

Biological Mechanisms and Related Natural Inhibitors of CD36 in Nonalcoholic Fatty Liver

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Abstract: Non-alcoholic fatty liver disease (NAFLD), a spectrum of liver disorders from non-alcoholic fatty liver (NAFL) to the more severe non-alcoholic steatohepatitis (NASH), is the leading etiology of chronic liver disease and its global prevalence is increasing. Hepatic steatosis, a condition marked by an abnormal buildup of triglycerides in the liver, is the precursor to NAFLD. Differentiated cluster 36 (CD36), a scavenger receptor class B protein, is a membrane receptor that recognizes multiple lipid and non-lipid ligands. It is generally agreed that CD36 contributes significantly to hepatic steatosis by taking part in fatty acid uptake as well as triglyceride storage and secretion. While there has not been any conclusive research on how CD36 inhibitors prevent NAFLD from progressing and no clinically approved CD36 inhibitors are currently available for use in NAFLD, CD36 remains a target worthy of further investigation in NAFLD. In recent years, the potential role of natural products acting through CD36 in treating non-alcoholic fatty liver disease has attracted much attention. This paper offers an overview of the pathogenesis of CD36 in NAFLD and summarizes some of the natural compounds or extracts that are currently being investigated for modulating NAFLD via CD36 or the CD36 pathway, providing an alternative approach to the development of CD36-related drugs in NAFLD.

Keywords: NAFLD, CD36, natural inhibitors, FFA, TG

Introduction

NAFLD is at the forefront of liver disease with a global prevalence of 25%.¹ NAFLD makes a huge impact on the quality of people's lives and has also exacted a growing economic burden.²⁻⁴ There are numerous unresolved issues, and there are no recognized treatments for NAFLD although continuous progress in understanding the pathogenesis of the disorder, finding therapeutic targets, and advancing drug development.⁵ Prevention and treatment remain increasing challenges.

NAFLD is associated with obesity, insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome.⁶ The pathogenesis of NAFLD is a complicated process. The traditional "two-hit" mechanism sees sedentary lifestyles, high-fat diets, and insulin resistance leading to a build-up of hepatic lipid accumulation, which can make the liver sensitive and further stigmatized as a "second hit" that triggers inflammation and fibrosis.⁷ However, the pathogenesis and progression of NAFLD are multifactorial and complex, it cannot be summarized in this simple way, and this fact has given rise to "multiple-hit", which are thought to include a combination of insulin resistance, lipotoxicity, nutritional factors, gut microbiota, and genetics acting in parallel to trigger the NAFLD development.^{8,9}

Differentiated cluster 36 (CD36), a multi-ligand receptor, is named "SR-B2".¹⁰ A variety of physiological processes are mediated by this membrane glycoprotein, which is found in hepatocytes, platelets, adipocytes, mononuclear phagocytes, myocytes, and some epithelial cells. Roles of CD36 in lipid accumulation, inflammatory signaling, energy reprogramming, and oxidative stress have been demonstrated.^{11,12} Recent research has also revealed that CD36 is

a common transcription target for multiple ligand-sensing and lipogenic transcription factors, including the aryl hydrocarbon receptor,¹³ and several nuclear hormone receptors, including progesterone X receptor (PXR), liver X receptor (LXR), and peroxisome proliferator-activated receptor γ (PPAR γ).¹⁴ Although CD36 expression is not high in liver cells under physiological conditions, it is highly induced when lipid overload or nuclear cell activation occurs.^{15,16} CD36 is a high-affinity receptor for long chain fatty acids (LCFAs), suggesting a potential role of CD36 in lipid metabolism. CD36 is associated with cellular uptake of free fatty acids and drives hepatic steatosis in the liver, possibly leading to the development of NASH.^{17,18} Several clinical studies have shown that Levels of CD36 are higher in patients with nonalcoholic fatty liver disease than in normal subjects.^{19,20} There are currently no FDA-approved CD36-related medications, but there have been numerous reports of natural substances treating NAFLD that work on CD36 or the CD36 pathway.^{21,22} CD36 and its transcriptional regulators are expected to be identified as new therapeutic targets for the treatment and prevention of NAFLD in the future.

The Role of CD36 in the Occurrence and Progression of NAFLD Fatty Acid Oxidative Impairmen

As we all know, CD36 is the main participant in metabolic tissue, primarily involved in the uptake of long-chain fatty acids (LCFAs).²³ CD36 is subject to various types of posttranslational modifications in a way that depends on the tissue, condition, and time-dependent manner, and one of the most common lipid modifications of CD36 is palmitoylation.²⁴ Mitochondrial fatty acid oxidative (FAO) impairment in hepatocytes leads to lipid accumulation, overproduction of mitochondrial reactive oxygen species (ROS), and oxidative damage, which further leads to NAFLD.²⁵ A recent study found that CD36 was present in hepatocyte mitochondria and that hindering CD36 palmitoylation greatly increases the distribution of CD36 to hepatocyte mitochondria. Long-chain acyl-CoA synthetase (ACSL) is a key enzyme that converts LCFAs into long-chain acyl-CoA and thus oxidizes them in mitochondria. When the localization of CD36 is increased, more ACSL1 and CD36 in the mitochondria interact to boost the transfer of additional LCFAs to ACSL1, which in turn promotes FAO and lessens NAFLD by increasing the production of long-chain acyl-CoA (Figure 1A).²⁶ It may be an effective method for the treatment of NAFLD to inhibit CD36 palmitoylation thereby reducing the localization of CD36 in mitochondria.

