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The effects of oleoylethanolamide, an endogenous PPAR-α agonist, on risk factors for NAFLD: A systematic review

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Summary

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease. Recently, some novel compounds have been investigated for the prevention and treatment of NAFLD. Oleoylethanolamide (OEA), an endogenous PPAR-α agonist, has exhibited a plethora of pharmacological properties for the treatment of obesity and other obesity-associated metabolic complications. This systematic review was performed with a focus on the effects of OEA on the risk factors for NAFLD. PubMed, Scopus, Embase, ProQuest, and Google Scholar databases were searched up to December 2018 using relevant keywords. All articles written in English evaluating the effects of OEA on the risk factors for NAFLD were eligible for the review. The evidence reviewed in this article illustrates that OEA regulates multiple biological processes associated with NAFLD, including lipid metabolism, inflammation, oxidative stress, and energy homeostasis through different mechanisms. In summary, many beneficial effects of OEA have led to the understanding that OEA may be an effective therapeutic strategy for the management of NAFLD. Although a wide range of studies have demonstrated the most useful effects of OEA on NAFLD and the associated risk factors, further clinical trials, from both in vivo studies and in vitro experiments, are warranted to verify these outcomes.

KEYWORDS

NAFLD, obesity, oleoylethanolamide, PPAR-α

Abbreviations: 2-AG, 2-arachidonoylglycerol; ABCA1, ATP binding cassette transporter A-1; ACC, acetyl-CoA carboxylase; AEA, arachidonoylethanolamide; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AP-1, activator protein type 1; APO, apolipoproteins; BAT, brown adipose tissue; BMI, body mass index; CB1R, cannabinoid receptor type 1; CB2R, cannabinoid receptor type 2; CCL2, chemokine (C-C motif) ligand 2; CNS, central nervous system; COX-1, cyclooxygenase-1; CPT-1, carnitine palmitoyltransferase 1; DStr, dorsal striatum; ECS, endocannabinoid system; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; FAAH, fatty acid amide hydrolase; FAS, fatty acid synthase; FAT/CD36, fatty acid translocase/cluster of differentiation 36; FFAs, free fatty acids; FGF21, fibroblast growth factor 21; GBS, gastric bypass surgery; GLP-1, glucagon-like peptide-1; GPR119, G protein-coupled receptor 119; HCC, hepatocellular carcinoma; HDC, histidine decarboxylase; HDL-C, high-density lipoproteins cholesterol; HFD, high-fat diet; HSCs, hepatic stellate cells; ICAM-1, intercellular adhesion molecule-1; IL-1B, interleukin 1 beta; IP, intraperitoneal; IR, insulin resistance; JNK, jun n-terminal kinase; LCFA, long-chain fatty acids; LEA, linoleoylethanolamine; L-FABP, liver fatty-acid binding protein; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LXRα, liver X-receptor alpha; MCD, methionine and choline-deficient; MMP2, matrix metalloproteinase 2; NAAA, n-acylethanolamine acid amidase; NAEs, n-acylethanolamines; NAFLD, non-alcoholic fatty liver disease; NAPE-PLD, n-acyl-phosphatidylethanolamine phospholipase D; NASH, non-alcoholic steatohepatitis; NAT, n-acetyltransferase; NEFA, nonesterified fatty acids; NF-kappa B, nuclear factor-kappa B; NO, nitric oxide; NOPE, n-oleoyl-phosphatidylethanolamine; OA, oleic acid; OEA, Oleoylethanolamide; PE, phosphatidylethanolamine; PEA, palmitoylethanolamide; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARs, peroxisome proliferator-activated receptors; PVN, paraventricular nuclei; ROS, reactive oxygen species; SCD1, stearoyl coenzyme A desaturase 1; SNPs, single nucleotide polymorphisms; SON, supraoptic nuclei; SREBP-1, sterol regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3; T2DM, type II diabetes mellitus; TGF-β1, transforming growth factor beta 1; TGs, triglycerides; TIMP1, tissue inhibitors of matrix metalloproteinase 1; TNF-α, tumour necrosis factor alpha; αSMA, α-smooth muscle actin; TLR4, toll-like receptor 4; TRPV1, transient receptor potential vanilloid 1; UCP-2, uncoupling protein 2; VCAM-1, vascular cell adhesion molecule-1.

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1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), as one of the most epidemic disorders worldwide, is caused by triglyceride accumulation in hepatic cells of more than 5% of liver weight.[1,2] NAFLD consists of a wide spectrum of hepatic dysfunctions, including simple steatosis, non-alcoholic steatohepatitis (NASH), necroinflammation, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[3] NAFLD is rapidly developing, and the global prevalence is estimated to be approximately 25% to 30% in the general adult population and more than 70% among adults with obesity and those with diabetes or metabolic syndrome.[4,5]

The most important theory in NAFLD pathogenesis is the two-hit theory.[6] In the first hit, obesity or insulin resistance (IR) leads to fat accumulation in hepatic cells.[6,7] In the second hit, oxidative stress has a preceding role that causes mitochondrial dysfunction that leads to impaired gene expression, altered protein synthesis, reduced mitochondrial content, and disrupted mitochondrial beta-oxidation.[8,9] Impaired beta-oxidation is a major cause in the pathogenesis of NAFLD and leads to triglyceride accumulation in hepatocytes, which results in the development of the disease.[10] Moreover, oxidative stress induces an inflammatory response and exacerbates insulin resistance and liver damage, stimulating steatohepatitis or fibrosis.[7,8,11] Nevertheless, the role of free fatty acids (FFAs) in liver damage has caused some changes in the definition of this theory. FFAs are either involved in beta-oxidation or esterification with glycerol to generate triglycerides (TGs), resulting in fat accumulation in the liver.[6] According to the evidence, FFAs increase oxidative stress and cause toxicity via direct activation of inflammatory pathways.[12] Therefore, it is speculated that hepatic TG accumulation may be a protective mechanism for inhibiting the adverse effects of nonesterified FFAs.[13]

There is no definitive treatment for NAFLD.[14] The current clinical therapies focus on improving the metabolic parameters involved in NAFLD pathogeneses, including weight loss, decreasing IR, lowering oxidative stress, and modulating blood glucose levels.[15] However, overweight and obesity are major risk factors for the initiation and progression of NAFLD.[2] Recently, some novel compounds have been investigated for the treatment of NAFLD.[16,17] For example, in the NAFLD and NASH research community, much attention has been paid to agonists of peroxisome proliferator-activated receptors (PPARs), as major therapeutic agents for NAFLD.[18]

PPARs are a group of nuclear hormone receptors that act as transcription factors, regulating the expression of genes and modulating metabolic programmes.[18,19] Distinct PPAR isotypes have different physiological functions that depend on their specific ligand activation and tissue distribution.[20] Of the three isotypes, namely, PPAR-α, PPAR-β/δ, and PPAR-γ, PPAR-α is one of the most abundantly expressed nuclear receptors in hepatocytes, where it modulates lipid metabolism and energy homeostasis.[18,21] However, mRNA transcripts for PPAR-α increasingly decrease as NASH develops in humans.[18,22] Whole-body and hepatocyte-specific PPAR-α deficient mice were diagnosed with acute liver steatohepatitis upon eating a high-fat diet (HFD) and a methionine and choline-deficient (MCD) diet.[23-25] According to novel findings, PPAR-α agonists regulate several biological processes associated with NAFLD, including metabolic dysfunction, inflammation, and oxidative stress. Thus, these drugs may be considered promising treatments for hepatic disorders.[18,26,27]

Oleoylethanolamide (OEA), an endogenous high-affinity ligand for PPAR-α, has shown major pharmacological effects in the treatment of obesity and obesity-associated metabolic complications.[23,26-28] In this systematic review, the current evidence on the therapeutic efficacy as well as mechanisms of action of OEA supplementation in the management of risk factors associated with NAFLD is discussed.

2 | METHODS

2.1 | Search strategy

PubMed, Scopus, Embase, ProQuest, and Google Scholar electronic databases were searched using the following keywords: "oleoylethanolamide" or "OEA" or "N-oleyl-phosphatidyl-ethanolamine" or "NOPE" and "non-alcoholic fatty liver disease" or "nonalcoholic steatohepatitis" or "hepatic steatosis" or "fatty liver" or "NAFLD" or "NASH" or "NAFL" or "hepatic liver" or "steatohepatitis" or "insulin resistance" or "insulin sensitivity" or "HOMA-IR" or "QUICKI" or "impaired glucose tolerance" or "glucose intolerance" or "glucose tolerance" or "impaired fasting glycemia" or "impaired fasting glucose" or "obese" or "obesity" or "fat mass" or "high fat diet" or "inflammation" or "oxidative stress" or "dyslipidemia." To minimize the loss of studies, we included all keywords related to the primary goals about the potential effects of OEA on the risk factors for NAFLD in the search strategy. Furthermore, we conducted this search strategy in several databases, which assures that most of the studies carried out thus far are discussed in this systematic overview. The search was limited to studies published in English until December 2018.

2.2 | Eligibility criteria

Studies were eligible to be included in this systematic review if they met the following criteria: (1) clinical trials, (2) experimental studies, (3) in vitro models, and (4) published in English. Studies that had insufficient information, were observational design, used OEA analogues, or included pregnant or lactating women were excluded from this review. In addition, studies on several diseases other than NAFLD-related conditions were not included in this study.

2.3 | Data extraction and quality assessment of previous studies

Two investigators independently retrieved the scientific literature, based on the inclusion criteria; studies were excluded from further review if they could not meet the predefined criteria. For quality assessment and data extract, eligible full-text studies were appraised based on a checklist consisting of the study aims, the research question, and the inclusion and exclusion criteria. Then, a third reviewer

assessed the accuracy, precision, and quality of the included data. Any disagreements regarding study eligibility and quality assessment were resolved by discussion and consensus.

