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REVIEW

Research Progress on Nanoformulations Based on Active Components from Traditional Chinese Medicine for MASLD

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disease with rising prevalence and disease burden. However, despite recent therapeutic advances, effective and broadly applicable treatment options remain limited, prompting continued efforts to develop novel therapeutic agents. Traditional Chinese Medicine (TCM) has attracted growing interest in MASLD management because its bioactive compounds can target multiple pathogenic processes. However, many TCM-derived compounds are limited by poor solubility, low bioavailability, and insufficient tissue specificity. Nanotechnology-based formulations enable controlled release and targeted delivery, offering a strategy to improve the utilization and therapeutic efficacy of TCM-derived active ingredients against MASLD. Based on a structured literature search across four databases, 45 representative studies were included and narratively synthesized according to nanoplatform type, design features, and mechanism-related therapeutic actions. Compared with previous broader reviews on TCM nanomedicine or MASLD-related nanotherapies, this review particularly emphasizes MASLD-oriented TCM nanoformulations from the perspectives of platform classification, design features, and mechanism-related therapeutic actions. We also discuss current challenges and future directions for clinical translation.

Keywords: metabolic dysfunction-associated steatotic liver disease, nanotechnology, Chinese herbal medicine, bioactive compounds, drug delivery

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic steatosis with cardiometabolic risk factors, exhibits a rising global trend and currently affects approximately 38% of the population.[1,2] MASLD is closely associated with systemic metabolic dysfunction and commonly coexists with multiple metabolic risk factors.[3] A subset of patients may progress to metabolic dysfunction-associated steatohepatitis (MASH), which represents a critical stage in disease progression.[4] Aligned with the updated international consensus, the terms MASLD and MASH are used herein, superseding the previous designations of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).[3]

The pathogenesis of MASLD involves a complex network characterized by the interplay of multidimensional mechanisms. Multiple factors, such as overnutrition, obesity, and insulin resistance (IR), induce an excessive influx of free fatty acids into the liver, leading to hepatic lipid deposition and lipotoxicity.[5,6] This, in turn, exacerbates hepatic IR to form a vicious cycle, further triggering hepatocyte injury via endoplasmic reticulum stress, mitochondrial dysfunction, oxidative stress, impaired lipophagy, and ferroptosis.[7,8] Concurrently, gut microbiota dysbiosis, compromised intestinal barrier integrity, and disrupted bile acid metabolism further aggravate hepatic injury via the gut–liver axis.[9,10] These multifaceted insults collectively promote hepatic inflammation and immune microenvironment remodeling, eventually resulting in hepatic stellate cells (HSCs) activation and fibrotic progression.[7,11,12]

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Although pharmacological development for MASLD has advanced in recent years, currently available therapies remain limited.[13] Obeticholic acid, once considered a promising candidate, did not receive U.S. Food and Drug Administration (FDA) approval for MASLD/MASH because of concerns over its overall benefit–risk profile.[13] By contrast, Resmetirom was approved by the FDA in 2024 as the first approved therapy for adults with non-cirrhotic MASH and moderate to advanced fibrosis.[14,15] However, the response rate in the Phase 3 Resmetirom trial was only about 30%,[15] while treatment cost remains high and long-term safety issues have yet to be fully resolved.[16] These data highlight the imperative to explore safer and more effective therapeutic strategies.

TCM has attracted increasing attention in the treatment of MASLD because many of its bioactive constituents, such as terpenoids, glycosides, polyphenols, and flavonoids, can act on multiple pathogenic processes involved in the disease.[17–20] Owing to their multitarget properties, these compounds exhibit multidimensional therapeutic potential against MASLD by simultaneously intervening in its interconnected metabolic, inflammatory, and fibrotic mechanisms.[21] This therapeutic relevance, together with the growing body of MASLD-related studies on TCM-derived compounds, highlights TCM as a particularly relevant therapeutic domain in MASLD research.[19,20,22]

However, the translational application of many TCM active compounds remains hindered by poor water solubility, low chemical stability, inadequate bioavailability, and insufficient tissue specificity.[23] Nanotechnology provides a practical bridge between the pharmacological potential of these compounds and the drug delivery demands of MASLD, as it can both enhance their therapeutic potential and improve delivery efficiency.[24] By increasing drug loading, protecting unstable compounds, enhancing targeting, and enabling controlled or stimuli-responsive release, nanoformulations may substantially improve the therapeutic efficacy of TCM active compounds.[25]

Several recent reviews have addressed nanomedicine for MASLD/MASH or nanocarrier-based delivery of TCM active compounds.[23,26–29] However, these studies have generally focused either on broad nanotechnology strategies for MASLD or on TCM nanocarriers across multiple diseases, rather than specifically on TCM-derived nanoformulations in MASLD. A focused synthesis of MASLD-oriented TCM nanoformulations, particularly one integrating platform classification, mechanistic relevance, and translational considerations, therefore remains lacking. Accordingly, this review, informed by a structured search strategy, summarizes current advances in TCM-derived nanoformulations for MASLD from the perspectives of nanoplatform types, design features, representative applications, and translational challenges.

Survey Methods

This review was conducted as a narrative review supported by a structured literature search. PubMed, Web of Science, Scopus, and Embase were searched for English-language publications published between January 2015 and December 2025, with additional manual screening of the reference lists of relevant articles. The search strategy combined controlled vocabulary and free-text terms related to nanotechnology, MASLD-related diseases, and active components derived from traditional Chinese medicine. Detailed inclusion and exclusion criteria are provided in Supplementary Document S1. Through the structured screening process, 45 original studies were included in the focused synthesis to summarize mechanistic evidence, delivery or targeting rationale, formulation innovation, therapeutic significance, and translational value of nanoformulations based on traditional Chinese medicine-derived active compounds in MASLD. The search and selection process is summarized in Figure 1, and the detailed search strategies are provided in Supplementary Table S1.

Barrier-Informed Design and Targeting Logic of MASLD-Oriented TCM Nanoformulations

The delivery performance of TCM nanoformulations in MASLD is determined not only by carrier composition but also by the disease-specific barrier landscape and the corresponding targeting requirements. As summarized in Figure 2, administration route and MASLD-specific barriers collectively determine how nanocarrier properties such as particle size, surface charge, and ligand decoration influence hepatic exposure, cell selectivity, and gut–liver-axis intervention.

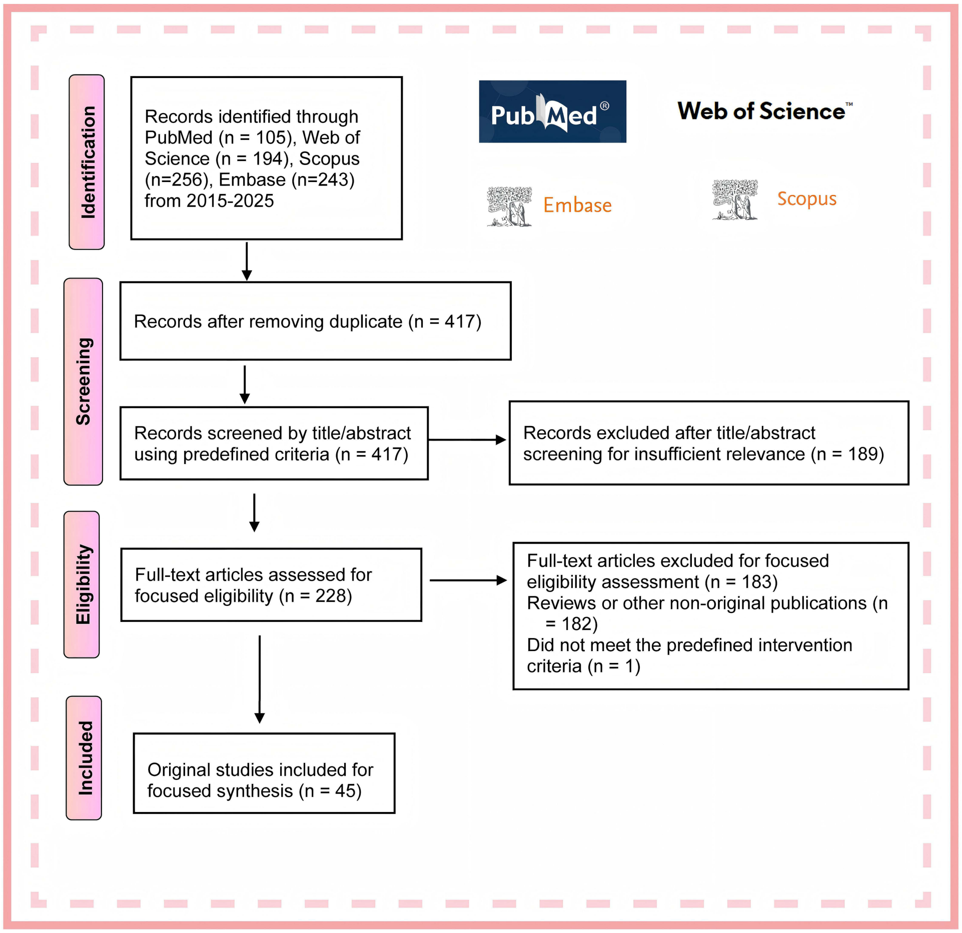

Figure 1 Flowchart of the structured literature search. (A total of 151 references were ultimately cited in this narrative review. Among them, 45 original studies identified through the structured screening process were included in the focused synthesis. Figure created by the authors).

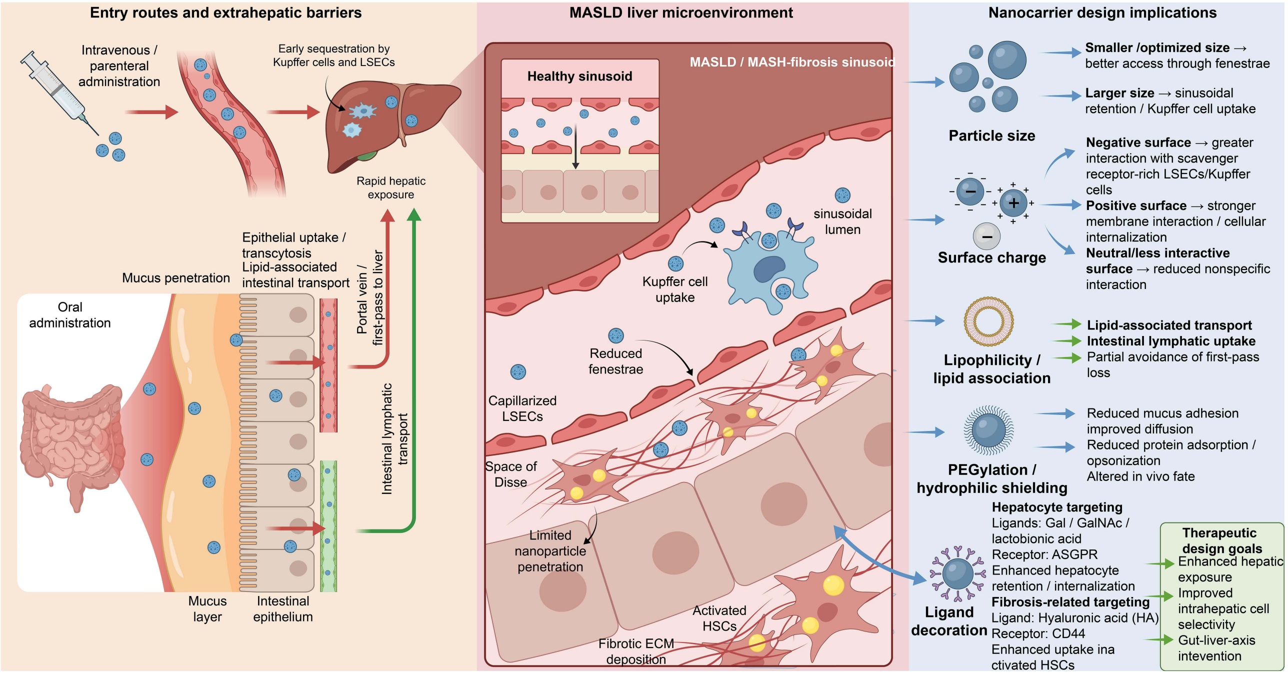

Figure 2 MASLD-specific delivery barriers and design implications for TCM nanoformulations. (Figure created by the authors).

MASLD-Specific Delivery Barriers and Nanocarrier Design Considerations

The design of TCM nanoformulations for MASLD should be interpreted against a disease-specific transport landscape rather than generic liver accumulation alone. In MASLD, liver sinusoidal endothelial cells (LSECs) undergo capillarization and fenestrae loss from early disease stages, and these changes become more pronounced with fibrosis, thereby reducing trans-sinusoidal exchange and limiting nanoparticle access to the space of Disse and hepatocytes.[30,31] At the same time, Kupffer cells and LSECs constitute a major hepatic clearance barrier, so liver accumulation does not necessarily indicate efficient delivery to the intended target cells.[32] As MASLD progresses toward MASH and fibrosis, fenestrae loss and excessive extracellular matrix deposition may further hinder nanoparticle penetration.[31,33]

These pathological changes have direct implications for nanocarrier design. Particle size influences whether nanoparticles can pass through sinusoidal fenestrae and gain access to the space of Disse.[32] Surface charge can also influence how nanoparticles are distributed among different hepatic cell populations.[32] Negatively charged nanoparticles tend to interact more readily with scavenger receptor-rich LSECs and Kupffer cells, whereas positively charged particles often show stronger membrane interactions and endocytosis, which may favor uptake by hepatocytes in some settings.[32] Surface chemistry also affects protein adsorption; compared with neutral or hydrophilic coatings, charged or hydrophobic surfaces are generally more likely to adsorb serum proteins, which may in turn modify opsonization and alter in vivo fate.[32,34] For orally administered systems, mucus and epithelial barriers must also be considered, because nanoparticle diffusion in mucus is strongly influenced by particle size and surface properties.[35] Therefore, nanocarrier design in MASLD should be aligned with the intended route, target cell population, and dominant pathological barrier in a given therapeutic scenario.[32]

Targeting Strategies of TCM Nanoformulations for MASLD: Passive, Active, and Gut–Liver-Axis-Oriented Delivery

Targeting strategies in MASLD-oriented TCM nanoformulations can be differentiated according to their principal therapeutic level of action. Passive targeting primarily aims to enhance hepatic exposure through nanoparticle physicochemical properties, whereas active targeting seeks to improve cell-type selectivity within the liver; by contrast, gut–liver-axis-oriented delivery acts mainly through extrahepatic regulation.[36,37]

After intravenous administration, passive liver-oriented delivery mainly arises from the intrinsic tendency of circulating nanoparticles to accumulate in the liver. However, such accumulation does not necessarily translate into efficient hepatocyte delivery, because a substantial fraction of nanoparticles is intercepted by Kupffer cells and LSECs.[32] After oral administration, by contrast, passive liver-oriented delivery is influenced more strongly by gastrointestinal barriers and transport processes, including mucus penetration, epithelial uptake/transcytosis, and, for some lipid-based systems, intestinal lymphatic transport, which may partially circumvent first-pass loss.[38,39]

Active targeting complements passive hepatic exposure by promoting nanoparticle retention and internalization in specific hepatic cell populations.[36,40] Among hepatocyte-targeted strategies, asialoglycoprotein receptor (ASGPR) remains the best-established receptor because it is predominantly expressed on hepatocytes and recognizes ligands bearing terminal galactose or GalNAc residues; accordingly, galactose-, GalNAc-, and lactobionic acid (Lac)-based modifications have been widely used to enhance hepatocyte uptake.[40] Beyond ASGPR, other hepatocyte surface receptors may also be exploited for active targeting, including scavenger receptor class B type 1 (SR-B1), which can mediate apolipoprotein A1 (Apo-A1)-guided uptake, as well as lectin-like carbohydrate-recognition pathways that may be engaged by polysaccharide ligands such as pullulan.[41,42] In contrast, negatively charged nanoparticles are more readily recognized by scavenger receptor-rich LSECs and Kupffer cells, which may compromise hepatocyte selectivity but can be advantageous when therapeutic modulation of non-parenchymal cells is desired.[32] Fibrosis-related targeting usually focuses on activated HSCs and the fibrotic microenvironment; in this context, hyaluronic acid (HA)/CD44-based targeting systems have shown enhanced uptake in activated HSCs.[43]

In addition, some MASLD nanoformulations are not designed for direct hepatocyte targeting but instead aim to intervene through the gut–liver axis. Oral systems with colon-targeting, mucus-adapted delivery, or microbiota-modulating functions may help restore intestinal barrier integrity and reshape microbial- or bile-acid-related signaling, thereby indirectly improving hepatic steatosis and inflammation.[37]

Overall, the key distinction among these strategies lies less in the mere introduction of a targeting ligand than in whether the principal therapeutic objective is to enhance hepatic exposure, improve intrahepatic cell selectivity, or regulate extrahepatic drivers of MASLD.[36,37,40] Nevertheless, in vivo efficacy remains limited by cross-platform factors, including protein adsorption/opsonization and corona formation, mononuclear phagocyte system clearance, and off-target accumulation/sequestration, which may uncouple apparent liver accumulation from true target-cell delivery.[32,44]

Engineering Nanocarriers to Deliver Active Components of TCM

Lipid-Based Nanocarriers

Liposomes

Liposomes are spherical vesicles formed by an amphiphilic phospholipid bilayer surrounding an aqueous core, typically ranging in size from 20 to 1000 nanometers.[45] This unique structure enables them to simultaneously encapsulate both hydrophilic and hydrophobic drugs.[46] As a mature nanodelivery platform, liposomes offer good biocompatibility and modifiability;[47] for example, cholesterol can improve membrane stability, whereas modification with polyethylene glycol (PEG) may prolong circulation.[47,48] These properties make liposomes a versatile platform for improving drug solubility and enabling surface engineering.