β -Oxidation and Inflammation

The function of CD36 largely depends on its position in the plasma membrane, and post-translational modification of palmitoylation can increase the modified protein's lipophilicity, controlling the distribution and function of CD36 within the cell. The expression of CD36 enhanced as the liver progressed from normal to simple steatosis (SS) and then to NASH. When compared to SS and liver cirrhosis, the dispersion of CD36 on the cell membrane of NASH patients' liver cells increased significantly.¹⁹ This suggests that the enhanced location of CD36 on hepatocyte plasma membranes may be a crucial aspect of NASH development.²⁷ One study showed that the increase of palmitoylation of CD36 promoted the transfer of CD36 to the plasma membrane of liver cells. The formation of the CD36/Lyn/Fyn complex is aided by palmitoylated CD36, which also aids FA absorption, and initiates c-JUN N-terminal kinase (JNK) which causes inflammation in adipose tissues, promotes Fyn-mediated LKB1 phosphorylation, and inhibits LKB1-mediated AMPK activation, and impair FA β -oxidation. Inhibiting palmitoylation of CD36 may enhance phosphorylation of AMP-activated protein kinase (AMPK) in the way of Fyn-LKB1 manner, improve FA β -oxidation and prevent steatosis. Furthermore, JNK signaling pathway inactivation is a crucial factor in CD36-mediated inflammation. The inhibition of palmitoylation of CD36 can block JNK signaling pathway inactivation, which reduces inflammation in the liver tissue (Figure 1B).²⁸ These results imply that in the future, targeting the palmitoylation site of CD36 may represent a novel research avenue for the treatment and prevention of NAFLD.

Lipotoxicity

Lipotoxicity refers to the harmful effects of high concentrations of lipids and lipid derivatives on cells.²⁹ Lipotoxicity occurs when lipid metabolism is misregulated. Evidence shows that hepatic injury is one of the key events in the pathophysiology of NAFLD.³⁰ When the high levels of peripheral free fatty acids or the new fat synthesis of the liver

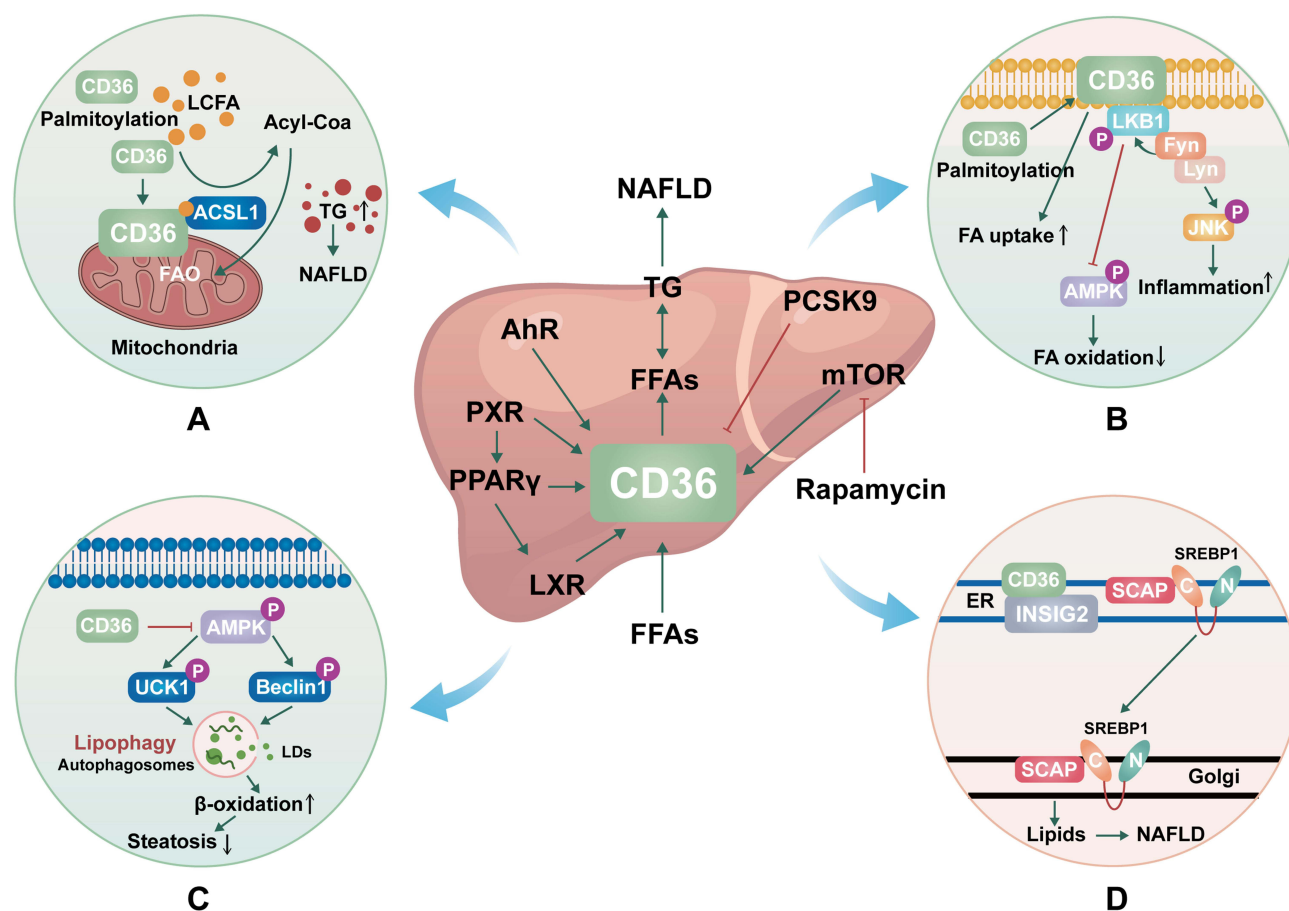


Figure 1 The mechanisms of CD36 in NAFLD. (A). Molecular mechanisms by which CD36 palmitoylation promotes FAO and NAFLD. (B). Molecular mechanisms by which CD36 palmitoylation promotes β -oxidation and inflammation. (C). Molecular mechanisms by which CD36 inhibits autophagy. (D). Molecular mechanisms by which CD36 promotes De novo lipogenesis.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CD36, differentiated cluster 36; LCFA, long chain fatty acid; ACSL, long-chain acyl-CoA synthetase; FAO, free fatty acid oxidation; TG, triglycerides; LKB1, live kinase B1; JNK, c-JUN N-terminal kinase; AMPK, AMP-activated protein kinase; Lyn, the kinase Lck/Yes-related novel protein tyrosine kinase; FA, Fatty acid; AhR, aryl hydrocarbon receptor; PXR, Pregnane X receptor; PPAR γ ; peroxisome proliferator-activated receptor; LXR, liver X receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; mTOR, mechanistic target of rapamycin; UCK1, uridine-cytidine kinase I; LDs, lipid droplets; ER, endoplasmic reticulum; SCAP, SREBP cleavage-activating protein; INSIG2, insulin-induced gene-2; SREBP1, sterol regulatory element-binding protein 1.

