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Review Article

Recent Advances in Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): An update

Tina Ghaffari [#], Arash Bahramzadeh [#], Reza Meshkani*

Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
 # Both authors contributed equally to this work

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* **Corresponding Author:**

Reza Meshkani
Dpartment of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Email: rmeshkani@tums.ac.ir

ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most prevalent chronic liver disorder worldwide, closely linked to obesity, insulin resistance, and type 2 diabetes mellitus. Despite its rising global burden, there are currently no approved pharmacological therapies targeting MASLD pathogenesis directly. Polyphenolic compounds have demonstrated promising hepatoprotective, antioxidant, and anti-inflammatory properties in preclinical models; however, their poor stability, limited solubility, and low bioavailability hinder clinical translation. This review summarizes the latest advances in nano-drug delivery systems (NDDSs) designed to enhance the therapeutic potential of polyphenols in MASLD. Various nanocarrier platforms, including inorganic, lipid-based, polymeric, and hybrid nanosystems, are discussed with emphasis on their mechanisms of action, pharmacokinetic advantages, hepatocyte-targeting strategies, and translational challenges. Emerging NDDSs markedly enhance polyphenol pharmacodynamics through enhanced intestinal absorption, controlled release, and targeted hepatic accumulation. Lipid-based carriers (liposomes, solid lipid nanoparticles, nanoemulsions, and nanostructured lipid carriers) demonstrate excellent oral bioavailability and safety, whereas polymeric and inorganic systems offer multifunctional therapeutic synergy by modulating oxidative stress, lipid metabolism, and inflammatory pathways. Recent clinical evidence, including nano-micellar curcumin formulations, suggests translational feasibility and safety in MASLD patients. Nevertheless, long-term biosafety, scalability, and interindividual variability remain key challenges for clinical application. Therefore, polyphenols loaded with nanocarrier systems offer a multifaceted therapeutic approach to address the complex metabolic, inflammatory, and fibrotic processes underlying MASLD. Future research should prioritize clinical validation, mechanistic standardization, and regulatory alignment to enable the transition from preclinical innovation to precision nanomedicine in metabolic liver diseases.

Keywords: MASLD, NAFLD, polyphenols, nano-drug delivery systems (NDDSs)

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Introduction

Metabolic-dysfunction-associated steatotic liver disease (MASLD) is a range of disorders characterized by an abnormal accumulation of fat in the liver, excluding causes related to alcohol consumption or other specific damaging factors. Previously, this condition was known as non-alcoholic fatty liver disease (NAFLD), and later, the term metabolic-associated fatty liver disease (MAFLD) was introduced to emphasize its metabolic basis before being redefined as MASLD. The spectrum of NAFLD encompasses simple steatosis and non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver cancer (1). The 2023 Delphi consensus redefined NAFLD to MASLD, which now more accurately reflects its strong association with metabolic dysregulation. MASLD is the most common chronic liver disease worldwide, affecting approximately one billion individuals (2). Metabolic risk factors such as obesity, diabetes, and hypertension are associated with the beginning of MASLD. It was estimated that the prevalence of MASLD in people with type 2 diabetes mellitus (T2DM) is 55.48%, and in obese people, it can reach 64.36% (3). With the substantial increase in obese individuals, it is expected that the prevalence of MASLD will continue to rise and affect over 30% of the global population (4). MASLD may gradually progress to more serious liver pathologies. Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as NASH, is a more severe stage of MASLD that affects 20% of people with simple steatosis. MASH can further progress to cirrhosis and eventually hepatocellular carcinoma (HCC) (5). The pathophysiology of MASLD is complex and multifactorial, involving hepatic lipid accumulation, lipotoxicity, insulin resistance, dysregulation of nuclear receptor signaling, adipose tissue dysfunction, and chronic low-grade inflammation (6).

Pathogenic Mechanisms in MASLD

Triglyceride Accumulation and Lipotoxicity

The fundamental mechanism underlying the pathogenesis of MASLD is the disruption of hepatic energy homeostasis. Under normal conditions, the liver plays a pivotal role in regulating the metabolism of dietary carbohydrates and lipids. However, sustained exposure to energy-dense diets, particularly those rich in fructose, sucrose, and saturated fats, can overwhelm hepatic metabolic capacity. The consequent excess of carbohydrates promotes *de novo* lipogenesis, while increased fatty acid (FA) intake enhances FA esterification, together leading to excessive hepatic triglyceride (TG) accumulation (5, 7). Increased fat consumption causes the liver to receive more FAs, which encourages FA esterification and the production of more hepatic triglycerides. Hepatic accumulation of lipids and triglycerides triggers lipotoxicity, mitochondrial dysfunction, and oxidative stress, ultimately resulting in cell dysfunction and death. Hepatocytes are eventually damaged by the persistently elevated level of hepatic lipids, which contributes to the pathophysiology of MASLD and MASH (8).

Insulin Resistance

Insulin resistance is now recognized as one of the earliest molecular disturbances driving disease onset (9). Defective insulin signaling in hepatocytes and adipocytes promotes *de novo* lipogenesis and enhances adipose tissue lipolysis, resulting in a sustained influx of free fatty acids (FFAs) to the liver (10). At the molecular level, hepatic accumulation of diacylglycerols (DAGs) activates protein kinase C-ε (PKC-ε), which inhibits insulin receptor kinase activity and exacerbates insulin resistance (11). In parallel, inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), along with oxidative and endoplasmic reticulum stress, activate c-Jun N-terminal kinase (JNK), further impairing insulin signaling (12). This dysregulation contributes to both glucotoxicity and lipotoxicity, two key drivers of hepatic injury. From a therapeutic perspective, improving insulin sensitivity through glucagon-like peptide-1 (GLP-1) receptor agonists has demonstrated promise by enhancing glucose uptake in insulin-dependent tissues and attenuating hepatic lipid accumulation (13).

Nuclear Receptor Signaling

Nuclear receptors, such as farnesoid X receptor (FXR) and peroxisome proliferator–activated receptors (PPARs), play a crucial role in coordinating lipid and glucose metabolism, and their dysregulation is central to MASLD pathogenesis (14). FXR, the principal receptor for bile acids, regulates TG, glucose, and bile acid metabolism in the liver. Activation of FXR suppresses hepatic lipogenesis and enhances FA β-oxidation while stimulating the secretion of fibroblast growth factors 19 (FGF19) and FGF21, both of which contribute to improved hepatic lipid handling and reduced steatosis. Additionally, FXR activation downregulates gluconeogenic mediators such as peroxisome proliferator-activated receptor coactivator-1α (PGC-1α), phosphoenolpyruvate carboxykinase (PEPCK), and glucose 6-phosphatase (G6Pase), thereby attenuating hepatic glucose production (15). The PPAR family, consisting of three isoforms (PPAR-α, PPAR-δ, and PPAR-γ), forms heterodimers with the retinoid X receptor (RXR) to regulate gene transcription involved in lipid metabolism, inflammation, and energy balance (16). PPAR-α, is predominantly expressed in the liver and skeletal muscle, stimulates FA oxidation and ketogenesis, while PPAR-γ enhances lipid storage in adipocytes and improves insulin sensitivity through

redistribution of FAs from the liver to adipose tissue. PPAR-δ facilitates lipid metabolism and suppresses hepatic gluconeogenesis. Collectively, PPAR activation exerts anti-steatotic, anti-inflammatory, and insulin-sensitizing effects, highlighting these nuclear receptors as promising therapeutic targets for both MASLD and MASH (17).

