ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 November 21; 30(43): 4597-4688

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 30 Number 43 November 21, 2024

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Editorial Board Member of *World Journal of Gastroenterology*, Giovanna Ferraioli, MD, FAIUM, Researcher, Department of Clinical Surgical, Diagnostic and Pediatric Sciences, Medical School University of Pavia, Viale Brambilla 74, Pavia 27100, Italy. giovanna.ferraioli@unipv.it

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The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJG* as 4.3; Quartile: Q1. The *WJG*'s CiteScore for 2023 is 7.8.

RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
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http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
November 21, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

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https://www.wjgnet.com/bpg/gerinfo/204

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World J Gastroenterol 2024 November 21; 30(43): 4660-4668

DOI: 10.3748/wjg.v30.i43.4660

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Elafibranor alleviates alcohol-related liver fibrosis by restoring intestinal barrier function

Yu-Qi Sun, Yang Wu, Meng-Ran Li, Yu-Yao Wei, Mei Guo, Zi-Li Zhang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Feng YR

Received: July 26, 2024

Revised: September 29, 2024

Accepted: October 18, 2024

Published online: November 21, 2024

Processing time: 97 Days and 3.7 Hours

Yu-Qi Sun, Yang Wu, Meng-Ran Li, Yu-Yao Wei, Mei Guo, Zi-Li Zhang, Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Co-corresponding authors: Mei Guo and Zi-Li Zhang.

Corresponding author: Zi-Li Zhang, MD, PhD, Professor, Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, Nanjing University of Chinese Medicine, No. 138 Xianlin Avenue, Nanjing 210023, Jiangsu Province, China. zilizhang@njucm.edu.cn

Abstract

We discuss the article by Koizumi *et al* published in the *World Journal of Gastroenterology*. Our focus is on the therapeutic targets for fibrosis associated with alcohol-related liver disease (ALD) and the mechanism of action of elafibranor (EFN), a dual agonist of peroxisome proliferator-activated receptor α (PPARα) and peroxisome PPAR δ (PPARδ). EFN is currently in phase III clinical trials for the treatment of metabolic dysfunction-associated fatty liver disease and primary biliary cholangitis. ALD progresses from alcoholic fatty liver to alcoholic steatohepatitis (ASH), with chronic ASH eventually leading to fibrosis, cirrhosis, and, in some cases, hepatocellular carcinoma. The pathogenesis of ALD is driven by hepatic steatosis, oxidative stress, and acetaldehyde toxicity. Alcohol consumption disrupts lipid metabolism by inactivating PPARα, exacerbating the progression of ALD. EFN primarily activates PPARα, promoting lipolysis and β-oxidation in ethanol-stimulated HepG2 cells, which significantly reduces hepatic steatosis, apoptosis, and fibrosis in an ALD mouse model. Additionally, alcohol disrupts the gut-liver axis at several interconnected levels, contributing to a proinflammatory environment in the liver. EFN helps alleviate intestinal hyperpermeability by restoring tight junction protein expression and autophagy, inhibiting apoptosis and inflammatory responses, and enhancing intestinal barrier function through PPARδ activation.

Key Words: Liver fibrosis; Ethanol; Gut barrier function; Apoptosis; Autophagy; Peroxisome proliferator-activated receptor

Core Tip: Peroxisome proliferator-activated receptor (PPAR) can inhibit the pathological process of alcohol-related liver disease (ALD). However, the dual PPARα/δ agonist elafibranor has been studied mainly in metabolic dysfunction-associated steatohepatitis and primary cholangitis, and its role in ALD and its mechanism need to be further explored.

Citation: Sun YQ, Wu Y, Li MR, Wei YY, Guo M, Zhang ZL. Elafibranor alleviates alcohol-related liver fibrosis by restoring intestinal barrier function. *World J Gastroenterol* 2024; 30(43): 4660-4668
URL: https://www.wjgnet.com/1007-9327/full/v30/i43/4660.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i43.4660

