Journal of Clinical and Translational Hepatology **2024** vol. 12(9) | 815–826
DOI: 10.14218/JCTH.2024.00019

Review Article

Mechanism of Metabolic Dysfunction-associated Steatotic Liver Disease: Important role of lipid metabolism

Xiaoxi Feng, Rutong Zhang, Zhenye Yang, Kaiguang Zhang* and Jun Xing*

Department of Digestive Disease, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China

Received: January 12, 2024 | **Revised:** August 02, 2024 | **Accepted:** August 08, 2024 | **Published online:** September 03, 2024

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease, has a high global prevalence and can progress to metabolic dysfunction-associated steatohepatitis, cirrhosis, and hepatocellular carcinoma. The pathogenesis of MASLD is primarily driven by disturbances in hepatic lipid metabolism, involving six key processes: increased hepatic fatty acid uptake, enhanced fatty acid synthesis, reduced oxidative degradation of fatty acids, increased cholesterol uptake, elevated cholesterol synthesis, and increased bile acid synthesis. Consequently, maintaining hepatic lipid metabolic homeostasis is essential for effective MASLD management. Numerous novel molecules and Chinese proprietary medicines have demonstrated promising therapeutic potential in treating MASLD, primarily by inhibiting lipid synthesis and promoting lipid oxidation. In this review, we summarized recent research on MASLD, elucidated the molecular mechanisms by which lipid metabolism disorders contribute to MASLD pathogenesis, and discussed various lipid metabolism-targeted therapeutic approaches for MASLD.

Citation of this article: Feng X, Zhang R, Yang Z, Zhang K, Xing J. Mechanism of Metabolic Dysfunction-associated Steatotic Liver Disease: Important role of lipid metabolism. J Clin Transl Hepatol 2024;12(9):815–826. doi: 10.14218/JCTH.2024.00019.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes that is not attributable to alcohol or other known liver-damaging factors. In 2023, non-alcoholic fatty liver disease was renamed MASLD following a Delphi consensus process. This renaming emphasizes the importance of metabolism in the disease and provides a more precise description. Consequently, we use the term MASLD instead of non-alcoholic fatty liver disease. MASLD is an acquired metabolic stress-associated liver injury closely related to insulin resistance and genetic susceptibility. It is one of the most common chronic diseases globally and a significant cause of liver injury in adults. The global prevalence of MASLD is approximately 29.8%.[1] According to the National Health and Nutrition Examination Survey III, the prevalence of MASLD in the United States is 18.8%, rising to 28% in the overweight population.[2] By 2018, the prevalence of MASLD in China had reached 32.9%, with the total population of MASLD in China expected to increase to 314.58 million people by 2030.[3]

The development of MASLD is closely linked to genetic alterations and environmental influences. The risk factors can be divided into genetic, epigenetic, and environmental factors.[4] Genetic factors include mutations in genes such as I148M PNPLA3, TM6SF2, MBOAT7, and GCKR, which increase susceptibility to MASLD.[5] Epigenetic factors include DNA methylation, chromatin remodeling, and non-coding RNAs. For instance, the M6A "writer" protein methyltransferase-like 3 ameliorates MASLD *via* RNA methylation.[6] Additionally, replication protein A1 can maintain lipid metabolism homeostasis and thus ameliorate MASLD by regulating chromatin structure.[7] Many non-coding RNAs involved in the regulation of lipid metabolism, such as miR-34a, miR-122, and miR-21, play a role in the development of MASLD.[8] Furthermore, environmental factors play a critical role in the progression of MASLD. These include dietary habits, exercise status, and socioeconomic factors. Unhealthy dietary habits, such as high sugar and fat consumption,[9] sedentary lifestyles, and infrequent exercise,[10,11] increase susceptibility to MASLD.

MASLD can be classified as simple steatosis or metabolic dysfunction-associated steatohepatitis (MASH). MASH is characterized by pathological histological lobular inflammation and ballooning of hepatocytes attributable to MASLD. Prolonged liver injury can lead to cirrhosis and hepatocellular carcinoma (HCC). A common clinical method to diagnose MASLD is the detection of hepatic fat density on MRI.[12] Additionally, plasma cytokeratin 18, a marker of hepatocyte apoptosis, has been widely used to assess MASLD.[13] In recent years, mutations in the PNPLA3 and TM6SF2 genes have been shown to correlate with the severity of MASLD, highlighting their potential as new diagnostic markers. Furthermore, autophagy-related markers, oxidative stress-related markers, inflammatory factors, and liver fibrosis-related markers can also be used to assess the progression of MASLD.

Keywords: MASLD; Lipid metabolism; Cholesterol metabolism; Lipogenesis; Lipolysis; lipid metabolism-targeted drugs; Chinese proprietary medicine.
***Correspondence to:** Jun Xing and Kaiguang Zhang, Department of Digestive Disease, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, 17 Lujiang Road, Luyang District, Hefei, Anhui 230001, China. ORCID: https://orcid.org/0000-0002-2771-6725 (JX) and https://orcid.org/0000-0001-9462-6335 (KZ). E-mail: xingjunjoy@hotmail.com (JX) and zhangkaiguang@ustc.edu.cn (KZ).

Many treatments have been developed for MASLD. First, dietary control and appropriate exercise habits can significantly alleviate MASLD. Second, glucagon-like peptide-1 (GLP-1) agonists, sterol-regulatory element binding protein (SREBP) inhibitors, acetyl-CoA carboxylase (ACC) inhibitors, fatty acid synthase (FASN) inhibitors, stearoyl coenzyme A desaturase (SCD) inhibitors, farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor (PPAR) agonists, and certain natural compounds are considered promising treatments. In recent years, there has been tremendous growth in research focused on treating MASLD by modulating lipid metabolism, with an increasing number of drugs in clinical development. However, the treatment of MASLD remains challenging due to population selection issues and the side effects of current drugs. Given the crucial role of lipid metabolism in MASLD, exploring new drugs and targets for lipid metabolism modulation has become a popular direction for treatment research.

Lipid metabolism

Lipids serve as crucial energy sources in the body, and various molecules involved in lipid metabolism play integral roles in different cellular functions. The development of MASLD is closely related to lipid metabolism, particularly the metabolism of triglycerides and cholesterol. Triglycerides are synthesized from fatty acids. In this review, we primarily focus on fatty acid and cholesterol metabolism. The maintenance of hepatic lipid metabolic homeostasis involves three aspects: uptake, synthesis, and catabolism. It is widely believed that an increase in fatty acid uptake and synthesis or a decrease in lipid degradation leads to the development of MASLD. Therefore, researchers have increasingly focused on these aspects, and various viewpoints have been proposed.

Fatty acid metabolism

Fatty acid intake

The hepatic uptake of fatty acids depends on fatty acid transport carriers, including fatty acid transport proteins (FATPs), cluster of differentiation 36 (CD36), and hepatic caveolin-1 (CAV-1).

FATPs: Six FATP isoforms have been identified, with FATP2 and FATP5 primarily found in the liver.[14] These transport proteins play crucial roles in the development of MASLD. Down-regulation of FATP2 in mice reduces fatty acid uptake and ameliorates hepatic steatosis induced by a high-fat diet.[15] Deletion of FATP2 in the mouse liver alters the metabolic landscape by increasing the expression of PPARα-regulated genes.[16] Knockdown of FATP5 leads to reduced hepatic fatty acid uptake, which in turn decreases hepatic lipid accumulation.[17] However, decreased hepatic FATP5 expression is associated with the histological progression of MASLD, which might be related to the reduction of hepatic lipid content as MASH advances to cirrhosis.[18] Thus, FATP5 might have a dual role in the development of MASLD.

CD36: Experiments have confirmed the involvement of CD36 in hepatic fatty acid uptake and lipid accumulation.[19] CD36 palmitoylation is an important factor in the pathogenesis of MASLD. *In vitro* and *in vivo* studies have demonstrated that inhibiting CD36 palmitoylation can ameliorate fatty acid metabolism disorders and reduce inflammatory reactions.[20] Inhibition of CD36 palmitoylation also attenuates MASLD by promoting CD36 localization to hepatocyte mitochondria.[21] The palmitoyltransferases DHHC4 and DHHC5 promote fatty acid uptake by targeting CD36.[22] Several upstream factors regulating CD36 are also involved in MASLD. Demethylation of the PPARγ DNA promoter increases CD36 expression, leading to excessive lipid accumulation.[23] Hepatic Dickkopf-1 enhances fatty acid uptake through the ERK–PPARγ–CD36 axis.[24] Deletion of methyltransferase-like 3 in hepatocytes increases CD36 expression and hepatic free fatty acid uptake, promoting MASH development. Hypoxia-inducible factor 1α interacts with the CD36 promoter to increase CD36 expression and enhance fatty acid uptake.[25] Additionally, non-coding RNAs such as miR-96-5p,[26] miR-100,[27] miR-26a,[28] and miR-195/miR4668[29] regulate CD36 expression and affect the development of MASLD.

CAV-1: The role of CAV-1 in the development of MASLD remains controversial due to its role in mediating lipid endocytosis. Although some studies have detected increased CAV-1 expression in the liver tissue of mice with MASLD-fed high-fat diets, others have found a significant reduction in its expression in mice with MASLD.[30] Knockdown of CAV-1 in LO2 and AML12 cells resulted in increased steatosis.[31] CAV-1 upregulation has been found to attenuate lipid accumulation and promote autophagy in mice with MASLD.[32] Interestingly, hepatocyte-specific CAV-1 knockdown significantly altered the gene profile in the development of MASLD without affecting hepatic steatosis and fibrosis.[33]

De novo fatty acid synthesis

De novo fatty acid synthesis is a process by which the body converts carbon from carbohydrates, such as glucose, and amino acids, including glutamine, into fatty acids. The raw material for *de novo* fatty acid synthesis is acetyl-CoA, which is derived from two sources. First, acetyl-CoA in mitochondria is condensed with oxaloacetate, catalyzed by citrate synthase, to form citric acid, which is then transported to the cytosol by tricarboxylic acid transport proteins in the mitochondrial membrane. Citric acid is subsequently modified by ATP citrate lyase (ACLY) to regenerate acetyl-CoA, which is used for fatty acid synthesis. This process is called the citrate shuttle. Second, acetic acid is linked to coenzyme A to synthesize acetyl-CoA, providing additional raw material for fatty acid synthesis, catalyzed by acetyl-CoA synthetase (ACSS). The generated acetyl-CoA is initially converted to malonyl coenzyme A by ACC, the key rate-limiting step. Malonyl coenzyme A is then converted to palmitic acid *via* FASN. Saturated palmitic acid (FA16:0) can undergo C-chain extension and desaturation by SCD to produce other fatty acid species. These fatty acids can be used to generate more complex lipids. The key enzymes involved in *de novo* fatty acid synthesis play important roles in the development of MASLD (Fig. 1).

SREBPs play critical roles in the development of MASLD by transcriptionally regulating key genes involved in hepatic lipid metabolism. SREBPs are divided into SREBP1 and SREBP2. SREBP1 has two transcripts, SREBP1a and SREBP1c, with SREBP1c being more widely expressed. SREBP1a is expressed in the intestinal epithelium, heart, and macrophages, while SREBP2 is primarily expressed in hepatic and adipose tissue. SREBPs can form trimers with SREBP cleavage-activating protein (SCAP) and INSIG, anchoring the protein in the endoplasmic reticulum (ER). The C-terminal region of SCAP interacts with the C-terminal structural domain of the ER, while the N-terminal region of SCAP contains a sterol-sensing domain sensitive to cholesterol levels. When cholesterol levels are high, SCAP binds with cholesterol and INSIG, resulting in the retention of the entire complex in the ER. Conversely, when cholesterol levels decrease, SCAP does not interact with INSIG, allowing the SREBP–SCAP complex to be internalized into COPII-containing vesicles, which are