In recent years, liposome engineering has increasingly focused on overcoming conventional loading limitations and improving delivery performance. For example, Tanshinone IIA (TSIIA) suffers from extremely poor water solubility.[49] To address this defect, Cai et al developed an innovative nanocrystal liposome technology (TNC@Lipo) Instead of the conventional loading of TSIIA directly into the lipid bilayer, this strategy involved the initial preparation of TSIIA into highly soluble nanocrystals (TNC) via anti-solvent precipitation combined with ultrasonication. Subsequently, the TNCs were encapsulated within the liposomal core to form a unique "crystal core-lipid shell" structure. This approach addressed the common limitation of low drug loading associated with conventional liposomes for hydrophobic drugs, while also significantly enhancing the physical stability of TSIIA. The system not only reduced the cytotoxicity of the free drug but also significantly enhanced the anti-fibrotic efficacy of TSIIA by increasing drug exposure at the lesion site.[50]

Furthermore, liposomal platforms can support co-delivery and multi-target intervention through flexible formulation and surface design. Chen et al designed a nano-liposome (DEAE-DEX@LSDBC) for the co-delivery of berberine (BER) and curcumin (CUR) This system achieved enhanced flexibility and stability by incorporating sodium deoxycholate into the lipid bilayer to form bilosomes. Surface coating with the cationic polymer diethylaminoethyl dextran (DEAE-DEX) further enhanced mucosal stability and oral absorption, which was associated with increased hepatic accumulation after oral administration. From a mechanistic perspective, the therapeutic effects of this system were associated with coordinated modulation of oxidative stress and inflammatory signaling, particularly the Nrf2-related antioxidant response and the NF-κB/TXNIP–NLRP3 axis.[51]

Moreover, similar liposome engineering strategies have been successfully applied to the delivery of flavonoid compounds, such as Chrysin,[52] Vitexin,[53] and baicalin,[54] significantly enhancing their therapeutic efficacy against MASLD by improving their pharmacokinetics.

Despite their versatility, liposomes in MASLD still face route-dependent translational limitations. After parenteral administration, plasma protein adsorption and mononuclear phagocyte system clearance may reduce effective hepatocyte exposure.[32,55] Although modification with PEG can prolong circulation, it does not fully prevent protein corona formation and may be further complicated by anti-PEG antibodies and accelerated blood clearance (ABC phenomenon) upon repeated dosing.[55,56] For oral delivery, conventional liposomes remain constrained by gastrointestinal instability and limited epithelial permeability, which explains why bile-salt-containing or other surface-engineered variants are often preferred.[57]

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Nanoemulsions, Microemulsions, and SMEDDS

Nanoemulsions, microemulsions, and self-microemulsifying drug delivery systems (SMEDDS) are closely related oral lipid-based carriers for hydrophobic TCM active ingredients. All three rely on oil-surfactant systems, often with a co-surfactant or cosolvent, to improve drug solubilization, but differ in how the dispersed state is generated and stabilized.[58,59] Nanoemulsions are preformed aqueous dispersions that generally require external energy input during preparation and remain kinetically stable, whereas microemulsions are spontaneously formed single-phase systems that are thermodynamically stable By comparison, SMEDDS are anhydrous preconcentrates that generate fine droplets only after contact with gastrointestinal fluids.[58–60]

To address the poor aqueous solubility and low stability of the flavonoid dihydromyricetin (DMY) for the treatment of MASLD,[61] Li et al developed a hybrid nanoemulsion (DMY-hNE) with a biomimetic "rigid-soft" core-shell structure[62] In this system, polylactic acid loaded with DMY forms the rigid core, while the outer layer consists of flexible lipids composed of phospholipids and cholesterol. This chylomicron-mimetic architecture facilitates intestinal mucus penetration and supports passive liver-oriented delivery through physiological lipid transport pathways.[62] By comparison, Lyu et al used a DMY-loaded SMEDDS constructed from D-α-tocopherol polyethylene glycol 1000 succinate and saponin, which improved oral absorption by enhancing drug solubilization and generating finely dispersed droplets after aqueous dilution.[63]

He et al further developed a curcumin/DHA-rich algal oil microemulsion for co-delivery. In PA-injured WRL-68 and LX2 cells, this formulation showed hepatoprotective and anti-fibrotic potential, while in HFD-fed mice it alleviated liver injury and lowered serum triglyceride and low-density lipoprotein cholesterol levels, accompanied by reduced expression of fatty acid synthase (FAS), 5-LOX, and cPLA2. A separate rat pharmacokinetic study further suggested improved oral exposure to the loaded cargos.[64]

Nanoemulsion-based systems can also intervene in MASLD through the gut–liver axis. In the case of BZEP-NE, therapeutic benefit was associated with remodeling of gut microbial composition, restoration of intestinal barrier function, and activation of the intestinal LXR–ABCA1–HDL pathway, through which high-density lipoprotein cholesterol (HDL-C) may neutralize and clear gut-derived lipopolysaccharide in portal circulation, thereby limiting downstream inflammatory activation.[65]

Despite their oral-delivery advantages, nanoemulsions, microemulsions, and SMEDDS present distinct translational trade-offs. Nanoemulsions remain only kinetically stable, so long-term storage and process robustness require careful control, whereas SMEDDS improve storage stability as anhydrous preconcentrates but may still face precipitation after dilution or dosage-form compatibility issues.[66] Microemulsions, although thermodynamically stable and relatively easy to form, share with the other two systems a frequent reliance on relatively high surfactant/co-surfactant levels. Across these systems, excessive excipient burdens may perturb intestinal epithelial function, making minimization of surfactant load an important design principle.[58,67] For translational development, the selected excipients should also be assessed for oral regulatory acceptability, such as GRAS status or prior inclusion in the FDA Inactive Ingredient Database.[67]

Nanostructured Lipid Carriers (NLC)

To overcome the limitations of solid lipid nanoparticles (SLN), such as low drug loading capacity and drug leakage during storage, nanostructured lipid carriers have been developed as a new generation of lipid-based nanocarriers.[68] NLCs are formed by mixing liquid lipids with solid lipids in the presence of surfactants, generating a less ordered or partially amorphous lipid matrix with an "imperfect crystal" arrangement. Compared with SLN, this less ordered matrix can generally accommodate more drug molecules and reduce the risk of drug expulsion during storage.[69,70]

NLC technology shows significant advantages in delivering hydrophobic TCM active components. For instance, to address the extremely low oral bioavailability of Naringenin (NGN) (approximately 15%),[71] Hu et al developed an NGN-loaded NLC system (NGN-NLC)[72] This system utilized stearic acid and glyceryl monostearate as the solid matrix, with oleic acid serving as the liquid lipid. It was prepared using emulsion evaporation and low-temperature solidification techniques. The resulting nanoparticles achieved a particle size of about 163 nm and a high drug loading capacity of 22.5%. Moreover, they successfully increased the drug's solubility by 115-fold. Mechanistically, inhibitor studies suggested that the enhanced intestinal absorption of NGN-NLC involved clathrin-mediated epithelial uptake together with reduced P-glycoprotein-related efflux. These mechanisms dually promote the intestinal epithelial absorption of NGN. Consequently, NGN-NLC demonstrated superior lipid-lowering and hepatoprotective efficacy compared to the free drug in MASLD mouse models.[72]

Furthermore, a study developed NLCs co-loaded with astaxanthin and kaempferol. This co-delivery system not only improved the stability and water dispersibility of the ingredients but also enhanced their overall bioactivity compared with astaxanthin-loaded NLCs alone. Specifically, the co-delivery system exhibited superior performance in antioxidant activity by reducing H_2O_2-induced cytotoxicity, and in anti-inflammatory activity by significantly inhibiting lipopolysaccharides (LPS) -induced NO production and the gene expression of inflammatory factors, such as iNOS, TNF-α, and IL-6. In terms of lipid metabolism, this co-loaded system inhibited the transcription of FAS and stearoyl-CoA desaturase 1 by upregulating Insig-2a gene expression and subsequently blocking SREBP-1c activation. It was also associated with activation of the LXRα/CYP7A1 axis to promote cholesterol conversion to bile acids and enhancement of PPARα/CPT-1-mediated fatty acid oxidation, thereby improving hepatocellular lipid homeostasis.[73]

However, the critical issue for NLCs is whether their delivery advantages can be consistently reproduced in robust and scalable formulations. Because NLC performance is highly dependent on formulation composition and internal structure, especially the solid/liquid lipid balance and surfactant system, small formulation or process variations may alter drug retention and other critical quality attributes, thereby affecting storage stability and batch reproducibility.[74,75] Therefore, for MASLD therapy, further development of NLCs should prioritize storage stability, formulation simplicity, and manufacturability.[75]

Polymer-Based Nanocarriers

Polymeric Micelles

Polymeric micelles are nanocarriers with a core-shell structure (typically 5–100 nm) formed by the self-assembly of amphipathic polymers in an aqueous phase.[76,77] Among these, the most commonly used amphiphilic polymers are block copolymers composed of two or more hydrophilic and hydrophobic polymer chains.[76,78] The hydrophobic core of polymeric micelles effectively enhances the solubility of hydrophobic drugs, while the hydrophilic shell contributes to colloidal stability and prolonged circulation, making them a useful platform for improving the pharmacokinetics of poorly soluble active ingredients from TCM.[76,77] Furthermore, polymeric micelles possess the advantage of ease of engineering, enabling active targeting and intelligent drug release via functional modification.

For instance, to address the limitation of the low bioavailability of resveratrol (Res) for the treatment of MASLD,[79] two independent studies adopted similar hepatocyte-targeting strategies. Teng et al constructed Gal-OSL/Res micelles using galactose-modified oxidized starch-lysozyme,[80] whereas Li et al developed Gly-LA-Lac/Res micelles using lactobionic-acid-modified natural glycogen.[81] In both systems, galactose-containing ligands promoted hepatocyte-directed delivery through ASGPR recognition. Gly-LA-Lac/Res reduced hepatic lipid accumulation and oxidative stress partly via modulation of the TLR4/NF-κB pathway,[81] whereas Gal-OSL/Res was shown to activate the AMPK/SIRT1 axis and improve hepatic insulin signaling by decreasing hepatic insulin receptor substrate-1 phosphorylation.[80] A distinct hepatocyte-targeting strategy was later reported for oral celastrol micelles (OPDEA-PCL/CEL).[42] Rather than relying on a preinstalled hepatocyte ligand, this system first achieved efficient oral absorption and then selectively adsorbed plasma high-density lipoprotein cholesterol (HDL) after entering the circulation, thereby exposing Apo-A1 and promoting SR-B1-mediated hepatocyte uptake. Mechanistically, OPDEA-PCL/CEL alleviated steatosis by activating AMPK and suppressing SREBP1/FAS-driven lipogenesis, while also reducing hepatic inflammation and mitigating celastrol-associated toxicity.[42]

Furthermore, polymeric micelles can be engineered as “smart” systems integrating diagnosis and treatment. Wang et al constructed innovative polymeric micelles (PGOD NPs) for the delivery of Glycyrrhetinic acid (GA) In this system, GA, PEG chains, and fluorescent probes are covalently linked via reactive oxygen species (ROS)-sensitive oxalate bonds. Upon activation in the high-ROS environment of MASLD lesions, the cleavage of oxalate bonds initially consumed ROS to alleviate oxidative stress. Subsequently, fluorescent probes with aggregation-induced emission characteristics were activated, enabling the real-time visualization of lipid droplets. Finally, the released GA activated the SIRT1/AMPK pathway, promoting lipophagy and reducing excess triglycerides. This system also increased GSH and GPX4 activity

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while lowering MDA accumulation, thereby alleviating hepatic lipotoxicity through multiple mechanisms. Notably, PGOD NPs showed concentration- and time-dependent H_2O_2-responsive fluorescence recovery, strong lipid-droplet colocalization (Pearson's r = 0.96), and a 30.6% reduction in intracellular TG; however, formal quantitative evaluation of imaging sensitivity and image–therapy correlation remained limited.[82]

Clinically, a trial of SinaCurcumin® (nanomicellar curcumin) reported reduced serum transaminase levels in patients with MASLD, providing preliminary human support for the micellization strategy.[83]

However, a practical limitation of polymeric micelles is that critical micelle concentration (CMC)-related dilution can compromise micellar integrity after administration; when polymer concentration falls below the CMC, micellar disassembly and premature drug release may occur, although this also depends on kinetic stability and drug–polymer interactions.[77] Clinical translation is also limited by reproducibility and scale-up, because commonly used preparation methods such as dialysis and thin-film hydration are process-sensitive and may lead to batch-to-batch inconsistency during large-scale production.[84]

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are solid-state nanocarriers made from natural or synthetic polymers, primarily existing as nanospheres or nanocapsules.[85–87] PNPs possess advantages such as good biocompatibility, controllable drug release kinetics, and easy functional modification. By selecting different polymer materials and fabrication strategies, PNPs can achieve diverse design goals, from drug solubilization and efficacy enhancement to precise drug targeting.[88,89]

Gut microbiota dysbiosis plays a critical role in the progression of MASLD. Consequently, delivering drugs precisely to the colon to modulate the microecology has emerged as an effective therapeutic approach. A prominent example is the colon-targeted delivery system for Luteolin.[90] Researchers encapsulated luteolin within an mPEG-PLGA core and subsequently coated the surface with the pH-sensitive anionic polymer Eudragit S100 to form core-shell nanoparticles (Lu-NPs). The Eudragit S100 shell minimized drug release in the gastric (pH 1.2) and small-intestinal (pH 6.8) environments but dissolved under colonic pH (pH 7.4) conditions, thereby enabling colon-directed release. This strategy modulated the gut microbiota and repaired the intestinal barrier, producing therapeutic effects through the gut–liver axis.[90,91]

In addition, alternative strategies focus on achieving efficient hepatic accumulation of drugs to address the core injury. Yu et al developed a multifunctional nanosystem (GCNp-Cur NPs) for the delivery of Curcumin (Cur).[92] This system utilized chitosan oligosaccharide as the backbone and integrated NAC and GA. Specifically, GA promoted hepatocyte-targeted liver accumulation of the system through GA-receptor recognition, whereas the introduction of NAC endowed the carrier itself with antioxidant properties. Thus, the carrier itself participated in therapy rather than serving only as a passive matrix. This system exhibited particular value in ferroptosis-oriented intervention. NAC not only served as a precursor of GSH but also directly chelated excessive intracellular Fe^{2+}, thereby suppressing the Fenton reaction and ROS burst at the source, while curcumin enhanced GPX4 expression. Direct evidence for this ferroptosis-oriented effect was provided by restoration of the GPX4/GSH axis together with reduced iron burden and oxidative/lipid-peroxidative stress, as well as protection against erastin-induced ferroptotic injury, supporting inhibition of ferroptosis-related hepatocellular damage in MASLD.[92]

Natural-polymer-based nanocomplexes have also been explored. For example, nanocomplexes constructed from gum arabic and xanthan gum improved curcumin solubility and prolonged intestinal retention through mucoadhesion, thereby enhancing absorption. These systems were associated with downregulation of hepatic CD36 expression and suppression of HMGB1-related inflammatory signaling, helping to limit progression from steatosis toward fibrosis.[93,94]

An important limitation of biodegradable PNPs is that degradation kinetics can affect safety as well as release behavior; in PLGA-based systems, hydrolysis may generate an acidic microenvironment that accelerates degradation and has been associated with reduced cell viability and pro-inflammatory macrophage responses.[95] Therefore, material safety issues need to be considered in translational applications.

