advanced fibrosis. However, their clinical efficacy remains limited because of poor solubility and stability. nanomedicine strategies address these limitations through shared design principles—enhancing drug accumulation at lesion sites via targeted delivery and achieving microenvironment-triggered release—thereby concurrently disrupting the oxidative-inflammatory cycle to unlock their full therapeutic potential.

Resveratrol (Res), a natural polyphenolic compound,[87] has multiple bioactivities, including anti-inflammatory, antioxidant, free radical scavenging, cardioprotective, and antitumor effects.[88,89] Studies have demonstrated that Res ameliorates hepatic steatosis, enhances insulin sensitivity, and reduces inflammatory/oxidative stress markers in rats fed a high-fat diet.[90–92] However, Res undergoes rapid systemic metabolism, with oral absorption reaching 75% yet bioavailability remaining below 1%,[93] primarily because of extensive postabsorptive metabolism into glucuronide and sulfate conjugates, resulting in negligible circulating levels of the parent compound. Coupled with poor aqueous solubility and photolability, these pharmacotechnical barriers hinder therapeutic plasma concentration attainment, collectively limiting the clinical translation of Res for metabolic disorders. To address these limitations, Li et al engineered a stabilized resveratrol-loaded nanoparticulate system (Res NPs) by synthesizing an amphiphilic glycine-modified α-lipoic acid and lactobionic acid conjugate (Gly-LA-Lac), which self-assembled in aqueous media to encapsulate resveratrol[94] This system effectively resolved bioavailability challenges: In vitro analyses demonstrated that compared with free drugs, Res NPs increased the cellular uptake of Res, alleviated oxidative stress, and reduced proinflammatory cytokine levels. In vivo studies validated the hepatotropic targeting of Res NPs, which significantly attenuated hepatic lipid deposition and oxidative stress while ameliorating liver injury in MASLD mice through modulation of the TLR4/NF-κB signaling axis.[94] This nanoplatform provides a transformative strategy to increase the bioavailability of resveratrol and improve its therapeutic efficacy against metabolic liver disorders.

Silymarin, a flavonoid compound sourced from the seeds of Silybum marianum, has been valued for centuries for its hepatoprotective properties, stemming from its antioxidant, anti-inflammatory, and antifibrotic effects.[95–98] The poor water solubility and low oral bioavailability (0.73%) of silymarin limit its clinical effectiveness in MASLD treatment. To address these challenges, strategies such as the development of lipid–polymer hybrid nanoparticles (LPNs) are being pursued. LPNs feature a core–shell structure that comprises a polymer core and a phospholipid shell.[99] Liang et al successfully engineered chitosan-modified silymarin-loaded LPNs (CS-LPNs) that exhibit 14.38-fold greater relative bioavailability than silymarin suspensions do.[100] These CS-LPNs have been shown to significantly reduce triglyceride levels, lower AST and ALT levels, alleviate hepatic lipid accumulation, and decrease vesicular steatosis, thereby enhancing the therapeutic efficacy of MASLD treatment (Figure 3).

Naringenin (NGN), a dihydroflavonoid from citrus,[101] has anti-inflammatory, antioxidant, and antitumor benefits[102,103] but is limited by low oral bioavailability because of solubility and oxidation issues. To address this, liposomal and solid lipid nanoparticle formulations have been developed to increase NGN stability and bioavailability.[104,105] In a study by Hu et al,[106] a 100 mg/kg/day dose of NGN significantly reduced liver fat in MASLD mice fed a methionine-choline deficiency (MCD) diet. They subsequently formulated NGN-loaded nanolipid carriers (NGN-NLCs) via an emulsification–evaporation and low-temperature curing technique, achieving a 22.5% drug loading capacity.[107] This formulation increased NGN release by 3.5 times that of pure NGN, bolstered transepithelial transport and intestinal absorption via intracellular pathways, circumvented p-gp efflux, and achieved equivalent pharmacokinetics at a reduced dose. Ultimately, NGN-NLCs enhanced liver distribution by 1.5-fold and decreased MCD-induced liver fat by threefold.

Studies indicate that low vitamin D3 levels are linked to hepatic steatosis and inflammation in MASH patients.[108,109] Active vitamin D3 may benefit MASH treatment by inhibiting immune cell activation, reducing collagen in hepatic stellate cells, and enhancing the intestinal–hepatic axis.[110] However, the clinical application of active vitamin D3 is limited because of its lack of efficacy at safe doses and the risk of hypercalcemia at higher doses.[111,112] Mu et al developed a novel nanolipid carrier (NLC) system to deliver active vitamin D3 directly to the intestines and liver for the

