pharmaceuticals

MDPI

Review

Nanostructured Natural Bioactives: A Promising Frontier for MASLD Therapy

Xu-Ting Shen [1], Qin-Mei Sun [2,3,4], Ru-Tao Lin [2,3], Xin Xin [2,3], Chen Zou [2,3], Ren-Qiang Zeng [2,3], Li-Li Shen [1], Jia Geng [5,6,7], Qin Feng [2,3,*] and Lei Shi [1,*]

1 Department of Clinical Laboratory, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
2 Institute of Liver Diseases, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
3 Key Laboratory of Liver and Kidney Diseases (Ministry of Education), Shuguang Hospital, Shanghai 200021, China
4 Institute of Interdisciplinary Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
5 Department of Laboratory Medicine, State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu 610041, China
6 Department of Laboratory Medicine, Clinical Laboratory Medicine Research Center, West China Hospital of Sichuan University, Chengdu 610041, China
7 Tianfu Jincheng Laboratory, City of Future Medicine, Chengdu 610000, China
* Correspondence: fengqin@shutcm.edu.cn (Q.F.); sg2800@shutcm.edu.cn (L.S.); Tel.: +86-21-20256185 (Q.F.); +86-13818226306 (L.S.)

Abstract

Background: Natural bioactives derived from medicinal plants and dietary sources have long been used to manage metabolic and hepatic disorders. However, their application in metabolic dysfunction-associated steatotic liver disease (MASLD) is restricted by poor solubility, instability, low bioavailability, rapid metabolism, and insufficient hepatic exposure. This review evaluates the pharmacological mechanisms and therapeutic potential of nanostructured natural bioactives for MASLD. **Methods**: Published preclinical and clinical evidence on natural bioactives and their nanostructured formulations for MASLD was narratively reviewed. Evidence was synthesized according to nanocarrier type, pharmacokinetic advantages, mechanisms of action, therapeutic outcomes, safety, and clinical translation. **Results**: The included studies primarily covered three categories: nanostructured natural small-molecule bioactives, bioactive fractions, and single-source therapeutics. Small-molecule bioactives constituted the largest group, encompassing flavonoids, polyphenols, terpenoids, alkaloids, and lignans. Liposomes, nanoemulsions, polymeric nanoparticles, and micelles were the principal delivery platforms used to improve effective exposure through encapsulation, protection, and controlled release. Mechanisms included modulation of AMPK, SREBP-1c/FAS-, and PPARα/CPT-1-related lipid metabolism, suppression of NF-κB-associated inflammation, and enhancement of Nrf2-related antioxidant defenses, collectively attenuating hepatic lipid accumulation and injury. Nanostructured bioactive fractions and single-source therapeutics additionally involved multicomponent interactions, intestinal barrier protection, and gut–liver axis modulation. Nanostructured small-molecule bioactives showed translational promise, with oral nano-curcumin providing preliminary clinical evidence, although its additional benefits on hepatic fat content were inconsistent. Naturally derived vesicle-like nanoparticles also showed potential, but their compositional standardization, in vivo behavior, and long-term safety require further investigation. **Conclusions**: Nanostructuring may improve the pharmacokinetic performance and pharmacological efficacy of natural bioactives against MASLD. Future studies

Check for updates

Academic Editors: Daniel Sepúlveda-Crespo and Silviya Petrova Zustiak

Received: 8 October 2026
Revised: 4 November 2026
Accepted: 11 November 2026
Published: 17 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

should prioritize standardized formulation characterization, dose–exposure–response relationships, direct comparisons with free bioactives, long-term safety, and clinical trials.

Keywords: nanostructure; liver disease; metabolic dysfunction-associated steatotic liver disease; therapeutic strategies; treatment

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed nonalcoholic fatty liver disease (NAFLD), is one of the most prevalent chronic liver disorders worldwide and is tightly linked to obesity, insulin resistance, type 2 diabetes, and metabolic syndrome [1]. Epidemiological estimates indicate that approximately 38% of adults and 7–14% of children and adolescents are affected, with projections suggesting that adult prevalence will exceed 55% by 2040 [2–4]. In certain Asian regions, the prevalence already surpasses 30% [5], and disease burden is even higher among individuals with obesity or diabetes, reaching 50–70% [6]. Driven by the global adoption of high-fat diets and population aging, MASLD is rapidly emerging as a major cause of liver fibrosis and hepatocellular carcinoma (Figure 1).



Figure 1. Progressive spectrum of MASLD from healthy liver to hepatocellular carcinoma. Continuous progression associated with MASLD from a healthy liver to hepatocellular carcinoma. Schematic illustration of the progressive spectrum of MASLD, depicting the transition from a healthy liver to simple steatosis, MASH, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma.

Despite the expanding global impact of MASLD, no pharmacotherapy has yet been approved by the U.S. Food and Drug Administration (FDA) for this indication. Current management relies predominantly on lifestyle therapy, including weight reduction, dietary control, and physical activity. Several approved drugs, such as glucagon-like peptide-1 receptor agonists, farnesoid X receptor agonists, and peroxisome proliferator-activated receptor modulators, have demonstrated certain efficacy in clinical trials; however, their efficacy is often limited and may be accompanied by notable adverse effects. Bioactive compounds derived from natural sources possess unique advantages in the treatment of metabolic-related liver diseases. Numerous small-molecule phytochemicals, including quercetin, berberine, and naringenin, have been shown to ameliorate steatosis, oxidative stress, inflammation, and fibrogenesis through modulation of key signaling pathways such as AMPK, Nrf2, and NF-κB [7–9]. However, these bioactive compounds generally exhibit unfavorable pharmacokinetic properties, including poor solubility, low oral absorption, uneven tissue distribution, and rapid metabolism, which substantially limit their clinical efficacy [10].

In recent years, advances in nanotechnology have provided promising opportunities to overcome these limitations. Nanostructured systems, including lipid nanoparticles, nanoemulsions, polymeric nanoparticles, inorganic nanomaterials, and exosome-mimetic nanovesicles, can effectively enhance drug solubility and stability, improve systemic pharmacokinetics, and enable liver-targeted delivery, ultimately increasing bioavailability and

therapeutic efficacy [11–14]. By enabling precise control over drug release kinetics and prolonging retention in target tissues, these nanostructures can enhance therapeutic efficacy and reduce adverse effects [15,16].

2. Pathophysiological Mechanisms of MASLD

MASLD is a complex metabolic disorder characterized by a multifactorial and multistage pathological progression. Its major pathogenic mechanisms include insulin resistance, dysregulated lipid metabolism, inflammatory responses, oxidative stress, gut microbiota dysbiosis with disruption of the gut–liver axis, and genetic susceptibility. These processes do not operate in isolation; rather, they interact in a tightly interconnected network that propels the transition from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and ultimately hepatocellular carcinoma.

Insulin resistance (IR) is widely regarded as a central driver of MASLD initiation and progression. Reduced insulin sensitivity in the liver and peripheral tissues enhances hepatic gluconeogenesis while attenuating insulin-mediated suppression of lipolysis in adipose tissue, resulting in an increased flux of free fatty acids (FFAs) to the liver. This influx promotes triglyceride synthesis and hepatic lipid accumulation [17,18]. Intracellular lipid overload further disrupts insulin signaling through activation of protein kinase C (PKC) and c-Jun N-terminal kinase 1 (JNK1), leading to aberrant serine phosphorylation of insulin receptor substrates (IRS-1 and IRS-2) rather than their physiological tyrosine phosphorylation. This impairs downstream insulin signaling and exacerbates hepatic insulin resistance [15,19–21].

Perturbations in lipid metabolism constitute the most direct mechanistic basis for hepatic steatosis and its progression. These disturbances encompass increased fatty acid influx, enhanced de novo lipogenesis (DNL), reduced fatty acid oxidation, and intrahepatic retention of very-low-density lipoproteins (VLDL). When lipid uptake and synthesis exceed hepatic export and oxidation, triglycerides accumulate within hepatocytes, leading to steatosis [22,23]. Beyond local lipid deposition, disordered lipid metabolism is closely linked to systemic metabolic dysfunction [18]. Patients with MASLD frequently exhibit hypertriglyceridemia, hyperinsulinemia, and other features of metabolic syndrome [24].

Lipotoxicity and oxidative stress activate resident hepatic immune cells, including Kupffer cells, which secrete pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β, thereby establishing a persistent pro-inflammatory microenvironment. Activated Kupffer cells also release profibrogenic mediators, notably transforming growth factor-β (TGF-β), which stimulate hepatic stellate cell (HSC) activation. Activated HSCs undergo phenotypic transdifferentiation into myofibroblast-like cells and produce excessive extracellular matrix (ECM), driving fibrogenesis [25–27]. Meanwhile, oxidative stress directly damages hepatocyte membranes and mitochondrial function and amplifies inflammatory signaling via pathways such as NF-κB, JNK, and the NLRP3 inflammasome. Sustained oxidative injury and inflammation promote hepatocyte apoptosis and necrosis, accelerating fibrotic remodeling and functional decline and ultimately facilitating progression toward cirrhosis and hepatocellular carcinoma [28,29].

Gut microbiota dysbiosis can disrupt the gut–liver axis, which plays a critical role in maintaining intestinal barrier integrity and hepatic homeostasis, thereby contributing to the initiation and progression of MASLD [30,31]. Increased intestinal permeability permits translocation of microbial products such as LPS into the portal circulation, triggering hepatic immune activation and promoting inflammatory and oxidative stress responses that exacerbate liver injury [32–35]. Short-chain fatty acids (SCFAs) and bile acids can regulate hepatic metabolism and insulin sensitivity, thereby contributing to disease progression [36].

Genetic susceptibility influences lipid accumulation and inflammatory responses, helping to explain interindividual differences in disease susceptibility and progression [37–40]. These genetic factors may act independently or synergistically to regulate hepatic lipid metabolism, inflammation, and fibrogenesis, thereby affecting disease severity (Figure 2).

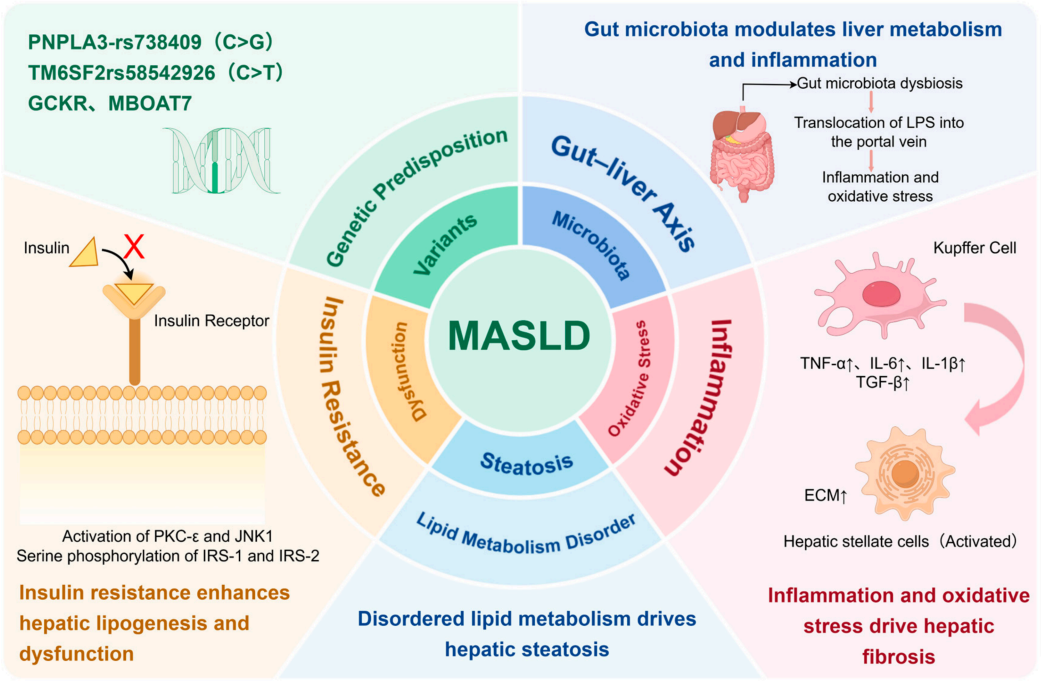


Figure 2. Multifactorial mechanisms underlying MASLD initiation and progression. Integrated pathogenic network underlying MASLD. Schematic overview of the interconnected mechanisms driving MASLD initiation and progression. Central features include insulin-resistance-mediated metabolic dysfunction, disordered hepatic lipid metabolism, oxidative stress, and chronic inflammation, which collectively promote the transition from hepatic steatosis to steatohepatitis and fibrosis. Genetic susceptibility variants (e.g., PNPLA3, TM6SF2, GCKR, and MBOAT7) modulate individual risk and disease severity. Dysbiosis of the gut microbiota and disruption of the gut–liver axis further exacerbate hepatic injury through lipopolysaccharide translocation, inflammatory cytokine release, and metabolic dysregulation. Crosstalk among hepatocytes, Kupffer cells, and hepatic stellate cells amplifies inflammatory and fibrogenic signaling, ultimately contributing to extracellular matrix deposition and liver fibrosis. This figure summarizes the multifactorial and network-based pathophysiology of MASLD and highlights key molecular and cellular pathways implicated in disease progression.

3. Representative Nanostructures for MASLD Therapy

Nanostructured systems can generally be classified into two categories: carrier-based and carrier-free nanostructures. Carrier-based nanostructures include liposomes, nanoemulsions, inorganic nanoparticles, polymeric nanoparticles, micelles, and nanogels. These systems rely on exogenous materials as drug carriers and offer advantages such as well-established fabrication methods, controlled drug release, and versatile surface modification. In contrast, carrier-free nanostructures are formed through the self-assembly of drug molecules themselves or in combination with small molecular excipients to generate nanoscale particles or vesicles. This strategy avoids the potential toxicity and immunogenicity associated with exogenous carrier materials while enabling higher drug-loading efficiency. Representative examples, including self-assembled nanostructures and vesicle-like nanoparticles, have increasingly been explored for MASLD intervention in recent years and have shown promising therapeutic potential.

3.1. Carrier-Based Nanostructures

3.1.1. Liposomes

Liposomes are vesicular nanocarriers composed of phospholipid bilayers or multilayers that encapsulate therapeutic agents within an aqueous core or lipid membrane. However, formulation stability remains an important limitation, particularly following oral administration. Orally administered liposomes encounter gastric acidity, bile salts, digestive enzymes, dilution, and mucus, which may cause membrane disruption, aggregation, oxidation, or premature drug leakage. Protective polymer coatings, suitable lipid composition, or enteric formulations may improve performance. Liposomes are particularly suitable for hydrophobic natural small molecules, such as flavonoids and terpenoids. Liposomal encapsulation enhances aqueous solubility, protects labile compounds from gastrointestinal degradation, prolongs circulation half-life, and facilitates hepatic accumulation through uptake by Kupffer cells and hepatocytes, thereby improving therapeutic efficacy in liver disease [41–44]. In MASLD models, natural products such as silybin, baicalin, and glycyrrhizin derivatives exhibit superior oral absorption, hepatic distribution, and anti-steatotic and anti-inflammatory effects when delivered via liposomal formulations compared with their free-drug counterparts [45].

3.1.2. Nanoemulsions

Nanoemulsions are colloidal systems consisting of nanoscale oil droplets dispersed in an aqueous phase and stabilized by surfactants. Although thermodynamically unstable, they are kinetically stable and typically range from 20 to 200 nm in diameter. Nanoemulsions offer high drug-loading capacity, improved bioavailability, and favorable stability, making them particularly suitable for lipophilic natural compounds such as curcumin, resveratrol, and vitamin E [46–48]. Following oral or intravenous administration, nanoemulsion-based formulations can significantly enhance solubility and systemic absorption of hydrophobic agents, thereby augmenting their therapeutic effects on hepatic steatosis, inflammation, and fibrosis [49].

3.1.3. Inorganic Nanoparticles

Inorganic nanoparticles are particles whose principal matrix is an inorganic material, including elemental selenium, metals, metal oxides (such as ZnO or CeO_2), and mesoporous silica [50]. They are distinguished from lipid- or polymer-based organic carriers. Depending on composition, they possess unique physicochemical properties such as intrinsic antioxidant or catalytic activity and versatile surface functionalization. These systems are commonly used either as therapeutic or adjunctive nanomedicines themselves or as delivery carriers for drugs and nucleic acids [51–53]. For instance, chitosan-stabilized selenium nanoparticles have demonstrated antioxidant activity, modulation of intestinal barrier integrity, and improvement of metabolic steatosis in experimental models. Nonetheless, the hepatic biocompatibility of inorganic nanomaterials varies widely. Some studies suggest that certain unmodified or high-dose inorganic nanoparticles may exacerbate lipid metabolic disturbances or induce oxidative stress in the liver [54,55]. Consequently, material selection and rigorous biocompatibility evaluation are critical considerations in the development and translational application of inorganic nanoplatforms for MASLD.

3.1.4. Polymeric Nanoparticles

Polymeric nanoparticles are nanoscale carriers fabricated from natural or synthetic polymers, most commonly poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG) [56]. These systems offer controlled drug release, favorable biocompatibility, and structural stability, and can be readily engineered through surface modification to

achieve targeted delivery. By enabling sustained release, ligand-mediated hepatic targeting, and optimized drug-loading capacity, polymeric nanoparticles have emerged as one of the principal platforms for delivering natural bioactive compounds [57,58]. In MASLD research, typical strategies include the use of chitosan or glycyrrhizin modifications to achieve liver localization while exploiting intrinsic antioxidant and anti-inflammatory properties of the carrier, as well as the use of PLGA-based systems to enable sustained delivery. Oral systems must first overcome digestive and epithelial barriers, whereas intravenous systems bypass intestinal absorption and initial presystemic first-pass loss but still undergo hepatic metabolism and systemic clearance [59,60].

3.1.5. Polymeric Micelles

Polymeric micelles are nanoscale assemblies formed by the spontaneous aggregation of amphiphilic molecules in aqueous environments, typically featuring a hydrophobic core and hydrophilic shell. This architecture is particularly advantageous for encapsulating highly hydrophobic natural products such as curcumin and flavonoids [61–63]. Compared with nanoemulsions or liposomes, polymeric micelles often exhibit improved in vivo stability and more controllable drug release profiles [64]. Functionalization with liver-targeting ligands at the polymer termini or side chains can further enhance hepatocyte uptake. Several studies have shown that receptor-targeted micelles achieve higher hepatic accumulation and produce more pronounced anti-steatotic and anti-inflammatory effects in vivo [63].