Other Polymer-Based Nanocarriers

Other polymeric nanostructures, such as nanogels and polymeric vesicles (polymersomes), have also demonstrated unique advantages in improving the delivery of active ingredients from TCM due to their distinct structural characteristics.

Polymeric nanogels are swollen, three-dimensional network structures formed by the physical or chemical cross-linking of hydrophilic polymers.[96] This hydrated network supports high drug loading and controlled release. During delivery, network swelling enlarges aqueous channels and promotes drug diffusion, whereas matrix degradation further releases entrapped cargo. Because both processes are modulated by cross-link density and the ionic environment, they directly affect intracellular release kinetics and delivery efficiency.[97] For example, Mauri et al constructed PEG/PEI nanogels (HT-NGs) for delivering hydroxytyrosol (HT), with a particle size of approximately 250 nm and a drug loading of 83%. The PEI component conferred a positive charge that enhanced membrane interaction and intracellular delivery, while the nanogel network enabled sustained intracellular HT release for up to 24 h, resulting in greater efficacy against hepatocyte lipid accumulation and lipotoxicity than free HT.[98]

Polymersomes are hollow spheres formed by the self-assembly of amphiphilic block copolymers. They possess a bilayer membrane structure similar to liposomes and can simultaneously encapsulate both hydrophilic and hydrophobic molecules, while typically exhibiting greater mechanical stability.[96,99] To address the extremely poor solubility of oridonin (ORI), Zhang et al first complexed ORI with hydroxypropyl-β-cyclodextrin to resolve its solubility issues and then co-assembled the inclusion complex with H9 peptide and miltefosine to form nanovesicles. This system achieved a high drug loading of 63.60%, and the introduction of HePC significantly enhanced the cellular endocytosis of the vesicles. In vivo experiments confirmed that these nanovesicles effectively accumulated in the liver, significantly reducing the formation of lipid droplet vacuoles and collagen deposition in MASLD models.[100,101]

Despite their structural versatility, further development of these polymer-based carriers for MASLD still requires reproducible formulation quality, evaluation of polymer-related safety, and regulatory assessment of physicochemical characterization, batch consistency, stability, and manufacturing standardization.[102]

Inorganic Nanocarriers

Inorganic nanocarriers, including metal/metal oxide nanoparticles (such as CeO_2 and ZnO), carbon-based materials (such as graphene), and elemental nanoparticles (such as selenium and silicon), have attracted significant attention due to their high specific surface area, controllable pore size, and unique physicochemical properties.[103–105]However, their application in MASLD treatment requires particular caution. Some materials, such as certain metal-based and carbon nanotubes may aggravate hepatic oxidative stress or inflammatory injury.[106–108] Beyond intrinsic toxicity, incomplete biodegradation or long-term tissue retention may further create chronic safety uncertainty.[109] Therefore, the biosafety of the carriers is the primary prerequisite for their application in this field. Currently, researchers have developed two main strategies to maximize advantages while mitigating risks.

One strategy involves the modification of potentially toxic carriers via "green synthesis". For example, Abdelmoneim et al developed naringenin-loaded reduced graphene oxide nanosheets (Nar-RGO), in which naringenin served both as the therapeutic cargo and as a green reducing agent to convert GO into lower-toxicity RGO. Owing to the high surface area and interaction capacity of RGO, the system achieved a drug loading of 68% and showed stronger suppression of SREBP-1c/FAS-driven lipogenesis and inflammatory cytokines than free naringenin in MASLD models.[110]

Another strategy is to exploit intrinsically bioactive inorganic carriers so that both the carrier and the drug contribute to therapy. For example, selenium is an essential human trace element and a powerful antioxidant.[111] Based on this, galactose-modified mesoporous selenium nanoparticles (GA-MSe) were constructed to deliver arctiin (AR). The galactose moiety was introduced to promote ASGPR-mediated hepatocyte targeting, while the mesoporous selenium structure improved AR loading; after cellular uptake, GA-MSe@AR showed transient lysosomal accumulation followed by efficient escape into the cytoplasm. In addition, selenium release promoted antioxidant selenoprotein-related activity and, together with AR, reduced intracellular ROS, protected mitochondrial integrity, and inhibited the IGF1/PI3K/AKT axis, thereby suppressing oxidative stress and excessive lipid synthesis.[111]

A related carrier-drug cooperative strategy was also observed in luteolin-zinc oxide nanoparticles (Lut/ZnO NPs), in which zinc ions exerted insulin-mimetic effects and, together with luteolin, upregulated the phosphorylation levels of the hepatic insulin signaling pathway (IRS/PI3K/AKT) and suppressed FoxO1-driven gluconeogenesis, while also reducing SREBP-1c-mediated lipogenesis.[112] Furthermore, CeO_2 hollow mesoporous nanocarriers leverage the cyclic redox conversion between Ce^{3+}/Ce^{4+} to scavenge ROS, thereby augmenting the therapeutic effect of resveratrol against MASLD.[113]

Bio-Derived and Bionic Nanoscale Systems

In addition to engineered nanocarriers, an emerging frontier in MASLD nanomedicine involves utilizing or mimicking nature's own transport systems. These bio-derived and biomimetic strategies typically exhibit superior biocompatibility, inherent bioactivity, and low immunogenicity.[114–116]

Endogenous Carriers and Natural Nanovesicles

Among these bio-derived strategies, the most direct approach is to utilize naturally occurring transport components. These mainly include endogenous biomolecules (such as proteins) and cell-secreted nanovesicles.

Endogenous Protein Carriers

Among the many endogenous components, serum albumin (especially human serum albumin and bovine serum albumin) has emerged as an ideal drug delivery platform. As early as 2005, the albumin-based nanodrug Abraxane® (albumin-bound paclitaxel) was approved by FDA for clinical use.[117] As the most abundant protein in plasma, albumin possesses excellent biocompatibility, biodegradability, and low immunogenicity. Furthermore, it inherently functions to transport hydrophobic molecules, such as fatty acids and hormones, as well as drugs.[118,119] Its three-dimensional structure provides high-affinity binding sites, such as Sudlow sites I and II, for hydrophobic drugs. However, these binding interactions are not unlimited, because albumin contains only a finite number of major drug-binding pockets and different cargos show unequal binding affinities.[120] Meanwhile, the recycling mechanism mediated by the neonatal Fc receptor confers a long circulatory half-life of approximately 19 days. Furthermore, albumin can specifically bind to the gp60 receptor and SPARC protein. This capability allows it to naturally accumulate in inflamed and diseased tissues.[117,118]

To address the bottlenecks hindering the clinical translation of celastrol in MASLD treatment, specifically its poor water solubility and systemic toxicity,[121] Fan et al designed a lactobionic acid-modified bovine serum albumin (Lac-BSA) nanosystem.[122] This system exploited the natural hydrophobic drug-carrying capacity of albumin while achieving ASGPR-mediated liver targeting through surface lactobionic acid ligands. As a result, it enhanced the anti-steatotic and anti-fibrotic effects of celastrol while reducing non-target exposure, and was associated with activation of the AMPK/SIRT/FAS/SREBP1c axis together with upregulation of fatty-acid-oxidation-related genes such as Acox-1 and Cpt-1.[122]

Similarly, the albumin-based nanomedicine of ginsenoside compound K (nabCK) achieved selective hepatic accumulation by leveraging the natural distribution characteristics of albumin. Multi-omics analysis suggested that nabCK alleviated lipotoxicity mainly through mTOR inhibition, thereby reducing FASN-associated lipogenesis, limiting lipid storage, and enhancing APOB-related hepatic lipid export. This remodeling of lipid homeostasis attenuated steatosis and fibrosis and was accompanied by an improved systemic lipid profile.[123]

Despite these advantages, albumin-based loading is constrained by the finite number of major binding sites and by cargo-dependent binding affinity, so loading capacity is not universally high across different drugs.[120] Moreover, because endogenous ligands and loaded drugs may compete for or perturb albumin binding, high loading efficiency does not necessarily guarantee stable drug retention, which can limit formulation flexibility for some cargos.[124]

Biogenic Nanovesicles

Bio-derived nanovesicles (BNVs) are natural lipid bilayer vesicles actively secreted by the living cells of organisms, such as plants, mammals, or microorganisms. They primarily include exosomes and other extracellular vesicles (EVs).[125,126] They carry bioactive substances derived from parent cells, such as proteins, lipids, and nucleic acids. These contents constitute the foundation of inter-kingdom cellular communication.[127] These natural nanosystems possess excellent biocompatibility and the capability for efficient transport across biological barriers. Moreover, their inherent bioactive contents often exhibit defined pharmacological activities. Consequently, they represent promising bioactive nanosystems for MASLD.

Nanovesicles derived from various TCM sources, such as tea,[128] *Artemisia capillaris*,[129] garlic,[130] *Pericarpium Citri Reticulatae*,[131] honey,[132] and honeysuckle,[133] have shown therapeutic activity in preclinical MASLD models, demonstrating the unique advantage of multi-target intervention in the MASLD pathological network. For example, tangerine-derived nanovesicles (TNVs) not only remodeled gut microbiota and restored intestinal barrier integrity but also promoted short-chain fatty acids (SCFAs) production and activated intestinal Farnesoid X receptor (FXR). This leads to increased FGF15/19 release and upregulated hepatic SHP expression to inhibit CYP7A1 activity, coupled with the regulation of bile acid transporters (eg, BSEP and NTCP), thereby comprehensively restoring bile acid homeostasis In parallel, TNVs downregulated gluconeogenic and lipogenic genes while enhancing fatty-acid-oxidation-related programs, ultimately alleviating IR and hepatic lipid accumulation.[131]

Furthermore, certain TCM-derived vesicles target the hepatic inflammatory and immune microenvironment. For instance, Xu et al isolated nanovesicles (ACDEs) from the traditional hepatoprotective herb *Artemisia capillaris*, and these ACDEs exhibited dual activity in MASLD models. Besides downregulating key lipogenic genes, they effectively inhibited NF-κB activation in hepatocytes and macrophages, as reflected by reduced phosphorylation of IKKβ and p65 and decreased production of TNF-α, IL-6, and IL-1β, thereby alleviating hepatic inflammatory burden. These effects may be related to the abundant small RNAs carried by ACDEs, such as gma-miR5368.[129] Honey vesicle-like nanoparticles (H-VLNs) exhibited a deeper anti-inflammatory mechanism. With natural tropism toward hepatic Kupffer cells, their bioactive cargos, including miR-5119, miR-5108, and luteolin, coordinately suppressed C-JUN/NF-κB signaling and NLRP3 inflammasome activation, thereby limiting the chronic inflammation that drives fibrosis at its source. This was accompanied by reduced expression of fibrosis-related genes such as Col1a1, Timp1, and Mmp13, together with decreased HSC activation and attenuation of fibrosis.[132] Furthermore, Garlic-derived exosomes (GDEs) demonstrated a distinct immunometabolic mechanism. After uptake by macrophages, vesicular miR-396e directly inhibited the mRNA expression of the glycolytic enzyme PFKFB3, thereby reducing energy supply required for excessive M1-type inflammatory responses. As a result, IL-1β and TNF-α release was decreased, and hepatocyte lipogenic genes such as FAS and ACC1 were indirectly downregulated through macrophage-hepatocyte crosstalk.[130]

Beyond their native forms, BNVs can be further engineered to enhance therapeutic efficacy. A distinctive engineered example is pullulan-modified exosomes loaded with naringenin (Pul-Exos@NGN). In this design, pullulan served not only as a hepatocyte-directed ligand through lectin-like receptor recognition, but also increased vesicle size, thereby favoring caveolae-mediated uptake after intravenous administration and helping reduce Kupffer-cell-dominated sequestration. Mechanistically, Pul-Exos@NGN promoted lipid-droplet turnover by enhancing ubiquitin–proteasome-system-dependent removal of the lipid-droplet coat protein PLIN2 together with lipophagy flux, thereby alleviating hepatic lipid accumulation.[41] Fucoxanthin-loaded *Lactobacillus paracasei*-derived EVs (LpEVs) likewise utilized the bacteria-derived lipid membrane structure to improve the stability of the hydrophobic cargo and, after glycyrrhetinic-acid modification, achieved liver-targeted delivery with downregulation of the SREBP-1/ACC1/FAS pathway.[134] Another strategy is donor-cell preprogramming: exosomes derived from curcumin-pretreated mesenchymal stem cells (MSCs/Exo-Cur) showed an altered cargo profile and were confirmed to downregulate the ASK-1/JNK/BAX apoptotic pathway, inhibit HSC activation, and exert sustained anti-MASH effects for up to 3 months.[135]

Despite their biological advantages, BNVs remain constrained by marked source- and process-related heterogeneity. Vesicles derived from different organisms cells can differ substantially in composition, bioactivity, and tropism, while commonly used isolation methods such as ultracentrifugation, precipitation, size-exclusion chromatography, or tangential-flow filtration may yield major differences in purity, recovery, production yield, and batch reproducibility.[136,137] Moreover, dosing metrics are not standardized across studies, because EV preparations are variably reported by particle number, protein amount, and/or other abundance-related measures, which complicates cross-study comparison and quality control.[136] Accordingly, further translation will require clearer characterization standards, GMP-compatible scalable manufacturing, and more explicit regulatory classification.[137,138]