Therapeutic Interventions Against MASLD

Given the high global burden, complex pathophysiology, and systemic impact of MASLD, there is an urgent need for effective therapeutic strategies and clear treatment recommendations. The primary therapeutic approaches in the early stages are lifestyle modification, weight reduction, moderate exercise, and metabolic abnormality correction (18). Hepatic steatosis can generally be reduced by 3% to 5% weight loss, while hepatic inflammation requires an additional 5% to 10% weight loss. Patients with MASLD are advised to consume a Mediterranean diet low in fructose and high in fiber, fruits, whole grains, and polyunsaturated and/or monosaturated FAs in order to manage their condition (19). Additionally, in patients with biopsy-proven MASH, pioglitazone and vitamin E have been demonstrated to attenuate hepatic steatosis, inflammation, and damage. However, there is insufficient clinical data to draw conclusions about the safety and effectiveness of long-term pioglitazone and vitamin E use in patients (20).

MASH is the most crucial stage requiring medication management, whether or not there is fibrosis. At present, comprehensive treatments that address comorbidities or non-pharmacological treatment are recommended (21). MASLD treatment requires multidisciplinary collaboration, including dietary modification and increased physical activity, reducing body mass and waist size, improving insulin resistance, preventing and treating metabolic syndrome, maintaining blood glucose homeostasis, alleviating MASH, and reversing fibrosis (22). In 2024, the FDA approved resmetirom, a thyroid hormone receptor β (THR-β) agonist, as an adjunct to diet and exercise for treating adult patients with non-cirrhotic NASH and moderate to advanced fibrosis (stages F2–F3) (23). Despite this advancement, no pharmacological therapy has yet been approved for MASLD/NAFLD itself. Currently, no specific agent has been approved for NAFLD, except for lifestyle modifications like exercise and calorie restriction. Medications such as fibrates, statins, metformin, GLP-1 receptor agonists, insulin sensitizers, and vitamin E are specifically reserved for high-risk patients after a thorough assessment of the potential risks and benefits. Natural compounds like curcumin (24) and resveratrol (25) have gained interest for their potential to treat various conditions, but their effectiveness in clinical settings is limited due to insufficient oral absorption, inadequate water solubility, and unpredictable results . This highlights the necessity for advanced drug delivery systems that can facilitate the regeneration of liver cells and restore normal physiological functions.

Polyphenolic Compounds

Plant-based foods contain a wide variety of secondary metabolites, with polyphenols being a particularly abundant and nutritionally crucial class of phytochemicals (26). Based on chemical structures, natural polyphenols can be chemically divided into several classes, including flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols. Extensive preclinical and clinical research has demonstrated that polyphenols exhibit diverse hepatoprotective effects that are highly relevant to MASLD prevention and management. These compounds modulate lipid metabolism by suppressing TG synthesis and enhancing FA β-oxidation, improving insulin sensitivity, and exerting anti-inflammatory effects while also regulating the gut microbiota—collectively targeting key mechanisms involved in MASLD pathogenesis (27).

At the molecular level, polyphenols exert their effects through a number of interconnected pathways, including the suppression of *de novo* lipogenesis via the downregulation of Sterol regulatory element-binding protein (SREBP)-1c, the activation of PPARα to stimulate β-oxidation, and the modulation of inflammatory cascades. In a systematic review encompassing 29 studies, Ranneh et al. assessed the effects of dietary polyphenol supplementation on NAFLD treatment, demonstrating that curcumin, silymarin, and hesperidin effectively reduce liver enzymes (AST, ALT, GGT), enhance lipid profiles (LDL, HDL, TC, TG), and attenuate inflammatory markers (TNF-α, IL-6, CRP) (28). However, one of the most significant challenges in the clinical application of polyphenols is their poor stability, rapid metabolism, inadequate absorption, and low bioavailability (29).

Polyphenols generally have low bioavailability and bioaccessibility due to their chemical structure, interactions with the food matrix, extensive metabolism, and poor solubility. These limitations can be partially overcome by nano-drug delivery systems (NDDSs). NDDSs have emerged as a promising strategy for enhancing efficacy, enabling liver-specific targeting, facilitating controlled release, and increasing target tissue concentrations (30). As the prevalence of MASLD continues to rise globally, the need for effective treatment strategies has become increasingly urgent, making the exploration of NDDSs particularly notable for advancing therapeutic options in liver diseases (31). In the past two years, numerous studies have explored the use of nanoparticles (NPs), nanoemulsions, nanoliposomes, nanofibers, metallic NPs, and hybrid systems for polyphenol delivery in the context of NAFLD.

Nano Drug Delivery Systems (NDDSs)

Nanomedicines are composed of NPs, typically characterized by dimensions up to 100 nm in at least one axis, though in some cases their overall size may extend to several hundred nanometers. These NPs are unique due to their minute dimensions and customizable surface functionalities. Owing to these, their small particle sizes and large surface areas modify molecular interactions, thereby enabling novel and diverse applications (32). NPs can carry many payloads, including small molecules, proteins, peptides, nucleic acids, and RNA oligonucleotides, allowing for targeted or non-targeted delivery (33). NDDSs enhance drug transport across epithelial and endothelial barriers, improve the delivery of macromolecules and poorly water-soluble agents, support combination therapies, and enable targeted delivery to specific tissues or cell types (34). Compared with conventional therapeutics, nanomedicines offer distinct advantages, including extended circulation time through reduced renal clearance and hepatic metabolism, targeted site-specific delivery, enhanced therapeutic index, and diminished systemic toxicity. Nanomedicine extends beyond conventional drug delivery, incorporating the concept of theranostics, in which next-generation NPs are engineered to serve both therapeutic and diagnostic functions (35). NDDSs have attracted a lot of interest in the study of several diseases, particularly MASLD, in recent years. They also optimize polyphenol-based therapies for MASLD by overcoming core limitations, with advantages including controlled release characteristics, reduced side effects, accurate targeting, and good biocompatibility (36). The primary NDDS platforms employed for polyphenol-based therapy in MASLD include inorganic nanocarriers, lipid-based systems, nanocrystals, polyphenol-derived NPs, and polymeric NPs, all of which are addressed in this review.

This review aims to review the advancements in the application of polyphenols in conjunction with NDDSs for MASLD treatment, focusing on mechanisms, nanocarrier platforms, existing challenges, and possible developments in clinical and research settings.

NDDSs for Polyphenols in MASLD

Inorganic Nanocarriers

Inorganic nanocarriers have emerged as multifunctional delivery platforms that can enhance the stability, bioavailability, and targeted delivery of polyphenols in MASLD. Several recent studies have demonstrated that metal- and metal oxide–based nanosystems not only improve pharmacokinetics but also synergize with polyphenols to modulate key metabolic and oxidative pathways. Luteolin, a natural flavonoid with poor aqueous solubility, was nano-formulated with zinc oxide to enhance its bioavailability and therapeutic efficacy against NAFLD. In a diabetic rat model of NAFLD induced by a high-fat diet and streptozotocin, treatment with Lut/ZnO NPs significantly ameliorated insulin resistance. The treatment also improved the serum lipid profile. Mechanistically, Lut/ZnO NPs activated the hepatic IRS/PI3K/AKT signaling pathway, leading to the inactivation of FoxO1 and the downregulation of its target G6Pase, thereby suppressing gluconeogenesis. Furthermore, the NPs downregulated the expression of SREBP1c, a master regulator of lipogenesis, which contributed to reduced hepatic lipid accumulation. Histopathological examination confirmed the hepatoprotective effects, showing a remarkable reduction in steatosis, ballooning, and necrosis compared to the diseased control groups (37). Similarly, Naringenin (Nar), a natural flavanone with poor bioavailability, was used as a reducing and stabilizing agent to synthesize naringenin-reduced graphene oxide nanosheets (Nar-RGO) for the treatment of NAFLD. In a rat model of NAFLD induced by a high-fat high-fructose diet (HFFD), oral administration of Nar-RGO was compared to an equivalent dose of free Nar. The results demonstrated that Nar-RGO was significantly more effective than free Nar in ameliorating HFFD-induced liver injury. Nar-RGO also significantly improved the serum lipid profile. Furthermore, Nar-RGO treatment markedly alleviated insulin resistance. Mechanistically, Nar-RGO significantly upregulated hepatic PPAR-α mRNA expression and downregulated SREBP-1c and fatty acid synthase (FAS) mRNA expression, suppressing *de novo* lipogenesis. It also exerted potent antioxidant effects by reducing hepatic MDA levels and elevating the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), and demonstrated anti-inflammatory activity by significantly reducing serum levels of IL-1β and IL-6 (38). Collectively, these studies underscore how inorganic carriers can amplify polyphenol-driven modulation of metabolic signaling cascades and oxidative stress.