3.1.6. Nanogels

Nanogels are nanoscale hydrogel particles composed of crosslinked hydrophilic polymers forming a three-dimensional network. This structure enables high drug-loading capacity and stimulus-responsive release in response to environmental triggers such as pH or temperature. Nanogels offer multiple advantages, including high loading efficiency, excellent biocompatibility, low toxicity, and tunable release kinetics [65,66]. When applied to natural compounds, nanogels can protect active ingredients from gastrointestinal degradation and can be surface-modified to achieve hepatic targeting or triggered release within inflammatory or oxidative microenvironments [67]. For natural products requiring sustained release or activity along the gut–liver axis, such as formulations designed to modulate intestinal barrier function and microbiota, nanogels represent a particularly attractive platform. In MASLD therapy, nanogels have also been explored for encapsulating water-soluble or macromolecular therapeutics, including peptides and proteins, enabling long-acting and stable drug delivery [11,68].

3.1.7. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) possess a core composed entirely of solid lipids that remain in the solid state at both room and body temperatures. SLNs encapsulate bioactive compounds within a solid lipid matrix, potentially improving the dispersibility, stability, and release profiles of lipophilic natural bioactives. Fucoxanthin-loaded SLNs administered by oral gavage to mice with high-fat-diet-induced obesity showed potential to attenuate hepatic lipid accumulation and inflammation and improve metabolic parameters [69]. In addition, Moin et al. developed piperine-loaded SLNs and evaluated their hepatoprotective effects in a mouse model of high-fat-diet-induced hyperlipidemia [70] (Figure 3).

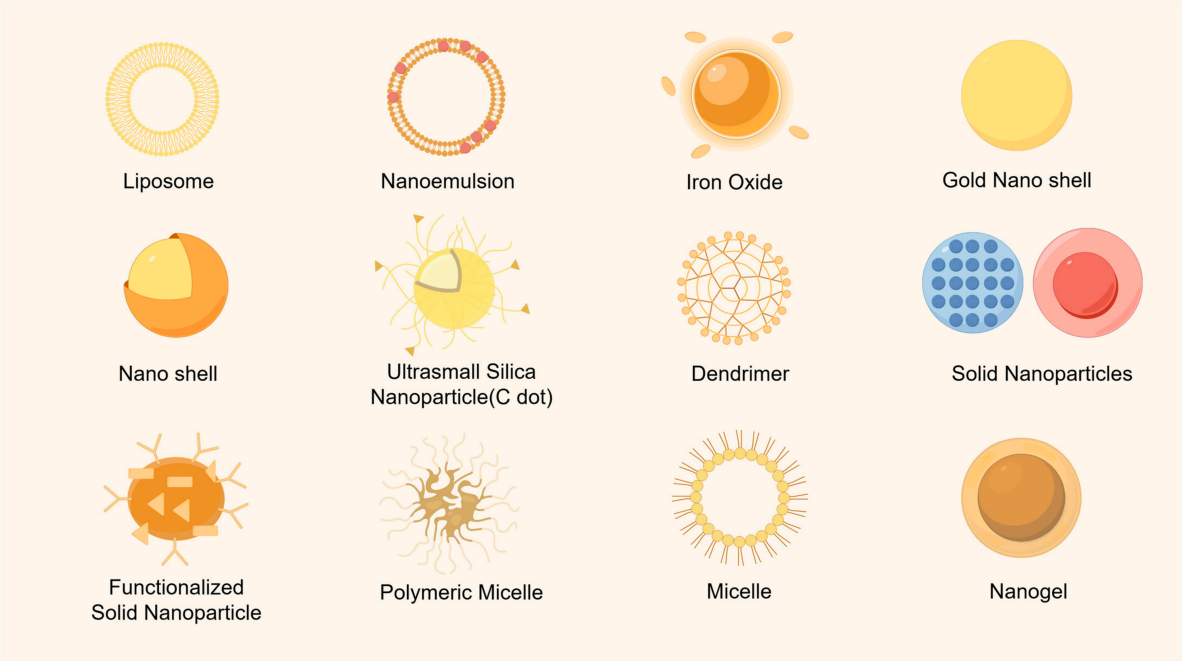


Figure 3. Carrier-based nanostructured delivery platforms for natural bioactive compounds in MASLD therapy. Representative nanostructured delivery platforms for natural bioactive compounds in MASLD therapy. Schematic illustration of major carrier-based nanostructures employed to enhance the pharmacokinetics, stability, and liver-targeting efficiency of natural products in MASLD. These include liposomes, nanoemulsions, inorganic nanoparticles, polymeric nanoparticles, polymeric micelles, dendrimers, solid nanoparticles, functionalized nanoparticles, and nanogels.

3.2. Carrier-Free Nanostructures

3.2.1. Self-Assembled Nanostructures

Carrier-free self-assembled systems refer to nanostructures formed through the spontaneous assembly of drug molecules themselves or through the co-assembly of drugs with small molecular excipients via non-covalent interactions. These assemblies can generate nanoscale particles or micelles, such as drug–drug assemblies or drug–lipid and drug–polymer co-assemblies. By eliminating the need for non-drug carrier materials, this strategy increases drug-loading efficiency while avoiding the potential toxicity or immunogenicity associated with conventional carriers. Self-assembled systems offer notable advantages in enhancing drug loading and enabling combination therapy; however, their formulation stability and in vivo pharmacokinetic behavior still require careful optimization [71,72].

3.2.2. Vesicle-like Nanoparticles

Vesicle-like nanoparticles represent another class of carrier-free nanostructures formed spontaneously from natural bioactive molecules and characterized by a hollow, membrane-like architecture. Unlike conventional liposomes formed by the assembly of natural-source phospholipids, the membranes of these vesicles are constructed from specific natural constituents, such as certain saponins, phospholipids, or polyphenolic compounds [73]. In the context of MASLD, biologically derived vesicles and engineered vesicle-mimetic nanostructures have been explored as vehicles for delivering natural compounds or nucleic acids with liver-targeting capability. These systems can modulate hepatic inflammatory and metabolic pathways while offering improved biocompatibility and intrinsic bioactivity [74,75]. However, compared with fully synthetic carriers, their translational advancement is constrained by challenges related to source variability, purification, and large-scale manufacturing (Figure 4).

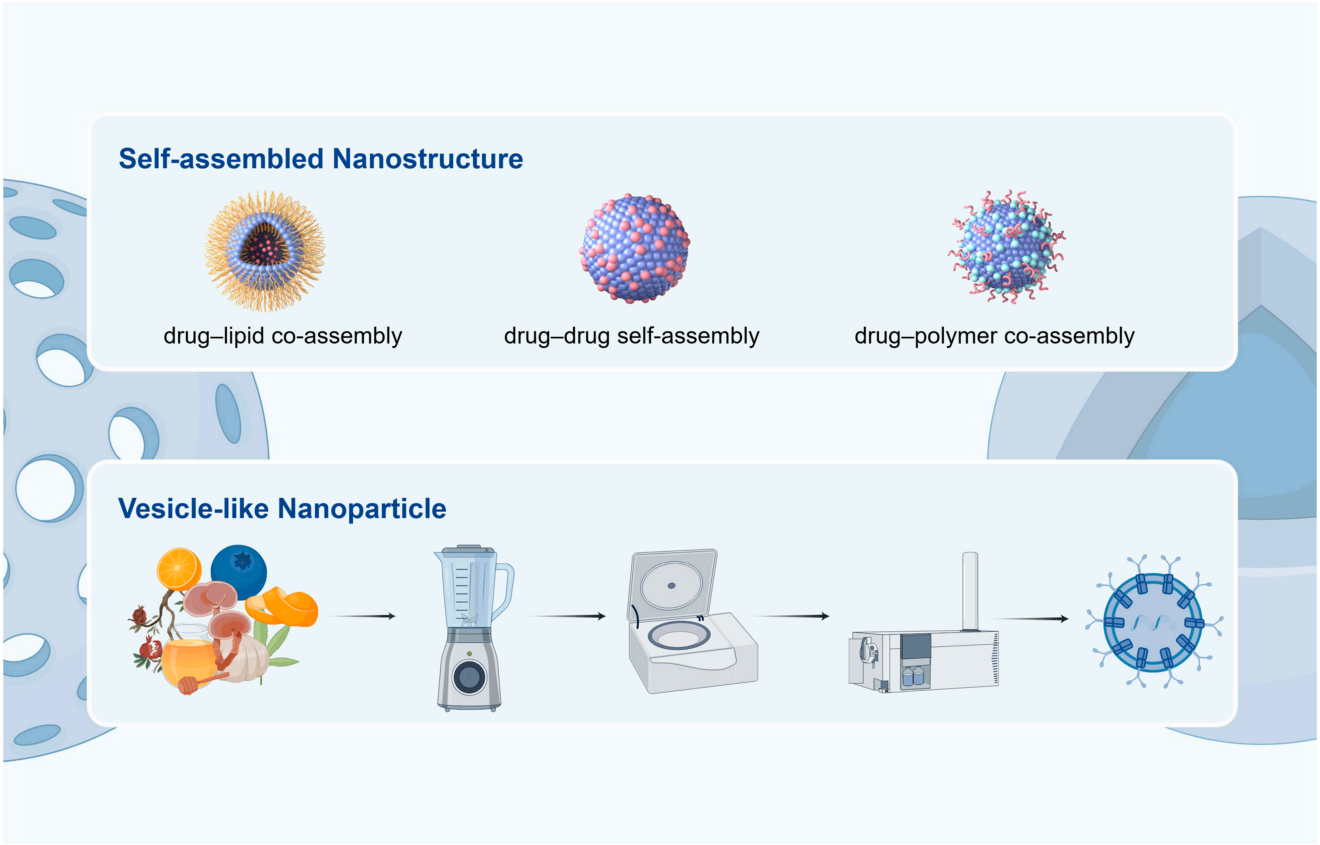


Figure 4. Carrier-free nanostructured delivery systems for natural bioactive compounds in MASLD therapy. Carrier-free nanostructured systems for the delivery of natural bioactive compounds in MASLD. Schematic illustration of representative carrier-free nanostructures designed to improve the therapeutic performance of natural bioactive agents in MASLD. The upper panel depicts self-assembled nanostructures formed via non-covalent interactions, including drug–lipid co-assemblies, drug–drug self-assemblies, and drug–polymer co-assemblies. The lower panel illustrates vesicle-like nanoparticles derived from natural constituents. Such biologically derived vesicle-mimetic nanostructures can facilitate liver-targeted delivery, improve biocompatibility, and modulate inflammatory and metabolic pathways relevant to MASLD.

4. Nanostructured Natural Bioactive Compounds for MASLD: Current Progress

Unlike conventional chemical drugs, natural therapeutics can exist in multiple forms, including structurally defined small-molecule compounds, mixtures containing multiple bioactive constituents, or whole-plant extracts derived from medicinal herbs. These different levels of drug forms vary in their chemical composition, pharmacological activities, and metabolic behaviors in vivo, and therefore require distinct nanostructuring strategies and delivery approaches. In the following sections, we summarize recent advances in nanostructured natural small-molecule bioactives, nanostructured natural bioactive component mixtures, and nanostructured single herbal medicines in the treatment of MASLD.

4.1. Natural Small-Molecule Bioactives Delivered by Nanostructures

Natural small-molecule compounds derived from natural sources possess well-defined chemical structures and exhibit diverse biological activities in regulating lipid metabolism, oxidative stress, and inflammatory responses. Small molecules investigated for MASLD therapy can generally be classified into several major categories, including flavonoids, polyphenols, terpenoids, alkaloids, and lignans. These classes differ in molecular scaf-

folds, polarity, and bioactivity profiles, which contribute to distinct mechanisms of action. The following sections systematically summarize the recent research advances in these representative classes of bioactive small molecules for MASLD (Table 1).

4.1.1. Flavonoids

Flavonoids represent one of the most extensively investigated classes of natural small molecules in this context. Encapsulation within liposomes, polymeric nanoparticles, or solid lipid nanoparticles generally enhances solubility, bioavailability, and hepatic targeting, leading to improved lipid-lowering and anti-inflammatory efficacy in MASLD models. For example, luteolin-loaded zinc oxide nanoparticles (Lut/ZnO NPs) markedly improved hepatic histopathology in a diabetic MASLD model and reduced serum ALT, AST, total cholesterol (TC), and triglycerides (TG), while also improving fasting glucose, insulin levels, and HOMA-IR indices [76].

An orally delivered quercetin-based nanocomposite (TMC-Zein-Q) demonstrated enhanced efficacy in high-fat-diet-fed mice and Caco-2 cells by activating AMPK signaling, improving energy metabolism and lipid homeostasis, and reducing hepatic steatosis while ameliorating dyslipidemia and glucose intolerance [77].

Nano-scutellarin using bovine serum albumin (BSA) suppressed interferon-γ-mediated JAK/STAT1 signaling, attenuating endothelial–mesenchymal transition and collagen deposition and thereby significantly alleviating fibrosis and inflammation in MASH models [78].

Orally administered icariin nanoparticles (ICA-NPs) significantly improved HFD-induced MASLD through liver-targeted delivery and reactive oxygen species (ROS) scavenging. ICA-NPs produced marked improvements across multiple parameters, including hepatic histopathology, liver lipid deposition, ALT/AST levels, serum lipid profiles, and blood glucose levels [79].

PEGylated vitexin liposomes exhibited pronounced anti-steatotic and anti-inflammatory effects in rats fed a high-fat/high-sucrose diet with fructose supplementation. These effects were associated with reduced reactive oxygen species (ROS) levels, enhanced antioxidant enzyme activity (SOD, CAT, and GSH-Px), downregulation of lipogenic factors (SREBP-1c and FAS), and upregulation of fatty acid oxidation-related genes (PPAR-α and CPT-1), ultimately mitigating hepatic injury and lipid droplet accumulation while lowering ALP, ALT, and AST. The vitexin study compared oral-gavage PEG-coated vitexin liposomes with uncoated liposomes administered intravenously, alongside free-vitexin controls. Because coating and administration routes differed between formulation groups, outcome differences cannot establish an isolated benefit of PEGylation or be interpreted simply as enhanced oral versus intravenous efficacy [80]. Similarly, a vitexin–rhamnoside nanoformulation significantly reduced hepatocellular lipid droplet deposition and necrosis and decreased hepatic TG and serum ALT and AST levels in MASLD models [81].

Apigenin encapsulated within poly(lactic-co-glycolic acid) (PLGA) nanoparticles (Api-NPs) improved liver histology, reduced adipocyte size, and suppressed weight gain in mice. The formulation also downregulated transcription factors associated with adipocyte differentiation, including aP2, lipid droplet-associated proteins, and PPARγ isoforms, suggesting modulation of adipogenesis [82]. Chrysin-loaded nanoliposomes significantly attenuated hepatic steatosis and reduced hepatic TG levels in methionine- and choline-deficient (MCD) diet-induced rat models while suppressing ALT and AST elevation [83]. Rutin incorporated into orally administered chitosan-coated emulsomes alleviated obesity and improved lipid profiles in hyperlipidemic rats, reducing serum TC, TG, and LDL-c while increasing HDL-c [84].

Orally administered naringenin delivered via lipid-based, protein-based, or other nanoparticles demonstrated improved solubility and oral absorption and produced robust

lipid-lowering and anti-inflammatory effects in high-fat-diet-fed mice. Mechanistically, these formulations upregulated PPAR-α and CPT-1 while downregulating SREBP-1c and FAS, thereby reducing hepatic lipid accumulation and inflammatory infiltration, inhibiting weight gain, lowering hepatic TG, TC, ALT, and AST levels, and improving fasting glucose and insulin resistance [85–91]. Baicalin-loaded nanoliposomes administered by oral gavage improved hepatic fibrosis and liver function by suppressing TLR4/MyD88/NF-κB signaling [88]. Phloretin incorporated into elastomeric nanocarriers modulated FAS, SREBP1c, and AMPK pathways, resulting in significant reductions in body weight, blood glucose, and lipid levels [92].

An orally administered biomimetic nanoemulsion of dihydromyricetin enhanced oral absorption and hepatic accumulation and improved lipid metabolism and inflammatory responses [13]. Blueberry anthocyanins encapsulated in composite nanoparticles composed of lecithin and gum arabic reduced hepatic lipid droplet accumulation and improved serum lipid profiles and liver enzyme levels [93,94].

Collectively, nanostructured flavonoids exert multifaceted therapeutic effects by modulating lipid synthesis and oxidation, improving insulin sensitivity, and suppressing inflammation and oxidative stress. Across histological, biochemical, and metabolic endpoints, including hepatic steatosis, serum lipids, liver enzymes, and glycemic control, these formulations consistently demonstrate hepatoprotective and metabolic regulatory potential in MASLD models.

4.1.2. Polyphenols

Nanostructured polyphenolic small molecules have demonstrated robust antioxidant, anti-inflammatory, and metabolic regulatory effects in experimental models of MASLD. For instance, orally gavaged epigallocatechin gallate (EGCG) formulated as a β-cyclodextrin inclusion nanoparticle (EGCG@β-CD NPs) reduced hepatic malondialdehyde (MDA) levels, increased CAT activity and apo-A1, and markedly attenuated steatosis and histopathological injury, accompanied by reductions in TC, LDL-c, and phospholipids (PL) [95].

Multiple nanoformulations of curcumin have demonstrated metabolic benefits. Notably, two oral clinical studies have evaluated nano-curcumin in MASLD. In one trial using Sinacurcumin® (a nano-curcumin formulation provided by Exir-Nano-Sina), oral nano-curcumin significantly reduced fatty liver grade compared with placebo and produced greater decreases in ALT and AST. It also improved lipid profiles (decreased TC, TG, and LDL-c; increased HDL-c) and significantly improved fasting blood glucose, glycated hemoglobin (HbA1c), and insulin resistance [96]. In another clinical trial, oral micellar nano-curcumin improved several liver enzyme endpoints, including ALT, AST, γ-glutamyl transferase (GGT), and lactate dehydrogenase (LDH) [97] (Table 2). An orally administered medium-chain fatty acid nanoemulsion (cNE-MCFA) alleviated hepatocellular steatosis and reduced AST, ALT, TC, TG, and LDL levels while increasing HDL [48]. In a high-fat/high-fructose (HFHF) metabolic syndrome model, an orally administered curcumin nanoemulsion improved insulin resistance and dyslipidemia, reducing ALT, AST, and blood glucose [98]. In high-fat diet (HFD)-induced metabolic dysfunction, a curcumin nanoemulsion suppressed reactive oxygen species (ROS) accumulation, reduced lipid droplet formation, and improved lipid profiles (TC↓, TG↓, LDL↓, and HDL↑) [99]. Curcumin incorporated into polyvinyl alcohol-gelatin nanofiber patches was administered transdermally (a non-oral route) and enhanced skin delivery, decreased whole-body fat volume by 4–7%, and significantly lowered serum TG levels [100].

Table 1. Advances in experimental studies of nanostructured natural small molecules for MASLD.