Bionic Assembly and TCM-Derived Nanodrugs

In contrast to directly utilizing natural components, another advanced strategy involves constructing "carrier-free" nanodrugs through biomimetic self-assembly or the direct nanonization of TCM ingredients. These approaches minimize the use of exogenous materials and can improve delivery efficiency while preserving the intrinsic bioactivity of TCM-derived components.[139,140] One important strategy is the spontaneous self-assembly of TCM ingredients into nanoparticles through the cooperative balance of non-covalent interactions, including hydrophobic interactions, hydrogen bonding, electrostatic forces, π–π stacking, and van der Waals interactions. In aqueous systems, assembly is favored when these interactions drive the molecules into a more stable state, often by clustering hydrophobic regions away from water.[115,139]

For example, celastrol and HA were reported to spontaneously co-assemble into nanoparticles (CHNPs) in aqueous solution through supramolecular interactions. This HA-templated assembly improved the solubility and stability of celastrol and, because HA is a natural ligand of CD44, enabled targeting of hepatic non-parenchymal cells. In experimental models, CHNPs inhibited LPS-induced M1 macrophage polarization, significantly alleviated hepatic lipid deposition and fibrosis, and also improved obesity, IR, and leptin resistance. Proteomic analysis further suggested involvement of the PPAR signaling pathway and CD36 regulation.[141]

Furthermore, TCM components themselves can be directly converted into functional nanomaterials with intrinsic therapeutic activity. Researchers synthesized highly water-soluble carbon dots (HCDs) directly from the TCM Hawthorn using a green hydrothermal method. HCDs inherited and amplified the bioactivity of Hawthorn. Consequently, they exhibited significant intrinsic antioxidant and anti-inflammatory capabilities. In high-fat diet-induced obese mouse models, it directly alleviates hepatic lipid accumulation and improves glucose metabolism. Simultaneously, it effectively remodels the gut microbiota structure, thereby it exerts therapeutic effects indirectly by regulating the gut-liver axis.[140]

Despite their carrier-free design, further translation of these systems remains challenging, because the final nanostructure can be affected by assembly conditions and source materials, making precise composition characterization, structural homogeneity, and batch reproducibility during scale-up difficult to standardize.[115,139] (Table 1)

Conclusion and Future Perspectives

This review summarizes current advances in TCM-derived nanoformulations for MASLD by integrating nanoplatform classification with a pathology-oriented overview of therapeutic mechanisms. As shown in Figure 3, current nano-TCM systems span engineered, bio-derived, and carrier-free platforms with distinct design logics. Figure 4 further maps representative mechanistic findings from these studies onto the major pathological processes of MASLD, providing an overview of how current nanoformulations may intervene in hepatic lipid dysregulation and hepatocyte stress, inflammatory and immune remodeling, gut–liver-axis dysfunction, fibrosis, and broader metabolic disturbances.

Taken together, different nanoplatforms appear to offer distinct but complementary strengths. Engineered systems are advantageous when improved drug loading, controlled release, or active targeting is required,[47,88,89] whereas bio-derived, biomimetic, and carrier-free systems may offer benefits in biocompatibility, intrinsic bioactivity, microenvironmental modulation, and reduced reliance on exogenous excipients.[114,115]

However, their translation remains limited by unresolved issues in long-term safety, in vivo fate, immunogenicity, scalable manufacturing, batch consistency, and quality control, while most current evidence still comes from small-animal models that do not fully reflect the heterogeneity and stage complexity of human MASLD.[106,110,137,138]

Looking ahead, further development of nano-TCM strategies for MASLD remains important, because these systems can improve the utilization efficiency of TCM-derived active ingredients, overcome limitations in solubility, bioavailability, and tissue specificity, and thereby more effectively intervene in the multiple interconnected pathological processes of MASLD. Future research should therefore focus on developing more precise and clinically relevant nanoformulations. In this context, a "reverse design" strategy should be advanced, in which nanoplatforms are selected or tailored according to clinically relevant requirements, such as disease stage, dominant pathological process, target cell population, route of administration, safety, and manufacturability. At the same time, advanced tools such as organoids and spatial transcriptomics should be used to deepen mechanistic studies and clarify the cell-specific and immunometabolic actions of nano-

Table 1 Overview of Literature Information on TCM-Derived Nanoparticles for MASLD Treatment

Type of NPs	NPs	Particle Size	Targeting/Surface Feature	Active Ingredient	Source TCM	Study Type	Experimental Model	Key Results Against MASLD	References
Liposome	TNC@Lipo (TSIIA nanocrystals@liposome)	230 nm	Passive targeted delivery; nanocrystal core–liposome shell hybrid	Tanshinone IIA	*Salvia miltiorrhiza*	in vivo + in vitro	CCl4-induced liver fibrosis mice; HSC-T6, LO-2, and RAW264.7 cells	Reversed liver fibrosis; reduced collagen deposition, serum ALT/AST, TNF-α, IL-6, and hepatic Hyp; improved liver histopathology	[50]
Liposome	DEAE-DEX@LSDBC (DEAE-DEX-coated bilosome with BER and CUR encapsulated)	150 nm	DEAE-DEX coating; bile salt-inserted bilosome; oral mucus-penetrating/co-delivery design	Berberine + Curcumin	*Coptis chinensis* + *Curcuma longa*	in vivo + in vitro	High fat and sucrose diet-induced NAFLD mice; FFA-treated LO2 cells	Reduced hepatic lipid accumulation and inflammatory foci; improved serum TC/TG/LDL-c, AST/ALT/ALP/GGT/LDH, MDA/SOD/GSH, and fasting serum glucose	[51]
Liposome	CH-NL (Chrysin nanoliposome)	121 ± 8 nm	Conventional nanoliposome; no active targeting ligand or surface modification reported	Chrysin	NR	in vivo	MCD diet-induced NASH in C57BL/6J mice	Reduced hepatic steatosis, liver injury, ROS generation, inflammatory cytokines/cell infiltration, and fibrosis; improved oral bioavailability and liver drug exposure	[52]
Liposome	PEG-VLPs (PEGylated vitexin liposomes)	458 nm	PEG coating; no active targeting ligand reported	Vitexin	NR	in vivo	CCl4/urethane-induced liver cirrhosis in female Sprague-Dawley rats	Improved liver histopathology, LFTs, liver/body weight, and ascites; PEG-VLPs showed better overall improvement than free vitexin and VLPs	[53]
Liposome	BA-NL (baicalin-loaded nanoliposomes)	81.41 nm	Conventional nanoliposome; no active targeting ligand or surface modification reported	Baicalin	*Scutellaria baicalensis* Georgi	in vivo	MCD-induced NAFLD mice	Reduced hepatic steatosis, liver injury, hepatocyte apoptosis, fibrosis, and macrophage/neutrophil infiltration; decreased serum ALT/AST and hepatic TG	[54]
Liposome	Gal-LNP-RSV (Galactose receptor-mediated hepatic targeting system: engineering of quinary cationic liposomes for resveratrol delivery against hepatic steatosis)	~100 nm	Galactose-modified quinary cationic liposome with Gal-PEG2000-DSPE for ASGPR-mediated hepatic targeting; tail-vein delivery	Resveratrol	*Polygonum cuspidatum*	in vivo + in vitro	HFD-induced NAFLD female BALB/c mice; OA/PA-induced steatotic HepG2 cells	Reduced hepatic and cellular lipid accumulation; lowered serum ALT/AST and TG/TC/LDL-C; improved HDL-C and hepatic oxidative stress indices	[142]
Nanoemulsion	DMY-hNE (DMY-loaded stiff-soft hybrid biomimetic nano drug delivery system	164.6 ± 2.9 nm	Stiff-soft core-shell biomimetic nano-emulsion; chylomicron-mimicking soft shell for passive liver-targeted oral delivery	Dihydromyricetin	Vine tea	in vivo	HFD-induced early NAFLD C57BL/6J mice	Reduced hepatic steatosis and liver index; improved plasma TG/TC/LDL/HDL and ALT/AST/ALP; reduced plasma MDA and liver NO/MDA	[62]
Nanoemulsion	BZEPWR (Atractylodes macrocephala extract crystallize self-microemulsion)	<100 nm	Conventional self-microemulsion for oral solubilization; no active targeting ligand reported	Atractylodes macrocephala extract crystallize (BZEP)	*Atractylodes macrocephala* Koidz.	in vivo	"High sugar, high fat, and excessive alcohol consumption"-induced MAFLD rats	Improved ALT/AST, TC/TG/LDL-C/HDL-C, hepatic TC/TG, GSH/SOD/ROS, liver steatosis, mild fibrosis, and ileum/colon pathology	[65]

(*Continued*)

Table 1 (Continued).

Type of NPs	NPs	Particle Size	Targeting/Surface Feature	Active Ingredient	Source TCM	Study Type	Experimental Model	Key Results Against MASLD	References
Nanoemulsion	CUR nanoemulsion (Curcumin nanoemulsion)	125 ± 7.52 nm	Conventional oral nanoemulsion prepared by spontaneous emulsification; no active targeting ligand reported	Curcumin	*Curcuma longa*	in vivo	HFHF diet-induced NAFLD/hepatic and cardiac complications in male Wistar rats	Improved insulin resistance and hyperlipidemia; reduced ALT/AST, serum and hepatic TC/TG, steatohepatitis grade, oxidative/nitrosative stress, oxidative DNA damage, and histopathological liver injury	[143]
SMEDDS	DMY-S (self-microemulsion delivery system for dihydromyricetin)	Mostly <100 nm	TPGS/QS-based self-microemulsion; oral absorption-enhancing design; no active targeting ligand reported	Dihydromyricetin	Vine tea	in vivo	HFD-fed male ICR mice	Prevented HFD-associated weight gain, adipose accumulation, hepatic steatosis, dyslipidemia, and liver injury; reduced hepatic TG and increased hepatic TBA	[63]
Microemulsion	Microemulsion co-delivering curcumin and DHA-rich algal oil	179.37 ± 2.90 nm	Conventional oral co-delivery microemulsion; no active targeting ligand reported	Curcumin + DHA-rich algal oil	*Curcuma longa* + NR	in vivo + in vitro	HFD-induced mild NAFLD mice; PA-treated WRL-68 cells and LX2 cells	Reduced serum TG and LDL-C; attenuated hepatic steatosis and liver injury; lowered ALT/AST and inflammatory cytokines; improved pharmacokinetics of curcumin and DHA	[64]
Nanostructured lipid carrier	NGN-NLC (Naringenin loaded nanostructured lipid carrier)	162.9 ± 11.7 nm	Conventional oral NLC; absorption-enhancing lipid carrier; no active targeting ligand reported	Naringenin	Citrus plants	in vivo + in vitro	MCD diet-induced NAFLD in C57BL/6 mice; MDCK monolayer transport model	Reduced hepatic lipid deposition and serum ALT/AST; increased liver NGN concentration; achieved comparable PK to free NGN at an 8-fold lower dose	[72]
Nanostructured lipid carrier	AK3 (Nanoastaxanthin/ kaempferol)	97 ± 1 nm	β-cyclodextrin-based co-encapsulation with lecithin/ Cremophor RH40; no active targeting ligand reported	Astaxanthin + Kaempferol	*Haematococcus pluvialis* + NR	in vitro	LPS-stimulated RAW264.7 cells; oleic acid-treated HepG2 cells	Reduced intracellular lipid accumulation and inflammatory responses; enhanced protection against oxidative stress	[73]
Polymeric Micelles	Gal-OSL/Res (Hepatic-targeted galactose-conjugated oxidized starch-lysozyme micelles loaded with resveratrol nanoparticles)	50 nm	Galactose-conjugated oxidized starch coating for ASGPR-mediated hepatocyte targeting; lysozyme micelle core	Resveratrol	Red grapes and nuts	in vivo + in vitro	HFD-induced NAFLD C57BL/6J mice; FFA-induced steatotic HepG2 cells	Reversed hepatic steatosis and improved insulin sensitivity; reduced hepatic TG/ NEFA/MDA and serum glucose/TG/LDL-C/ ALT	[80]
Polymeric Micelles	Res NPs (Resveratrol-loaded liver-targeted glycogen-based nanoparticles)	288.9 ± 0.35 nm	Lactobionic acid-modified glycogen nanoparticle for ASGPR-mediated liver targeting; α-lipoic acid-based redox-responsive release	Resveratrol	Grapes and mulberries	in vivo + in vitro	HFD-induced NAFLD male Balb/c mice; PA-treated HepG2 cells	Reduced hepatic steatosis, serum/liver lipid accumulation, ALT/AST/TBIL, oxidative stress, inflammatory cytokines, and liver histopathological injury; improved liver biodistribution and retention	[81]
Polymeric Micelles	PGOD NPs (Polyethylene Glycol-Glycyrrhetinic Acid-Oxalate Ester-Probe D Self-Assembled Fluorescent Nanoplatform)	135.6 ± 5.4 nm	ROS-responsive PEGylated self-assembled polymer nanoplatform with lipid droplet-targeting fluorescent probe D	18β-Glycyrrhetinic acid	NR	in vivo + in vitro	Tetracycline-induced NAFLD ICR mice; FFA-treated HepG2 cells	Reduced intracellular and hepatic lipid droplet accumulation, hepatic TG, and oxidative stress; improved liver histology; enabled lipid droplet fluorescence imaging in cells and liver tissue	[82]

Polymeric Micelles	SinaCurcumin$^{®}$ /nano-micelle	NR	Conventional oral nano-micelle; no active targeting ligand reported	Curcumin	*Curcuma longa*	Clinical	Patients with ultrasonography-diagnosed NAFLD; double-blind randomized placebo-controlled trial	Significantly reduced serum ALT and AST after 60 days; no significant effect on ALP	[83]
Polymeric Micelles	NS (Nano-silymarin)	NR	Conventional oral micelle formulation; no active targeting ligand reported	Silymarin	*Silybum marianum*	in vivo	HFD-induced NAFLD in adult male Wistar rats	Reduced serum TG and significantly decreased hepatic fat vacuoles and steatosis grade; no significant reduction in ALT or AST	[144]
Polymeric Micelles	OPDEA-PCL/CEL micelles (Oral celastrol micelles forming high-density lipoprotein corona targeting hepatocytes for MASLD treatment)	63.2 ± 0.1 nm	OPDEA-PCL micelle forming HDL corona for SR-B1-mediated hepatocyte targeting; oral mucus-penetrating/transcytosis design	Celastrol	NR	in vivo + in vitro	HFD-induced MASLD C57BL/6J mice; OA-treated AML12 cells	Reduced body weight, abdominal fat, hepatic lipid droplet accumulation, serum TC/LDL/AST/ALT, and hepatic inflammation; improved liver CEL exposure and mitigated CEL toxicity	[42]
Polymeric nanoparticle	Lu-NPs (Eudragit S100-coated Lu/mPEG-PLGA NPs)	197.45 ± 20.09 nm	Eudragit S100 coating; pH-responsive colon-targeted mPEG-PLGA nanoparticle	Luteolin	NR	in vivo + in vitro	Normal colonic epithelial cells (NCM460); healthy Wistar rats	By enabling pH-dependent release and preserving drug integrity in the gastrointestinal tract, it ensured efficient colonic accumulation of luteolin and indirectly supported the treatment of NAFLD through the gut–liver axis	[90]
Polymeric nanoparticle	GCNp-Cur NPs (Curcumin-loaded GCNp)	132.5 ± 9.8 nm	GA receptor-targeted chitosan oligosaccharide-N-acetylcysteine polymer coating; Cur-Lip/polymer composite design	Curcumin	Turmeric	in vivo + in vitro	Tetracycline-induced NAFLD mice; FFA-treated HepG2 cells	Improved liver injury and steatosis; reduced serum TG/TC and hepatic oxidative damage; alleviated lipid accumulation	[92]
Polymeric nanoparticle	NC-CS/PT-NPs (Dual-Stimuli-Responsive Gut Microbiota-Targeting Nitidine Chloride-CS /PT-Nanoparticles)	255.9 ± 5.10 nm	Chitosan/pectin polyelectrolyte nanoparticle; dual pH- and gut microbiota-responsive colon-targeted oral delivery	Nitidine chloride	*Zanthoxylum nitidum* (Roxb). DC.	in vivo	HFD-induced NAFLD C57 mice	Reduced body weight gain, serum ALT/AST and lipid levels; improved hepatic steatosis and liver/intestinal inflammation; altered gut microbiota diversity	[145]
Polymeric nanoparticle	NP-NAR (Naringenin cationic lipid-modified nanoparticles)	NR	DOTAP-containing cationic lipid-assisted PEG-b-PLA nanoparticle; no active targeting ligand reported	Naringenin	Citrus fruits	in vivo	HFD-induced MASLD C57BL/6J mice	Reduced body weight gain, fat accumulation, hepatic steatosis, AST, hepatic TG/NEFA/VLDL, oxidative stress, inflammatory cytokines, and insulin resistance; improved gut microbiota and fecal SCFAs	[146]
Polymeric nanoparticle	Gal-PEG10K-TK-PCL15K @BA-Mg (Gal-PEG10K-TK-PCL15K@BA-Mg ROS-responsive liver inflammation-targeted nanoparticles)	151.4 ± 1.48 nm	Galactose-modified PEG-TK-PCL polymer for ASGPR-mediated liver targeting; thioketal-based ROS-responsive release	Baicalin magnesium	*Scutellaria baicalensis* Georgi	in vivo	HFD-induced MAFLD male C57BL/6 mice	Reduced hepatic lipid deposition, inflammation, oxidative stress, and liver injury; improved serum biochemical indices and liver histopathology; superior to BA-Mg	[147]

(*Continued*)

Table 1 (Continued).

