World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

*World J Gastroenterol* 2025 January 14; 31(2): 99549

DOI: 10.3748/wjg.v31.i2.99549

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

LETTER TO THE EDITOR

# Prospects of elafibranor in treating alcohol-associated liver diseases

Wei-Tong Cui, Hua-Ru Xue, Dian-Fang Wei, Xiao-Yu Feng, Kai Wang

**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 B, Grade C

**Novelty:** Grade B, Grade B

**Creativity or Innovation:** Grade A, Grade B

**Scientific Significance:** Grade A, Grade B

**P-Reviewer:** Qiang Z; Zheng L

**Received:** July 24, 2024

**Revised:** October 8, 2024

**Accepted:** November 25, 2024

**Published online:** January 14, 2025

**Processing time:** 146 Days and 13.4 Hours

**Wei-Tong Cui, Dian-Fang Wei, Xiao-Yu Feng, Kai Wang,** School of Basic Medicine, Qilu Medical University, Zibo 255300, Shandong Province, China

**Hua-Ru Xue,** School of Medical Imaging, Qilu Medical University, Zibo 255300, Shandong Province, China

**Co-first authors:** Wei-Tong Cui and Hua-Ru Xue.

**Corresponding author:** Wei-Tong Cui, MD, Professor, School of Basic Medicine, Qilu Medical University, No. 1678 West Renmin Road, Zibo 255300, Shandong Province, China. klnr727@qlmu.edu.cn

## Abstract

Alcohol-related liver disease (ALD), which is induced by excessive alcohol consumption, is a leading cause of liver-related morbidity and mortality. ALD patients exhibit a spectrum of liver injuries, including hepatic steatosis, inflammation, and fibrosis, similar to symptoms of nonalcohol-associated liver diseases such as primary biliary cholangitis, metabolic dysfunction-associated steatotic liver disease, and nonalcoholic steatohepatitis. Elafibranor has been approved for the treatment of primary biliary cholangitis and has been shown to improve symptoms in both animal models and *in vitro* cell models of metabolic dysfunction-associated steatotic liver disease and nonalcoholic steatohepatitis. However, the efficacy of elafibranor in treating ALD remains unclear. In this article, we comment on the recent publication by Koizumi *et al* that evaluated the effects of elafibranor on liver fibrosis and gut barrier function in an ALD mouse model. Their findings indicate the potential of elafibranor for ALD treatment, but further experimental investigations and clinical trials are warranted.

**Key Words:** Elafibranor; Alcohol-associated liver diseases; Peroxisome proliferator-activated receptor; Lipid; Apoptosis; Steatosis; Inflammation; Fibrosis

**Core Tip:** Elafibranor is an oral dual peroxisome proliferator-activated receptor α/δ agonist that has demonstrated efficacy in improving hepatic steatosis and inhibiting inflammation and fibrosis associated with nonalcoholic liver diseases. Alcohol-related liver disease (ALD), resulting from excessive alcohol consumption, also presents symptoms such as hepatic steatosis, inflammation, and fibrosis. However, the effectiveness of elafibranor in treating ALD remains unclear. A recent study by Koizumi *et al* revealed that elafibranor significantly reduced hepatic steatosis, apoptosis, and fibrosis in a mouse model of ALD. Despite the potential of elafibranor for ALD treatment appears promising, further experimental investigations and clinical trials are warranted.

**Citation:** Cui WT, Xue HR, Wei DF, Feng XY, Wang K. Prospects of elafibranor in treating alcohol-associated liver diseases. *World J Gastroenterol* 2025; 31(2): 99549
**URL:** https://www.wjgnet.com/1007-9327/full/v31/i2/99549.htm
**DOI:** https://dx.doi.org/10.3748/wjg.v31.i2.99549

## TO THE EDITOR

Elafibranor is an oral dual peroxisome proliferator-activated receptor (PPAR) α/δ agonist that mediates many physiological processes, such as lipid metabolism, glucose metabolism balance, and inflammatory responses, by activating PPARα and PPARδ[1]. Elafibranor has shown great potential in the treatment of liver disease and has been approved for the treatment of primary biliary cholangitis (PBC) in the United States[2]. Several studies have revealed that elafibranor treatment ameliorates steatosis, inflammation, and fibrogenesis resulting from conditions such as metabolic dysfunction-associated steatotic liver disease (MASLD), also known as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and chronic hepatic diseases[3-10], in mouse models and *in vitro* liver cell or slice models.

Alcohol is one of the most common causes of liver disease worldwide and induces a wide range of direct liver damage, including steatosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma[11-13]. Alcohol-related liver disease (ALD) also involves lipid metabolism disorders and inflammation[14,15], but whether elafibranor is effective in treating ALD remains unknown. The mechanisms by which elafibranor treats ALD have been explored by studies using animal models. Li *et al*[16] reported that elafibranor reduced intestinal epithelial destruction and liver inflammation/apoptosis/steatosis in a mouse model of alcoholic steatohepatitis, thereby reducing the severity of liver injury. Recent findings of Koizumi *et al*[17] demonstrated that elafibranor reduced ALD related fibrosis by inhibiting lipid accumulation and suppressed inflammatory responses by restoring intestinal barrier function in a mouse model of NASH. Moreover, several studies have shown that the application of PPARα or PPARδ agonists alone could improve symptoms of ALD[18-20]. For example, PPARα agonists alleviate steatohepatitis in ALD mouse models by increasing lipid oxidation, increasing the expression level of antioxidant enzymes, downregulating the expression of proinflammatory factors[18-20], and enhancing autophagy by directly increasing the expression of autophagy genes[21], whereas PPARδ agonists alleviate alcohol-induced liver injury in mice and improve intestinal barrier function[22]. These findings lay a foundation for the application of elafibranor in ALD.