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Flavone	Luteolin	Type 2 diabetes mellitus MASLD model induced by HFD combined with intraperitoneal streptozotocin administration	/	ZnO NPs	Intraperitoneal injection	Activates the PI3K/AKT signaling cascade, leading to suppression of FoxO1 activity and consequent improvement in hepatic insulin sensitivity. In parallel, Lut/ZnO NP treatment downregulates SREBP-1c expression.	[76]
	Quercetin	HFD-induced mouse	Caco-2 cells	TMC-Zein-Q	Oral gavage	Activates AMPK signaling pathway, thereby regulating lipid metabolism and restoring cellular energy homeostasis.	[77]
	Scutellarin	Mouse induced with HFD combined with CCl_4 administration	TGF-β1-stimulated activation of hepatic stellate cells	Scutellarin @BSA	Not explicitly reported	Disrupts the interaction between IFN-γ and JAK, suppressing activation of the JAK/STAT1 signaling pathway and thereby significantly reducing collagen deposition and exerting antifibrotic effects.	[78]
	Icariin	HFD-induced mouse	FAFM-induced steatotic HepG2 hepatocellular carcinoma cells.	PLGA-PEG	Oral gavage	Activates the Nrf2/HO-1 signaling pathway, enhances SOD activity, reduces MDA levels, and scavenges ROS, thereby alleviating oxidative stress and ameliorating MASLD.	[79]
	Vitexin	HFD-induced rat with fructose-enriched drinking water	HepG2 hepatocellular carcinoma cells	PEG-VLPs	Oral gavage	Reduces ROS, enhances the activity of SOD, CAT, and GSH-Px; suppresses the expression of inflammatory cytokines, including TNF-α and IL-6, thereby alleviating inflammatory infiltration, and downregulates SREBP-1c and FAS while upregulating PPAR-α and CPT-1, ultimately improving lipid metabolism.	[80]
	Vitexin–rhamnoside	HFD-induced mouse	/	Zein-VR-Pectin	Oral gavage	Alleviates HFD-induced lipid metabolic dysregulation, chronic inflammation, and liver injury through modulation of the gut microbiota.	[81]
	Apigenin	HFD-induced mouse	3T3-L1 preadipocytes	PLGA	Subcutaneous injection	Promotes the polarization of adipose tissue macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, thereby reducing the expression of inflammatory cytokines in adipose tissue and alleviating inflammation.	[82]
	Chrysin	MCD-induced mouse	HepG2 and AML12 cells	CH-NL	Oral gavage	Inhibits activation of the TLR4 signaling pathway induced by the MCD diet, leading to downregulation of TLR4 as well as reduced phosphorylation of p38 and p65.	[83]

Table 1. *Cont.*

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Flavone	Rutin	HFD-induced rat	/	Nanoemulsion	Oral	Alleviates HFD-induced lipid metabolic dysregulation, chronic inflammation, and liver injury through modulation of the gut microbiota.	[84]
	Naringenin	HFD-induced mouse	/	NP-NAR	Oral gavage	Upregulates PPAR-α and CPT-1 while downregulating SREBP-1c and FAS. Cationic lipid modification enhances the adhesion of the nanoparticles to the intestinal mucosa and facilitates trans-epithelial transport, thereby improving drug efficacy.	[85]
		MCD-induced mouse	/	Liposome	Oral gavage	Suppresses hepatocellular lipid accumulation, thereby ameliorating MASLD.	[86]
		HFD-induced obesity mouse	HepG2 cells or 3T3-L1 adipocytes.	Liposome	Oral	Downregulates hepatic mRNA expression of Vanin-1, iNOS, and MCP-1, and modulates the expression of lipid metabolism-related molecules in the liver by reducing SREBP-1c, p-AMPK, and PPAR-α levels, thereby exerting antioxidant and anti-inflammatory effects.	[87]
		HFD-induced mouse	/	NAR-rGO	Oral	Downregulates pro-inflammatory cytokines (TNF-α, IL-6, and MCP-1), reduces hepatic lipid accumulation, and ameliorates dysregulated lipid metabolism.	[88]
		MCD-induced mouse	Caco-2 cells	Liposome	Oral delivery	Reduces pro-inflammatory cytokines (TNF-α and IL-6) and lipid peroxidation levels while enhancing antioxidant enzyme activity, simultaneously improving intestinal absorption and increasing plasma concentrations.	[89]
		HFD-induced obesity mouse	HepG2 cells or Caco-2 cells.	GC NPs	Oral gavage	It can be recognized by hepatocytes through galactose-specific recognition sites, thereby exhibiting enhanced lipid-lowering effects.	[90]
	Baicalin	MCD-induced mouse	HepG2 cells/RAW264.7 macrophages	BA-NLs	Oral gavage	Inhibits the TLR4/MyD88/NF-κB signaling pathway, alleviates hepatocyte apoptosis, and attenuates liver fibrosis.	[91]
	Phloretin	HFD-induced obesity mouse	3T3-L1 preadipocytes/HepG2 cells	PTN-NSLs	Oral	Regulate FAS, SREBP-1c, and AMPK, modulates lipid metabolism, enhances energy expenditure, and suppresses lipid accumulation.	[92]
	Dihy-dromyricetin (DMY)	HFD-induced mouse	HepG2 cells/RAW264.7 macrophages	DMY-hNE	Oral	Enhance oral absorption and hepatic accumulation, thereby improving lipid metabolism and exerting anti-inflammatory effects.	[13]
	blueberry anthocyanin	HFD-induced mouse	3T3-L1 adipocytes	Lipo/GA-ACN NPs	Oral gavage	Reduces hepatic lipid droplet accumulation and attenuates lipid deposition in the liver.	[93]

Table 1. *Cont.*

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Polyphenols	Epigallocatechin-3-Gallate, EGCG	HFD-induced rat	/	EGCG@β-CD NPs	Oral gavage	Reduces hepatic MDA levels and increases hepatic catalase (CAT) activity and apolipoprotein A1 (apo-A1) levels.	[95]
	Curcumin	Hepatic steatosis rat	/	cNE-MCFA	Oral	Improves lipid metabolism and alleviates inflammation and oxidative stress, thereby attenuating fructose-induced hepatic steatosis.	[48]
		HFHF-induced rat	/	Nanoemulsion	Oral	Reduces oxidative stress in liver and heart tissues, therefore alleviating insulin resistance and hyperlipidemia.	[98]
		HFD-induced mouse	HepG2 cells	Nanoemulsion	Oral gavage	Inhibits ROS accumulation, thereby reducing lipid peroxidation and oxidative-stress-induced hepatic injury. Meanwhile, the upregulation of SREBP-1 and increased expression of PPAR-γ2 contribute to the attenuation of hepatic steatosis.	[99]
		HFD-induced obesity rat	/	PVA-Gelatin	Transdermal	Modulates lipid metabolic pathways, suppresses lipid accumulation, and alleviates obesity-related symptoms through attenuation of inflammatory responses.	[100]
	Resveratrol	HFD-induced mouse	HepG2 cells	Gly-LA-Lac	Oral	Enhances hepatic delivery and controls the release of resveratrol, thereby suppressing inflammation and oxidative stress, reducing the intrahepatic lipid burden, and ultimately improving liver enzyme profiles, lipid parameters, and glycemic indices.	[101]
		HFD-induced mouse	HepG2 cells and AML12 hepatocytes	Gal-OSL/Res	Intravenous	Activates the AMPK/SIRT1 signaling axis, downregulates FAS and SREBP-1c, and improves IRS-1 phosphorylation at Ser307 to restore insulin signaling, therefore ameliorating hepatic steatosis and improving lipid and glucose metabolism.	[102]
		HFD-induced rat	/	Liposomes	Oral gavage	Suppresses the hepatic expression of Toll-like receptor 3 (TLR3) and its adaptor protein TRIF. Attenuates chronic inflammatory signaling and potentially modulates downstream pathways, ultimately improving lipid clearance and metabolic homeostasis.	[103]
		HFD-induced mouse	/	tFNAs-RSV	Parenteral injection	Suppresses the activation of Th1 and Th17 responses and promotes Th2 and Treg polarization, thereby improving glucose homeostasis and insulin sensitivity.	[104]

Table 1. *Cont.*

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Polyphenols		HFD-induced mouse	HepG2 cells	Res@H-CeO_2-Gal	Intravenous	Galactose-mediated hepatic targeting enables nanoparticle enrichment in hepatocytes and sustained release of resveratrol. Reduces lipid droplet accumulation and hepatic lipid content, alleviates inflammation, and ultimately ameliorates the NASH phenotype.	[105]
	Syringic acid	HFD-induced mouse	/	Self-microemulsifying drug delivery system, SMEDDS	Oral	This strategy primarily enhances bioavailability and liver targeting through an optimized delivery system, leading to improved lipid profiles, reduced intrahepatic lipid accumulation and ALT levels, and overall histopathological recovery.	[106]
		HFFD-induced rat	/	CS-NPs	Oral	Reduces fasting blood glucose, HbA1c, and MDA levels, while increasing GSH and the activities of SOD and catalase. Decreases the levels of inflammatory markers, including IL-6, IL-8, and NF-κB.	[107]
	Pterostilbene	HFD-induced rat	3T3-L1 adipocytes	PS/HPβCD-NPs	Oral	Suppresses lipogenesis by downregulating key lipogenic genes (SREBP-1c and FAS) while promoting fatty acid catabolism through upregulation of PPARα and CPT1.	[108]
Terpene	Astaxanthin	HFD-induced mouse	HepG2 cells	AST @TPP-WPI-Gal	Oral gavage	Reduces hepatic ROS levels and enhances antioxidant enzyme activities (SOD and CAT); suppresses lipogenic gene expression (SREBP-1c and FAS) while promoting fatty acid oxidation (CPT1α↑ and PPARα↑); and preserves mitochondrial function by maintaining mitochondrial membrane potential and limiting mitochondrial damage.	[109]
		HFD-induced mouse	HepG2 cells/RAW264.7 macrophages	AXT @TWG @LBGs	Oral gavage	Scavenges ROS and enhances antioxidant enzyme activities (SOD, CAT, and GSH). Suppresses NF-κB-mediated inflammatory signaling, leading to reduced expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Downregulates lipogenic genes (SREBP-1c, ACC, and FASN) and upregulates fatty-acid-oxidation-related genes (PPARα and CPT-1α). Inhibits hepatic lipogenesis and promotes β-oxidation, thereby reducing ALT/AST levels, improving serum and hepatic lipid profiles, alleviating insulin resistance, and attenuating hepatic inflammation and fibrosis.	[110]
	Lycopene	HFD-induced rat	/	Nanostructured lipid carriers (NLCs)	Intragastric administration	Upregulates SMO, GLI-1, and PTCH-1 gene expression and enhances insulin signaling sensitivity, accompanied by a reduction in the HOMA-IR index.	[111]

Table 1. *Cont.*

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Terpene	Fucoxanthin	HFD-induced mouse	3T3-L1 adipocytes	Solid lipid nanoparticles (SLNs)	Oral gavage	Downregulates hepatic MCP-1 protein expression, indicating attenuation of hepatic inflammation, thereby improving FBG, TG, ALT, and AST levels and resulting in notable histological recovery of the liver.	[69]
		HFD-induced obesity rat	/	Nanoemulsion	Oral gavage	Upregulates UCP-1 and the β3-adrenergic receptor (Adrb3) in white adipose tissue, thereby exerting anti-obesity effects. Modulates lipid-metabolism-related gene expression and strengthens antioxidant and metabolic pathways by activating the Nrf2 axis and downstream antioxidant enzymes (SOD, CAT, and GST), as well as the PPAR-α/CPT-1 pathway, ultimately alleviating oxidative stress and enhancing fatty acid β-oxidation.	[112]
	Celastrol	HFD-induced mouse	3T3-L1 adipocytes	PEG-PCL	Oral gavage	Inhibits the NF-κB signaling pathway, reduces expression of pro-inflammatory cytokines such as TNF-α and IL-6. Improves lipid metabolism by suppressing lipogenesis (SREBP-1c↓, FAS↓) and promoting fatty acid oxidation (CPT1↑), ultimately ameliorating insulin resistance.	[113]
		HFD-induced mouse	/	Cel-LANPs	Intraperitoneal injection	Specifically targets hepatocytes, facilitating efficient cellular internalization of the nanoparticles and markedly enhancing hepatic accumulation of celastrol. Alleviates hepatic steatosis by modulating lipid metabolism, suppressing inflammatory signaling, and reducing oxidative stress.	[114]
		HFD-induced mouse	RAW264.7 macrophages/3T3-L1 adipocytes	Celastrol-BSA-NPs	Oral gavage	Suppresses expression of M1-associated pro-inflammatory markers (IL-6, IL-1β, TNF-α, CCL-2, and CXCL-10) while upregulating M2 markers (Arg-1 and IL-10).	[115]
	β-Carotene	HFD-induced mouse	HepG2 cells	NP-BC	Oral gavage	Ameliorates lipid metabolic dysregulation by inhibiting the PI3K/Akt/mTOR signaling pathway and downregulating PPARγ expression.	[116]
	Oridonin	intraperitoneal injection of tetracycline	HepG2 cells	ORI/HP-β-CD/H9-HeP	Intravenous	Enhanced targeting and cellular uptake → increased intrahepatic drug exposure → improvement in lipid accumulation and fibrotic phenotypes.	[117]

Table 1. *Cont.*

Type	Compound	Model		Nanostructure	Route of Administration	Mechanism and Outcomes	Reference
		In Vivo	In Vitro				
Alkaloid	Berberine	HFD-induced mouse	HepG2 cells/RAW264.7 macrophages/primary mouse hepatocytes	BBR-CTA-Mic	Oral gavage	Prolongs intrahepatic retention time while producing comparatively smaller increases in plasma and extrahepatic tissues relative to free BBR. Enhances the hepatic expression and activation of key metabolic regulators, including the insulin receptor (InsR), AMPK, LDLR, and AKT.	[118]
		HFD-induced Apoe$^{-/-}$ mouse	RAW264.7 macrophages	BBR-TPGS1500	Oral gavage	Enhances berberine deposition in the liver and adipose tissue, increasing tissue accumulation. Modulates metabolic inflammatory signaling by upregulating p-AMPK and suppressing NF-κB expression in both liver and adipose tissues, while disrupting the pro-inflammatory crosstalk between adipocytes and macrophages.	[119]
		HFD-induced rat	3T3-L1 adipocytes/HepG2 cells	Ber/Gu-AGNCs	Oral	Enhances the bioavailability and metabolic regulatory potential of berberine by improving oral absorption and systemic stability, increasing tissue distribution with sustained release, and attenuating oxidative stress and metabolic inflammatory signaling pathways.	[120]
	Nitidine Chloride	HFD-induced mouse with fructose-supplemented drinking water	HepG2 cells	CS/PT-NPs	Oral gavage	Suppresses lipogenic gene expression (FAS and SREBP-1c) and activates fatty acid oxidation through the AMPK/ACC signaling pathway, thereby reprogramming hepatic lipid metabolism toward reduced lipid synthesis and enhanced β-oxidation.	[121]
Lignan	Arctiin	HFD-induced rat	HepG2 cells	GA-MSe @AR	Intravenous	Elevates hepatic MDA and GSSG levels and reduces GSH levels and the GSH/GSSG ratio. GA-MSe @AR also downregulates key lipogenic proteins, including FASN, PPARγ, and SREBP-1c, and inhibits the IGF1/PI3K/Akt signaling pathway.	[16]

Abbreviations: HFD, high-fat diet; MCD, methionine- and choline-deficient diet; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; FoxO1, Forkhead box O1; SREBP-1c, sterol regulatory element-binding protein 1c; AMPK, AMP-activated protein kinase; IFN-γ, interferon gamma; JAK, Janus kinase; STAT1, signal transducer and activator of transcription 1; MDA, malondialdehyde; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; PPAR-α, peroxisome proliferator-activated receptor alpha; CPT-1, carnitine palmitoyltransferase 1; TLR4, Toll-like receptor 4; FAS, fatty acid synthase; Vanin-1, vascular non-inflammatory molecule 1; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; p-AMPK, phosphorylated AMP-activated protein kinase; MyD88, myeloid differentiation primary response 88; apo-A1, apolipoprotein A1; SIRT1, sirtuin 1; IRS-1, insulin receptor substrate 1; TLR3, Toll-like receptor 3; NASH, nonalcoholic steatohepatitis; HbA1c, hemoglobin A1c; GSH, glutathione; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SMO, smoothened; GLI-1, GLI family zinc finger 1; FBG, fasting blood glucose; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UCP-1, uncoupling protein 1; IL-6, interleukin 6; IL-1β, interleukin 1 beta; CCL-2, C-C motif chemokine ligand 2; CXCL-10, C-X-C motif chemokine ligand 10; Arg-1, arginase-1; IL-10, interleukin 10; NRF2, nuclear factor erythroid 2-related factor 2.

Resveratrol-based nanoformulations have also shown broad therapeutic potential. Gly-LA-Lac core-shell nanoparticles, described as supplementation in the HFD (oral dietary administration), improved hepatic delivery, reduced lipid droplet accumulation, and lowered ALT, AST, blood lipids, and glucose [101]. Intravenously administered resveratrol loaded into oxidized starch-lysozyme (OSL) liver-targeting nanocarriers activated AMPK/SIRT1 signaling, suppressed FAS and SREBP-1c, restored insulin signaling, and significantly reduced hepatic TG, serum ALT, lipids, and glucose levels [102]. Resveratrol liposomes administered by oral gavage attenuated inflammation and dyslipidemia by downregulating the TLR3/TRIF pathway, reducing TC, TG, and LDL-c while increasing HDL-c [103]. Tetrahedral framework nucleic acids loaded with resveratrol (tFNAs-RSV), evaluated in a study reporting injection-based animal treatment, improved insulin sensitivity through immunomodulatory mechanisms, reduced lipid deposition, and significantly lowered blood glucose while improving glucose tolerance [104]. Intravenously administered resveratrol delivered via cerium oxide nanozyme carriers (Res @H-CeO_2-Gal) exhibited antioxidant and hepatotropic properties, reducing hepatic TG, nonesterified fatty acids (NEFAs), and inflammatory cytokines while ameliorating NASH phenotypes [105].

Orally administered syringic acid formulated in a self-microemulsifying drug delivery system (SMEDDS) significantly improved liver histology and reduced serum ALT, TC, TG, and LDL-c while increasing HDL-c [106]. Orally administered syringic acid chitosan nanoparticles (SANPs) reduced fasting glucose, HbA1c, and MDA; increased GSH, SOD, and CAT activity; and suppressed IL-6, IL-8, and NF-κB signaling, resulting in reduced lipid accumulation and inflammatory infiltration and improved lipid and glycemic profiles [107].

Pterostilbene encapsulated in chitosan nanoparticles and administered by oral gavage downregulated SREBP-1c and FAS to inhibit lipogenesis while upregulating PPARα and CPT1 to promote fatty acid oxidation, improving adipose morphology and lipid profiles (LDL-c↓, VLDL-c↓, and HDL-c↑) [108].

Collectively, these findings indicate that nanostructured polyphenols exert multifaceted therapeutic effects through antioxidant and anti-inflammatory activity, regulation of lipid metabolism, and improvement of insulin sensitivity, leading to consistent improvements across histological, biochemical, and metabolic endpoints.