increases, the liver's ability to utilize, store and export free fatty acids is covered, which is the cause of lipotoxicity.³¹ The mechanisms of lipotoxicity involve several cellular processes, such as endoplasmic reticulum stress, mitochondrial dysfunction, and lysosomal permeability, which ultimately lead to triggering apoptosis.^{32,33} The increase in intake and utilization of free fatty acids is significantly influenced by CD36. Excessive circulating free fatty acids can cause cytotoxicity and apoptosis. As mentioned earlier, palm acylation of CD36 promotes the intake of fatty acids and increases the accumulation of lipids in the liver. The relationship between palm acylation of CD36 lipid toxicity needs further study.²⁶ Gaemers IC et al³⁴ established a mouse model of NAFLD by high-fat liquid diet (HFLD) overfeeding which liver steatosis developed and NASH developed. In the mouse model, adipocytes experienced metabolic changes, which resulted in a decrease in lipid storage capacity and an increase in lipid outflow, which led to lipotoxicity in peripheral organs. And CD36 was found to be induced in the livers of mice overfed with HFLD.³⁵ In a word, it is very important to understand the molecular mechanism of CD36 for inhibiting or alleviating lipotoxicity and adverse consequences during nonalcoholic fatty liver disease.

Autophagy

In addition to playing a role in fatty acid uptake, CD36 has also been shown to affect lipid autophagy, which is the defense mechanism of hepatocytes against NAFLD.³⁶ This is a selective mass degradation system, which swallows

solute and regulates the hepatic metabolic pathway. Lipid autophagy is a form of selective autophagy, which cuts off some lipid droplets and fuses them with lysosomes, promoting lipid decomposition, and then producing energy and ketones through β -oxidative catabolism.³⁷ It has been shown that CD36 knockdown induces autophagy in hepatocytes due to increased autophagosome formation in autophagic flow, while CD36 overexpression inhibits autophagy.³⁸ AMP-activated protein kinase (AMPK) directly phosphorylates autophagy activating kinase 1 (ULK1) and Beclin1 is critical for autophagy.^{39,40} In CD36 gene knockout hepatocytes, lipid phagocytosis increased through the AMPK-ULK1/Beclin pathway, which contributed to the increase of β -oxidation and the alleviation of steatosis. CD36 acts as a negative regulator of autophagy, which is responsible for lipid accumulation in liver cells and mice. Inhibition of CD36 can enhance fatty acid clearance by inducing autophagy, which has become a new therapeutic strategy for NAFLD and other metabolic diseases (Figure 1C).⁴¹

De novo Lipogenesis

De novo lipogenesis (DNL) or de novo fatty acid (FA) synthesis is a metabolic pathway that synthesizes fatty acids from excess carbohydrate.⁴² Studies have shown that enhanced DNL in hepatocytes is a major cause of NAFLD.⁴³ Overexpression of CD36 is related to the exacerbation of steatosis, and its mechanism involves the increase of FFA uptake and TG storage in the hepatic. There is growing evidence that CD36 goes far beyond FFA transport.^{41,44} In a recent study, CD36 was found to have a novel role in the resynthesis of fat that goes beyond the known FFA transporter function. CD36 promotes liver lipid homeostasis by regulating Sterol regulatory element-binding protein 1 (SREBP1) processing. CD36 is coupled with insulin-induced gene-2 (INSIG2) to eliminate the interaction between INSIG2 and the SREBP cleavage-activating protein (SCAP)-SREBP complex, thereby leading to the translocation of SREBP1 from ER to Golgi for processing, leading to lipogenesis.^{45,46} Thus, CD36-mediated DNL in hepatocytes is a key driver of NAFLD development and provides an intervention strategy for the treatment of hepatic steatosis (Figure 1D).

Regulation of CD36 Targets in Lipid Metabolism

PCSK9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is expressed mainly in the liver and is thought to induce the degradation of low-density lipoprotein receptor (LDLR) in the liver, thus leading to an increase in the levels of circulating LDLC.^{47,48} Recent studies have shown that PCSK9 induces CD36 degradation via intracellular or extracellular pathways, reducing CD36 levels on the cell surface, and thereby affecting the metabolism of long-chain fatty acids and triglycerides in the livers of the lysosome adipocytes and mice. PCSK9 interacts directly with CD36. Functionally, the internalization of ligands like oxidized LDL in liver cells and analogs of palmitic acid in adipocytes was considerably diminished by the lower CD36 levels. In contrast, by inhibiting PCSK9 expression with small interfering RNA, CD36 and LDLR protein levels in HepG2 hepatocytes were significantly increased. In vivo, recombinant PCSK9 was injected into wild-type C57BL/6 mice, causing the degradation of CD36 in the liver. Conversely, loss of PCSK9 resulted in a significant rise in CD36 protein expression in the liver and other tissues, which is linked to an increase in fatty acid absorption and triglyceride levels in the liver. PCSK9 induces the degradation of CD36 in the acidic compartment of the posterior endoplasmic reticulum through a proteasome sensitive mechanism. In tissues with significant lipid flow, including the visceral adipose tissue and liver, PCSK9-mediated control of CD36 levels may restrict fatty acid uptake and triglyceride accumulation and offer additional mechanistic support for the function of PCSK9 in triglyceride metabolism.⁴⁹ Similarly, Lebeau PF et al⁵⁰ found that PCSK9 prevents the uptake and accumulation of CD36-mediated FA in cultured hepatocytes. It was observed that the increase of CD36 expression significantly led to the increase of intracellular lipid levels in liver cell lines with reduced PCSK9 expression.