Recent innovations have expanded inorganic platforms beyond conventional oxides. Aptamer-functionalized copper oxide nanobubbles co-loaded with resveratrol (Apt-NBs@Res@$Cu_{5.4}O$) represent a sophisticated approach combining ultrasound-triggered release, aptamer-mediated hepatic targeting, and redox synergy between copper and resveratrol. This system significantly suppressed TNF-α production and attenuated hepatic TG accumulation in FFA-treated HepG2 cells, highlighting the potential of ultrasound-assisted nanotheranostics in NAFLD (39). Likewise, galactose-modified mesoporous selenium nanoparticles encapsulating arctiin (GA-MSe@AR) achieved selective liver accumulation via asialoglycoprotein receptor (ASGPR) targeting and delivered robust metabolic and anti-inflammatory benefits in high-fat diet (HFD)-induced models, primarily through IGF1/PI3K/Akt inhibition and enhancement of the hepatic antioxidant defense system. Selenium's intrinsic

antioxidant properties appear to synergize with arctiin, emphasizing the advantage of combining therapeutic and carrier functionalities within a single platform (40). Finally, galactose-conjugated hollow cerium oxide nanocarriers loaded with resveratrol (Res@H-CeO_2-Gal) demonstrated potent anti-steatotic and anti-inflammatory activities by leveraging CeO_2's ROS-scavenging capability. This dual-function design, integrating both the catalytic and delivery roles, exemplifies the emerging paradigm of bioactive inorganic nanocarriers (41). Despite encouraging preclinical evidence, a key translational challenge remains: inorganic nanomaterials often face issues of long-term accumulation, potential metal ion toxicity, and unclear clearance pathways. Addressing these limitations through surface modification, degradable hybridization, or controlled dosing strategies will be crucial for clinical advancement. Overall, inorganic nanosystems represent a promising yet complex class of delivery vehicles for polyphenols in MASLD, offering mechanistic synergy between the carrier and cargo. Future efforts should emphasize systematic toxicological evaluation, scalable synthesis, and comparative studies across different inorganic frameworks to define the optimal balance between therapeutic efficacy and biosafety.

Lipid-Based Nanocarriers

Lipid-based nanocarriers have attracted substantial attention as versatile platforms for the delivery of polyphenolic compounds in MASLD. Their inherent biocompatibility, ability to encapsulate hydrophobic and amphiphilic molecules, and preferential hepatic accumulation make them particularly suited for chronic metabolic disorders characterized by lipid dysregulation, oxidative stress, and inflammation. In recent years, research has progressed beyond simple bioavailability enhancement toward the design of multifunctional lipid systems capable of modulating specific hepatic pathways, including AMPK, PPARα, NF-κB, and Nrf2, thereby addressing the multifactorial nature of MASLD. Collectively, these advancements highlight how structural optimization of lipid nanocarriers translates into targeted pharmacological and metabolic benefits.

Early investigations employed conventional liposomal systems to overcome solubility and stability barriers of plant-derived bioactives. Naringenin (NRG), a natural dihydroflavone with demonstrated bioactivities including regulation of lipid metabolism and insulin sensitivity, was encapsulated into nanoliposomes (NRG-Nanolipo) to overcome its poor aqueous solubility and low oral bioavailability for the treatment of NAFLD. The NRG-Nanolipo was prepared using a thin-film rehydration method. *In vitro* release studies demonstrated a sustained release profile, significantly higher than that released from the crude NRG suspension. Pharmacokinetic studies in mice revealed that the nanoliposomal formulation markedly enhanced the oral absorption of NRG, compared to the crude NRG. In a methionine and choline-deficient (MCD) diet-induced NAFLD mouse model, the therapeutic efficacy was evaluated. While the crude NRG showed dose-dependent protective effects, the NRG-Nanolipo at a low dose achieved comparable or superior outcomes to the high dose of crude NRG. Specifically, NRG-Nanolipo significantly reduced serum ALT and AST levels, decreased hepatic TG content, and markedly attenuated lipid accumulation in the liver, as confirmed by Oil Red O staining (42). Building on this foundation, Liu et al. developed baicalin-loaded nanoliposomes. Baicalin (BA), a natural flavonoid with known hepatoprotective and anti-inflammatory properties but poor aqueous solubility and low oral bioavailability, was encapsulated into nanoliposomes (BA-NL) to enhance its delivery for the treatment of NAFLD. The BA-NL formulation was prepared using a film rehydration method. *In vitro* release studies demonstrated that BA-NL provided a slower and more sustained release of baicalin compared to free BA. In a MCD diet-induced NAFLD mouse model, both free BA and BA-NL were evaluated. BA-NL was significantly more effective than free BA in ameliorating MCD-induced liver injury, as shown by greater reductions in serum ALT and AST levels, and more substantial improvements in liver morphology and liver index. BA-NL also markedly reduced hepatocyte apoptosis, hepatic lipid accumulation, and liver fibrosis. Furthermore, BA-NL more potently inhibited the infiltration of macrophages and neutrophils into the liver (43). Similarly, Liang et al. engineered chitosan-coated lipid–polymer hybrid nanoparticles containing silymarin. Silymarin, a hepatoprotective flavonoid with low oral bioavailability due to poor solubility and permeability, was encapsulated in chitosan-functionalized lipid-polymer hybrid nanoparticles (CS-LPNs) for the treatment of NAFLD. The formulation exhibited a very high encapsulation efficiency. *In vitro*, chitosan modification significantly enhanced the cellular uptake of the nanoparticles in both Caco-2 intestinal cells and fat-emulsion-induced HepG2 fatty liver cells. Furthermore, CS-LPNs demonstrated a superior concentration-dependent reduction in intracellular TG levels in the fatty liver cells compared to uncoated nanoparticles. A pharmacokinetic study in rats showed that the oral bioavailability of silymarin from CS-LPNs was higher than from a silymarin suspension and uncoated S-LPNs. In a pharmacodynamic study using transgenic mice fed an HFD, treatment with CS-LPNs was significantly more effective than silymarin suspension or uncoated S-LPNs. The CS-LPNs markedly improved liver function by exerting a potent lipid-lowering effect by reducing serum TG and total cholesterol (TC). The enhanced efficacy was attributed to the combined effects of improved oral bioavailability, increased cellular uptake mediated by chitosan's mucoadhesive properties, and the inherent hepatoprotective and lipid-lowering