4.1.3. Terpenoids

Nanoformulated terpenoids, including astaxanthin, lycopene, and celastrol, have demonstrated potent anti-inflammatory and antioxidant effects in MASLD models. Astaxanthin delivered by oral gavage via PLGA-based nanocarriers (AST @TPP-WPI-Gal) reduced hepatic oxidative stress, suppressed lipogenic factors (SREBP-1c and FAS), and enhanced fatty acid oxidation through upregulation of CPT1α and PPARα, thereby reducing hepatic TG, TC, and NEFA accumulation and improving ALT, AST, lipid profiles, and insulin resistance [109]. A protein-based dual-targeting nanoparticle (AXT @TWG @LBGs), administered by oral gavage, similarly reduced steatosis, inflammation, and fibrosis in NASH models while improving glucose tolerance, insulin sensitivity, and fasting metabolic parameters [112].

Table 2. Clinical studies of nanoformulated curcumin in MASLD.

Nanostructure	Intervention	Duration	Primary Outcomes	Key Findings	References
Sinacurcumin® (Exir-Nano-Sina)	Oral administration: 84 participants randomized to nano-curcumin (n=42) or placebo (n=42). Intervention group received two 40 mg capsules daily after meals (total dose: 80 mg/day) for 12 weeks.	12 weeks	Ultrasonographic fatty liver grade; liver function (ALT and AST); glycometabolic indices (FBG, HbA1c, and HOMA-IR); lipid profile (TG, TC, LDL-c, and HDL-c).	Compared with placebo, nano-curcumin significantly reduced ultrasound-assessed steatosis grade and produced greater reductions in ALT and AST. Significant improvements were also observed in lipid parameters (TC↓, TG↓, LDL-c↓, and HDL-c↑) and glycemic control (FBG↓ and HbA1c↓), accompanied by improved insulin resistance.	[96]
Nano-curcumin micellar soft capsules	Oral administration: 55 participants randomized to nano-curcumin (n = 27) or placebo (n = 28). Nano group received 40 mg nano-curcumin per capsule, twice daily (total dose: 80 mg/day) for 16 weeks. Placebo group received maltodextrin capsules. Both groups received standardized lifestyle intervention (dietary modification and increased physical activity).	16 weeks	Liver fibrosis stage assessed by transient elastography (FibroScan; F0–F4); hepatic fat content assessed by controlled attenuation parameter (CAP).	Both groups showed significant reductions in hepatic fat content following lifestyle interventions; however, nano-curcumin did not confer an additional significant reduction in CAP values compared with placebo. Nano-curcumin significantly reduced ALT, AST, GGT, and LDH, indicating hepatoprotective effects despite limited additive impact on steatosis.	[97]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase.

Lycopene-loaded nanoliposomes administered intragastrically (oral gavage) significantly improved hepatic histology in MASLD rats, lowered ALT and AST, reduced serum TC, TG, and LDL-c, increased HDL-c, and improved fasting glucose and insulin levels [111]. Fucoxanthin administered by oral gavage as solid lipid nanoparticles reduced hepatic MCP-1 expression, attenuated inflammation, decreased lipid droplet accumulation, and lowered ALT, AST, TG, and fasting glucose in obese mice [69]. A fucoxanthin nanoemulsion further enhanced lipid oxidation and thermogenesis by upregulating UCP-1 and β3-adrenergic receptor expression and activating the PPARα/CPT-1 axis [112].

Celastrol delivered by oral gavage via PEG-PCL nanomicelles suppressed NF-κB signaling, downregulated SREBP-1c and FAS, and upregulated CPT1, leading to reduced body weight and lipid accumulation and improved glycemic control and insulin sensitivity [113]. Lactosylated albumin nanoparticles (Cel-LANPs), administered by intraperitoneal injection (non-oral), enabled hepatocyte-targeted delivery, reducing steatosis and inflammation and improving ALT, AST, TC, glucose tolerance, and insulin sensitivity [114]. Celastrol-loaded albumin nanoparticles administered by oral gavage further promoted macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, reducing lipid deposition and inflammation and improving metabolic outcomes [115]. These celastrol studies should be compared within their respective routes: oral PEG-PCL micelles and oral BSA nanoparticles address enteral delivery, whereas intraperitoneal lactosylated BSA nanoparticles test post-injection distribution.

β-Carotene delivered via cationic lipid-assisted nanoparticles (NP-BC), administered by oral gavage, corrected lipid metabolic dysregulation through inhibition of the PI3K/AKT/mTOR pathway and PPARγ expression, reducing hepatic FFA and body weight, lowering AST, TG, TC, LDL-c, and VLDL-c, increasing HDL-c, and improving glycemic control and insulin sensitivity [116].

Oridonin encapsulated in HP-β-CD/H9-HePC peptide nanovesicles administered intravenously exhibited high hepatic exposure and rapid lipid-lowering effects in tetracycline-induced MASLD models, significantly reducing lipid droplets, collagen deposition, and liver weight [117].

Overall, nanoformulated terpenoids enhance hepatic targeting, anti-inflammatory and antioxidant activity, and metabolic pathway modulation, leading to systemic improvements in histological and metabolic endpoints in preclinical MASLD models.

4.1.4. Alkaloids

Alkaloids constitute another important class of natural compounds investigated for MASLD therapy, with berberine and evodiamine among the most studied. Liver-targeted berberine microspheres (BBR-CTA-Mic), administered by oral gavage, achieved higher intrahepatic concentrations and prolonged retention in HFD-fed mice and in HepG2, RAW264.7, and primary hepatocytes. These formulations activated InsR, AMPK, LDLR, and AKT signaling, reduced hepatocellular lipid accumulation, suppressed weight gain and hepatic steatosis, lowered ALT, and decreased TG, TC, and LDL-c levels, accompanied by reduced blood glucose [118]. Berberine delivered by oral gavage via TPGS1500 micelles increased deposition in liver and adipose tissue, upregulated p-AMPK, and inhibited NF-κB-mediated inflammation, thereby attenuating adipocyte–macrophage inflammatory crosstalk and reducing lipid accumulation and circulating lipids, although ALT and AST reductions were not significant in this study [119]. Berberine loaded into guar gum/arabic gum nanocomposites (Ber/Gu-AGNCs), administered orally, improved histopathology in HFD models, reducing liver weight, lipid droplets, AST, ALT, TC, TG, LDL-c, and VLDL-c while increasing HDL-c and lowering glucose levels [120].

A pH/gut-microbiota-responsive system of NC nanoparticles (NC-CS/PT-NPs), administered by oral gavage, reduced lipid accumulation and improved ALT, AST, TC, TG, and LDL through suppression of FAS and SREBP-1c and activation of AMPK/ACC signaling in HFD plus fructose MASLD models [121].

Overall, nanostructured alkaloids achieve higher hepatic exposure and prolonged pharmacological activity and exert multi-targeted effects via AMPK activation, inhibition of lipogenesis, and suppression of inflammation.

4.1.5. Lignans

Among lignans, intravenously administered arctiin delivered via nanocarriers (GA-MSe @AR) demonstrated antioxidant and lipid-regulatory effects in HFD-induced MASLD models and hepatocyte systems. Treatment reduced MDA and oxidized glutathione (GSSG), increased the GSH/GSSG ratio, and suppressed FASN, PPARγ, SREBP-1c, and IGF1/PI3K/Akt signaling, collectively producing lipid-lowering, antioxidant, anti-inflammatory, and insulin-sensitizing effects [16] (Figure 5).

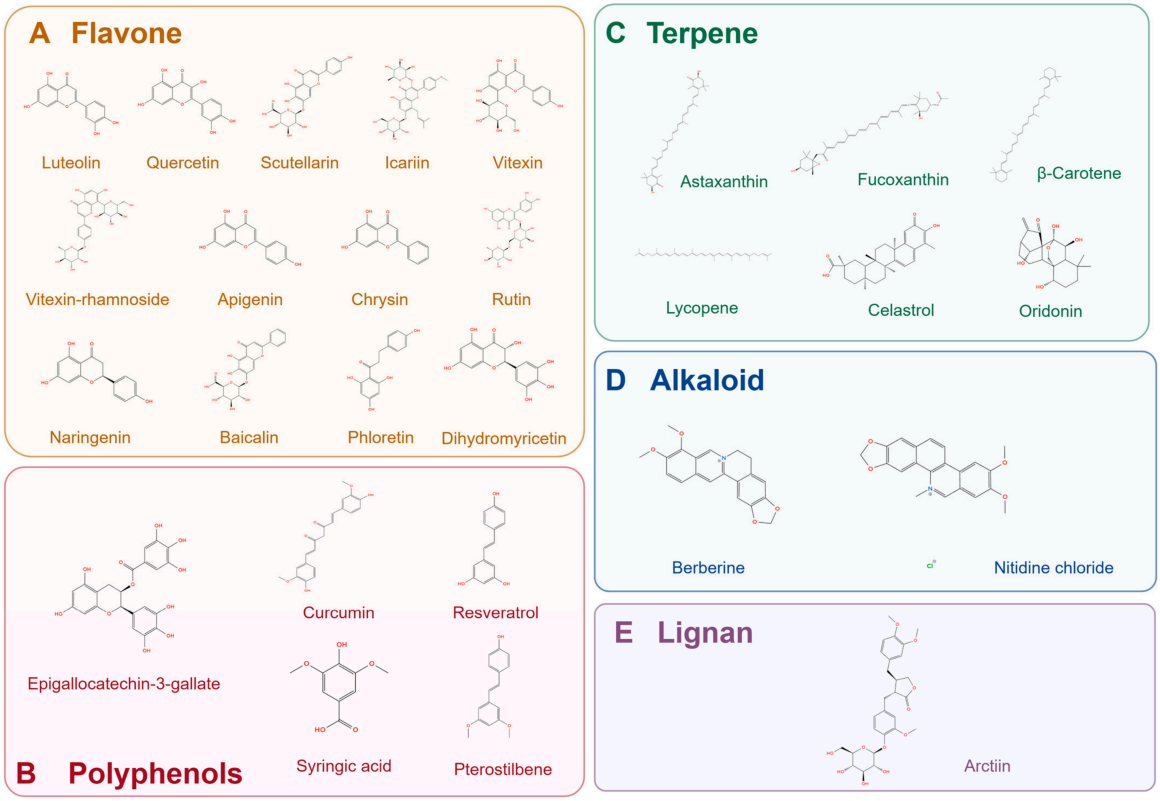


Figure 5. Natural small-molecule bioactives in nanostructured delivery systems for MASLD therapy. Representative classes of natural small-molecule bioactives incorporated into nanostructured delivery systems for MASLD therapy. Schematic overview of major categories of natural small molecules that have been formulated into nanostructured delivery platforms for the treatment of MASLD. The figure classifies representative compounds into five principal groups: (**A**) flavonoids (e.g., luteolin, quercetin, scutellarin, icariin, vitexin, apigenin, chrysin, rutin, naringenin, baicalin, phloretin, and dihydromyricetin), (**B**) polyphenols (e.g., curcumin, resveratrol, epigallocatechin gallate, syringic acid, and pterostilbene), (**C**) terpenoids (e.g., astaxanthin, fucoxanthin, β-carotene, lycopene, celastrol, and oridonin), (**D**) alkaloids (e.g., berberine and nitidine chloride), and (**E**) lignans (e.g., arctiin).

Overall, nanostructured natural bioactive small molecules generally demonstrate enhanced hepatic targeting and improved bioavailability, accompanied by coordinated effects on lipid metabolism remodeling and the attenuation of oxidative stress and inflammatory

responses. Their therapeutic actions primarily involve key metabolic and inflammatory regulatory pathways, including AMPK, Nrf2, SREBP-1c, PPARα, and NF-κB signaling axes. However, most available evidence is still derived from cellular and animal studies. Future investigations should therefore focus on comprehensive pharmacokinetic evaluation and well-designed clinical trials to further validate their therapeutic potential.

4.2. Nanostructured Natural Bioactive Fractions

In the field of natural product research, in addition to structurally well-defined single small molecules, another important category comprises bioactive fractions. These refer to biologically active extracts derived from natural medicines or traditional herbal materials. Such fractions usually consist of multiple chemical constituents, such as polysaccharides, polyphenols, flavonoids, or saponins, but do not correspond to a single defined chemical structure or molecular formula.

In studies related to MASLD, various nanoformulations incorporating natural bioactive fractions have demonstrated significant metabolic benefits. For instance, orally administered silymarin encapsulated in chitosan-containing lipid–polymer hybrid nanoparticles (CS-LPNs) enhances hepatocellular uptake and reduces lipid accumulation. In a high-fat diet (HFD)-induced MASLD mouse model, this formulation markedly alleviated macrovesicular steatosis and significantly reduced serum levels of ALT, AST, TG, and TC [122]. The oral route makes intestinal transport and formulation stability relevant to performance.

Similarly, *Ganoderma lucidum* spore polysaccharide-loaded selenium nanoparticles (GLP-SeNPs) have been shown to attenuate lipid deposition and oxidative stress in HFD-induced MAFLD models through activation of the NRF2 signaling pathway. These nanoparticles also ameliorate ferroptosis via multiple mechanisms, including SLC40A1-mediated iron metabolism, ACSL4-regulated lipid metabolic pathways, and the NRF2–GSH–GPX4 antioxidant axis. Both cellular and animal studies demonstrated significant reductions in lipid droplet accumulation, as well as in hepatic TG and TC levels [123].

4.3. Nanostructured Single-Source Therapeutics

In contrast to structurally defined small-molecule compounds or isolated bioactive fractions, single natural medicines generally refer to whole extracts derived from a single medicinal material or natural biological resource, characterized by complex chemical compositions. In studies related to MASLD, increasing attention has been directed toward single natural medicines derived from plants, animals, or microorganisms, as well as their corresponding nanoformulations. In particular, recently identified natural exosome-like nanovesicles and nano-engineered systems based on natural extracts have opened new avenues for exploring the therapeutic potential of single natural medicines in MASLD. The following section summarizes recent research progress on nanostructured single natural medicines and their applications in MASLD.

In an HFS-induced NASH model, oral administration of citrus peel extract formulated with metal oxide nanoparticles (MgO/ZnO) downregulates TLR4/NF-κB signaling and multiple pro-inflammatory mediators while suppressing lipogenesis through inhibition of SREBP-1c. These effects translate into marked improvements in hepatic steatosis and inflammation, reductions in ALT, AST, TC, TG, and LDL-c, and increased HDL-c levels [124].

A nanoemulsion containing ω-5 fatty acid (punicic acid) derived from pomegranate seed oil, administered by oral gavage, demonstrates optimal efficacy when administered during the seventh week in HFD-induced MASLD, significantly promoting fatty acid oxidation and antioxidant responses, reducing hepatic lipid droplets, lowering fasting blood glucose, and improving glucose tolerance. Mild decreases in ALT and AST are observed, although serum lipid profiles show limited improvement [125].

Orally administered basil essential oil nanoemulsions (BNOs) attenuate steatosis and hepatic inflammation in fructose-saturated fatty acid-induced NASH models by downregulating IL-6 and LCN2, improving gut microbiota composition, and reducing hepatic lipid burden, with significant decreases observed primarily in serum TG [126].

Orally administered Spirulina peptide-loaded liposomes and chitosan-modified liposomes (SP-LP and SP-Ch-LP) suppress lipogenesis and promote lipid oxidation through activation of the AMPK–ACC signaling axis while modulating cholesterol metabolism. These formulations significantly reduce hepatic lipid droplets and inflammation, lower hepatic TG and TC and serum ALT and AST levels, improve serum TG, TC, LDL, and HDL profiles, and reduce fasting blood glucose and HOMA-IR. Notably, SP-Ch-LP exhibits more pronounced metabolic improvements than SP-LP [127,128].

Natural exosome-like nanovesicles have recently emerged as promising therapeutic platforms for MASLD. Orally administered honey-derived vesicle-like nanoparticles (H-VLNs) suppress c-JUN and NF-κB transcriptional activity in aging mouse liver models and AML12 cells, thereby attenuating chronic inflammation and fibrogenesis and reducing fibrotic deposition. However, hepatic TAG content and lipogenic gene expression remain largely unchanged, and serum ALT shows only a downward trend [129].

Blueberry-derived exosome-like nanoparticles (BELNs), administered by oral gavage, promote nuclear translocation of Nrf2 and enhance antioxidant defenses while suppressing FAS and ACC1 expression, resulting in improved insulin resistance and reduced hepatic lipid accumulation. These changes are accompanied by decreases in ALT, AST, TC, TG, and LDL-c, increases in HDL-c, and improvements in fasting blood glucose, insulin levels, glucose tolerance, and HOMA-IR [130].

Poria cocos-derived exosome-like nanovesicles (PCELNs), administered by intraperitoneal injection (non-oral), reduce oxidized mitochondrial DNA and inhibit the NLRP3–caspase-1–IL-1β inflammatory axis, significantly decreasing hepatic lipid droplets and inflammatory infiltration. Correspondingly, ALT, AST, TC, TG, and LDL-c levels decline, HDL-c increases, and hepatic architecture approaches normal morphology [131].

Garlic-derived exosome-like nanoparticles (GDEs), administered by oral gavage, regulate inflammation and lipid metabolism through the miR-396e-PFKFB3 axis between macrophages and hepatocytes, reducing hepatocellular vacuolation and lipid droplets, lowering ALT and AST, decreasing serum TC, and increasing HDL-c [132].

Tangerine peel-derived exosome-like nanovesicles (TPNVs), administered orally, suppress lipogenesis, enhance fatty acid oxidation, and modulate gut microbiota in type 2 diabetes-associated fatty liver models. These effects significantly reduce ALT, AST, TG, TC, LDL-c, fasting glucose, insulin, and HOMA-IR, while increasing HDL-c [133].

Pomegranate-derived exosome-like nanovesicles (PNVs), administered orally, ameliorate MASLD by restoring intestinal barrier integrity, reshaping gut microbiota, and suppressing oxidative stress and lipogenesis, thereby reducing hepatic lipid droplets and inflammatory foci and lowering hepatic TG, serum ALT, AST, and fasting glucose levels [134].

Orally administered exosome-like nanovesicles from hemp seedlings (HSNVs) inhibit TLR4-mediated inflammatory signaling and reduce expression of TGF-β, α-SMA, collagen, and MMPs, while modulating the P-AMPK/SREBP-1 pathway and improving intestinal barrier function. These coordinated effects decrease hepatic lipid accumulation, inflammation, and fibrosis, accompanied by reductions in serum ALT, AST, TG, and hepatic TG [135].

Bovine colostrum-derived exosome-like vesicles (BCEVs), administered by oral gavage, modulate gut microbiota and cholesterol metabolism while suppressing intestinal inflammation and hepatic fibrosis, significantly reducing MASLD activity scores and steatotic area and lowering ALT and AST levels in NASH models [136].