Although there is a large body of data suggesting that PCSK9 affects circulating cholesterol more than it does circulate and peripheral triglyceride levels.^{51,52} However, PCSK9 can reduce CD36 levels and prevent the accumulation of long-chain fatty acids and triglycerides, thus preventing endoplasmic reticulum stress, fibrosis, and liver injury, which is still worthy of our attention and further research.

PPAR/RXR/LXR

Through engaging the lipogenic transcription factor sterol regulatory element-binding protein (SREBP-1c) and its target gene, the liver X receptor (LXR) is considered to induce adipogenesis.^{53–55} There is increasing evidence that LXR may have additional transcription targets. It may promote steatosis by regulating CD36 directly or indirectly through peroxisome proliferator-activated receptor (PPAR) γ , this activation is liver-specific.^{56,57} Similarly, it has been demonstrated that the Pregnane X receptor (PXR) controls CD36 either directly or indirectly through PPAR γ , and PXR activation of CD36 is also liver-specific.⁵⁸ Along with LXR and PXR, the activation of PPAR γ may also encourage CD36 activation and steatosis. Recent studies have shown that LXR, PXR, and PPAR γ synergistically contribute to promoting CD36 expression, which in turn promotes hepatic steatosis. In addition, Hajri T et al⁵⁹ showed that palmitic acid (PA) stimulation of liver cells reduced PPAR γ promoter-specific DNA methylation, strongly induced CD36 and, very low-density lipoprotein (VLDL) expression, and increased liver fat storage, which further led to hepatic steatosis. To assess the efficacy of an intervention for adipogenic therapy, CD36, a common target for adipogenic nuclear receptors, maybe a trustworthy liver indicator.

AhR

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor belonging to the basic helix-loop-helix (bHLH)/Per-Arnt-Sim (PAS) family of proteins.⁶⁰ AhR and its ligands have been found to have a philanthropic effect on AhR gene expression and lipid metabolism. Lee JH et al⁶¹ reported a CA-AhR transgenic mouse by eliminating the minimum ligand-binding domain of AhR (amino acid 287–422). CA-AhR transgenic mice showed spontaneously hepatic steatosis in contrast to wild mice. In addition, the steatosis effect of AhR agonists was eliminated in CD36 knockout mice, suggesting that AhR activation promotes steatosis through activation of CD36 expression. Yao L et al⁶² found that hyperhomocysteine (HHcy) induced hepatic steatosis and increased hepatic expression of CD36, which was associated with the activation of AhR. In another study, Kawano Y et al⁶³ found that the AhR agonist 3-methylcholanthrene (3MC) enhanced CD36 expression in mouse and human hepatocellular carcinoma cells HepG2 and induced hepatic steatosis. In addition, the study by Yuan P and others found that compared with low-dose TCDF (a kind of have to human body health of toxic organic pollutants 2,3,7,8-tetrachlorodibenzofuran) treatment in mice, high dose treatment showed the ratio of liver to body weight of mice increased significantly, as well as a significant rise in the liver triglyceride levels, TCDF exposure activates AhR and its target genes Cyp1a1 and CD36.⁶⁴ Jin J et al⁶⁵ found a qualitative increase in liver steatosis in Ahre/e mice (a type of systemic AhR excised mouse). CD36 was increased by PCB126 (activators of AhR) exposure and Ahre/e genotype. Liver steatosis and injury were increased in Ahre/e mice. This may be partly due to increased lipid uptake of liver CD36 receptors. These studies may be helpful to establish AhR and its target CD36 as new targets for the therapy and averting the development of NAFLD.

mTOR

The mammalian target of rapamycin (mTOR) has been proved to play a role in the activation of inflammatory stress and metabolic syndrome.⁶⁶ Rapamycin, a specific inhibitor of mTOR in mammalian cells, has been used as an immunosuppressant to prevent transplant rejection. Research has indicated that the lipid metabolism enzymes SREBP1c, SREBP2, FASN, acetyl-coa carboxylase (ACC), stearoyl-coa desaturase-1 (SCD1), and LDLR can be inhibited by rapamycin, which also reduces hepatic steatosis.^{67–70} Rapamycin has been shown in studies to have a pleiotropic anti-lipid deposition impact in hepatic steatosis.⁷¹ Rapamycin significantly reduced lipid accumulation in the liver of HepG2 hepatocytes treated with palmitic acid or C57BL/6J mice fed with HFD, which indicated that rapamycin had a protective effect on reducing hepatic steatosis.⁷² Although CD36 mRNA expression was not affected by rapamycin, CD36 protein expression was. Rapamycin altered the expression of the CD36 protein in the liver at the post-transcriptional level as opposed to the transcriptional level because CD36 is essential for the rapamycin-mediated remission of induced hepatic steatosis. Rapamycin inhibits the mTOR signaling pathway's partial inflammatory stress-induced increased phosphorylation and reduced CD36 translational efficiency, which lowers the quantity of CD36 protein. mTOR signaling pathway mediates inflammatory stress and enhance the expression of CD36 protein. In addition, rapamycin can significantly reduce the

intake of FFA in vitro and in vivo, reduce the lipid accumulation in the liver, overcomes the influence of inflammatory stress, and provide a protective effect in reducing liver steatosis.⁷³ Inflammation significantly increases FFA uptake, while rapamycin reduced FFA uptake, which is one of the mechanisms of fat accumulation in cells in addition to the fat formation, expressed by CD36. Rapamycin reduces CD36 translation efficiency and mTOR signaling, which may represent a novel molecular mechanism of hepatic steatosis and adds to the data supporting the use of mTOR inhibitors to treat NAFLD in patients with metabolic syndrome.