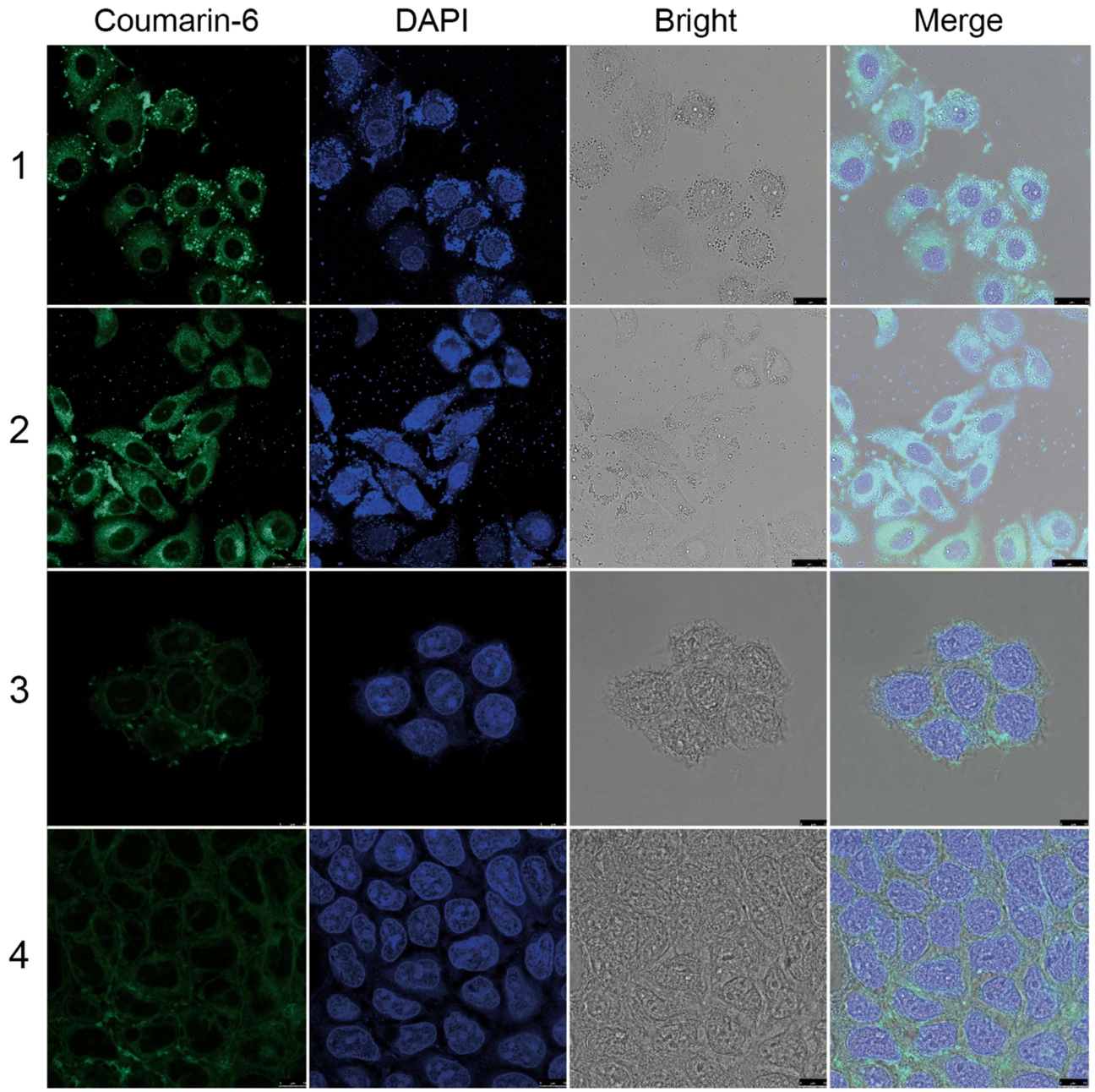


Figure 3 Confocal laser scanning microscopy images. Reprinted with permission from Liang J, Liu Y, Liu J, et al Chitosan-functionalized lipid-polymer hybrid nanoparticles for oral delivery of silymarin and enhanced lipid-lowering effect in NAFLD. J Nanobiotechnology. 2018;16:64. Licensed under CC BY 4.0.[99]

treatment of MASH.[113] Importantly, this NLC system was effective at reducing intestinal barrier permeability and alleviating liver steatosis, inflammation, and fibrosis in the MASH model, all of which are within a safe dosage range.

Notably, close pathological crosstalk occurs among insulin resistance, oxidative stress, and inflammation in MASLD, forming a vicious cycle that mutually exacerbates these conditions. On the one hand, oxidative stress and chronic inflammation can aggravate peripheral and hepatic insulin resistance by interfering with insulin signaling. On the other hand, insulin resistance-induced lipid metabolic disorders and lipotoxicity can further trigger oxidative stress and inflammatory responses. Consequently, therapeutic strategies aimed at improving insulin resistance often involve synergistic or overlapping mechanisms with anti-inflammatory and antioxidant effects. The next section explores strategies employing nanotechnology for the delivery of insulin sensitizers, which not only improve insulin signaling pathways but also frequently effectively modulate oxidative stress and inflammation.

Nevertheless, several challenges still need to be addressed before these anti-inflammatory and antioxidant nanomedicines can reach clinical application. Most current systems rely on passive targeting via the enhanced permeability and retention (EPR) effect, which may be less reliable in MASLD patients because of heterogeneous hepatic vascular remodeling and fibrosis. Additionally, issues related to batch-to-batch reproducibility, scale-up manufacturing, and long-term stability under physiological conditions warrant further optimization. The safety profiles of nanomedicines themselves—including potential chronic toxicity, immunogenicity, and off-target accumulation—also require more thorough evaluation. Furthermore, many preclinical studies employ prophylactic or early-intervention regimens that do not fully recapitulate the clinical scenario of advanced MASH with fibrosis. Looking forward, with rational design of active targeting ligands, adoption of scalable and reproducible fabrication techniques (eg., microfluidics), and rigorous toxicological assessment in clinically relevant animal models, these nanomedicines hold promise for future clinical translation beyond simply improving pharmacokinetics.

Nanomedicines for Improving Insulin Resistance in MASLD

The liver serves as a pivotal metabolic organ alongside skeletal muscle and adipose tissue[114] and is regulated primarily by the insulin signaling pathway IRS/PI3K/AKT/FoxO1,[115] which also modulates the cell cycle, growth, and apoptosis.[116] In MASLD patients, the ability of insulin to suppress adipose tissue lipolysis has been demonstrated in multiple studies[117–119] and is strongly correlated with steatosis severity, indicating its role as a causal driver.[120,121] This evidence confirms that insulin resistance is the core metabolic abnormality in MASLD, particularly characterized by resistance to insulin-mediated suppression of lipolysis, leading to persistent influx of nonesterified fatty acids (NEFAs) into the liver and exacerbating intrahepatic lipid accumulation and lipotoxicity.[122] Consequently, antidiabetic medications, especially those that improve insulin sensitivity, show promising potential for MASLD treatment.[123]

Metformin, a first-line therapeutic for T2DM[124–126] with inherent anti-inflammatory properties, has demonstrated limited clinical efficacy against MASLD because of its suboptimal bioavailability (50–60%). To address this, Sarkar et al[127] engineered a CD44-targeting nanoplatform using hyaluronic acid-functionalized graphene oxide quantum dots (GOQD-HAs) for metformin delivery, which achieved enhanced bioavailability (Figure 4). GOQD-HA exhibits exceptional chemical stability, facile functionalization capacity, low toxicity, and good biocompatibility,[128,129] with its large surface area enabling an enhanced drug payload to substantially improve metformin bioavailability.[130] In vitro in palmitate-treated RAW264.7 macrophages and in vivo MASLD mice, GOQD-HA-Met demonstrated dose-sparing efficacy: significantly suppressing proinflammatory cytokines while enhancing the antioxidant marker; furthermore, it potentiated the antisteatotic effects of metformin and ameliorated insulin resistance, outperforming conventional metformin therapy.[127]

Luteolin (LUT), a flavonoid isolated from traditional Chinese medicinal herbs, has ameliorative effects on diet-induced obesity-associated insulin resistance.[131] Ahmed ESA et al[132] engineered LUT/ZnO nanoparticles through the conjugation of luteolin with zinc oxide, establishing a novel phytochemical–metal hybrid nanosystem. LUT/ZnO nanoparticles have been shown to increase hepatic insulin sensitivity via the activation of the PI3K/AKT signaling pathway and the suppression of FoxO1, thereby ameliorating insulin resistance. This therapeutic intervention increased hepatic function and antioxidant capacity while mitigating oxidative stress, effectively reducing the intrahepatic lipid content and circulating lipid profile. Notably, intrinsic PI3K/AKT pathway modulation by ZnO nanoparticles has been independently validated,[133] indicating that the synergistic combination of ZnO nanoparticles with luteolin significantly amplifies insulin resistance amelioration beyond monotherapeutic paradigms.