Similarly, orally administered bovine milk-derived exosome-like vesicles (B-mEVs) enhance intestinal barrier integrity and immune function and suppress intrahepatic inflammatory signaling pathways (including iNOS and IRAK4) in MCD-induced NASH models, leading to marked reductions in hepatic lipid droplets, inflammatory foci, and fibrotic regions [137].

Fermentation with *Acetobacter* reduces particle size and increases the abundance of tea-derived exosome-like nanovesicles, which, after oral administration, significantly improve hepatic lipid droplets, serum transaminases, and lipid parameters in HFD-fed mice [138].

Exosome-like nanovesicles obtained from turmeric decoction and administered by oral gavage exhibit lipid-lowering and anti-inflammatory effects, reduce PLIN2-associated lipid droplets, and improve hepatic lipid accumulation, ALT/AST levels, and serum lipid profiles in HFD models [139]. Similarly, arugula-derived exosome-like nanovesicles administered intragastrically activate p-AMPK/p-Akt signaling and suppress FASN/PPARγ, thereby reducing lipid accumulation and improving both lipid and glucose metabolism [140]. For orally delivered natural vesicles, intestinal persistence and barrier effects may contribute to liver benefits even when intact-vesicle systemic absorption has not been established [139,141].

Collectively, these findings suggest that nanostructured natural bioactive components exert broad therapeutic effects on MASLD phenotypes across histological, biochemical, and metabolic parameters. Their mechanisms converge on multi-layered regulation of inflammation, oxidative stress, lipid synthesis and oxidation, and intestinal barrier integrity, highlighting the translational potential of nanotechnology-enabled natural products for MASLD intervention (Figure 6).

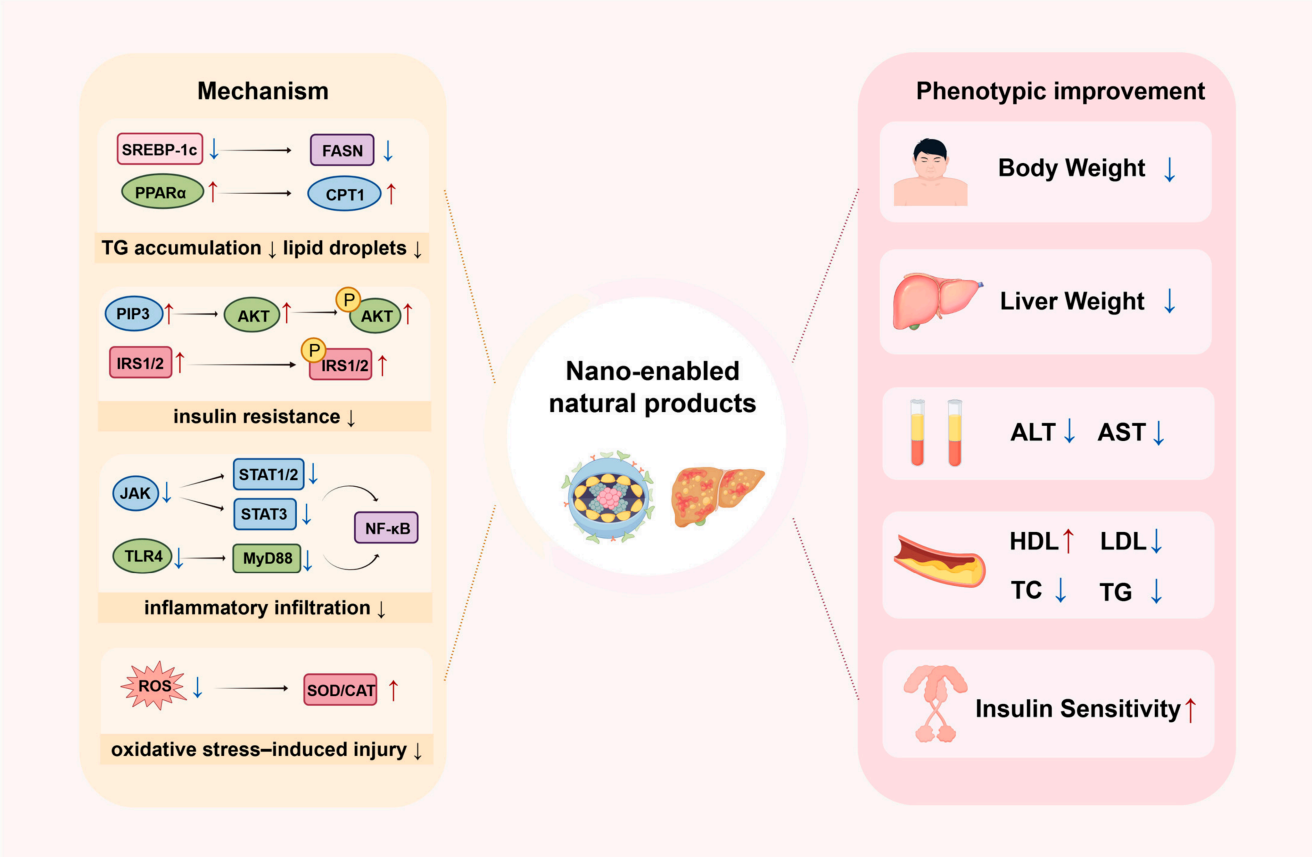


Figure 6. Molecular mechanisms and associated phenotypic improvements of nano-enabled natural products in MASLD. Mechanistic actions and phenotypic improvements mediated by nano-enabled natural products in MASLD. Schematic summary of the principal molecular mechanisms (left panel)

and corresponding phenotypic outcomes (right panel) associated with nanostructured natural bioactive compounds in MASLD. At the mechanistic level, nano-enabled natural products modulate key metabolic and inflammatory signaling pathways, including suppression of lipogenesis (downregulation of SREBP-1c and FASN) and enhancement of fatty acid oxidation (upregulation of PPARα and CPT1), reduction of hepatic triglyceride accumulation and lipid droplet formation, improvement of insulin signaling via IRS-1/AKT activation, inhibition of inflammatory cascades (e.g., TLR4-MyD88-NF-κB and JAK/STAT pathways), and attenuation of oxidative stress through increased antioxidant defenses and reduced ROS-mediated injury. These coordinated molecular effects translate into measurable phenotypic improvements, including reduced body and liver weight, decreased serum ALT and AST levels, improved lipid profiles (decreased TC, TG, and LDL with increased HDL), and enhanced insulin sensitivity.

4.4. Delivery Characteristics and Mechanisms of Different Nanostructures

Different nanostructures may enhance the effects of natural bioactives on MASLD-related pathological processes by improving effective exposure, cellular uptake, and release, or by modulating local intestinal effects. Although these systems influence common processes involving lipid metabolism, inflammation, and oxidative stress, their mechanistic profiles should be interpreted in the context of the payload, administration route, and experimental model.

Studies of liposomal formulations primarily demonstrate coordinated effects on lipid metabolism and inflammatory signaling. Encapsulated natural bioactives modulate AMPK-ACC-, SREBP-1c/FAS-, and PPARα/CPT-1-related processes to suppress lipogenesis and promote fatty acid oxidation. Concurrent inhibition of TLR4/MyD88/NF-κB- or TLR3/TRIF-associated inflammation, together with enhanced antioxidant defenses, contributes to reductions in hepatic lipid accumulation and injury [80,83,91,103,127,128]. The extent of these effects depends on membrane stability, release behavior, and administration route.

Nanoemulsions primarily improve the dispersion and absorption of hydrophobic compounds, thereby enhancing their antioxidant and metabolic regulatory effects. Reported mechanisms include reductions in ROS and lipid peroxidation, modulation of Nrf2-associated defenses, and enhancement of PPARα/CPT-1-mediated fatty acid oxidation, collectively alleviating hepatic metabolic stress. Some formulations also indirectly attenuate hepatic steatosis by promoting adipose tissue thermogenesis or modulating the gut microbiota [48,98,99,112,125,126]. Their effects therefore encompass hepatic protection, systemic energy metabolism, and gut–liver axis regulation.

The effects of inorganic nanoparticles may arise from both improved delivery and the intrinsic biological activity of the constituent materials. Reported mechanisms involve modulation of PI3K/AKT/FoxO1-mediated insulin signaling, suppression of TLR4/NF-κB-associated inflammation, and regulation of the NRF2–GSH–GPX4 axis and iron metabolism, thereby attenuating lipid accumulation, oxidative injury, and ferroptosis-related pathological changes [76,105,123,124]. Because material composition can directly influence redox processes, mechanistic interpretation requires consideration of the respective contributions of the bioactive payload and inorganic components.

Polymeric nanoparticles support metabolic and immune modulation by protecting bioactive compounds, facilitating transport across biological barriers, and modifying tissue and cellular exposure. Their reported mechanisms encompass AMPK-related metabolic regulation and suppression of lipogenesis, Nrf2/HO-1-mediated antioxidant defense, inhibition of JAK/STAT1-associated fibrogenic responses, and modulation of macrophage phenotypes and the gut microbiota [77–79,81,82,109,110,115,121].

Micellar systems primarily enhance effective exposure, supporting coordinated metabolic regulation and suppression of inflammation. Representative studies report AMPK activation, NF-κB inhibition, downregulation of SREBP-1c and FAS, and upregulation of CPT1, leading to reduced lipid accumulation, metabolic inflammation, and insulin resistance [113,119]. However, a clinical study of micellar nano-curcumin reported improvements in liver enzymes without a significant additional benefit in hepatic fat content, indicating that its clinical efficacy and underlying mechanisms require further validation [97].

Current evidence for nanogels primarily supports hepatocellular protection through improved intracellular delivery and release. In an in vitro model, hydroxytyrosol-loaded nanogels reduced intracellular triglyceride accumulation and free-fatty-acid-induced injury more effectively than non-encapsulated hydroxytyrosol [68]. These effects suggest enhanced intracellular delivery, reduced lipid burden, and preservation of cell viability, although specific signaling mechanisms and in vivo efficacy remain to be established.

Available mechanistic evidence for solid lipid nanoparticles primarily concerns attenuation of inflammation. A fucoxanthin formulation downregulated hepatic MCP-1 expression, accompanied by improvements in lipid parameters, glycemia, liver enzymes, and hepatic histology, suggesting that reduced inflammatory responses may contribute to its hepatoprotective effects [69]. These findings are insufficient to establish a common mechanism of metabolic regulation across this nanostructure class.

Self-assembled nanoparticles may enhance therapeutic potential by optimizing assembly behavior, improving tissue exposure, or enabling co-delivery [71,72]. Although their delivery advantages have some supporting evidence, the pathway-level findings summarized in this review remain limited, precluding a mechanistic synthesis as well defined as that available for liposomes or polymeric nanoparticles.

Naturally derived vesicle-like nanoparticles exhibit multilevel effects on the gut–liver axis, oxidative stress, and immune-inflammatory responses. Reported mechanisms combine improvements in intestinal barrier function and gut microbiota composition with Nrf2-associated antioxidant defenses, suppression of lipogenesis, and modulation of TLR4/NF-κB, NLRP3-caspase-1-IL-1β, and intercellular signaling, thereby attenuating hepatic lipid accumulation, inflammation, and fibrosis [129–137,139,140]. Local intestinal effects following oral administration should, however, be distinguished from systemic absorption of intact vesicles and direct hepatic delivery.

Overall, the effects of these nanostructures converge on suppression of lipogenesis, enhancement of fatty acid oxidation, attenuation of oxidative injury, and inhibition of inflammation. The more clearly supported differences concern how they modify effective exposure and sites of action, rather than an exclusive association with individual signaling pathways. Current evidence does not allow the observed pathway responses to be attributed solely to carrier structure, nor does it support an efficacy ranking across nanostructure classes (Figure 7).

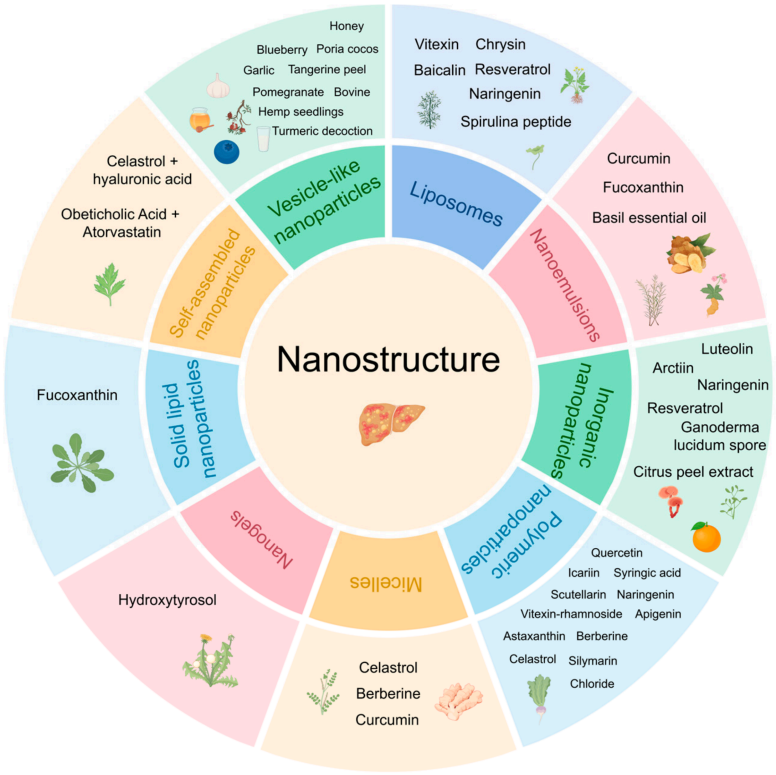


Figure 7. Nanostructure classes and their corresponding naturally derived bioactives. The inner ring depicts nine nanostructure classes: liposomes, nanoemulsions, inorganic nanoparticles, polymeric nanoparticles, micelles, nanogels, solid lipid nanoparticles, self-assembled nanoparticles, and vesicle-like nanoparticles. The outer ring lists the representative small-molecule bioactives, bioactive fractions, and single-source natural medicines investigated in the corresponding studies.

5. Main Outcomes and Future Perspectives

This review systematically summarizes recent advances in nanostructured natural bioactive substances for the treatment of MASLD. Based on the chemical composition and pharmacological forms of natural products, the available studies are categorized into three major groups: nanostructured natural bioactive small molecules, nanostructured natural bioactive fractions, and nanostructured single-source medicines. Among these, the bioactive small-molecule category can be further subdivided into five principal subclasses: flavonoids, polyphenols, terpenoids, alkaloids, and lignans. Notably, two nanoformulated curcumin-based therapies have already progressed to clinical studies. Overall, the evidence summarized in this review demonstrates that nanostructuring markedly enhances the therapeutic potential of natural bioactive substances in MASLD.

These nanoformulations exert beneficial effects across multiple pathological dimensions, including improvements in hepatic histology and the reduction of hepatic lipid accumulation, the normalization of serum liver enzymes, the amelioration of dyslipidemia, and the improvement of glucose metabolism.

MASLD evolves along a continuum from steatosis to inflammation and fibrosis, encompassing lipid metabolic dysregulation, insulin resistance, oxidative stress, and chronic inflammatory signaling. Accordingly, therapeutic strategies capable of simultaneously targeting metabolic and inflammatory pathways are conceptually better aligned with the pathophysiology of the disease. The present review focuses on nanostructured natural bioactive agents, including carrier-based systems such as liposomes, nanoemulsions, polymeric nanoparticles, micelles, and nanogels, that encapsulate natural small molecules, as well as carrier-free self-assembled nanostructures, vesicle-like nanoparticles, and exosome-

like nanovesicles derived from natural sources. Despite their structural diversity, these strategies share a common objective: to enhance the efficacy and safety profile of natural bioactive compounds.

Natural small molecules possess intrinsic pharmacological advantages, including multi-pathway modulation, anti-inflammatory and antioxidant activity, and broad metabolic regulatory capacity. However, their therapeutic translation is frequently constrained by poor aqueous solubility due to hydrophobicity, low oral bioavailability, rapid systemic metabolism, and heterogeneous tissue distribution, all of which result in insufficient and fluctuating hepatic exposure. Consequently, maintaining an effective intrahepatic concentration remains challenging, and therapeutic responses are often sensitive to dose variation and interindividual differences. A central bottleneck in the transition from mechanistic studies to clinical application is whether adequate and reproducible hepatic exposure can be achieved in a safe and controllable manner. As highlighted throughout this review, improving pharmacokinetics via nanostructuring has therefore emerged as a critical research direction.

The core value of nanostructuring extends beyond improving solubility or absorption; rather, it lies in enhancing the predictability of the exposure–response relationship. Carrier-based nanostructures, such as liposomes, nanoemulsions, polymeric nanoparticles, micelles, and nanogels, offer well-established fabrication methods, controlled-release properties, and high modifiability. These systems can improve aqueous solubility, protect compounds from gastrointestinal degradation, and promote hepatic accumulation through uptake by Kupffer cells, hepatocytes, or receptor-mediated targeting, thereby enhancing therapeutic efficacy [71,141–143]. Inorganic nanomaterials require particular caution in an already oxidatively stressed and inflamed MASLD liver. Depending on composition, dose, surface chemistry, and dissolution, silica or metal oxide particles may promote oxidative stress, disturb lipid handling, or counteract the intended antioxidant action of their payload. Abulikemu et al. reported aggravated steatosis, inflammatory injury, and disturbed amino acid and lipid metabolism after silica nanoparticle exposure in ApoE-deficient mice, accompanied by oxidative stress [54].

The disease models also constrain interpretation. Many studies reviewed here use HFD or methionine- and choline-deficient (MCD) diets. HFDs reproduce aspects of obesity and metabolic dysfunction, but their inflammatory and fibrotic phenotypes vary with diet, strain, and duration. MCD feeding can rapidly produce steatohepatitis but often causes weight loss and lacks the systemic insulin resistance characteristic of many patients [144]. Neither approach captures the full multisystem metabolic and histological heterogeneity of human MASLD/MASH. Future validation should span disease stages and metabolic backgrounds and incorporate human multicellular liver organoids; diet-induced obese nonhuman primates may provide additional evidence when scientifically and ethically justified [145,146].