2.4 | Findings

A flow chart depicting the study selection process is shown in Supplemental Figure 1 In total, 362 potentially articles were retrieved by the search strategy. Following removal of duplicate articles, 236 studies remained for further screening. Of these, 194 articles were excluded because of not providing the inclusion criteria. Overall, 42 full-text studies were reviewed. After evaluating the full texts of these articles, 12 studies were removed due to the exclusion criteria, leaving 30 articles for qualitative synthesis (Supplemental Table 1). As obesity and NAFLD are deeply connected, information in this table is divided into obesity-related outcomes and liver-related endpoints, and within each part, the studies are arranged by their design (cell line, goldfish, mice, rats, and humans).

3 | OLEOYLETHANOLAMIDE, A MULTIFUNCTIONAL FAT DERIVED FROM OLEIC ACID

3.1 | The endocannabinoid system and OEA

In the current epidemiological studies on obesity, atherosclerosis, and other metabolic disorders, such as neurodegenerative and inflammatory-related diseases, OEA is considered an endocannabinoid-like lipid as well as a derivative of unsaturated oleic acid (OA).[59,60] The endocannabinoid system (ECS) is one of the most important systems involved in physiological functions both in the brain and in the peripheral organs.[61] The ability of the ECS system to modulate appetite, food intake, and energy balance has recently attracted much attention.[62] This system consists of the membrane cannabinoid receptors (cannabinoid receptor type 1 [CB1R] and type 2 [CB2R]), endogenous ligands (endcannabinoids), and enzymes responsible for the synthesis and degradation of ligands, leading to greater food consumption by binding and activating related receptors.[61,62] Endocannabinoid-like lipids are bioactive lipid mediators with common biosynthetic and metabolic procedures, similar to endocannabinoids that function in a cannabinoid receptor-independent manner.[59,61] Dietary long-chain fatty acids (LCFA) act as activating ligands or agonists in this system.[63] OEA, belonging to the N-acylethanolamine (NAE) group, has a saturated fatty acid and/or unsaturated fatty acid amide with a group of ethanol amines (Figure 1).[59] Among these bioactive lipids, unsaturated arachidonoylethanolamide (AEA, anandamide) and 2-arachidonoylglycerol (2-AG) are endogenous ligands of the cannabinoid receptor.[64] Endocannabinoid-like compounds, such as saturated palmitoylethanolamide (PEA), unsaturated linoleoylethanolamide (LEA), and OEA, function in a CB1 receptor-independent manner.[65] AEA and 2-AG, the most important endocannabinoids, are considered major compounds of energy conservation.[63,66] These compounds enhance energy intake and reduce energy expenditure via both central and peripheral mechanisms involved in the hedonic processing of sweet and fatty meals as well as in the storage of their energy content for future utilization.[66]

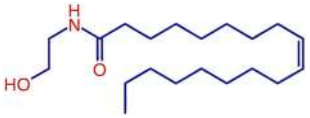


FIGURE 1 Biochemical structure of the N-oleoylethanolamide [Colour figure can be viewed at wileyonlinelibrary.com]

OEA is a monounsaturated analogue of anandamide; however, contrary to anandamide, OEA does not productively bind to cannabinoid receptors but does bind to PPAR-α.[32] OEA functions through a cannabinoid receptor-independent mechanism and causes hypophagia.[40,67] Thus, OEA is involved in the control of food intake and the regulation of feeding behaviour.[38,68,69]

3.2 | Dietary sources of OEA

Oatmeal, nuts, and cacao powder are the main dietary sources of OEA.[70] However, limited amounts are present in these foods, typically less[70] than 2 μg/g. Dietary OA acts as the main substrate for OEA production.[71] Several human studies indicate that consuming foods containing OA increases the circulating levels of OEA by elevating the availability of its precursors.[71,72] Small intestinal concentrations of OEA decrease during food deprivation, while its endogenous levels are enhanced when nutrients are available.[38] The work performed by Schwartz et al[73] demonstrated that among numerous types of fats, only OA prompted intestinal OEA production in animals. However, prolonged exposure to dietary fat reduces the levels of OEA in the small intestine.[74,75] Joosten et al[76] illustrated that the plasma levels of OEA were positively associated with serum concentrations of FFAs and the associated specific fatty acid precursor, OA, in humans.

3.3 | Biosynthesis and degradation of OEA

Endogenous production of OEA in the intestine is accomplished through several biochemical reactions in which OA and phosphatidylethanolamine (PE) are used as fundamental substrates.[77,78] In the first stage, OA enters the enterocytes through the fatty acid translocase/cluster of differentiation 36 (FAT/CD36) glycoprotein.[78] Translocated OA is used to produce N-oleoyl-phosphatidylethanolamine (NOPE) via the calcium-dependent N-acetyltransferase (NAT).[59] NAT catalyses the transfer of an acyl group from the sn-1 position of phosphatidylcholine to the amine group of PE, generating NOPE.[59] Eventually, NOPE is hydrolysed through N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) and produces OEA (Figure 2).[79] As evidence shows, the complete depletion of the NAPE-PLD gene in mice attenuates OEA biosynthesis.[80] However, OEA was not completely suppressed in these mice, indicating that OEA synthesis occurs in a

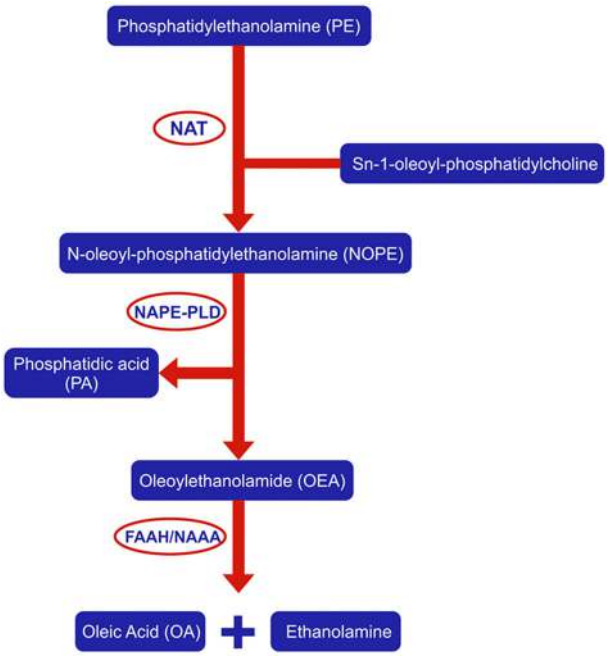


FIGURE 2 Biosynthesis and decomposition of oleoylethanolamide (OEA) in mammalian cells. FAAH/NAAA, fatty acid amide hydrolase/N-acylethanolamine acid amidase; NAT, Nacetyltransferase; NAPEPLD, N-acyl phosphatidylethanolamine phospholipase D [Colour figure can be viewed at wileyonlinelibrary.com]

NAPE-PLD-dependent and NAPE-PLD-independent manner.[80,81] Although fat consumption is the main stimulator of OEA production and mobilization, the sympathetic nervous system also contributes to the endogenous production of OEA.[82] OEA is also generated in the astrocytes, neurons, fat tissue, liver, kidney, lungs, spleen, pancreas, muscles, and heart.[71,83,84] OEA degradation into OA and ethanolamide occurs by either of the following two structurally distinct enzymes: fatty acid amide hydrolase (FAAH) and N-acylethanolamine acid amidase (NAAA).[85] The former is highly expressed in the liver, small intestine, and central nervous system (CNS).[79] The latter is a lysosomal cysteine hydrolase located primarily in the macrophages.[79] Saturated NAEs, such as PEA, are mainly hydrolysed by NAAA, while monounsaturated and polyunsaturated NAEs, such as OEA and AEA, are substantially hydrolysed through FAAH.[60]

4 | MAJOR MECHANISMS OF ACTION OF OEA IN THE MANAGEMENT OF NAFLD RISK FACTORS

The major mechanisms of action of OEA in the management of NAFLD risk factors are discussed in three sections and include obesity (the anorectic actions of OEA and its effects on the activation of GPR119 and TRPV1), metabolic factors, oxidative stress, and inflammatory parameters, as presented in the following section.

4.1 | The effects of OEA on obesity-induced NAFLD

NAFLD prevalence is enhanced as body mass index (BMI) increases.[2,86] Histological liver analyses of liver donors, car accident victims, dissection results, and clinical liver biopsy specimens have shown that the prevalence of steatosis and steatohepatitis is approximately 15% and 3% in nonobese individuals, 65% and 20% in persons with classes I and II obesity (BMI $\geq$30 kg/m^2), and 85% and 40% in individuals with extreme obesity (BMI $\geq$40 kg/m^2), respectively.[2,87] Due to the close association between NAFLD and obesity, medical or nutritional supplements efficient in treating obesity are widely encouraged for NAFLD management.[87,88] Gradual weight loss results in improved hepatic enzymes, reduced fat accumulation in the liver and, in some cases, decreased degree of inflammation and liver fibrosis.[87,89] Several studies have claimed that OEA is involved in energy homeostasis and feeding behaviour (Supplemental Table 1).[32,33,41,42,46,49-52]

Rodriguez et al[38] first demonstrated that administration of OEA (5, 10, and 20 mg/kg, intraperitoneally [i.p.]) inhibited food intake in rats. Later, studies demonstrated that the anorectic potency of OEA depended on the feeding status in animals.[39,42] In free-feeding rats, OEA treatment, either i.p. or orally, prolonged the feeding latency in a dose-dependent manner without affecting the meal size.[39,46] OEA treatment postponed the onset of feeding and decreased the meal size in food-deprived animals.[39] In Zucker rats, OEA administration (5 mg/kg, i.p.) attenuated food intake, diminished weight gain, and reduced both serum cholesterol and triglyceride (TG) levels.[57] Additionally, serum levels of alanine aminotransferase (ALT) were reduced in OEA-treated mice.[57] In the same study, a combination therapy with OEA and CB1R antagonist (5 mg/kg OEA plus 1 mg/kg rimonabant) decreased liver steatosis, liver fat content, and plasma levels of ALT and cholesterol in mice. The combined treatment was also associated with a reduction in stearoyl coenzyme A desaturase 1 (SCD1) expression, which plays a role in fatty acid and triglyceride synthesis, linked to obesity phenotypes.[57,90] SCD1 deficiency prevented IR and diet-induced obesity in mice.[91] Furthermore, the results of a recent study supported the simultaneous use of CB1R antagonists and OEA for obesity-induced dyslipidaemia and NAFLD.[57] In all, the results of numerous human studies indicate that obesity plays a pivotal role in NAFLD development and progression.