In addition, hepatic hypoxia-inducible factor 2 α (HIF-2 α) was identified as a major regulator of hepatic lipid metabolism through the upregulation of CD36.⁷⁴ Likewise, krueppel-like factor 9 (KLF9) can regulate hepatic lipid metabolism and development of NAFLD by promoting the expression of CD36,⁷⁵ sex determining region Y-box 2 (SOX2) was proved to play a role in FFA-induced lipid accumulation in hepatocytes by up-regulating CD36 expression.⁷⁶ Other studies have found that some microRNAs (miRNAs) potentially target CD36 and influence liver lipid accumulation by modulating the receptor. Among them, miR-29a was found to improve hepatocellular steatosis and liver fibrosis by targeting its 3'-untranslated region (UTR) to inhibit CD36 expression.⁷⁷ Similarly, MiR-20a-5p inhibits CD36 expression by binding to CD36's 3' UTR.⁷⁸ Another study found that a protective role of miR-100 in HFD induced metabolic syndrome and liver steatosis, partially mediated by the direct repression of CD36 and attenuation of hepatic lipid storage.⁷⁹

Natural Products That Affect the Occurrence and Development of NAFLD by Acting on CD36

Berberine (BBR) is an isoquinoline alkaloid derived from *Rhizoma Coptidis*. Data from extensive research have conclusively shown that BBR can enhance insulin sensitivity and improve glucose metabolism.⁸⁰ Yu M et al⁸¹ found that BBR significantly reversed the HFD-fed mice liver CD36 protein level elevation. Besides, the mice intestinal protein levels of CD36 elevation caused by HFD-fed were also reversed by the treatment of BBR. BBR relieves hepatic steatosis by inhibiting the protein levels of hepatic and intestinal CD36 fatty acid uptake. It is worth noting, Choi YJ et al⁸² found that BBR induces phosphorylation of AMPK in HepG2 cells and mouse primary hepatocytes, leading to the activation of extracellular signal-regulated kinases 1/2 (ERK1/2) and CCAAT/enhancer-binding protein β (C/EBP β), resulting in increased CD36 expression. Similarly, prolonged activation of AMPK by BBR in HepG2 cells and mice increased CD36 expression and fatty acid uptake, which may lead to hepatocellular lipid accumulation and fatty liver. This difference may be ascribed to the use of different dosages of berberine in the two studies, which may be one of the keys to determining the toxicity of berberine. Further research is needed to clarify the distinction between the beneficial and harmful effects of berberine (Table 1).

Curcumin, a polyphenol derived from *turmeric* roots, has been shown in several studies to reduce inflammation, atherosclerosis, and obesity.^{83–85} In recent years, curcumin has been shown to affect lipid metabolism in mouse models of NAFLD. Liu Y et al⁸⁶ found that curcumin significantly reversed the liver relative mRNA level of CD36 in mice fed with a high-fat and high-fructose diet (HFHFr)-diet, and reduced fatty acid uptake.

Oxidative stress is considered a key component in NASH pathogenesis.^{87,88} An increase in oxygen consumption in the liver has been linked to oxidative stress and activation of hypoxia-inducible factor (HIF) leading to CD36 overexpression.⁸⁹ β -patchoulene (β -PAE) is one of the active natural tricyclic sesquiterpene isolated from the essential oil of *patchouli*. It has exhibited unexpected anti-inflammatory and antioxidative effects.⁹⁰ Wu J et al⁹¹ found that β -PAE decreased body weight gain, liver index, and epididymal adipocyte weight in NASH rats, and decreased serum CD36 content. In the liver of NASH rats, β -PAE treatment resulted in reduced expression of the CD36 proteins. In addition, when CD36 was highly expressed, AMPK activation in NASH rats is significantly inhibited, and β -PAE therapy reverses this trend. It was suggested that β -PAE might reduce hypoxia in liver tissue and improve hepatic lipid metabolism balance through CD36/AMPK signaling pathway.

Naringin, a naturally occurring flavonoid compound, extracted from traditional Chinese medicine (TCM), is believed to promote anti-inflammatory, anti-oxidative, and prevention of fibrosis in the liver.^{92,93} The latest research suggests that naringin can adjust NAFLD caused by a high fat diet in mice of the intestinal flora and metabolic function to give play

Table I Natural products which treat NAFLD through CD36

Name	Classification	Sources	Type of Study	Dosage	Medical Effects	References
Berberine	Alkaloids	Coptis chinensis	In vivo	blended into the ^A HFD at 1.4 g/kg	↓ Protein levels of CD36	[81]
			In vivo and in vitro	In vitro: 10 μM In vivo: 10 mg/kg/day	In vitro: ↑ mRNA expression and protein levels of CD36 transcriptional activation of CD36 In vivo: ↑ mRNA expression and protein levels of CD36	[82]
Curcumin	Phenols	Turmeric	In vivo	50 mg/kg and 100 mg/kg	↓ mRNA Expression of CD36	[86]
β-patchoulene	Terpenoids	Pogostemonis Herba or “Guang-Huo-Xiang”	In vivo	10, 20 and 40 mg/kg	↓ Hepatic CD36 expression	[91]
Naringin	Flavonoids	Grapefruit and oranges	In vivo	In vitro: 10 μM	↓ mRNA expression and protein levels of CD36	[94]
The extract of Syzygium simile leaves	Extracts	Syzygium simile leaves	In vitro	50 and 100 μg/mL	↓ mRNA and Protein Expression of CD36 in Huh7 cells ↓ the expression of CD36 in both macrophage and enterocyte cells	[95]
Siphonaxanthin	Carotenoid	Green algae such as Codium fragile, Umbraulva japonica, and Caulerpa lentillifera	In vitro	0.5, 1.0, and 2.0 μM	↓ The transcriptional levels of CD36	[96]
Dolichos lablab water extract	Extracts	Dolichos lablab Linne	In vitro	1, 10, 100, and 250 μM	↓ mRNA level of CD36	[97]
Cinnamic acid	Phenylpropanoids	Citrus fruits and grape and vegetables	In vivo and in vitro	In vitro: 25, 50, and 100 μM In vivo: 20 mg/kg	In vitro: ↓ The mRNA expression of CD36 In vivo: ↓ the mRNA expression of CD36	[101]

(Continued)

Table 1 (Continued).