Table 1. Key Studies on Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyphenol	Nanocarrier Platform	Study Type	Model	Size (nm)	Dose / Duration	Key Mechanisms	Clinical Translation Potential	Ref
Curcumin	Nano-micelle (SinaCurcumin®)	Human	RCT, MASLD (n=56 completers)	NR	160 mg/day, 2 months	↓ ALT/AST ($p<0.01$); ↓ hepatic inflammation; no change in BMI/lipid profile	First human RCT with nano-micelle curcumin; safe, scalable, GMP-grade; no adverse events	(55)
Silibinin	Liposome (Sil-Lip)	In vivo + In vitro	HFD-induced MASLD mice model + FFA-HepG2	< 130 nm	~ 50 mg/kg daily oral for 4 w	↑ GI stability, mucus permeation, oral absorption; ↓ insulin resistance (IRS-1/PI3K/Akt) & NF-κB inflammation; Extrahepatic: gut microbiota modulation (↑ alpha-diversity, e.g., Sobs/Chao; adjusted phyla/families) Transcriptome/16S rRNA: multi-hit targeting	High, ↑ Oral bioavailability, FDA-aligned liposomes; 5.2× ↑AUC; mucus-penetrating; scalable thin-film method 9.45× BA boost; dual hepatic/gut effects on "multiple-hit" pathology	(46)
Curcumin	O/W nanoemulsions stabilized with MCFA-enriched MAG/DAG (cNE-MCFA)	In vivo	Fructose-induced hepatic steatosis rat model	174.8 ± 1.11	20 mg/kg daily oral gavage for 5 w	↓AST/ALT ratio; ↓steatosis, ↓LDL-c, cholesterol; ↓ steatosis extent, inflammation, brown adipose tissue	Non-commercial emulsifiers viable; food-grade potential; nanoemulsion improves bioavailability; effective in short-term model	(52)
Curcumin + Berberine	DEAE-DEX-coated bilosome (DEAE DEX@LSDBC)	In vivo + In vitro (drug release study)	High fat & sucrose diet induced MASLD mice model	150-200	45 mg/kg BER + 15 mg/kg CUR daily Oral for 8 w	↓ MDA, ↑SOD; synchronized liver targeting; anti-oxidant/anti-inflammatory synergy	Combination therapy; prolonged circulation; enhanced oral absorption; Low cytotoxicity	(54)
Luteolin	ZnO nanoparticles (Lut/ZnO NPs)	In vivo	HFD-induced MASLD + STZ diabetic rat model	~17	IP 12 mg/kg, 3×/week, 3 weeks	↓Hyperglycemia; ↑PI3K/AKT, ↓FoxO1; ↓TG/TC, ↑antioxidants , ↑ hepatic cells Insulin sensitivity	Metal-polyphenol synergy; potential for diabetic MASLD	(37)
Quercetin	Nanocrystals glycyrrhizic acid stabilized (QT-NCs/GL)	In vitro + In vivo	Healthy rats	~ 130	IV, dose 50 mg/kg	Liver-targeted (2.5× vs. poloxamer NCs); ↑solubility/dissolution	Herbal stabilizer; reduced crystallinity; high liver accumulation	(57)

Continued Table 1. Key Studies on Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyphenol	Nanocarrier Platform	Study Type	Model	Size (nm)	Dose / Duration	Key Mechanisms	Clinical Translation Potential	Ref
Resveratrol	Solid lipid nanoparticles (Gelucire/Tween 80)	In vivo + In vitro (drug release study)	HFD-induced MASLD rat model	208 ± 48	20 mg/kg daily oral gavage for 6 w	↑EE (75%); sustained release; ↓lipid profile, ↓ALT/AST; histological improvement	Scalable hot homogenization; High clinical translation potential	(47)
Curcumin	Nanoemulsion	In vivo	HFHF-induced MASLD rat model	~ 125 ± 7.52	High dose 10 and Low dose 5 mg/kg, 2 w	↓Insulin resistance, ↓leptin, ↑adiponectin; ↓DNA damage; ↓ALT/AST; ↓ glucose, Insulin, HOMA-IR and IGF-1	×5-10 lower dose vs. powder; cardiac + hepatic protection	(50)
Naringenin	Nanostructured Lipid Carriers (NGN-NLC)	In vivo + In vitro (drug release study)	MCD-diet induced MASLD mice model	162.9 ± 11.7	12.5 mg/kg daily oral gavage for 1 w	↑ Cmax/AUC; ↑intestinal absorption (jejunum/ileum); ↓hepatic lipid; ↓hepatic TG; accumulation	High EE (99.9%), accelerated transepithelial transport	(49)
Naringenin	Reduced graphene oxide (Nar-RGO)	In vivo	HFFD-induced MASLD rats	NR	50 mg/kg daily oral gavage for 8 w	↓Lipid peroxidation, ↓TG, ↑GSH; improved steatosis/inflammation	2D nanomaterial; redox modulation; emerging platform	(38)
Resveratrol	Glycogen-based NPs (Gly–LA–Lac)	In vivo + In vitro (Cellular uptake)	HepG2 and L02 cells (cellular uptake) + HFD-induced MASLD mice model	~90	100 mg/kg daily oral gavage for 6 w	Liver-targeted, redox-responsive; ↑GSH, SOD; ↓TLR4/NF-κB; ↓lipid accumulation; ↓TNF-α, IL 1β, and IL-6	Biocompatible polymer; ROS scavenging; high targeting	(58)
Resveratrol	Galactose-modified lipid NPs (Gal-LNPs)	In vivo+ In (Cellular uptake) vivo	HFD-induced MASLD mice model	100	Gal-LNP-RSV, IV, 100 mg/kg RSV, every 3 days for 6 weeks	↑ × 3.49 cellular uptake; ↓ALT/AST (48–59%); reduced steatosis; ↓lipid accumulation	ASGPR targeting; superior to free RSV	(45)
Naringenin	Cationic lipid-modified NPs (NP-NAR)	In vivo	HFD-induced MASLD mice model	NR	50 mg/kg daily oral gavage for 8 w	↓CD36/ACC/FASN; ↑PPAR; modulated gut microbiota/SCFAs	Gut-liver axis targeting; lipid homeostasis restoration	(53)
Resveratrol	Hepatic-targeted nano-enzyme	In vitro + In vivo	NASH mice model	N/A	N/A	↓Fibrosis, ↓oxidative damage; improved histology	Enzyme-mimetic; hepatic targeting potential	(41)
Resveratrol + CuNPs	Aptamer-functionalized US nanobubbles	In vitro + In vivo	HepG2 + MASLD model induced by high fatty acids	193.73	310 nM, 24 h after steatosis induction	Synergistic ROS scavenging; liver-targeted delivery	Liver-targeted aptamer nanobubbles co-delivering Res + CuNPs effectively reduced MASLD inflammation; proposed as	(39)

Continued Table 1. Key Studies on Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyphenol	Nanocarrier Platform	Study Type	Model	Size (nm)	Dose / Duration	Key Mechanisms	Clinical Translation Potential	Ref
							a safe, targeted therapy platform	
Baicalin	Nanoliposomes (BA-NL)	In vivo + In vitro (drug release study)	MCD-induced MASLD mice model	81.41	50 mg/kg daily oral gavage for 4 w	↓Lipid/inflammation/fibrosis/apoptosis; ↓TLR4 cascade	More effective than free baicalin; scalable liposomal tech	(43)
Curcumin	Nanocomplexes (CNCs)	In vivo	Opisthorchis + HFHF diet-induced MASH hamster model	NR	25, 50, 100 mg/kg weekly for 3 months	↓Lipid uptake genes, ↓TLR4/NF-κB; ↓ ↓fat accumulation, ↓fibrosis, ↓inflammation, ↓CD36, ↓HMGB1,↓ α-SMA optimal at 50 mg/kg	Infection-associated NASH model; long-term efficacy	(59)
Resveratrol	PLGA nanoparticles (RSV-PLGA-NPs)	In vitro	Oleic acid-induced hepatic steatosis HepG2	176.1	12.5 to 100 μM	↑Stability/solubility; EE 97.25%; ↓lipogenesis, ↑lipolysis	Sustained release; clinical-grade polymer	(60)
Naringenin	Nanoliposomes (NRG-Nanolipo)	In vivo	MCD-diet induced MASLD mice model	~ 98 ± 5	25 mg/kg daily oral gavage for 4 w	Comparable efficacy at 1/4 dose vs crude naringenin significantly reduced the lipid accumulation; ↓steatosis/inflammation; ↓ALT and AST; ↓ Liver TG/TC	High oral absorption; dose reduction potential (Comparable efficacy to crude NRG at 4-fold lower dose)	(42)
Silybin	Liposome	In vivo + In vitro	T2DM-MASLD rats + primary hepatocytes	~ 119.76	70 mg/kg daily oral gavage for 4 w	↑AMPK phosphorylation; ↓TGF-β1/Smad2/3; ↓hepatic fibrosis/inflammation; improved glucose/lipid metabolism	Enhanced insulin sensitivity; AMPK-mediated antifibrotic effects; scalable liposomal tech; addresses T2DM comorbidity; low toxicity	(56)
Berberine	Solid Lipid Nanoparticles (BBR-SLN)	In vivo	db/db mice hepatosteatosis/MASLD model	NR	High dose BBR-SLN 100 mg/kg, Low dose BBR-SLN 50 mg/kg oral gavage for 4 w	↓Hepatic lipid accumulation and lipid droplet sizes; improved insulin sensitivity; ↓inflammation/fibrosis; ↓ The expression of lipogenic genes, (especially in High dose group)	Liver-concentrated delivery 20-fold higher than the blood; 2–3× ↑bioavailability; scalable SLN platform; effective in genetic MASLD models; potential for obesity-related diseases	(48)
Resveratrol	Galactose-modified oxidized starch-lysozyme	In vivo + In vitro	HFD-induced MASLD mice + steatotic HepG2 cells	50	200 mg/ kg, once every two days, IV	↑AMPK/SIRT1; ↓FAS/SREBP1c lipid synthesis; ↓IRS-1 Ser307 phosphorylation; improved insulin resistance	Hepatic-targeted (ASGPR); 3–4× ↑liver accumulation; sustained release; food-grade	(61)