Type of NPs	NPs	Particle Size	Targeting/Surface Feature	Active Ingredient	Source TCM	Study Type	Experimental Model	Key Results Against MASLD	References
Polymeric Nanogels	HT-loaded nanogel (HT/NG)	262 nm	PEG/PEI nanogel; no active targeting ligand reported; sustained-release intracellular delivery design	Hydroxytyrosol	Olive	in vitro	FFA-induced hepatic steatosis in HepG2/ C3A cells	Reduced intracellular triglyceride accumulation and lipotoxicity; restored cell viability; outperformed non-encapsulated hydroxytyrosol; no oxidative stress induction	[98]
Polymeric Vesicles	ORI/HP-β-CD/H9-HePC NVs (Oridonin loaded hydroxypropyl-β-cyclodextrin /H9 peptide-hexadecylphosphocholine nanovesicles)	195.6 ± 11.49 nm	Amphiphilic peptide H9-HePC nanovesicle; HP-β-CD inclusion-complex loading; liver accumulation after tail-vein injection; no active targeting ligand reported	Oridonin	*Rabdosia rubescens*	in vivo + in vitro	Tetracycline-induced NAFLD mice; FFA-induced HepG2 cells	Reduced cellular lipid accumulation and total cholesterol; reduced liver index, hepatic lipid accumulation, and fibrosis; improved liver histopathology	[101]
Inorganic Nanocarriers	Nar-RGO (Naringenin-reduced graphene oxide nanosheets)	NR	Naringenin-reduced graphene oxide nanosheet; green-reduction/encapsulation design; no active targeting ligand reported	Naringenin	Citrus fruits	in vivo	HFFD-induced NAFLD in male Sprague–Dawley rats	Improved hepatic steatosis, insulin resistance, oxidative stress, and inflammation; reduced serum ALT/AST, TC/ TAG/LDL; increased HDL and adiponectin	[110]
Inorganic Nanocarriers	GA-MSe@AR (Arctiin-loaded galactose-modified mesoporous selenium nanoparticles)	~30 nm	Galactose-modified mesoporous selenium nanoparticle for ASGPR-mediated liver targeting; acidic pH-responsive AR release	Arctiin	*Arctium lappa* L.	in vivo + in vitro	HFD-fed C57BL/6J mice; FFA-treated LO2 and AML12 cells	Reduced hepatic lipid deposition, oxidative stress, inflammation, blood glucose, TC/TG, and ALT/AST; improved pancreatic function	[111]
Inorganic Nanocarriers	Lut/ZnO NPs (Luteolin/ZnO nano-dispersions)	172.6 nm	Conventional ZnO-based nanodispersion; no active targeting ligand reported	Luteolin	NR	in vivo	HFD- and HFD+STZ-induced NAFLD in male Wistar rats	Reduced hepatic steatosis, insulin resistance, hyperglycemia, dyslipidemia, oxidative stress, and liver injury; improved ALT/AST, hepatic TG/FFA, and histopathology	[112]
Inorganic Nanocarriers	Res@H CeO2 Gal (Galactose-modified Hollow Mesoporous Cerium Oxide Nanocarriers Loaded with Resveratrol)	~120 nm	Galactose-modified hollow mesoporous CeO2 nano-enzyme for ASGPR-mediated hepatic targeting; sustained-release design	Resveratrol	Grapes/berries	in vivo + in vitro	HFD-induced NASH mice; FFA-induced steatotic HepG2 cells	Reduced hepatic and intracellular lipid accumulation; decreased liver TG/NEFA, inflammatory cytokines, and macrophage infiltration; improved liver histology	[113]
Inorganic Nanocarriers	ZnO NPs-*Citrus reticulata*/ MgO NPs-*Citrus reticulata* (*Citrus reticulata*-loaded Zinc Oxide Nanoparticles/*Citrus reticulata*-loaded Magnesium Oxide Nanoparticles)	22.5 ± 1.3 nm (ZnO); 18.3 ± 1.5 nm (MgO)	Green-synthesized extract-capped metal oxide nanoparticles; no active targeting ligand reported	*Citrus reticulata* peel extract	*Citrus reticulata*	in vivo	HFS diet-induced NASH mice	Reduced hepatic steatosis, inflammation, fibrosis, ALT/AST, body/liver/fat weights, dyslipidemia, and oxidative stress; MgO formulation showed the strongest effect	[148]

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Endogenous Protein Carriers	CEL-Lac-BSA (Celastrol-loaded lactosylated BSA nanoparticles)	158.6 ± 3.4 nm	Lactose-modified BSA nanoparticle for ASGPR-mediated liver targeting; sustained-release albumin carrier	Celastrol	*Tripterygium wilfordii* Hook.f.	in vivo + in vitro	HFD-induced NAFLD C57BL/6N mice; oleate/palmitate-treated HepG2 cells	Reduced hepatic lipid deposition and fibrosis; improved glucose tolerance, insulin sensitivity, serum TC, ALT/AST, and liver histopathology	[122]
Endogenous Protein Carriers	nabCK (Albumin-bound ginsenoside CK)	272 nm	Albumin-based liver-selected nanoparticle; no additional targeting ligand reported	Ginsenoside C–K	Ginseng	in vivo + in vitro	HFD-induced NAFLD C57BL/6J mice; PA/HF-treated HepG2 cells; 3T3-L1 adipocytes	Reduced hepatic steatosis and fibrosis; improved plasma TG/TC/HDL-C/LDL-C and liver histology; alleviated NAFLD-associated cardiac injury	[123]
Bio-derived Systems	Targeted tFNAs (Aptamer-mediated liver-targeted curcumin delivery system based on tetrahedral framework nucleic acids)	NR	Liver-specific aptamer (M15B/M15BT)-conjugated tetrahedral framework nucleic acids; tail-vein liver-targeted delivery	Curcumin	*Curcuma longa*	in vivo + in vitro	HFD-induced NAFLD C57BL/6 mice; AML12, RAW264.7, and GES-1 cells	Reduced body weight, adipose tissue weight, liver TG, plasma TG/TC, and ALT/AST; showed stronger efficacy than free curcumin and untargeted tFNAs	[149]
Biogenic Nanovesicles	TNVs (Tangerine Peel-Derived Exosome-Like Nanovesicles)	172.1 ± 3.7 nm	Plant-derived exosome-like nanovesicle; oral liver-selective biodistribution reported; no engineered targeting ligand	Tangerine peel-derived exosome-like nanovesicles	*Citrus reticulatae* Pericarpium (Chenpi)	in vivo + in vitro	db/db mice; PA-treated AML-12 cells and differentiated 3T3-L1 adipocytes	Reduced hepatic steatosis, insulin resistance, ALT/AST, TG/TC/LDL-c, and hepatic glycogen/collagen accumulation; increased HDL-c and GSH-PX; restored intestinal barrier and gut microbiota homeostasis	[131]
Biogenic Nanovesicles	ACDEs (*Artemisia capillaris*-derived exosomes)	201.1 nm	Plant-derived exosome; oral gastrointestinal/liver biodistribution reported; no engineered targeting ligand	*Artemisia capillaris*-derived exosomes	*Artemisia capillaris*	in vivo + in vitro	MCD diet-induced NAFLD mice; PA-treated AML12 cells	Reduced hepatic steatosis, collagen deposition, ALT/AST, and hepatic lipid accumulation; decreased cellular TG/TC and lipid droplets; suppressed inflammatory responses	[129]
Biogenic Nanovesicles	H-VLNs (Honey vesicle-like nanoparticles)	142 nm	Food-derived vesicle-like nanoparticle; oral liver accumulation with predominant Kupffer cell uptake; no engineered targeting ligand reported	Honey vesicle-like nanoparticles	Manuka honey	in vivo + in vitro	Naturally aged male C57BL/6J mice with spontaneous NASH; LPS-treated BMDMs	Reduced hepatic chronic inflammation and curtailed fibrosis and liver nodule formation in aged mice	[132]
Biogenic Nanovesicles	GDE (Garlic-derived exosomes)	160.61 nm	Plant-derived exosome; no engineered targeting ligand reported	Garlic-derived exosomes	*Allium sativum* Linn.	in vivo + in vitro	HFD-fed C57BL/6 mice; LPS-treated differentiated THP-1 macrophages and conditioned medium-cultured LO2 hepatocytes	Reduced hepatic lipid droplet accumulation and improved liver dysfunction; decreased serum TC, AST, and ALT and hepatic inflammatory responses	[130]
Biogenic Nanovesicles	AC10 TELNs (Dark tea-derived exosome-like nanoparticles)	127.00 ± 6.09 nm	Fermentation-modified tea-derived exosome-like nanovesicle; no engineered targeting ligand reported	Tea-derived exosome-like nanoparticles	*Camellia sinensis* L. (dark tea)	in vivo	HFD-induced NAFLD C57BL/6J mice	Reduced hepatic lipid accumulation and serum TC/TG/LDL-C, ALT/AST, IL-6, and TNF-α; fermented TELNs showed stronger efficacy than unfermented TELNs	[128]

(*Continued*)

Table 1 (Continued).

Type of NPs	NPs	Particle Size	Targeting/Surface Feature	Active Ingredient	Source TCM	Study Type	Experimental Model	Key Results Against MASLD	References
Biogenic Nanovesicles	GA-LpEVs-FX (Glycyrrhetinic acid-modified L. paracasei EVs loaded with Fucoxanthin)	NR	Glycyrrhetinic acid-modified *Lactobacillus paracasei*-derived biomimetic extracellular vesicle for liver parenchymal cell targeting; oral delivery design	Fucoxanthin	Algae/ plankton / shellfish	in vivo + in vitro	HFD-induced NAFLD mice; OA-induced HepG2 cells	Reduced hepatic and intracellular lipid accumulation; improved serum T-CHO/TG/ LDL-C/HDL-C and ALT/AST; reduced liver MDA and NEFA	[134]
Biogenic Nanovesicles	MSCs/Exo-Cur (Curcumin-preconditioned MSCs derived exosomes)	60–130 nm	Curcumin-preconditioned MSC-derived exosome; no engineered targeting ligand reported	Curcumin-preconditioned MSC-derived exosomes	*Curcuma longa*	in vivo + in vitro	MCD-induced NASH mice; PA-treated HepG2 cells	Reduced hepatic steatosis, fibrosis, ALT/ AST, liver TG/Ch, LDL, inflammatory cytokines, and lipotoxicity; maintained protective effects for 3 months after treatment	[135]
Biogenic Nanovesicles	HNVs (Honeysuckle-derived exosome-like nanovesicles)	152.7 nm	Plant-derived exosome-like nanovesicle; oral enterohepatic distribution reported; no engineered targeting ligand	Honeysuckle-derived exosome-like nanovesicles	*Lonicera japonica*	in vivo	HFD-induced MAFLD C57BL/6 mice	Reduced hepatic fat vacuoles, lipid droplet deposition, collagen fibrosis, ALT/AST, TC/ TG, insulin resistance, and oxidative stress; restored gut barrier integrity	[133]
Biogenic Nanovesicles	Pul-Exos@NGN(Pullulan-modified exosomes loaded with naringenin)	498.3 ± 67.1 nm	Pullulan-modified exosome for lectin-like receptor-mediated hepatic targeting; enlarged size for caveolae-mediated endocytosis; intravenous liver targeting	Naringenin	Citrus plants	in vivo + in vitro	HFD-induced MASLD C57BL/6 mice; OA-treated AML12 hepatocytes	Reduced serum and liver TC/TG, ALT/AST, liver weight/body weight ratio, and hepatic lipid droplet accumulation; improved liver histology	[41]
Bionic Assembly and Traditional Chinese Medicine-Derived Nanodrugs	HCD (Hawthorn carbon dots)	2.42 ± 0.53 nm	Biomass-derived carbon dot prepared by green hydrothermal carbonization; no engineered targeting ligand reported	Hawthorn carbon dots	Hawthorn	in vivo + in vitro	HFD-induced obesity mice; LPS-stimulated RAW264.7 cells	Reduced body weight gain, hepatic lipid accumulation, ALT/AST, liver vacuolization, and inflammatory indices; improved glucose tolerance and insulin resistance	[140]
Bionic Assembly and Traditional Chinese Medicine-Derived Nanodrugs	CHNPs (Celastrol-HA co-assembled nanoparticles)	135.2 ± 1.0 nm	HA-templated carrier-free self-assembled nanoparticle; intrinsic HA-mediated liver-targeting capability without chemical modification	Celastrol	*Tripterygium wilfordii*	in vivo + in vitro	HFD-fed C57BL/6J mice; LPS-stimulated RAW264.7 cells and OA-treated HepG2 cells	Reduced hepatic lipid deposition, liver TG, ALT/AST, inflammatory cytokines, body weight, visceral fat, and mild fibrosis; improved glucose tolerance and insulin sensitivity	[141]

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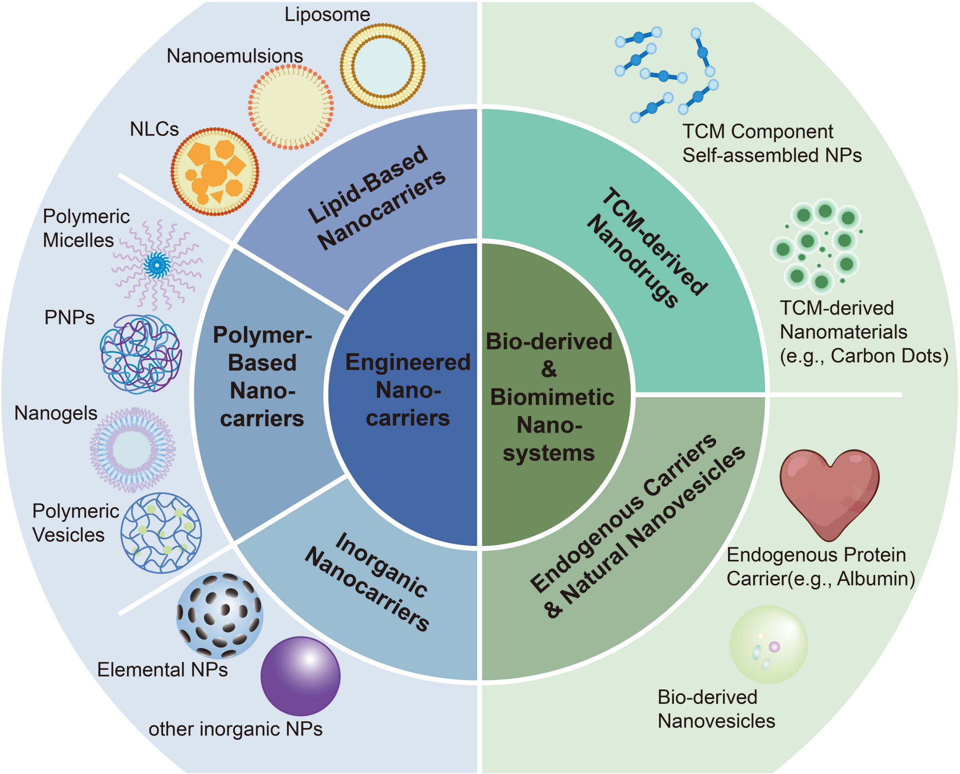

Figure 3 Classification of traditional Chinese medicine nanoparticles for the treatment of MASLD. (Figure created by the authors.).