Organic/inorganic nanomedicines show promise in ameliorating MASLD-associated insulin resistance. ZnO nanoparticles allow precise physicochemical tuning (morphology/size/crystallinity) via solvent/pH/temperature control, optimizing bioactivity. ZnO outperforms conventional metal oxides in terms of biocompatibility and redox activity. The GOQD-HA nanocomposite synergizes the ROS scavenging ability of GOQDs[134,135] with the CD44-targeted anti-inflammatory effects of HA,[136] enabling dual therapeutic-carrier action: enhanced bioavailability, redox homeostasis modulation, and metabolic tissue targeting. Scalability challenges in nanomanufacturing (eg., GOQD-HA reaction kinetics) remain translational bottlenecks.

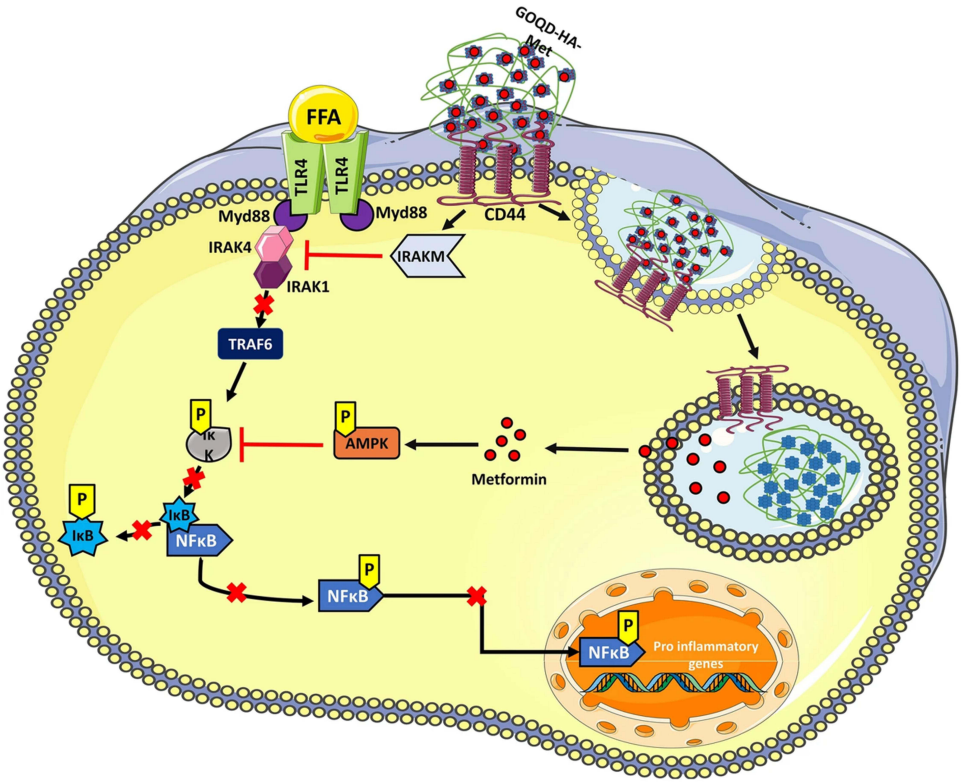


Figure 4 Proposed anti-inflammatory mechanism through which GOQD-HA-Met affects free fatty acid-induced macrophage activation. Reprinted with permission from BioMed Central. Sarkar K, Bank S, Chatterjee A et al Hyaluronic acid-graphene oxide quantum dots nanoconjugate as dual purpose drug delivery and therapeutic agent in meta-inflammation. Journal of Nanobiotechnology. 2023;21(1). Creative Commons.[127]

Several unresolved issues temper the promise of these insulin-sensitizing nanomedicines. The long-term biodegradation and tissue retention of inorganic nanomedicines such as ZnO and GOQD-HA remain poorly characterized, leaving uncertainty about their chronic safety. Moreover, the current data do not clearly elucidate whether improved insulin sensitivity stems from enhanced drug delivery or from direct signaling modulation by the nanomedicine itself (eg., ZnO-mediated PI3K/AKT activation). Most preclinical studies also rely on short-term efficacy end points, which may not capture the chronic, progressive nature of insulin resistance in human MASLD. Finally, the manufacturing complexity of systems such as GOQD-HA—particularly their sensitive reaction kinetics—poses practical barriers to batch-to-batch reproducibility and scale-up. Future progress will require systematic long-term toxicological evaluation, clearer mechanistic attribution of nanomedicine versus cargo effects, and the development of robust, scalable fabrication protocols before clinical translation can be realistically considered.

Application of Nanomedicines in the Treatment of MASLD with Relevant Gene Drugs

Key gene regulation and associated signaling pathway alterations are central to the pathogenesis and progression of MASLD.[137] Evidence suggests that targeted modulation of hepatic gene expression can effectively ameliorate lipid metabolism disorders and inflammation,[138] suggesting a promising treatment strategy for MASLD. However, in vivo gene therapy faces challenges such as delivery efficiency, biocompatibility, toxicity, and stability. An optimal delivery system must ensure precise targeting of genes to hepatocytes and minimize immune responses and toxicity, which is critical for enhancing the therapeutic efficacy, safety, and clinical translation of gene therapies.

MicroRNAs (miRNAs), noncoding RNAs approximately 22 nucleotides long, posttranscriptionally regulate gene expression and are vital for oxidative stress and liver lipid metabolism,[139] making them promising targets for MASLD treatment. Notably, miR-146b is significantly downregulated in the livers of MASLD mice and exerts anti-inflammatory effects by negatively regulating the Toll-like receptor 4 (TLR-4) signaling pathway and inhibiting hepatic steatosis.[140] He

et al[141] innovatively developed a lactosylated PDMAEMA (Lac-PDMAEMA) cationic polymer carrier, which complexes with miR-146b mimics to form a gene delivery system. The experimental results revealed that compared with free miR-146b mimics, the Lac-PDMAEMA complex exhibited superior hepatocyte targeting ability. Compared with those in the control group, the expression levels of peroxisome proliferator-activated receptor γ (PPARγ), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were significantly lower ($P<0.05$). Pathologically, H&E and Oil Red O staining revealed markedly reduced inflammation and lipid droplet formation, effectively alleviating hepatic steatosis in MASLD mice. This system represents a novel therapeutic strategy for MASLD intervention.