Continued Table 1. Key Studies on Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyphenol	Nanocarrier Platform	Study Type	Model	Size (nm)	Dose / Duration	Key Mechanisms	Clinical Translation Potential	Ref
	nanoparticles (Gal-OSL)						materials; scalable for MASLD/metabolic syndrome	
Arctiin	Galactose-modified mesoporous selenium nanoparticles (GA-MSe@AR)	In vivo + In vitro (cellular uptake and drug release study)	HFD-induced MASLD mice	~ 30	5 mg/kg, IV (tail vein), twice weekly for 16 weeks	↓Lipid deposition (↓TG/TC); ↓oxidative stress (↓ROS/MDA, ↑SOD/GSH); ↓inflammation (↓TNF-α/IL-6)	Dual lipid-lowering/antioxidant; liver-targeted (GA-ASGPR); improved glucose/lipids/pancreatic function; selenium synergy; scalable for MASLD with metabolic complications	(40)
Celastrol	Chondroitin sulfate-derived hybrid micelles (CS-Hybrid/CLT)	In vivo + In vitro	HFD-induced MASLD rat model + HepG2 cells	N/A	N/A	↓ Hepatic lipid accumulation and FFAs levels; ↓inflammation; improved pathologic liver histology	Enhanced cellular uptake efficiencies in HePG2 cells; enhance liver-targeted delivery, improving bioavailability and efficacy in MASLD treatment by overcoming solubility barriers and enabling site-specific accumulation in hepatocytes	(63)
Celastrol	Celastrol loaded Lactosylated albumin nanoparticles (CEL-Lac-BSA)	In vivo	HFD-induced MASLD mice model	158.6 ± 3.4	N/A	↓Lipid accumulation; ↓oxidative stress; ↓TGF-β1/fibrosis; ↑antioxidant enzymes; ↑AMPK, SIRT1, FASN, SREBP1c; ↑ Insulin Sensitivity	Hepatic-targeted; ↑Hepatocyte uptake and hepatic deposition sustained; release; IV efficacy; albumin biocompatibility; fibrosis reversal	(62)
Curcumin	O/W nanoemulsions stabilized with MCFA-enriched MAG/DAG	In vivo	Fructose-induced hepatic steatosis rat model	174.8±1.11	20 mg/kg daily oral gavage for 5 w	↓ Body weight and adipose tissue; ↓ steatosis; ↓ cholesterol, LDL-C, insulin, HOMA-IR ↓ TG; ↓ FATP5 ↑ FATP2, FABP↓; improved AST/ALT ratio, atherogenic index	Non-commercial MCFA-enriched emulsifier boosts bioavailability and enables direct enterocyte uptake; reverses multiple MAFLD hallmarks in a prolonged model; supports scalable,	(51)

Continued Table 1. Key Studies on Nanodelivery Systems for Polyphenols in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyphenol	Nanocarrier Platform	Study Type	Model	Size (nm)	Dose / Duration	Key Mechanisms	Clinical Translation Potential	Ref
							solvent-free glycerolysis production	
Silymarin	Chitosan-functionalized lipid-polymer hybrid nanoparticles (CS-LPNs)	In vivo + In vitro	HepG2 fatty liver cells; PNPLA3 I148M transgenic mice with HFD	286.5	20 mg/kg daily oral gavage for 4 w	14.38-fold ↑ oral BA vs. suspension, 14.4× higher oral bioavailability, 1.9× greater uptake by hepatic cells, stronger TG reduction, improved liver function ↓ AST/ALT, less hepatic fat accumulation and macrovesicular steatosis	High; demonstrates potential as an oral nanocarrier for MASLD therapeutics with improved efficacy, but requires further human studies for translation	(44)

Note: All studies originally used the term NAFLD; MASLD is the updated nomenclature (Rinella et al., Hepatology 2023). Human studies prioritized at top. Translational impact graded by clinical readiness, scalability, and bioavailability enhancement. N/A; Not available; NR: Not reported; RCT: Randomized controlled trial; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; GI: Gastrointestinal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; FFAs: Free fatty acids; W: weeks; IRS-1: Insulin receptor substrate 1; PI3K: Phosphoinositide 3-kinases; AKT: Protein kinase B; NF-κB *: Nuclear factor kappa B; AUC: Area under the curve; BA: Bioavailability; Cmax: Maximum plasma concentration; ALP: Alkaline phosphatase; LDL-c: low-density lipoprotein; ; W: week ; HFD: High-fat diet ; bw: Body weight; O/W: Oil/Water; MCFA: Medium Chain Fatty Acids; MAG: Monoacylglycerides; DAG: Diacylglycerides; NE: Nanoemulsion; BER: Berberine; CUR: Curcumin; RSV: Resveratrol; MDA: Malondialdehyde; SOD: Superoxide dismutase; DEAE-DEX: Diethylaminoethyl dextran; HFFD: high-fat-fructose diet; EE: Encapsulation efficiency; STZ: Streptozotocin ; HFFD: high-fat-fructose diet; MCD: methionine choline deficient; GSH: Glutathione; TG: Triglycerides; TC: Total Cholesterol; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor alpha ; IL 1β: Interleukin-1 beta; IL-6: : Interleukin-6 ; Gal: Galactose; FOXO1: Forkhead box protein O1; PPAR: Peroxisome proliferator-activated receptor; SCFAs: Short-chain fatty acids; AMPK: Adenosine monophosphate-activated protein kinase; HMGB1:High mobility group box 1; TGF-β1 : Transforming growth factor beta 1; Ser: Serine; ROS: Reactive oxygen species; Naringenin :NRG; SLN: Solid Lipid Nanoparticles; CS: Chitosan; FASN: Fatty acid Synthase; ACC: Acetyl-CoA carboxylase; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; FABP: Fatty Acid Binding Protein; FATP2: Fatty Acid Transport Protein-2; FATP5: Fatty Acid Transport Protein-5; Celastrol included as triterpenoid (quinone methide; polyphenol-like activity per lit.).*

activities of chitosan itself (44).

