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REVIEW

Therapeutic Nanomaterials in NAFLD: Current Advances and Potential Applications in Patients with Concurrent HBV Infection

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Abstract: Due to the high prevalence of non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis B virus (HBV) infection, a significant proportion of patients suffer from both conditions simultaneously. The management of NAFLD in patients with concurrent HBV infection presents unique challenges, primarily due to the complex interplay between these two diseases. Nanomaterials have gained widespread attention due to their ability to overcome the limitations of conventional therapies. This review provides an overview of the current advances in therapeutic nanomaterials for NAFLD and explores their potential applications for personalized and effective management in patients with concurrent HBV infection. Furthermore, we discuss the challenges and future directions in the development of nanomaterials for the treatment of coexisting liver diseases.

Keywords: nonalcoholic fatty liver disease, chronic hepatitis B virus infection, nanomaterials

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, encompassing a spectrum ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). Amid the epidemic of obesity and diabetes, the global prevalence of NAFLD is estimated to be 25% and still rising.[1,2] Furthermore, while NAFLD generally progresses slowly, 20% of patients experience accelerated disease progression, particularly in the fibrotic stage.[1,2]

At present, no specific agent has been approved for NAFLD, except for lifestyle modifications (exercise and dietary restrictions). Pharmacological therapy, such as lipid-lowering drugs (fibrates and statins), antihyperglycemic drugs (metformin), incretin hormone [glucagon-like peptide-1 (GLP-1) analogs], insulin sensitizers, and antioxidants (vitamin E), should only be prescribed to patients with multiple risk factors after a thorough assessment of the potential risks and benefits.[3] In addition, several natural extracts, such as curcumin[4] and resveratrol,[5] have entered the spotlight due to the pharmacological properties. However, poor oral absorption, low water solubility, limited bioavailability, and uncertain efficacy of these drugs, significantly restrict their clinical application.[6,7]

Chronic hepatitis B virus (HBV) infection is another major etiology of chronic liver disease with 296 million existing infected individuals worldwide. Furthermore, although effective HBV vaccines are available, new infections still occur as limited access to prophylaxis objectively exists in some regions. Currently, the clinically available antiviral treatments include nucleos(t)ide analogues and pegylated-interferon α, but due to the inability of these drugs to fully eliminate the viruses, 20%-30% of the patients still experience recurrent inflammation and progression to liver cirrhosis or hepatocellular carcinoma (HCC).[8,9]

In the past, NAFLD was strictly defined as occurring only in the absence of other factors, such as viral hepatitis, autoimmune diseases, or excessive alcohol intake.[10] Recently, NAFLD has been redesignated as metabolic dysfunction-

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associated fatty liver disease (MAFLD), reflecting its metabolic origins rather than being an exclusive diagnosis.[11,12] Therefore, it can coexist with conditions like chronic hepatitis B, which synergistically contribute to disease progression.[13] Given the high prevalence of MAFLD and chronic HBV infection, it is imperative to investigate novel therapies that effectively target MAFLD and offer additional benefits for patients with concurrent chronic HBV infection.

Nanomaterials, which emerged in 1981, such as lipid-based nanoparticles, polymeric nanoparticles, inorganic nanoparticles, and nanogels, have found widespread application in medicine due to their ability to overcome the limitations of conventional drugs.[14,15] These nanomaterials improve bioavailability,[16–20] reduce side effects,[21–25] and optimize the drug distribution across tissues[7,21,23,26–30] by enhancing the stability of pharmaceuticals and enabling targeted delivery in NAFLD/MAFLD.

In this review, we will summarize potential therapeutic nanomaterials for MAFLD and chronic HBV infection, aiming to provide new insights into the treatment of patients with both conditions. For clarity, we will consistently refer to the disease as NAFLD throughout this paper, given the variation in definitions across studies.

Pathogenesis of NAFLD and Chronic HBV Infection

NAFL is the initial stage of NAFLD, characterized by the accumulation of lipid droplets in more than 5% of hepatocytes, with or without inflammation. NASH, a more aggressive form with a higher risk of progressing to end-stage liver disease, is defined by the coexistence of hepatic steatosis, lobular inflammation, and hepatocyte injury, with or without fibrosis. Recently, the "multiple-hit" hypothesis, which asserts that the synergistic interaction of multiple parallel factors leads to the development and progression of NAFLD in genetically predisposed individuals, has replaced the "two-hit" theory and gained widespread acceptance[31] (Figure 1). Lipids accumulate in the liver in the form of triglycerides, accompanied

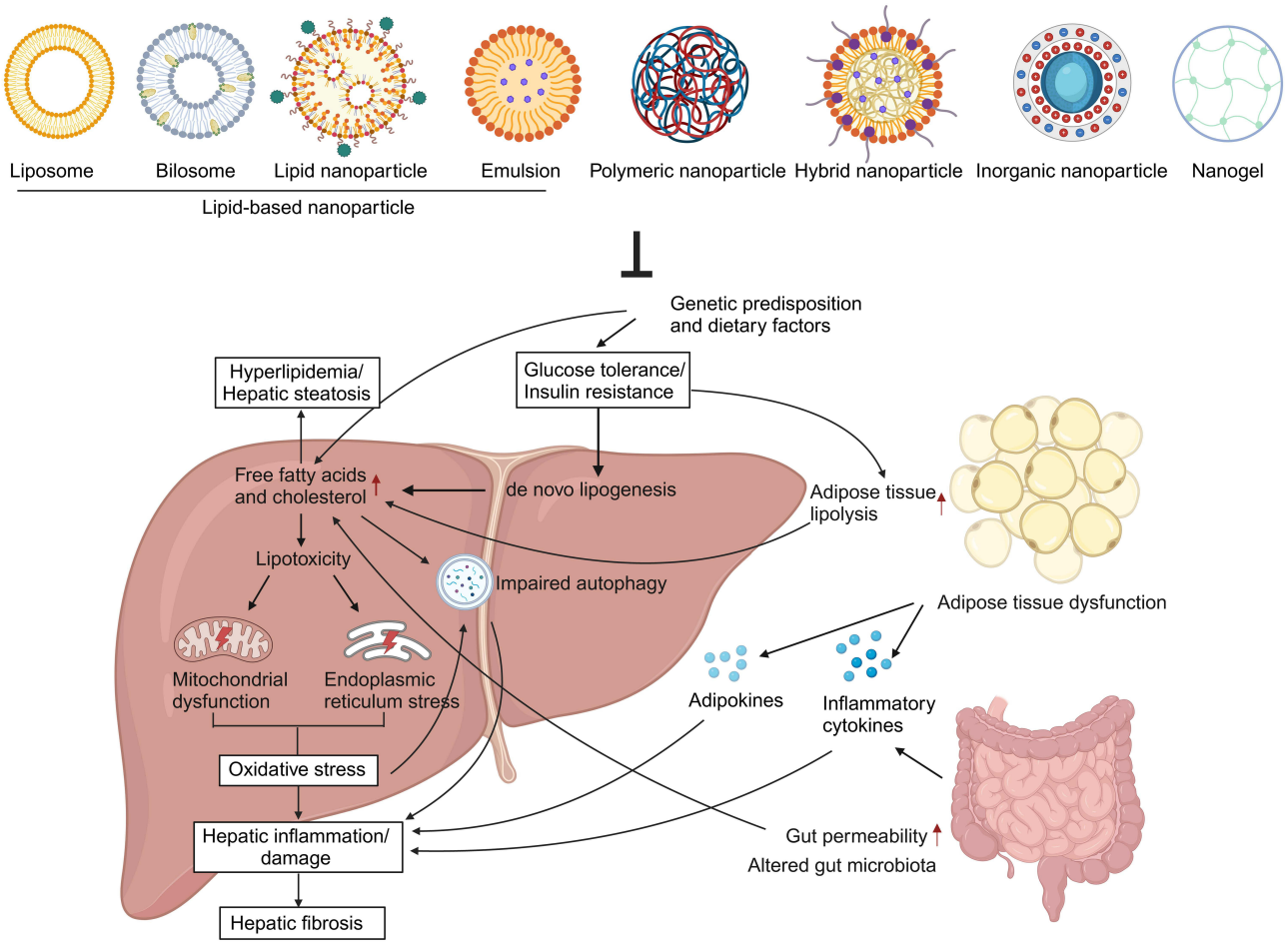

Figure 1 The pathogenesis and representative therapeutic nanomaterials of NAFLD.
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by increased lipotoxicity due to elevated levels of free fatty acids and cholesterol, leading to mitochondrial dysfunction, reactive oxygen species (ROS) production, oxidative stress, and endoplasmic reticulum (ER) stress.[31] Impaired autophagy induced by oxidative stress further exacerbates the accumulation of damaged organelles and lipids in hepatocytes.[31] Insulin resistance increases hepatic de novo lipogenesis while inducing adipose tissue lipolysis and dysfunction, resulting in an elevated influx of free fatty acids to the liver and altering the production and secretion of adipokines and inflammatory cytokines.[31] Additionally, altered gut microbiota further promotes the production of fatty acids in the intestines, increases small bowel permeability, and enhances fatty acid absorption, thereby triggering the release of proinflammatory cytokines and activating inflammatory pathways.[31] These factors collectively contribute to chronic hepatic inflammation and injury, rather than acting through a simple, stepwise accumulation of insults over time.