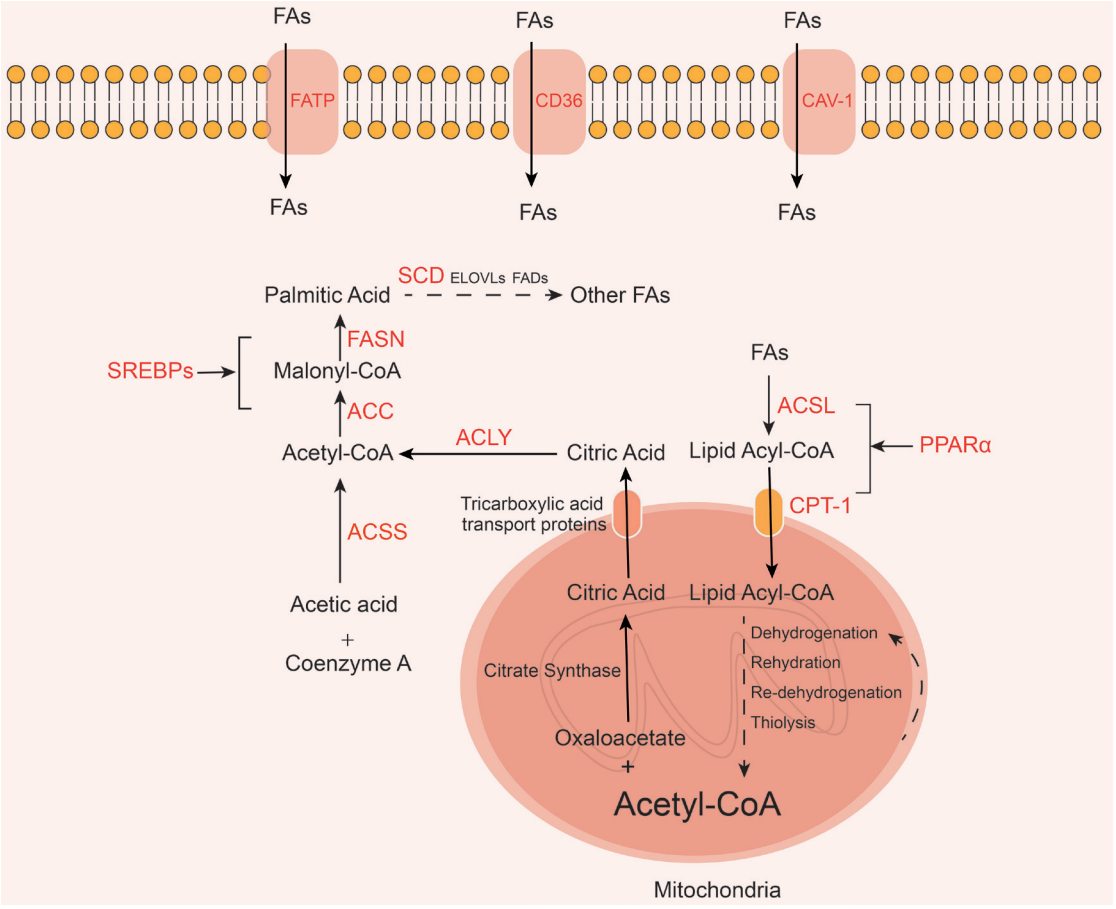

Fig. 1. Fatty acid metabolism. Fatty acid uptake by the liver depends on fatty acid transport carriers, including FATP, CD36, and CAV-1. The raw material for *de novo* fatty acid synthesis is acetyl-CoA, which can be obtained via the citrate shuttle pathway or from acetic acid. ACC and FASN catalyze the conversion of acetyl-CoA into saturated palmitic acid, which can be further modified into other fatty acids by enzymes such as SCD. *De novo* fatty acid synthesis is promoted by SREBPs. Conversely, the β-oxidation of fatty acids occurs in the mitochondria. Fatty acids are converted into fatty acyl-CoA by ACSL and transported via CPT-1 before being oxidized to acetyl-CoA. Fatty acid β-oxidation is promoted by PPARα. FAs, fatty acids; FASN, fatty acid synthase; SREBP, sterol-regulatory element binding protein; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ACSS, acetyl-CoA synthetase; ACSL, acyl-CoA synthetase; PPAR, peroxisome proliferator-activated receptor; CPT-1, carnitine palmitoyltransferase-1.

transported to the Golgi apparatus. Within the Golgi, SREBPs are sequentially cleaved by site-1 protease and site-2 protease, releasing their N-terminal bHLH structural domain into the cytoplasm, where it acts as a transcription factor. The bHLH structural domain migrates to the nucleus, dimerizes, and forms a complex with transcriptional co-activators, activating the transcription of genes with SRE motifs. SREBP1 mainly regulates fatty acid synthesis and LDLR expression, while SREBP2 primarily regulates the expression of cholesterol biosynthetic genes.

ACLY and ACSS: Inhibiting ACLY can reduce hepatic lipid accumulation by suppressing *de novo* fatty acid synthesis. Recent research has clarified the involvement of ACLY in MASLD. In steatotic cells, ACLY mRNA is efficiently translated in a cap-independent manner, promoting adipogenesis.[34] The sirtuin 2–ACLY axis is also involved in MASLD progression, with sirtuin 2 inhibiting ACLY and lipid accumulation.[35] Additionally, ACLY is degraded by HMG-CoA reductase degradation protein *via* ubiquitination, thereby attenuating MASLD.[36] ACSS is involved in the synthesis of acetyl-CoA, which promotes hepatic steatosis. Silencing ACSS2 can effectively inhibit the conversion of fructose to acetyl-CoA and fatty acids in mice.[37]

ACC: ACC, a key enzyme in *de novo* fatty acid synthesis, plays a significant role in MASLD development. Liver-specific ACC1 knockdown reduces hepatic lipid accumulation and impairs hepatocyte *de novo* fatty acid synthesis in mice.[38] AMPK activates the phosphorylation of ACC1 (Ser79Ala) and ACC2 (Ser212Ala), inhibiting the enzymatic activity of ACC and thereby suppressing lipid synthesis. Mutations at these sites are associated with increased *de novo* fatty acid synthesis and steatosis in the liver.[39]

FASN and SCD: FASN and SCD are markers of lipid synthesis and are both upregulated in MASLD. FASN regulation plays an important role in MASLD. Sorting nexin 8 can prevent MASLD by promoting FASN degradation, making the sorting nexin 8–FASN axis a promising target for MASLD prevention and treatment.[40] miR-103 can also inhibit hepatic steatosis by targeting FASN and SCD1, which can attenuate MASLD.[41] Slug binds to the FSAN promoter, while Slug-associated LSD1 catalyzes H3K9 demethylation, stimulating FASN expression and lipogenesis.[42] Furthermore, in MASLD, the levels of mitochondrial pyruvate carrier 1 are positively correlated with hepatic lipid deposition, and mitochondrial pyruvate carrier 1 knockdown affects FASN lactylation at K673, ultimately inhibiting FASN activity.[43]

SREBP1: SREBP1c induces the expression of ACC, FASN, and SCD, promoting hepatic fatty acid and triglyceride synthesis. Increased SREBP1 expression is observed in patients with MASLD, and SREBP1c overexpression in mice increases hepatic triglyceride levels.[44] However, exercise and strength training can reduce hepatic lipid accumulation by downregulating SREBP1.[45,46] Activated AMPK phosphorylates SREBPs, reducing their activity and inhibiting hepatic lipid accumulation. VEGFB,[47] MD2,[48] and protectin DX[49] are involved in MASLD development through the AMPK–SREBP1 pathway. mTOR promotes the maturation and nucleation of SREBP1, enhancing lipid synthesis.[50] Pancreatic progenitor cell differentiation and proliferation factor reduces hepatic steatosis by inhibiting mTOR/SPRBP1.[51] CD36 promotes *de novo* lipogenesis through INSIG2-dependent SREBP1 hydrolytic processing.[52] Additionally, non-coding RNAs including miR-23a/b-3p,[53] miR-33-5p,[54] and miR-130b-5p[55] regulate SREBP1 expression. ZBTB7A,[56] ceramide synthase,[57] and dihydroxytryptamine[58] are believed to upregulate SREBP1, promoting lipid synthesis. Interestingly, although SREBP1a does not contribute to hepatic lipogenesis, its absence in hepatocytes or macrophages exacerbates methionine- and choline-deficient diet-induced MASLD.[59]

SREBP2: The high-fat, choline-deficient, amino acid-defined diet model is a newly established mouse model of MASH that activates the SREBP2/SCD2 gene and drives liver fibrosis through high-fat feeding.[60] The expression of SCD, FASN, and SREBP2 is increased in rats fed a Western diet.[61] Moreover, SREBP2 is regulated by the AMPK signaling pathway, and increased expression of SREBP2 alleviates autophagic dysfunction in MASLD.[62]

Fatty acid β-oxidation

Fatty acid oxidation refers to the process by which fatty acids are degraded in the presence of oxygen to release energy for various biological processes. The most common pathway is the β-oxidation of fatty acids. β-oxidation of long-chain fatty acids occurs in the mitochondria, whereas very-long-chain fatty acids are oxidized in peroxisomes. Mitochondrial β-oxidation consists of three steps. First, fatty acids are activated to fatty acyl-CoA, a reaction catalyzed by acyl-CoA synthetase (ACSL). Second, while the enzyme system catalyzing fatty acid β-oxidation is located in the mitochondrial matrix, long-chain fatty acyl-CoA requires a carrier, namely carnitine palmitoyltransferase-1 (CPT-1), to be transported through the inner mitochondrial membrane. Finally, the β-oxidation of fatty acyl-CoA in the mitochondrial matrix proceeds through a four-step reaction involving dehydrogenation, hydration, re-dehydrogenation, and thiolysis, ultimately producing one molecule of acetyl-CoA and a new molecule of fatty acyl-CoA with two fewer carbons. This cycle repeats several times to gradually produce more acetyl-CoA. Peroxisomal β-oxidation is similar to mitochondrial β-oxidation, but the first step is catalyzed by lipid acyl-CoA oxidase (Fig. 1).

The PPAR system, particularly PPARα, plays an important role in the regulation of lipid metabolism. Activated PPARs form heterodimers with the retinoid X receptor and bind to peroxisome proliferator-responsive elements upstream of certain genes to activate enzymes related to lipid metabolism. PPARα has various roles in lipid metabolism, including promoting fatty acid β-oxidation and inhibiting MASLD development.

ACSL: TANK-binding kinase 1 acts as a scaffolding protein to localize ACSL1 to mitochondria and promote fatty acid oxidation.[63] Although ACSL4 is weakly expressed in the liver, it is upregulated in patients with MASLD, which contradicts the conventional belief that ACSL4 promotes fatty acid β-oxidation and inhibits MASLD.[64] This might be attributable to ACSL4's ability to promote inflammation[65] and its involvement in ferroptosis.[66] Additionally, P115 interacts with ACSL4 and degrades it. P115 is significantly upregulated in the livers of high-fat diet-fed mice, resulting in the downregulation of ACSL4 protein.[67] ACSL5 knockdown in mice increases energy expenditure and insulin sensitivity and delays fat absorption.[68]

CPT-1: Exercise can lead to CPT-1 downregulation, thereby reducing the disruption of lipid metabolism in MASLD.[69,70]

PPARα: Metabolomic and lipidomic screening revealed that PPARα plays an important role in the progression of MASH to HCC.[71] In a mouse model, obese female offspring fed a high-fat diet exhibited impaired hepatic PPARα activation.[72] Moreover, PPARα is sex-selective, making male mice more susceptible to MASLD.[73] Mechanistically, PPARα can reduce hepatic steatosis by rebuilding the intestinal barrier and regulating the distribution of the intestinal flora.[74] Intestinal PPARα in mice with MASLD can promote MASH progression by regulating fatty acid uptake.[75] Several molecules can also affect MASLD by influencing PPARα. For example, the anti-adipogenic factor coenzyme Q10 regulates MASLD by upregulating PPARα and CPT-1.[76] Programmed cell death 4,[77] obesity-associated protein,[78] and mothers against decapentaplegic homolog family member 4[79] promote hepatocyte lipid deposition by inhibiting PPARα-mediated fatty acid oxidation.

Cholesterol metabolism

Cholesterol uptake

The uptake of dietary cholesterol by intestinal epithelial cells is facilitated by Niemann–Pick type C1-like 1 (NPC1L1). The accumulated cholesterol is then esterified by cholesterol acyltransferases, also known as sterol O-acyltransferases, for hepatic uptake.[80]

NPC1L1: Expression of the human NPC1L1 gene in the mouse liver exacerbates high-fat diet-induced steatosis.[81,82]

Cholesterol synthesis

Cholesterol synthesis originates from acetyl-CoA through a complex process involving nearly 30 enzymatic steps. This process can be roughly divided into three stages: synthesis of isopentenyl pyrophosphate from acetyl-CoA, synthesis of squalene, and conversion of squalene to cholesterol (Fig. 2). The key enzymes involved in this process are mammalian 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGCR/HMFR) and squalene monooxygenase (SM/SQLE). HMGCR catalyzes the conversion of HMG-CoA to mevalonate in the first phase, while squalene is oxidized by SM in the third stage to produce 2,3-oxidized squalene, a precursor of cholesterol and sterols.