4.1.1 | Mechanisms for the anorectic actions of OEA

The appetite-suppressing effect of OEA can be mediated by different mechanisms. It has been suggested that OEA modulates food intake by increasing feeding latency, promoting control of energy intake, decreasing meal size, and increasing the intervals between meals by boosting the expression of genes associated with satiety.[45,92] The major action of OEA in regulating food intake is mediated by PPAR-α activation, an important transcriptional regulator of energy balance and fat metabolism.[40,93] OEA is considered to be a high-affinity PPAR-α agonist.[40,43] PPAR-α has the ability to abolish the expression of nitric oxide (NO) synthase, an important enzyme involved in feeding stimulation.[32] Thus, the prevention of NO synthase expression by PPAR-α may play a role in satiety-inducing effects of OEA.[32,39] A recent

clinical trial revealed that oral supplementation with OEA can elevate PPAR-α gene expression, improve appetite sensations, and reduce anthropometric measurements, including weight, BMI, waist circumference, and fat mass in patients with obesity.[52]

OEA induces satiety by PPAR-α-mediated activation of the afferent vagus nerve from the gut to the CNS.[32,59] Within the brain, there are two pathways involved in satiety-inducing effects of OEA as follows: (1) OEA administration induces the expression of oxytocin neurotransmission in neurons within the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus, involved primarily in energy homeostasis and control of food intake; and (2) brain histamine levels may also contribute to satiety effects of OEA.[94,95] A study by Provensi et al[95] showed that the deletion of the histidine decarboxylase (HDC), the only histamine-synthesizing enzyme, reduces the anorectic action of OEA.

Previous studies have reported that dysfunction of the dopamine system can cause overeating and subsequent overweight or obesity; therefore, dopamine signalling plays a critical role in the control of food intake.[96] Tellez et al[35] investigated the effect of OEA (10 mg/kg, i.p.) on extracellular dopamine concentrations in the dorsal striatum (DStr), a brain region that mediates hedonic reactions, in mice fed normal chow or HFD. In that study, intragastric lipid infusion was accompanied by microdialysis samples of dopamine in the DStr. In chow-fed mice, intragastric infusion of lipid induced elevated DStr dopamine levels, although this was not observed in HFD mice.[35] Therefore, the HFD impaired signalling pathways, mediating the dopamine action in the DStr. Interestingly, OEA treatment prior to lipid infusion restored this dopamine deficiency in HFD mice.[35] In chow-fed mice, OEA reduced the oral consumption of both low- and high-calorie emulsions.[35] It was also reported that OEA resulted in a decrease in the intake of high-calorie emulsion in chow-fed mice and an increase in the intake of low-calorie emulsion in HFD-fed mice.[35] These findings indicate that OEA may change preferences towards low-calorie emulsion consumption.

The anorectic properties of OEA may also be mediated via the attenuation of hedonic CBR1 signalling, which can lead to reduced food intake.[59,79] OEA also reduces fat mass and exhibits an "anti-obesity" effect by decreasing fat transport into adipocytes.[30,34] In HFD-fed mice, oral administration of OEA (100 mg/kg body weight) resulted in a decrease in adipose FAT/CD36 and fatty acid transport into adipose tissue, which in turn reduced adiposity in these mice.[34] Montecucco et al[30] demonstrated that OEA (10^{-7}M to 10^{-5}M) may play a role in the decrease of inflammation induced by gastric bypass surgery (GBS). OEA directly lowered the secretion of the proinflammatory chemokine (C—C motif) ligand 2 (CCL2) from adipocytes in a dose-dependent manner through the activation of ERK1/2-mediated pathways.[30] Overall, both animal and human trials indicate that the lipid-amide OEA can be considered a potentially useful therapeutic agent for weight management and treatment of obesity-induced NAFLD.

4.1.2 | Effects of OEA on the activation of GPR119 and TRPV1

In addition to PPAR-α, OEA can also interact with two other receptors, namely, transient receptor potential vanilloid 1 (TRPV1) and G protein-coupled receptor 119 (GPR119).[29,97,98] In addition to their analgesic and thermosensation effects, TRPV1 receptors are likely to modulate energy homeostasis, by either the control of food intake or energy expenditure, or both.[59] There is evidence suggesting that OEA suppressed food intake in TRPV1-knockout mice.[59,99] This implies that TRPV1 plays no role in the anorectic effects of OEA. However, TRPV1 mediates the proalgesic effects of high-dose OEA (50 μg) in wild-type mice.[100]

Evidence indicates that food intake could also be reduced through the administration of OEA in both GPR119 wild-type and knockout mice.[101] This result suggests that the existence of GPR119 is not essential for the anorectic properties of OEA, as well. The only established role for GPR119 activation by OEA is glucagon-like peptide-1 (GLP-1) release.[29] In this context, Lauffer et al[29] showed that OEA administration (10 μmol/L) stimulated GPR119, a G protein-coupled receptor, in ileum L-cells to secrete GLP-1, a gut hormone that delays gastric emptying and exerts anorectic effects, in the mouse GLUTag cell line. Yang et al[102] demonstrated that the activation of GPR119 induced the phosphorylation and activation of AMP-activated protein kinase (AMPK) and thereby inhibited the expression of sterol regulatory element-binding protein-1 (SREBP-1) in hepatocytes. The downregulation of SREBP-1 decreased lipogenic enzyme gene expression, including acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and SCD1, resulting in a reduction in hepatic lipid accumulation.[103]

GPR119 is considered part of the ECS.[102] In patients with NAFLD, the hepatic expression of CB1R/CB2R and the serum levels of the endocannabinoid 2-AG were increased.[104,105] The activation of CB1 in hepatocytes stimulates lipid accumulation by activating SREBP-1-dependent lipogenesis or suppressing AMPK-dependent fatty acid oxidation.[106] In GPR119 knockout hepatocytes, expression of lipogenic enzymes was elevated. Overall, evidence demonstrated that GPR119 activation attenuates hepatic lipogenesis and steatosis as well as triggers GLP-1 and insulin secretion. Hence, the activation of GPR119 may be a promising therapeutic intervention in the management of NAFLD.[103]

4.2 | The effects of OEA on NAFLD metabolic risk factors

4.2.1 | Lipid profile

OEA plays a pivotal role in lipid metabolism by modulating lipids in circulation and tissues in addition to its satietogenic effect.[71] Several experimental studies have shown the useful effects of OEA on lipid profiles (Supplemental Table 1).[31,40,43,45,48,55] Further investigations have indicated that the lipolytic activity of OEA and its effects on fatty acid mobilization by activating PPAR-α and PPAR-α target genes contribute to lipid metabolism.[32,43,45] PPAR-α regulates hepatic lipid metabolism by enhancing beta-oxidation and omega-oxidation.[25,107] PPAR-α also promotes the oxidation of fatty acids and reduces TG resources by enhancing the transcription of the carnitine palmitoyltransferase 1 (CPT-1) gene, the main regulatory enzyme in

oxidation of LCFA.[108] Hepatocyte-specific PPAR-α deletion debilitates whole-body fatty acid catabolism during fasting, resulting in hepatic lipid accumulation.[25] Additionally, hepatic PPAR-α activity modulates lipid metabolism by regulating the expression of apolipoproteins (APO) and PPAR-α response elements, which have been recognized in the promoters of APOA1, APOA2, APOA4, APOA5, and lipoprotein lipase (LPL) genes.[109-111] PPAR-α agonists promote LPL activity and reduce the expression of APO CIII, leading to enhanced lipolysis of triglyceride-rich lipoproteins.[112,113] PPAR-α activation lowers cholesterol esterification and absorption and augments high-density lipoprotein cholesterol (HDL-C) secretion by stimulating APOA1 and ATP binding cassette transporter A-1 (ABCA1).[18,114] In fact, the activation of PPAR-α induces ABCA1 expression and consequently results in cholesterol removal from macrophages.[115]

The results of both in vitro and in vivo studies illustrate that OEA stimulates lipid utilization by inducing fatty acid uptake, lipolysis, and fatty acid beta-oxidation.[18] The incubation of adipocytes derived from rats with OEA (1μM-20μM) induced the release of nonesterified fatty acids (NEFA) and glycerol from adipocytes via a dose-dependent effect without impacting glucose uptake or oxidation.[40] It was also shown that OEA enhanced NEFA release from rat adipocytes in a dose-dependent manner.[45] Nonetheless, a 2-hour incubation of adipocytes with a high dose of OEA (30μM) suppressed the release of NEFA.[45] Likewise, OEA enhanced the mRNA levels of FAT/CD36, a transmembrane glycoprotein that plays a pivotal role in LCFA cellular translocation in the mitochondria in a dose-dependent manner.[45,116] The results of in vivo studies demonstrated that OEA administration (5 mg/kg, i.p.) increased plasma glycerol and NEFA concentrations as well as 3-hydroxybutyrate, an efficient indicator of hepatic fatty acid oxidation.[40] Furthermore, Misto et al[117] showed that the release of histamine from mast cells into the hepatic portal vein increased during fasting. Histamine entered into the hepatocytes where it induced OEA synthesis.[117] OEA through activation of PPAR-α led to ketogenesis in liver mitochondria.[40,118]