TO THE EDITOR

In 2019, the World Health Organization estimated that 4.4% of diagnosed cancers and 401000 cancer-related deaths globally were attributable to alcohol consumption. Alcohol-related liver disease (ALD) is a significant global health crisis, accounting for approximately 20% of liver cancer-related deaths[1]. Approximately 90% of ingested alcohol is metabolized in the liver, where alcohol dehydrogenase (ADH) oxidizes it to acetaldehyde, a highly reactive and toxic compound[1]. Acetaldehyde interferes with DNA synthesis and repair and binds to proteins, altering their structure and function. These alterations include mitochondrial structural damage, reduced adenosine triphosphate (ATP) production through the respiratory chain, generation of reactive oxygen species (ROS), lipid peroxidation, and the formation of toxic byproducts such as 4-hydroxynonenal and malondialdehyde[2-4]. Research suggests that alcohol, *via* its metabolite acetaldehyde, can directly or indirectly regulate the transcription of proliferator-activated receptor A (encoding PPARα), leading to its inactivation[5]. This inactivation hinders fatty acid metabolism, promoting alcoholic fatty liver and contributing to the progression of fibrosis and cirrhosis.

The gut-liver axis describes the bidirectional relationship between the gut microbiota and the liver, integrating signals from diet, genetics, and environmental factors[6]. Studies have shown that ethanol metabolites, such as acetaldehyde, increase the permeability of Caco-2 cell monolayers, disrupting tight junctions and compromising gut barrier integrity[7]. Gut inflammation is another critical factor in gut barrier dysfunction. Pathological bacterial translocation and elevated plasma levels of gut-derived microbial products, such as lipopolysaccharides (LPS), increase with gut permeability[8]. LPS, a component of gram-negative bacterial outer membranes, is a potent trigger of inflammation and immune responses and has been identified as a key contributor to the development of ALD[9].

Elafibranor (EFN; GFT505), a dual PPARα/δ agonist, has progressed to phase III clinical trials for the treatment of metabolic dysfunction-associated fatty liver disease[10], and PPAR has been identified as a promising pharmacological target for chronic liver diseases, including ALD[11,12]. Could EFN be a viable treatment option for ALD? This possibility remains largely unexplored. EFN protects the liver by acting on several key pathways associated with nonalcoholic steatohepatitis (NASH) pathogenesis, reducing steatosis, improving liver function, and inhibiting the expression of proinflammatory and profibrogenic genes[13,14]. EFN may follow a similar pathway to mitigate the pathological progression of ALD. Li *et al*[15] suggest that restoring alcohol-impaired PPARα and PPARδ function could reduce the severity of ASH, potentially through alcohol-induced autophagy in adipose tissue.

MECHANISMS OF ALD-RELATED FIBROSIS

ALD primarily results from the toxic effects of ethanol and its metabolite acetaldehyde. Acetaldehyde, a highly reactive compound, interferes with several hepatocyte functions, inducing endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and tissue damage[16]. The oxidation of ethanol and acetaldehyde results in the production of large amounts of reduced NADH, which promotes fat synthesis and inhibits mitochondrial fatty acid oxidation, leading to the development of fatty liver[17].

Histological fibrosis staging is a critical prognostic factor in both compensated and decompensated ALD patients. Hepatic fibrosis is a dynamic process involving the excessive accumulation of extracellular matrix components, which is sustained by hepatic myofibroblasts[18]. Fibrosis is a major determinant of the prognosis of ALD patients. Alcoholic hepatic fibrosis is characterized by perivenular fibrosis and venous occlusion, whereas liver injury manifests through macrovesicular steatosis, lobular inflammation, hepatocellular swelling, and necrosis[17]. Some morphological features of ALD can also be observed in nonalcoholic fatty liver disease; however, widespread microvesicular steatosis, cholestasis, and hepatic venular occlusive injuries are more specific to ALD[1]. Acetaldehyde is a key mediator of alcoholic liver fibrosis, activating quiescent hepatic stellate cells (qHSCs), which lose their characteristic cytoplasmic lipid droplets (LDs) and transdifferentiate into activated myofibroblasts (aHSCs)[19]. It also stimulates the synthesis of transforming growth factor β1 (TGF-β1) in HSCs, with secreted TGF-β1 promoting the expression of α-smooth muscle actin and collagen type I [20]. In addition, ROS and endogenous liver LPS contribute to liver fibrosis[21]. The metabolism of alcohol in the liver follows two main pathways[22]. First, ethanol is metabolized to acetaldehyde by ADH, generating byproducts such as ROS, which cause lipid peroxidation and other toxic effects[23-25]. Second, the mitochondrial ethanol oxidizing system, which involves cytochrome P450 (CYP) enzymes, also metabolizes ethanol. Chronic alcohol consumption increases the expression of CYP2E1, which generates large amounts of ROS[26,27] during the metabolism of ethanol to acetaldehyde.