HMGCR: Dysregulated cholesterol metabolism can exacerbate MASLD. The development of MASLD is associated with increased HMGCR expression and reduced HMGCR phosphorylation.[83] A genomic analysis of a high-fat-fed mouse model of MASLD showed a 2.06-fold upregulation of HMGCR.[84] HMGCR is regulated by Dicer1/miR-29, indicating that the Dicer1–miR-29–HMGCR axis is involved in free cholesterol accumulation in the livers of mice with MASLD.[85]

SM/SQLE: SM/SQLE is implicated in the progression of MASLD to HCC. It is the most significantly overexpressed metabolic gene in patients with MASLD and HCC, and its expression accelerates the development of HCC induced by a high-fat, high-cholesterol diet in mice.[86–88] The underlying mechanisms include the promotion of MASH and HCC development through the induction of cholesterol biosynthesis, the SQLE–CA3 axis-mediated lipogenesis,[88] and P53-mediat-

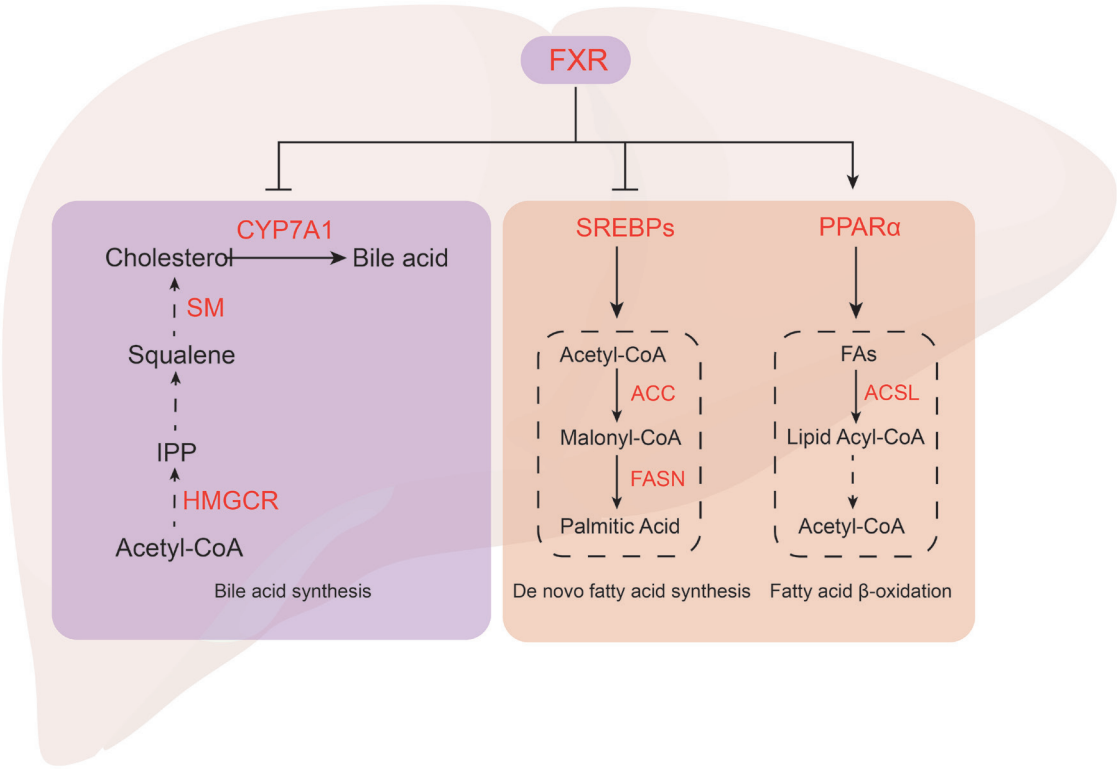

Fig. 2. Cholesterol metabolism. The process of cholesterol synthesis is complex and can be roughly divided into three stages: synthesis of IPP from acetyl-CoA, synthesis of squalene, and conversion of squalene to cholesterol. HMGCR and SM are the key enzymes in cholesterol synthesis. The primary route of cholesterol production is bile acid synthesis catalyzed by CTP7A1. FXR is an important regulator of cholesterol metabolism; Its activation inhibits CTP7A1, leading to the inhibition of bile acid synthesis. FXR, farnesoid X receptor; CYP7A1, cholesterol 7α-hydroxylase; SM, squalene monooxygenase; HMGCR, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase; IPP, isopentenyl pyrophosphate; SREBP, sterol-regulatory element binding protein; PPAR, peroxisome proliferator-activated receptor; FAs, fatty acids; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ACLY, ATP citrate lyase.

ed transcriptional regulation of SQLE to suppress cholesterol synthesis and tumor growth.[89]

Bile acid synthesis

Bile-acid synthesis is the primary pathway for cholesterol catabolism, and the key enzyme in this process is cholesterol 7α-hydroxylase (CYP7A1). Patients with MASLD often exhibit disordered bile acid metabolism. Hepatic bile acid synthesis is mainly regulated by FXR, and FXR activation inhibits *de novo* bile acid synthesis (Fig. 2).

CYP7A1: Bioinformatic analysis has revealed that CYP7A1 is involved in the development of MASLD, MASH, and HCC.[90,91] In MASLD, CYP7A1 mRNA expression is increased.[92] However, CYP7A1 mRNA levels decline with the progression of MASH-associated liver fibrosis.[93]

FXR: FXR plays a crucial role in the development of MASLD. On one hand, FXR activation promotes the production of short heterodimer partner, which downregulates the rate-limiting enzyme CYP7A1, ultimately inhibiting bile acid synthesis. Studies have demonstrated that FXR activation can prevent MASLD by reducing lipid uptake in a bile acid-dependent manner.[94] On the other hand, FXR activation decreases hepatic lipid accumulation by inhibiting triglyceride synthesis, achieved through the induction of short heterodimer partner expression and the downregulation of SREBP1 and FASN.

FXR deficiency in mice results in hepatic steatosis, lipid droplet accumulation in hepatocytes, disturbed glucose metabolism, and elevated blood lipid levels.[95] FXR functions as a nuclear transcription factor that regulates glucose and lipid metabolic homeostasis through pyruvate dehydrogenase kinase 4.[95] Furthermore, FXR sulfation, a post-translational modification influenced by endogenous hepatic cystathionine γ lyase/hydrogen sulfide, promotes FXR activity, thereby improving MASLD.[96] MiR-552-3p ameliorates hepatic lipid metabolism disorders by regulating the transcriptional activity of FXR.[97]

Drugs that treat MASLD by regulating lipid metabolism

The FDA has approved Rezdiffra (resmetirom), a thyroid hormone receptor β-1 agonist, as the first treatment for MASH. Resmetirom selectively activates thyroid hormone receptor β-1, resulting in a reduction of free thyroxine (T4) levels by approximately 16–19%. Notably, it does not influence the levels of thyrotropin or free triiodothyronine.[98] Resmetirom also significantly reduces cholesterol and triglyceride levels and enhances fatty acid oxidation, demonstrating substantial potential for the treatment of MASLD. Meanwhile, there has been increasing interest in developing new drugs for MASLD treatment. In this section, we review recent articles exploring molecular drugs and Chinese proprietary medicines (CPMs) that inhibit MASLD. Most of these drugs/CPMs work by inhibiting fatty acid uptake and synthesis while promoting fatty acid oxidation. Similarly, the inhibition of cholesterol uptake and synthesis, as well as bile acid synthesis, can also be used to improve MASLD. CPMs have shown great potential in MASLD treatment. The modification of inhibitors and activators targeting key regulatory genes, such as GLP-1, SREBP, ACC,

Table 1. Clinical trials of GLP-1 agonists

Drugs	Conclusions	Phase	References
Dulaglutide	Improvement in patients with type 2 diabetes and MASLD	\	114
Efinopegdutide	Improvement of MASH and MASLD	Phase II	107
Exenatide	Improvement in patients with type 2 diabetes and MASLD	\	115
Liraglutide	Improvement of MASH and MASLD	Phase II/III	116–118
	Improvement in patients with type 2 diabetes and MASLD	Phase IV	119
	No improvement in patients with type 2 diabetes and MASLD	Phase IV	120
Semaglutide	Improvement of MASH but not liver fibrosis	Phase I/II	121,122
	Improvement of health-related quality of life in patients with MASH and liver fibrosis	Phase II	103

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

FASN, SCD1, PPARα, and FXR, has gained increasing attention in recent years. Improving the therapeutic efficacy of drugs and reducing their potential side effects have become major research goals in this field.

GLP-1 agonists: GLP-1 regulates insulin and glucagon secretion and modulates intestinal motility, and its agonists have been considered promising therapeutics in recent years for reducing the risk of MASLD and its associated mortality.[99] GLP-1 agonists, such as semaglutide and liraglutide, effectively treat MASLD by reducing visceral and hepatic fat content.[100–102] Semaglutide improves the health-related quality of life in patients with MASLD,[103] with daily dosing proving more effective.[104] Mechanistically, semaglutide induces modifications in the gut microbiota and ameliorates MASLD.[105] Dual GLP-1/GLP-2 receptor agonists,[106] as well as dual GLP-1 receptor/glucagon receptor agonists like ALT-801, NN1177, and efinopegdutide,[107–109] have shown good therapeutic efficacy in MASLD. The combination of GLP-1 activators with other drugs is also the focus of an increasing number of studies. Combined treatment with semaglutide and the FXR agonist cilofexor, the ACC inhibitor firsocostat, and the ACLY inhibitor has demonstrated better therapeutic efficacy than monotherapy.[110,111] Novel GLP-1 activators, such as cinchonine and exendin-4, are also under development.[112,113]

The findings of clinical trials on GLP-1 agonists are listed in Table 1.[103,107,114-122] "\" indicates that no phasing information for the clinical trial could be found.

SREBP inhibitors: Betulin is a specific inhibitor of SREBP maturation. It inhibits the transport of SREBP to the Golgi via SCAP,[52] thereby inhibiting the processes of fatty acid and cholesterol synthesis. Betulin has shown potential in the treatment of MASLD.[123–126] PF-429242 is a specific inhibitor of the proteasome site-1 protease, which inhibits the cleavage and release of the SREBP precursor protein. It is also considered to have potential in MASLD control.[127]

ACC inhibitors: ACC inhibition reduces lipid accumulation in hepatocytes and inhibits pro-fibrosis activity in liver stem cells, suggesting that small-molecule inhibitors of ACC can attenuate liver fibrosis by reducing hepatocyte lipotoxicity and preventing liver stem cell activation. These findings provide a mechanistic basis for the treatment of patients with MASH and advanced liver fibrosis.[128] However, while ACC inhibitors have been found to reverse MASLD, they may also promote hypertriglyceridemia.[129] GS-0976 (Firsocostat) has shown promise in alleviating MASH in Phase II clinical trials.[130,131] However, firsocostat can cause hyperlipidemia, which can be alleviated by fenofibrate.[132,133] The ACC inhibitor ND-654, which mimics the action of ACC phosphorylation, inhibits hepatic de novo fatty acid synthesis.[39] In mouse models, treatment with selective ACC1 inhibitors significantly ameliorated hepatic steatosis and liver fibrosis, supporting their use as new therapies for MASLD/MASH.[134] Additionally, both the dual ACC1/ACC2 inhibitor PF-05221304[135] and the novel ACC1/ACC2 inhibitor WZ66[136] have been shown to alleviate MASH in mouse models.

FASN or SCD1 inhibitors: In patients with MASLD, FASN inhibitors such as TVB-2640 (Denifanstat)[137] and FT-4101[138] reduce hepatic *de novo* lipogenesis and steatosis. FASstatin may be useful in treating MASLD by targeting and degrading FASN.[139] Both the SCD1 inhibitor CAY10566 and a novel SCD1 inhibitor have inhibited hepatic lipid accumulation in mice, suggesting that SCD1 may be an effective target for the treatment of MASLD.[140,141]

PPAR agonists: Fibrates are clinically available PPARα agonists for MASLD treatment. The literature indicates that PPARα-mediated peroxisome adaptation is crucial for fenofibrate-mediated improvements in MASLD.[142] Combining PPARα with other dual-receptor agonists has shown great potential in MASLD treatment. The novel PPARα/γ agonists G4 and G5 effectively inhibited hepatic steatosis while avoiding the side effects of pioglitazone.[143] The PPARα/γ agonist aleglitazar significantly reduced hepatic steatosis and fibrosis.[144] The PPARα/δ agonist compound H11, which exhibits effective and balanced PPARα/δ agonist activity, has shown promise in MASH treatment.[145] Additionally, ZLY18, a quadruple free fatty acid receptor 1 and PPARα/γ/δ agonist, might be a highly effective anti-MASLD drug.[146]

The findings of the clinical trials on PPAR agonists are listed in Table 2.[144,147–150] "\" indicates that no phasing information for the clinical trial could be found.

FXR agonists: Although traditional FXR agonists have been used in the clinic, their side effects have limited their application to some extent. The traditional FXR agonist, obeticholic acid, has been abandoned for MASLD treatment. New FXR agonists, such as nidufexor (LMB763),[151] cilofexor,[152] and EDP-305,[153] have entered clinical trials for the treatment of MASLD or MASH. In recent years, the development of FXR agonists with stronger activity and fewer side effects has received increasing attention. For instance, 1-adamantylcarbonyl-4-phenylpiperazine is an FXR agonist, and its derivative compound 10A was found to be more effective in ameliorating hyperlipidemia, hepatic steatosis, and insulin resistance.[154] Additionally, structural optimization of non-bile acid FXR agonists led to the development of compound 42 as an FXR agonist with high efficiency and selectivity for alleviating MASH.[155] MET409, an FXR agonist with a unique chemical structure, significantly suppressed hepatic fat content without causing significant or severe

Table 2. Clinical trials of PPAR agonists

Drugs	Targets	Conclusions	Phase	References
Aleglitazar	PPARα/γ	Improvement of MASLD and liver fibrosis	\	144
Elafibranor	PPARα/δ	Improvement of MASH	Phase II	147
Lanifibranor	Pan-PPAR	Improvement of MASH and liver fibrosis	Phase III	148
Saroglitazar	PPARα/γ	Improvement of MASH and MASLD	Phase II	149,150

PPAR, peroxisome proliferator-activated receptor; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

Table 3. Clinical trials of FXR agonists

Drugs	Conclusions	Phase	References
Cilofexor	Improvement of MASH	Phase II	152,159
MET409	Improvement of MASH	Phase I	156
Obeticholic acid	Improvement in patients with type 2 diabetes and MASH	Phase II	160
Tropifexor	Improvement of MASH	Phase II	161
Vonafexor	Improvement of liver and kidney function in patients with MASH and liver fibrosis	Phase II	162

MASH, metabolic dysfunction-associated steatohepatitis.

side effects in patients with MASH.[156] Moreover, tissue-selective FXR agonists have been studied. For example, (E)-3-(3-((2-cyano-4′-dimethylaminobiphenyl-4-ylmethyl) cyclohexanecarbonylamino)-5-fluorophenyl) acrylic acid methyl ester is an entero-selective FXR partial agonist that significantly reduced the extent of liver fibrosis and decreased the levels of fibrosis markers and serum AST.[157] BMS-986339 exhibited potent FXR activation and anti-fibrotic efficacy despite its tissue selectivity, reducing the activation of certain genes in the liver.[158]