OEA injection (5 mg/kg, i.p.) significantly reduced both serum levels of TG and cholesterol without having any effect on HDL-C and glucose levels.[43,45] Levels of serum TG, but not glucose, were also reduced via OEA treatment (5 μg/g body weight) in goldfish, indicating the protective effects of OEA on TG levels in vertebrates.[31] Fu et al[43] reported increased PPAR-α gene expression and other PPAR-α target genes, including liver fatty-acid binding protein (L-FABP), uncoupling protein 2)UCP-2(, and FAT/CD36 after OEA administration (5 mg/kg, i.p.). Moreover, liver lipid content, serum cholesterol, and TG levels as well as food intake and body weight markedly decreased after OEA administration (5 mg/kg, i.p.).[43]

OEA treatment led to an increase in PPAR-α gene expression in the liver, small intestine, adipose tissue, and muscle in animal models.[32,40,43] The results from in vitro rodent models showed that OEA administration promoted FAT/CD36 expression in most tissues, including liver, small intestine, adipose tissue, and muscle.[32,45] Furthermore, the expression of UCP-2, a mitochondrial protein involved in energy metabolism, increased in the liver, adipose tissue, and muscle by OEA injection (5 mg/kg, i.p.).[43] The thermogenic effect of UCP-2 increased mitochondrial function and fatty acid oxidation, thereby contributing to the management of obesity.[119] Two studies have also demonstrated an enhancement in the expression of L-FABP, participating in cellular fatty acid trafficking, after OEA treatment (5 mg/kg, i.p.).[32,43] As a whole, the evidence reveals that beneficial effects of OEA on lipid metabolism in NAFLD prevention are mediated by activation of PPAR-α, induction of hepatic fatty acid oxidation, modulation of circulatory lipid levels, elevation of lipolysis, and the release of fatty acids from the adipose tissue for uptake in oxidative tissues.

4.2.2 | Glycemic parameters

In animal models of type II diabetes mellitus (T2DM), PPAR-α agonists improved glucose metabolism by promoting insulin sensitivity in adipose tissue and muscle in addition to lowering the lipotoxicity and risk of liver steatosis.[120-122] Furthermore, PPAR-α agonists attenuated the progression of T2DM by preserving pancreatic β-cell function.[123] In relation to the effects of OEA on glucose metabolism, some studies claimed that OEA did not cause modifications in blood glucose concentrations (Supplemental Table 1).[31,40,43] There is only one study that demonstrated that mice treated with OEA (5 mg/kg) had glucose intolerance.[44] However, serum levels of insulin were not reduced by OEA treatment.[44] In comparison with the control group, the influence of OEA on plasma glucose levels was examined via a glucose tolerance test in mice treated with OEA.[44] OEA-treated animals had markedly high plasma glucose levels after 30 minutes of glucose load. However, there were no significant differences in other time settings for the short-term influence of OEA on glucose intolerance without diabetic effects.[44] Only high-dose OEA (20 mg/kg) significantly induced higher glucose levels at 60-minute post-glucose. However, the levels of glucose returned to normal levels after 120-minute post-glucose.[44] Dissociated rat adipocytes showed that OEA inhibited glucose uptake and insulin activity up to 30%.[44] Nevertheless, this evidence may not completely justify the glucose intolerance observed in rats in vivo because there is limited data on the inhibitory effect of OEA on glucose transportation in adipocytes.[70] Similarly, OEA did not have any effects on glucose uptake and oxidation in isolated adipocytes and muscles from rats in another study.[40] Overall, evidence regarding the effects of OEA on glycaemic parameters is yet to be confirmed. Further studies of the impacts of OEA on glycaemic variables are warranted.

4.3 | The effects of OEA on oxidative stress- and inflammation-induced NAFLD

There is cumulative evidence in humans indicating that inflammation is the main precursor in NAFLD progression.[124,125] Proinflammatory cytokines and oxidative stress are the most important markers of liver dysfunction; thus, inflammation suppression is a potential therapeutic strategy for ameliorating hepatic inflammatory disorders associated with IR.[125,126] Inflammation plays a fundamental role in the disruption of insulin signalling-induced NAFLD.[127] Increased serum levels of tumour necrosis factor alpha (TNF-α), an important inflammatory adipocytokine for NAFLD progression, are positively associated with

the severity of NAFLD.[128,129] TNF-α is capable of activating nuclear factor-kappa B (NF-κB) signalling, which is involved in inflammation and inducing the c-Jun N-terminal kinase (JNK), known as the stress-activated protein pathway, resulting in the downregulation of PPAR-α target gene expression in the liver.[130-132] Hepatic JNK deficiency in HFD-fed mice was associated with enhanced fibroblast growth factor 21 (FGF21) expression and its plasma levels, leading to improved systematic metabolism.[132] Studies have demonstrated that ligand-activated PPAR-α alleviates inflammation by interfering with NF-κB and activator protein type 1 (AP-1) signalling pathways, which are involved in the transcriptional activation of proinflammatory mediators in the intestine.[107,133] PPAR-α had not only protective effects on hepatic ischaemia and/or reperfusion injury in rats but also hepatoprotective properties by the detoxification of hydrogen peroxide and reduction of hepatic reactive oxygen species (ROS).[134,135] The anti-inflammatory and anti-fibrotic effects of PPAR-α are linked to its ability to suppress inflammatory and fibrogenic gene transcription, which are independent of its effects on the expression of genes involved in fatty acid oxidation and hepatic steatosis.[18,24] Hepatic anti-inflammatory and anti-fibrosis properties of PPAR-α led to a diminished number of activated macrophages, lowered levels of proinflammatory cytokines, including IL-1B, IL-6, and TNF-α, and ameliorated hepatic endothelial dysfunction through reduced cyclooxygenase-1 (COX-1) protein levels.[24,25,136] Notably, the expression of inflammatory factors, such as interleukin 1 beta (IL-1B) and TNF-α, in the liver and adipose tissue increased in the PPAR-α knockout mouse model.[54] The results of both in vivo and in vitro studies suggest that OEA exhibits potent anti-inflammatory and anti-fibrosis properties by enhancing PPAR-α expression and reversing essential inflammatory signalling pathways (Supplemental Table 1).[54,56] OEA exposure can also inhibit liver injury and oxidative stress associated with NAFLD.[58]

Activated PPAR-α suppresses lipopolysaccharide (LPS)-induced proinflammatory cytokines, such as TNF-α, IL-1β, COX-2, and IL-6, in various cell types.[137,138] According to an in vitro study, OEA (10μM, 20μM, and 40μM) had anti-inflammatory effects on the LPS-induced human acute monocytic leukaemia cell line (THP-1) by promoting PPAR-α signalling, inhibiting the Toll-like receptor 4 (TLR4)-mediated NF-κB signalling pathway, attenuating extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and reversing signal transducer and activator of transcription 3 (STAT3) cascades.[54] It is well established that the activation of these pathways triggers inflammatory and immune responses.[139] Administration of OEA (5 mg/kg, i.p.) significantly suppressed hepatic fibrosis progression in an experimental animal model by inhibiting the activation of hepatic stellate cells (HSCs), which play a pivotal role in liver fibrosis.[56] In addition, OEA reversed transforming growth factor beta 1 (TGF-β1), a profibrotic cytokine, and genes involved in the TGF-β1 signalling pathway.[56] OEA injection decreased serum concentrations of ALT, AST, and TG as well as diminished the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) proteins, which play important roles in inflammatory and immunological responses.[56,140,141] In chronic liver disease, the process of tissue remodelling progresses; therefore, suppression of matrix remodelling enzyme gene activation may be a therapeutic strategy for the prevention and treatment of liver fibrosis.[56,142] Matrix remodelling enzyme genes, including matrix metalloproteinase 2 (MMP2), MMP9, and tissue inhibitors of matrix metalloproteinase 1 (TIMP1), were reduced by OEA treatment in rats fed an MCD diet.[56] An in vitro study revealed that OEA (30μM, 10μM, and 3μM) suppressed the activation of TGF-β1, the expression of α-smooth muscle actin (αSMA), and the expression of collagen type 1a/3a, which contributes greatly to hepatic fibrosis progression.[56] However, these protective effects of OEA on liver fibrosis were not observed in PPAR-α-deficient mice.[56] All these findings are suggestive of hepatoprotective roles of OEA via the activation of PPAR-α and reversing inflammatory and oxidative mediators involved in the development and progression of NAFLD.

5 | COMPARISON OF OEA WITH OTHER COMMONLY USED PPAR-A AGONISTS

Fibrates, such as fenofibrate, are widely used as PPAR-α agonist drugs in dyslipidaemia treatment.[143] Numerous studies have revealed that fibrates play a crucial role in reducing plasma and liver TG concentrations as well as improving IR in NAFLD patients.[144,145] Nevertheless, because of the relatively low affinity of fibrates for PPAR-α receptors and dose-related side effects,[146,147] the use of novel agonists of PPAR-α with greater potency and efficacy has been considered in the treatment of NAFLD. Notably, due to the relatively weak potency of fenofibrates at PPAR-α, these compounds do not play a significant role in controlling food intake.[40,58] In comparison with fenofibrate, OEA has a higher binding affinity for PPAR-α receptors and favourable effects in ameliorating obesity, atherosclerosis, and other metabolic disorders.[36,60] As mentioned above, OEA exerts its effects both via its major binding partner PPAR-α and other receptors such as TRPV1 and GRP119. Because of that, physiological functions of OEA are more diverse than that of other PPAR-α agonists such as Wy-14643 and fenofibrate.[29,97,102] In the MCD model of liver disease, Wy-1464 reduced steatohepatitis and liver fibrosis; nevertheless, Wy-1464 was not effective in diminishing the expression of enhanced TGF-β1 transcription factor.[148] An increase in the expression of TGF-β1, a profibrotic cytokine, plays an important role in the development of hepatic fibrosis; thus, the long-term effects of Wy-14643 treatment are still unclear.[56]

OEA administration (5 mg/kg, i.p.) had a protective influence on HFD-induced NAFLD in rats by modulating plasma levels of TG, total cholesterol, AST, ALT, and inflammatory cytokines,[58] such as TNF-α and IL-6. In the same study, OEA and fenofibrate (10 mg/kg, i.p.) both stimulated lipid beta-oxidation by boosting the expression of PPAR-α. OEA reduced the expression of lipogenic genes, including SCD-1, SREBP-1, and ACC.[58] Fenofibrate exhibited the inverse effectiveness, which indicated that OEA had a safer and superior effect over fenofibrate in the treatment of NAFLD.[58]

Overall, the literature review indicates that the satiety-inducing compound OEA regulates multiple biological processes associated with NAFLD, including energy homeostasis, lipid metabolism,

inflammation, and oxidative stress. Figure 3 shows the proposed mechanisms of action for OEA in the management of NAFLD.