Mammalian sterile 20-like kinase 1 (MST1), a conserved serine/threonine kinase, is central to cell proliferation, differentiation, apoptosis, autophagy, and the immune response.[142–144] Additionally, it modulates hepatic lipid metabolism by regulating Sirt1 ubiquitination and ROS levels.[145–147] Li et al[148] developed redox-responsive Hep@PGEA polymeric nanoparticles. These nanoparticles, enriched with surface hydroxyl groups, exhibit prolonged systemic circulation and enable intelligent drug release triggered by high intracellular glutathione (GSH) concentrations in hepatocytes. This study confirmed that Hep@PGEA efficiently delivered MST1 to the livers of MASLD model mice. Compared with the control, activation of the AMP-activated protein kinase (AMPK)/sterol regulatory element-binding protein-1c (SREBP-1c) pathway significantly ameliorated insulin resistance, attenuated liver injury, and reduced hepatic lipid accumulation in MASLD mice ($P<0.05$). No adverse effects were observed, indicating strong potential for clinical application.

Circular RNAs (circRNAs), characterized by covalently closed-loop structures, contribute to the pathogenesis of MASLD through interactions with RNA-binding proteins or miRNAs.[149–151] Notably, circRNA_0001805 is significantly downregulated in MASLD.[152,153] To address this, Li et al[153] developed a glycyrrhetinic acid–zinc ion–based metal–organic framework (GZ) complexed with a circRNA_0001805 plasmid (designated GZ/PL). This complex was further encapsulated within a galactose-modified erythrocyte membrane to construct the targeted nanodrug GA-RM/GZ/PL (Figure 5). The delivery system specifically increased circRNA_0001805 levels in hepatocytes, where it competitively bound to miR-106a-5p and miR-320a, thereby regulating the expression of ATP-binding cassette transporter A1 (ABCA1) and carnitine palmitoyltransferase 1 (CPT1). Concurrently, it suppressed nuclear factor-kappa B (NF-κB) signaling, significantly mitigating lipid accumulation and inflammation in both free fatty acid (FFA)-treated primary hepatocytes and MASLD model mice. Furthermore, the GZ system—a MOF nanomedicine—exhibits dual functionality: its synthesis is facile, and the glycyrrhetinic acid ligand confers intrinsic anti-MASLD bioactivity (eg., attenuating lipid dysmetabolism and inflammation). This synergistic design overcomes the limitations of conventional carriers by integrating gene delivery with bioactive components.

Overall, nanomedicine is revolutionizing drug delivery, with advantages such as precise targeting, reduced systemic toxicity, and increased bioavailability.[27] These systems, typically fabricated through mechanical processing or bottom-up self-assembly, can overcome biological barriers such as epithelial and endothelial layers, enabling efficient delivery of macromolecular and poorly soluble therapeutics.[154,155] The targeted accumulation and controlled release features significantly improve treatment precision and efficacy. By delaying renal clearance and hepatic metabolism, they also prolong circulation time, collectively leading to a broader therapeutic window, reduced side effects, and better treatment outcomes.[156,157]

There is often a gap between sophisticated design and practical reality in these gene delivery studies. Cationic polymers such as Lac-PDMAEMA and MOF-based systems such as GZ work reasonably well in simplified models, but their transfection efficiency in real liver tissue remains modest, and off-target gene modulation in organs such as the gut or spleen has rarely been examined. Immunogenicity is another concern—these carriers and their nucleic acid payloads could trigger innate immune responses, especially given that chronic MASLD would likely require repeated dosing. The long-term tissue fate of non-biodegradable or slowly degrading carrier materials is also poorly understood, leaving chronic toxicity largely uncharacterized. Even the delivered genes themselves have unclear intracellular fates, whether they persist as episomes, integrate into the host genome, or are rapidly degraded. Manufacturing complexity adds a further hurdle, as multi-component systems such as erythrocyte membrane-camouflaged MOFs demand stringent quality control and scalable production methods. Getting these gene nanomedicines to actual MASLD patients will require these mundane but critical problems to be solved first.

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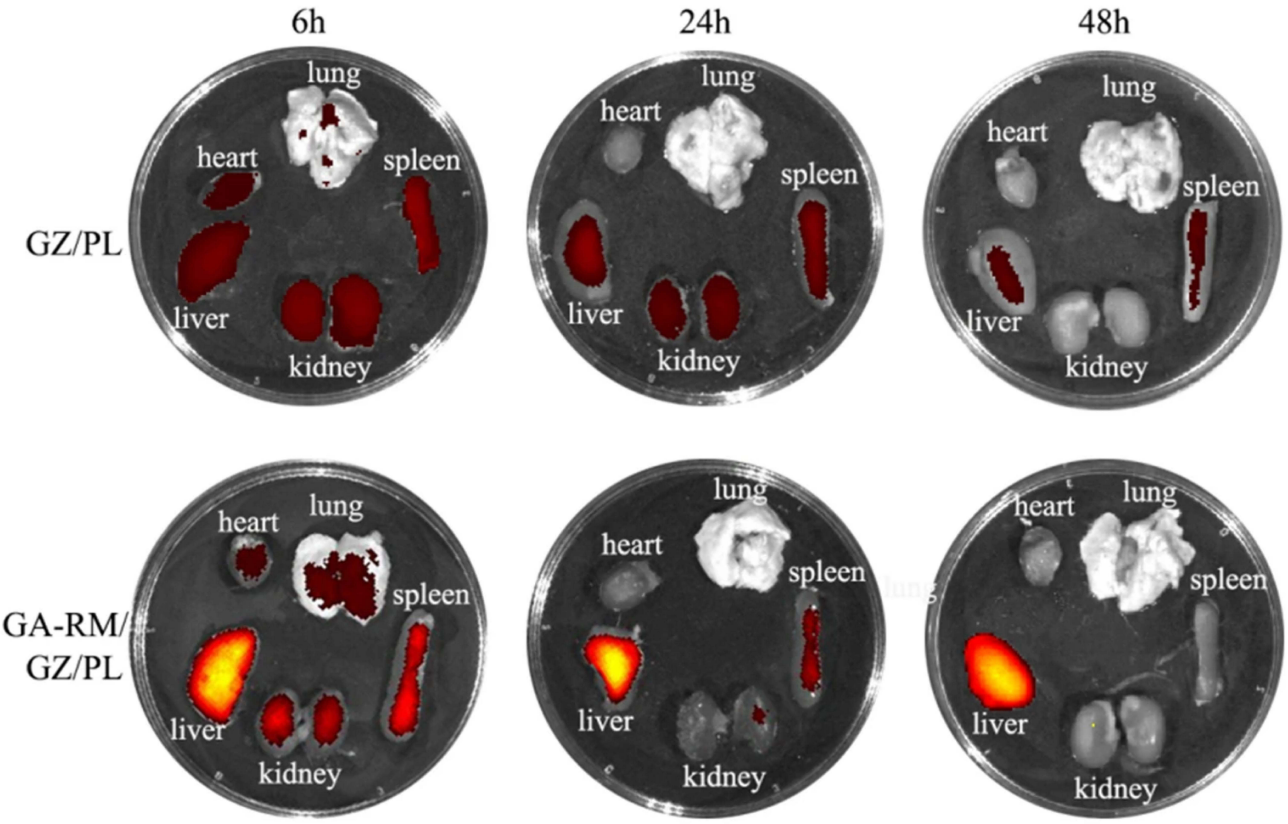