The pathogenesis of chronic HBV infection involves both direct viral effects and immune-mediated processes. On one hand, the expression and accumulation of viral proteins, resulting from HBV replication or integration, can lead to oxidative stress, mitochondrial dysfunction, and ER stress.[32,33] On the other hand, the host's prolonged immune response, particularly through cytotoxic T lymphocytes, initiates the recognition and clearance of HBV-infected hepatocytes.[34] These two mechanisms synergize to exacerbate liver damage and accelerate fibrosis progression. Additionally, HBV integration into the host genome, or the interference of the HBx protein in cellular signaling pathways, DNA repair, and apoptosis, contributes to hepatocarcinogenesis, even in the absence of cirrhosis.[35]

Liver-Targeted Delivery Systems

For therapeutic nanomaterials, tissue-targeted delivery systems can significantly reduce toxicity and improve bioavailability. Currently, liver-targeted delivery systems are commonly used for the treatment of NAFLD and chronic HBV infection.[36] The absence of a basement membrane and the presence of fenestrations in liver sinusoidal endothelial cells (LSECs) provide the physiological basis for the passive accumulation of nanomaterials in the liver. Besides, the mononuclear phagocyte system, including Kupffer cells, monocytes, and splenic macrophages, helps sequester the majority of nanomaterials in the liver.[37] Phagocytosis by the mononuclear phagocyte system is influenced by the route of administration and the properties of nanomaterials, such as size, shape, charge, and rigidity. Nanomaterials ranging from 50 to 250 nm in size, with non-spherical shapes, high charge density, and surface hydrophobicity, are more likely to be captured by the hepatic mononuclear phagocyte system upon entering the bloodstream, thereby facilitating hepatic accumulation.[37,38] This effect may result from opsonization, in which opsonins bind to the nanomaterials, enhancing their recognition and uptake by macrophages.[38] Additionally, albumin-based formulations target the liver by leveraging the transcytosis of albumin through LSECs, facilitating precise delivery to the space of Disse.[39] Moreover, long half-life, high stability, and capacity to bind hydrophobic molecules enhance albumin's accumulation, making it an effective drug delivery vehicle for liver diseases.[40]

Several characteristics of the liver can be utilized for active liver-targeted strategies:[36] (1) The larger pore size of LSECs compared to capillary walls in most tissues: Macromolecules can enter liver tissue and accumulate. For instance, the accumulation of dextran in the liver is tissue-dependent based on molecular weight. (2) Various major uptake transporters on hepatocyte membranes: The Na^+-taurocholate co-transporting polypeptide, which is liver-specific and responsible for conjugated bile acid transport, serves as an effective mechanism for liver-targeted delivery. (3) Other receptors on hepatocytes, LSECs and Kupffer cells: The asialoglycoprotein receptor (ASGPR) on hepatocytes binds to sugars, enabling targeted delivery of nanomaterials conjugated to sugar chains, such as galactose (Gal), lactose, N-acetylgalactosamine (GalNAc), and asialofetuin. Moreover, glycyrrhizic acid binds to multiple sites on the hepatocyte membrane and can be used to enhance liver-targeting properties of nanomaterials. Active targeting strategies offer a more precise approach to liver-specific delivery by addressing some limitations of passive targeting, such as uneven drug distribution and the potential for non-specific uptake.

Notably, as liver fibrosis and HCC progress, the structural and microenvironmental changes in liver tissue, along with the unique characteristics of liver cancer cells, necessitate distinct liver-targeted delivery strategies. After the onset of liver fibrosis, the loss of fenestrations in LSECs as well as the microvilli in hepatocytes impair the delivery of blood-borne substances, which can be addressed by targeting activated hepatic stellate cells via specific receptors.[36] In HCC, while carcinogenic transformation impairs the effective delivery of drugs, the enhanced permeability and retention effect of the highly vascular tumor environment can be leveraged for passive targeted delivery.[36] Highly expressed antigens and enzymes can be utilized for HCC-targeted delivery, though their expression should be evaluated due to individual variations.[41]

Additionally, the characteristics, such as low pH and increased ROS, allow for the design of environment-responsive nanomaterials that are sensitive to pH or redox conditions.[36] Furthermore, the complex interactions between the liver, gut and adipose tissue during the progression of liver diseases suggest that nanomaterials designed to target the gut and adipose tissue may exert indirect therapeutic effects on liver conditions.

Application of Nanomaterials in NAFLD

Nanomaterials Loaded With Approved Drugs

Hypolipidemic Drugs

Fenofibrate (FNB) is used clinically to treat dyslipidemia by acting as an agonist of peroxisome proliferator-activated receptor (PPAR) α, which enhances triglyceride hydrolysis and increases high-density lipoprotein synthesis.[42] Beyond its lipid-lowering effects, FNB also impacts inflammation, oxidation, and apoptosis.[42] Statins, including rosuvastatin, simvastatin and atorvastatin, are commonly used for lowering low-density lipoprotein-cholesterol (LDL-C) by inhibiting HMG-CoA reductase, the key enzyme in cholesterol biosynthesis.[19] Furthermore, statins can enhance oxidase activity, reduce lipid peroxidation, protect liver endothelium, and even stabilize or reverse fibrosis by inhibiting HSC proliferation.[43] However, these drugs suffer from inconsistent oral absorption, low solubility, and limited bioavailability, which hinder their clinical effectiveness.[19,42,43]

Nanoliposomes, bilayered spherical nanoparticles formed by phospholipids, are biodegradable and less toxic, protecting drugs from degradation and enabling sustained drug release in the gastrointestinal tract, thereby increasing plasma drug concentration.[44] Moreover, water-based polyurethane nanoparticles can inhibit macrophage polarization to the M1 phenotype by reducing secretion of inflammatory cytokines.[45] Previous studies demonstrated that both FNB-loaded nanoliposomes and polyurethane nanoparticles significantly enhanced the oral absorption of FNB and exhibited superior efficacy in inhibiting NAFLD compared to crude FNB.[44,45] Furthermore, a recent study has revealed that FNB-loaded polymer-lipid hybrid nanoparticles, utilizing DSPE-PEG and ROS-responsive peroxalate ester derived from vitamin E (OVE), achieve higher drug-loading efficiency via π–π stacking interactions between FNB and OVE compared to other formulations like FNB nanoliposomes.[42] FNB-loaded nanoparticles significantly reduced hepatic lipid accumulation by upregulating PPARα expression and suppressed oxidative stress via OVE's synergistic antioxidant effect.[42] Similarly, FNB and ketoprofen share benzophenone structures, facilitating π-π stacking interactions. A co-assembled nanosystem combining FNB with ketoprofen-$G^DF^DF^DF^DY$, which exhibited strong self-assembly properties and selectively inhibited cyclooxygenase-2, significantly improved hepatic lipid accumulation and inflammation, further emphasizing the promising potential of FNB-based nanoparticle systems in the treatment of NAFLD via a series of synergistic mechanisms.[16]

For statins, in an in vitro model, self-assembled rosuvastatin-loaded cell membrane-derived nanoparticles significantly reduced the accumulation of intracellular triglycerides and cholesterol.[19] Likewise, simvastatin-loaded liposomal nanoparticles effectively reduced oxidative stress through the enhancement of the kruppel-like factor 2-nitric oxide signaling pathway, and also decreased pro-inflammatory cytokines and collagen I expression.[43]