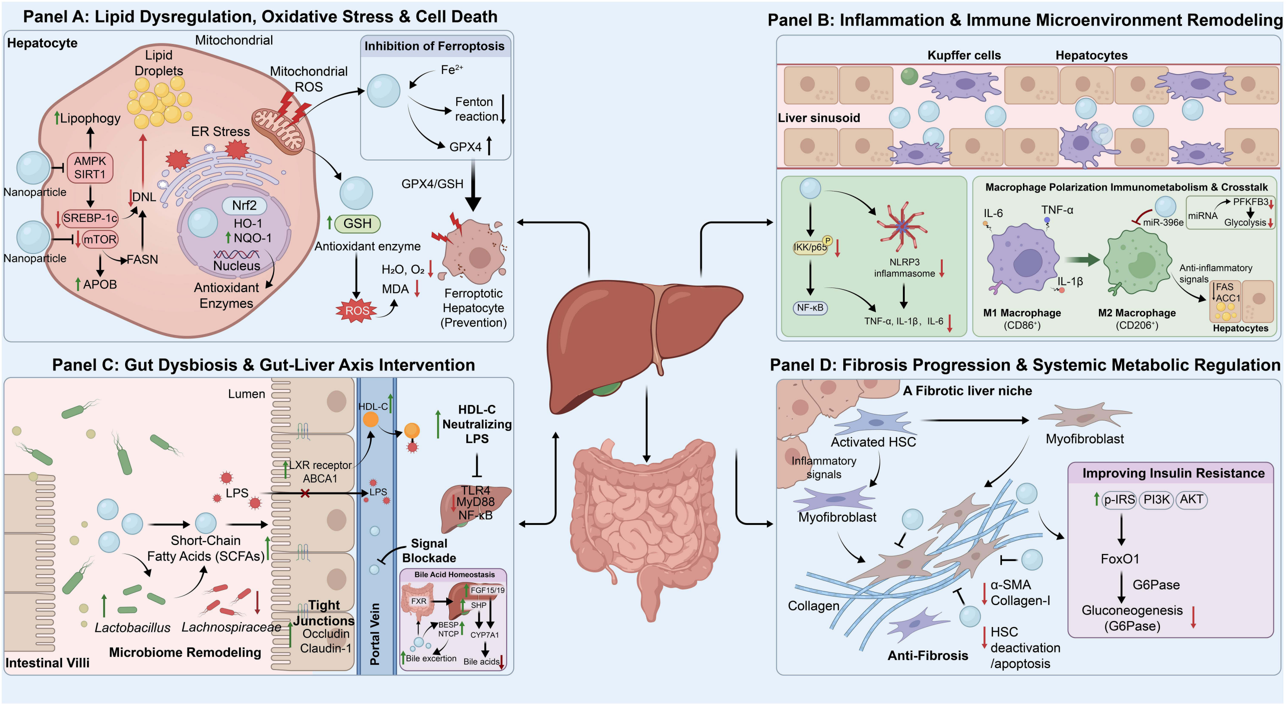

Figure 4 Multi-target mechanisms of TCM-derived nanomedicine in treating MASLD. (This schematic illustrates the therapeutic mechanisms of various TCM-derived nanoformulations across the pathological progression of MASLD, highlighting both shared and distinct pathways. For clarity, all nanoformulations are represented by a uniform spherical symbol rather than their specific nanostructures. Green upward arrows indicate promotion, enhancement, or upregulation of biological processes/ targets, while red downward arrows denote inhibition, reduction, or downregulation. Panel (**A**) Regulation of hepatic lipid metabolism and alleviation of hepatocyte stress and death. Panel (**B**) Remodeling of hepatic inflammation and the immune microenvironment. Panel (**C**) Modulation of gut microbiota and intervention in the gut-liver axis. Panel (**D**) Inhibition of liver fibrosis and improvement of systemic metabolic disorders. Figure created by the authors.).

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TCM systems in MASLD.[150] In addition, interdisciplinary collaboration should be strengthened to connect platform design with standardized production and clinical evaluation.[151]

Overall, TCM-derived nanoformulations show broad mechanistic potential in MASLD, but their clinical value will depend on translating that potential into safe, standardized, and clinically relevant therapies.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT in order to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Abbreviations

MASLD, Metabolic dysfunction–associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic dysfunction-associated fatty liver disease; FDA, U.S. Food and Drug Administration; IR, insulin resistance; MDA, malondialdehyde; TCM, Traditional Chinese medicine; nanoparticles, NPs; NLC, Nanostructured Lipid Carriers; SLN, solid lipid nanoparticles; EVs, extracellular vesicles; SCFAs, short-chain fatty acids; LPS, lipopolysaccharides; HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells; ASGPR, asialoglycoprotein receptor; SR-B1, scavenger receptor class B type 1; Apo-A1, apolipoprotein A1; SOD, superoxide dismutase; GSH, Glutathione; Nrf2, nuclear factor erythroid 2-related factor 2; SMEDDS, Self-Microemulsifying Drug Delivery Systems; LXR, liver X receptor; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; FAS, fatty acid synthase; Lac, lactobionic acid; ROS, reactive oxygen species; Gal, galactose; IRS-1, insulin receptor substrate-1; PNPs, polymeric nanoparticles; NAC, N-acetyl-L-cysteine; GA, glycyrrhetinic acid; GPX4, glutathione peroxidase 4; PEG, polyethylene glycol; PEI, polyethyleneimine; HePC, H9 peptide and miltefosine; GO, Graphene oxide; RGO, reduced graphene oxide; FXR, Farnesoid X receptor; HA, hyaluronic acid; PA, palmitic acid; OA, oleic acid; MCD, methionine-choline-deficient; HFD, high-fat diet; STZ, streptozotocin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Tacke F, Horn P, Wong VW, et al. EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81(3):492–542. doi:10.1016/j.jhep.2024.04.031
2. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2023;8(1):20–30. doi:10.1016/s2468-1253(22)00317-x
3. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. *Lancet Diabetes Endocrinol*. 2025;13(2):134–148. doi:10.1016/s2213-8587(24)00318-8

4. Hagström H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction-associated steatotic liver disease. *Lancet Gastroenterol Hepatol*. 2024;9(10):944–956. doi:10.1016/s2468-1253(24)00193-6
5. Guo X, Yin X, Liu Z, Wang J. Non-Alcoholic Fatty Liver Disease (NAFLD) pathogenesis and natural products for prevention and treatment. *Int J Mol Sci*. 2022;23(24). doi:10.3390/ijms232415489
6. Nassir F. NAFLD: mechanisms, treatments, and biomarkers. *Biomolecules*. 2022;12(6). doi:10.3390/biom12060824
7. Lee KC, Wu PS, Lin HC. Pathogenesis and treatment of non-alcoholic steatohepatitis and its fibrosis. *Clin Mol Hepatol*. 2023;29(1):77–98. doi:10.3350/cmh.2022.0237
8. Li C, Deng D, Jiang Q, Shi J, Xu L, Liu Y. Ferroptosis in NAFLD: insights and the therapeutic potential of exercise. *Front Med*. 2025;12:1462145. doi:10.3389/fmed.2025.1462145
9. Long Q, Luo F, Li B, et al. Gut microbiota and metabolic biomarkers in metabolic dysfunction-associated steatotic liver disease. *Hepatol Commun*. 2024;8(3). doi:10.1097/hc9.0000000000000310
10. Simbrunner B, Paternostro R, Reiberger T, Trauner M. Bile acid signaling in MASLD: from pathogenesis to therapeutic applications. *Hepatology*. 2025. doi:10.1097/hep.0000000000001539
11. He Y, Chen Y, Qian S, et al. Immunopathogenic mechanisms and immunoregulatory therapies in MASLD. *Cell Mol Immunol*. 2025;22(10):1159–1177. doi:10.1038/s41423-025-01307-5
12. Kuchay MS, Choudhary NS, Ramos-Molina B. Pathophysiological underpinnings of metabolic dysfunction-associated steatotic liver disease. *Am J Physiol Cell Physiol*. 2025;328(5):C1637–c1666. doi:10.1152/ajpcell.00951.2024
13. Wei S, Wang L, Evans PC, Xu S. NAFLD and NASH: etiology, targets and emerging therapies. *Drug Discov Today*. 2024;29(3):103910. doi:10.1016/j.drudis.2024.103910
14. Hasan AH, Abid MA, Abid MH, Suhail L, Nazir A. A new hope for the patients of non-alcoholic steatohepatitis: FDA gives green signal for resmetirom use. *Health Sci Rep*. 2025;8(1):e70394. doi:10.1002/hsr2.70394
15. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of in NASH with liver fibrosis. *N Engl J Med*. 2024;390(6):497–509. doi:10.1056/NEJMoa2309000
16. Bittla P, Paidimarri SP, Ayuthu S, et al. Resmetirom: a systematic review of the revolutionizing approach to non-alcoholic steatohepatitis treatment focusing on efficacy, safety, cost-effectiveness, and impact on quality of life. *Cureus*. 2024;16(9):e69919. doi:10.7759/cureus.69919
17. He C, Zhang Q, Zhu R, Tse G, Wong WT. Asperuloside activates hepatic NRF2 signaling to stimulate mitochondrial metabolism and restore lipid homeostasis in high fat diet-induced MAFLD. *Eur J Pharmacol*. 2024;983:177003. doi:10.1016/j.ejphar.2024.177003
18. Yasmin T, Menon SN, Pandey A, et al. Resveratrol attenuates hepatic oxidative stress and preserves gut mucosal integrity in high-fat diet-fed rats by modulating antioxidant and anti-inflammatory pathways. *Sci Rep*. 2025;15(1):25162. doi:10.1038/s41598-025-08450-z
19. Liu WJ, Chen WW, Chen JY, et al. Baicalin attenuated metabolic dysfunction-associated fatty liver disease by suppressing oxidative stress and inflammation via the p62-Keap1-Nrf2 signalling pathway in db/db mice. *Phytother Res*. 2025;39(4):1663–1678. doi:10.1002/ptr.8010
20. Li D, Chen J, Ye C, et al. Celastrol ameliorates fibrosis in Western diet/tetrachloromethane-induced nonalcoholic steatohepatitis by suppressing Notch/osteopontin signaling. *Phytomedicine*. 2025;137:156369. doi:10.1016/j.phymed.2025.156369
21. Chen M, Xie Y, Gong S, et al. Traditional Chinese medicine in the treatment of nonalcoholic steatohepatitis. *Pharmacol Res*. 2021;172:105849. doi:10.1016/j.phrs.2021.105849
22. Ji L, Li Q, He Y, et al. Therapeutic potential of traditional Chinese medicine for the treatment of NAFLD: a promising drug Potentilla discolor Bunge. *Acta Pharm Sin B*. 2022;12(9):3529–3547. doi:10.1016/j.apsb.2022.05.001
23. Wei D, Yang H, Zhang Y, et al. Nano-traditional Chinese medicine: a promising strategy and its recent advances. *J Mater Chem B*. 2022;10(16):2973–2994. doi:10.1039/d2tb00225f
24. Li X, Zhang M, Wang X, Ma P, Song Y. Carrier-Free nanomedicine based on celastrol and methotrexate for synergistic treatment of breast cancer via folate targeting. *Int J Nanomed*. 2025;20:8291–8304. doi:10.2147/ijn.S516921
25. Huang L, Huang XH, Yang X, et al. Novel nano-drug delivery system for natural products and their application. *Pharmacol Res*. 2024;201:107100. doi:10.1016/j.phrs.2024.107100
26. Qin X, Liu J. Nanoformulations for the diagnosis and treatment of metabolic dysfunction-associated steatohepatitis. *Acta Biomater*. 2024;184:37–53. doi:10.1016/j.actbio.2024.06.014
27. Yang Y, Wang X. Nano-drug delivery systems (NDDS) in metabolic dysfunction-associated steatotic liver disease (MASLD): current status, prospects and challenges. *Front Pharmacol*. 2024;15:1419384. doi:10.3389/fphar.2024.1419384
28. Li F, Yuan R, Zhang J, Su B, Qi X. Advances in nanotechnology for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease. *Asian J Pharm Sci*. 2025;20(2):101025. doi:10.1016/j.ajps.2025.101025
29. Qiu C, Zhang JZ, Wu B, et al. Advanced application of nanotechnology in active constituents of Traditional Chinese Medicines. *J Nanobiotechnology*. 2023;21(1):456. doi:10.1186/s12951-023-02165-x
30. Dai Q, Ain Q, Seth N, Rooney M, Zipprich A. Liver sinusoidal endothelial cells: friend or foe in metabolic dysfunction- associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis. *Dig Liver Dis*. 2025;57(5):493–503. doi:10.1016/j.dld.2025.01.189
31. Rautou PE, Chotkoe S, Biquard L, et al. Altered liver sinusoidal endothelial cells in MASLD and their evolution following lanifibranor treatment. *JHEP Rep*. 2025;7(6):101366. doi:10.1016/j.jhepr.2025.101366
32. He Y, Wang Y, Wang L, Jiang W, Wilhelm S. Understanding nanoparticle-liver interactions in nanomedicine. *Expert Opin Drug Deliv*. 2024;21(6):829–843. doi:10.1080/17425247.2024.2375400
33. Armillotta MG, Lizzi L, Massimi M. Nanoparticle-based systems for liver therapy: overcoming fibrosis and enhancing drug efficacy. *World J Hepatol*. 2025;17(10):108810. doi:10.4254/wjh.v17.i10.108810
34. Öztürk K, Kaplan M, Çalış S. Effects of nanoparticle size, shape, and zeta potential on drug delivery. *Int J Pharm*. 2024;666:124799. doi:10.1016/j.ijpharm.2024.124799
35. Liu C, Jiang X, Gan Y, Yu M. Engineering nanoparticles to overcome the mucus barrier for drug delivery: design, evaluation and state-of-the-art. *Med Drug Discovery*. 2021;12:100110. doi:10.1016/j.medidd.2021.100110
36. Kaps L, Limeres MJ, Schneider P, et al. Liver cell type-specific targeting by nanoformulations for therapeutic applications. *Int J Mol Sci*. 2023;24(14). doi:10.3390/ijms241411869