The findings of the clinical trials on FXR agonists are listed in Table 3.[152,156,159–162]

Natural compounds: Many natural compounds, including CPMs, are considered promising in the treatment of MASLD. Recent studies on natural compounds and their molecular mechanisms are listed in Table 4.[163–187] However, the use of many CPMs for the treatment of MASLD still needs to be tested in rigorous clinical trials. Nevertheless, CPMs remain

Table 4. Drugs that treat MASLD by regulating lipid metabolism

Drugs	Mechanism	References
Andrographolide	Inhibits FATP2	163
Baicalein	Inhibits fatty acid synthesis; promotes fatty acid oxidation; activates AMPK; inhibits SREBP1	164,165
Berberine/oxyberberine	Inhibits fatty acid synthesis; promotes fatty acid oxidation; regulates SIRT3/AMPK/ACC; downregulates SIRT1/FoxO1/SREBP2; inhibits cholesterol synthesis	166–170
Curcumin	Inhibits CD36, SLC13A5, and ACLY; regulates CYP2E1, SREBP1c, and PPARα	171–173
Extract of *Dillenia indica* L.	Regulates SIRT1/pLKB1/AMPK, HMGCR, and PPARα signaling pathways	174
Extract of *Liriope platyphylla*	Inhibits fatty acid uptake and synthesis	175
Extract of root from *Arctium lappa* L.	Activates AMPK/ACC/CPT1	176
Jian Pi Qing Gan Yin decoction	Activates AMPK/PPARα; inhibits LXRα/SREBP1/NF-κB	177
Kangtaizhi Granule	Regulates PPARγ, SREBP1, pAKT, FAS, and SIRT1	178
Limonin	AMPK agonist; downregulates FASN and SREBP1	179,180
Naringenin	Activates the CaMKKβ/AMPK/ACC pathway	181
Paeoniflorin	Activates LKB1/AMPK and PPARα	182,183
Puerarin	Inhibits fatty acid uptake and synthesis; promotes fatty acid oxidation; inhibits FASN, SREBP1c; activates AMPK	184,185
Saikosaponin	Inhibits SREBP1c; activates PPARα; inhibits FASN; promotes ACOX1 and CPT1	186,187

FATP, fatty acid transport protein; AMPK, AMP-activated protein kinase; SREBP, sterol regulatory element-binding protein; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; PPAR, peroxisome proliferator-activated receptor; HMGCR, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase; CPT1, carnitine palmitoyltransferase-1; FASN, fatty acid synthase.

a valuable resource in modern medicine and have significant potential for the future treatment of MASLD.

Discussion

MASLD represents a continuum of liver diseases that includes simple steatosis and metabolic dysfunction-associated steatohepatitis. The global prevalence of MASLD is estimated to be as high as 29.8%, making it one of the most significant diseases. Most patients with MASLD are asymptomatic and only present with incidental findings of hepatomegaly or slight-to-moderate increases in ALT and AST levels during routine physical examinations. The current primary approach for treating MASLD is reducing hepatic steatosis by regulating lipid metabolism. Dietary control and appropriate exercise can significantly improve the symptoms of MASLD. Additionally, drugs such as FXR agonists, PPARα agonists, and SREBP1 inhibitors have been explored for MASLD treatment because of their ability to regulate lipid metabolism.

The pathology of MASLD is characterized by hepatic steatosis, the development of which is mainly related to dysregulated hepatic lipid metabolism. The development of MASLD is generally attributed to six factors: increased hepatic fatty acid uptake and synthesis, decreased fat oxidation, increased cholesterol uptake and synthesis, and increased bile acid synthesis. (1) Regarding increased fatty acid uptake, FATP and CD36 are upregulated in MASLD. Although CAV-1 is involved in fat uptake, its role in MASLD remains controversial. (2) Concerning increased *de novo* lipogenesis, ACLY, ACSS, ACC, FASN, and SCD, key enzymes involved in *de novo* fatty acid synthesis, are upregulated in MASLD. Among them, SREBP1 can sense cholesterol levels and affect MASLD by transcriptionally regulating key genes involved in hepatic lipid metabolism. SREBP1 induces ACC, FASN, SCD, and other lipid synthesis genes to promote hepatic fatty acid and triglyceride synthesis. SREBP1 has been considered to have great potential as a treatment target for MASLD. (3) Inhibition of fatty acid oxidation can also lead to MASLD. Inhibition of ACSL and CPT-1, key enzymes in lipolysis, can exacerbate hepatic steatosis. Fatty acid oxidation can be regulated by PPARα, and PPARα activation promotes CPT1 expression, thereby enhancing fatty acid β-oxidation. Dysregulated cholesterol metabolism is also involved in the development of MASLD. (4) Increased cholesterol uptake can exacerbate MASLD through increased NPC1L1 expression. (5) Regarding increased cholesterol synthesis, HMGCR, a key enzyme for cholesterol synthesis, is upregulated in MASLD. SM has also been found to play an important role in the progression of MASLD to HCC. (6) Finally, increased bile acid synthesis is involved in the development of MASLD. CYP7A1, a key enzyme involved in bile acid synthesis, has elevated expression in MASLD. Hepatic bile acid synthesis is mainly regulated by FXR, and FXR activation inhibits *de novo* bile acid synthesis, thereby ameliorating MASLD.

Conclusions

Although much research has investigated the mechanisms of MASLD development, some unanswered questions remain. Peroxisomes are involved in the β-oxidation of extra-long-chain fatty acids, but little research has assessed the connection between peroxisomes and MASLD. Current models of MASLD are mainly based on oleic acid-induced cells and high-fat diet-fed mice, which do not fully capture the dynamic process of MASH fibrosis that can progress to cirrhosis and HCC. Thus, the need for novel, low-cost, and rapid MASLD models for life science research is evident. Despite numerous new drugs, including molecule drugs and CPMs, entering clinical trials in recent years, the treatment of MASLD remains ineffective given the large MASLD population. Lipid metabolism, as an important mechanism in the development of MASLD, has been the primary focus of MASLD treatment. Therefore, the exploration of new drugs and targets that regulate lipid metabolism for MASLD treatment is an area that requires in-depth research.

Funding

This work was supported by the Research Start-up Funding for the First Affiliated Hospital of USTC (RC2021012) and the Fundamental Research Funds for Central Universities (WK9110000004).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

XF and JX contributed to the writing of the first draft. RZ, ZY and KZ contributed to the correction and revision of the manuscript. All authors have approved the final version and publication of the manuscript.

References

[1] Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y, *et al*. 2019 global nafld prevalence: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2022;20(12):2809–2817.e2828. doi:10.1016/j.cgh.2021.12.002, PMID:34890795.
[2] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, *et al*. Nonalcoholic fatty liver disease in lean individuals in the united states. Medicine (Baltimore) 2012;91(6):319–327. doi:10.1097/MD.0b013e3182779d49, PMID:23117851.
[3] Zhou J, Zhou F, Wang W, Zhang XJ, Ji YX, Zhang P, *et al*. Epidemiological features of nafld from 1999 to 2018 in china. Hepatology 2020;71(5):1851–1864. doi:10.1002/hep.31150, PMID:32012320.
[4] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73–84. doi:10.1002/hep.28431, PMID:26707365.
[5] Eslam M, Valenti L, Romeo S. Genetics and epigenetics of nafld and nash: Clinical impact. J Hepatol 2018;68(2):268–279. doi:10.1016/j.jhep.2017.09.003, PMID:29122391.
[6] Qin Y, Li B, Arumugam S, Lu Q, Mankash SM, Li J, *et al*. M(6)a mrna methylation-directed myeloid cell activation controls progression of nafld and obesity. Cell Rep 2021;37(6):109968. doi:10.1016/j.celrep.2021.109968, PMID:34758326.
[7] Yin Q, Li Y, Zhou Z, Li X, Li M, Liu C, *et al*. Rpa1 controls chromatin architecture and maintains lipid metabolic homeostasis. Cell Rep 2022;40(2):111071. doi:10.1016/j.celrep.2022.111071, PMID:35830798.
[8] Hochreuter MY, Dall M, Treebak JT, Barrès R. Micrornas in non-alcoholic fatty liver disease: Progress and perspectives. Mol Metab 2022;65:101581. doi:10.1016/j.molmet.2022.101581, PMID:36028120.
[9] Leslie T, Pawloski L, Kallman-Price J, Escheik C, Hossain N, Fang Y, *et al*. Survey of health status, nutrition and geography of food selection of chronic liver disease patients. Ann Hepatol 2014;13(5):533–540. PMID:25152986.
[10] Gerber L, Otgonsuren M, Mishra A, Escheik C, Birerdinc A, Stepanova M, *et al*. Non-alcoholic fatty liver disease (nafld) is associated with low level of physical activity: A population-based study. Aliment Pharmacol Ther 2012;36(8):772–781. doi:10.1111/apt.12038, PMID:22958053.
[11] Patel AH, Peddu D, Amin S, Elsaid MI, Minacapelli CD, Chandler TM, *et al*. Nonalcoholic Fatty Liver Disease in Lean/Nonobese and Obese Individuals: A Comprehensive Review on Prevalence, Pathogenesis, Clinical Outcomes, and Treatment. J Clin Transl Hepatol 2023;11(2):502–515. doi:10.14218/JCTH.2022.00204, PMID:36643037.
[12] Wong VW, Adams LA, de Lédinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in nafld and nash - current progress and future promise. Nat Rev Gastroenterol Hepatol 2018;15(8):461–478. doi:10.1038/s41575-018-0014-9, PMID:29844588.
[13] Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, *et al*. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58(6):1930–1940. doi:10.1002/hep.26455, PMID:23696515.
[14] Koo SH. Nonalcoholic fatty liver disease: Molecular mechanisms for the hepatic steatosis. Clin Mol Hepatol 2013;19(3):210–215. doi:10.3350/cmh.2013.19.3.210, PMID:24133660.