Excess ROS can activate apoptotic and autophagic pathways[28], as well as lipid peroxidation[29], exacerbating liver injury. ROS also induce oxidative stress, including ER stress and mitochondrial damage, while amplifying the inflammatory effects of LPS[30]. Interestingly, LPS-induced ROS production is also exacerbated by alcohol[31], impairing intestinal barrier function and increasing permeability. This allows LPS to cross the intestinal barrier and enter the portal circulation, directly affecting the liver[3]. Elevated levels of LPS activate Kupffer cells, promoting hepatic injury[32,33], whereas increased intestinal permeability further increases LPS levels in the liver. Therefore, ROS and LPS act synergistically in the progression of liver disease, exacerbating liver injury[34].

Increasing attention is being given to the treatment of alcoholic liver fibrosis. Nataraj *et al*[35] reported that estrogens protect female mice from alcohol-induced liver fibrosis by promoting protein arginine N-methyltransferase 6 expression and inhibiting integrin genes. Wu *et al*[36] reported that cluster of differentiation 73 (CD73) may regulate autophagy in HSCs through the AMPK/AKT/mTOR signaling pathway, thereby exerting an antifibrotic effect on ALD. Koizumi *et al*[37] demonstrated that EFN reduces liver enlargement, steatosis, and necroinflammation in mice with ALD. Consistent with the reduction in steatosis, EFN significantly decreases hepatic triglyceride (TG) and free fatty acid (FFA) levels, confirming that EFN can mitigate alcohol-induced steatohepatitis in mice. This raises the following question: Can EFN also alleviate lipid metabolism disorders induced by the alcohol metabolite acetaldehyde? These results indicate that while EFN does not alter the expression of lipogenesis-related markers, it significantly increases the expression of lipolysis- and fatty acid oxidation-related markers.

FFAs are absorbed by hepatocytes and converted into TGs, which are stored in LDs alongside cholesterol. The regulatory and functional similarities between autophagy, lipolysis, and lysosomal lipid degradation suggest that autophagy may contribute to the degradation of LDs and TGs[38]. Interestingly, EFN can increase autophagy, promote lipolysis and reduce hepatocyte apoptosis. *In vivo*, EFN significantly improved alcohol-induced liver injury and inhibited the progression of liver fibrosis in mice. However, intriguingly, *in vitro*, EFN does not directly affect LX2 cells but appears to modulate HepG2 cell activity, autophagy, and antioxidative responses through PPARα activation, thereby playing an antifibrotic role in ALD[37].

PPAR SUBTYPES AND THEIR ROLES

PPARs are fatty acid-activated transcription factors belonging to the nuclear hormone receptor superfamily and play a key role in regulating energy metabolism. Three subtypes of PPARs have been identified: PPARα, PPARγ, and PPARβ/δ [39]. PPARα is involved in fatty acid transport, esterification, and oxidation, whereas PPARβ/δ, which is ubiquitously expressed, not only regulates fatty acid oxidation but also plays a role in glucose metabolism. Evidence suggests that PPARα has anti-inflammatory effects by directly acting on adipocytes. The proposed mechanism involves sirtuin 1 (SIRT1), an NAD (+)-dependent deacetylase that inhibits TNF-α-induced CD40 expression *via* SIRT1-dependent signaling pathways[40,41]. PPARα also appears to promote macrophage polarization toward an anti-inflammatory phenotype. The known PPAR agonists and their functions are outlined in Table 1. Li *et al*[42] reported that Huang Qin Tang regulates fatty acid metabolism and mediates M2 macrophage polarization through the FFAR4-AMPK-PPARα pathway. PPARβ/δ influences lipid metabolism by regulating adipokine expression[43] and improving insulin sensitivity[44]. It also reduces acute liver inflammation, as administering PPARβ/δ agonists protects mice from chemically induced hepatotoxicity and downregulates the expression of proinflammatory mediators, including TNF-α and human macrophage chemoattractant protein-1 (MCP-1), by inhibiting nuclear factor κB (NF-κB) activation[45].