Figure 5 Fluorescence images of the main organs upon treatment with GZ/PL and GA-RM/GZ/PL for 6 h, 24 h and 48 h. Reprinted with permission from Li J, Qin J, Tang Y, et al A nanodrug system overexpressed circRNA_0001805 alleviates nonalcoholic fatty liver disease via miR-106a-5p/miR-320a and ABCA1/CPT1 axis. J Nanobiotechnology. 2021;19:373. Licensed under CC BY 4.0.[153]

Biological Effects of Nanomedicines: Beyond Drug Delivery

Carriers as Functional Therapeutic Units

Emerging evidence has demonstrated that nanomedicines function not only as passive delivery vehicles but also as active therapeutic components capable of modulating hepatic pathophysiology through intrinsic biological activities. Zinc oxide nanoparticles (ZnO NPs) exemplify this paradigm and exhibit potent hepatoprotective effects via the SIRT1-LKB1-AMPK signaling axis. In high-fat-diet-fed mice, ZnO NPs significantly attenuated hepatic steatosis by restricting SREBP-1c within the cytosol, thereby ameliorating de novo lipogenesis independent of any drug cargo.[158] This intrinsic metabolic regulatory activity positions ZnO NPs as dual-action therapeutic platforms that simultaneously serve as delivery vehicles and direct modulators of lipid metabolism.

Graphene oxide (GO) nanoparticles demonstrate remarkable intrinsic antioxidant and anti-inflammatory capabilities that are relevant to MASLD pathogenesis. GO exhibits exceptional ability to scavenge reactive oxygen species (ROS) and increase superoxide dismutase activity, leading to decreased oxidative stress and activation of the Nrf2/HO-1 antioxidant pathway.[159] Notably, GO also regulates macrophage polarization toward the anti-inflammatory M2 phenotype and reduces lipotoxicity through the downregulation of SREBP-1c expression, thereby addressing multiple pathological hallmarks of MASLD simultaneously.

Chitosan-based nanoparticles possess inherent immunomodulatory properties that complement their drug delivery functions. These carriers exhibit mucoadhesive characteristics ideal for oral delivery and can modulate gut microbiota–liver axis homeostasis, attenuating MASLD progression through the restoration of intestinal barrier function and the suppression of TLR4-mediated hepatic inflammation.[160] The modulation of the gut–liver axis represents a unique carrier-intrinsic mechanism that extends therapeutic impact beyond direct hepatic drug delivery.

Carrier–Drug Synergistic Mechanisms

The therapeutic efficacy of nanomedicines frequently exceeds the sum of individual carrier and drug effects through mechanistic synergy in MASLD treatment. Lipid nanoparticles (LNPs) illustrate this principle through apolipoprotein E (ApoE)-mediated hepatocyte targeting. Upon intravenous administration, LNPs bind serum ApoE, which drives structural rearrangement and enables specific recognition by hepatocyte LDL receptors, facilitating efficient cellular uptake.[161] This intrinsic targeting mechanism ensures that encapsulated drugs (such as siRNA against SREBP-1c or silibinin) achieve concentrated hepatic delivery that would be impossible with free drug administration.[162]

The interaction between carrier physicochemical properties and biological responses creates opportunities for optimized MASLD therapy. ZnO NPs combined with luteolin demonstrate synergistic insulin-sensitizing effects: ZnO provides intrinsic PI3K/AKT pathway activation and FoxO1 suppression, whereas luteolin contributes to flavonoid-mediated anti-inflammatory effects, resulting in enhanced metabolic benefits exceeding those of monotherapeutic paradigms.[132] Similarly, glycyrrhetinic acid-zinc MOF systems integrate the intrinsic anti-inflammatory and antistalkatotic properties of glycyrrhetinic acid with gene delivery functionality, achieving dual therapeutic action through both carrier ligand bioactivity and nucleic acid cargo.[163]

Covalent organic frameworks (COFs) exemplify carriers as functional therapeutic units, enabling programmable drug delivery through tunable pore structures and stimuli-responsive release mechanisms tailored to pathological hepatic microenvironments.[164] Their structural versatility permits the integration of ROS-responsive linkages for targeted release under MASLD-specific oxidative stress conditions. Bioactive hydrogels (Bio-HyGs) represent another innovative class of carriers with inherent therapeutic bioactivity. By combining three-dimensional polymeric networks with intrinsic biological activities, these platforms enable sustained drug release while providing tissue engineering scaffolds for cellular regeneration. Their stimuli-responsive gelation and degradation mechanisms make them particularly suitable for chronic liver diseases requiring prolonged intervention and tissue remodeling.[165]

However, the dose-dependent hepatotoxicity of certain carriers necessitates careful safety evaluation. Silica nanoparticles (SiNPs) at doses exceeding 3 mg/kg body weight aggravated MASLD progression in ApoE-deficient mice through amino acid metabolism disturbance and oxidative stress exacerbation, demonstrating that carrier-intrinsic effects can be deleterious when exposure thresholds are exceeded.[166] These findings underscore the critical importance of comprehensive safety profiling that distinguishes therapeutic carrier concentrations from potentially harmful doses.

The recognition of carriers as functional therapeutic units necessitates revised evaluation frameworks for nanomedicine development in MASLD. Future designs should strategically exploit carrier-intrinsic bioactivities—whether metabolic regulatory, antioxidant, or immunomodulatory—to complement drug mechanisms and achieve superior therapeutic indices while maintaining rigorous safety standards.

Clinical Translation: Reality and Challenges

Although nanomedicines have demonstrated significant potential to enhance therapeutic efficacy and drug utilization in MASLD treatment (Table 3), their clinical translation continues to face a series of profound challenges. Despite substantial investment and encouraging laboratory findings, no nanomedicine-based therapy has yet achieved regulatory approval specifically for MASLD, underscoring the complexity of this translational pathway.

Clinical-Stage Nanomedicines

While MASLD-specific nanotherapies remain in development, the clinical success of hepatic-targeted nanomedicines for other indications provides valuable translational insights. Six small interfering RNA (siRNA) drugs have received FDA approval since 2018, all of which leverage liver-targeted delivery: patisiran (Onpattro), givosiran (Givlaari), lumasiran (Oxlumo), inclisiran (Leqvio), vutrisiran (Amvuttra), and nedosiran (Rivfloza).[167] These therapeutics predominantly utilize lipid nanoparticles (LNPs) or GalNAc conjugation to achieve hepatocyte-specific delivery, establishing a proof of concept for hepatic nanomedicine translation.