[15] Falcon A, Doege H, Fluitt A, Tsang B, Watson N, Kay MA, *et al*. Fatp2 is a hepatic fatty acid transporter and peroxisomal very long-chain acyl-coa synthetase. Am J Physiol Endocrinol Metab 2010;299(3):E384–393. doi:10.1152/ajpendo.00226.2010, PMID:20530735.
[16] Perez VM, Gabell J, Behrens M, Wase N, DiRusso CC, Black PN. Deletion of fatty acid transport protein 2 (fatp2) in the mouse liver changes the metabolic landscape by increasing the expression of ppara-regulated genes. J Biol Chem 2020;295(17):5737–5750. doi:10.1074/jbc.RA120.012730, PMID:32188695.
[17] Doege H, Grimm D, Falcon A, Tsang B, Storm TA, Xu H, *et al*. Silencing of hepatic fatty acid transporter protein 5 in vivo reverses diet-induced non-alcoholic fatty liver disease and improves hyperglycemia. J Biol Chem 2008;283(32):22186–22192. doi:10.1074/jbc.M803510200, PMID:18524776.
[18] Enooku K, Tsutsumi T, Kondo M, Fujiwara N, Sasako T, Shibahara J, *et al*. Hepatic fatp5 expression is associated with histological progression and loss of hepatic fat in nafld patients. J Gastroenterol 2020;55(2):227–243. doi:10.1007/s00535-019-01633-2, PMID:31602526.
[19] Koonen DP, Jacobs RL, Febbraio M, Young ME, Soltys CL, Ong H, *et al*. Increased hepatic cd36 expression contributes to dyslipidemia associated with diet-induced obesity. Diabetes 2007;56(12):2863–2871. doi:10.2337/db07-0907, PMID:17728375.
[20] Zhao L, Zhang C, Luo X, Wang P, Zhou W, Zhong S, *et al*. Cd36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis. J Hepatol 2018;69(3):705–717. doi:10.1016/j.jhep.2018.04.006, PMID:29705240.
[21] Zeng S, Wu F, Chen M, Li Y, You M, Zhang Y, *et al*. Inhibition of fatty acid translocase (fat/cd36) palmitoylation enhances hepatic fatty acid β-oxidation by increasing its localization to mitochondria and interaction with long-chain acyl-coa synthetase 1. Antioxid Redox Signal 2022;36(16-18):1081–1100. doi:10.1089/ars.2021.0157, PMID:35044230.
[22] Wang J, Hao JW, Wang X, Guo H, Sun HH, Lai XY, *et al*. Dhhc4 and dhhc5 facilitate fatty acid uptake by palmitoylating and targeting cd36 to the plasma membrane. Cell Rep 2019;26(1):209–221.e205. doi:10.1016/j.celrep.2018.12.022, PMID:30605677.
[23] Hajri T, Zaiou M, Fungwe TV, Ouguerram K, Besong S. Epigenetic regulation of peroxisome proliferator-activated receptor gamma mediates high-fat diet-induced non-alcoholic fatty liver disease. Cells 2021;10(6):1355. doi:10.3390/cells10061355, PMID:34072832.
[24] Yang Z, Huang X, Zhang J, You K, Xiong Y, Fang J, *et al*. Hepatic dkk1-driven steatosis is cd36 dependent. Life Sci Alliance 2023;6(1):e202201665. doi:10.26508/lsa.202201665, PMID:36410795.
[25] Pan X, Queiroz J, Hussain MM. Nonalcoholic fatty liver disease in clock mutant mice. J Clin Invest 2020;130(8):4282–4300. doi:10.1172/jci132765, PMID:32396530.
[26] El-Derany MO, AbdelHamid SG. Upregulation of mir-96-5p by bone marrow mesenchymal stem cells and their exosomes alleviate non-alcoholic steatohepatitis: Emphasis on caspase-2 signaling inhibition. Biochem Pharmacol 2021;190:114624. doi:10.1016/j.bcp.2021.114624, PMID:34052187.
[27] Smolka C, Schlösser D, Hohnloser C, Bemtgen X, Jänich C, Schneider L, *et al*. Mir-100 overexpression attenuates high fat diet induced weight gain, liver steatosis, hypertriglyceridemia and development of metabolic syndrome in mice. Mol Med 2021;27(1):101. doi:10.1186/s10020-021-00364-6, PMID:34488621.
[28] Ding D, Ye G, Lin Y, Lu Y, Zhang H, Zhang X, *et al*. Microrna-26a-cd36 signaling pathway: Pivotal role in lipid accumulation in hepatocytes induced by pm(2.5) liposoluble extracts. Environ Pollut 2019;248:269–278. doi:10.1016/j.envpol.2019.01.112, PMID:30798028.
[29] Guo J, Fang W, Sun L, Lu Y, Dou L, Huang X, *et al*. Ultraconserved element uc.372 drives hepatic lipid accumulation by suppressing mir-195/mir4668 maturation. Nat Commun 2018;9(1):612. doi:10.1038/s41467-018-03072-8, PMID:29426937.
[30] Qiu Y, Liu S, Chen HT, Yu CH, Teng XD, Yao HT, *et al*. Upregulation of caveolin-1 and sr-b1 in mice with non-alcoholic fatty liver disease. Hepatobiliary Pancreat Dis Int 2013;12(6):630–636. doi:10.1016/s1499-3872(13)60099-5, PMID:24322749.
[31] Li M, Chen D, Huang H, Wang J, Wan X, Xu C, *et al*. Caveolin1 protects against diet induced hepatic lipid accumulation in mice. PLoS One 2017;12(6):e0178748. doi:10.1371/journal.pone.0178748, PMID:28570612.
[32] Xue W, Wang J, Jiang W, Shi C, Wang X, Huang Y, *et al*. Caveolin-1 alleviates lipid accumulation in nafld associated with promoting autophagy by inhibiting the akt/mtor pathway. Eur J Pharmacol 2020;871:172910. doi:10.1016/j.ejphar.2020.172910, PMID:31926991.
[33] Han M, Piorońska W, Wang S, Nwosu ZC, Sticht C, Wang S, *et al*. Hepatocyte caveolin-1 modulates metabolic gene profiles and functions in non-alcoholic fatty liver disease. Cell Death Dis 2020;11(2):104. doi:10.1038/s41419-020-2295-5, PMID:32029710.
[34] Siculella L, Giannotti L, Testini M, Gnoni GV, Damiano F. In steatotic cells, atp-citrate lyase mrna is efficiently translated through a cap-independent mechanism, contributing to the stimulation of de novo lipogenesis. Int J Mol Sci 2020;21(4):1206. doi:10.3390/ijms21041206, PMID:32054087.
[35] Guo L, Guo YY, Li BY, Peng WQ, Chang XX, Gao X, *et al*. Enhanced acetylation of atp-citrate lyase promotes the progression of nonalcoholic fatty liver disease. J Biol Chem 2019;294(31):11805–11816. doi:10.1074/jbc.RA119.008708, PMID:31197036.
[36] Li K, Zhang K, Wang H, Wu Y, Chen N, Chen J, *et al*. Hrd1-mediated acly ubiquitination alleviate nafld in db/db mice. Metabolism 2021;114:154349. doi:10.1016/j.metabol.2020.154349, PMID:32888949.
[37] Zhao S, Jang C, Liu J, Uehara K, Gilbert M, Izzo L, *et al*. Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature 2020;579(7800):586–591. doi:10.1038/s41586-020-2101-7, PMID:32214246.
[38] Mao J, DeMayo FJ, Li H, Abu-Elheiga L, Gu Z, Shaikenov TE, *et al*. Liver-specific deletion of acetyl-coa carboxylase 1 reduces hepatic triglyceride accumulation without affecting glucose homeostasis. Proc Natl Acad Sci U S A 2006;103(22):8552–8557. doi:10.1073/pnas.0603115103, PMID:16717184.
[39] Lally JSV, Ghoshal S, DePeralta DK, Moaven O, Wei L, Masia R, *et al*. Inhibition of acetyl-coa carboxylase by phosphorylation or the inhibitor nd-654 suppresses lipogenesis and hepatocellular carcinoma. Cell Metab 2019;29(1):174–182.e175. doi:10.1016/j.cmet.2018.08.020, PMID:30244972.
[40] Hu Y, He W, Huang Y, Xiang H, Guo J, Che Y, *et al*. Fatty acid synthase-suppressor screening identifies sorting nexin 8 as a therapeutic target for nafld. Hepatology 2021;74(5):2508–2525. doi:10.1002/hep.32045, PMID:34231239.
[41] Zhang M, Tang Y, Tang E, Lu W. Microrna-103 represses hepatic de novo lipogenesis and alleviates nafld via targeting fasn and scd1. Biochem Biophys Res Commun 2020;524(3):716–722. doi:10.1016/j.bbrc.2020.01.143, PMID:32035613.
[42] Liu Y, Lin H, Jiang L, Shang Q, Yin L, Lin JD, *et al*. Hepatic slug epigenetically promotes liver lipogenesis, fatty liver disease, and type 2 diabetes. J Clin Invest 2020;130(6):2992–3004. doi:10.1172/jci128073, PMID:32365055.
[43] Gao R, Li Y, Xu Z, Zhang F, Xu J, Hu Y, *et al*. Mitochondrial pyruvate carrier 1 regulates fatty acid synthase lactylation and mediates treatment of nonalcoholic fatty liver disease. Hepatology 2023;78(6):1800–1815. doi:10.1097/hep.0000000000000279, PMID:36651176.
[44] Shimano H, Horton JD, Shimomura I, Hammer RE, Brown MS, Goldstein JL. Isoform 1c of sterol regulatory element binding protein is less active than isoform 1a in livers of transgenic mice and in cultured cells. J Clin Invest 1997;99(5):846–854. doi:10.1172/jci119248, PMID:9062341.
[45] Bae JY. Resistance exercise regulates hepatic lipolytic factors as effective as aerobic exercise in obese mice. Int J Environ Res Public Health 2020;17(22):8307. doi:10.3390/ijerph17228307, PMID:33182720.
[46] Dos Santos GF, Veras ASC, de Freitas MC, McCabe J, Seraphim PM, Teixeira GR. Strength training reduces lipid accumulation in liver of obese wistar rats. Life Sci 2019;235:116834. doi:10.1016/j.lfs.2019.116834, PMID:31493478.
[47] Li R, Li Y, Yang X, Hu Y, Yu H, Li Y. Reducing vegfb accelerates nafld and insulin resistance in mice via inhibiting ampk signaling pathway. J Transl Med 2022;20(1):341. doi:10.1186/s12967-022-03540-2, PMID:35907871.
[48] Luo W, Ye L, Hu XT, Wang MH, Wang MX, Jin LM, *et al*. Md2 deficiency prevents high-fat diet-induced ampk suppression and lipid accumulation through regulating tbk1 in non-alcoholic fatty liver disease. Clin Transl Med 2022;12(3):e777. doi:10.1002/ctm2.777, PMID:35343085.
[49] Jung TW, Kyung EJ, Kim HC, Shin YK, Lee SH, Park ES, *et al*. Protectin dx ameliorates hepatic steatosis by suppression of endoplasmic reticulum stress via ampk-induced orp150 expression. J Pharmacol Exp Ther 2018;365(3):485–493. doi:10.1124/jpet.117.246686, PMID:29572342.
[50] Han J, Li E, Chen L, Zhang Y, Wei F, Liu J, *et al*. The creb coactivator crtc2 controls hepatic lipid metabolism by regulating srebp1. Nature 2015;524(7564):243–246. doi:10.1038/nature14557, PMID:26147081.
[51] Ma N, Wang YK, Xu S, Ni QZ, Zheng QW, Zhu B, *et al*. Ppdpf alleviates hepatic steatosis through inhibition of mtor signaling. Nat Commun 2021;12(1):3059. doi:10.1038/s41467-021-23285-8, PMID:34031390.
[52] Zeng H, Qin H, Liao M, Zheng E, Luo X, Xiao A, *et al*. Cd36 promotes de novo lipogenesis in hepatocytes through insig2-dependent srebp1 processing. Mol Metab 2022;57:101428. doi:10.1016/j.molmet.2021.101428, PMID:34974159.
[53] Li L, Zhang X, Ren H, Huang X, Shen T, Tang W, *et al*. Mir-23a/b-3p promotes hepatic lipid accumulation by regulating srebp-1c and fas. J Mol Endocrinol 2021;68(1):35–49. doi:10.1530/jme-20-0324, PMID:34723832.
[54] Pan JH, Cha H, Tang J, Lee S, Lee SH, Le B, *et al*. The role of microrna-33 as a key regulator in hepatic lipogenesis signaling and a potential serological biomarker for nafld with excessive dietary fructose consumption in c57bl/6n mice. Food Funct 2021;12(2):656–667. doi:10.1039/d0fo02286a, PMID:33404569.
[55] Liu X, Chen S, Zhang L. Downregulated microrna-130b-5p prevents lipid accumulation and insulin resistance in a murine model of nonalcoholic fatty liver disease. Am J Physiol Endocrinol Metab 2020;319(1):E34–e42. doi:10.1152/ajpendo.00528.2019, PMID:32228319.
[56] Zhou JP, Ren YD, Xu QY, Song Y, Zhou F, Chen MY, *et al*. Obesity-induced upregulation of zbtb7a promotes lipid accumulation through srebp1. Biomed Res Int 2020;2020:4087928. doi:10.1155/2020/4087928, PMID:31998789.
[57] Kim YR, Lee EJ, Shin KO, Kim MH, Pewzner-Jung Y, Lee YM, *et al*. Hepatic triglyceride accumulation via endoplasmic reticulum stress-induced srebp-1 activation is regulated by ceramide synthases. Exp Mol Med 2019;51(11):1–16. doi:10.1038/s12276-019-0340-1, PMID:31676768.
[58] Seidu T, McWhorter P, Myer J, Alamgir R, Eregha N, Bogle D, *et al*. Dht causes liver steatosis via transcriptional regulation of scap in normal weight female mice. J Endocrinol 2021;250(2):49–65. doi:10.1530/joe-21-0040, PMID:34060475.
[59] Araki M, Nakagawa Y, Saito H, Yamada Y, Han SI, Mizunoe Y, *et al*. Hepatocyte- or macrophage-specific srebp-1a deficiency in mice exacerbates methionine- and choline-deficient diet-induced nonalcoholic fatty liver disease. Am J Physiol Gastrointest Liver Physiol 2022;323(6):G627–g639. doi:10.1152/ajpgi.00090.2022, PMID:36283088.
[60] Wei G, An P, Vaid KA, Nasser I, Huang P, Tan L, *et al*. Comparison of murine steatohepatitis models identifies a dietary intervention with robust fibro-