EFFECT OF EFN ON MACROPHAGES

Macrophages, crucial components of the innate immune system, are essential for immune defense, inflammation regulation, tissue remodeling, and homeostasis. Macrophages can be polarized into two phenotypes: M1-like (proinflammatory) and M2-like (anti-inflammatory) macrophages. M1 macrophages are primarily activated by LPS and interferon-gamma (IFN-γ), whereas M2 macrophages are induced by interleukin-4 (IL-4) and IL-13[46]. M1 macrophages secrete large amounts of proinflammatory cytokines, including IL-1β, inducible nitric oxide synthase, and TNF-α[47], whereas M2 macrophages primarily produce anti-inflammatory cytokines, such as IL-10 and *Arg-1*[47].

In the context of ALD, Kupffer cell activation plays a pivotal role, and monocyte macrophages are recruited to the liver, where they polarize into M1 or M2 phenotypes depending on the hepatic microenvironment[48]. Voican *et al*[49] reported reduced macrophage infiltration and increased M2 macrophage polarization in subcutaneous adipose tissue in ALD patients after alcohol withdrawal. Furthermore, M2 macrophages induce hepatocyte senescence *via* IL-6, mitigating alcohol-induced hepatocyte apoptosis and hepatic steatosis[50]. Thus, macrophage polarization, particularly toward the M2 phenotype, appears to play a key role in resolving ALD. Toll-like receptor 4 (TLR4), an innate immune receptor on macrophages, recognizes pathogen-associated molecular patterns and is the primary receptor for LPS[51]. During ALD progression, the LPS/TLR4 pathway is crucial for activating hepatic macrophages[52]. Increased intrahepatic LPS levels trigger the LPS/TLR4 pathway, leading to M1 macrophage polarization. However, EFN significantly inhibits the expression of LPS-binding protein, Tlr4, and its coreceptor Cd14, reducing the expression of the proinflammatory cytokine TNF-α (Tnfa) in the liver. EFN also decreases the expression of M1 macrophage markers such as Tnfa, Il1b, and Nos2 while increasing the expression of the M2 macrophage marker Arg in the gut of ALD mice. These findings suggest that EFN promotes autophagy in intestinal epithelial cells (IECs), increasing cell survival and maintaining intestinal barrier function[37]. Additionally, Hakeem *et al*[53] reported that in NASH, EFN reduces ileal inflammation by

Table 1 Roles of elafibranor and other peroxisome proliferator-activated receptor agonists

Agonists	Roles
PPARα agonists	
Bezafibrate	Bezafibrate promotes fatty acid β-oxidation and ketogenesis while reducing abnormal lipid metabolism, inflammation, oxidative stress, and insulin resistance[71]. It ameliorates steatosis, alters lipid composition, and increases mitochondrial mass in the liver[72]
Fenofibrate	Fenofibrate has been shown to improve hepatic steatosis and increase TFEB activation, leading to lower levels of LDL and VLDL. It also elevates HDL levels and decreases TG levels[73]
Ciprofibrate	Ciprofibrate stimulates the expression of the *CETP* gene and alters cholesterol flow through reverse cholesterol transport, facilitating plasma cholesterol removal *via* LDL[74]
PPARα/δ agonists	
Elafibranor	EFN promotes lipolysis and β-oxidation, enhances autophagy and antioxidant capacity, inhibits Kupffer cell-mediated inflammatory responses, and impairs the LPS and TLR4/NF-κB signaling pathways. Additionally, EFN improves intestinal barrier hyperpermeability by restoring tight junction proteins, enhancing autophagy, and inhibiting both apoptosis and inflammatory responses[37]
PPARγ agonists	
Rosiglitazone	Rosiglitazone increases the expression of adipogenic and energetic genes in adipose tissue, as well as defense genes in macrophages[71]. It is primarily used to treat type 2 diabetes, enhancing glucose utilization by cells, which subsequently lowers blood sugar levels[75]
Pioglitazone	Pioglitazone reduces glucose production in the liver, lowers triglyceride levels, and increases HDL, thus improving insulin sensitivity[76]

PPAR: Peroxisome proliferator-activated receptor; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; CETP: Cholesteryl ester transfer protein; EFN: Elafibranor; LPS: Lipopolysaccharides; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor κB.

promoting M2 macrophage polarization, likely through the protective effects of PPARα against intestinal injury *via* IFN-γ inhibition. Briand *et al*[54] demonstrated that EFN significantly improves NASH induced by the HFCC/CDX diet (which consists of C57BL6/J mice fed a diet containing 60.00% high-fat, 1.25% cholesterol, and 0.50% cholic acid, along with 2.00% cyclodextrin in drinking water) by suppressing the innate immune system. This includes a reduction in Kupffer cells and natural killer T cells, thereby ameliorating the pathological progression of NASH. This raises the question of whether EFN could also inhibit the progression of ALD by promoting M2 macrophage polarization or by decreasing the overall number of immune cells in the ALD model.