Hypoglycemic Agents

Exenatide (EXE), a GLP-1 analog that enhances glucose-dependent insulin secretion and suppresses glucagon release, is now being widely studied in clinical trials for its potential to treat NAFLD.[46] Besides the effects on glucose metabolism, EXE also influences lipid metabolism through the activation of sirtuin-1 (SIRT1).[47] As reported, SIRT1 suppresses lipid synthesis, reduces oxidative stress, and promotes fatty acid β-oxidation through deacetylation of PPARγ as well as interaction with two other metabolic regulators: the farnesoid X receptor (FXR) and miR-34a.[47] FXR agonists, like ursodeoxycholic acid (UDCA) and obeticholic acid (OCA), reduce steatosis, fibrosis, and inflammation by inhibiting lipogenesis and enhancing fatty acid β-oxidation.[47] In contrast, miR-34a promotes the progression of NASH.[47] Importantly, FXR activation not only suppresses miR-34a but also increases SIRT1 expression, which in turn further enhances FXR activity, creating a positive feedback loop that improves lipid metabolism and attenuates NASH progression.[47]

A previous study demonstrated that oral lipid nanocapsules loaded with EXE improved glucose homeostasis, showing greater effectiveness than subcutaneous injections.[48] However, it did not completely resolve NASH in either high fat (HF) diet-fed foz/foz mice or western diet plus fructose-fed C57BL/6J mice.[48] Chitosan is a natural, biocompatible, and biodegradable polysaccharide that regulates carbohydrate/lipid metabolism and improves insulin resistance. A novel UDCA-based

oligochitosan derivative nanoparticle encapsulating EXE was developed for NAFLD treatment.[47] This nanoparticle overcame the incompatibility between UDCA and EXE, enabled esterase-responsive release of drugs, and reduced lipid accumulation via the SIRT1 pathway.[47] Likewise, UDCA-based oligochitosan derivative nanoparticles loaded with OCA and miR-34a antagomir also prevented NAFLD progression.[49] To address the elevated LDL-C levels associated with OCA administration, carrier-free OCA-atorvastatin nanocrystals, formed through weak non-covalent interactions, were developed to enhance bioavailability, improve liver targeting, and effectively reverse NAFLD with fewer side effects.[22]

Nanomaterials Loaded With Natural Extracts

Polyphenolic Compounds

Curcumin, a natural polyphenol from turmeric, has garnered attention for its antioxidant, anti-fibrotic, anti-inflammatory, and anti-lipidemic properties. In hamsters fed a high-fat, high-fructose diet and infected with Opisthorchis viverrini, curcumin-loaded nanocomplexes reduced hepatic steatosis and decreased the expression of genes linked to fatty acid uptake, inflammation, and fibrosis.[50] Similarly, berberine, a natural alkaloid, showed the potential to slow NAFLD progression by improving insulin sensitivity, stabilizing LDL receptor mRNA, reducing oxidative stress, and modulating the AMP-activated protein kinase (AMPK) pathway. To overcome the poor oral bioavailability of both berberine and curcumin, diethylaminoethyl dextran, a cationic polymer, was applied to enhance nanoparticle stability and promote hepatocyte uptake via the ASGPR.[6] Furthermore, clinical studies have demonstrated that curcumin-loaded nanoparticles improve glucose levels, lipid profiles, fatty liver, liver enzymes, and inflammatory markers in NAFLD patients.[51,52]

Another natural polyphenolic compound that has received widespread attention is resveratrol, known for reducing liver damage through its antioxidant and anti-inflammatory effects. NAFLD-targeted nanobubbles, modified with aptamers and loaded with resveratrol and ultra-small copper-based nanoparticles that possess enzymatic activity and ROS scavenging capabilities, demonstrated synergistic anti-inflammatory effects in vitro.[26] Resveratrol-loaded polymeric nanoparticles also demonstrated enhanced efficacy in reducing lipogenesis and hepatocellular proliferation.[53] α-Lipoic acid with disulfide bonds serves as a cross-linking agent in redox-responsive drug carriers. Lactobionic acid, containing Gal residues, targets hepatocytes by binding to the ASGPR. Glycogen-based nanoparticles, modified with α-lipoic acid and lactobionic acid to deliver resveratrol, effectively reduced lipid accumulation, oxidative stress and inflammation via the toll-like receptor 4 (TLR4)/ nuclear factor kappa B (NF-κB) pathway,[28] while the Gal-modified oxidized starch lysozyme nanocarrier reduced lipid accumulation and improved insulin sensitivity via the AMPK/SIRT1/ fatty acid synthase (FASN)/ sterol regulatory element-binding protein-1c (SREBP-1c) pathway.[7]

In addition, it was demonstrated that hydroxytyrosol delivered via nanogels significantly reduced intracellular triglyceride accumulation.[54] Exosome-like nanoparticles derived from blueberry rich in polyphenols enhanced insulin sensitivity, regulated detoxifying and antioxidant gene expression through nuclear factor erythroid 2-related factor 2 (NRF2) activation, improved liver function, reduced vacuole formation, and decreased lipid droplet accumulation.[55]

Flavonoid Compounds

A series of flavonoid compounds, including naringenin, vitexin, baicalin and silymarin, have been reported to exert anti-inflammatory, antioxidant, and anticancer effects, showing potential for treating NAFLD. Among these, pegylated vitexin-loaded nanoliposomes,[56] as well as naringenin-loaded nanoliposomes[57] and nanostructured lipid carriers[17,58] further reduced hepatic triglycerides and enzymes in rats treated with CCl_4 and urethane, or in methionine and choline deficient (MCD) diet-fed mice, respectively. Similarly, baicalin-loaded nanoliposomes mitigated lipid accumulation, hepatocyte apoptosis, fibrosis, and immune cell infiltration through the inhibition of TLR4 signaling and inflammatory mediator production.[59] Furthermore, silymarin-loaded chitosan-modified lipid-polymer hybrid nanoparticles significantly enhanced therapeutic effectiveness in the livers of PNPLA3 I148M transgenic mice.[18]

Terpenoid Compounds

Celastrol and oridonin, both plant-derived terpenoids, exhibit potential in treating metabolic disorders. Celastrol enhances insulin sensitivity, upregulates antioxidant genes, and promotes anti-inflammatory macrophage polarization[27] while

oridonin possesses antioxidant, anti-inflammatory, and anti-fibrotic properties, along with the ability to maintain lipid and glucose homeostasis.[60]

Liver-targeted celastrol-loaded lactosylated albumin nanoparticles have shown superior performance in reducing body weight, improving insulin sensitivity, lowering cholesterol and triglyceride levels by downregulating lipogenesis genes and boosting lipolysis genes, which in turn mitigates liver fibrosis.[27] Hexadecylphosphorylcholine can integrate into cell membranes, enhancing nanovesicle uptake and serving as a stable nanomaterial with high encapsulation efficiency. In addition, hydroxypropyl-β-cyclodextrin improves the solubility of hydrophobic compounds like oridonin. Accordingly, oridonin/hydroxypropyl-β-cyclodextrin/H9-hexadecylphosphorylcholine nanovesicles, designed to enhance stability and minimize leakage compared to traditional liposomes, showed efficacy in reducing hepatic steatosis and fibrosis in tetracycline-induced mice.[60] The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway plays a critical role in metabolic disorders, oxidative stress, and inflammation. A ROS-scavenging nanomedicine co-delivering oridonin and LY294002, an inhibitor of the PI3K/AKT pathway, effectively alleviated NAFLD-induced systemic and hepatic oxidative stress, insulin resistance, inflammation, and fibrosis by modulating insulin-PI3K/AKT, transforming growth factor β and NF-κB pathways, demonstrating good biocompatibility.[61]

Others

Several natural compounds have shown therapeutic potential in NAFLD, particularly when delivered through nanoparticles to enhance bioavailability and targeting.

For instance, a combination of cordyceps extract and withaferin A, both known for their ability to reduce lipid accumulation, demonstrated enhanced lipid-lowering effects in vitro when delivered in oxygen nanobubble water.[62] Nitidine chloride, an alkaloid with liver-protective, anti-inflammatory, and anti-cancer properties, was successfully delivered using chitosan-pectin nanoparticles.[63] This nanosystem utilized ionic interactions between chitosan and pectin to form a polyelectrolyte complex at low pH, which slowed nitidine chloride release in the gastrointestinal tract, allowing it to reach the colon. There, the higher pH and gut microbiota degraded the chitosan and pectin, releasing the drug. This targeted release mechanism effectively reduced hyperlipidemia and liver damage by improving gut microbiota balance and lowering inflammatory cytokines.[63] Similarly, nanocarriers delivering astaxanthin, a carotenoid from the lutein group known for its potent antioxidant properties, significantly enhanced insulin sensitivity, reduced hepatic fat accumulation, and effectively reversed NAFLD to a healthy state.[64] In addition, a formulation combining the ginsenoside compound K with albumin improved ginsenoside compound K's solubility and liver targeting, consequently slowing the progression of steatosis and fibrosis while also protecting cardiac tissues from lipotoxicity.[65] Moreover, natural antibiotic extracts, platensimycin delivered in a liposomal formulation[66] and rapamycin delivered via methoxy PEG- PLGA nanoparticles[67] effectively reduced liver steatosis by modulating key metabolic genes, such as FASN, SREBP1c and PPARα, in western diet and CCl_4-treated mice or HF diet-fed mice, respectively.