The inclisiran (Leqvio) case exemplifies successful clinical translation: this LNP-formulated siRNA targeting PCSK9 demonstrates that robust manufacturing scalability, well-defined pharmacokinetics, and clear clinical endpoints can

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Table 3 Examples of the Application of Nanomedicines in MASLD Drug Therapy

Treatment Strategies	Nanomedicines	Delivered Drugs	Therapeutic Efficacy	Route of Administration	Animal Model	Treatment Duration	Cell Distribution Data	Comparative Effectiveness	Ref.
Lipid-lowering therapy	β-Cyclodextrin Nanospheres	Atorvastatin Calcium	AC-NS effectively enhance the oral bioavailability of AC, decrease the concentration of blood lipids in mice, and ameliorate liver steatosis.	Oral gavage	Fatty liver rats (HFD)	Pharmacokinetic study	No data	Yes vs. plain AC	[77]
	Nanoliposomes	Fenofibrate	The FNB-Nanolipo could not only significantly prevent but also efficiently treat MASLD.	Intraperitoneal	MCD diet mice	7 days (20 mg/kg)	Yes Hepatic uptake	Yes vs. free FNB	[72]
	Polyurethane nanoparticles	Fenofibrate	Compared with FNB crude drugs, FNB-PU has higher drug loading and sustained release ability, which can enhance cell uptake of FNB and reduce lipid accumulation in liver more significantly.	Oral gavage	MCD diet mice	In vivo study	Yes HepG2 cells	Yes vs. crude FNB	[73]
	Formation of nanoparticles based on OVE and DSPE-PEG	Fenofibrate	FNB-NP promoted the release of FNB in the liver and significantly reduced the lipid deposition in the liver. At the same time, the oxidative stress of MASLD was significantly inhibited after administration of FNB-NP.	Intravenous	MCD diet mice	In vivo study	Yes Liver targeting	Yes vs. FNB alone	[74]
	PBP-NPs	Inducers of heme oxygenase-1	PBP-NPs are found to target prohibitin overexpressed fatty liver in the MASH model and inhibit hepatic uptake of circulating lipids.	Intravenous (tail vein)	MASH mice (HFD+fructose)	4 weeks (once weekly)	Yes vWAT targeting	Yes vs. free HO-1	[80]
Anti-inflammatory and antioxidant therapy	LPNs (CS-LPNs)	Silymarin	After CS-LPNs treatment, the blood lipid level (TG) was effectively reduced, the liver function (AST and ALT) was improved, and the lipid accumulation in the liver was reduced.	Oral gavage	PNPLA3 1148M transgenic mice (HFD)	In vivo study	Yes HepG2 uptake	Yes vs. silymarin susp.	[100]
	Nanolipid carriers (NLC)	Naringenin	NLC preparation significantly enhanced the inhibitory effect of NGN on MASLD, and increased oral bioavailability and liver NGN distribution.	Oral gavage	MCD diet mice	1 week (12.5 mg/kg)	Yes Liver distribution	Yes vs. NGN crude	[107]
	Gly-LA-Lac	Resveratrol	ResNPs showed liver targeting and redox reaction release behavior, which improved the liver injury of nonalcoholic fatty liver mice.	Oral gavage	HFD-induced MASLD mice	6 weeks (100 mg/kg)	Yes HepG2/L02 uptake	No data	[94]
	Nanolipid carriers (NLC)	Active vitamin D3	At safe doses where free vitamin D3 did not show efficacy, NLC inhibited intestinal permeability and improved MASH symptoms.	Oral application	MCD diet MASH mice	In vivo study	Yes Intestine/Liver	Yes vs. free vit D3	[113]

Improve insulin resistance therapy	ZnO	Luteolin	LUT/ZnO nanoparticles can effectively reduce hyperglycemia and hyperinsulinemia, improve insulin resistance and liver function, and reduce the markers of oxidative stress.	Intraperitoneal	HFD+STZ diabetic rats	12 weeks	Yes Hepatic uptake	Yes vs. luteolin alone	[132]
	GOQD-HA	Metformin	GOQD-HA-Met successfully downregulated the expression of pro-inflammatory cytokines and restored antioxidation at lower doses.	Oral gavage	HFD-fed mice	10 days	Yes RAW264.7 uptake	Yes vs. free Metformin	[127]
Gene therapy	Lac-PDMAEMA	miR-146b	Lac-PDMAEMA/miR-146b mimetic administration reduced mRNA levels of tumor necrosis factor-α and IL-6 compared to controls, effectively reducing hepatic steatosis in MASLD mice.	Intravenous (tail vein)	MCD diet MASLD mice	In vivo study	Yes Hepatocyte targeting	Yes vs. controls	[141]
	Hep@PGEA	MST1	Hep@PGEA vector can effectively deliver concentrated functional nucleic acid MST1 to liver of MASLD mice, upregulate MST1 expression, significantly improve liver insulin resistance sensitivity, reduce liver injury and lipid accumulation.	Intravenous (tail vein)	HFD-induced MASLD mice	3 weeks (once weekly)	Yes Liver enriched	Yes vs. PBS control	[148]
	Glycyrrhizic acid and zinc ion (GZ)	circRNA_0001805	The nanopharmaceutical system (GA-RM/GZ/PL) was able to specifically overexpress circRNA_0001805 in hepatocytes, effectively reducing lipid droplet accumulation, lipid metabolism disorder and inflammation in MASLD mice.	Intravenous (tail vein)	HFD-fed mice	In vivo study	Yes Hepatocytespecific	Yes vs. glycyrrhizic acid	[153]

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overcome regulatory hurdles. However, critical distinctions exist between these successes and MASLD nanomedicine development. Approved siRNA therapeutics target rare genetic diseases or cardiovascular indications with unambiguous biomarkers, whereas MASLD presents heterogeneous pathophysiology with complex, multifactorial etiology lacking single molecular targets.[163]

Current MASLD therapeutic development has witnessed both breakthroughs and setbacks. Resmetirom, a thyroid hormone receptor-β agonist (not a nanomedicine), became the first FDA-approved therapy for noncirrhotic MASH with moderate-to-advanced fibrosis in March 2024, establishing histological endpoints (MASH resolution and fibrosis improvement) as viable regulatory pathways.[163] Semaglutide received FDA approval for MASH treatment in August 2025, further validating metabolic modulation strategies. These approvals intensify the competitive landscape for nanomedicine approaches, which must demonstrate clear advantages over these established oral therapies.