The evolution of lipid systems subsequently advanced toward active hepatocyte targeting through receptor-mediated endocytosis. Liang et al. engineered Galactose-modified lipid nanoparticles (Gal-LNPs) for the targeted hepatic delivery of resveratrol (RSV) to treat NAFLD. *In vitro* studies in HepG2 cells demonstrated that Gal-LNP-RSV significantly enhanced cellular uptake, higher than unmodified LNPs via ASGPR-mediated endocytosis. In an HFD-induced NAFLD mouse model, Gal-LNP-RSV treatment markedly reduced hepatic lipid accumulation, and oxidative stress markers, outperforming both free RSV and non-targeted LNP-RSV. The study highlighted Gal-LNPs as a promising liver-targeted delivery platform that enhances the intracellular bioavailability and therapeutic efficacy of resveratrol for NAFLD treatment (45).

Silibinin (Sil), a natural flavonoid with poor water solubility and low oral bioavailability, was encapsulated into a liposomal formulation (Sil-Lip) to enhance its therapeutic efficacy against NAFLD. Pharmacokinetic studies in rats revealed that Sil-Lip significantly improved oral bioavailability of silibinin compared to free Sil. In an HFD-induced NAFLD mouse model, oral administration of Sil-Lip markedly reduced body weight gain, liver weight, and hepatic steatosis, as confirmed by H&E and Oil Red O staining. Mechanistically, Sil-Lip downregulated key lipogenic proteins (SREBP-1, FAS, CD36, FATP2) and suppressed inflammatory cytokines (TNF-α, IL-6, IL-1β) both *in vivo* and *in vitro* (46).

Parallel efforts explored solid lipid nanoparticles (SLNs) as a more stable and scalable alternative. Resveratrol was encapsulated into solid lipid nanoparticles (Res-SLN1) using an emulsification and homogenization method to enhance its delivery for the treatment of NAFLD. *In vitro* release studies demonstrated a sustained release profile. In a rat model of NAFLD induced by HFD, oral administration of Res-SLN1 significantly ameliorated the serum lipid profile. Furthermore, Res-SLN1 effectively normalized liver function. Histopathological examination of liver tissues confirmed the therapeutic efficacy, showing that Res-SLN1 treatment drastically reduced hepatocyte ballooning, cytoplasmic vacuolization, and inflammatory cell infiltration compared to the diseased group. The study concluded that formulating resveratrol into solid lipid nanoparticles significantly enhanced its therapeutic potential against NAFLD by improving its delivery (47). Likewise, Berberine, a natural alkaloid with poor oral bioavailability, was encapsulated into solid lipid nanoparticles (BBR-SLNs) to enhance its liver-targeting efficacy for the treatment of hepatosteatosis in db/db mice. In this study, oral administration of BBR-SLNs significantly increased the concentration of berberine in the liver, reaching levels 20 times higher than in the blood, indicating preferential hepatic accumulation. Treatment with BBR-SLNs effectively suppressed body weight gain and reduced liver weight, along with significant decreases in serum ALT levels and hepatic TG content, suggesting improved liver function and reduced steatosis. These findings demonstrate that BBR-SLNs ameliorate hepatosteatosis through enhanced liver targeting and modulation of lipid metabolism pathways (48). Moreover, nanostructured lipid carriers (NLCs), which integrate both solid and liquid lipids, have been developed to increase entrapment capacity and release flexibility. Naringenin (NGN) was encapsulated into a nanostructured lipid carrier (NGN-NLC) to enhance its oral bioavailability and efficacy against NAFLD. The NGN-NLC significantly improved the *in vitro* release rate of NGN compared to the crude NGN. The NLC formulation enhanced transepithelial transport across MDCK cell monolayers via the clathrin-mediated pathway and bypassed P-glycoprotein efflux, which was identified as a limiting factor for free NGN absorption. In everted gut sac models, NGN-NLC showed superior intestinal absorption, particularly in the ileum, compared to the crude NGN. Pharmacokinetic studies in mice revealed that a much lower dose of NGN-NLC achieved comparable AUC and extended half-life relative to a free NGN. In a MCD diet-induced NAFLD mouse model, the low-dose NGN-NLC treatment significantly reduced hepatic TG accumulation, lipid droplet formation, outperforming the higher doses of free NGN. The study demonstrated that the NLC system markedly improved the solubility, stability, intestinal absorption, and liver distribution of NGN, leading to a potent and dose-efficient therapeutic strategy for NAFLD (49).

Nanoemulsions have also been widely applied to enhance the solubility, absorption, and systemic stability of curcumin and other hydrophobic polyphenols. Curcumin, a polyphenol with poor aqueous solubility, was formulated into a nanoemulsion (CUR-NE) to enhance its bioavailability and investigate its effects on high-fat/high-fructose (HFHF) diet-induced hepatic and cardiac complications. In a rat model, oral administration of CUR-NE was compared to a conventional curcumin powder. Results demonstrated that the high-dose CUR-NE was superior to both conventional curcumin and the low-dose nanoemulsion in ameliorating HFHF-induced metabolic disturbances. It effectively normalized insulin resistance. CUR-NE treatment significantly improved the serum lipid profile in both serum and liver tissue. The therapeutic efficacy of CUR-NE was linked to its potent antioxidant and anti-nitrosative effects, evidenced by increased hepatic GSH levels and decreased levels of MDA and nitrates/nitrites. The study concluded that the curcumin nanoemulsion was a highly effective strategy for concurrently mitigating HFHF diet-induced NAFLD, outperforming conventional curcumin due to its enhanced bioavailability and multi-faceted protective mechanisms (50). Agame-Lagunes et al. further investigated curcumin nanoemulsions prepared with medium-chain mono- and diacylglycerols. Curcumin

was encapsulated in oil-in-water (O/W) nanoemulsions stabilized with a non-commercial emulsifier composed of mono- and diacylglycerides enriched with medium-chain fatty acids (MAG-DAG MCFA) for the treatment of fructose-induced hepatic steatosis, the curcumin-loaded nanoemulsion (cNE-MCFA) and the emulsifier-only nanoemulsion (NE-MCFA). In a Wistar rat model of MAFLD, oral administration of the nanoformulations was evaluated. The NE-MCFA group showed a marked reduction in serum glucose and TGs, while both NE-MCFA and cNE-MCFA treatments significantly decreased cholesterol, LDL-C, insulin levels, and the HOMA-IR index, indicating improved insulin resistance and atherogenic profile. Analysis of FA transporter gene expression showed that the NE-MCFA group decreased the expression of FATP 5, while the cNE-MCFA group increased FATP 2 and decreased the fatty acid binding protein (FABP). The study concludes that these specially designed nanoemulsions, particularly the one containing curcumin, confer significant hepatoprotective effects against MAFLD, though the specific impact on serum triglycerides was more pronounced with the emulsifier alone, suggesting a complex interaction between curcumin and the MCFA-rich emulsifier (51, 52).

The structural versatility of lipid nanoparticles has also enabled the creation of hybrid and cationic systems with enhanced intestinal retention and cellular uptake. Naringenin was efficiently encapsulated into cationic lipid-assisted nanoparticles (NP-NAR) to overcome its inherent hydrophobicity and low oral bioavailability. The NP-NAR formulation was prepared using a double emulsion-solvent evaporation technique with the cationic lipid DOTAP, resulting in positively charged nanoparticles with a size below 200 nm, which is favorable for liver targeting. In an HFD-induced MASLD mouse model, oral administration of NP-NAR was compared to an equivalent dose of free naringenin (NAR) and a positive control (Vitamin E). The results demonstrated that NP-NAR was significantly more effective than free NAR in alleviating obesity and metabolic disturbances. It more potently inhibited body weight gain and fat accumulation without suppressing appetite, and more effectively improved dyslipidemia, as well as hepatic levels of non-esterified fatty acids (NEFA) and VLDL. Furthermore, NP-NAR exhibited enhanced antioxidant capacity by increasing hepatic GSH and SOD activities while reducing MDA, and demonstrated stronger anti-inflammatory effects by more significantly suppressing hepatic levels of TNF-α, IL-6, and IL-1β. Mechanistic investigations through transcriptomic and molecular analyses revealed that NP-NAR alleviated MASLD by activating the PPAR signaling pathway to promote FA β-oxidation, while simultaneously inhibiting hepatic lipid uptake and *de novo* lipogenesis by downregulating the expression of CD36, acetyl-coenzymeA carboxylase alpha (ACCα), and FAS (53).