Nanomaterials Loaded With Chemically Synthesized Compounds

Some nanoparticles loaded with synthetic compounds exert the protective effects directly by modulating the lipid metabolism in NAFLD. Bilirubin acts as a hormone by binding directly to the nuclear receptor PPARα. Bilirubin nanoparticles enhanced the PPARα pathway, effectively lowering hepatic lipid accumulation and enzyme levels through boosting β-oxidation, regulating lipid transport, inhibiting lipid synthesis and decreasing ceramide production.[68,69] Endocannabinoids are lipid ligands that bind to cannabinoid receptors CB1R and CB2R, promoting lipogenesis, insulin resistance and dyslipidemia. Rimonabant, the first compound targeting CB1R, was effective in delaying the progression of NAFLD but had neuropsychiatric side effects. To retain its metabolic benefits while minimizing risks, liver-targeted PLGA-encapsulated rimonabant nanoparticles were developed, showing potential in improving hepatic steatosis, liver injury, and insulin resistance.[21] Additionally, BAM15, an oral mitochondrial uncoupler that enhanced lipid oxidation and reduced inflammation, was formulated into BAM15-albumin nanoparticles to improve low bioavailability and short half-life, effectively targeting the liver and reducing hepatic steatosis.[23] Chitosan nanoparticles combined with nicotinamide reduced hepatotoxicity and improved insulin resistance, oxidative stress, and liver enzyme levels by restoring the homeostasis of nicotinamide adenine dinucleotide.[25]

Some nanoparticles regulate lipid metabolism in NAFLD by modulating the autophagy process. Nifedipine, a calcium channel blocker, prevented the accumulation of autophagy-related p62 and ubiquitinated proteins by restoring cytosolic calcium balance. Through this mechanism, intravenous administration of water-soluble nifedipine polymeric nanoparticles alleviated insulin resistance and reduced hepatic steatosis.[70] Tat-Beclin, a peptide with a Tat cell-penetrating sequence and a segment from Beclin-1, promoted the release of Beclin-1 from the autophagy-inactive Golgi, enabling autophagosome formation. As a result, polymeric nanoparticle-formulated Tat-Beclin significantly reduced lipid droplet accumulation in -vitro.[30] Additionally, acid-activated nanoparticles restored lysosomal acidity, thereby reactivating autophagy and improving mitochondrial function, which ultimately reversed fasting-induced hyperglycemia and hepatic steatosis.[71]

Other nanoparticles play a role in the progression of NAFLD primarily by modulating inflammation. For example, dextran-based nanocarriers combined with dexamethasone shifted the pro-inflammatory phenotype of adipose tissue macrophages to the anti-inflammatory phenotype, improving liver inflammation and fibrosis.[72] MCC950, an orally available NOD-like receptor protein 3 inflammasome inhibitor, was delivered via PEG-stabilized liposomes decorated with an anti-Frizzled-1 antibody, which targeted the plasma membrane receptor of inflammasome-activated THP-1 cells. This formulation effectively reduced inflammasome activation and liver inflammation, while slowing fibrosis progression.[73]

Nanomaterials Loaded With Gas Molecules

Gas molecules play important roles as signaling molecules, influencing various biological processes, including inflammation and oxidative stress. Gas-releasing nanomaterials offer a targeted and controlled release of these therapeutic gases, enhancing their bioavailability and reducing potential side effects. A previous study demonstrated that styrene maleic acid copolymer encapsulating carbon monoxide-releasing molecule exhibited enhanced bioavailability compared to natural carbon monoxide-releasing molecule.[20] This nanoparticle effectively mitigated steatohepatitis and liver fibrosis by regulating carbon monoxide release and suppressing the inflammatory response.[20] Additionally, hydrogen-rich water has been found to mildly reduce hepatic lipid accumulation in NAFLD patients. However, its delivery is limited, providing only about 19.4 mL of hydrogen gas per liter. Hydrogen nanocapsules by encapsulating ammonia borane into hollow mesoporous silica nanoparticles facilitated prolonged and high-dose hydrogen release in the gut, which effectively relieved metabolic disorders likely due to the reprogramming of lipid metabolism.[74] Furthermore, N-(3-triethoxysilylpropyl) gluconamide modified magnesium silicide nanosheets, a novel hepatocyte-targeted hydrogen delivery system, enabled a localized, abundant, and sustained release of hydrogen directly into hepatocytes, suppressing hepatic inflammation and ferroptosis while improving liver metabolic function, achieving significant efficacy in preventing NAFLD.[75]

Nanomaterials Loaded With Nucleic Acids or Proteins

Nanomaterials can serve as delivery systems for therapeutic nucleic acids (eg, DNA, mRNA, small activating RNA, siRNA, or miRNA) or proteins, targeting hepatocytes to modulate key pathways involved in NAFLD progression, such as lipid metabolism, inflammation, autophagy, and mitochondrial function.

Interleukin-22 (IL-22) can improve glucose tolerance and insulin sensitivity while alleviating hepatic steatosis. When combined with apolipoprotein A1, which reduced hepatic steatosis, inflammation, and oxidative stress, IL-22 could be effectively delivered to the liver using self-assembling nanocarriers composed of chitosan, metformin, penetratin, and DSPE-PEG.[29] This approach not only prolonged the half-life of IL-22 but also reduced off-target toxicity. In a similar vein, lipid nanoparticles were engineered to enhance gene delivery to the liver. For instance, replacing DSPC with POPC in lipid nanoparticles significantly improved the delivery of CTP cytidylyltransferase α mRNA, which promoted phosphatidylcholine synthesis, mitigating lipid accumulation, inflammation, oxidative stress, and fibrosis in NAFLD.[76] Furthermore, the heparin-based polycationic vector was effective in delivering mammalian sterile 20-like kinase 1 mRNA to hepatocytes, where it activated the AMPK/SREBP-1c pathway, improving insulin sensitivity and reducing liver damage.[77] Other polymeric nanocarriers, like 5-(G5)-triethanolamine-core polyamidoamine dendrimers loaded with small activating RNA targeting hepatocyte nuclear factor 4α, demonstrated the potential to improve lipid metabolism and regulate glucose homeostasis.[78]

As for siRNA, nanomaterials loaded with siRNA targeting the inositol-requiring enzyme 1α-X-box binding protein 1 (IRE1α-XBP1) pathway, which is critical for the unfolded protein response, reduced lipid accumulation and collagen deposition, as well as restored intestinal barrier integrity in NAFLD.[79] Additionally, nanoparticles loaded with siRNA

targeting methylation-controlled J protein, a mitochondrial inhibitor that restricts Complex I activity, improved mitochondrial function without increasing ROS levels, thereby reducing lipid accumulation and fibrosis.[80] Furthermore, Rubicon, the interacting protein of Beclin-1 involved in the progression of NAFLD, could be targeted through hepatocyte-specific sgRubicon lipid nanoparticles, thus reducing hepatic steatosis.[81] Moreover, nanoparticles loaded with siRNA targeting CD98, a key regulator of liver inflammation, effectively alleviated NAFLD.[82] Methyltransferase-like 3 (METTL3), an m6A methyltransferase, has been implicated in immune evasion by decreasing $CD8^+$ T cell infiltration in tumors through enhanced cholesterol biosynthesis. Correspondingly, siRNA targeting METTL3 delivered by nanoparticles activated cytotoxic $CD8^+$ T cells, boosting anti-tumor immunity in NAFLD related HCC mouse model.[83]

For miRNA, targeted delivery of miR-146b mimic to hepatocytes by lactosylated PDMAEMA nanoparticles reduced proinflammatory cytokines as well as PPARγ, likely by degrading TLR4-related markers, consequently alleviating hepatic steatosis and inflammation.[84] Additionally, metal-organic nanocarriers, composed of glycyrrhizic acid and zinc ions, were loaded with the circRNA_0001805 plasmid, and coated with a Gal-modified red blood cell membrane for targeted delivery.[85] These nanocarriers overexpressed circRNA_0001805, which interacted with miR-106a-5p/miR-320a, restoring genes involved in lipid metabolism and inhibiting NF-κB signaling to protect against NAFLD.[85]

The HB-ATV-8 vaccine used a synthetic peptide in micellar nanoparticles to induce anti-cholesteryl-ester transfer protein antibodies, reducing plasma triglycerides and mitigating liver damage.[86] Additionally, nanoparticles loaded with glial cell line-derived neurotrophic factor also protected against hepatic steatosis and liver fibrosis by downregulating PPAR-γ, PPAR-α, SREBP1 while activating the p38 mitogen-activated protein kinase (MAPK) signaling pathway.[87]

Other Forms of Nanomaterials

Nanoemulsions offer a promising approach to enhance the pharmacological efficacy of poorly soluble drugs by increasing the surface area for absorption and improving bioavailability through lipid content. Curcumin nanoemulsions,[88] liver-targeted lovastatin nanoemulsomes designed with bile acid and fatty acids,[89] and Vitamin D nanoemulsions[90] demonstrated superior therapeutic effects over conventional forms in alleviating steatosis and inflammation.