6 | KNOWLEDGE GAPS AND FUTURE DIRECTIONS

As noted above, there have been several in vitro and in vivo studies assessing the protective effects of OEA. However, there is a lack of clinical trials to determine the safety and beneficial therapeutic utilization of OEA in humans. The major knowledge gap is therefore the functions of OEA in patients with NAFLD. Thus, clinical trials at larger scales with precise insights into the underlying mechanisms of OEA in the management of NAFLD and related risk factors are crucial. Dietary OA acts as a precursor to OEA formation.[71] Therefore, future clinical trials should also address the effectiveness of dietary fat consumption rich in OA on NAFLD. Although the cumulative evidence in humans has demonstrated that high-OA diets elevate circulating OEA levels, there are fewer studies on the effect of dietary OA on OEA concentrations in tissues, such as hepatocytes, in humans. This lack of evidence requires clarification from future clinical trials.

OA could stimulate mRNA synthesis of liver X-receptor alpha (LXRα) in human neutrophils.[149] It can also reduce intracellular lipid levels and inflammatory markers.[150] Conversely, OA induced hepatic steatosis through the upregulation of p38 signalling in an in vitro model.[149] As a result, a dual effect has been suggested for OA in patients with NAFLD[151]; therefore, future robust human clinical trials are needed in this area.

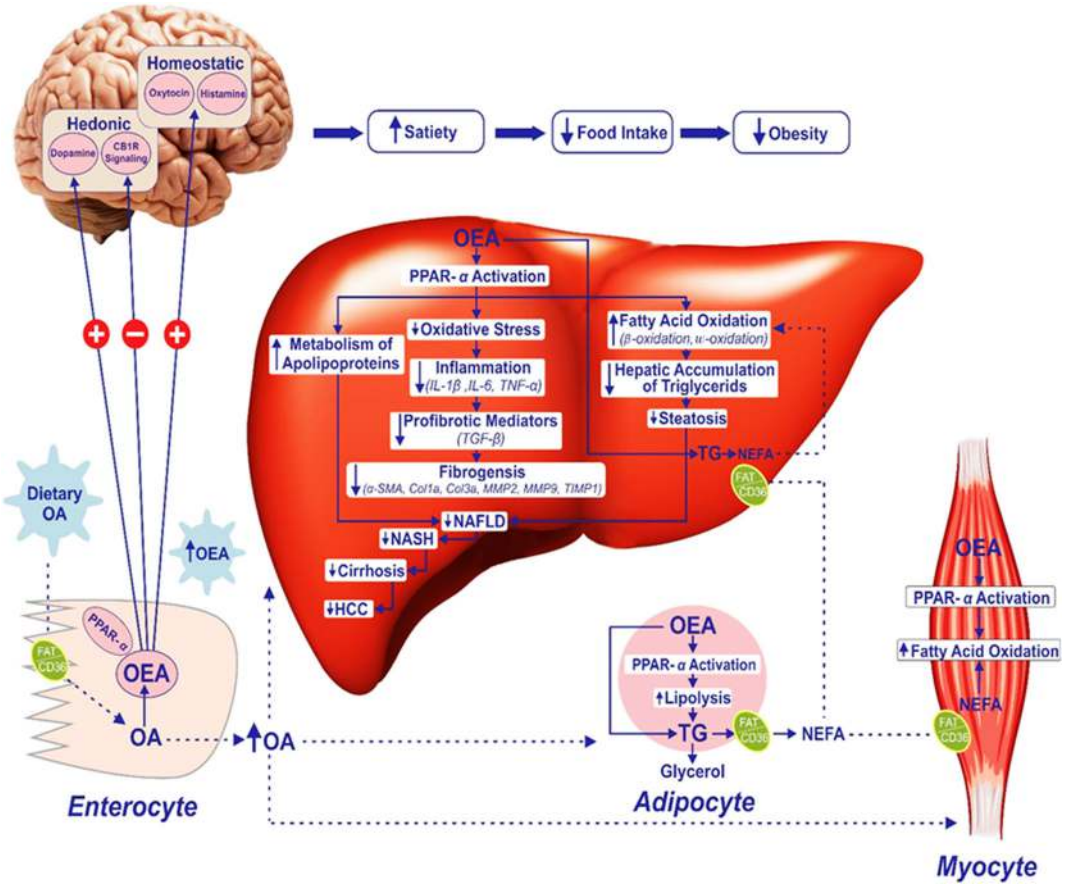


FIGURE 3 Proposed mechanisms of action for OEA in the management of NAFLD. Dietary OA enters the enterocytes through the FAT/CD36 transporter and causes the production and mobilization of OEA, which can interact with PPAR-α in the enterocyte to regulate gene transcription. Dietary OA is transferred to the tissues and OEA is produced in the peripheral tissues. OEA can bind to PPAR-α in the adipocyte and cause lipid droplet lipolysis and the release of fatty acids from the adipose tissue for uptake in oxidative tissues. Activation of PPAR-α by OEA in hepatocytes and muscle promotes fat utilization via elevated uptake of fatty acids and fatty acid oxidation, as well as increased fatty acid transport in muscle and decreased hepatic triglyceride accumulation through the breakdown of lipid droplets. In addition, OEA-PPAR-α interaction in the liver reverses oxidative stress and inflammation by attenuating the secretion of proinflammatory mediators involved in NAFLD development and progression. OEA decreases feeding and attenuates obesity-induced NAFLD by stimulating the hedonic dopamine pathways and lowering hedonic CB1R signalling as well as boosting homeostatic oxytocin and brain histamine. Dashed lines trace the path. Col1a, type I collagen; Col3a, type III collagen; FAT/CD36, fatty acid translocase/cluster of differentiation 36; HCC, hepatocellular carcinoma; IL-1β, interleukin 1 beta; IL-6, interleukin 6; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NEFA, nonesterified fatty acid; OA, oleic acid; OEA, oleoylethanolamide; PPAR-α, peroxisome proliferator-activated receptor α; α-SMA, alpha-smooth muscle actin; TG, triglyceride; TGF-β, transforming growth factor beta; TIMP1, tissue inhibitor of metalloproteinase-1; TNF-α, tumour necrosis factor alpha (gene); ↑, increased; ↓, decreased [Colour figure can be viewed at wileyonlinelibrary.com]

Overweight and obesity conditions, sex hormones, and genetic variations, such as single nucleotide polymorphisms (SNPs), may affect the individual response to nutrition-specific interventions. Thus, further research is required to confirm the effects of nutrition interventions in attenuating food consumption, inflammation, and fibrosis as well as in reducing hepatic TG and liver steatosis. Human clinical trials with subject selection based on the selected SNP-related genotypes are also required. Additionally, biopsy specimens of the liver, adipose, and muscle tissues will provide important data on the ability of OEA to stimulate gene expression in the liver and in oxidative tissues, enabling this conceptual framework to be examined in humans.

Future clinical trials are also required to investigate the effects of OEA on the factors involved in the AMPK signalling pathway, such as sirtuin-1, FGF-21, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). The evidence indicates that the interaction of AMPK with sirtuin-1 and FGF-21 may result in increased expression of the PGC-1α gene.[152] Overexpression of PGC-1α increases peroxisomal activity and mitochondrial fatty acid oxidation.[153] Furthermore, the activation of the AMPK signalling pathway in the liver leads to the reduction of the gene expression of the lipogenic enzymes, and the suppression of SREBP-1c, and ACC expression.[154] Therefore, research is required to investigate the effects of OEA on the factors involved in the AMPK signalling pathway. A simplified possible mechanism about the actions of OEA in the liver is shown in Supplemental Figure 2.

7 | CONCLUSIONS

The findings of this review indicate that the lipid-amide OEA contributes to NAFLD prevention and treatment by (1) increasing the expression of PPAR-α and other PPAR-α target genes; (2) modulating the energy homeostasis and feeding behaviour, leading to the control of food intake; (3) enhancing fatty acid uptake, lipolysis, and oxidation; (4) regulating lipid levels in circulation and tissues; (5) improving the metabolism of apolipoproteins; (6) decreasing the hepatic accumulation of TG in the liver, leading to the inhibition of hepatic steatosis; and (7) reversing oxidative stress and inflammation by interfering with the activation of inflammatory and profibrotic signalling pathways.

In summary, the beneficial effects of OEA, together with its greater potency and efficacy compared with other PPAR-α agonists, have led to the conclusion that OEA may be a suitable and effective therapeutic strategy for improving and reducing the progression of NAFLD. Although a wide range of studies have demonstrated the most useful effects of OEA on NAFLD and the associated risk factors, further clinical trials, from both in vivo studies and in vitro experiments, are warranted to verify these outcomes.

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CONFLICT OF INTEREST

No conflict of interest was declared.