sis, ductular reaction, and rapid progression to cirrhosis and cancer. Am J Physiol Gastrointest Liver Physiol 2020;318(1):G174–g188. doi:10.1152/ajpgi.00041.2019, PMID:31630534.
[61] Gabbia D, Roverso M, Guido M, Sacchi D, Scaffidi M, Carrara M, *et al*. Western diet-induced metabolic alterations affect circulating markers of liver function before the development of steatosis. Nutrients 2019;11(7):1602. doi:10.3390/nu11071602, PMID:31311123.
[62] Cheng C, Deng X, Xu K. Increased expression of sterol regulatory element binding protein-2 alleviates autophagic dysfunction in nafld. Int J Mol Med 2018;41(4):1877–1886. doi:10.3892/ijmm.2018.3389, PMID:29336468.
[63] Huh JY, Reilly SM, Abu-Odeh M, Murphy AN, Mahata SK, Zhang J, *et al*. Tank-binding kinase 1 regulates the localization of acyl-coa synthetase acsl1 to control hepatic fatty acid oxidation. Cell Metab 2020;32(6):1012–1027.e1017. doi:10.1016/j.cmet.2020.10.010, PMID:33152322.
[64] Duan J, Wang Z, Duan R, Yang C, Zhao R, Feng Q, *et al*. Therapeutic targeting of hepatic acsl4 ameliorates nash in mice. Hepatology 2022;75(1):140–153. doi:10.1002/hep.32148, PMID:34510514.
[65] Singh AB, Kan CFK, Kraemer FB, Sobel RA, Liu J. Liver-specific knockdown of long-chain acyl-coa synthetase 4 reveals its key role in vldl-tg metabolism and phospholipid synthesis in mice fed a high-fat diet. Am J Physiol Endocrinol Metab 2019;316(5):E880–e894. doi:10.1152/ajpendo.00503.2018, PMID:30721098.
[66] Wei S, Qiu T, Wang N, Yao X, Jiang L, Jia X, *et al*. Ferroptosis mediated by the interaction between mfn2 and irea promotes arsenic-induced nonalcoholic steatohepatitis. Environ Res 2020;188:109824. doi:10.1016/j.envres.2020.109824, PMID:32593899.
[67] Sen P, Kan CFK, Singh AB, Rius M, Kraemer FB, Sztul E, *et al*. Identification of p115 as a novel acsl4 interacting protein and its role in regulating acsl4 degradation. J Proteomics 2020;229:103926. doi:10.1016/j.jprot.2020.103926, PMID:32736139.
[68] Bowman TA, O'Keeffe KR, D'Aquila T, Yan QW, Griffin JD, Killion EA, *et al*. Acyl coa synthetase 5 (acsl5) ablation in mice increases energy expenditure and insulin sensitivity and delays fat absorption. Mol Metab 2016;5(3):210–220. doi:10.1016/j.molmet.2016.01.001, PMID:26977393.
[69] Luo Y, Chen Q, Zou J, Fan J, Li Y, Luo Z. Chronic intermittent hypoxia exposure alternative to exercise alleviates high-fat-diet-induced obesity and fatty liver. Int J Mol Sci 2022;23(9):5209. doi:10.3390/ijms23095209, PMID:35563600.
[70] Zheng F, Cai Y. Concurrent exercise improves insulin resistance and nonalcoholic fatty liver disease by upregulating ppar-γ and genes involved in the beta-oxidation of fatty acids in apoe-ko mice fed a high-fat diet. Lipids Health Dis 2019;18(1):6. doi:10.1186/s12944-018-0933-z, PMID:30611282.
[71] Ahmed EA, El-Derany MO, Anwar AM, Saied EM, Magdeldin S. Metabolomics and lipidomics screening reveal reprogrammed signaling pathways toward cancer development in non-alcoholic steatohepatitis. Int J Mol Sci 2022;24(1):210. doi:10.3390/ijms24010210, PMID:36613653.
[72] Heinecke F, Mazzucco MB, Fornes D, Roberti S, Jawerbaum A, White V. The offspring from rats fed a fatty diet display impairments in the activation of liver peroxisome proliferator activated receptor alpha and features of fatty liver disease. Mol Cell Endocrinol 2020;511:110818. doi:10.1016/j.mce.2020.110818, PMID:32298755.
[73] Smati S, Polizzi A, Fougerat A, Ellero-Simatos S, Blum Y, Lippi Y, *et al*. Integrative study of diet-induced mouse models of nafld identifies pparα as a sexually dimorphic drug target. Gut 2022;71(4):807–821. doi:10.1136/gutjnl-2020-323323, PMID:33903148.
[74] Silva-Veiga FM, Miranda CS, Vasques-Monteiro IML, Souza-Tavares H, Martins FF, Daleprane JB, *et al*. Peroxisome proliferator-activated receptor-alpha activation and dipeptidyl peptidase-4 inhibition target dysbiosis to treat fatty liver in obese mice. World J Gastroenterol 2022;28(17):1814–1829. doi:10.3748/wjg.v28.i17.1814, PMID:35633911.
[75] Yan T, Luo Y, Yan N, Hamada K, Zhao N, Xia Y, *et al*. Intestinal peroxisome proliferator-activated receptor α-fatty acid-binding protein 1 axis modulates nonalcoholic steatohepatitis. Hepatology 2023;77(1):239–255. doi:10.1002/hep.32538, PMID:35460276.
[76] Chen K, Chen X, Xue H, Zhang P, Fang W, Chen X, *et al*. Coenzyme q10 attenuates high-fat diet-induced non-alcoholic fatty liver disease through activation of the ampk pathway. Food Funct 2019;10(2):814–823. doi:10.1039/c8fo01236a, PMID:30675881.
[77] Du X, Osoro EK, Chen Q, Yan X, Gao D, Wu L, *et al*. Pdcd4 promotes lipid deposition by attenuating pparα-mediated fatty acid oxidation in hepatocytes. Mol Cell Endocrinol 2022;545:111562. doi:10.1016/j.mce.2022.111562, PMID:35051553.
[78] Wei X, Zhang J, Tang M, Wang X, Fan N, Peng Y. Fat mass and obesity-associated protein promotes liver steatosis by targeting pparα. Lipids Health Dis 2022;21(1):29. doi:10.1186/s12944-022-01640-y, PMID:35282837.
[79] Qin G, Wang GZ, Guo DD, Bai RX, Wang M, Du SY. Deletion of smad4 reduces hepatic inflammation and fibrogenesis during nonalcoholic steatohepatitis progression. J Dig Dis 2018;19(5):301–313. doi:10.1111/1751-2980.12599, PMID:29696816.
[80] Ko CW, Qu J, Black DD, Tso P. Regulation of intestinal lipid metabolism: Current concepts and relevance to disease. Nat Rev Gastroenterol Hepatol 2020;17(3):169–183. doi:10.1038/s41575-019-0250-7, PMID:32015520.
[81] Toyoda Y, Takada T, Yamanashi Y, Suzuki H. Pathophysiological importance of bile cholesterol reabsorption: Hepatic npc1l1-exacerbated steatosis and decreasing vldl-tg secretion in mice fed a high-fat diet. Lipids Health Dis 2019;18(1):234. doi:10.1186/s12944-019-1179-0, PMID:31883528.
[82] Yamanashi Y, Takada T, Tanaka Y, Ogata Y, Toyoda Y, Ito SM, *et al*. Hepatic niemann-pick c1-like 1 exacerbates non-alcoholic fatty liver disease by re-absorbing specific biliary oxysterols. Biomed Pharmacother 2022;156:113877. doi:10.1016/j.biopha.2022.113877, PMID:36270257.
[83] Min HK, Kapoor A, Fuchs M, Mirshahi F, Zhou H, Maher J, *et al*. Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. Cell Metab 2012;15(5):665–674. doi:10.1016/j.cmet.2012.04.004, PMID:22560219.
[84] Li T, Yan H, Geng Y, Shi H, Li H, Wang S, *et al*. Target genes associated with lipid and glucose metabolism in non-alcoholic fatty liver disease. Lipids Health Dis 2019;18(1):211. doi:10.1186/s12944-019-1154-9, PMID:31805951.
[85] Liu MX, Gao M, Li CZ, Yu CZ, Yan H, Peng C, *et al*. Dicer1/mir-29/hmgcr axis contributes to hepatic free cholesterol accumulation in mouse non-alcoholic steatohepatitis. Acta Pharmacol Sin 2017;38(5):660–671. doi:10.1038/aps.2016.158, PMID:28112179.
[86] Liang JQ, Teoh N, Xu L, Pok S, Li X, Chu ESH, *et al*. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. Nat Commun 2018;9(1):4490. doi:10.1038/s41467-018-06931-6, PMID:30367044.
[87] Liu D, Wong CC, Fu L, Chen H, Zhao L, Li C, *et al*. Squalene epoxidase drives nafld-induced hepatocellular carcinoma and is a pharmaceutical target. Sci Transl Med 2018;10(437):eaap9840. doi:10.1126/scitranslmed.aap9840, PMID:29669855.
[88] Liu D, Wong CC, Zhou Y, Li C, Chen H, Ji F, *et al*. Squalene epoxidase induces nonalcoholic steatohepatitis via binding to carbonic anhydrase iii and is a therapeutic target. Gastroenterology 2021;160(7):2467–2482.e2463. doi:10.1053/j.gastro.2021.02.051, PMID:33647280.
[89] Sun H, Li L, Li W, Yang F, Zhang Z, Liu Z, *et al*. P53 transcriptionally regulates sqle to repress cholesterol synthesis and tumor growth. EMBO Rep 2021;22(10):e52537. doi:10.15252/embr.202152537, PMID:34459531.
[90] Jia X, Zhai T. Integrated analysis of multiple microarray studies to identify novel gene signatures in non-alcoholic fatty liver disease. Front Endocrinol (Lausanne) 2019;10:599. doi:10.3389/fendo.2019.00599, PMID:31551930.
[91] Wu C, Zhou Y, Wang M, Dai G, Liu X, Lai L, *et al*. Bioinformatics analysis explores potential hub genes in nonalcoholic fatty liver disease. Front Genet 2021;12:772487. doi:10.3389/fgene.2021.772487, PMID:34777484.
[92] Jiao N, Baker SS, Chapa-Rodriguez A, Liu W, Nugent CA, Tsompana M, *et al*. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in nafld. Gut 2018;67(10):1881–1891. doi:10.1136/gutjnl-2017-314307, PMID:28774887.
[93] Suga T, Yamaguchi H, Ogura J, Shoji S, Maekawa M, Mano N. Altered bile acid composition and disposition in a mouse model of non-alcoholic steatohepatitis. Toxicol Appl Pharmacol 2019;379:114664. doi:10.1016/j.taap.2019.114664, PMID:31306673.
[94] Clifford BL, Sedgeman LR, Williams KJ, Morand P, Cheng A, Jarrett KE, *et al*. Fxr activation protects against nafld via bile-acid-dependent reductions in lipid absorption. Cell Metab 2021;33(8):1671–1684.e1674. doi:10.1016/j.cmet.2021.06.012, PMID:34270928.
[95] Deng W, Fan W, Tang T, Wan H, Zhao S, Tan Y, *et al*. Farnesoid x receptor deficiency induces hepatic lipid and glucose metabolism disorder via regulation of pyruvate dehydrogenase kinase 4. Oxid Med Cell Longev 2022;2022:3589525. doi:10.1155/2022/3589525, PMID:35251469.
[96] Xu W, Cui C, Cui C, Chen Z, Zhang H, Cui Q, *et al*. Hepatocellular cystathionine γ lyase/hydrogen sulfide attenuates nonalcoholic fatty liver disease by activating farnesoid x receptor. Hepatology 2022;76(6):1794–1810. doi:10.1002/hep.32577, PMID:35586979.
[97] Fan L, Lai R, Ma N, Dong Y, Li Y, Wu Q, *et al*. Mir-552-3p modulates transcriptional activities of fxr and lxr to ameliorate hepatic glycolipid metabolism disorder. J Hepatol 2021;74(1):8–19. doi:10.1016/j.jhep.2020.07.048, PMID:32818571.
[98] Kokkorakis M, Boutari C, Hill MA, Kotsis V, Loomba R, Sanyal AJ, *et al*. Resmetirom, the first approved drug for the management of metabolic dysfunction-associated steatohepatitis: Trials, opportunities, and challenges. Metabolism 2024;154:155835. doi:10.1016/j.metabol.2024.155835, PMID:38508373.
[99] Krishnan A, Schneider CV, Hadi Y, Mukherjee D, AlShehri B, Alqahtani SA. Cardiovascular and mortality outcomes with glp-1 receptor agonists vs other glucose-lowering drugs in individuals with nafld and type 2 diabetes: A large population-based matched cohort study. Diabetologia 2024;67(3):483–493. doi:10.1007/s00125-023-06057-5, PMID:38117293.
[100] Liao C, Liang X, Zhang X, Li Y. The effects of glp-1 receptor agonists on visceral fat and liver ectopic fat in an adult population with or without diabetes and nonalcoholic fatty liver disease: A systematic review and meta-analysis. PLoS One 2023;18(8):e0289616. doi:10.1371/journal.pone.0289616, PMID:37616255.
[101] Gu Y, Sun L, Zhang W, Kong T, Zhou R, He Y, *et al*. Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (sglt-2) inhibitor and 4 glucagon-like peptide-1 (glp-1) receptor agonist drugs in non-alcoholic fatty liver disease: A grade-assessed systematic review and network meta-analysis of randomized controlled trials. Front Pharmacol 2023;14:1102792. doi:10.3389/fphar.2023.1102792, PMID:36992825.
[102] Gu Y, Sun L, He Y, Yang L, Deng C, Zhou R, *et al*. Comparative efficacy of glucagon-like peptide 1 (glp-1) receptor agonists, pioglitazone and vitamin e for liver histology among patients with nonalcoholic fatty liver disease: Systematic review and pilot network meta-analysis of randomized controlled trials. Expert Rev Gastroenterol Hepatol 2023;17(3):273–282. doi:10.1080/17474124.2023.2172397, PMID:36689199.
[103] Romero-Gómez M, Armstrong MJ, Funuyet-Salas J, Mangla KK, Ladelund S, Sejling AS, *et al*. Improved health-related quality of life with semaglutide in people with non-alcoholic steatohepatitis: A randomised trial. Aliment Pharmacol Ther 2023;58(4):395–403. doi:10.1111/apt.17598, PMID:37328931.
[104] Yuan X, Gao Z, Yang C, Duan K, Ren L, Song G. Comparing the effec-