Moreover, metal and metal oxide nanoparticles show potential in treating NAFLD through various mechanisms. As reported, zinc oxide nanoparticles protected against hepatic steatosis and insulin resistance via inhibition of SREBP-1c-mediated lipogenesis.[91] Luteolin-conjugated zinc oxide nanoparticles,[92] cerium dioxide nanoparticles[24,93–99] and cerium/zinc nanocomposites[100] exhibited enhanced antioxidant effects, improved insulin sensitivity, and reduced hyperlipidemia. Selenium nanoparticles[101,102] alleviated lipid deposition, oxidative stress and liver injury by activating the PPARα and NRF2 pathways, while amorphous selenium nanodots[103] mitigated liver inflammation and improved liver function via p38 MAPK signaling pathway.

Other innovative nanomaterials, such as surface-deacetylated chitin nanofibers, provided hepatoprotection by dual mechanisms of lipid adsorption and gut microbiota modulation, thus reducing oxidative stress and hepatic inflammation.[104] Carbon quantum dots, including carbon quantum dots-lactoferrin complexes[105] and Fe^{3+}-chelating carbon dots,[106] exhibited antioxidant effects that reduced liver fibrosis and managed iron-overload-induced liver conditions.

Overview of Therapeutic Nanomaterials in Chronic HBV Infection

The recurrence of chronic hepatitis B, even in "functionally cured" patients with negative HBsAg, is primarily due to the inability of current antiviral drugs to eliminate nuclear covalently closed circular DNA (cccDNA).[107] Additionally, HBV DNA integrates into the host genome during replication, contributing to chronic infection and HCC.[35] With the development of nanomaterial properties and optimization of fabrication techniques, nanomaterials may improve treatment outcomes and advance toward an HBV cure by drug delivery and gene editing.

Due to the small size and customizable surface properties, nanomaterials, such as polymer nanoparticles, lipid nanoparticles and metal nanoparticles, effectively delivered nucleos(t)ide analogues, improving bioavailability and therapeutic efficacy while reducing drug resistance and minimizing side effects.[108–111] In particular, polymer nanoparticles could control drug release, extending therapeutic effects and reducing dosing frequency.[108]

Moreover, nanomaterials, including polymeric nanoparticles, lipid nanoparticles, conjugate nanoparticles and lipid-like nanoparticles, could carry engineered nucleases,[112,113] siRNA[114] or gene-editing tools, such as CRISPR-Cas9,

enabling precise cleavage and deactivation of HBV DNA for effective viral inhibition or potential eradication.[108] More importantly, nanomaterials not only improved delivery efficiency in gene therapy but also minimized off-target effects. As reported, ionizable lipidoid nanoparticles and advanced lyophilization technology could deliver siRNA targeting HBV, suppressing viral RNA, antigens and DNA.[115] Apart from the common strategies for liver targeting, preS peptide-guided biomimetic nanoparticles also precisely delivered HBV siRNA to hepatocytes.[116] Interestingly, recent studies have demonstrated novel biomimetic nanoparticles create stable and targeted CRISPR/Cas9 nanodrugs.[117,118] By modifying the vehicle with red blood cell or hepatocyte membranes, these nanoparticles enabled efficient gene editing with immune evasion properties and enhanced clearance of cccDNA.[117,118]

Some nanovaccines focused on enhancing HBV-specific cellular and humoral immune responses, including mRNA encoding HBV antibodies,[119] acting as adjuvants,[120,121] and targeting molecules that regulate immune cell functions.[122] Additionally, nanomaterials have been engineered for the codelivery of multiple therapeutic agents with different mechanisms of action, including siRNA for direct viral targeting and immune modulation.[123]

Discussion

For NAFLD or chronic HBV infection, ideal nanomaterials should possess high liver-targeting specificityto minimize off-target effects, strong biocompatibility to prevent immune responses, and controlled release capabilities to maintain consistent therapeutic levels and reduce dosing frequency. Efficient metabolism and clearance after treatment are also crucial to prevent long-term accumulation and potential toxicity.

The development of therapeutic nanomaterials for NAFLD concurrent with chronic HBV infection faces unique challenges, particularly due to the complex interplay between these two conditions.[124] For instance, HBV activates mitophagy to clear damaged mitochondria, preventing host cell death and thereby facilitating viral replication.[125] In contrast, NAFLD experiences impaired mitophagy, resulting in the accumulation of damaged mitochondria, which further exacerbates liver damage.[125] This disparity in mitochondrial function hints that therapeutic approaches must carefully balance HBV persistence and NAFLD-induced cellular stress. Furthermore, it has been revealed that metabolic and immune alterations accompanying NAFLD progression can suppress HBV replication directly or stimulate antiviral immune responses indirectly.[124] However, the heightened activity of immune cells can also aggravate hepatic inflammation and injury. Thus, it should be careful to modulate immune responses to avoid exacerbating liver damage in patients with coexisting conditions.

Altogether, managing NAFLD concurrent with chronic HBV infection requires addressing overlapping molecular and pathological mechanisms. It has been reported that HBx enhances the activity of liver X receptor on the SREBP-1c promoter, thereby upregulating the expression of SREBP-1c and its downstream lipogenic genes.[126] Furthermore, HBx induces expression of PPARγ by increasing the level and activity of its activator, CCAAT/enhancer-binding protein α, which plays a crucial role in hepatic lipogenesis.[126] Through the upregulation of these transcription factors and downstream lipid metabolism pathways, HBV facilitates its own replication and infectivity.[126] These lipid synthesis regulators may serve as potential targets for therapeutic nanomaterials in the management of NAFLD coexisting with chronic HBV infection. Moreover, both NAFLD and chronic HBV infection lead to oxidative stress, a key pathogenic mechanism that induces hepatocyte damage, activates hepatic stellate cells, and accelerates fibrosis progression, potentially leading to HCC.[127] Consequently, reducing non-specific hepatic inflammatory damage by targeting shared signaling pathways in NAFLD and chronic HBV infection, along with the use of anti-inflammatory drugs and antioxidants, may serve as potential strategies for therapeutic nanomaterials. Furthermore, a recent study demonstrated that in the NASH-HCC model, the residency and exhaustion of $CD8^+$ T cell paradoxically contributed to HCC progression following the administration of immune checkpoint inhibitors.[128] This finding highlights that early intervention with immunomodulatory nanomaterials may mitigate NAFLD-associated immune exhaustion and enhance HBV-specific antiviral responses.