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REFERENCES

1. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274-285.
2. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology*. 2010;51(2):679-689.
3. Tiniakos DG, Vos MB, Brunt EM. Nonalcoholic fatty liver disease: pathology and pathogenesis. *Annu Rev Pathol*. 2010;5(1):145-171.
4. Ahmed M. Non-alcoholic fatty liver disease in 2015. *World J Hepatol*. 2015;7(11):1450-1459.
5. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. *Liver Int*. 2017;37:81-84.
6. Dowman JK, Tomlinson J, Newsome P. Pathogenesis of non-alcoholic fatty liver disease. *QJM*. 2009;103:71-83.
7. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
8. Masarone M, Rosato V, Dallio M, et al. Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. *Oxid Med Cell Longev*. 2018;2018:9547613.
9. Ucar F, Sezer S, Erdogan S, Akyol S, Armutcu F, Akyol O. The relationship between oxidative stress and nonalcoholic fatty liver disease: its effects on the development of nonalcoholic steatohepatitis. *Redox Rep*. 2013;18(4):127-133.
10. Wei Y, Rector RS, Thyfault JP, Ibdah JA. Nonalcoholic fatty liver disease and mitochondrial dysfunction. *World J Gastroenterol*. 2008;14:193-199.
11. Benedict M, Zhang X. Non-alcoholic fatty liver disease: an expanded review. *World J Hepatol*. 2017;9(16):715-732.
12. Feldstein AE, Werneburg NW, Canbay A, et al. Free fatty acids promote hepatic lipotoxicity by stimulating TNF-α expression via a lysosomal pathway. *Hepatology*. 2004;40:185-194.
13. Yamaguchi K, Yang L, McCall S, et al. Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis. *Hepatology*. 2007;45(6):1366-1374.
14. Hung CK, Bodenheimer HC Jr. Current treatment of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Clin Liver Dis*. 2018;22(1):175-187.
15. Romero-Gomez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol*. 2017;67(4):829-846.
16. Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. *J Hepatol*. 2015;62(1):S65-S75.

17. Barb D, Portillo-Sanchez P, Cusi K. Pharmacological management of nonalcoholic fatty liver disease. *Metabolism*. 2016;65:1183-1195.

18. Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol*. 2017;13:36-49.

19. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: a family of nuclear receptors role in various diseases. *J Adv Pharm Technol Res*. 2011;2:236-240.

20. Hummasti S, Tontonoz P. The peroxisome proliferator-activated receptor N-terminal domain controls isotype-selective gene expression and adipogenesis. *Mol Endocrinol*. 2006;20(6):1261-1275.

21. Lefebvre P, Chinetti G, Fruchart JC, Staels B. Sorting out the roles of PPARα in energy metabolism and vascular homeostasis. *J Clin Invest*. 2006;116(3):571-580.

22. Francque S, Verrijken A, Caron S, et al. PPARα gene expression correlates with severity and histological treatment response in patients with non-alcoholic steatohepatitis. *J Hepatol*. 2015;63:164-173.

23. Abdelmegeed MA, Yoo SH, Henderson LE, Gonzalez FJ, Woodcroft KJ, Song BJ. PPARα expression protects male mice from high fat-induced nonalcoholic fatty liver. *J Nutr*. 2011;141:603-610.

24. Pawlak M, Bauge E, Bourguet W, et al. The transrepressive activity of peroxisome proliferator-activated receptor alpha is necessary and sufficient to prevent liver fibrosis in mice. *Hepatology*. 2014;60(5):1593-1606.

25. Montagner A, Polizzi A, Fouche E, et al. Liver PPARα is crucial for whole-body fatty acid homeostasis and is protective against NAFLD. *Gut*. 2016;65(7):1202-1214.

26. Ip E, Farrell GC, Robertson G, Hall P, Kirsch R, Leclercq I. Central role of PPARα-dependent hepatic lipid turnover in dietary steatohepatitis in mice. *Hepatology*. 2003;38(1):123-132.

27. Liss KH, Finck BN. PPARs and nonalcoholic fatty liver disease. *Biochimie*. 2017;136:65-74.

28. Igarashi M, DiPatrizio NV, Narayanaswami V, Piomelli D. Feeding-induced oleoylethanolamide mobilization is disrupted in the gut of diet-induced obese rodents. *Biochim Biophys Acta*. 1851;2015:1218-1226.

29. Lauffer LM, Iakoubov R, Brubaker PL. GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. *Diabetes*. 2009;58(5):1058-1066.

30. Montecucco F, Lenglet S, Quercioli A, et al. Gastric bypass in morbid obese patients is associated with reduction in adipose tissue inflammation via N-oleoylethanolamide (OEA)-mediated pathways. *Thromb Haemost*. 2015;113(4):838-850.

31. Tinoco AB, Armirotti A, Isorna E, Delgado MJ, Piomelli D, de Pedro N. Role of oleoylethanolamide as a feeding regulator in goldfish. *J Exp Biol*. 2014;217:2761-2769.

32. Fu J, Gaetani S, Oveisi F, et al. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-α. *Nature*. 2003;425(6953):90-93.

33. Thabuis C, Destaillats F, Landrier JF, Tissot-Favre D, Martin JC. Analysis of gene expression pattern reveals potential targets of dietary oleoylethanolamide in reducing body fat gain in C3H mice. *J Nutr Biochem*. 2010;21(10):922-928.

34. Thabuis C, Destaillats F, Lambert DM, et al. Lipid transport function is the main target of oral oleoylethanolamide to reduce adiposity in high-fat-fed mice. *J Lipid Res*. 2011;52:1373-1382.

35. Tellez LA, Medina S, Han W, et al. A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science*. 2013;341:800-802.

36. Romano A, Coccurello R, Giacovazzo G, Bedse G, Moles A, Gaetani S. Oleoylethanolamide: a novel potential pharmacological alternative to cannabinoid antagonists for the control of appetite. *Biomed Res Int*. 2014;2014:10.

37. Brown JD, McAnally D, Ayala JE, et al. Oleoylethanolamide modulates glucagon-like peptide-1 receptor agonist signaling and enhances exendin-4-mediated weight loss in obese mice. *Am J Physiol Regul Integr Comp Physiol*. 2018;315(4):R595-R608.

38. Rodriguez de Fonseca F, Navarro M, Gomez R, et al. An anorexic lipid mediator regulated by feeding. *Nature*. 2001;414:209-212.

39. Gaetani S, Oveisi F, Piomelli D. Modulation of meal pattern in the rat by the anorexic lipid mediator oleoylethanolamide. *Neuropsychopharmacology*. 2003;28(7):1311-1316.

40. Guzman M, Lo Verme J, Fu J, Oveisi F, Blazquez C, Piomelli D. Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-alpha). *J Biol Chem*. 2004;279:27849-27854.

41. Nielsen MJ, Petersen G, Astrup A, Hansen HS. Food intake is inhibited by oral oleoylethanolamide. *J Lipid Res*. 2004;45:1027-1029.

42. Oveisi F, Gaetani S, Eng KT, Piomelli D. Oleoylethanolamide inhibits food intake in free-feeding rats after oral administration. *Pharmacol Res*. 2004;49(5):461-466.

43. Fu J, Oveisi F, Gaetani S, Lin E, Piomelli D. Oleoylethanolamide, an endogenous PPAR-α agonist, lowers body weight and hyperlipidemia in obese rats. *Neuropharmacology*. 2005;48(8):1147-1153.

44. González-Yanes C, Serrano A, Bermúdez-Silva FJ, et al. Oleylethanolamide impairs glucose tolerance and inhibits insulin-stimulated glucose uptake in rat adipocytes through p38 and JNK MAPK pathways. *Am J Physiol Endocrinol Metab*. 2005;289(5):E923-E929.

45. Yang Y, Chen M, Georgeson KE, Harmon CM. Mechanism of oleoylethanolamide on fatty acid uptake in small intestine after food intake and body weight reduction. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(1):R235-R241.

46. Azari EK, Ramachandran D, Weibel S, et al. Vagal afferents are not necessary for the satiety effect of the gut lipid messenger oleoylethanolamide. *Am J Physiol Regul Integr Comp Physiol*. 2014;307(2):R167-R178.

47. Romano A, Karimian Azari E, Tempesta B, et al. High dietary fat intake influences the activation of specific hindbrain and hypothalamic nuclei by the satiety factor oleoylethanolamide. *Physiol Behav*. 2014;136:55-62.

48. Suarez J, Rivera P, Arrabal S, et al. Oleoylethanolamide enhances beta-adrenergic-mediated thermogenesis and white-to-brown adipocyte phenotype in epididymal white adipose tissue in rat. *Dis Model Mech*. 2014;7:129-141.

49. Rondanelli M, Opizzi A, Solerte SB, Trotti R, Klersy C, Cazzola R. Administration of a dietary supplement (N-oleyl-phosphatidylethanolamine and epigallocatechin-3-gallate formula) enhances compliance with diet in healthy overweight subjects: a randomized controlled trial. *Br J Nutr*. 2009;101(03):457-464.

50. Barbaro D, Menasci A, Baldini B, Pasquini C, Lapi P. The dietary supplement EGCG: NOPE (N-Oleyl-Phosphatidyletathanolamine and Epigallocatechin-3-Gallato formula) helps patients to follow a flexible dietary regimen and induces loss of weight in patients who had previously experienced no response to other weight loss intervention. *J Obes Weig los Ther*. 2011;1:1.

51. Mangine GT, Gonzalez AM, Wells AJ, et al. The effect of a dietary supplement (N-oleyl-phosphatidyl-ethanolamine and epigallocatechin gallate) on dietary compliance and body fat loss in adults who are

overweight: a double-blind, randomized control trial. *Lipids Health Dis*. 2012;11(1):127.