In contrast, carrier-free self-assembled or vesicle-like nanoparticles can achieve high drug loading while minimizing the introduction of exogenous materials, thereby reducing potential toxicity and immunogenicity and offering structural advantages for combination therapy [147,148]. Exosomes are lipid bilayer vesicles secreted by cells, with diameters of approximately 30–150 nm, and are naturally found in bodily fluids such as blood and saliva. Plant extracellular vesicles can be isolated from extracellular compartments such as leaf apoplastic fluid [149]; preparations obtained by homogenizing or processing edible tissues may additionally contain intracellular membrane fragments, reassembled vesicles, and non-vesicular particles. Where extracellular origin and biogenesis have not been demonstrated, plant-derived nanovesicles or vesicle-like nanoparticles are more defensible terms than exosomes. Plant-derived vesicles retain source-specific lipids, proteins, and other biomolecules,

which may influence receptor recognition, cellular uptake, and tissue distribution. For synthetic nanocarriers, particle size, surface charge, ligand modification, and the protein corona formed upon entry into living organisms all influence cellular recognition and clearance. However, the fact that plant-derived vesicles possess a natural membrane structure does not mean that they can avoid protein adsorption, phagocytosis, or intracellular degradation. Current research on plant vesicles has primarily provided evidence regarding cellular uptake and tissue localization; quantitative evidence concerning the circulation half-life of intact vesicles, their degradation products, and their excretion via the hepatobiliary or renal pathways remains insufficient. Consequently, it cannot yet be established that plant vesicles are cleared more slowly or accumulate less in vivo than synthetic carriers [150].

Comparative evidence between nanostructured and non-nanostructured compounds generally supports the notion that nanostructuring enhances both the magnitude and stability of improvements in hepatic and metabolic endpoints, consistent with findings from previous preclinical and clinical studies. For example, β-carotene delivered via cationic lipid-assisted nanoparticles (NP-BC) produced greater histological improvement than free β-carotene, reduced hepatic free fatty acid levels, suppressed weight gain, and improved lipid and glucose metabolism. Notably, the nanoformulation exerted a more pronounced effect on AST reduction, suggesting that enhanced hepatic exposure and sustained action may amplify measurable therapeutic endpoints. Clinical studies of nano-curcumin provide additional support. In one trial involving 84 participants, Sinacurcumin® (80 mg/day for 12 weeks) significantly improved ultrasound-based steatosis grading, reduced ALT and AST, and improved lipid and glycemic parameters. In another study using micellar nano-curcumin (80 mg/day for 16 weeks) in conjunction with lifestyle intervention, both treatment and control groups showed reductions in liver fat content as assessed by FibroScan CAP, with no additional significant reduction in hepatic fat in the nano-curcumin group. However, nano-curcumin significantly lowered ALT, AST, GGT, and LDH. Collectively, these findings suggest that nanostructuring may more readily translate into improvements in liver enzymes and metabolic biochemical markers, whereas endpoints highly sensitive to behavioral intervention, such as hepatic fat content, may require longer treatment duration, larger sample sizes, and baseline stratification to reveal incremental benefits. However, issues related to source standardization, purification methods, and batch-to-batch consistency remain major challenges for clinical translation. It is worth mentioning that complex botanical mixtures and vesicle-like products create related regulatory challenges because both active composition and delivery structure may be incompletely defined. Botanical drug guidance offers a framework for controlling complex mixtures, but classification and evidence requirements must be determined for the specific product and jurisdiction [151].

Safety remains a decisive factor in determining the clinical feasibility of MASLD therapies. Nanostructured natural bioactive agents offer dual potential in this regard. On one hand, improved hepatic exposure and controlled release may enable stronger therapeutic effects at lower or comparable doses, thereby reducing systemic exposure and dose-related risks. On the other hand, carrier-free self-assembled systems and exosome-like nanovesicles may reduce the burden of exogenous materials and improve physiological compatibility. Nonetheless, nanostructured formulations should not be assumed to be inherently safe. Biocompatibility varies considerably among inorganic nanomaterials, and certain nanoparticles, particularly when unmodified or administered at high doses, may exacerbate hepatic lipid metabolic disturbances or induce oxidative stress. Therefore, material selection and comprehensive biocompatibility assessment are critical in MASLD research and translation. Future work should establish systematic safety evaluation frameworks encompassing chronic exposure, immune responses, tissue accumulation and clearance pathways, and interactions with the metabolic syndrome milieu. Such frameworks should be integrated

with dose–exposure–effect analyses to meet the requirements of long-term therapy for chronic disease.

Looking forward, nanostructured natural bioactive agents hold considerable promise for MASLD intervention and may offer improved efficacy with favorable safety profiles. Mechanistically, hepatocytes, Kupffer cells, hepatic stellate cells, and the gut–liver axis represent key nodes for targeted delivery and therapeutic modulation [152–154]. Nanostructures incorporating liver-targeting ligands or microenvironment-responsive release mechanisms may further enhance therapeutic efficiency. Carrier-free self-assembled systems and exosome-like nanovesicles are particularly attractive due to their potential for combination therapy, reduced carrier burden, and improved biocompatibility. These systems have already demonstrated the capacity to reduce ALT and AST, improve lipid metabolism, and modulate inflammatory metabolic signaling in MASLD models. Manufacturing reproducibility is especially important for nanostructured natural products. Scale-dependent changes in mixing, homogenization, solvent removal, purification, and drying may alter size distribution, surface properties, free versus encapsulated constituents, and release. Future clinical studies should adopt standardized and comparable endpoint frameworks that integrate imaging, histological, and metabolic outcomes, and should be designed within the context of lifestyle intervention with appropriate stratification to determine whether nanostructuring can provide clinically meaningful benefits beyond those of the active compound alone in real-world settings.

In summary, natural bioactive compounds possess pharmacological advantages that align with the multi-pathway pathological network of MASLD, yet their pharmacokinetic and distributional limitations remain key barriers to clinical translation. Nanostructured formulations improve solubility, stability, hepatic accumulation, and controlled release, thereby enhancing the actionable, sustained, and predictable intrahepatic exposure required for therapeutic efficacy. Early clinical data have yielded encouraging signals. With continued advances in material safety, manufacturing standardization, and clinical endpoint evaluation, nanostructured natural bioactive agents may emerge as an important strategy for long-term MASLD management that balances safety with enhanced therapeutic efficacy.

Author Contributions: Conceptualization, Q.-M.S., R.-T.L., X.X., C.Z., R.-Q.Z., L.-L.S., J.G., Q.F., and L.S.; Resources, J.G., Q.F., and L.S.; Writing—original draft, X.-T.S.; Writing—review and editing, J.G., Q.F., and L.S.; Supervision, Q.-M.S., R.-T.L., X.X., C.Z., R.-Q.Z., L.-L.S., J.G., Q.F., and L.S.; Funding acquisition, X.-T.S., Q.F., and L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by The Siming Fund, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, grant number SGKJ-202522; Science and Technology Development Program of Shanghai University of Traditional Chinese Medicine, grant number 25KPZX01; Shanghai Oriental Talent Top-notch Program, grant number BJWS2025018; Clinical Research Project initiated by researchers from Shanghai Pudong New Area Health Commission, grant number 2026-PWDL-12 and Shuguang Hospital IIT Program, grant number SGYYIIT-2025-198.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: Figures were created using the Figdraw 2.0 platform.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Younossi, Z.M.; Golabi, P.; Paik, J.M.; Henry, A.; Van Dongen, C.; Henry, L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): A systematic review. *Hepatology* **2023**, *77*, 1335–1347. [CrossRef]
2. Younossi, Z.M.; Kalligeros, M.; Henry, L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. *Clin. Mol. Hepatol.* **2025**, *31*, S32–S50. [CrossRef]
3. Miao, L.; Targher, G.; Byrne, C.D.; Cao, Y.Y.; Zheng, M.H. Current status and future trends of the global burden of MASLD. *Trends Endocrinol. Metab.* **2024**, *35*, 697–707. [CrossRef]
4. Stroes, A.R.; Vos, M.; Benninga, M.A.; Koot, B.G.P. Pediatric MASLD: Current understanding and practical approach. *Eur. J. Pediatr.* **2024**, *184*, 29. [CrossRef]
5. Wong, V.W.; Ekstedt, M.; Wong, G.L.; Hagström, H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J. Hepatol.* **2023**, *79*, 842–852. [CrossRef]
6. van Kleef, L.A.; Pustjens, J.; Savas, M.; Ayada, I.; Li, P.; Pan, Q.; van Rossum, E.F.C.; Janssen, H.L.A.; Brouwer, W.P. MASLD, At-Risk MASH and Increased Liver Stiffness Are Associated With Young Adulthood Obesity Without Residual Risk After Losing Obesity. *Liver Int.* **2025**, *45*, e16169. [CrossRef]
7. Kozłowska, A. Clinical Insights into Non-Alcoholic Fatty Liver Disease and the Therapeutic Potential of Flavonoids: An Update. *Nutrients* **2025**, *17*, 956. [CrossRef]
8. Wu, Q.; Chen, Z.; Ding, Y.; Tang, Y.; Cheng, Y. Protective effect of traditional Chinese medicine on non-alcoholic fatty liver disease and liver cancer by targeting ferroptosis. *Front. Nutr.* **2022**, *9*, 1033129. [CrossRef]
9. Song, Z.; Bu, S.; Sang, S.; Li, J.; Zhang, X.; Song, X.; Ran, Y. The Active Components of Traditional Chinese Medicines Regulate the Multi-Target Signaling Pathways of Metabolic Dysfunction-Associated Fatty Liver Disease. *Drug Des. Devel Ther.* **2025**, *19*, 2693–2715. [CrossRef]
10. Dai, X.; Feng, J.; Chen, Y.; Huang, S.; Shi, X.; Liu, X.; Sun, Y. Traditional Chinese Medicine in nonalcoholic fatty liver disease: Molecular insights and therapeutic perspectives. *Chin. Med.* **2021**, *16*, 68. [CrossRef]
11. Moghtadaie, A.; Mahboobi, H.; Fatemizadeh, S.; Kamal, M.A. Emerging role of nanotechnology in treatment of non-alcoholic fatty liver disease (NAFLD). *Excli J.* **2023**, *22*, 946–974. [CrossRef]
12. Wang, C.; Ren, K.; Yang, M.; Li, X.; Li, N.; Li, P.; Yang, H.; Zhang, G.; Wei, X. How Traditional Chinese Medicine Can Play a Role In Nanomedicine? A Comprehensive Review of the Literature. *Int. J. Nanomed.* **2025**, *20*, 6289–6315. [CrossRef]
13. 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*, 1303. [CrossRef]
14. Li, Y.; Zhang, W.; Zhao, R.; Zhang, X. Advances in oral peptide drug nanoparticles for diabetes mellitus treatment. *Bioact. Mater.* **2022**, *15*, 392–408. [CrossRef]
15. Batsukh, T.; Tsend-Ayush, A. Herbal drug-based nanotherapy for hepatocellular carcinoma: Quercetin-contained nanocarrier as a multipurpose therapeutic agent against hepatocellular carcinoma (Review). *Biomed. Rep.* **2025**, *22*, 29. [CrossRef]
16. 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. [CrossRef]
17. Bugianesi, E.; Moscatiello, S.; Ciaravella, M.F.; Marchesini, G. Insulin Resistance in Nonalcoholic Fatty Liver Disease. *Curr. Pharm. Des.* **2010**, *16*, 1941–1951. [CrossRef]
18. Mungamuri, S.K.; Sinha, S.N.; Javvadi, Y. Understanding the Alterations in Lipid Metabolism in NAFLD Progression: Current Trends and Future Directions. *Crit. Rev. Oncog.* **2021**, *26*, 35–49. [CrossRef]
19. Samuel, V.T.; Shulman, G.I. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. *J. Clin. Investig.* **2016**, *126*, 12–22. [CrossRef]
20. Zhang, C.H.; Zhou, B.G.; Sheng, J.Q.; Chen, Y.; Cao, Y.Q.; Chen, C. Molecular mechanisms of hepatic insulin resistance in nonalcoholic fatty liver disease and potential treatment strategies. *Pharmacol. Res.* **2020**, *159*, 104984. [CrossRef]
21. Kitade, H.; Chen, G.; Ni, Y.; Ota, T. Nonalcoholic Fatty Liver Disease and Insulin Resistance: New Insights and Potential New Treatments. *Nutrients* **2017**, *9*, 387. [CrossRef]
22. Pei, K.; Gui, T.; Kan, D.; Feng, H.; Jin, Y.; Yang, Y.; Zhang, Q.; Du, Z.; Gai, Z.; Wu, J.; et al. An Overview of Lipid Metabolism and Nonalcoholic Fatty Liver Disease. *Biomed. Res. Int.* **2020**, *2020*, 4020249. [CrossRef]
23. Shen, S.; Shen, M.; Kuang, L.; Yang, K.; Wu, S.; Liu, X.; Wang, Y.; Wang, Y. SIRT1/SREBPs-mediated regulation of lipid metabolism. *Pharmacol. Res.* **2024**, *199*, 107037. [CrossRef]
24. Petrescu, M.; Vlaicu, S.I.; Ciumărnean, L.; Milaciu, M.V.; Mărginean, C.; Florea, M.; Vesa Ș, C.; Popa, M. Chronic Inflammation-A Link between Nonalcoholic Fatty Liver Disease (NAFLD) and Dysfunctional Adipose Tissue. *Medicina* **2022**, *58*, 641. [CrossRef]
25. Lee, Y.A.; Friedman, S.L. Inflammatory and fibrotic mechanisms in NAFLD-Implications for new treatment strategies. *J. Intern. Med.* **2022**, *291*, 11–31. [CrossRef]
26. Song, C.; Long, X.; He, J.; Huang, Y. Recent evaluation about inflammatory mechanisms in nonalcoholic fatty liver disease. *Front. Pharmacol.* **2023**, *14*, 1081334. [CrossRef]

27. Chen, J.; Deng, X.; Liu, Y.; Tan, Q.; Huang, G.; Che, Q.; Guo, J.; Su, Z. Kupffer Cells in Non-alcoholic Fatty Liver Disease: Friend or Foe? *Int. J. Biol. Sci.* **2020**, *16*, 2367–2378. [CrossRef]
28. Delli Bovi, A.P.; Marciano, F.; Mandato, C.; Siano, M.A.; Savoia, M.; Vajro, P. Oxidative Stress in Non-alcoholic Fatty Liver Disease. An Updated Mini Review. *Front. Med.* **2021**, *8*, 595371. [CrossRef]
29. Rives, C.; Fougerat, A.; Ellero-Simatos, S.; Loiseau, N.; Guillou, H.; Gamet-Payrastre, L.; Wahli, W. Oxidative Stress in NAFLD: Role of Nutrients and Food Contaminants. *Biomolecules* **2020**, *10*, 1702. [CrossRef]
30. Wang, L.; Zhang, K.; Zeng, Y.; Luo, Y.; Peng, J.; Zhang, J.; Kuang, T.; Fan, G. Gut mycobiome and metabolic diseases: The known, the unknown, and the future. *Pharmacol. Res.* **2023**, *193*, 106807. [CrossRef]
31. Du, L.; Ding, X.; Tian, Y.; Chen, J.; Li, W. Effect of anthocyanins on metabolic syndrome through interacting with gut microbiota. *Pharmacol. Res.* **2024**, *210*, 107511. [CrossRef]
32. Song, Q.; Zhang, X. The Role of Gut-Liver Axis in Gut Microbiome Dysbiosis Associated NAFLD and NAFLD-HCC. *Biomedicines* **2022**, *10*, 524. [CrossRef]
33. Sharma, S.; Tiwari, N.; Tanwar, S.S. The current findings on the gut-liver axis and the molecular basis of NAFLD/NASH associated with gut microbiome dysbiosis. *Naunyn Schmiedebergs Arch. Pharmacol.* **2025**, *398*, 11541–11579. [CrossRef]
34. Pandey, H.; Goel, P.; Srinivasan, V.M.; Tang, D.W.T.; Wong, S.H.; Lal, D. Gut microbiota in non-alcoholic fatty liver disease: Pathophysiology, diagnosis, and therapeutics. *World J. Hepatol.* **2025**, *17*, 106849. [CrossRef]
35. Rodriguez-Diaz, C.; Taminiau, B.; García-García, A.; Cueto, A.; Robles-Díaz, M.; Ortega-Alonso, A.; Martín-Reyes, F.; Daube, G.; Sanabria-Cabrera, J.; Jimenez-Perez, M.; et al. Microbiota diversity in nonalcoholic fatty liver disease and in drug-induced liver injury. *Pharmacol. Res.* **2022**, *182*, 106348. [CrossRef]
36. Plaza-Díaz, J.; Solís-Urra, P.; Rodríguez-Rodríguez, F.; Olivares-Arancibia, J.; Navarro-Oliveros, M.; Abadía-Molina, F.; Álvarez-Mercado, A.I. The Gut Barrier, Intestinal Microbiota, and Liver Disease: Molecular Mechanisms and Strategies to Manage. *Int. J. Mol. Sci.* **2020**, *21*, 8351. [CrossRef]
37. Sodum, N.; Kumar, G.; Bojja, S.L.; Kumar, N.; Rao, C.M. Epigenetics in NAFLD/NASH: Targets and therapy. *Pharmacol. Res.* **2021**, *167*, 105484. [CrossRef]
38. Anstee, Q.M.; Day, C.P. The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on PNPLA3 and TM6SF2. *Semin. Liver Dis.* **2015**, *35*, 270–290. [CrossRef]
39. Gu, Z.; Bi, Y.; Yuan, F.; Wang, R.; Li, D.; Wang, J.; Hu, X.; He, G.; Zhang, L.; Liu, B.C. FTO Polymorphisms are Associated with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) Susceptibility in the Older Chinese Han Population. *Clin. Interv. Aging* **2020**, *15*, 1333–1341. [CrossRef]
40. Zhu, X.; Xia, M.; Gao, X. Update on genetics and epigenetics in metabolic associated fatty liver disease. *Ther. Adv. Endocrinol. Metab.* **2022**, *13*, 20420188221132138. [CrossRef]
41. Stojiljković, N.; Ilić, S.; Stojanović, N.; Janković-Veličković, L.; Stojnev, S.; Kocić, G.; Radenković, G.; Arsić, I.; Stojanović, M.; Petković, M. Nanoliposome-encapsulated ellagic acid prevents cyclophosphamide-induced rat liver damage. *Mol. Cell Biochem.* **2019**, *458*, 185–195. [CrossRef]
42. AbouSamra, M.M. Liposomal nano-carriers mediated targeting of liver disorders: Mechanisms and applications. *J. Liposome Res.* **2024**, *34*, 728–743. [CrossRef]
43. Böttger, R.; Pauli, G.; Chao, P.H.; Al Fayez, N.; Hohenwarter, L.; Li, S.D. Lipid-based nanoparticle technologies for liver targeting. *Adv. Drug Deliv. Rev.* **2020**, *154–155*, 79–101. [CrossRef]
44. Bai, Y.; Nan, Y.; Wu, T.; Zhu, A.; Xie, X.; Sun, Y.; Deng, Y.; Dou, Z.; Hu, X.; Zhou, R.; et al. Lipid Nanoparticle-Mediated Delivery of CRISPR-Cas9 Against Rubicon Ameliorates NAFLD by Modulating CD36 Along with Glycerophospholipid Metabolism. *Adv. Sci.* **2024**, *11*, e2400493. [CrossRef]
45. Yan, B.; Zheng, X.; Wang, Y.; Yang, J.; Zhu, X.; Qiu, M.; Xia, K.; Wang, Y.; Li, M.; Li, S.; et al. Liposome-Based Silibinin for Mitigating Nonalcoholic Fatty Liver Disease: Dual Effects via Parenteral and Intestinal Routes. *ACS Pharmacol. Transl. Sci.* **2023**, *6*, 1909–1923. [CrossRef]
46. Zaafar, D.; Khalil, H.M.A.; Elkhouly, G.E.; Sedeky, A.S.; Ahmed, Y.H.; Khalil, M.G.; Abo-Zeid, Y. Preparation and characterization of Sorafenib nano-emulsion: Impact on pharmacokinetics and toxicity; an in vitro and in vivo study. *Drug Deliv. Transl. Res.* **2024**, *14*, 3089–3111. [CrossRef]
47. Qushawy, M.; Mortagi, Y.; Alshaman, R.; Mokhtar, H.I.; Hisham, F.A.; Alattar, A.; Liang, D.; Enan, E.T.; Eltrawy, A.H.; Alamrani, Z.H.; et al. Formulation and Characterization of O/W Nanoemulsions of Hemp Seed Oil for Protection from Steatohepatitis: Analysis of Hepatic Free Fatty Acids and Oxidation Markers. *Pharmaceuticals* **2022**, *15*, 864. [CrossRef]
48. Agame-Lagunes, B.; Grube-Pagola, P.; García-Varela, R.; Alexander-Aguilera, A.; García, H.S. Effect of Curcumin Nanoemulsions Stabilized with MAG and DAG-MCFAs in a Fructose-Induced Hepatic Steatosis Rat Model. *Pharmaceutics* **2021**, *13*, 509. [CrossRef]
49. Preeti; Sambhakar, S.; Malik, R.; Bhatia, S.; Al Harrasi, A.; Rani, C.; Saharan, R.; Kumar, S.; Geeta; Sehrawat, R. Nanoemulsion: An Emerging Novel Technology for Improving the Bioavailability of Drugs. *Scientifica* **2023**, *2023*, 6640103. [CrossRef]