EFFECT OF EFN ON THE INTEGRITY OF THE INTESTINAL BARRIER AND ON PERMEABILITY

The gut-liver axis refers to the dynamic relationship between the gut microbiota and the liver[55]. Approximately 70% of the liver's blood supply comes from the intestine *via* the portal vein, where it carries products derived from food, the gut microbiota, and toxins. An early manifestation of impaired intestinal mucosal barrier function is increased permeability. The interface between the liver and microbiota forms the intestinal mucosal barrier, which separates the gut microbiota from host immune cells to maintain homeostasis. The integrity of the intestinal mucosa depends on several functional components: A protective mucin layer on the luminal surface of IECs and tight junction proteins (TJPs) between intestinal epithelial and immune cells[56,57]. Key TJPs include claudins, occludins, adhesion molecules, and zonula occludens (ZOs)[58]. Decreases in TJPs or alterations in IECs can result in increased mucosal permeability[59].

Alcohol intake increases the levels of acetaldehyde, a metabolite that damages tight junctions, leading to gut dysbiosis and increased intestinal permeability. This allows bacterial endotoxins, such as LPS, to enter the portal vein, where they activate TLRs on Kupffer cells and hepatocytes, promoting inflammation and fibrosis and exacerbating the pathophysiology of ALD[60]. In an ALD mouse model[37], increased expression of genes such as Ftcd and Sox9, which are associated with reduced TJPs and inflammation and inhibited epithelial cell proliferation, was observed, whereas the expression of Dhrs9, FoxM1, S100G, and Mgl2, which promote intestinal barrier function and have anti-inflammatory effects, decreased. EFN significantly mitigated these changes, effectively reducing the loss of TJPs, improving intestinal permeability, and restoring mucosal barrier integrity.

EFN has been shown to increase the expression of key TJPs, such as ZO-1 and occludin[37], thereby restoring intestinal barrier function. The intestinal epithelium, which is composed of a single layer of closely connected columnar epithelial cells, serves as the first line of defense for the intestinal mucosa. Increased permeability is closely linked with the apoptosis and autophagy of IECs[61,62]. Autophagy is crucial for cell survival under stress[15] and reinforces the epithelial barrier by preserving proteins such as ZO-1 and occludin[63,64]. While apoptosis is a natural protective mechanism, excessive apoptosis can hinder the repair and regeneration of IECs, leading to barrier dysfunction. Kim *et al*[65] reported that PPARα promotes intestinal tissue repair by inhibiting pigment epithelium-derived factor and encouraging intestinal stem cell proliferation, thereby supporting barrier integrity. Abdulqadir *et al*[66] demonstrated that PPARγ prevents the TNFα-induced increase in epithelial permeability by inhibiting the NF-κB p50/p65 signaling pathway and activating the myosin light chain kinase gene[66]. Similarly, Sohn *et al*[67] reported that PPARγ in Lactoba-

cillus paracasei acts similarly to PPARδ. As a dual agonist of PPARα and PPARδ, the role of EFN in intestinal permeability and barrier function is significant. EFN has been reported to inhibit apoptosis in IECs by activating autophagy[15], which reduces the level of IL-1β/MCP-1 and restores the intestinal barrier. Koizumi *et al*[37] demonstrated accelerated apoptosis of intestinal cells in ALD mice, along with decreased expression of antiapoptotic markers such as Bcl-2 and Mcl-1. EFN treatment inhibits the autophagy-induced apoptosis of damaged epithelial cells. *In vitro* studies using Caco-2 cells revealed that EFN improved hyperpermeability by restoring TJPs, enhancing autophagy, and reducing both apoptosis and proinflammatory responses. In summary, EFN promotes the expression of TJPs, inhibits apoptosis, and enhances autophagy in IECs, thereby reducing intestinal permeability and restoring the intestinal barrier. Additionally, EFN promotes macrophage M2 polarization, which reduces intestinal injury. Its beneficial effects on intestinal barrier function appear to be primarily mediated through PPARδ activation rather than PPARα[37].