Additionally, nanomaterials offer an opportunity for the co-delivery of multiple therapeutic agents targeting both the viral infection and the metabolic disturbances of NAFLD. A previous report indicated that an optimized lipid-like nanoparticle formulation enabled effective delivery of Cas9 mRNA and single-guide RNA to the liver, achieving in vivo targeting of both HBV DNA and the proprotein convertase subtilisin/kexin type 9 gene, an essential therapeutic target in hypercholesterolemia.[129]

Notably, the molecular interactions between NAFLD and chronic HBV infection remain incompletely elucidated, posing challenges for the precise design of nanomaterials. Moreover, chronic HBV infection exhibits distinct virological

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Table 1 Characteristics of Nanomaterials for NAFLD Treatment

Study	Category	Nanomaterials	Formulation	Animal Model	LT	Improvements on NAFLD					Characteristics			
						HG/HS	OS	GT/IR	HI/HD	HF	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficacy (%)	Drug Loading (%)
Lipid-based nanoparticle														
Cao 2016[44]	Liposome	Fenofibrate nanoliposome	SPC, cholesterol, fenofibrate	MCD diet-fed mice		√					122.1±1.40	−2.92	96.6±1.60	7.44±4.39
Chen 2017[57]	Liposome	Naringenin nanoliposome	SPC, cholesterol, naringenin	MCD diet-fed mice		√			√		98±5	/	96.66±1.03	8.43±0.45
Liu 2020[59]	Liposome	Baicalin nanoliposomes	SPC, cholesterol, baicalin	MCD diet-fed mice		√			√	√	81.41	−13.9 ±5.74	81.10	6.90
Su 2021[66]	Liposome	Platensimycin nanoliposome/mannose-modified nanoliposome	DPPC, cholesterol, DSPE-PEG-Mannose, platensimycin	Western diet and CCl_4-treated mice		√		√			135±2.57/ 138±3.46	14.2±0.35/ 13.2±0.39	36.7±1.4/38.2 ±2.3	8.30±0.24/ 8.70±0.31
Farooq 2022[56]	Liposome	PEGylated vitexin nanoliposomes	DPPC, cholesterol, PEG, vitexin	CCl_4/Urethane co-administration-induced rats					√	√	458	−0.3	80	/
Negro 2023[73]	Liposome	PEG-stabilized, anti-FZD1 antibody-decorated, MCC950-loaded liposomes	L-α-phosphatidylcholine /stearylamine/cholesterol, DSPE-PEG2000-COOH, sulfo-NHS, EDC, MCC950	HF diet-fed mice					√	√	151±1	−22±2	60±3	7.5±0.4
Xin 2023[61]	Liposome	Oridonin- and LY294002-loaded liposomes	DOPC, cholesterol, DSPE–PEG2000, oridonin, LY294002	CCl_4-treated mice	√	√	√	√	√	√	125.47±2.11	−23.09 ±0.53	/	/
Parsa 2024[43]	Liposome	Simvastatin nanoliposome	DSPC, cholesterol, simvastatin	/			√		√	√	139.5	−56.8±1.1	/	/
Chen 2021[6]	Bilosome	Diethylaminoethyl dextran-coated, berberine- and curcumin-loaded bilosomes	Bile salts-SDC, SPC, cholesterol, ODA, curcumin, berberine	HFHS diet-fed mice	√	√	√	√	√		~150	<1	/	~7 (berberine); ~3(curcumin)
He 2018[84]	Lipid nanoparticle	miRNA-146b mimic-loaded, lactosylated PDMAEMA nanoparticles	DODAP, Lac-DOPE, DOPE, DMG-PEG, gramicidin A, miRNA-146b mimic	MCD diet-fed mice	√	√			√	√	168.9	10.3	/	/
Barbier-Torres 2020[80]	Lipid nanoparticle	siMCJ-loaded lipid nanoparticles	Lipid nanoparticle Invivofectamine, N-Acetylgalactosamine-siMCJ	MCD/CDHF/ HFHF diet-fed mice; CCl_4-treated mice	√	√	√	√	√	√	/	/	/	/

Bai 2024[81]	Lipid nanoparticle	Rubicon-targeting CRISPR-Cas9-loaded nanoparticles	Dlin-MC3-DMA, DOPE, cholesterol, DMG-PEG2000, sgRubicon plasmid	HF diet-fed mice		√		√	√		112	−0.36	94%	/
Guo 2024[76]	Lipid nanoparticle	mCCTα-loaded lipid nanoparticles	POPC, Dlin-MC3-DMA, cholesterol, DMG-PEG2000, mCCTα	HF/MCD diet-fed mice	√	√	√		√	√	55.5±10.8	/	/	/
El-Sherbiny 2018[90]	Emulsion	Vitamin D nanoemulsion	Soluble pea protein, canola oil, vitamin D	HF diet-fed rats		√			√	√	/	/	/	/
Elbaset 2022[88]	Emulsion	Curcumin nanoemulsion	Curcumin	HFHF diet-fed rats		√	√	√	√		125±7.52	−19.40 ± 2.58	/	/
Hu 2021[17]	Nanostructured lipid carrier	Naringenin-loaded nanostructured lipid carrier	SPC, labrafac lipophile WL 13492, glycerol trilaurate, naringenin	MCD diet-fed mice		√			√		162.9±11.7	−6.4±0.4	94.5±5.6	22.5±1.7
Hu 2021[58]	Nanostructured lipid carrier	Naringenin-loaded nanostructured lipid carrier	SPC, stearic acid, monostearin, oleic acid, naringenin	MCD diet-fed mice		√			√		171.9±2.0	−2.3±0.1	99.9±0.0	23.7±0.3
Faran 2024[89]	Nanostructured lipid carrier	Lovastatin nanoemulsome	Ginger and garlic oils, stearic acid, phospholipon, UDCA, linoleic acid, lovastatin	HF diet-fed rats	√	√			√		270±27.4	−23.8±3.5	81.36±3.4	/
Polymeric nanoparticle														
Mwangi 2016[87]	Polymeric nanoparticle	PVA-covered, GDNF-loaded nanoparticles	PVA, BSA-FITC, GNDF protein	HF diet-fed mice		√				√	376.8±12.7	−27.1±3.5	/	/
Canup 2017[82]	Polymeric nanoparticle	CD98 siRNA-loaded nanoparticles	PLA, PVA, CD98 siRNA	HF diet-fed mice		√		√	√	√	273.1±19.3	−12.84 ±2.70	/	/
Wan 2018[53]	Polymeric nanoparticle	Resveratrol-loaded nanoparticles	PLGA, resveratrol	/		√					176.1	−22.6	97.25	14.9
Lee 2019[70]	Polymeric nanoparticle	Nifedipine-loaded nanoparticles	PLGA, ethyl acetate, PVA, nifedipine	HF diet-fed mice		√		√			258	−13.2	/	/
Hinds 2020;[68] Kipp 2023[69]	Polymeric nanoparticle	Pegylated bilirubin	Bilirubin-IX-alpha, mPEG2000-NH2	HF diet-fed mice		√			√		94±12	28	/	/
Li 2022[28]	Polymeric nanoparticle	Glycogen-based, resveratrol-loaded nanoparticles	Glycogen, α-lipoicacid, lactobionic acid, DCC/DMAP, resveratrol	HF diet-fed mice	√	√	√	√	√		288.9±0.35	−4.3±0.3	98	11.8

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Table 1 (Continued).

Study	Category	Nanomaterials	Formulation	Animal Model	LT	Improvements on NAFLD					Characteristics			
						HG/HS	OS	GT/IR	HI/HD	HF	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficacy (%)	Drug Loading (%)
Zagkou 2022[30]	Polymeric nanoparticle	Tat-Beclin nanoparticles	Poly(L-Lactide)/poly(D-Lactide), Tat-Beclin	/		√					202±4.0	33.0±4.0	81.0±3.0	49±2.0
Cui 2023[20]	Polymeric nanoparticle	CO-releasing molecule-encapsulated styrene-maleic acid copolymer	Styrene-maleic acid copolymer, CO-releasing molecule, water-soluble carbodiimide	HF-MCD diet-fed mice		√	√		√	√	20 to 100	−17.12	/	10.5
Hirsch 2023[21]	Polymeric nanoparticle	Rimonabant-loaded nanoparticles	DCM containing PLGA, PVA, rimonabant	HF diet-fed mice	√	√		√			250	−18.9 ±10.7	32.53±6.1	3.6±0.13
Pan 2023[83]	Polymeric nanoparticle	METTL3 siRNA-loaded nanoparticles	PEG-PLGA, METTL3 siRNA	CDHF diet-fed mice		√					/	/	/	/
Zeng 2023[71]	Polymeric nanoparticle	Acidic nanoparticles	Di-acid monomers tetrafluorosuccinic acid, succinic acid, ethylene glycol, DCM, acetonitrile, SDS	HF diet-fed mice		√		√	√		100	−25~-30	/	/
Huang 2020[78]	Dendrimer	HNF4A small activating RNA-loaded dendrimer nanoparticles	Triethanolamine core, HNF4A-small activating RNA	HF diet-fed rats		√		√	√		/	/	/	/
Abd-Allah 2020[25]	Chitosan-based nanoparticle	Chitosan/TPP nanoparticles	Chitosan/TPP, nicotinamide	HFHF diet-fed rats		√	√	√	√		174.7±10.6	22.5±0.56	/	/
Xie 2022[47]	Chitosan-based nanoparticle	Exenatide-loaded UBC nanovesicles	UDCA, oligochitosan, NHS, EDC·HCl, exenatide	HF diet-fed mice	√	√			√		237.6±8.2	0.53 ±0.03	85.7 ±1.8	17.1 ±0.2
Kong 2023[49]	Chitosan-based nanoparticle	OCA/anta-miRNA-34a-loaded UBC nanovesicles	UDCA, oligochitosan, NHS, EDC·HCl, OCA, miRNA-34a antagomir	HF diet-fed mice	√	√		√	√		/	/	82.7 (OCA); 89.3 (miRNA-34a antagomir)	8.90 (OCA); 2.13 (miRNA-34a antagomir)
Goto 2020[104]	Polysaccharide-based nanoparticle	Surface-deacetylated chitin nanofibers	Powdered chitin	HFHC diet-fed SHRSP5/Dmcr rats		√	√	√	√	√	/	/	/	/
Li 2022[77]	Polysaccharide-based nanoparticle	Redox-unlockable MST1 mRNA-loaded nanoparticle	Heparin nanoparticle, PGEA, MST1 mRNA	HF diet-fed mice	√	√		√	√		180	25	/	/