Name	Classification	Sources	Type of Study	Dosage	Medical Effects	References
Alisol B	Triterpenoids	<i>Alisma orientalis</i>	In vivo and in vitro	In vitro: 10 μ M In vivo: 100 mg/kg	In vivo: \downarrow mRNA and protein level of CD36 In vivo: \downarrow mRNA and protein level of CD36	[102]
Quercetin	Flavonoids	Flowers, leaves, and fruits of many plants, particularly alfalfa.	In vivo	100 mg/kg bw	\downarrow The mRNA and protein expression of CD36	[103]
Gypenosides	Triterpenoids	<i>Gynostemma pentaphyllum</i> , perennial vines widely grown in Asian	In vivo	300 mg/kg	\downarrow The mRNA levels of CD36	[104]
Raw Bowl Tea polyphenols	Phenols	Bowl Tea	In vivo	In vivo: 50 and 100 mg/kg	\downarrow The mRNA and protein expression of CD36	[105]
The aqueous extract of the aerial part of <i>Angelica tenuissima</i> Nakai	Extracts	<i>Angelica tenuissima</i> Nakai	In vivo and in vitro	In vitro: 50, 100, and 200 μ g/mL In vivo: 10 or 50 mg/kg	In vivo: \downarrow The mRNA and protein expression of CD36 In vitro: \downarrow The protein expression of CD36	[106]
Piceatannol	Phenols	Grapes, whites tea, passion fruit, and Japanese knotweed	In vitro	100 μ M	\downarrow The mRNA expression of CD36	[107]
Magnolol	Lignans	<i>Magnolia officinalis</i>	In vivo and in vitro	In vitro: 8 μ g/mL In vivo: 10 mg/kg	In vivo: \downarrow The mRNA expression of Cd36 In vitro: \downarrow The protein and mRNA expression of cd36	[108]
A pomegranate fruit extract	Extracts	Pomegranate	In vivo	In vivo: 1%	\downarrow CD36	[109]
Cordycepin	Alkaloids	<i>Cordyceps militaris</i> .	In vivo	In vivo: 50 mg/kg	\downarrow The mRNA and protein expression of CD36	[110]
<i>Liriope platyphylla</i> root ethanolic extract	Extracts	<i>Liriope platyphylla</i>	In vivo and in vitro	In vitro: 50, 100 μ g/mL In vivo: 100, and 250 mg/kg	In vivo: \downarrow The protein expression of CD36 In vitro: \downarrow The protein expression of CD36	[112]

(Continued)

Table I (Continued).

Name	Classification	Sources	Type of Study	Dosage	Medical Effects	References
Sweroside	Iridoids	Swertia pseudochinensis Hara	In vivo	In vivo: 60, 120, 240 mg/kg	↓ The mRNA levels of CD36	[113]
Ginsenoside Rg1	Triterpenoids	Ginseng	In vitro	In vitro: 25, 50 μM	↓ The mRNA and protein expression of CD36	[114]
Extracts of Ficus hirta Vahl.	Extracts	Ficus hirta Vahl.	In vivo and in vitro	In vivo: 5, 10 mg/kg In vitro: 15, 30 mg/mL	In vivo: ↓ The mRNA and protein levels of CD36 In vitro: ↓ The mRNA and protein levels of CD36	[115]
Betaine	Alkaloids	Beta vulgaris	In vivo	In vivo: 1% (w/v)	↓ The mRNA and protein levels of CD36	[116]
Abelmoschus esculentus subfractions	Extracts	Abelmoschus esculentus	In vitro	In vitro: 1, 2.5, and 5 μg/mL	↓ The mRNA and protein levels of CD36	[118]
Hydroethanolic extract of Dillenia indica leaf	Extracts	Dillenia indica leaf	In vitro	5, and 10 μg/mL	↓ The protein levels of CD36	[120]
Salvianolic acid B	Phenylpropanoids	The root of Salvia miltiorrhiza	In vivo	10 and 20 mg/kg/d	↓ The mRNA levels of CD36	[122]
Puerarin	Flavonoids	The root of Pueraria lobata	In vivo	0.1% and 0.2%	↓ The mRNA levels of CD36	[124]
Gallic acid	Phenols	Fruits and nuts	In vitro	In vitro: 50, 100, and 200 μM	↓ The mRNA and protein levels of CD36	[126]
Theobromine	Alkaloids	A variety of plants such as Theobroma cacao, Cola aluminate, Paullinia cupana, and Ilex aquifolium.	In vivo and in vitro	In vitro: 0, 10, 100 μM In vivo: 100 mg/kg/d	In vivo: ↓ The protein expression of CD36 In vitro: ↓ The protein expression of CD36	[129]

Abbreviations: [^]HFD, high-fat diet.

the role of lipid-lowering. Zhang X et al⁹⁴ studies show that naringin reduced the accumulation of lipid droplets within the liver cells, decreased intracellular triglyceride levels and inhibited alanine transaminase (ALT) elevation. CD36 mRNA and protein levels in tissue-engineered fatty (TEF) livers were downregulated by Naringin treatment. Additionally, by molecular docking, naringin was proved to bind directly to the CD36 domain and inhibits FFA uptake.

Syzygium simile is a kind of the Myrtaceae family, distributed in Taiwan and the Philippines and other regions. Yen CH et al⁹⁵ by utilizing an image-based high-throughput screening found that the extract of *Syzygium simile leaves* (SSLE) can reduce, including liver, bowel and macrophages of several cell types in the accumulation of lipid droplets. Further research proves that SSLE suppresses the mRNA and protein expression in vitro in a dose-dependent manner, blocking fatty acid uptake and subsequently preventing fatty acid uptake by liver cells. In addition, the lipid accumulation and CD36 expression in macrophages and intestinal epithelial cell lines were also inhibited after SSLE treatment.

Siphonaxanthin (SPX) is a marine carotenoid abundant in *green algae*, which has been reported to have antiangiogenesis, anti-degranulation, and anti-obesity effects. Zheng J et al⁹⁶ showed that SPX significantly inhibited the accumulation of TAG in HepG2 hepatocytes in a concentration-dependent manner. CD36 mRNA levels are significantly downregulated by SPX.

Hung WL et al⁹⁷ *Dolichos lablab* water extract (DLL-Ex) can protect liver in an in vitro model of NAFLD. THE study found that DLL-Ex inhibited lipid accumulation induced by free fatty acids in HepG2 hepatocytes and reduced FFA uptake in HepG2 hepatocytes. The expression levels of CD36 were significantly and dose-dependently decreased when HepG2 cells are treated with the DLL-Ex (100 and 250 μ g/mL).