DISCUSSION

In a recent issue of the *World Journal of Gastroenterology*, Koizumi *et al*[37] published an intriguing paper titled "Effects of elafibranor on liver fibrosis and gut barrier function in a mouse model of alcohol-associated liver disease". This study addresses a critical question: How does EFN mitigate the pathological progression of ALD-related liver fibrosis?

EFN significantly alleviated hepatic steatosis, apoptosis, and liver fibrosis in the ALD mouse model. It primarily activates PPARα, promoting fat breakdown and β-oxidation in ethanol (EtOH)-stimulated HepG2 cells while enhancing autophagy and antioxidant capacity. Moreover, EFN inhibits Kupffer cell-mediated inflammatory responses, reducing liver exposure to LPS and downregulating the TLR4/NF-κB signaling pathway. EFN also improves intestinal barrier function by restoring TJPs, enhancing autophagy, and suppressing cell apoptosis and inflammatory responses. The protective effect of EFN on intestinal barrier integrity in EtOH-stimulated Caco-2 cells is largely mediated through PPARδ activation.

In contrast to a previously published article[15], which focused on a different aspect, Koizumi *et al*[37] emphasized the liver fibrosis process induced by ALD, a topic not highlighted by Li *et al*[15]. However, a question arises: While EFN significantly reduces liver fibrosis in the ALD mouse model, it does not notably affect LX2 cells. Could this suggest a novel therapeutic approach: Targeting ALD-related liver fibrosis through mechanisms that bypass LX2 cells? Additionally, given that HepG2 cells are derived from a hepatocellular carcinoma line, future research should focus on analyzing the effects of EFN on primary cultured liver cells.

The literature suggests that PPARα activation can influence IECs[68]. In Caco-2 cells, treatment with the PPARα agonist fenofibrate preserves barrier function, reduces junctional curling, and increases Claudin-1 expression after exposure to high glucose or inflammatory cytokines. However, Koizumi *et al*[37] revealed limited effects of PPARα on intestinal barrier function in Caco-2 cells treated with EFN, possibly due to differences in experimental models. A diagram illustrating the specific mechanisms of action of EFN in ALD mice is presented in Figure 1.