52. Payahoo L, Khaje-Bishak Y, Barzgar A, et al. Oleoylethanolamide increases the expression of PPAR-α and reduces appetite and body weight in obese people: a clinical trial. *Appetite*. 2018;128:44-49.
53. Payahoo L, Khajebishak Y, Asghari Jafarabadi M, Ostadrahimi A. Oleoylethanolamide supplementation reduces inflammation and oxidative stress in obese people: a clinical trial. *Adv Pharm Bull*. 2018;8(3):479-487.
54. Yang L, Guo H, Li Y, et al. Oleoylethanolamide exerts anti-inflammatory effects on LPS-induced THP-1 cells by enhancing PPARα signaling and inhibiting the NF-κB and ERK1/2/AP-1/STAT3 pathways. *Sci Rep*. 2016;6:34611.
55. Gomez-Boronat M, Velasco C, Isorna E, De Pedro N, Delgado MJ, Soengas JL. The satiety factor oleoylethanolamide impacts hepatic lipid and glucose metabolism in goldfish. *J Comp Physiol B*. 2016;186:1009-1021.
56. Chen L, Li L, Chen J, et al. Oleoylethanolamide, an endogenous PPAR-α ligand, attenuates liver fibrosis targeting hepatic stellate cells. *Oncotarget*. 2015;6(40):42530-42540.
57. Serrano A, Del Arco I, Javier Pavon F, Macias M, Perez-Valero V, Rodriguez de Fonseca F. The cannabinoid CB1 receptor antagonist SR141716A (Rimonabant) enhances the metabolic benefits of long-term treatment with oleoylethanolamide in Zucker rats. *Neuropharmacology*. 2008;54(1):226-234.
58. Li L, Li L, Chen L, et al. Effect of oleoylethanolamide on diet-induced nonalcoholic fatty liver in rats. *J Pharmacol Sci*. 2015;127(3):244-250.
59. Brown JD, Karimian Azari E, Ayala JE. Oleoylethanolamide: a fat ally in the fight against obesity. *Physiol Behav*. 2017;176:50-58.
60. Piomelli D. A fatty gut feeling. *Trends Endocrinol Metab*. 2013;24:332-341.
61. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *Int J Mol Sci*. 2018;19:833.
62. Li C, Jones PM, Persaud SJ. Role of the endocannabinoid system in food intake, energy homeostasis and regulation of the endocrine pancreas. *Pharmacol Ther*. 2011;129(3):307-320.
63. Naughton SS, Mathai ML, Hryciw DH, McAinch AJ. Fatty acid modulation of the endocannabinoid system and the effect on food intake and metabolism. *Int J Endocrinol*. 2013;2013:11.
64. Crawley JN, Corwin RL, Robinson JK, Felder CC, Devane WA, Axelrod J. Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents. *Pharmacol Biochem Behav*. 1993;46:967-972.
65. Lo Verme J, Fu J, Astarita G, et al. The nuclear receptor peroxisome proliferator-activated receptor-α mediates the anti-inflammatory actions of palmitoylethanolamide. *Mol Pharmacol*. 2005;67(1):15-19.
66. DiPatrizio NV, Piomelli D. The thrifty lipids: endocannabinoids and the neural control of energy conservation. *Trends Neurosci*. 2012;35(7):403-411.
67. Sarro-Ramirez A, Sanchez-Lopez D, Tejeda-Padron A, Frias C, Zaldivar-Rae J, Murillo-Rodriguez E. Brain molecules and appetite: the case of oleoylethanolamide. *Cent Nerv Syst Agents Med Chem*. 2013;13:88-91.
68. Proulx K, Cota D, Castaneda TR, et al. Mechanisms of oleoylethanolamide-induced changes in feeding behavior and motor activity. *Am J Physiol Regul Integr Comp Physiol*. 2005;289(3):R729-R737.
69. Dipasquale P, Romano A, Cianci S, Righetti L, Gaetani S. Oleoylethanolamide: a new player in energy metabolism control. Role in food intake. *Drug Discov Today Dis Mech*. 2010;7:e169-e174.
70. Thabuis C, Tissot-Favre D, Bezelgues JB, et al. Biological functions and metabolism of oleoylethanolamide. *Lipids*. 2008;43:887-894.
71. Bowen KJ, Kris-Etherton PM, Shearer GC, West SG, Reddivari L, Jones PJH. Oleic acid-derived oleoylethanolamide: a nutritional science perspective. *Prog Lipid Res*. 2017;67:1-15.
72. Mennella I, Savarese M, Ferracane R, Sacchi R, Vitaglione P. Oleic acid content of a meal promotes oleoylethanolamide response and reduces subsequent energy intake in humans. *Food Funct*. 2015;6:204-210.
73. Schwartz GJ, Fu J, Astarita G, et al. The lipid messenger OEA links dietary fat intake to satiety. *Cell Metab*. 2008;8:281-288.
74. Diep TA, Madsen AN, Krogh-Hansen S, et al. Dietary non-esterified oleic Acid decreases the jejunal levels of anorectic N-acylethanolamines. *PLoS One*. 2014;9(6):e100365.
75. Diep TA, Madsen AN, Holst B, et al. Dietary fat decreases intestinal levels of the anorectic lipids through a fat sensor. *FASEB J*. 2011;25(2):765-774.
76. Joosten MM, Balvers MG, Verhoeckx KC, Hendriks HF, Witkamp RF. Plasma anandamide and other N-acylethanolamines are correlated with their corresponding free fatty acid levels under both fasting and non-fasting conditions in women. *Nutr Metab (Lond)*. 2010;7:49.
77. Romano A, Tempesta B, Provensi G, Passani MB, Gaetani S. Central mechanisms mediating the hypophagic effects of oleoylethanolamide and N-acylphosphatidylethanolamines: different lipid signals? *Front Pharmacol*. 2015;6:137.
78. Guijarro A, Fu J, Astarita G, Piomelli D. CD36 gene deletion decreases oleoylethanolamide levels in small intestine of free-feeding mice. *Pharmacol Res*. 2010;61:27-33.
79. Sihag J, Jones PJH. Oleoylethanolamide: the role of a bioactive lipid amide in modulating eating behaviour. *Obes Rev*. 2018;19:178-197.
80. Tsuboi K, Okamoto Y, Ikematsu N, et al. Enzymatic formation of N-acylethanolamines from N-acylethanolamine plasmalogen through N-acylphosphatidylethanolamine-hydrolyzing phospholipase D-dependent and -independent pathways. *Biochim Biophys Acta*. 1811;2011:565-577.
81. Simon GM, Cravatt BF. Characterization of mice lacking candidate N-acyl ethanolamine biosynthetic enzymes provides evidence for multiple pathways that contribute to endocannabinoid production in vivo. *Mol Biosyst*. 2010;6:1411-1418.
82. Fu J, Dipatrizio NV, Guijarro A, Schwartz GJ, et al. Sympathetic activity controls fat-induced oleoylethanolamide signaling in small intestine. *J Neurosci*. 2011;31(15):5730-5736.
83. Cadas H, di Tomaso E, Piomelli D. Occurrence and biosynthesis of endogenous cannabinoid precursor, N-arachidonoyl phosphatidylethanolamine, in rat brain. *J Neurosci*. 1997;17(4):1226-1242.
84. Fu J, Astarita G, Gaetani S, et al. Food intake regulates oleoylethanolamide formation and degradation in the proximal small intestine. *J Biol Chem*. 2007;282:1518-1528.
85. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature*. 1996;384(6604):83-87.
86. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2003;124:71-79.
87. Marchesini G, Petta S, Dalle GR. Diet, weight loss, and liver health in nonalcoholic fatty liver disease: pathophysiology, evidence, and practice. *Hepatology*. 2016;63:2032-2043.