Another innovative direction involves the co-delivery of synergistic polyphenols within unified lipid carriers. The combination of berberine (BER) and curcumin (CUR) has demonstrated therapeutic potential for NAFLD, but its efficacy is limited by the poor and discrepant oral bioavailability and biodistribution of the two polyphenols. To address this, the researchers developed dextran-coated bilosomes for the co-delivery of BER and CUR (DEAE-DEX@ LSDBC). *In vitro* studies demonstrated that DEAE-DEX@LSDBC significantly enhanced permeation across a mucus layer and a Caco-2 cell monolayer, with the transport mechanism involving both paracellular and energy-dependent transcellular pathways. An *in vivo* pharmacokinetic study in mice showed that DEAE-DEX@LSDBC profoundly improved the oral absorption of both polyphenols. It also prolonged their circulation time and, crucially, achieved a synchronized biodistribution, with the highest simultaneous accumulation observed in the liver. In a mouse model of NAFLD induced by a high-fat and high-sucrose diet, oral administration of DEAE-DEX@LSDBC resulted in superior therapeutic outcomes compared to the free polyphenols combination. These outcomes included a significant reduction in body weight gain and fat accumulation, improved serum lipid profiles, decreased fasting serum glucose, and ameliorated liver injury markers. Mechanistic studies revealed that the enhanced efficacy was primarily mediated through potent anti-oxidative effects, via activation of the Nrf2 pathway and upregulation of downstream proteins (NQO-1, HO-1, TrxR-1), and anti-inflammatory effects, via suppression of the NF-κB/NLRP3 inflammasome pathway (54).

In a double-blind, randomized clinical trial, the efficacy of nano-micelle curcumin for the treatment of NAFLD was investigated. Patients with NAFLD were randomly assigned to receive either nano-micelle curcumin (SinaCurcumin®) or a placebo. The results demonstrated that supplementation with nano-micelle curcumin led to a significant reduction in key liver enzymes. The study highlighted that the nano-micelle formulation used was 100% pure, offering superior bioavailability compared to the impure gross substances used in some prior studies. The authors concluded that short-term supplementation with nano-micelle curcumin is beneficial for the treatment of NAFLD, primarily through the reduction of serum ALT and AST levels, and proposed that its combination with lifestyle modification represents an effective therapeutic approach (55).

MASLD frequently coexists with T2DM, necessitating dual-targeted therapeutic approaches. Silybin (SLB), a natural flavonolignan with known hepatoprotective effects but poor oral bioavailability, was encapsulated in liposomes to enhance its delivery and efficacy for the treatment of T2DM complicated with NAFLD. In a rat model of T2DM-NAFLD induced by HFD and streptozotocin, liposomal SLB was compared to free SLB and metformin. The results

showed that liposomal SLB significantly improved insulin resistance. It also ameliorated dyslipidemia by increasing HDL-C and decreasing TC and TG levels, and improved liver function by reducing serum ALT and AST activities. Additionally, it reduced serum levels of pro-inflammatory cytokines. Mechanistically, liposomal SLB activated the AMPK pathway while inhibiting the TGF-β1/Smad signaling axis, leading to decreased expression of fibrogenic markers and improved glycolipid metabolism. The study concludes that liposomal SLB offers a superior therapeutic strategy for T2DM-NAFLD by enhancing SLB bioavailability and targeting key metabolic and fibrotic pathways (56).

Nanocrystals

Nanocrystal technology has recently gained attention as a simple yet powerful strategy to enhance the solubility, bioavailability, and tissue specificity of poorly water-soluble bioactives in metabolic liver diseases. Unlike polymeric or lipidic nanocarriers, nanocrystals consist solely of pure drug particles reduced to the nanoscale and stabilized by minimal amounts of surfactants or functional ligands, thereby maximizing drug loading while minimizing excipient-related toxicity. Their large surface area and high saturation solubility enable rapid dissolution and enhanced absorption, whereas surface modification allows for organ-directed delivery. A representative example of this approach was presented by Shen et al., who developed Quercetin nanocrystals (QT-NCs) stabilized by glycyrrhizic acid (GL) using the wet media milling technique to achieve liver-targeted delivery for the treatment of liver diseases. The optimized QT-NCs/GL indicate good colloidal stability. Compared to raw QT, the nanocrystals showed a 160-fold increase in solubility and a significant improvement in drug release. *In vivo* pharmacokinetic and tissue distribution studies in rats following intravenous administration revealed that while QT-NCs/GL and poloxamer 188-stabilized QT-NCs (QT-NCs/P188) showed similar plasma profiles, QT-NCs/GL exhibited significantly higher liver accumulation. This enhanced liver targeting is attributed to the presence of specific receptors for GL on hepatocytes. The study demonstrates that GL can function as both a stabilizer and a targeting ligand in nanocrystal formulations to promote site-specific drug delivery to the liver (57).

Polymeric Nanocarriers

Polymeric nanoparticles have emerged as highly versatile carriers for the delivery of polyphenolic compounds in MASLD, offering tunable physicochemical characteristics, controlled release profiles, and the potential for site-specific targeting. Their chemical adaptability enables surface functionalization, responsiveness to physiological stimuli such as pH or redox gradients, and incorporation of biodegradable polymers that prolong circulation time while reducing systemic toxicity. These features collectively provide a means to overcome the intrinsic drawbacks of polyphenols, including poor solubility, rapid metabolism, and limited hepatic accumulation. Recent research has focused on polymeric systems ranging from conventional biodegradable matrices like poly (lactic-co-glycolic acid) (PLGA) to advanced polysaccharide- and protein-based carriers functionalized for hepatocyte-specific recognition.

A representative example of this approach is the Resveratrol-loaded glycogen-based nanoparticles (Res NPs), which developed for liver-targeted and redox-responsive delivery to treat NAFLD. The amphiphilic copolymer Gly–LA–Lac, synthesized by conjugating glycogen (Gly) with α-lipoic acid (α-LA) and lactobionic acid (Lac), self-assembled into nanoparticles that efficiently encapsulated resveratrol. *In vitro* studies in HepG2 cells revealed enhanced cellular uptake and significant reductions in oxidative stress (ROS, MDA) and inflammatory cytokines (TNF-α, IL-1β, IL-6), particularly in the presence of GSH. In an HFD-induced NAFLD mouse model, Res NPs markedly reduced hepatic lipid accumulation, serum ALT and AST levels, and oxidative stress, while improving the lipid profile. Histopathological analyses confirmed the alleviation of steatosis and restoration of liver architecture. *In vivo* biodistribution studies demonstrated preferential accumulation and prolonged retention of the nanoparticles in the liver. The therapeutic effects were linked to the suppression of the TLR4/NF-κB signaling pathway (58). Parallel to resveratrol, curcumin has been extensively explored within polymeric matrices owing to its multifaceted antioxidant and anti-inflammatory properties, but poor aqueous solubility. Sithirach et al. encapsulated curcumin into polymeric nanocomplexes (CNCs) to treat NASH in a complex pathological model involving both dietary and parasitic triggers. In hamsters co-exposed to a high-fat, high-fructose diet and infection with Opisthorchis viverrini (OV), hepatic injury progressed from simple steatosis to advanced NASH. Oral administration of CNCs markedly ameliorated the severity of liver damage. Molecular analysis demonstrated downregulation of CD36, a key mediator of FA uptake, as well as HMGB-1 and α-SMA, markers of inflammation and fibrosis, respectively (59). Among synthetic biodegradable systems, PLGA-based nanoparticles have been widely regarded. Resveratrol (RSV) was encapsulated in poly (lactic-co-glycolic acid) nanoparticles (RSV-PLGA-NPs) using an oil-in-water emulsion solvent evaporation method to enhance its properties for NAFLD therapy. *In vitro* release studies showed a sustained and slow-release profile, particularly under acidic conditions, which is advantageous for oral delivery and gastrointestinal transit. In a steatotic HepG2 cell model induced by oleic acid (OA), RSV-PLGA-NPs were effectively internalized and demonstrated superior bioactivity compared to free RSV. They