Animal Models: Strengths and Limitations

The predominant reliance on animal models for preclinical validation of MASLD nanomedicine presents substantial translational risks. Current literature overwhelmingly cites studies using a methionine-choline deficient (MCD) diet, a high-fat diet (HFD), or genetic models (ob/ob, db/db mice), yet a systematic discussion of their applicability limitations remains inadequate.[168]

The MCD diet model induces rapid, severe steatohepatitis via impaired β-oxidation and altered lipoprotein secretion, leading to oxidative stress and inflammatory cascades reminiscent of human MASH. However, fundamental metabolic discrepancies undermine its translational validity: MCD-fed animals develop disease without obesity, insulin resistance, or dyslipidemia—the core features of human MASLD. This disconnect likely explains the recurrent pattern of promising preclinical efficacy followed by clinical failure.

The Ldlr-/-. The Leiden mouse model, which involves obesity-associated metabolic dysfunction, has been proposed to be more translationally relevant. However, even when this advanced model failed to predict cenicriviroc (CVC) clinical outcomes, whereas CVC demonstrated antifibrotic efficacy in multiple preclinical models, the Phase 3 AURORA trial was terminated after one year because of a lack of improvement in fibrosis.[169] This discrepancy highlights that macrophage-driven mechanisms in murine fibrosis may not accurately reflect human MASH pathophysiology, where metabolic and immune pathways exhibit greater complexity.[170]

Species-specific pharmacokinetic differences further complicate translation. Physiologically based pharmacokinetic modeling has demonstrated that while plasma exposure may scale reasonably across mice, rats, and dogs, hepatic and splenic nanoparticle distribution kinetics differ substantially.[171] Compared with human hepatocytes, mouse liver sinusoidal cells exhibit distinct endocytic capacities and protein corona formation patterns, potentially altering targeted delivery efficiency. Kupffer cell density varies two- to threefold between species, affecting nanoparticle clearance and hepatocyte accessibility.

Disease severity mismatch represents another critical limitation. Preclinical models typically produce severe, rapidly progressive disease amenable to dramatic therapeutic intervention, whereas human MASLD evolves over decades with substantial interpatient variability. The efficacy of nanomedicine demonstrated in acute, severe murine models may overestimate the clinical benefit in slowly progressive human disease with established compensatory mechanisms.

Long-Term Biosafety of Nanomedicines

The evaluation framework for long-term nanomedicine biosafety remains underdeveloped, presenting significant obstacles to clinical translation. While acute toxicity assessments are routinely performed, chronic exposure risks associated with repeated nanomedicine administration require more comprehensive characterization.

Despite being considered among the most biocompatible nanomaterials, gold nanoparticles (AuNPs) demonstrate prolonged hepatic retention with the potential for subtle chronic toxicity. Long-term biodistribution studies revealed that 20 nm spherical AuNPs maintained substantial tissue levels at 120 days post-administration, with only a 39% reduction in hepatic burden despite minimal circulating concentrations.[172] This persistent accumulation induces low-grade, non-resolving inflammation characterized by fibrotic remodeling, extracellular matrix deposition, and a disrupted sinusoidal

architecture that may impair hepatic function and drug metabolism over time.[173] Importantly, these pathological changes often remain undetected in short-term toxicological assessments focused on acute cytotoxicity or organ burden.

Nickel-containing nanoparticles illustrate dose-dependent toxicity concerns relevant to metal-based nanomedicine development. These materials exhibit cytotoxicity, genotoxicity, and carcinogenicity in lung tissues, with IC_{50} values ranging from 10–100 μg/mL, but preferentially accumulate in the liver, spleen, and kidneys, with elimination half-lives exceeding 30 days.[174] Released metal ions may interfere with intracellular calcium homeostasis and disrupt mitochondrial function, generating oxidative stress and inflammatory responses even at sublethal doses. Carbon nanoparticles (CNPs) induce hepatotoxicity characterized by dose-dependent hepatocyte vacuolation, sinusoidal congestion, and inflammatory infiltration.[175] These findings underscore that even "inert" carbon-based materials can provoke immune reactions and cellular degeneration upon chronic hepatic accumulation.

For MASLD specifically, where patients may require years of continuous therapy, these chronic toxicity risks are highly significant. The subtle immune alterations and fibrotic changes induced by long-term nanoparticle exposure could paradoxically exacerbate the very disease processes that nanomedicines aim to treat. Comprehensive safety assessments must extend beyond traditional acute toxicity endpoints to evaluate immune remodeling, histopathological changes, and recovery of immune competence following prolonged nanoparticle exposure.

Lessons from Failed Development

A critical analysis of discontinued development programs provides essential guidance for future MASLD nanomedicine design. The cenicriviroc (CVC) case represents the most instructive failure: Despite promising Phase 2b CENTAUR results showing fibrosis improvement without worsening steatohepatitis, the phase 3 AURORA study (n=1,778) was terminated because of a lack of efficacy.[163] This failure likely reflects the complexity of MASH pathogenesis involving diverse immune and metabolic pathways that single-target approaches cannot adequately address.[176] The translational disconnect between robust preclinical efficacy and clinical failure emphasizes that murine macrophage-driven fibrosis mechanisms differ fundamentally from those of human disease, where multiple compensatory pathways may offset single-target inhibition.[170]

The MRX34 liposomal miR-34a mimic trial (NCT01829971) illustrates RNA nanoparticle-specific failure modes. This study was terminated in 2016 following four treatment-related deaths among 85 patients, with adverse events including sepsis, cytokine release syndrome, and liver failure.[177] These severe toxicities were attributed not to the liposomal carrier (SMARTICLES®), which had proven safe in other trials, but to the unmodified miRNA payload that triggered excessive immune activation. This case highlights that nanomedicine safety does not ensure therapeutic safety when complex biological payloads are involved and that chemical modifications (eg., 2′-O-methylation) may be essential for suppressing the immunogenicity of RNA-based nanomedicines. Manufacturing and scalability challenges have terminated multiple development programs. The Translate Bio mRNA nanoparticle trial (NCT03767270) for ornithine transcarbamylase deficiency was withdrawn in September 2019 because of poor pharmacokinetics and concerning safety profiles observed in preclinical studies, highlighting how inadequate formulation optimization can preclude clinical advancement. Alnylam's reformulation of DLinDMA to DLin-MC3-DMA ionizable lipids increased therapeutic efficacy by two orders of magnitude, demonstrating that subtle chemical modifications determine clinical viability.

For MASLD nanomedicine specifically, these failures suggest several critical design principles: (1) multitarget approaches addressing metabolic, inflammatory, and fibrotic pathways simultaneously may be necessary given disease heterogeneity; (2) rigorous immunogenicity assessment is essential for nucleic acid-containing formulations; (3) manufacturing scalability and batch consistency must be established early in development; and (4) clinically relevant endpoints (histological MASH resolution and fibrosis improvement) should be prioritized over biochemical markers alone. The path forward requires the integration of advanced preclinical models—including human organoids and microfluidic liver-on-a-chip systems—with rigorous manufacturing protocols and early engagement with regulatory frameworks. Only through systematic addressing of these translational bottlenecks can nanomedicine realize its theoretical potential for MASLD treatment (Figure 6).