Sitthirach 2022[50]	Polysaccharide-based nanoparticle	Curcumin-loaded nanocomplexes	Ethylcellulose, methylcellulose, arabic gum, xanthan gum, curcumin	HFHF diet-fed hamsters infected with Opisthorchis viverrini		√			√	√	/	/	/	/
Che 2023[64]	Polysaccharide-based nanoparticle	Astaxanthin-loaded nanocarriers	WPI, Gal, TPP, EDC, NHS, astaxanthin	HF diet-fed mice	√	√	√	√	√		75.8	/	/	3.77±0.36
Martínez-Sánchez 2023[72]	Polysaccharide-based nanoparticle	Dextran-nanocarrier conjugated with dexamethasone	Dexamethasone succinic acid, aminated dextran, NOTA, tetramethylrhodamine	HF/HFHC diet-fed mice		√			√	√	/	/	/	/
Lu 2024[63]	Polysaccharide-based nanoparticle	Nitidine chloride-loaded chitosan/pectin nanoparticles	Chitosan, pectin, TPP, nitidine chloride	HF diet-fed mice		√			√		255.9±5.10	29.30±0.77	72.83±2.13	4.65±0.44
Cao 2018[45]	Polyurethane based nanoparticle	Fenofibrate-loaded polyurethane nanoparticles	Isophorone diisocyanate, poly(ε-caprolactone)diol, 2.2-bis(hydroxymethyl)propionic acid, ethylene diamine, fenofibrate	MCD diet-fed mice		√					57.7±14.1	−45.6±0.9	/	/
Wang 2020[16]	Peptide-based nanoparticle	Co-assembly of fenofibrate and ketoprofen peptide	Fenofibrate and Kep-G^{D}F^{D}F^{D}Y	HF diet-fed mice		√			√		9.5	/	/	/
Fan 2022[27]	Protein-based nanoparticle	Celastrol-loaded lactosylated albumin nanoparticles	D-lactose monohydrate, BSA	HF diet-fed mice	√	√		√	√	√	158.6±3.4	−25.7±0.4	79.0	13.62
Jing 2022[23]	Protein-based nanoparticle	BAM15-albumin nanocomposites	BAM15, BSA	HF diet-fed mice	√	√	√	√		√	331	−20.1	/	/
Yue 2023[65]	Protein-based nanoparticle	Nanodrug composed of ginsenoside compound K and albumin	Human serum albumin, ginsenoside compound K	HF diet-fed mice	√	√				√	272	−28	/	/
Gutiérrez-Vidal 2018[86]	Polymeric micelle	Vaccine HB-ATV-8 composed of micellar nanoparticles	Caldarchaeol, L-a-phosphatidylcholine, L-HPC, a synthetic peptide of cholesteryl-ester transfer protein	HF diet-fed pig		√			√	√	/	/	/	/
Zhu 2023[79]	Polymeric micelle	XBP1 siRNA-loaded nanomicelles	Folic acid-TPGS, RhB-siXBP1, 1.4-dioxane	HFHFHC diet-fed mice		√			√	√	/	/	/	/

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Table 1 (Continued).

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Zhao 2020[67]	Block copolymer-based nanoparticle	Rapamycin-loaded nanoparticles	Methoxy PEG-PLGA, PVA, rapamycin	HF diet-fed mice		√			√		157.5±19.5	−33.7±0.5	77.9	23.8
Hybrid nanoparticle														
Liang 2018[18]	Hybrid nanoparticle	Silymarin-loaded chitosan-modified lipid-polymer hybrid nanoparticles	PLGA, SPC, DSPE-PEG2000, silymarin	PNPLA3 1148M transgenic mice		√			√		286.5±23.8	45.3±8.9	97.05±0.01	/
Zai 2019[29]	Hybrid nanoparticle	Poly-metformin and penetratin-based hybrid nanoparticles	Biguanide modified chitosan, penetratin, DSPE-PEG2000, plasmid expressing a fusion gene by tethering IL-22 to ApoA-I	HF diet-fed mice	√	√		√	√		100	30	/	/
Teng 2019[7]	Polymer-protein hybrid nanoparticle	Lysozyme micelles coated with Gal and conjugated oxidized starch polymer	Oxidized starch, galactose-NH2, EDC, NHS, lysozyme peptides, resveratrol	HF diet-fed mice	√	√	√	√	√		50	−18.6	/	14.3
Eilenberger 2021[99]	Hybrid nanoparticle	Supramolecular complex composed of ZnMFA, HPβ-CD, and cerium dioxide nanoparticles	Cerium dioxide nanoparticles, ZnMFA, HPβ-CD	/					√		/	/	/	/
Jin 2021[74]	Hybrid nanoparticle	Hydrogen nanocapsule by encapsulating ammonia borane into hollow mesoporous silica nanoparticles	Hollow mesoporous silica, ammonia borane, PEG	HF diet-fed mice		√		√			120	/	/	/
Li 2021[85]	Hybrid nanoparticle	Nanodrug system overexpressing circRNA_0001805	Glycyrrhizic acid, Zn(NO3)2, polyethylene imine, nanoscale red blood cell membrane, Gal, DSPE-PEG2000, EDC, NHS, circRNA_0001805 plasmid	HF diet-fed mice	√	√			√		141	−25	76.5 (Gal); 94.3 (plasmid DNA)	23.6 (Gal); 14.6 (plasmid DNA)

Guo 2022[26]	Hybrid nanoparticle	NAFLD-specific aptamers-modified, resveratrol- and ultrasmall copper-based nanoparticles- loaded nanobubbles	DPPC, DSPE-PEG2000-maleimide, NAFLD aptamer, resveratrol, ultrasmall copper-based nanoparticles	/	√				√		193.73	27.39	90	/
Domingues 2023[48]	Hybrid nanoparticle	Exenatide-loaded lipid nanocapsules	Labrafac® WL1349, Span 80®, Peceol®, Lipoid®S100, Kolliphor®HS15, exenatide	HF diet-fed foz/foz mice; Western diet plus fructose-fed mice		√		√			~180	−6.5±1.9	78.2 ±4.2	/
Du 2023[42]	Hybrid nanoparticle	Fenofibrate-loaded nanoparticles based on OVE and DSPE-PEG	α-tocopherol, oxalyl chloride, DSPE-PEG, fenofibrate	MCD diet-fed mice		√	√		√		197.0±0.2	−49.6±0.6	97.25±0.6	29.67±0.1
Inorganic nanoparticle														
Kobyliak 2016;[24] Kobyliak 2017;[93] Carvajal 2019;[96] Carvajal 2019;[97] Abbasi 2021;[95] Wasef 2021[94]	Inorganic nanoparticle	Cerium oxide nanoparticles	/	HF diet-fed rats; MCD diet-fed rats; MSG-induced rats; fipronil-induced rats		√	√		√	√	2~5	/	/	/
Dogra 2019[91]	Inorganic nanoparticle	Zinc oxide nanoparticles	/	HF diet-fed mice		√		√	√		165.1±70.04	−16.6 ±4.61	/	/
Zhu 2022[103]	Inorganic nanoparticle	Amorphous selenium nanodots	Selenium powder, aqueous sodium sulfite solution, BSA	HF diet-fed rats		√	√		√		/	/	/	/
Ahmed 2022[92]	Inorganic nanoparticle	Luteolin-loaded zinc oxide nanoparticles	Zinc acetate, luteolin	HFD and streptozotocin induced rats		√	√	√	√		174.7	/	/	/
Zhao 2023[75]	Inorganic nanoparticle	N-(3-triethoxysilylpropyl) gluconamide modified magnesium silicide nanosheets	Magnesium silicide nanosheets powder, gluconamide	CDAHF diet-fed mice	√	√	√		√	√	300	/	/	/
El-Seidy 2023[100]	Inorganic nanoparticle	Cerium/zinc nanocomposites	Cerium chloride heptahydrate, PEG, zinc acetate dihydrate	HFHS diet-fed rats		√	√	√			40.53~45.01 (Cerium oxide); 24.50~36.68 (ZnO)	/	/	/
Lei 2024;[102] Shen 2024[101]	Inorganic nanoparticle	Selenium nanoparticles	/	Polystyrene microplastics-induced mice		√	√		√		100–200	/	/	/

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Table 1 (Continued).