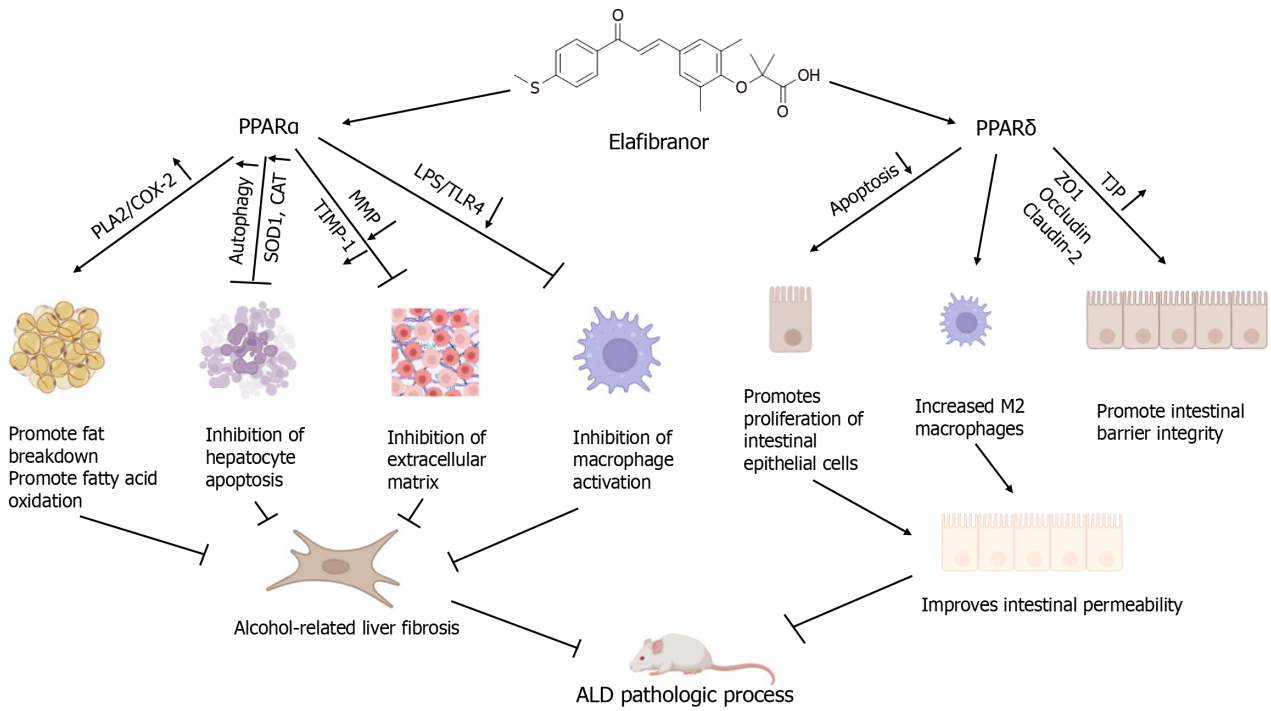

Figure 1 Effects of elafibranor on alcohol-associated liver disease in mice. Elafibranor (EFN) activates peroxisome proliferator-activated receptor α

(PPARα), inhibiting liver fibrosis in alcoholic liver disease through four primary mechanisms. First, it increases the expression of phospholipase A2 and cyclooxygenase-2, promoting lipid breakdown and fatty acid oxidation. Second, it enhances hepatocyte autophagy and increases antioxidant activity, specifically, superoxide dismutase 1 and catalase, thereby preventing hepatocyte apoptosis. Third, EFN reduces extracellular matrix production by regulating the activity of matrix metalloproteinases and tissue inhibitors of metalloproteinases. Finally, it suppresses macrophage activation by inhibiting the lipopolysaccharide/Toll-like receptor 4 signaling pathway. Moreover, PPARδ activation improves intestinal permeability by preventing intestinal epithelial cell apoptosis and promoting M2 macrophage polarization. It also enhances intestinal barrier integrity by upregulating tight junction proteins, such as zonula occludens-1, occludin, and claudin-2. PPAR: Peroxisome proliferator-activated receptor; ALD: Alcoholic liver disease; PLA2: Phospholipase A2; COX2: Cyclooxygenase-2; SOD1: Superoxide dismutase 1; CAT: Catalase; MMPs: Matrix metalloproteinases; TIMP-1: Tissue inhibitors of metalloproteinases; LPS: Lipopolysaccharides; TLR4: Toll-like receptor 4; TJPs: Tight junction proteins; ZO-1: Zonula occludens-1.

While compounds that activate multiple PPAR subtypes (dual agonists) or all PPARs (panagonists) may benefit lipid and glucose metabolism[69], the reduced target specificity of such agonists could lead to more adverse effects[70]. Therefore, although EFN shows promise in inhibiting the progression of ALD-related liver fibrosis, further investigations are needed to assess its potential side effects.

CONCLUSION

EFN, a dual agonist of PPARα and PPARδ, has demonstrated potential not only in treating metabolic disorders associated with hepatic steatosis and primary biliary cholangitis but also in inhibiting the development of EtOH + CCl4-induced liver fibrosis in ALD model mice. These findings suggest that EFN could be a promising therapeutic option for ALD. Furthermore, Koizumi *et al*[37] proposed the intriguing hypothesis that EFN may exert anti-ALD liver fibrosis effects without directly affecting LX2 cells, a notion that warrants further investigation and validation.

In conclusion, EFN holds promise as a therapeutic agent for ALD because of its dual activation of PPARα/δ, which enhances lipid metabolism, reduces inflammation, and strengthens gut barrier function. Additional clinical trials are essential to confirm EFN's efficacy and safety in treating ALD and to explore its potential applications in other liver diseases.

FOOTNOTES

Author contributions: Sun YQ, Li MR, Wei YY, Guo M, and Zhang ZL contributed to this paper; Zhang ZL designed the overall concept and outline of the manuscript; Guo M and Sun YQ contributed to the discussion and design of the manuscript; Sun YQ, Wu Y, Li MR, and Wei YY contributed to the writing, and editing the manuscript, illustrations, and review of literature; Guo M and Zhang ZL contributed equally to this work as co-corresponding authors; and all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 82474164, No. 82305046, and No. 82000572; Natural Science Foundation of Jiangsu Province, No. BK20220467; Major Project of the Natural Science Research of Jiangsu Higher Education Institutions, No. 22KJB310013; and Science and Technology Project of Jiangsu Province, No. BK20200840.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Country of origin: China

ORCID number: Yang Wu 0000-0002-0906-9667; Zi-Li Zhang 0000-0002-2618-0308.

S-Editor: Chen YL
L-Editor: A
P-Editor: Zheng XM

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