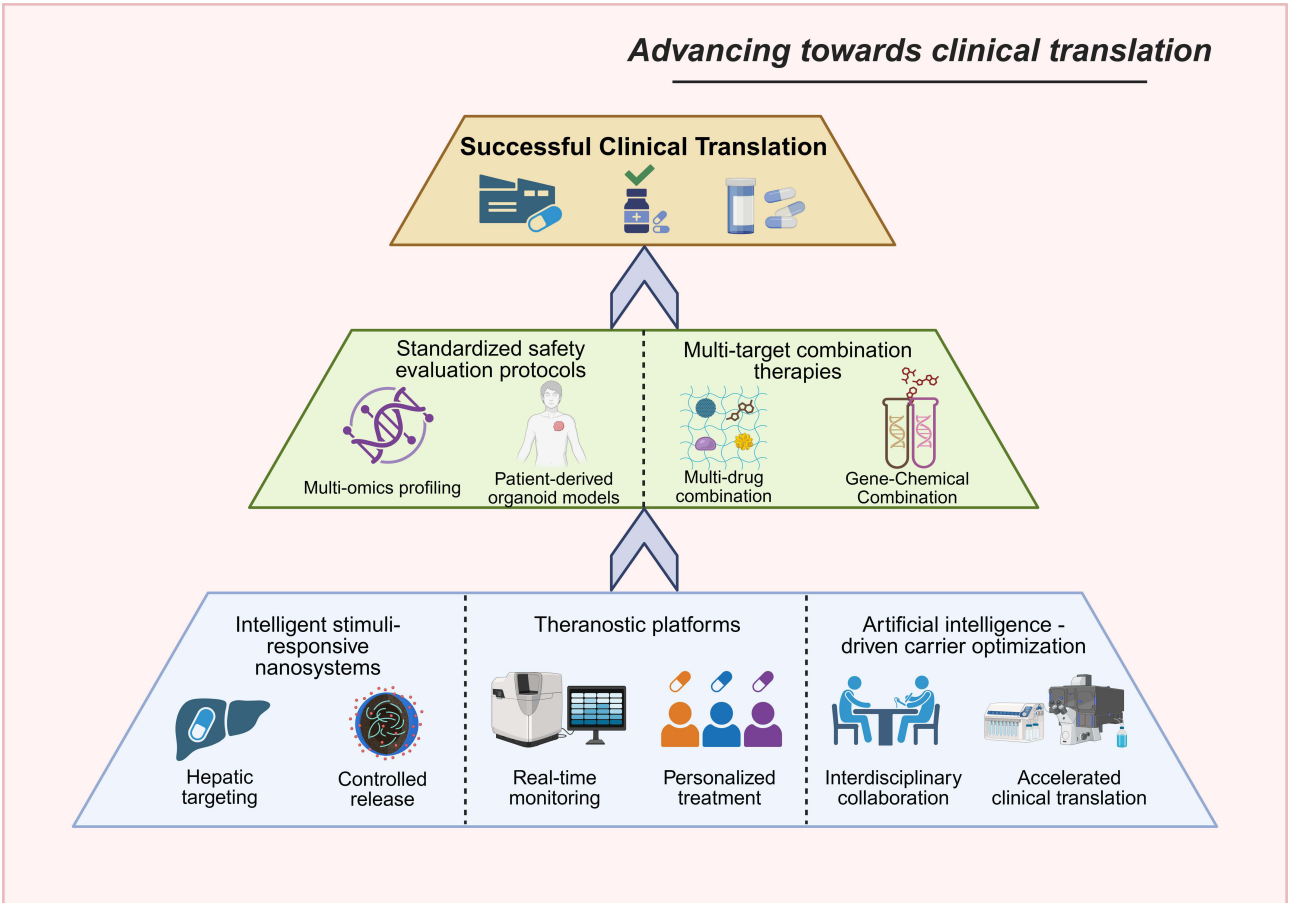

Figure 6 Future path of nanomedicine in the clinical management of MASLD. Created with BioRender.com.

Conclusion

The current clinical landscape for MASLD has been fundamentally reshaped by the 2024 FDA approval of resmetirom and the 2025 approval of semaglutide for MASH with fibrosis. These milestones establish histological endpoints—NASH resolution and fibrosis improvement—as viable regulatory pathways while simultaneously intensifying the competitive pressure on nanomedicine approaches. To achieve clinical relevance, nanotherapeutics must demonstrate clear differentiation from these oral standards: addressing nonresponders to semaglutide/resmetirom, enabling combination regimens that simultaneously target multiple pathological hits, or providing theranostic capabilities for real-time treatment monitoring.

Translational realism demands acknowledgment that MASLD nanomedicine remains predominantly preclinical. On the basis of current development trajectories and regulatory requirements, we project the following: near-term (2025–-2028) opportunities for repurposing approved hepatic nanomedicines (eg., siRNA-LNPs) from rare diseases to MASLD subpopulations with defined genetic drivers; medium-term (2028–2032) entry of first-generation MASLD-specific nanotherapeutics into Phase II–III trials, contingent upon the resolution of manufacturing scalability and the establishment of long-term safety databases; and long-term (post-2032) realization of personalized nanomedicine integrating AI-assisted design, patient stratification biomarkers, and closed-loop theranostic systems. This timeline assumes successful resolution of critical bottlenecks: human-relevant preclinical models, standardized regulatory frameworks for complex nanomaterials, and demonstrated cost-effectiveness against emerging oral competitors.

Priority future directions should focus on four domains: (1) intelligent carrier design leveraging machine learning to predict structure–activity relationships and optimize multiparameter performance; (2) theranostic integration combining diagnostic imaging with therapeutic delivery to enable dynamic, personalized treatment adjustment based on real-time

liver tissue responses; (3) combination nanoplatforms codelivering metabolic modulators, anti-inflammatory agents, and antifibrotics to address MASLD heterogeneity more effectively than single-mechanism approaches; and (4) advanced preclinical validation incorporating human organoid systems and microphysiological models to improve translational predictability beyond conventional animal studies.

The path from laboratory concepts to clinical reality for MASLD nanomedicine is measured in decades, not years. Success requires sustained commitment to mechanistic understanding, rigorous safety evaluation, and collaborative engagement with regulatory frameworks—positioning nanotechnology not as a revolutionary displacement of existing therapies but as an incremental yet potentially transformative contributor to the evolving MASLD therapeutic armamentarium.

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Disclosure

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