Cinnamic acid (CA), a kind of natural polyphenols, contains nine carbon atoms, was reported to have antibacterial, anti-inflammatory, antioxidant, and the effect of anti-diabetes.^{98–100} Research has shown that cinnamic acid on a high-fat diet induced animal models of obesity and lipid levels, Adisakwattana et al¹⁰¹ found that cinnamic acid decreased liver cancer cell accumulation of lipid droplets, after cinnamic acid treatment, the mRNA expression of CD36 in obese rats were significantly down-regulated, and fatty acid uptake in hepatocytes was inhibited.

Alisol B is a natural compound derived from the plant *Alisma orientalis (Sam)*. Zhao Z et al¹⁰² discovered that Alisol B reduced hepatic steatosis, inflammation, and fibrosis in NASH mice induced by a high-fat diet plus carbon tetrachloride (DIO+CCl₄) and choline-deficient and amino acid-defined (CDA) diet. Alisol B dramatically decreased CD36 expression and controlled retinol metabolism in DIO+CCl₄ and CDA-diet-induced NASH mice. Similarly, Alisol B inhibited the mRNA and protein levels of CD36 in a dose-dependent manner in mouse primary hepatocytes. Alisol B Inhibited Oxidative Stress and Inflammation in Primary Hepatocytes in a CD36-Dependent Manner. Further research has found that Alisol B has previously unknown therapeutic benefits against NASH via a unique mechanism by modulating the RAR-PPAR-CD36 cascade, indicating Alisol B as a prospective lead chemical for the treatment of NASH.

Quercetin, the special subclass of flavonoid, has anti-inflammatory and anti-oxidant actions. Liu L et al¹⁰³ found that quercetin inhibited the mRNA and protein expression of CD36 in HFD-fed mice, thereby decreasing excessive deposition of hepatic oxidized low-density lipoprotein (ox-LDL), and alleviating long-term HFD-induced liver damage.

Gypenosides (GP) extracted from *Gynostemma pentaphyllum Makino* have a significant role in reducing serum lipid levels and treating fatty liver diseases. Huang XGP et al¹⁰⁴ showed that administration of GP alleviates steatohepatitis and reversed the upregulated CD36 levels in mice fed an HFHC (high-fat and high-cholesterol) diet.

Raw Bowl Tea polyphenols (RBTP) contain numerous polyphenolic compounds, including Gallic acid, (-)-epigallocatechin, catechin, L-epicatechin, (-)-epigallocatechin gallate, (-)-gallocatechin gallate, and (-)-epicatechin gallate (ECG), and high levels of caffeine, (-)-epigallocatechin (EGC), and ECG. Liu B showed et al¹⁰⁵ showed that RBTP could effectively down-regulated the expression of CD36 located in the brush border membrane of small intestine villus cells of NAFLD mice, and prevented NAFLD by regulating intestinal function.

Lee W et al¹⁰⁶ showed that the aqueous extract of the aerial part of *Angelica tenuissima Nakai* (ATX) inhibited oleic acid-induced neutral lipid accumulation in HepG2 cells, and decreased the mRNA and protein levels of CD36.

Piceatannol, a natural stilbene, has an effect on cancer prevention, neuro-protection, and anti-diabetic. Yang J et al¹⁰⁷ found that piceatannol significantly reduced fat accumulation and inhibited fatty acid uptake by reducing CD36 mRNA expression in fat-induced HepG2 cells.

Magnolol (MG) is a bioactive polyphenolic compound isolated from the *Magnolia officinalis* that exert the accumulation of oxidative stress and plays a significant role via a variety of mechanisms. Kuo NC et al¹⁰⁸ found that MG reversed the elevated mRNA levels of CD36 in NAFLD Rats induced by Tyloxapol (a nonionic surfactant that

blocks plasma lipolytic functions) treatment. In addition, MG inhibited fatty acid uptake by reducing CD36 mRNA expression in PA-induced steatotic HepG2 cells.

Pfohl M et al¹⁰⁹ showed that pomegranate fruit extract (PE) alleviated diet-induced fatty liver and suppressed the mRNA levels of CD36 in HFD-fed mice.

Gong X et al¹¹⁰ showed that the Cordycepin (CRD), a nucleotide analogue derived from traditional Chinese medicine *cordyceps*, suppresses the mRNA and protein expression of CD36 on HFD-induced obesity with NAFLD mice and reduces hepatic lipid accumulation.

Liriope platyphylla is traditional medicine, which suggested a protective role of LPE in anti-obesity and anti-inflammatory effects.¹¹¹ Le TNH et al¹¹² showed that the treatment with *Liriope platyphylla* root ethanolic extract (LPE) reduced the protein expression of CD36 both in vivo and in vitro, leading to reduced fatty acid uptake.

Swertiamarin is a kind of secoiridoid glycoside, which is the active ingredient of *Swertia chinensis*. Yang et al¹¹³ found that the mRNA level of CD36 is markedly decreased in mice with sweroside treatment, which may ameliorate obesity with fatty liver via the regulation of lipid metabolism and inflammatory responses.

Gao Y et al¹¹⁴ found that Ginsenoside Rg1 (G-Rg1) inhibits FFA-induced lipid uptake to reduce hepatic steatosis of HepG2 cells by downregulating the mRNA and protein expression of CD36.

Quan T et al¹¹⁵ found that *Ficus hirta* Vahl. (FV) suppressed the expression and activity of CD36 in HepG2 cell lines induced by palmitate (PA) and mouse model fed with a high-fat diet (HFD), and FV treatment can reverse the exacerbated effects of CD36 on lipid metabolism and inflammation.

Betaine is widely present in plants and microorganisms exerting beneficial effects on the organism. Li Y et al¹¹⁶ found that betaine reduced both mRNA and protein levels of CD36. Betaine attenuates hepatic steatosis of HFD-fed mice via targeting the PPAR γ /CD36 pathway in the liver.