88. Lu FB, Hu ED, Xu LM, et al. The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2018;12:491-502.
89. Tilg H, Moschen A. Weight loss: cornerstone in the treatment of non-alcoholic fatty liver disease. *Minerva Gastroenterol Dietol*. 2010;56(2):159-167.
90. Brown JM, Rudel LL. Stearoyl-coenzyme A desaturase 1 inhibition and the metabolic syndrome: considerations for future drug discovery. *Curr Opin Lipidol*. 2010;21(3):192-197.
91. Miyazaki M, Sampath H, Liu X, et al. Stearoyl-CoA desaturase-1 deficiency attenuates obesity and insulin resistance in leptin-resistant obese mice. *Biochem Biophys Res Commun*. 2009;380:818-822.
92. Fu J, Kim J, Oveisi F, Astarita G, Piomelli D. Targeted enhancement of oleoylethanolamide production in proximal small intestine induces across-meal satiety in rats. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(1):R45-R50.
93. Silva AKS, Peixoto CA. Role of peroxisome proliferator-activated receptors in non-alcoholic fatty liver disease inflammation. *Cell Mol Life Sci*. 2018;75:2951-2961.
94. Gaetani S, Fu J, Cassano T, et al. The fat-induced satiety factor oleoylethanolamide suppresses feeding through central release of oxytocin. *J Neurosci*. 2010;30:8096-8101.
95. Provensi G, Coccurello R, Umehara H, et al. Satiety factor oleoylethanolamide recruits the brain histaminergic system to inhibit food intake. *PNAS*. 2014;111:11527-11532.
96. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci*. 2010;13:635-641.
97. Ahern GP. Activation of TRPV1 by the satiety factor oleoylethanolamide. *J Biol Chem*. 2003;278:30429-30434.
98. Wang X, Miyares RL, Ahern GP. Oleoylethanolamide excites vagal sensory neurones, induces visceral pain and reduces short-term food intake in mice via capsaicin receptor TRPV1. *J Physiol*. 2005;564:541-547.
99. Lo Verme J, Gaetani S, Fu J, Oveisi F, Burton K, Piomelli D. Regulation of food intake by oleoylethanolamide. *Cell Mol Life Sci*. 2005;62:708-716.
100. LoVerme J, Russo R, La Rana G, et al. Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-alpha. *J Pharmacol Exp Ther*. 2006;319:1051-1061.
101. Lan H, Vassileva G, Corona A, et al. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. *J Endocrinol*. 2009;201(2):219-230.
102. Yang JW, Kim HS, Choi YW, Kim YM, Kang KW. Therapeutic application of GPR119 ligands in metabolic disorders. *Diabetes Obes Metab*. 2018;20(2):257-269.
103. Yang JW, Kim HS, Im JH, et al. GPR119: a promising target for non-alcoholic fatty liver disease. *FASEB J*. 2016;30:324-335.
104. Mendez-Sanchez N, Zamora-Valdes D, Pichardo-Bahena R, et al. Endocannabinoid receptor CB2 in nonalcoholic fatty liver disease. *Liver Int*. 2007;27(2):215-219.
105. Liu J, Zhou L, Xiong K, et al. Hepatic cannabinoid receptor-1 mediates diet-induced insulin resistance via inhibition of insulin signaling and clearance in mice. *Gastroenterology*. 2012;142(5):1218-1228.
106. Osei-Hyiaman D, Liu J, Zhou L, et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J Clin Invest*. 2008;118:3160-3169.
107. Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *J Hepatol*. 2015;62:720-733.
108. Song S, Attia RR, Connaughton S, et al. Peroxisome proliferator activated receptor alpha (PPARα) and PPAR gamma coactivator (PGC-1α) induce carnitine palmitoyltransferase IA (CPT-1A) via independent gene elements. *Mol Cell Endocrinol*. 2010;325(1-2):54-63.
109. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, et al. PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J*. 1996;15(19):5336-5348.
110. Berthou L, Duverger N, Emmanuel F, et al. Opposite regulation of human versus mouse apolipoprotein A-I by fibrates in human apolipoprotein A-I transgenic mice. *J Clin Invest*. 1996;97:2408-2416.
111. Vu-Dac N, Gervois P, Jakel H, et al. Apolipoprotein A5, a crucial determinant of plasma triglyceride levels, is highly responsive to peroxisome proliferator-activated receptor alpha activators. *J Biol Chem*. 2003;278:17982-17985.
112. Crosby J, Peloso GM, Auer PL, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371(1):22-31.
113. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014;371(1):32-41.
114. Colin S, Briand O, Touche V, et al. Activation of intestinal peroxisome proliferator-activated receptor-α increases high-density lipoprotein production. *Eur Heart J*. 2013;34(32):2566-2574.
115. Chinetti G, Lestavel S, Bocher V, et al. PPAR-α and PPAR-γ activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. *Nat Med*. 2001;7(1):53-58.
116. Campbell SE, Tandon NN, Woldegiorgis G, Luiken JJ, Glatz JF, Bonen A. A novel function for fatty acid translocase (FAT)/CD36: involvement in long chain fatty acid transfer into the mitochondria. *J Biol Chem*. 2004;279:36235-36241.
117. Misto A, Provensi G, Vozella V, Passani MB, Piomelli D. Mast cell-derived histamine regulates liver ketogenesis via oleoylethanolamide signaling. *Cell Metab*. 2019;29(1):91-102.
118. Grabacka M, Pierzchalska M, Dean M, Reiss K. Regulation of ketone body metabolism and the role of PPARα. *Int J Mol Sci*. 2016;17:2093.
119. Crowley V, Vidal-Puig AJ. Mitochondrial uncoupling proteins (UCPs) and obesity. *Nutr Metab Cardiovasc Dis*. 2001;11:70-75.
120. Kim H, Haluzik M, Asghar Z, et al. Peroxisome proliferator–activated receptor-α agonist treatment in a transgenic model of type 2 diabetes reverses the lipotoxic state and improves glucose homeostasis. *Diabetes*. 2003;52:1770-1778.
121. Chou CJ, Haluzik M, Gregory C, Dietz KR, et al. WY14,643, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, improves hepatic and muscle steatosis and reverses insulin resistance in lipoatrophic A-ZIP/F-1 mice. *J Biol Chem*. 2002;277:24484-24489.
122. Guerre-Millo M, Gervois P, Raspe E, et al. Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. *J Biol Chem*. 2000;275(22):16638-16642.
123. Lalloyer F, Vandewalle B, Percevault F, et al. Peroxisome proliferator-activated receptor alpha improves pancreatic adaptation to insulin resistance in obese mice and reduces lipotoxicity in human islets. *Diabetes*. 2006;55:1605-1613.
124. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology*. 2010;52(5):1836-1846.

125. Streba LA, Vere CC, Rogoveanu I, Streba CT. Nonalcoholic fatty liver disease, metabolic risk factors, and hepatocellular carcinoma: an open question. *World J Gastroenterol*. 2015;21(14):4103-4110.
126. Spahis S, Delvin E, Borys JM, Levy E. Oxidative stress as a critical factor in nonalcoholic fatty liver disease pathogenesis. *Antioxid Redox Signal*. 2017;26(10):519-541.
127. Asrih M, Jornayvaz FR. Inflammation as a potential link between nonalcoholic fatty liver disease and insulin resistance. *J Endocrinol*. 2013;218(3):R25-R36.
128. Stojsavljevic S, Gomercic Palcic M, Virovic Jukic L, Smircic Duvnjak L, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20:18070-18091.
129. du Plessis J, Korf H, van Pelt J, et al. Pro-inflammatory cytokines but not endotoxin-related parameters associate with disease severity in patients with NAFLD. *PLoS One*. 2016;11(12):e0166048.
130. Paredes-Turrubiarte G, Gonzalez-Chavez A, Perez-Tamayo R, et al. Severity of non-alcoholic fatty liver disease is associated with high systemic levels of tumor necrosis factor alpha and low serum interleukin 10 in morbidly obese patients. *Clin Exp Med*. 2016;16(2):193-202.
131. Lin X, Zhang Z, Chen JM, et al. Role of APN and TNF-alpha in type 2 diabetes mellitus complicated by nonalcoholic fatty liver disease. *Genet Mol Res*. 2015;14(2):2940-2946.
132. Vernia S, Cavanagh-Kyros J, Garcia-Haro L, et al. The PPARα-FGF21 hormone axis contributes to metabolic regulation by the hepatic JNK signaling pathway. *Cell Metab*. 2014;20:512-525.
133. Mogilenko DA, Kudriavtsev IV, Shavva VS, et al. Peroxisome proliferator-activated receptor α positively regulates complement C3 expression but inhibits tumor necrosis factor α-mediated activation of C3 gene in mammalian hepatic-derived cells. *J Biol Chem*. 2013;288:1726-1738.
134. Yue TL, Bao W, Jucker BM, et al. Activation of peroxisome proliferator-activated receptor α protects the heart from ischemia/reperfusion injury. *Circulation*. 2003;108(19):2393-2399.
135. Toyama T, Nakamura H, Harano Y, et al. PPARα ligands activate antioxidant enzymes and suppress hepatic fibrosis in rats. *Biochem Biophys Res Commun*. 2004;324(2):697-704.
136. Rodriguez-Vilarrupla A, Lavina B, Garcia-Caldero H, et al. PPARα activation improves endothelial dysfunction and reduces fibrosis and portal pressure in cirrhotic rats. *J Hepatol*. 2012;56(5):1033-1039.
137. Delerive P, De Bosscher K, Besnard S, et al. Peroxisome proliferator-activated receptor α negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-κB and AP-1. *J Biol Chem*. 1999;274(45):32048-32054.
138. Xu J, Storer PD, Chavis JA, Racke MK, Drew PD. Agonists for the peroxisome proliferator-activated receptor-α and the retinoid X receptor inhibit inflammatory responses of microglia. *J Neurosci Res*. 2005;81:403-411.
139. Tao Z, Cheng M, Wang SC, et al. JAK2/STAT3 pathway mediating inflammatory responses in heatstroke-induced rats. *Int J Clin Exp Pathol*. 2015;8(6):6732-6739.
140. Volpes R, Van Den Oord JJ, Desmet VJ. Vascular adhesion molecules in acute and chronic liver inflammation. *Hepatology*. 1992;15(2):269-275.
141. Volpes R, van den Oord JJ, Desmet VJ. Immunohistochemical study of adhesion molecules in liver inflammation. *Hepatology*. 1990;12:59-65.
142. Baiocchini A, Montaldo C, Conigliaro A, et al. Extracellular matrix molecular remodeling in human liver fibrosis evolution. *PLoS One*. 2016;11(3):e0151736.
143. Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol*. 2010;30(5):894-899.
144. Kostapanos MS, Kei A, Elisaf MS. Current role of fenofibrate in the prevention and management of non-alcoholic fatty liver disease. *World J Hepatol*. 2013;5(9):470-478.
145. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088-2093.
146. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. *J Med Chem*. 2000;43:527-550.
147. Fruchart JC. Selective peroxisome proliferator-activated receptor α modulators (SPPARMα): the next generation of peroxisome proliferator-activated receptor α-agonists. *Cardiovasc Diabetol*. 2013;12(1):82.
148. Ip E, Farrell G, Hall P, Robertson G, Leclercq I. Administration of the potent PPARα agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice. *Hepatology*. 2004;39(5):1286-1296.
149. Reyes-Quiroz ME, Alba G, Saenz J, Santa-Maria C, et al. Oleic acid modulates mRNA expression of liver X receptor (LXR) and its target genes ABCA1 and SREBP1c in human neutrophils. *Eur J Nutr*. 2014;53:1707-1717.
150. Carrillo C, Cavia Mdel M, Alonso-Torre S. Role of oleic acid in immune system; mechanism of action; a review. *Nutr Hosp*. 2012;27:978-990.
151. Juarez-Hernandez E, Chavez-Tapia NC, Uribe M, Barbero-Becerra VJ. Role of bioactive fatty acids in nonalcoholic fatty liver disease. *Nutr J*. 2016;15:72.
152. Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1α. *Proc Natl Acad Sci U S a*. 2007;104(29):12017-12022.
153. Supruniuk E, Miklosz A, Chabowski A. The implication of PGC-1α on fatty acid transport across plasma and mitochondrial membranes in the insulin sensitive tissues. *Front Physiol*. 2017;8:923.
154. Viollet B, Foretz M, Guigas B, et al. Activation of AMP-activated protein kinase in the liver: a new strategy for the management of metabolic hepatic disorders. *J Physiol*. 2006;574(1):41-53.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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