37. Schnabl B, Damman CJ, Carr RM. Metabolic dysfunction-associated steatotic liver disease and the gut microbiome: pathogenic insights and therapeutic innovations. *J Clin Invest*. 2025;135(7). doi:10.1172/jci186423
38. Wang Y, Mo Y, Sun Y, et al. Intestinal nanoparticle delivery and cellular response: a review of the bidirectional nanoparticle-cell interplay in mucosa based on physiochemical properties. *J Nanobiotechnology*. 2024;22(1):669. doi:10.1186/s12951-024-02930-6
39. Zhang Z, Lu Y, Qi J, Wu W. An update on oral drug delivery via intestinal lymphatic transport. *Acta Pharm Sin B*. 2021;11(8):2449–2468. doi:10.1016/j.apsb.2020.12.022
40. Ramírez-Cortés F, Ménová P. Hepatocyte targeting via the asialoglycoprotein receptor. *RSC Med Chem*. 2025;16(2):525–544. doi:10.1039/d4md00652f
41. Hua Z, Li X, Yu L, et al. Liver-targeting exosomes loaded naringenin ameliorate metabolic dysfunction-associated steatotic liver disease through ubiquitin-proteasome system initiated lipophagy. *Chem Eng J*. 2025;523:168040. doi:10.1016/j.cej.2025.168040
42. Xu C, Zhu H, Wang K, et al. Oral celastrol micelles forming high-density lipoprotein corona targeting hepatocytes for MASLD treatment. *Adv Sci*. 2025;12(45):e00854. doi:10.1002/advs.202500854
43. Shinn J, Park S, Lee S, et al. Antioxidative hyaluronic acid-bilirubin nanomedicine targeting activated hepatic stellate cells for anti-hepatic-fibrosis therapy. *ACS Nano*. 2024;18(6):4704–4716. doi:10.1021/acsnano.3c06107
44. Guo F, Luo S, Wang L, et al. Protein Corona, influence on drug delivery system and its improvement strategy: a review. *Int J Biol Macromol*. 2024;256(Pt 2):128513. doi:10.1016/j.ijbiomac.2023.128513
45. Rideau E, Dimova R, Schwille P, Wurm FR, Landfester K. Liposomes and polymersomes: a comparative review towards cell mimicking. *Chem Soc Rev*. 2018;47(23). doi:10.1039/c8cs00162f
46. Fulton MD, Najahi-Missaoui W. Liposomes in cancer therapy: how did we start and where are we now. *Int J Mol Sci*. 2023;24(7). doi:10.3390/ijms24076615
47. Pande S. Liposomes for drug delivery: review of vesicular composition, factors affecting drug release and drug loading in liposomes. *Artif Cells Nanomed Biotechnol*. 2023;51(1):428–440. doi:10.1080/21691401.2023.2247036
48. Guimarães D, Cavaco-Paulo A, Nogueira E. Design of liposomes as drug delivery system for therapeutic applications. *Int J Pharm*. 2021;601:120571. doi:10.1016/j.ijpharm.2021.120571
49. Pi D, Liang Z, Pan J, et al. Tanshinone IIA inhibits the endoplasmic reticulum stress-induced unfolded protein response by activating the PPARα/FGF21 axis to ameliorate nonalcoholic steatohepatitis. *Antioxidants*. 2024;13(9). doi:10.3390/antiox13091026
50. Cai C, Liu K, Yang D, et al. The nanocrystal-loaded liposome of tanshinone IIA with high drug loading and stability towards efficient liver fibrosis reversion. *Nanomedicine*. 2025;63:102797. doi:10.1016/j.nano.2024.102797
51. Chen Y, Jiang Z, Xu J, et al. Improving the ameliorative effects of berberine and curcumin combination via dextran-coated bilosomes on non-alcohol fatty liver disease in mice. *J Nanobiotechnology*. 2021;19(1):230. doi:10.1186/s12951-021-00979-1
52. Liu H, Jiang N, Kuang G, et al. Chrysin and its nanoliposome ameliorated non-alcoholic steatohepatitis via inhibiting TLR4 signalling pathway. *J Pharm Pharmacol*. 2023;75(8):1046–1057. doi:10.1093/jpp/rgad031
53. Farooq A, Iqbal A, Rana NF, et al. A novel sprague-dawley rat model presents improved NASH/NAFLD symptoms with PEG coated vitexin liposomes. *Int J Mol Sci*. 2022;23(6). doi:10.3390/ijms23063131
54. Liu J, Yuan Y, Gong X, et al. Baicalin and its nanoliposomes ameliorates nonalcoholic fatty liver disease via suppression of TLR4 signaling cascade in mice. *Int Immunopharmacol*. 2020;80:106208. doi:10.1016/j.intimp.2020.106208
55. Imperlini E, Di Marzio L, Cevenini A, et al. Unraveling the impact of different liposomal formulations on the plasma protein Corona composition might give hints on the targeting capability of nanoparticles. *Nanoscale Adv*. 2024;6(17):4434–4449. doi:10.1039/d4na00345d
56. Pan J, Wang Y, Chen Y, et al. Emerging strategies against accelerated blood clearance phenomenon of nanocarrier drug delivery systems. *J Nanobiotechnology*. 2025;23(1):138. doi:10.1186/s12951-025-03209-0
57. He H, Lu Y, Qi J, Zhu Q, Chen Z, Wu W. Adapting liposomes for oral drug delivery. *Acta Pharm Sin B*. 2019;9(1):36–48. doi:10.1016/j.apsb.2018.06.005
58. Musakhanian J, Osborne DW. Understanding microemulsions and nanoemulsions in (Trans)Dermal delivery. *AAPS Pharm Sci Tech*. 2025;26(1):31. doi:10.1208/s12249-024-02997-2
59. Silberstein S, Spierings ELH, Kunkel T. Celecoxib oral solution and the benefits of Self-Microemulsifying Drug Delivery Systems (SMEDDS) technology: a narrative review. *Pain Ther*. 2023;12(5):1109–1119. doi:10.1007/s40122-023-00529-7
60. Priani SE, Fakih TM, Wilar G, Chaerunisaa AY, Sopyan I. Quality by design and in silico approach in SNEDDS development: a comprehensive formulation framework. *Pharmaceutics*. 2025;17(6). doi:10.3390/pharmaceutics17060701
61. Yang Y, Qiu W, Xiao J, Sun J, Ren X, Jiang L. Dihydromyricetin ameliorates hepatic steatosis and insulin resistance via AMPK/PGC-1α and PPARα-mediated autophagy pathway. *J Transl Med*. 2024;22(1):309. doi:10.1186/s12967-024-05060-7
62. Li J, Yin M, Tian M, Fang J, Xu H. Stiff-Soft hybrid biomimetic nano-emulsion for targeted liver delivery and treatment of early nonalcoholic fatty liver disease. *Pharmaceutics*. 2024;16(10). doi:10.3390/pharmaceutics16101303
63. Lyu Q, Chen L, Lin S, Cao H, Teng H. A designed self-microemulsion delivery system for dihydromyricetin and its dietary intervention effect on high-fat-diet fed mice. *Food Chem*. 2022;390:132954. doi:10.1016/j.foodchem.2022.132954
64. He J, Chen W, Chen S, et al. Microemulsion co-delivering curcumin and DHA-rich algal oil alleviates nonalcoholic fatty liver disease. *Journal of Functional Foods*. 2024;112:105998. doi:10.1016/j.jff.2023.105998
65. Li B, Jiang XF, Dong YJ, et al. The effects of Atractylodes macrocephala extract BZEP self-microemulsion based on gut-liver axis HDL/LPS signaling pathway to ameliorate metabolic dysfunction-associated fatty liver disease in rats. *Biomed Pharmacother*. 2024;175:116519. doi:10.1016/j.biopha.2024.116519
66. Uttreja P, Karnik I, Adel Ali Youssef A, et al. Self-Emulsifying Drug Delivery Systems (SEDDS): transition from liquid to solid-a comprehensive review of formulation, characterization, applications, and future trends. *Pharmaceutics*. 2025;17(1). doi:10.3390/pharmaceutics17010063
67. Silva-Neto AF, De Carvalho Amaral AR, Danda LJA, et al. Decoding excipients in lipid-based self-emulsifying drug delivery systems: insights into physicochemical properties and therapeutic outcomes. *Int J Pharm*. 2025;683:126018. doi:10.1016/j.ijpharm.2025.126018

68. Liu M, Wang F, Pu C, Tang W, Sun Q. Nanoencapsulation of lutein within lipid-based delivery systems: characterization and comparison of zein peptide stabilized nano-emulsion, solid lipid nanoparticle, and nano-structured lipid carrier. *Food Chem*. 2021;358:129840. doi:10.1016/j.foodchem.2021.129840
69. Madkhali OA. Perspectives and prospective on solid lipid nanoparticles as drug delivery systems. *Molecules*. 2022;27(5). doi:10.3390/molecules27051543
70. Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. *Pharmaceutics*. 2023;15(6). doi:10.3390/pharmaceutics15061593
71. Naeini F, Namkhah Z, Ostadrahimi A, Tutunchi H, Hosseinzadeh-Attar MJ. A comprehensive systematic review of the effects of naringenin, a citrus-derived flavonoid, on risk factors for nonalcoholic fatty liver disease. *Adv Nutr*. 2021;12(2):413–428. doi:10.1093/advances/nmaa106
72. Hu R, Liu S, Anwaier G, et al. Formulation and intestinal absorption of naringenin loaded nanostructured lipid carrier and its inhibitory effects on nonalcoholic fatty liver disease. *Nanomedicine*. 2021;32:102310. doi:10.1016/j.nano.2020.102310
73. Oanh HT, Hoai Thu NT, Van Hanh N, Hoang MH, Minh Hien HT. Co-encapsulated astaxanthin and kaempferol nanoparticles: fabrication, characterization, and their potential synergistic effects on treating non-alcoholic fatty liver disease. *RSC Adv*. 2023;13(50):35127–35136. doi:10.1039/d3ra06537e
74. Jeitler R, Glader C, König G, et al. On the structure, stability, and cell uptake of nanostructured lipid carriers for drug delivery. *Mol Pharm*. 2024;21(7):3674–3683. doi:10.1021/acs.molpharmaceut.4c00392
75. Buya AB, Mahlangu P, Witika BA. From lab to industrial development of lipid nanocarriers using quality by design approach. *Int J Pharm X*. 2024;8:100266. doi:10.1016/j.ijpx.2024.100266
76. Hari SK, Gauba A, Shrivastava N, Tripathi RM, Jain SK, Pandey AK. Polymeric micelles and cancer therapy: an ingenious multimodal tumor-targeted drug delivery system. *Drug Deliv Transl Res*. 2023;13(1):135–163. doi:10.1007/s13346-022-01197-4
77. Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: from nanoformulation to clinical approval. *Adv Drug Deliv Rev*. 2020;156:80–118. doi:10.1016/j.addr.2020.09.009
78. Biswas S. Polymeric micelles as drug-delivery systems in cancer: challenges and opportunities. *Nanomedicine*. 2021;16(18):1541–1544. doi:10.2217/nnm-2021-0081
79. He X, Li Y, Deng X, Xiao X, Zeng J. Integrative evidence construction for resveratrol treatment of nonalcoholic fatty liver disease: preclinical and clinical meta-analyses. *Front Pharmacol*. 2023;14:1230783. doi:10.3389/fphar.2023.1230783
80. Teng W, Zhao L, Yang S, et al. The hepatic-targeted, resveratrol loaded nanoparticles for relief of high fat diet-induced nonalcoholic fatty liver disease. *J Control Release*. 2019;307:139–149. doi:10.1016/j.jconrel.2019.06.023
81. Li X, Chen XX, Xu Y, et al. Construction of glycogen-based nanoparticles loaded with resveratrol for the alleviation of high-fat diet-induced nonalcoholic fatty liver disease. *Biomacromolecules*. 2022;23(1):409–423. doi:10.1021/acs.biomac.1c01360
82. Wang Q, Huang X, Zhao Z, Li Z. Oxidative stress-responsive fluorescent polymer nanoplatform regulate lipid metabolism through lipophagy. *Spectrochim Acta A Mol Biomol Spectrosc*. 2025;344(Pt 1):126695. doi:10.1016/j.saa.2025.126695
83. Beheshti Namdar A, Ahadi M, Hoseini SM, et al. Effect of nano-micelle curcumin on hepatic enzymes: a new treatment approach for non-alcoholic fatty liver disease (NAFLD). *Avicenna J Phytomed*. 2023;13(6):615–625. doi:10.22038/ajp.2023.21919
84. Cho S, Rasoulianboroujeni M, Kang RH, Kwon GS. From conventional to next-generation strategies: recent advances in polymeric micelle preparation for drug delivery. *Pharmaceutics*. 2025;17(10). doi:10.3390/pharmaceutics17101360
85. Beach MA, Nayanathara U, Gao Y, et al. Polymeric nanoparticles for drug delivery. *Chem Rev*. 2024;124(9):5505–5616. doi:10.1021/acs.chemrev.3c00705
86. Lima AL, Gratieri T, Cunha-Filho M, Gelfuso GM. Polymeric nanocapsules: a review on design and production methods for pharmaceutical purpose. *Methods*. 2022;199:54–66. doi:10.1016/j.ymeth.2021.07.009
87. Leyva-Gómez G, Piñón-Segundo E, Mendoza-Muñoz N, Zambrano-Zaragoza ML, Mendoza-Elvira S, Quintanar-Guerrero D. Approaches in polymeric nanoparticles for vaginal drug delivery: a review of the state of the art. *Int J Mol Sci*. 2018;19(6). doi:10.3390/ijms19061549
88. El-Say KM, El-Sawy HS. Polymeric nanoparticles: promising platform for drug delivery. *Int J Pharm*. 2017;528(1–2):675–691. doi:10.1016/j.ijpharm.2017.06.052
89. Floyd TG, Gurnani P, Rho JY. Characterisation of polymeric nanoparticles for drug delivery. *Nanoscale*. 2025;17(13):7738–7752. doi:10.1039/d5nr00071h
90. Liu X, Zhang M, Tian Y, et al. Development, characterization, and investigation of in vivo targeted delivery efficacy of luteolin-loaded, eudragit S100-Coated mPEG-PLGA nanoparticles. *AAPS Pharm Sci Tech*. 2022;23(4):100. doi:10.1208/s12249-022-02255-3
91. Liu X, Sun R, Li Z, et al. Luteolin alleviates non-alcoholic fatty liver disease in rats via restoration of intestinal mucosal barrier damage and microbiota imbalance involving in gut-liver axis. *Arch Biochem Biophys*. 2021;711:109019. doi:10.1016/j.abb.2021.109019
92. Yu Y, Wang Q, Huang X, Li Z. GA receptor targeted chitosan oligosaccharide polymer nanoparticles improve non-alcoholic fatty liver disease by inhibiting ferroptosis. *Int J Biol Macromol*. 2024;278(Pt 2):134779. doi:10.1016/j.ijbiomac.2024.134779
93. Jantawong C, Priprem A, Intuyod K, et al. Curcumin-loaded nanocomplexes: acute and chronic toxicity studies in mice and hamsters. *Toxicol Rep*. 2021;8:1346–1357. doi:10.1016/j.toxrep.2021.06.021
94. Sitthirach C, Charoensuk L, Pairojkul C, et al. Curcumin-loaded nanocomplexes ameliorate the severity of nonalcoholic steatohepatitis in hamsters infected with Opisthorchis viverrini. *PLoS One*. 2022;17(9):e0275273. doi:10.1371/journal.pone.0275273
95. Ma S, Feng X, Liu F, Wang B, Zhang H, Niu X. The pro-inflammatory response of macrophages regulated by acid degradation products of poly (lactide-co-glycolide) nanoparticles. *Eng Life Sci*. 2021;21(10):709–720. doi:10.1002/elsc.202100040
96. Zhai Z, Niu J, Xu L, Xu J. Advanced application of polymer nanocarriers in delivery of active ingredients from traditional chinese medicines. *Molecules*. 2024;29(15). doi:10.3390/molecules29153520
97. Delgado-Pujol EJ, Martínez G, Casado-Jurado D, et al. Hydrogels and nanogels: pioneering the future of advanced drug delivery systems. *Pharmaceutics*. 2025;17(2). doi:10.3390/pharmaceutics17020215
98. Mauri E, Gori M, Giannitelli SM, et al. Nano-encapsulation of hydroxytyrosol into formulated nanogels improves therapeutic effects against hepatic steatosis: an in vitro study. *Mater Sci Eng C Mater Biol Appl*. 2021;124:112080. doi:10.1016/j.msec.2021.112080
99. Karchilakis G, Varlas S, Johnson EC, et al. Capturing enzyme-loaded diblock copolymer vesicles using an aldehyde-functionalized hydrophilic polymer brush. *Langmuir*. 2024;40(27):14086–14098. doi:10.1021/acs.langmuir.4c01561