Abelmoschus esculentus (AE) fruit is a traditional functional food that has a significant effect on possessing hypoglycemic and anti-oxidative qualities.¹¹⁷ A study by Peng CH et al¹¹⁸ found that subfractions F2 (having large amounts of carbohydrates and polysaccharides) isolated from AE extract demonstrate a superior effect to down-regulate the lipid uptake. F2 downregulates OAPA (oleic acid and palmitic acid with the ratio of 2:1)-induced elevation of the CD36 mRNA and protein expression in HepG2 cells. The study also found that F2 has better effects at 5 μ g/mL doses.

Dillenia indica L. is a medicinal plant from the Dilleniaceae family, traditionally used to treat jaundice, dysentery, and other diseases.¹¹⁹ The latest research by Poornima MS et al¹²⁰ found that the hydroethanolic extract of *Dillenia indica* leaf (DI-HET) can significantly lower intracellular lipid accumulation in OA-treated HepG2 cells. After DI-HET treatment, the level of CD36 protein decreased and its activity decreased.

Salvianolic acid B (SalB) is a polyphenolic compound isolated from the root of *Salvia miltiorrhiza*, which has many pharmacological effects, such as protecting vascular endothelium, anti-fibrosis, anti-liver injury, etc.¹²¹ Meng LC et al¹²² found that SalB might prevent NAFLD by inhibiting the accumulation of lipids. SalB decreased the mRNA levels of CD36 and reduced lipid accumulation in the liver of ob/ob mice. SalB decreased the mRNA levels of CD36 and reduce lipid accumulation in the liver of ob/ob mice.

Puerarin, one of the main isoflavonoid components of the root of *Pueraria lobata*, has anti-inflammation, antioxidant, and insulin resistance-reducing effects, and is commonly used for the treatment of liver damage, allergic diseases, and neuronal protective.¹²³ Zhou J et al¹²⁴ found that puerarin ameliorated the levels of lipids in the serum and liver. Puerarin reversed the high-fat and high-fructose diet (HFFD) resulting in increased expressions of CD36 in rats and reduced the rate of fatty acid uptake by the liver.

Gallic acid (GA), a natural polyphenol, has a wide range of pharmacological effects on anti-obesity, anti-inflammation, and anti-cancer activities.¹²⁵ A recent study by Tanaka M al.¹²⁶ found that GA inhibits lipid accumulation, capable of preventing NASH progression. GA effectively suppressed the mRNA and protein expression of CD36 in HepG2 cells and prevent hepatic steatosis.

Theobromine is a methylxanthine that occurs in a variety of plants such as *Theobroma cacao*, *Cola aluminata*, *Paullinia cupana*, and *Ilex aquifolium*.¹²⁷ Theobromine has a variety of pharmacological activities and therapeutic effects, including anti-inflammatory, antioxidant stress, and antimicrobial activity.¹²⁸ A recent study showed that theobromine regulated lipid metabolism in hepatocytes in vivo and in vitro. Theobromine reversed HFD-diet-induced

elevation of CD36 mRNA and protein expression in mice. Similar results were obtained in experiments in vitro. Theobromine also reduced the mRNA and protein expression CD36 in AML-12 cells.¹²⁹

Conclusions and Prospects

Nonalcoholic fatty liver disease (NAFLD) is now a leading cause of liver disease worldwide and a worldwide health problem.^{1–3} Although the pathogenesis and therapeutic targets of NAFLD have been further studied and some progress has been made in drug development, there are still some problems to be solved, for example, no approved medical treatment exists so far.¹³⁰ CD36 is a membrane glycoprotein widely found in platelets, monocytes, adipocytes and skeletal muscle, etc.¹³¹ It plays an important role in lipid accumulation, inflammatory signaling, energy reprogramming, and oxidative stress.^{11,12} The mechanism of CD36 action is partially elucidated. However, the exact roles of CD36 in NAFLD remain to be determined. Natural compounds derived from plants are an important resource for drug development, and targeting CD36 may be a potential therapy for non-alcoholic fatty liver disease. Some natural compounds have been found to alleviate NAFLD by targeting CD36 or through the CD36 pathway, presenting a promising therapeutic prospect, Cinnamic acid,¹⁰¹ Alisol B,¹⁰² Magnolol,¹⁰⁸ etc., are potential CD36 inhibitors. Compared with the standard drug, natural compounds do not need synthetic, readily available.¹³² Although the role of these natural compounds in vivo or in vitro was widely studied, clinical application research is still less, and future research can be aimed at improving pharmacokinetic and pharmacodynamic properties of these drugs, make it a useful drug for the treatment and reverse NAFLD.

By summarizing current experimental evidence, we believe that natural products that inhibit CD36 have potential clinical effects in preventing NAFLD. It cannot be ignored that some but not all studies are limited to in vitro studies, such as Siphonaxanthin,⁹⁶ Piceatannol,¹⁰⁷ Ginsenoside Rg1,¹¹⁴ etc. The effectiveness of natural inhibitors of CD36 in treating NAFLD should also be addressed by using a more reliable and appropriate in vivo model of NAFLD. Besides, considering separating the single compound from extracts is difficult, our study includes not only single compounds but extracts, such as Dolichos lablab water extract,⁹⁷ the aqueous extract of the aerial part of *Angelica tenuissima* Nakai,¹⁰⁶ pomegranate fruit extract,¹⁰⁹ etc. The drug activity of these extracts is usually attributed to the synergistic and simultaneous action of multiple compounds.^{133,134} It will be interesting in future research to focus on this synergy.

Nevertheless, the safety of natural inhibitors must also be carefully evaluated to ensure their safety. For example, berberine can increase CD36 expression and fatty acid uptake when it exceeds its optimal dosage, which means that the possible safety, dose-limiting toxicity, and maximum tolerated dose determination of these compounds also need further evaluation.⁸² In addition, it will also be very interesting to research the synergistic effects of synthetic compounds with natural products for NAFLD treatment. Natural inhibitors of CD36 mentioned in this review are not drugs in themselves, but they provided new ideas for developing new NAFLD drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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