tiveness of long-term use of daily and weekly glucagon-like peptide-1 receptor agonists treatments in patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus: A network meta-analysis. Front Endocrinol (Lausanne) 2023;14:1170881. doi:10.3389/fendo.2023.1170881, PMID:37342259.
[105] Mao T, Zhang C, Yang S, Bi Y, Li M, Yu J. Semaglutide alters gut microbiota and improves nafld in db/db mice. Biochem Biophys Res Commun 2024;710:149882. doi:10.1016/j.bbrc.2024.149882, PMID:38583231.
[106] Kim ER, Park JS, Kim JH, Oh JY, Oh IJ, Choi DH, *et al*. A glp-1/glp-2 receptor dual agonist to treat nash: Targeting the gut-liver axis and microbiome. Hepatology 2022;75(6):1523–1538. doi:10.1002/hep.32235, PMID:34773257.
[107] Romero-Gómez M, Lawitz E, Shankar RR, Chaudhri E, Liu J, Lam RLH, *et al*. A phase iia active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. J Hepatol 2023;79(4):888–897. doi:10.1016/j.jhep.2023.05.013, PMID:37355043.
[108] Nestor JJ, Parkes D, Feigh M, Suschak JJ, Harris MS. Effects of alt-801, a glp-1 and glucagon receptor dual agonist, in a translational mouse model of non-alcoholic steatohepatitis. Sci Rep 2022;12(1):6666. doi:10.1038/s41598-022-10577-2, PMID:35461369.
[109] Monfeuga T, Norlin J, Bugge A, Gaalsgaard ED, Prada-Medina CA, Latta M, *et al*. Evaluation of long acting glp1r/gcgr agonist in a dio and biopsy-confirmed mouse model of nash suggest a beneficial role of glp-1/glucagon agonism in nash patients. Mol Metab 2024;79:101850. doi:10.1016/j.molmet.2023.101850, PMID:38065435.
[110] Desjardins EM, Wu J, Lavoie DCT, Ahmadi E, Townsend LK, Morrow MR, *et al*. Combination of an acly inhibitor with a glp-1r agonist exerts additive benefits on nonalcoholic steatohepatitis and hepatic fibrosis in mice. Cell Rep Med 2023;4(9):101193. doi:10.1016/j.xcrm.2023.101193, PMID:37729871.
[111] Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, *et al*. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase ii trial. J Hepatol 2022;77(3):607–618. doi:10.1016/j.jhep.2022.04.003, PMID:35439567.
[112] Xue H, Xing HJ, Wang B, Fu C, Zhang YS, Qiao X, *et al*. Cinchonine, a potential oral small-molecule glucagon-like peptide-1 receptor agonist, lowers blood glucose and ameliorates non-alcoholic steatohepatitis. Drug Des Devel Ther 2023;17:1417–1432. doi:10.2147/dddt.S404055, PMID:37197367.
[113] Mahalingam S, Bellamkonda R, Arumugam MK, Perumal SK, Yoon J, Casey C, *et al*. Glucagon-like peptide 1 receptor agonist, exendin-4, reduces alcohol-associated fatty liver disease. Biochem Pharmacol 2023;213:115613. doi:10.1016/j.bcp.2023.115613, PMID:37209859.
[114] Kuchay MS, Krishan S, Mishra SK, Choudhary NS, Singh MK, Wasir JS, *et al*. Effect of dulaglutide on liver fat in patients with type 2 diabetes and nafld: Randomised controlled trial (d-lift trial). Diabetologia 2020;63(11):2434–2445. doi:10.1007/s00125-020-05265-7, PMID:32865597.
[115] Liu L, Yan H, Xia M, Zhao L, Lv M, Zhao N, *et al*. Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes. Diabetes Metab Res Rev 2020;36(5):e3292. doi:10.1002/dmrr.3292, PMID:31955491.
[116] Khoo J, Hsiang JC, Taneja R, Koo SH, Soon GH, Kam CJ, *et al*. Randomized trial comparing effects of weight loss by liraglutide with lifestyle modification in non-alcoholic fatty liver disease. Liver Int 2019;39(5):941–949. doi:10.1111/liv.14065, PMID:30721572.
[117] Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, *et al*. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64(2):399–408. doi:10.1016/j.jhep.2015.08.038, PMID:26394161.
[118] Khoo J, Hsiang J, Taneja R, Law NM, Ang TL. Comparative effects of liraglutide 3 mg vs structured lifestyle modification on body weight, liver fat and liver function in obese patients with non-alcoholic fatty liver disease: A pilot randomized trial. Diabetes Obes Metab 2017;19(12):1814–1817. doi:10.1111/dom.13007, PMID:28503750.
[119] Petit JM, Cercueil JP, Loffroy R, Denimal D, Bouillet B, Fourmont C, *et al*. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: The lira-nafld study. J Clin Endocrinol Metab 2017;102(2):407–415. doi:10.1210/jc.2016-2775, PMID:27732328.
[120] Smits MM, Tonneijck L, Muskiet MH, Kramer MH, Pouwels PJ, Pieters-van den Bos IC, *et al*. Twelve week liraglutide or sitagliptin does not affect hepatic fat in type 2 diabetes: A randomised placebo-controlled trial. Diabetologia 2016;59(12):2588–2593. doi:10.1007/s00125-016-4100-7, PMID:27627981.
[121] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, *et al*. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384(12):1113–1124. doi:10.1056/NEJMoa2028395, PMID:33185364.
[122] Flint A, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, *et al*. Randomised clinical trial: Semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2021;54(9):1150–1161. doi:10.1111/apt.16608, PMID:34570916.
[123] Farage AE, Abdo W, Osman A, Abdel-Kareem MA, Hakami ZH, Alsulimani A, *et al*. Betulin prevents high fat diet-induced non-alcoholic fatty liver disease by mitigating oxidative stress and upregulating nrf2 and sirt1 in rats. Life Sci 2023;322:121688. doi:10.1016/j.lfs.2023.121688, PMID:37030617.
[124] Kim KD, Jung HY, Ryu HG, Kim B, Jeon J, Yoo HY, *et al*. Betulinic acid inhibits high-fat diet-induced obesity and improves energy balance by activating ampk. Nutr Metab Cardiovasc Dis 2019;29(4):409–420. doi:10.1016/j.numecd.2018.12.001, PMID:30799179.
[125] Mu Q, Wang H, Tong L, Fang Q, Xiang M, Han L, *et al*. Betulinic acid improves nonalcoholic fatty liver disease through yy1/fas signaling pathway. Faseb j 2020;34(9):13033–13048. doi:10.1096/fj.202000546R, PMID:32777136.
[126] Quan HY, Kim DY, Kim SJ, Jo HK, Kim GW, Chung SH. Betulinic acid alleviates non-alcoholic fatty liver by inhibiting srebp1 activity via the ampk-mtor-srebp signaling pathway. Biochem Pharmacol 2013;85(9):1330–1340. doi:10.1016/j.bcp.2013.02.007, PMID:23435355.
[127] Bitter A, Nüssler AK, Thasler WE, Klein K, Zanger UM, Schwab M, *et al*. Human sterol regulatory element-binding protein 1a contributes significantly to hepatic lipogenic gene expression. Cell Physiol Biochem 2015;35(2):803–815. doi:10.1159/000369739, PMID:25634759.
[128] Bates J, Vijayakumar A, Ghoshal S, Marchand B, Yi S, Kornyeyev D, *et al*. Acetyl-coa carboxylase inhibition disrupts metabolic reprogramming during hepatic stellate cell activation. J Hepatol 2020;73(4):896–905. doi:10.1016/j.jhep.2020.04.037, PMID:32376414.
[129] Goedeke L, Bates J, Vatner DF, Perry RJ, Wang T, Ramirez R, *et al*. Acetyl-coa carboxylase inhibition reverses nafld and hepatic insulin resistance but promotes hypertriglyceridemia in rodents. Hepatology 2018;68(6):2197–2211. doi:10.1002/hep.30097, PMID:29790582.
[130] Lawitz EJ, Coste A, Poordad F, Alkhouri N, Loo N, McColgan BJ, *et al*. Acetyl-coa carboxylase inhibitor gs-0976 for 12 weeks reduces hepatic de novo lipogenesis and steatosis in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2018;16(12):1983–1991.e1983. doi:10.1016/j.cgh.2018.04.042, PMID:29705265.
[131] Loomba R, Kayali Z, Noureddin M, Ruane P, Lawitz EJ, Bennett M, *et al*. Gs-0976 reduces hepatic steatosis and fibrosis markers in patients with nonalcoholic fatty liver disease. Gastroenterology 2018;155(5):1463–1473.e1466. doi:10.1053/j.gastro.2018.07.027, PMID:30059671.
[132] Dandan M, Han J, Mann S, Kim R, Li K, Mohammed H, *et al*. Acetyl-coa carboxylase inhibitor increases ldl-apob production rate in nash with cirrhosis: Prevention by fenofibrate. J Lipid Res 2023;64(3):100339. doi:10.1016/j.jlr.2023.100339, PMID:36737040.
[133] Lawitz EJ, Bhandari BR, Ruane PJ, Kohli A, Harting E, Ding D, *et al*. Fenofibrate mitigates hypertriglyceridemia in nonalcoholic steatohepatitis patients treated with cilofexor/firsocostat. Clin Gastroenterol Hepatol 2023;21(1):143–152.e143. doi:10.1016/j.cgh.2021.12.044, PMID:34999207.
[134] Tamura YO, Sugama J, Iwasaki S, Sasaki M, Yasuno H, Aoyama K, *et al*. Selective acetyl-coa carboxylase 1 inhibitor improves hepatic steatosis and hepatic fibrosis in a preclinical nonalcoholic steatohepatitis model. J Pharmacol Exp Ther 2021;379(3):280–289. doi:10.1124/jpet.121.000786, PMID:34535562.
[135] Ross TT, Crowley C, Kelly KL, Rinaldi A, Beebe DA, Lech MP, *et al*. Acetyl-coa carboxylase inhibition improves multiple dimensions of nash pathogenesis in model systems. Cell Mol Gastroenterol Hepatol 2020;10(4):829–851. doi:10.1016/j.jcmgh.2020.06.001, PMID:32526482.
[136] Gao YS, Qian MY, Wei QQ, Duan XB, Wang SL, Hu HY, *et al*. Wz66, a novel acetyl-coa carboxylase inhibitor, alleviates nonalcoholic steatohepatitis (nash) in mice. Acta Pharmacol Sin 2020;41(3):336–347. doi:10.1038/s41401-019-0310-0, PMID:31645659.
[137] Loomba R, Mohseni R, Lucas KJ, Gutierrez JA, Perry RG, Trotter JF, *et al*. Tvb-2640 (fasn inhibitor) for the treatment of nonalcoholic steatohepatitis: Fascinate-1, a randomized, placebo-controlled phase 2a trial. Gastroenterology 2021;161(5):1475–1486. doi:10.1053/j.gastro.2021.07.025, PMID:34310978.
[138] Beysen C, Schroeder P, Wu E, Brevard J, Ribadeneira M, Lu W, *et al*. Inhibition of fatty acid synthase with ft-4101 safely reduces hepatic de novo lipogenesis and steatosis in obese subjects with non-alcoholic fatty liver disease: Results from two early-phase randomized trials. Diabetes Obes Metab 2021;23(3):700–710. doi:10.1111/dom.14272, PMID:33289350.
[139] Xu S, Wu X, Wang S, Xu M, Fang T, Ma X, *et al*. Trim56 protects against nonalcoholic fatty liver disease by promoting the degradation of fatty acid synthase. J Clin Invest 2024;134(5):e166149. doi:10.1172/jci166149, PMID:38206764.
[140] Kurikawa N, Takagi T, Wakimoto S, Uto Y, Terashima H, Kono K, *et al*. A novel inhibitor of stearoyl-coa desaturase-1 attenuates hepatic lipid accumulation, liver injury and inflammation in model of nonalcoholic steatohepatitis. Biol Pharm Bull 2013;36(2):259–267. doi:10.1248/bpb.b12-00702, PMID:23370355.
[141] Zhou Y, Zhong L, Yu S, Shen W, Cai C, Yu H. Inhibition of stearoyl-coenzyme a desaturase 1 ameliorates hepatic steatosis by inducing ampk-mediated lipophagy. Aging (Albany NY) 2020;12(8):7350–7362. doi:10.18632/aging.103082, PMID:32324591.
[142] Jiang S, Uddin MJ, Yu X, Piao L, Dorotea D, Oh GT, *et al*. Peroxisomal fitness: A potential protective mechanism of fenofibrate against high fat diet-induced non-alcoholic fatty liver disease in mice. Diabetes Metab J 2022;46(6):829–842. doi:10.4093/dmj.2021.0274, PMID:35746892.
[143] Guru B, Tamrakar AK, Manjula SN, Prashantha Kumar BR. Novel dual pparα/γ agonists protect against liver steatosis and improve insulin sensitivity while avoiding side effects. Eur J Pharmacol 2022;935:175322. doi:10.1016/j.ejphar.2022.175322, PMID:36228743.
[144] Grobbee EJ, de Jong VD, Schrieks IC, Tushuizen ME, Holleboom AG, Tardif JC, *et al*. Improvement of non-invasive tests of liver steatosis and fibrosis as indicators for non-alcoholic fatty liver disease in type 2 diabetes mellitus patients with elevated cardiovascular risk profile using the ppar-α/γ agonist aleglitazar. PLoS One 2022;17(11):e0277706. doi:10.1371/journal.pone.0277706, PMID:36378671.
[145] Feng Z, Xiang J, Liu H, Li J, Xu X, Sun G, *et al*. Design, synthesis, and