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						HG/HS	OS	GT/IR	HI/HD	HF	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficacy (%)	Drug Loading (%)
Others														
Mauri 2021[54]	Nanogel	Hydroxytyrosol nanogels	PEG, rhodamine-conjugated PEI, hydroxytyrosol	/		√					262	0.90	83	/
Lu 2024[22]	Nanocrystal	Nanocrystal of obeticholic acid and atorvastatin	Obeticholic acid, atorvastatin	HF diet-fed mice	√	√	√		√		130	−15.3 ±0.78	/	/
Zhao 2022[55]	Biomimetic nanoparticle	Blueberry-derived exosome-like nanoparticles	Blueberry	HF diet-fed mice		√	√	√	√		150~250	−2.52	/	/
Zahid 2024[19]	Biomimetic nanoparticle	Cell membrane-derived nanoparticles	HepG2 cells, rosuvastatin	/		√			√		11~20	~-15	~50	55.85±3.34
Zhang 2024[60]	Cyclodextrin-based nanoparticle	Oridonin loaded peptide nanovesicles	HPβ-CD, hexadecylphosphorylcholine, H9 peptide, oridonin	Tetracycline-induced mice		√				√	195.6±11.49	17.5±0.98	84.46±1.34	63.60±1.71
Han 2023[62]	Nanobubble-based nanoparticle	Cordyceps extract- and withaferin A-loaded Oxygen nanobubble water	Cordyceps extract, withaferin A	/		√					<200	~-30	/	/
Yu 2021[106]	Carbon-based nanoparticle	Fe^{3+}-chelating carbon dots	Egg white	Fe^{2+} plus thioacetamide-incubated zebrafish		√	√		√		2.4±0.6	/	/	/
García-Topete 2024[105]	Carbon-based nanoparticle	Carbon quantum dots bioconjugated with lactoferrin	Citric acid	/			√		√	√	11.7	−21.86	/	/

Abbreviations: LT, liver-targeted; HG/HS, hyperlipidemia/hepatic steatosis; OS, oxidative stress; GT/IR, glucose tolerance/insulin resistance; HI/HD, hepatic inflammation/damage; HF, hepatic fibrosis; FZD1, frizzled-1; MCJ, methylation-controlled J protein; mCCTα, CTP phosphocholine cytidylyltransferase α mRNA; GDNF, glial cell line derived neurotrophic factor; CO, carbon monoxide; METTL3, methyltransferase-like 3; HNF4A, hepatocyte nuclear factor 4α; OCA, obeticholic acid; MST1, mammalian sterile 20-like kinase 1; XBP1, X-box binding protein 1; SPC, soybean lecithin; DPPC, dipalmitoylphosphatidylcholine; DSPE, 1.2-distearoyl-sn-glycero-3-phosphoethanolamine; SDC, sodium deoxycholate; ODA, octadecylamine; PEG, polyethylene glycol; NHS, N-hydroxysuccinimide; EDC·HCl, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DOPC, 1.2-dioleoyl-sn-glycero-3-phosphocholine; DSPC, 1.2-distearoyl-sn-glycero-3-phosphocholine; DODAP, 1.2-dioleoyl-3-dimethylammonium-propane; Lac-DOPE, lactose-conjugated 1.2-dioleoyl-sn-glycero-3-phosphoethanolamine; DMG, dimyristoylphosphatidylglycerol; Dlin-MC3-DMA, (2,3-dilinoleoyloxy)propyl)-dimethyl-ammonium-propane; POPC, 1-palmitoyl-2-oleoylphosphatidylcholine; UDCA, ursodeoxycholic acid; PVA, polyvinylic alcohol; BSA, bovine serum albumin; FITC, fluorescein Isothiocyanate; PLA, polylactic acid; PLGA, poly (D,L-lactide-co-glycolide acid; DCC/DMAP, N,N′-dicyclohexylcarbodiimide/4-dimethylaminopyridine; DCM, dichloromethane; SDS, sodium dodecylsulfate; TPP, sodium tripolyphosphate; PGEA, ethanolamine-modified poly(glycidyl methacrylate); WPI, whey protein isolate; Gal, D(+)-galactose; NOTA, 1,4,7-triazacyclononane-1,4,7-triacetic acid; L-HPC, 1-lauroyl-2-hydroxy-sn-glycero-3 phosphocholine; TPGS, D-α-tocopheryl polyethylene glycol 1000 succinate; ZnMFA, zinc salt of mefenamic acid; HPβ-CD, hydroxypropyl-β cyclodextrin; OVE, peroxalate ester derived from vitamin E; PEI, polyethyleneimine; MCD, methionine choline deficient; HFHS, high-fat high-sucrose; HFHF, high-fat high-fructose; CDHF, choline-deficient high-fat; HFHC, high-fat high-cholesterol; HFHFHC, high-fat high-fructose, high-cholesterol; MSG, monosodium glutamate; CDAHF, choline-deficient L-amino acid-defined high-fat; SHRSP5, stroke-prone spontaneously hypertensive 5.

and immune features at different stages of the disease and across HBV genotypes. In the future, multi-omics approaches should be prioritized to identify key targets of NAFLD-HBV comorbidity and inform the functional modification of nanomaterials. Furthermore, the non-specific hepatic uptake of nanoparticles, particularly by Kupffer cells, and concerns about the long-term safety of nanomaterial degradation products, including potential hepatotoxicity and immunogenicity, hinder clinical translation. The application of biomimetic nanotechnology may facilitate immune evasion and enable targeted drug delivery. Thus, the development of more representative preclinical models that accurately mimic the coexistence of NAFLD and HBV infection is crucial for evaluating the therapeutic efficacy of nanomaterials, as most existing animal models focus on a single disease and have inherent flaws. For instance, NAFLD animal models vary in terms of modeling techniques and dietary formulations, only partially reflecting the characteristics of NAFLD patients. And simulating the chronic HBV infection state remains a challenge, especially in the presence of HBV-specific immune responses.[130] In addition, from a pharmaceutical perspective, the complex synthesis of multifunctional nanomaterials and the high costs require careful assessments of the balance between therapeutic efficacy and economic feasibility.

In summary, therapeutic nanomaterials hold significant promise in the management of NAFLD (Table 1), especially in patients with concurrent HBV infection, by enabling targeted drug delivery, modulating immune responses, and reducing hepatic inflammation, thus offering a potential approach for more effective, personalized treatments for patients with coexisting conditions.

Abbreviations

AKT, protein kinase B; AMPK, AMP-activated protein kinase; ASGPR, asialoglycoprotein receptor; cccDNA, covalently closed circular DNA; ER, endoplasmic reticulum; EXE, exenatide; FASN, fatty acid synthase; FNB, fenofibrate; FXR, farnesoid X receptor; Gal, galactose; GalNAc, N-acetylgalactosamine; GLP-1, glucagon-like peptide-1; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HF, high-fat; IL-22, interleukin-22; LDL-C, low-density lipoprotein -cholesterol; LSECs, liver sinusoidal endothelial cells; MAFLD, metabolic dysfunction-associated fatty liver disease; MAPK, mitogen-activated protein kinase; MCD, methionine and choline deficient; METTL3, methyltransferase-like 3; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa B; NRF2, nuclear factor erythroid 2-related factor 2; OCA, obeticholic acid; OVE, peroxalate ester derived from vitamin E; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SIRT1, sirtuin-1; SREBP1c, sterol regulatory element-binding protein-1c; TLR4, toll-like receptor 4; UDCA, ursodeoxycholic acid.

Disclosure

The authors declare that there are no conflicts of interest in this work.

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