50. Joudeh, N.; Linke, D. Nanoparticle classification, physicochemical properties, characterization, and applications: A comprehensive review for biologists. *J. Nanobiotechnol.* **2022**, *20*, 262. [CrossRef]
51. Elfaky, M.A.; Sirwi, A.; Ismail, S.H.; Awad, H.H.; Gad, S.S. Hepatoprotective Effect of Silver Nanoparticles at Two Different Particle Sizes: Comparative Study with and without Silymarin. *Curr. Issues Mol. Biol.* **2022**, *44*, 2923–2938. [CrossRef]
52. Cai, J.; Peng, J.; Feng, J.; Li, R.; Ren, P.; Zang, X.; Wu, Z.; Lu, Y.; Luo, L.; Hu, Z.; et al. Antioxidant hepatic lipid metabolism can be promoted by orally administered inorganic nanoparticles. *Nat. Commun.* **2023**, *14*, 3643. [CrossRef]
53. Man, S.; Liu, W.; Bi, J.; Bai, J.; Wu, Q.; Hu, B.; Hu, J.; Ma, L. Smart Mesoporous Silica Nanoparticles Loading Curcumin Inhibit Liver Cancer. *J. Agric. Food Chem.* **2024**, *72*, 25743–25754. [CrossRef]
54. Abulikemu, A.; Zhao, X.; Xu, H.; Li, Y.; Ma, R.; Yao, Q.; Wang, J.; Sun, Z.; Li, Y.; Guo, C. Silica nanoparticles aggravated the metabolic associated fatty liver disease through disturbed amino acid and lipid metabolisms-mediated oxidative stress. *Redox Biol.* **2023**, *59*, 102569. [CrossRef]
55. He, Y.; Wang, Y.; Wang, L.; Jiang, W.; Wilhelm, S. Understanding nanoparticle-liver interactions in nanomedicine. *Expert. Opin. Drug Deliv.* **2024**, *21*, 829–843. [CrossRef]
56. Joglekar, M.; Trewyn, B.G. Polymer-based stimuli-responsive nanosystems for biomedical applications. *Biotechnol. J.* **2013**, *8*, 931–945. [CrossRef]
57. Ferreira Soares, D.C.; Domingues, S.C.; Viana, D.B.; Tebaldi, M.L. Polymer-hybrid nanoparticles: Current advances in biomedical applications. *Biomed. Pharmacother.* **2020**, *131*, 110695. [CrossRef]
58. Mandal, B.; Bhattacharjee, H.; Mittal, N.; Sah, H.; Balabathula, P.; Thoma, L.A.; Wood, G.C. Core-shell-type lipid-polymer hybrid nanoparticles as a drug delivery platform. *Nanomedicine* **2013**, *9*, 474–491. [CrossRef]
59. 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*, 134779. [CrossRef]
60. Zhao, R.; Zhu, M.; Zhou, S.; Feng, W.; Chen, H. Rapamycin-Loaded mPEG-PLGA Nanoparticles Ameliorate Hepatic Steatosis and Liver Injury in Non-alcoholic Fatty Liver Disease. *Front. Chem.* **2020**, *8*, 407. [CrossRef]
61. Bagherian, A.; Roudi, B.; Masoudian, N.; Mirzaei, H. Anti-glioblastoma effects of nanomicelle-curcumin plus erlotinib. *Food Funct.* **2021**, *12*, 10926–10937. [CrossRef]
62. Hatamipour, M.; Sahebkar, A.; Alavizadeh, S.H.; Dorri, M.; Jaafari, M.R. Novel nanomicelle formulation to enhance bioavailability and stability of curcuminoids. *Iran. J. Basic. Med. Sci.* **2019**, *22*, 282–289. [CrossRef]
63. Wang, A.L.; Mishkit, O.; Mao, H.; Arivazhagan, L.; Dong, T.; Lee, F.; Bhattacharya, A.; Renfrew, P.D.; Schmidt, A.M.; Wadghiri, Y.Z.; et al. Collagen-targeted protein nanomicelles for the imaging of non-alcoholic steatohepatitis. *Acta Biomater.* **2024**, *187*, 291–303. [CrossRef]
64. Chen, G.; Mao, D.; Wang, X.; Chen, J.; Gu, C.; Huang, S.; Yang, Y.; Zhang, F.; Tan, W. Aptamer-based self-assembled nanomicelle enables efficient and targeted drug delivery. *J. Nanobiotechnol.* **2023**, *21*, 415. [CrossRef]
65. Ahmed, S.; Alhareth, K.; Mignet, N. Advancement in nanogel formulations provides controlled drug release. *Int. J. Pharm.* **2020**, *584*, 119435. [CrossRef]
66. Shah, S.; Rangaraj, N.; Laxmikeshav, K.; Sampathi, S. Nanogels as drug carriers—Introduction, chemical aspects, release mechanisms and potential applications. *Int. J. Pharm.* **2020**, *581*, 119268. [CrossRef]
67. Kamenova, K.; Radeva, L.; Yoncheva, K.; Ublekov, F.; Ravutsov, M.A.; Marinova, M.K.; Simeonov, S.P.; Forys, A.; Trzebicka, B.; Petrov, P.D. Functional Nanogel from Natural Substances for Delivery of Doxorubicin. *Polymers* **2022**, *14*, 3694. [CrossRef]
68. Mauri, E.; Gori, M.; Giannitelli, S.M.; Zancla, A.; Mozetic, P.; Abbruzzese, F.; Merendino, N.; Gigli, G.; Rossi, F.; Trombetta, M.; 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. [CrossRef]
69. Ding, L.; Luo, X.; Wen, W. Fucoxanthin-Loaded Solid Lipid Nanoparticles Exert Potent Therapeutic Efficacy in Combating High-Fat Diet Induced Obesity in Mice. *Int. J. Mol. Sci.* **2025**, *26*, 5249. [CrossRef]
70. Moin, A.; Ram, S.; Boregowda, S.S.; Hussain, T.; Abu Lila, A.S.; Jayaramu, R.A.; Rizvi, S.M.D.; Anwar, S.; Chandan, K. Piperine-loaded solid lipid nanoparticles: A promising nano-phytomedicine for the treatment of non-alcoholic fatty liver disease. *Front. Pharmacol.* **2025**, *16*, 1646530. [CrossRef]
71. Zheng, T.; Gan, X.; Luo, J.; Shi, Z.; Zhao, Y.; Wang, Y.; Chen, J.; Yu, C. Hyaluronic acid act as drug self-assembly chaperone and co-assembled with celalstrol for ameliorating non-alcoholic steatohepatitis. *Int. J. Biol. Macromol.* **2024**, *282*, 137289. [CrossRef]
72. Lu, H.; Ban, Z.; Xiao, K.; Sun, M.; Liu, Y.; Chen, F.; Shi, T.; Chen, L.; Shao, D.; Zhang, M.; et al. Hepatic-Accumulated Obeticholic Acid and Atorvastatin Self-Assembled Nanocrystals Potentiate Ameliorative Effects in Treatment of Metabolic-Associated Fatty Liver Disease. *Adv. Sci.* **2024**, *11*, e2308866. [CrossRef]
73. Subudhi, P.D.; Bihari, C.; Sarin, S.K.; Baweja, S. Emerging Role of Edible Exosomes-Like Nanoparticles (ELNs) as Hepatoprotective Agents. *Nanotheranostics* **2022**, *6*, 365–375. [CrossRef]
74. Chen, X.; Liu, B.; Li, X.; An, T.T.; Zhou, Y.; Li, G.; Wu-Smart, J.; Alvarez, S.; Naldrett, M.J.; Eudy, J.; et al. Identification of anti-inflammatory vesicle-like nanoparticles in honey. *J. Extracell. Vesicles* **2021**, *10*, e12069. [CrossRef]

75. Chen, X.; Zhou, Y.; Yu, J. Exosome-like Nanoparticles from Ginger Rhizomes Inhibited NLRP3 Inflammasome Activation. *Mol. Pharm.* **2019**, *16*, 2690–2699. [CrossRef]
76. Ahmed, E.S.; Mohamed, H.E.; Farrag, M.A. 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. [CrossRef]
77. Dai, Z.; Yin, W.; Li, J.; Ma, L.; Chen, F.; Shen, Q.; Hu, X.; Xue, Y.; Ji, J. Zein and Trimethyl Chitosan-Based Core-Shell Nanoparticles for Quercetin Oral Delivery to Enhance Absorption by Paracellular Pathway in Obesity Mice. *Biomater. Res.* **2025**, *29*, 0193. [CrossRef]
78. Wang, T.; Liu, B.; Huang, J.; Zhao, Q.; Shen, H.; Bi, T.; Liu, Z.; Dai, Y.; Sun, Q. IFN-γ-mediated inhibition of JAK/STAT signaling via nano-scutellarin treatment is an efficient strategy for ameliorating liver fibrosis. *J. Transl. Med.* **2025**, *23*, 195. [CrossRef]
79. Fan, S.; Ma, N.; Li, J.; Wang, B.; Zhao, Y.; Yao, Y.; Chai, X.; Zhou, Z. Oral Icariin Nanoparticles Ameliorate Nonalcoholic Fatty Liver Disease by Alleviating Oxidative Stress. *ACS Appl. Mater. Interfaces* **2025**, *17*, 67581–67594. [CrossRef]
80. Farooq, A.; Iqbal, A.; Rana, N.F.; Fatima, M.; Maryam, T.; Batool, F.; Rehman, Z.; Menaa, F.; Azhar, S.; Nawaz, A.; et al. A Novel Sprague-Dawley Rat Model Presents Improved NASH/NAFLD Symptoms with PEG Coated Vitexin Liposomes. *Int. J. Mol. Sci.* **2022**, *23*, 3131. [CrossRef]
81. Huang, X.; Hu, X.; Li, S.; Li, T. Vitexin-rhamnoside encapsulated with zein-pectin nanoparticles relieved high-fat diet induced lipid metabolism disorders in mice by altering the gut microbiota. *Int. J. Biol. Macromol.* **2024**, *264*, 130704. [CrossRef]
82. Mohaghegh, N.; Iyer, A.; Wang, E.; Balajam, N.Z.; Kang, H.; Akbari, M.; Barnhill, M.S.; Khademhosseini, A.; Pearson, R.M.; Hassani Najafabadi, A. Apigenin-loaded nanoparticles for obesity intervention through immunomodulation and adipocyte browning. *J. Control Release* **2025**, *382*, 113670. [CrossRef]
83. Liu, H.; Jiang, N.; Kuang, G.; Gong, X.; Hu, J.; Liu, J.; Yin, X.; Wu, S.; Wan, J. Chrysin and its nanoliposome ameliorated non-alcoholic steatohepatitis via inhibiting TLR4 signalling pathway. *J. Pharm. Pharmacol.* **2023**, *75*, 1046–1057. [CrossRef]
84. Asfour, M.H.; Salama, A.A.A. Coating with tripolyphosphate-crosslinked chitosan as a novel approach for enhanced stability of emulsomes following oral administration: Rutin as a model drug with improved anti-hyperlipidemic effect in rats. *Int. J. Pharm.* **2023**, *644*, 123314. [CrossRef]
85. Dong, L.; Lou, W.; Xu, C.; Wang, J. Naringenin cationic lipid-modified nanoparticles mitigate MASLD progression by modulating lipid homeostasis and gut microbiota. *J. Nanobiotechnol.* **2025**, *23*, 168. [CrossRef]
86. Hu, R.; Liu, S.; Shen, W.; Chen, C.; Cao, Y.; Su, Z.; Sun, M.; Qi, R. Study on the Inhibitory Effects of Naringenin-Loaded Nanostructured Lipid Carriers Against Nonalcoholic Fatty Liver Disease. *J. Biomed. Nanotechnol.* **2021**, *17*, 942–951. [CrossRef]
87. Salah, A.; Mohammed El-Laban, N.; Mafiz Alam, S.; Shahidul Islam, M.; Abdalla Hussein, M.; Roshdy, T. Optimization of Naringenin-loaded nanoparticles for targeting of Vanin-1, iNOS, and MCP-1 signaling pathway in HFD-induced obesity. *Int. J. Pharm.* **2024**, *654*, 123967. [CrossRef]
88. Abdelmoneim, D.; Eldomany, E.B.; El-Adl, M.; Farghali, A.; El-Sayed, G.; El-Sherbini, E.S. Possible protective effect of natural flavanone naringenin-reduced graphene oxide nanosheets on nonalcoholic fatty liver disease. *Naunyn Schmiedebergs Arch. Pharmacol.* **2025**, *398*, 4071–4086. [CrossRef]
89. Hu, R.; Liu, S.; Anwaier, G.; Wang, Q.; Shen, W.; Shen, Q.; Qi, R. Formulation and intestinal absorption of naringenin loaded nanostructured lipid carrier and its inhibitory effects on nonalcoholic fatty liver disease. *Nanomedicine* **2021**, *32*, 102310. [CrossRef]
90. Zhang, H.; Liu, R.; Wang, J.; Cui, S.W.; Wang, S.; Wang, B.; Zhang, N.; Yang, X.; Li, J.; Wang, H. Fabrication, characterization, and lipid-lowering effects of naringenin-zein-sodium caseinate-galactosylated chitosan nanoparticles. *Int. J. Biol. Macromol.* **2023**, *230*, 123150. [CrossRef]
91. Liu, J.; Yuan, Y.; Gong, X.; Zhang, L.; Zhou, Q.; Wu, S.; Zhang, X.; Hu, J.; Kuang, G.; Yin, 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. [CrossRef]
92. Alamir, M.; Hussein, M.A.; Aboud, H.M.; Khedr, M.H.; Zanaty, M.I. Optimization of Phloretin-loaded Nanospanlastics for Targeting of FAS/SREBP1c/AMPK/OB-Rb Signaling Pathway in HFD-induced Obesity. *Curr. Pharm. Biotechnol.* **2024**, *26*, 92–107. [CrossRef]
93. Cheng, Z.; Wei, W.; Chen, Y.; Xu, A.; Wang, Y.; Li, B. Construction of nanoparticles from blueberry anthocyanins-lecithin/gum Arabic improves lipid droplet accumulation and gut microbiota disturbance in HFD-induced obese mice. *Int. J. Biol. Macromol.* **2024**, *264*, 130595. [CrossRef]
94. Zhang, H.; Qi, X.; Yang, L.; Xia, P.; Ling, J.; Zheng, X.; Liang, J.; Yang, P.; Chen, Y.; Liu, X.; et al. Advances in anthocyanin nanoparticle delivery systems in anti-inflammatory therapies. *Pharmacol. Res.* **2025**, *222*, 108038. [CrossRef]
95. Chen, Z.; Liu, B.; Gong, Z.; Huang, H.; Gong, Y.; Xiao, W. Metagenomics Approach to the Intestinal Microbiome Structure and Abundance in High-Fat-Diet-Induced Hyperlipidemic Rat Fed with (-)-Epigallocatechin-3-Gallate Nanoparticles. *Molecules* **2022**, *27*, 4894. [CrossRef]