significantly reduced intracellular TG accumulation and promoted lipolysis, as indicated by increased glycerol release. The study concluded that PLGA-based nanoencapsulation significantly enhanced the stability, solubility, and therapeutic bioactivity of resveratrol, making RSV-PLGA-NPs a promising delivery system for the treatment of NAFLD (60). Another innovative design was proposed by Teng et al., who developed galactose-conjugated oxidized starch–lysozyme nanoparticles (Gal-OSL/Res) for hepatocyte-targeted delivery of resveratrol. The nanoparticles displayed high stability and selective binding to the ASGPR expressed on hepatocytes. This receptor-mediated endocytosis facilitated enhanced cellular uptake in HepG2 cells and efficient reduction of lipid accumulation in FFA-induced steatosis models, outperforming free resveratrol. *In vivo* imaging confirmed preferential hepatic deposition and extended circulation following intravenous administration in HFD-fed mice. Treatment markedly attenuated hepatic steatosis, decreased lipid droplet density, reduced levels of hepatic TGs, malondialdehyde, and non-esterified FA, and improved systemic metabolic parameters, including fasting glucose, triglycerides, and LDL-C. Mechanistically, Gal-OSL/Res activated the AMPK/SIRT1 signaling cascade, suppressed SREBP-1c and FAS expression, and alleviated insulin resistance by reducing inhibitory IRS-1 phosphorylation at Ser307. These molecular effects collectively restored hepatic energy homeostasis and lipid turnover. By integrating biocompatible natural polymers (starch and lysozyme) with galactose-mediated targeting, this system achieved both biodegradability and receptor specificity, illustrating how polymeric nanocarriers can be engineered for precision hepatotherapy in NAFLD (61).

Protein-based polymeric carriers have also shown promise in delivering highly hydrophobic molecules such as celastrol, a potent anti-inflammatory and anti-obesity triterpenoid with limited solubility and systemic toxicity at higher doses. Fan et al. developed lactosylated bovine serum albumin nanoparticles for the targeted delivery of celastrol (CEL) to treat NAFLD. The synthesized CEL-loaded Lac-BSA nanoparticles (CEL-Lac-BSA) displayed a spherical morphology with a narrow size distribution and a high drug-loading efficiency. The Lac-BSA nanosystem not only enhanced hepatocyte uptake and hepatic deposition of CEL but also outperformed free CEL in reducing hepatic lipid accumulation, improving liver function, and enhancing insulin sensitivity in a diet-induced NAFLD mouse model. Mechanistic investigations revealed that CEL-Lac-BSA more effectively downregulated genes related to lipogenesis (e.g., SREBP1c, FASN) and upregulated those involved in lipolysis, by activating the AMPK/SIRT1 signaling pathway (62). Further innovation in polymeric design has extended to polysaccharide-based hybrid micelles capable of dual functionalization and ROS scavenging. Pan et al. constructed CD44-targeted hybrid micelles from chondroitin sulfate (CS) for the delivery of celastrol (CLT) to treat NAFLD. The nanosystem was fabricated from two CS-derived amphiphiles—CS-PBE, which provides ROS scavenging ability, and CS-PFM, which enhances hepatocyte internalization—to form CLT-loaded hybrid micelles (CS-Hybrid/CLT). The resulting micelles demonstrated excellent stability, enhanced cellular uptake in steatotic HepG2 cells, and a marked ability to alleviate intracellular lipid accumulation. In a diet-induced NAFLD rat model, CS-Hybrid/CLT treatment significantly reduced hepatic lipid deposits, lowered FFA levels, improved liver histology, and suppressed inflammation. These results position CS-based hybrid micelles as a promising targeted delivery strategy for NAFLD therapy (63).

NDDSs Clinical Translation and Regulatory Considerations

The clinical translation of polyphenol nanotherapeutics for MASLD faces several regulatory and technical challenges. Early-phase clinical trials have shown promise, as evidenced by the safety and effectiveness of nano-micellar curcumin in lowering liver enzymes in patients with MASLD. For instance, a 2023 randomized controlled trial demonstrated that short-term supplementation with nano-micelle curcumin significantly reduced AST and ALT levels, proving beneficial for MASLD treatment. However, larger, multicenter RCTs are needed to assess long-term outcomes, including fibrosis reversal and cardiovascular benefits, with endpoints like MRI-PDFF for steatosis quantification and biopsy-confirmed histological improvements. Patient stratification based on metabolic profiles (e.g., T2DM comorbidity) and interindividual variability (e.g., gut microbiota or genetic polymorphisms affecting polyphenol metabolism) must be incorporated to personalize therapies and minimize adverse events (55, 64).

Regulatory considerations demand strict compliance with FDA and EMA nanomedicine guidelines, focusing on thorough characterization of physicochemical attributes—such as particle size, zeta potential, and polydispersity—under ICH Q6A/Q6B standards, coupled with detailed toxicological studies to mitigate risks of nanomaterial accumulation, immunogenicity, or off-target effects. For instance, Abraxane (nab-paclitaxel), an albumin-based nanodrug approved by the FDA in 2005 for metastatic breast cancer and later in 2013 for pancreatic cancer, with EMA approvals in 2008 and 2014 for similar indications, serves as a comparative model (65, 66); it illustrates regulatory pathways for protein nanocarriers that could apply to nanoformulated polyphenols in MASLD, though no specific nanodrug for MASLD has been approved yet, and the emphasis remains on preclinical studies. Scale-up issues, including GMP-grade production and consistent batch-to-batch

quality, necessitate standardized synthesis methods, for instance thin-film hydration for liposome preparations. Protecting intellectual property on new formulations and conducting cost-benefit assessments for reimbursement are essential. Closer collaboration among academia, industry, and regulators, possibly via accelerated routes like the FDA's Breakthrough Therapy Designation, can speed approvals and help establish these platforms as practical solutions for MASLD precision medicine.

Future Directions

Future research should prioritize translational validation through well-designed phase I/II clinical trials assessing pharmacokinetics, liver-specific accumulation, and biomarker-based efficacy of nanoformulated polyphenols. Studies comparing different types of nanocarriers are needed to determine the optimal design parameters – including particle size, surface charge, and ligand density – that enable effective targeting of the liver while minimizing off-target deposition. Mechanistic insight obtained through multi-omics profiling and advanced imaging will be essential for delineating the interactions between nano-polyphenols and hepatocytes, Kupffer cells, and the gut-liver axis. Moreover, next-generation hybrid platforms—such as stimuli-responsive systems that respond to pH, redox, or magnetic cues, or multifunctional theranostic nanoparticles—could embed imaging features that enable real-time assessment of hepatic delivery and disease evolution. Investigating under-explored polyphenols like lignans or stilbenes, and pairing them with established drugs such as resmetirom or GLP-1 agonists, may produce synergistic benefits, particularly for advanced MASH or fibrotic stages. Likewise, modulating the gut-liver axis through microbiota-targeted nanoscale delivery could amplify extrahepatic advantages, given dysbiosis's role in MASLD. Using AI-driven design to optimize nanoparticle compositions and predict pharmacokinetic modeling will accelerate innovation, ensuring scalable, cost-effective solutions tailored to patient subgroups. Finally, exploration of sustainable and green nanofabrication strategies employing biopolymers or plant-derived materials should enhance clinical acceptability and environmental safety.

Conflict of Interest

The authors declared that they have no conflict of interest.

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Reference

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