biological evaluation of triazolone derivatives as potent pparα/δ dual agonists for the treatment of nonalcoholic steatohepatitis. J Med Chem 2022;65(3):2571–2592. doi:10.1021/acs.jmedchem.1c02002, PMID:35060744.
[146] Zhou Z, Ren Q, Jiao S, Cai Z, Geng X, Deng L, *et al*. Discovery of new and highly effective quadruple ffa1 and pparα/γ/δ agonists as potential anti-fatty liver agents. Eur J Med Chem 2022;229:114061. doi:10.1016/j.ejmech.2021.114061, PMID:34954593.
[147] Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, *et al*. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150(5):1147–1159.e1145. doi:10.1053/j.gastro.2016.01.038, PMID:26874076.
[148] Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, *et al*. A randomized, controlled trial of the pan-ppar agonist lanifibranor in nash. N Engl J Med 2021;385(17):1547–1558. doi:10.1056/NEJMoa2036205, PMID:34670042.
[149] Gawrieh S, Noureddin M, Loo N, Mohseni R, Awasty V, Cusi K, *et al*. Saroglitazar, a ppar-α/γ agonist, for treatment of nafld: A randomized controlled double-blind phase 2 trial. Hepatology 2021;74(4):1809–1824. doi:10.1002/hep.31843, PMID:33811367.
[150] Siddiqui MS, Idowu MO, Parmar D, Borg BB, Denham D, Loo NM, *et al*. A phase 2 double blinded, randomized controlled trial of saroglitazar in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2021;19(12):2670–2672. doi:10.1016/j.cgh.2020.10.051, PMID:33152542.
[151] Chianelli D, Rucker PV, Roland J, Tully DC, Nelson J, Liu X, *et al*. Nidufexor (lmb763), a novel fxr modulator for the treatment of nonalcoholic steatohepatitis. J Med Chem 2020;63(8):3868–3880. doi:10.1021/acs.jmedchem.9b01621, PMID:31940200.
[152] Patel K, Harrison SA, Elkhashab M, Trotter JF, Herring R, Rojter SE, *et al*. Cilofexor, a nonsteroidal fxr agonist, in patients with noncirrhotic nash: A phase 2 randomized controlled trial. Hepatology 2020;72(1):58–71. doi:10.1002/hep.31205, PMID:32115759.
[153] Ratziu V, Rinella ME, Neuschwander-Tetri BA, Lawitz E, Denham D, Kayali Z, *et al*. Edp-305 in patients with nash: A phase ii double-blind placebo-controlled dose-ranging study. J Hepatol 2022;76(3):506–517. doi:10.1016/j.jhep.2021.10.018, PMID:34740705.
[154] Qin T, Gao X, Lei L, Zhang W, Feng J, Wang X, *et al*. Structural optimization and biological evaluation of 1-adamantylcarbonyl-4-phenylpiperazine derivatives as fxr agonists for nafld. Eur J Med Chem 2023;245(Pt 1):114903. doi:10.1016/j.ejmech.2022.114903, PMID:36375336.
[155] Li J, Liu M, Li Y, Sun DD, Shu Z, Tan Q, *et al*. Discovery and optimization of non-bile acid fxr agonists as preclinical candidates for the treatment of nonalcoholic steatohepatitis. J Med Chem 2020;63(21):12748–12772. doi:10.1021/acs.jmedchem.0c01065, PMID:32991173.
[156] Harrison SA, Bashir MR, Lee KJ, Shim-Lopez J, Lee J, Wagner B, *et al*. A structurally optimized fxr agonist, met409, reduced liver fat content over 12 weeks in patients with non-alcoholic steatohepatitis. J Hepatol 2021;75(1):25–33. doi:10.1016/j.jhep.2021.01.047, PMID:33581174.
[157] Shim S, Krishnaiah M, Sankham MR, Kim I, Lee Y, Shin I, *et al*. Discovery of (e)-3-(3-((2-cyano-4′-dimethylaminobiphenyl-4-ylmethyl) cyclohexanecarbonylamino)-5-fluorophenyl)acrylic acid methyl ester, an intestine-specific, fxr partial agonist for the treatment of nonalcoholic steatohepatitis. J Med Chem 2022;65(14):9974–10000. doi:10.1021/acs.jmedchem.2c00641, PMID:35797110.
[158] Nara SJ, Jogi S, Cheruku S, Kandhasamy S, Jaipuri F, Kathi PK, *et al*. Discovery of bms-986339, a pharmacologically differentiated farnesoid x receptor agonist for the treatment of nonalcoholic steatohepatitis. J Med Chem 2022;65(13):8948–8960. doi:10.1021/acs.jmedchem.2c00165, PMID:35704802.
[159] Younis IR, Kirby BJ, Billin AN, Xiao D, Song Q, Watkins TR, *et al*. Pharmacokinetics, pharmacodynamics, safety and tolerability of cilofexor, a novel nonsteroidal farnesoid x receptor agonist, in healthy volunteers. Clin Transl Sci 2023;16(3):536–547. doi:10.1111/cts.13469, PMID:36573450.
[160] Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, *et al*. Efficacy and safety of the farnesoid x receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145(3):574–582.e571. doi:10.1053/j.gastro.2013.05.042, PMID:23727264.
[161] Sanyal AJ, Lopez P, Lawitz EJ, Lucas KJ, Loeffler J, Kim W, *et al*. Tropifexor for nonalcoholic steatohepatitis: An adaptive, randomized, placebo-controlled phase 2a/b trial. Nat Med 2023;29(2):392–400. doi:10.1038/s41591-022-02200-8, PMID:36797481.
[162] Ratziu V, Harrison SA, Loustaud-Ratti V, Bureau C, Lawitz E, Abdelmalek M, *et al*. Hepatic and renal improvements with fxr agonist vonafexor in individuals with suspected fibrotic nash. J Hepatol 2023;78(3):479–492. doi:10.1016/j.jhep.2022.10.023, PMID:36334688.
[163] Ran LS, Wu YZ, Gan YW, Wang HL, Wu LJ, Zheng CM, *et al*. Andrographolide ameliorates hepatic steatosis by suppressing fatp2-mediated fatty acid uptake in mice with nonalcoholic fatty liver disease. J Nat Med 2023;77(1):73–86. doi:10.1007/s11418-022-01647-w, PMID:36115008.
[164] Li P, Zhang R, Wang M, Chen Y, Chen Z, Ke X, *et al*. Baicalein prevents fructose-induced hepatic steatosis in rats: In the regulation of fatty acid de novo synthesis, fatty acid elongation and fatty acid oxidation. Front Pharmacol 2022;13:917329. doi:10.3389/fphar.2022.917329, PMID:35847050.
[165] Sun W, Liu P, Wang T, Wang X, Zheng W, Li J. Baicalein reduces hepatic fat accumulation by activating ampk in oleic acid-induced hepg2 cells and high-fat diet-induced non-insulin-resistant mice. Food Funct 2020;11(1):711–721. doi:10.1039/c9fo02237f, PMID:31909773.
[166] Li QP, Dou YX, Huang ZW, Chen HB, Li YC, Chen JN, *et al*. Therapeutic effect of oxyberberine on obese non-alcoholic fatty liver disease rats. Phytomedicine 2021;85:153550. doi:10.1016/j.phymed.2021.153550, PMID:33831691.
[167] Shan MY, Dai Y, Ren XD, Zheng J, Zhang KB, Chen B, *et al*. Berberine mitigates nonalcoholic hepatic steatosis by downregulating sirt1-foxo1-srebp2 pathway for cholesterol synthesis. J Integr Med 2021;19(6):545–554. doi:10.1016/j.joim.2021.09.003, PMID:34686466.
[168] Sharma A, Anand SK, Singh N, Dwarkanath A, Dwivedi UN, Kakkar P. Berbamine induced activation of the sirt1/lkb1/ampk signaling axis attenuates the development of hepatic steatosis in high-fat diet-induced nafld rats. Food Funct 2021;12(2):892–909. doi:10.1039/d0fo02501a, PMID:33411880.
[169] Yu M, Alimujiang M, Hu L, Liu F, Bao Y, Yin J. Berberine alleviates lipid metabolism disorders via inhibition of mitochondrial complex i in gut and liver. Int J Biol Sci 2021;17(7):1693–1707. doi:10.7150/ijbs.54604, PMID:33994854.
[170] Zhang YP, Deng YJ, Tang KR, Chen RS, Liang S, Liang YJ, *et al*. Berberine ameliorates high-fat diet-induced non-alcoholic fatty liver disease in rats via activation of sirt3/ampk/acc pathway. Curr Med Sci 2019;39(1):37–43. doi:10.1007/s11596-019-1997-3, PMID:30868489.
[171] Lee M, Nam SH, Yoon HG, Kim S, You Y, Choi KC, *et al*. Fermented curcuma longa l. Prevents alcoholic fatty liver disease in mice by regulating cyp2e1, srebp-1c, and ppar-α. J Med Food 2022;25(4):456–463. doi:10.1089/jmf.2021.K.0098, PMID:35438556.
[172] Mun J, Kim S, Yoon HG, You Y, Kim OK, Choi KC, *et al*. Water extract of curcuma longa l. Ameliorates non-alcoholic fatty liver disease. Nutrients 2019;11(10):2536. doi:10.3390/nu11102536, PMID:31640183.
[173] Sun Q, Niu Q, Guo Y, Zhuang Y, Li X, Liu J, *et al*. Regulation on citrate influx and metabolism through inhibiting slc13a5 and acly: A novel mechanism mediating the therapeutic effects of curcumin on nafld. J Agric Food Chem 2021;69(31):8714–8725. doi:10.1021/acs.jafc.1c03105, PMID:34323067.
[174] Poornima MS, Sindhu G, Billu A, Sruthi CR, Nisha P, Gogoi P, *et al*. Pretreatment of hydroethanolic extract of dillenia indica l. Attenuates oleic acid induced nafld in hepg2 cells via modulating sirt-1/p-lkb-1/ampk, hmgcr & ppar-α signaling pathways. J Ethnopharmacol 2022;292:115237. doi:10.1016/j.jep.2022.115237, PMID:35351574.
[175] Le TNH, Choi HJ, Jun HS. Ethanol extract of liriope platyphylla root attenuates non-alcoholic fatty liver disease in high-fat diet-induced obese mice via regulation of lipogenesis and lipid uptake. Nutrients 2021;13(10):3338. doi:10.3390/nu13103338, PMID:34684339.
[176] Ma K, Sheng W, Gao R, Feng J, Huang W, Cui L, *et al*. Ethanolic extract of root from arctium lappa l ameliorates obesity and hepatic steatosis in rats by regulating the ampk/acc/cpt-1 pathway. J Food Biochem 2022;46(12):e14455. doi:10.1111/jfbc.14455, PMID:36183168.
[177] Liu W, Shang J, Deng Y, Han X, Chen Y, Wang S, *et al*. Network pharmacology analysis on mechanism of jian pi qing gan yin decoction ameliorating high fat diet-induced non-alcoholic fatty liver disease and validated in vivo. J Ethnopharmacol 2022;295:115382. doi:10.1016/j.jep.2022.115382, PMID:35577161.
[178] Zhang J, Du H, Shen M, Zhao Z, Ye X. Kangtaizhi granule alleviated nonalcoholic fatty liver disease in high-fat diet-fed rats and hepg2 cells via ampk/mtor signaling pathway. J Immunol Res 2020;2020:3413186. doi:10.1155/2020/3413186, PMID:32884949.
[179] Li Y, Yang M, Lin H, Yan W, Deng G, Ye H, *et al*. Limonin alleviates nonalcoholic fatty liver disease by reducing lipid accumulation, suppressing inflammation and oxidative stress. Front Pharmacol 2021;12:801730. doi:10.3389/fphar.2021.801730, PMID:35046824.
[180] Wang SW, Lan T, Chen HF, Sheng H, Xu CY, Xu LF, *et al*. Limonin, an ampk activator, inhibits hepatic lipid accumulation in high fat diet fed mice. Front Pharmacol 2022;13:833705. doi:10.3389/fphar.2022.833705, PMID:35140621.
[181] Yang Y, Wu Y, Zou J, Wang YH, Xu MX, Huang W, *et al*. Naringenin attenuates non-alcoholic fatty liver disease by enhancing energy expenditure and regulating autophagy via ampk. Front Pharmacol 2021;12:687095. doi:10.3389/fphar.2021.687095, PMID:34163366.
[182] Hao R, Shan S, Yang D, Zhang H, Sun Y, Li Z. Peonidin-3-o-glucoside from purple corncob ameliorates nonalcoholic fatty liver disease by regulating mitochondrial and lysosome functions to reduce oxidative stress and inflammation. Nutrients 2023;15(2):372. doi:10.3390/nu15020372, PMID:36678243.
[183] Li YC, Qiao JY, Wang BY, Bai M, Shen JD, Cheng YX. Paeoniflorin ameliorates fructose-induced insulin resistance and hepatic steatosis by activating lkb1/ampk and akt pathways. Nutrients 2018;10(8):1024. doi:10.3390/nu10081024, PMID:30081580.
[184] Pham TH, Lee GH, Jin SW, Lee SY, Han EH, Kim ND, *et al*. Puerarin attenuates hepatic steatosis via g-protein-coupled estrogen receptor-mediated calcium and sirt1 signaling pathways. Phytother Res 2022;36(9):3601–3618. doi:10.1002/ptr.7526, PMID:35871535.
[185] Zhou J, Zhang N, Aldhahrani A, Soliman MM, Zhang L, Zhou F. Puerarin ameliorates nonalcoholic fatty liver in rats by regulating hepatic lipid accumulation, oxidative stress, and inflammation. Front Immunol 2022;13:956688. doi:10.3389/fimmu.2022.956688, PMID:35958617.
[186] Gu Y, Duan S, Ding M, Zheng Q, Fan G, Li X, *et al*. Saikosaponin d attenuates metabolic associated fatty liver disease by coordinately tuning pparα and insig/srebp1c pathway. Phytomedicine 2022;103:154219. doi:10.1016/j.phymed.2022.154219, PMID:35691075.
[187] Li X, Ge J, Li Y, Cai Y, Zheng Q, Huang N, *et al*. Integrative lipidomic and transcriptomic study unravels the therapeutic effects of saikosaponins a and d on non-alcoholic fatty liver disease. Acta Pharm Sin B 2021;11(11):3527–3541. doi:10.1016/j.apsb.2021.03.018, PMID:34900534.