96. Jazayeri-Tehrani, S.A.; Rezayat, S.M.; Mansouri, S.; Qorbani, M.; Alavian, S.M.; Daneshi-Maskooni, M.; Hosseinzadeh-Attar, M.J. Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): A double-blind randomized placebo-controlled clinical trial. *Nutr. Metab.* **2019**, *16*, 8. [CrossRef]
97. Gerami, H.; Mozaffari-Khosravi, H.; Mansour, A.; Sohrabpour, A.A.; Poustchi, H.; Hashemi Taheri, A.P.; Jaafari, M.R.; Jambarsang, S.; Khayyatzadeh, S.S. Effect of nano-curcumin supplementation on liver fibrosis in patients with NAFLD-associated fibrosis: A double-blind randomized controlled trial. *Sci. Rep.* **2025**, *15*, 38043. [CrossRef]
98. Elbaset, M.A.; Nasr, M.; Ibrahim, B.M.M.; Ahmed-Farid, O.A.H.; Bakeer, R.M.; Hassan, N.S.; Ahmed, R.F. Curcumin nanoemulsion counteracts hepatic and cardiac complications associated with high-fat/high-fructose diet in rats. *J. Food Biochem.* **2022**, *46*, e14442. [CrossRef]
99. Lee, E.J.; Hwang, J.S.; Kang, E.S.; Lee, S.B.; Hur, J.; Lee, W.J.; Choi, M.J.; Kim, J.T.; Seo, H.G. Nanoemulsions improve the efficacy of turmeric in palmitate- and high fat diet-induced cellular and animal models. *Biomed. Pharmacother.* **2019**, *110*, 181–189. [CrossRef]
100. Ariamoghaddam, A.R.; Ebrahimi-Hosseinzadeh, B.; Hatamian-Zarmi, A.; Sahraeian, R. In vivo anti-obesity efficacy of curcumin loaded nanofibers transdermal patches in high-fat diet induced obese rats. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2018**, *92*, 161–171. [CrossRef]
101. Li, X.; Chen, X.X.; Xu, Y.; Xu, X.B.; Wu, W.F.; Zhao, Q.; Hu, J.N. Construction of Glycogen-Based Nanoparticles Loaded with Resveratrol for the Alleviation of High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease. *Biomacromolecules* **2022**, *23*, 409–423. [CrossRef]
102. Teng, W.; Zhao, L.; Yang, S.; Zhang, C.; Liu, M.; Luo, J.; Jin, J.; Zhang, M.; Bao, C.; Li, D.; 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. [CrossRef]
103. Beheshtkhoo, N.; Jadidi Kouhbanani, M.A.; Daghighi, S.M.; Shakouri Nikjeh, M.; Esmaeili, Z.; Khosravani, M.; Adabi, M. Effect of oral resveratrol-loaded nanoliposomes on hyperlipidemia via toll-like receptor 3 and TIR domain-containing adaptor inducing interferon-β protein expression in an animal model. *J. Liposome Res.* **2025**, *35*, 225–251. [CrossRef]
104. Li, Y.; Gao, S.; Shi, S.; Xiao, D.; Peng, S.; Gao, Y.; Zhu, Y.; Lin, Y. Tetrahedral Framework Nucleic Acid-Based Delivery of Resveratrol Alleviates Insulin Resistance: From Innate to Adaptive Immunity. *Nanomicro Lett.* **2021**, *13*, 86. [CrossRef]
105. 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*, e202200468. [CrossRef]
106. Sun, C.; Li, W.; Zhang, H.; Adu-Frimpong, M.; Ma, P.; Zhu, Y.; Deng, W.; Yu, J.; Xu, X. Improved Oral Bioavailability and Hypolipidemic Effect of Syringic Acid via a Self-microemulsifying Drug Delivery System. *AAPS PharmSciTech* **2021**, *22*, 45. [CrossRef]
107. Rasheed, A.; Kamran, S.H.; Hameed, M.; Siddique, F.; Latif, S.; Bibi, M.; Rizwan, R. Syringic acid loaded chitosan nanoparticles mitigate glycation associated oxidative stress and inflammation in hyperglycaemic rat model. *Sci. Rep.* **2025**, *15*, 22778. [CrossRef]
108. Heikal, L.A.; El-Kamel, A.H.; Mehanna, R.A.; Khalifa, H.M.; Hassaan, P.S. Improved oral nutraceutical-based intervention for the management of obesity: Pterostilbene-loaded chitosan nanoparticles. *Nanomedicine* **2022**, *17*, 1055–1075. [CrossRef]
109. Che, T.; Song, Y.; Su, W.; Xing, S.; Wang, H.; Tan, M. Hepatic parenchymal cell and mitochondrial-targeted astaxanthin nanocarriers for relief of high fat diet-induced nonalcoholic fatty liver disease. *Food Funct.* **2023**, *14*, 2908–2920. [CrossRef]
110. Zhang, X.; Liu, R.; Chen, Y.; Wang, H.; Su, W.; Song, Y.; Tan, M. Dual-Targeted Nanoparticles Hitchhiking on Lactobacillus rhamnosus Bacterial Ghosts to Alleviate Nonalcoholic Steatohepatitis. *ACS Nano* **2025**, *19*, 14010–14027. [CrossRef]
111. Salem, G.A.; Mohamed, A.A.; Khater, S.I.; Noreldin, A.E.; Alosaimi, M.; Alansari, W.S.; Shamlan, G.; Eskandrani, A.A.; Awad, M.M.; El-Shaer, R.A.A.; et al. Enhancement of biochemical and genomic pathways through lycopene-loaded nano-liposomes: Alleviating insulin resistance, hepatic steatosis, and autophagy in obese rats with non-alcoholic fatty liver disease: Involvement of SMO, GLI-1, and PTCH-1 genes. *Gene* **2023**, *883*, 147670. [CrossRef]
112. Oliyaei, N.; Tanideh, N.; Moosavi-Nasab, M.; Dehghanian, A.R.; Iraji, A. Development and characterization of a fucoidan-based nanoemulsion using Nigella sativa oil for improvement of anti-obesity activity of fucoxanthin in an obese rat model. *Int. J. Biol. Macromol.* **2023**, *235*, 123867. [CrossRef]
113. Zhao, J.; Luo, D.; Zhang, Z.; Fan, N.; Wang, Y.; Nie, H.; Rong, J. Celastrol-loaded PEG-PCL nanomicelles ameliorate inflammation, lipid accumulation, insulin resistance and gastrointestinal injury in diet-induced obese mice. *J. Control Release* **2019**, *310*, 188–197. [CrossRef]
114. Fan, N.; Zhao, J.; Zhao, W.; Zhang, X.; Song, Q.; Shen, Y.; Shum, H.C.; Wang, Y.; Rong, J. Celastrol-loaded lactosylated albumin nanoparticles attenuate hepatic steatosis in non-alcoholic fatty liver disease. *J. Control Release* **2022**, *347*, 44–54. [CrossRef]
115. Fan, N.; Zhao, J.; Zhao, W.; Shen, Y.; Song, Q.; Shum, H.C.; Wang, Y.; Rong, J. Biodegradable celastrol-loaded albumin nanoparticles ameliorate inflammation and lipid accumulation in diet-induced obese mice. *Biomater. Sci.* **2022**, *10*, 984–996. [CrossRef]
116. Dong, L.; Lou, W.; Wang, J. β-Carotene-loaded cationic nanoparticles ameliorate MASLD via modulating lipid homeostasis and gut microbiome. *Food Res. Int.* **2025**, *205*, 115816. [CrossRef]
117. 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*, 123–130. [CrossRef]

118. Guo, H.H.; Feng, C.L.; Zhang, W.X.; Luo, Z.G.; Zhang, H.J.; Zhang, T.T.; Ma, C.; Zhan, Y.; Li, R.; Wu, S.; et al. Liver-target nanotechnology facilitates berberine to ameliorate cardio-metabolic diseases. *Nat. Commun.* **2019**, *10*, 1981. [CrossRef]
119. Ma, X.; Zhang, T.; Luo, Z.; Li, X.; Lin, M.; Li, R.; Du, P.; Yu, X.; Ma, C.; Yan, P.; et al. Functional nano-vector boost anti-atherosclerosis efficacy of berberine in Apoe ((-/-)) mice. *Acta Pharm. Sin. B* **2020**, *10*, 1769–1783. [CrossRef]
120. Bakshi, J.; Lather, P.; Verma, A.; Lather, D.; Grewal, S.; Dhingra, D.; Kumari, S. Potentiation and in vivo evaluation of anti-obesity activity of berberine through encapsulation in guar-acacia gum nanocomplexes. *Naunyn Schmiedebergs Arch. Pharmacol.* **2025**, *398*, 7041–7055. [CrossRef]
121. Lu, J.; Zeng, Y.; Zhong, H.; Guo, W.; Zhang, Y.; Mai, W.; Qin, Y.; Su, X.; Zhang, B.; Wu, W.; 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. [CrossRef]
122. Liang, J.; Liu, Y.; Liu, J.; Li, Z.; Fan, Q.; Jiang, Z.; Yan, F.; Wang, Z.; Huang, P.; Feng, N. Chitosan-functionalized lipid-polymer hybrid nanoparticles for oral delivery of silymarin and enhanced lipid-lowering effect in NAFLD. *J. Nanobiotechnol.* **2018**, *16*, 64. [CrossRef]
123. Xiao, Z.; Zhou, J.; Chen, H.; Chen, X.; Wang, L.; Liu, D.; Kang, X. Synthesis, characterization and MAFLD prevention potential of Ganoderma lucidum spore polysaccharide-stabilized selenium nanoparticles. *Int. J. Biol. Macromol.* **2024**, *282*, 136962. [CrossRef]
124. Elhady, S.S.; Wahba, A.S.; Ibrahim, A.K.; El-Sayyad, G.S.; El-Batal, A.I.; Wahba, N.S.; Nafie, M.S.; Ahmed, S.A.; Ibrahim, A.K.; Badr, J.M.; 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*, 36178–36202. [CrossRef]
125. Zamora-López, K.; Noriega, L.G.; Estanes-Hernández, A.; Escalona-Nández, I.; Tobón-Cornejo, S.; Tovar, A.R.; Barbero-Becerra, V.; Pérez-Monter, C. Punica granatum L.-derived omega-5 nanoemulsion improves hepatic steatosis in mice fed a high fat diet by increasing fatty acid utilization in hepatocytes. *Sci. Rep.* **2020**, *10*, 15229. [CrossRef]
126. Al-Okbi, S.Y.; Amin, M.A.; Mohamed, A.E.A.; Edris, A.E.; Sharaf, O.M.; Mabrok, H.B.; Ramadan, A.A. Basil Essential Oil and Its Nanoemulsion Mitigate Non Alcoholic Steatohepatitis in Rat Model with Special Reference to Gut Microbiota. *J. Oleo Sci.* **2020**, *69*, 913–927. [CrossRef]
127. Karimzadeh, K.; Unniappan, S.; Zahmatkesh, A. Spirulina platensis Peptide-Loaded Nanoliposomes Alleviate Hepatic Lipid Accumulation in Male Wistar Rats by Influencing Redox Homeostasis and Lipid Metabolism via the AMPK Signaling Pathway. *Appl. Biochem. Biotechnol.* **2025**, *197*, 1696–1725. [CrossRef]
128. Xu, K.; Wu, Q.; Lingyun, Z.; Nguyen, R.; Safri, F.; Yang, W.; Xu, Y.; Ye, Y.; Kwan, H.Y.; Wang, Q.; et al. Extracellular vesicles as a promising platform of precision medicine in liver cancer. *Pharmacol. Res.* **2025**, *217*, 107800. [CrossRef]
129. Liu, B.; Nguyen, P.L.; Yu, H.; Li, X.; Wang, H.; Nguyen, T.G.B.; Sahoo, P.K.; Sur, M.; Reddy, J.; Sillman, S.; et al. Honey vesicle-like nanoparticles protect aged liver from non-alcoholic steatohepatitis. *Acta Pharm. Sin. B* **2024**, *14*, 3661–3679. [CrossRef]
130. Zhao, W.J.; Bian, Y.P.; Wang, Q.H.; Yin, F.; Yin, L.; Zhang, Y.L.; Liu, J.H. Blueberry-derived exosomes-like nanoparticles ameliorate nonalcoholic fatty liver disease by attenuating mitochondrial oxidative stress. *Acta Pharmacol. Sin.* **2022**, *43*, 645–658. [CrossRef]
131. Wang, T.; Zhao, J.; Li, Q.Y.; Yang, H.Q.; Li, M.; Duan, R.; Zhang, M.; Qi, Y.; Yu, J.; Yang, X.X. Poria cocos-Derived Exosome-like Nanovesicles Alleviate Metabolic Dysfunction-Associated Fatty Liver Disease by Promoting Mitophagy and Inhibiting NLRP3 Inflammasome Activation. *Int. J. Mol. Sci.* **2025**, *26*, 2253. [CrossRef]
132. Liu, J.; Li, W.; Bian, Y.; Jiang, X.; Zhu, F.; Yin, F.; Yin, L.; Song, X.; Guo, H.; Liu, J. Garlic-derived exosomes regulate PFKFB3 expression to relieve liver dysfunction in high-fat diet-fed mice via macrophage-hepatocyte crosstalk. *Phytomedicine* **2023**, *112*, 154679. [CrossRef]
133. Zou, J.; Song, Q.; Shaw, P.C.; 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. [CrossRef]
134. Kim, J.S.; Song, B.J.; Cho, Y.E. Pomegranate-Derived Exosome-Like Nanovesicles Containing Ellagic Acid Alleviate Gut Leakage and Liver Injury in MASLD. *Food Sci. Nutr.* **2025**, *13*, e70088. [CrossRef]
135. Kim, J.S.; Eom, J.Y.; Kim, H.W.; Ko, J.W.; Hong, E.J.; Kim, M.N.; Kim, J.; Kim, D.K.; Kwon, H.J.; Cho, Y.E. Hemp sprout-derived exosome-like nanovesicles as hepatoprotective agents attenuate liver fibrosis. *Biomater. Sci.* **2024**, *12*, 5361–5371. [CrossRef]
136. Mun, D.; Ryu, S.; Lee, D.J.; Kwak, M.J.; Choi, H.; Kang, A.N.; Lim, D.H.; Oh, S.; Kim, Y. Bovine colostrum-derived extracellular vesicles protect against non-alcoholic steatohepatitis by modulating gut microbiota and enhancing gut barrier function. *Curr. Res. Food Sci.* **2025**, *10*, 101039. [CrossRef]
137. Tong, L.; Zhang, S.; Liu, Q.; Huang, C.; Hao, H.; Tan, M.S.; Yu, X.; Lou, C.K.L.; Huang, R.; Zhang, Z.; et al. Milk-derived extracellular vesicles protect intestinal barrier integrity in the gut-liver axis. *Sci. Adv.* **2023**, *9*, eade5041. [CrossRef]
138. Guo, M.; Song, C.; Tang, J.; Li, Y.; Zeng, Z.; Hu, X.; Huang, X.; Wei, S.; Chen, C.; Tang, Y.; 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*, 36504–36513. [CrossRef]

139. Li, Y.; Yao, H.; Guo, M.; Zeng, Z.; Hu, X.; Wang, Y.; Zhang, Y.; Chen, C.; Huang, R.; Song, C.; et al. Effects of Alcohol Extraction of Turmeric Decoction-Derived Exosome-Like Nanoparticles on Amelioration of Metabolic Dysfunction-Associated Steatotic Liver Disease. *J. Nutr.* **2026**, *156*, 101243. [CrossRef]
140. d'Adduzio, L.; Fanzaga, M.; Marangon, D.; Carrillo-Vico, A.; Cruz-Chamorro, I.; Bollati, C.; Lecca, D.; Lammi, C. Multifunctional Biological Activity Assessment of Plant-Derived Nanovesicles from Arugula Leaves: In Vitro and In Vivo Studies. *Antioxidants* **2025**, *14*, 1421. [CrossRef]
141. Sitthirach, C.; Charoensuk, L.; Pairojkul, C.; Chaidee, A.; Intuyod, K.; Pongking, T.; Thongpon, P.; Jantawong, C.; Hongsrichan, N.; Waraasawapati, S.; et al. Curcumin-loaded nanocomplexes ameliorate the severity of nonalcoholic steatohepatitis in hamsters infected with Opisthorchis viverrini. *PLoS ONE* **2022**, *17*, e0275273. [CrossRef]
142. Beheshti Namdar, A.; Ahadi, M.; Hoseini, S.M.; Vosoghinia, H.; Rajablou, H.; Farsi, S.; Zangouei, A.; Rahimi, H.R. Effect of nano-micelle curcumin on hepatic enzymes: A new treatment approach for non-alcoholic fatty liver disease (NAFLD). *Avicenna J. Phytomed.* **2023**, *13*, 615–625. [CrossRef]
143. Jin, Z.; Sun, Y.; Yang, T.; Tan, L.; Lv, P.; Xu, Q.; Tao, G.; Qin, S.; Lu, X.; He, Q. Nanocapsule-mediated sustained H(2) release in the gut ameliorates metabolic dysfunction-associated fatty liver disease. *Biomaterials* **2021**, *276*, 121030. [CrossRef]
144. Rinella, M.E.; Green, R.M. The methionine-choline deficient dietary model of steatohepatitis does not exhibit insulin resistance. *J. Hepatol.* **2004**, *40*, 47–51. [CrossRef]
145. Shively, C.A.; Appt, S.E.; Vitolins, M.Z.; Uberseder, B.; Michalson, K.T.; Silverstein-Metzler, M.G.; Register, T.C. Mediterranean versus Western Diet Effects on Caloric Intake, Obesity, Metabolism, and Hepatosteatosis in Nonhuman Primates. *Obesity* **2019**, *27*, 777–784. [CrossRef]
146. Ouchi, R.; Togo, S.; Kimura, M.; Shinozawa, T.; Koido, M.; Koike, H.; Thompson, W.; Karns, R.A.; Mayhew, C.N.; McGrath, P.S.; et al. Modeling Steatohepatitis in Humans with Pluripotent Stem Cell-Derived Organoids. *Cell Metab.* **2019**, *30*, 374–384.e376. [CrossRef]
147. Esim, O.; Adatepe, S.; Aksoy, O.A.; Goksel, B.A.; Yilmaz, T.; Baykal, B.; Yucel, Ç.; Kablan, S.E.; Eylem, C.C.; Kocak, E.; et al. Targeted hepatic delivery of ezetimibe via red blood cell-coated nanoparticles for the treatment of non-alcoholic fatty liver disease through inflammation modulation. *Int. J. Pharm.* **2025**, *685*, 126241. [CrossRef]
148. Wang, S.; Zhang, Y.; Zeng, Y.; Luo, X.; Chen, J.; Deng, Q.; Xiao, P.; Lin, R.; Chen, X.; Ding, X.; et al. Plant-derived vesicle-like nanoparticles for immunomodulation: Mechanisms and applications. *Bioact. Mater.* **2026**, *55*, 171–204. [CrossRef]
149. Rutter, B.D.; Innes, R.W. Extracellular Vesicles Isolated from the Leaf Apoplast Carry Stress-Response Proteins. *Plant Physiol.* **2017**, *173*, 728–741. [CrossRef]
150. Welsh, J.A.; Goberdhan, D.C.I.; O'Driscoll, L.; Buzas, E.I.; Blenkiron, C.; Bussolati, B.; Cai, H.; Di Vizio, D.; Driedonks, T.A.P.; Erdbrügger, U.; et al. Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches. *J. Extracell. Vesicles* **2024**, *13*, e12404. [CrossRef]
151. Wu, C.; Lee, S.L.; Taylor, C.; Li, J.; Chan, Y.M.; Agarwal, R.; Temple, R.; Throckmorton, D.; Tyner, K. Scientific and Regulatory Approach to Botanical Drug Development: A U.S. FDA Perspective. *J. Nat. Prod.* **2020**, *83*, 552–562. [CrossRef]
152. Zhang, X.; Lau, H.C.; Yu, J. Pharmacological treatment for metabolic dysfunction-associated steatotic liver disease and related disorders: Current and emerging therapeutic options. *Pharmacol. Rev.* **2025**, *77*, 100018. [CrossRef]
153. Kumar, S.; Duan, Q.; Wu, R.; Harris, E.N.; Su, Q. Pathophysiological communication between hepatocytes and non-parenchymal cells in liver injury from NAFLD to liver fibrosis. *Adv. Drug Deliv. Rev.* **2021**, *176*, 113869. [CrossRef]
154. Shinn, J.; Park, S.; Lee, S.; Park, N.; Kim, S.; Hwang, S.; Moon, J.J.; Kwon, Y.; Lee, Y. Antioxidative Hyaluronic Acid-Bilirubin Nanomedicine Targeting Activated Hepatic Stellate Cells for Anti-Hepatic-Fibrosis Therapy. *ACS Nano* **2024**, *18*, 4704–4716. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.