100. Zhu Y, Ruan S, Shen H, Guan Q, Zhai L, Yang Y. Oridonin regulates the polarized state of Kupffer cells to alleviate nonalcoholic fatty liver disease through ROS-NF-κB. *Int Immunopharmacol*. 2021;101(Pt B):108290. doi:10.1016/j.intimp.2021.108290
101. Zhang L, Yu Y, Wang Q, Huang X, Feng Z, Li Z. Oridonin loaded peptide nanovesicles alleviate nonalcoholic fatty liver disease in mice. *Pharm Dev Technol*. 2024;29(2):123–130. doi:10.1080/10837450.2024.2315460
102. Mahmud MM, Pandey N, Winkles JA, Woodworth GF, Kim AJ. Toward the scale-up production of polymeric nanotherapeutics for cancer clinical trials. *Nano Today*. 2024;56. doi:10.1016/j.nantod.2024.102314
103. Falsafi SR, Topuz F, Bajer D, et al. Metal nanoparticles and carbohydrate polymers team up to improve biomedical outcomes. *Biomed Pharmacother*. 2023;168:115695. doi:10.1016/j.biopha.2023.115695
104. Sajjadi M, Nasrollahzadeh M, Jaleh B, Soufi GJ, Iravani S. Carbon-based nanomaterials for targeted cancer nanotherapy: recent trends and future prospects. *J Drug Target*. 2021;29(7):716–741. doi:10.1080/1061186x.2021.1886301
105. Tao Y, Xu S, Wang J, et al. Delivery of microRNA-33 antagomirs by mesoporous silica nanoparticles to ameliorate lipid metabolic disorders. *Front Pharmacol*. 2020;11:921. doi:10.3389/fphar.2020.00921
106. Jiang M, Tao X, Pang Y, Qin Z, Song E, Song Y. Copper oxide nanoparticles induce non-alcoholic fatty liver disease by disrupting bile acid homeostasis and perturbing the intestinal microbial homeostasis. *J Hazard Mater*. 2024;480:136416. doi:10.1016/j.jhazmat.2024.136416
107. Jia J, Li F, Zhou H, et al. Oral exposure to silver nanoparticles or silver ions may aggravate fatty liver disease in overweight mice. *Environ Sci Technol*. 2017;51(16):9334–9343. doi:10.1021/acs.est.7b02752
108. Chen H, Zhou S, Chen W, et al. PEG-GNPs aggravate MCD-induced steatohepatitic injury and liver fibrosis in mice through excessive lipid accumulation-mediated hepatic inflammatory damage. *NanoImpact*. 2023;31:100469. doi:10.1016/j.impact.2023.100469
109. Saker R, Regdon G, Sovány T. Pharmacokinetics and toxicity of inorganic nanoparticles and the physicochemical properties/factors affecting them. *J Drug Delivery Sci Technol*. 2024;99:105979. doi:10.1016/j.jddst.2024.105979
110. Abdelmoneim D, Eldomany EB, El-Adl M, Farghali A, El-Sayed G, El-Sherbini ES. Possible protective effect of natural flavanone naringenin-reduced graphene oxide nanosheets on nonalcoholic fatty liver disease. *Naunyn Schmiedebergs Arch Pharmacol*. 2025;398(4):4071–4086. doi:10.1007/s00210-024-03495-9
111. Lei S, Wu Q, Zhang B, Lu M, Xia Y, Li N. Liver-Targeting nanoparticles GA-MSe@AR Treat NAFLD through dual lipid-lowering and antioxidant efficacy. *Int J Nanomed*. 2025;20:5017–5037. doi:10.2147/ijn.S510577
112. Ahmed ES, Mohamed HE, Farrag MA. Luteolin loaded on zinc oxide nanoparticles ameliorates non-alcoholic fatty liver disease associated with insulin resistance in diabetic rats via regulation of PI3K/AKT/FoxO1 pathway. *Int J Immunopathol Pharmacol*. 2022;36:3946320221137435. doi:10.1177/03946320221137435
113. Tong Y, Yu X, Huang Y, Zhang Z, Mi L, Bao Z. Hepatic-targeted nano-enzyme with resveratrol loading for precise relief of nonalcoholic steatohepatitis. *ChemMedChem*. 2023;18(5):e202200468. doi:10.1002/cmdc.202200468
114. Baruah H, Sarma A, Basak D, Das M. Exosome: from biology to drug delivery. *Drug Deliv Transl Res*. 2024;14(6):1480–1516. doi:10.1007/s13346-024-01515-y
115. Kuang Y, Li Z, Chen H, Wang X, Wen Y, Chen J. Advances in self-assembled nanotechnology in tumor therapy. *Colloids Surf B Biointerfaces*. 2024;237:113838. doi:10.1016/j.colsurfb.2024.113838
116. Sitia L, Saccomandi P, Bianchi L, et al. Combined ferritin nanocarriers with ICG for effective phototherapy against breast cancer. *Int J Nanomed*. 2024;19:4263–4278. doi:10.2147/ijn.S445334
117. Qu N, Song K, Ji Y, et al. Albumin nanoparticle-based drug delivery systems. *Int J Nanomed*. 2024;19:6945–6980. doi:10.2147/ijn.S467876
118. Spada A, Emami J, Tuszynski JA, Lavasanifar A. The uniqueness of albumin as a carrier in nanodrug delivery. *Mol Pharm*. 2021;18(5):1862–1894. doi:10.1021/acs.molpharmaceut.1c00046
119. Karami E, Mesbahi Moghaddam M, Kazemi-Lomedasht F. Use of albumin for drug delivery as a diagnostic and therapeutic tool. *Curr Pharm Biotechnol*. 2024;25(6):676–693. doi:10.2174/1389201024666230807161200
120. Ashraf S, Qaiser H, Tariq S, et al. Unraveling the versatility of human serum albumin - A comprehensive review of its biological significance and therapeutic potential. *Curr Res Struct Biol*. 2023;6:100114. doi:10.1016/j.crstbi.2023.100114
121. Wang X, Abu Bakar MH, Liqun S, Kassim MA, Shariff KA, Karunakaran T. Targeting metabolic diseases with celastrol: a comprehensive review of anti-inflammatory mechanisms and therapeutic potential. *J Ethnopharmacol*. 2025;344:119560. doi:10.1016/j.jep.2025.119560
122. Fan N, Zhao J, Zhao W, et al. Celastrol-loaded lactosylated albumin nanoparticles attenuate hepatic steatosis in non-alcoholic fatty liver disease. *J Control Release*. 2022;347:44–54. doi:10.1016/j.jconrel.2022.04.034
123. Yue C, Li D, Fan S, et al. Long-term and liver-selected ginsenoside C-K nanoparticles retard NAFLD progression by restoring lipid homeostasis. *Biomaterials*. 2023;301:122291. doi:10.1016/j.biomaterials.2023.122291
124. Guzzi R, Bartucci R. Thermal effects and drugs competition on the palmitate binding capacity of human serum albumin. *Biochem Biophys Res Commun*. 2024;722:150168. doi:10.1016/j.bbrc.2024.150168
125. Ailuno G, Baldassari S, Lai F, Florio T, Caviglioli G. Exosomes and extracellular vesicles as emerging theranostic platforms in cancer research. *Cells*. 2020;9(12). doi:10.3390/cells9122569
126. Dad HA, Gu TW, Zhu AQ, Huang LQ, Peng LH. Plant exosome-like nanovesicles: emerging therapeutics and drug delivery nanoplatforms. *Mol Ther*. 2021;29(1):13–31. doi:10.1016/j.ymthe.2020.11.030
127. Wang X, Chen W, Zeng W, et al. Extracellular vesicles as biomarkers and drug delivery systems for tumor. *Acta Pharm Sin B*. 2025;15(7):3460–3486. doi:10.1016/j.apsb.2025.04.033
128. Guo M, Song C, Tang J, et al. Changes in tea exosome-like nanoparticles fermented by Aspergillus cristatus and the preventive effects on non-alcoholic fatty liver disease. *RSC Adv*. 2025;15(43):36504–36513. doi:10.1039/d5ra03044g
129. Xu M, Ma L, Liang H, Tang W, Gu S. Protective effects of small RNAs encapsulated in *Artemisia capillaris*-derived exosomes against non-alcoholic fatty liver disease. *Front Pharmacol*. 2024;15:1476820. doi:10.3389/fphar.2024.1476820
130. Liu J, Li W, Bian Y, et al. Garlic-derived exosomes regulate PFKFB3 expression to relieve liver dysfunction in high-fat diet-fed mice via macrophage-hepatocyte crosstalk. *Phytomedicine*. 2023;112:154679. doi:10.1016/j.phymed.2023.154679
131. Zou J, Song Q, Shaw PC, Wu Y, Zuo Z, Yu R. Tangerine peel-derived exosome-like nanovesicles alleviate hepatic steatosis induced by type 2 diabetes: evidenced by regulating lipid metabolism and intestinal microflora. *Int J Nanomed*. 2024;19:10023–10043. doi:10.2147/ijn.S478589

132. Liu B, Nguyen PL, Yu H, et al. Honey vesicle-like nanoparticles protect aged liver from non-alcoholic steatohepatitis. *Acta Pharm Sin B*. 2024;14(8):3661–3679. doi:10.1016/j.apsb.2024.05.002
133. Li P, Wu QY, Zhou YH, et al. Honeysuckle-derived exosome-like nanovesicles ameliorate metabolic-associated fatty liver disease by modulating gut microbiota and its metabolites. *Nano Research*. 2025;18(12):94907986. doi:10.26599/NR.2025.94907986
134. Wu C, Xiang S, Wang H, et al. Orally deliverable sequence-targeted fucoxanthin-loaded biomimetic extracellular vesicles for alleviation of nonalcoholic fatty liver disease. *ACS Appl Mater Interfaces*. 2024;16(8):9854–9867. doi:10.1021/acsami.3c18029
135. Tawfeek GA, Kasem HA. Curcumin preconditioned mesenchymal stem cells derived exosomes transplantation ameliorate and protect against non- alcoholic steatohepatitis by regulation the expression of key genes of inflammation and oxidative stress. *Transpl Immunol*. 2023;78:101837. doi:10.1016/j.trim.2023.101837
136. Welsh JA, Goberdhan DCI, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13(2):e12404. doi:10.1002/jev2.12404
137. Thakur A, Rai D. Global requirements for manufacturing and validation of clinical grade extracellular vesicles. *J Liq Biopsy*. 2024;6:100278. doi:10.1016/j.jlb.2024.100278
138. Verma N, Arora S. Navigating the global regulatory landscape for exosome-based therapeutics: challenges, strategies, and future directions. *Pharmaceutics*. 2025;17(8). doi:10.3390/pharmaceutics17080990
139. Fu S, Li G, Zang W, Zhou X, Shi K, Zhai Y. Pure drug nano-assemblies: a facile carrier-free nanoplatform for efficient cancer therapy. *Acta Pharm Sin B*. 2022;12(1):92–106. doi:10.1016/j.apsb.2021.08.012
140. Lin S, Zheng YJ, Xu YZ, et al. Hawthorn carbon dots: a novel therapeutic agent for modulating body weight and hepatic lipid profiles in high-fat diet-fed mice. *Nanoscale*. 2025;17(5):2668–2681. doi:10.1039/d4nr04486j
141. Zheng T, Gan X, Luo J, et al. Hyaluronic acid act as drug self-assembly chaperone and co-assembled with celalstrol for ameliorating non-alcoholic steatohepatitis. *Int J Biol Macromol*. 2024;282(Pt 5):137289. doi:10.1016/j.ijbiomac.2024.137289
142. Liang Z, Li J, Luo S, et al. Galactose receptor-mediated hepatic targeting system: engineering of quinary cationic liposomes for resveratrol delivery against hepatic steatosis. *RSC Adv*. 2025;15(25):19786–19801. doi:10.1039/d5ra02554k
143. Elbaset MA, Nasr M, Ibrahim BMM, et al. Curcumin nanoemulsion counteracts hepatic and cardiac complications associated with high-fat/high-fructose diet in rats. *J Food Biochem*. 2022;46(12):e14442. doi:10.1111/jfbc.14442
144. Mohebbati R, Momeni-Moghaddam MA, Asghari R, et al. The comparison of the effects of nano-silymarin and silymarin on high-fat diet-induced fatty liver of adult male rats. *Avicenna J Phytomed*. 2024;14(3):365–375. doi:10.22038/ajp.2024.23734
145. Lu J, Zeng Y, Zhong H, et al. Dual-Stimuli-responsive gut microbiota-targeting nitidine Chloride-CS/PT-NPs improved metabolic status in NAFLD. *Int J Nanomed*. 2024;19:2409–2428. doi:10.2147/ijn.S452194
146. Dong L, Lou W, Xu C, Wang J. Naringenin cationic lipid-modified nanoparticles mitigate MASLD progression by modulating lipid homeostasis and gut microbiota. *J Nanobiotechnology*. 2025;23(1):168. doi:10.1186/s12951-025-03228-x
147. Shi J, Yu B, Zhang J, et al. Reactive oxygen species-responsive liver-targeting nanoparticles enhance the therapeutic effect of baicalin magnesium in metabolic dysfunction-associated fatty liver disease. *Int J Pharm*. 2025;686:126354. doi:10.1016/j.ijpharm.2025.126354
148. Elhady SS, Wahba AS, Ibrahim AK, et al. Hepatoprotective potential of green synthesized nanoparticles from *Citrus reticulata* peel extract against HFS Diet-Induced NASH in mice, integrated with chemical profiling and molecular modeling. *ACS Omega*. 2025;10(32):36178–36202. doi:10.1021/acsomega.5c03992
149. Chen S, Liu Y, Ma S, et al. Aptamer-mediated liver-targeted curcumin delivery system based on tetrahedral framework nucleic acids for NAFLD. *Drug Deliv*. 2025;32(1):2576222. doi:10.1080/10717544.2025.2576222
150. Han X, Cai C, Deng W, et al. Landscape of human organoids: ideal model in clinics and research. *Innovation*. 2024;5(3):100620. doi:10.1016/j.xinn.2024.100620
151. Witten J, Raji I, Manan RS, et al. Artificial intelligence-guided design of lipid nanoparticles for pulmonary gene therapy. *Nat Biotechnol*. 2025;43(11):1790–1799. doi:10.1038/s41587-024-02490-y