## EFFICACY OF ELAFIBRANOR IN THE TREATMENT OF NONALCOHOLIC LIVER DISEASE

In addition to PBC, elafibranor has also been used for the treatment of liver fibrosis, NAFLD, primary sclerosing cholangitis, dyslipidemia, abdominal obesity and other diseases, but many clinical trials have terminated in stages 2 or 3. In clinical trials to treat PBC, researchers have tested two doses of elafibranor (80 mg and 120 mg per day)[23,24]. Both doses significantly reduced the serum levels of alkaline phosphatase (ALP) and total bilirubin, which are biomarkers of PBC, but the 120 mg group showed little improvement compared with the 80 mg group[23,24]. Notably, 16-30 days after treatment with elafibranor, the ALP level of the PBC patients increased again to the pretreatment level[24], indicating that although elafibranor could improve the plasma biochemical parameters of PBC patients, it did not fundamentally solve the problem of cholestasis.

The slow pace of drug development for liver disease is partly due to the lack of adequate tools to evaluate the efficacy of potential new drug candidates; thus, animal and cellular models of liver disease are important tools for studying disease pathogenesis and evaluating drug candidates[25,26]. Perakakis *et al*[4] evaluated the effects of elafibranor on a mouse model of NAFLD and reported that elafibranor (30 mg/kg/day) had profound effects on the hepatic lipidome, manifested by a reduction in triglycerides, increases in phospholipids, and beneficial regulation of fatty acid oxidation, inflammation, and oxidative stress. Baandrup Kristiansen *et al*[27] reported that although elafibranor (30 mg/kg/day) could significantly reduce the liver fat content in a NASH mouse model, it tended to exacerbate hepatomegaly. Van den Hoek *et al*[6] reported that oral administration of elafibranor (15 mg/kg/day) significantly reduced hepatic steatosis and liver inflammation and prevented the progression of liver fibrosis in a NASH mouse model, which was consistent with the results obtained by Briand *et al*[28] with 20 mg/kg/day of elafibranor. Briand *et al*[7] also reported that 20 mg/kg/day elafibranor had liver-protective effects on NASH model hamsters, greatly improving liver lesions and reducing the expression of genes associated with inflammation (*e.g.*, tumor necrosis factor-α and interleukin-1β) and fibrosis (collagen 1 alpha 1).

Hammoutene *et al*[29] constructed a 3D model of MASLD using patient-derived precision cut liver slices (PCLS) and reported that aspartate aminotransferase and lactate dehydrogenase leakage in PCLS culture supernatants was not significantly affected by elafibranor treatment. Four clinical trials of elafibranor in the treatment of NAFLD patients also demonstrated that elafibranor significantly reduced serum ALT levels, but there was no significant change in aspartate aminotransferase[30], which was consistent with the results obtained *via* PCLS[29].

van Os *et al*[26] established functional multicellular liver spheroid (MCLS) cultures using primary mouse hepatocytes, hepatic stellate cells, liver sinusoidal endothelial cells, and Kupffer cells and reported that elafibranor (30 μmol/L) inhibited steatosis and liver fibrosis. Gore *et al*[31] reported that improved fibrosis and inflammation occurred only in NASH model mice treated with elafibranor (15 mg/kg, administered orally twice a day), but not *in vitro* in mouse-derived PCLS treated with 0.2 or 1 μmol/L elafibranor, which increased the expression of only PPARα-regulated genes. Elafibranor (10 μmol/L) also decreased triglycerides and reduced inflammation in MAFLD patient-derived PCLS but had no effect on the expression of liver fibrosis-related markers, such as alpha smooth muscle actin, collagen 1 alpha 1, and collagen 1 alpha 2[29]. These studies indicate that the responses of animal models and MCLS/PCLS to elafibranor are different, but the differences may be caused by the different doses of elafibranor used in these studies.

Boeckmans *et al*[25] established *in vitro* models of NASH using primary human hepatocytes (PHHs), HepaRG cells, and human skin stem cell-derived hepatic progenitor cells (hSKP-HPCs) and reported that the transcriptomes of these models were similar to those of NASH human livers. Transcriptome analysis revealed that 60 μmol/L elafibranor reduced the toll-like receptor-dependent inflammatory response in NASH models of PHHs and hSKP-HPCs, and three genes (*ANGPTL4*, *PDK4*, and *PLIN2*) that promote fat production and accumulation were strongly upregulated. Nevertheless, elafibranor did not increase the expression of these three genes in the clinical samples of NASH patients. Moreover, the transcriptomes of PHHs, HepaRG cells, and hSKP-HPCs overlapped 35% with the transcriptomes of liver sample from NASH patients. Other comparative transcriptomic studies revealed that, after activation by wy14643 (a PPARα agonist), only 20% of the upregulated and 12% of the downexpressed genes overlapped between humans and mice[32], with genes involved in glycolysis and gluconeogenesis pathways being specifically upregulated only in mice, whereas genes involved in heterologous metabolism and the apolipoprotein synthesis pathway were specifically upregulated only in human hepatocytes[32,33]. These findings indicate large differences in gene expression and regulation between animal models and humans and may explain the failure of elafibranor in many clinical trials.

## DOSAGES OF ELAFIBRANOR AND ITS SAFETY

Doses of 80 mg or 120 mg elafibranor per person per day were adopted in clinical trials for MAFLD and NASH in both adults and children[5,23,24]. The common doses are 15, 20, or 30 mg/kg/day for animal models[4,6,7,27,28], and 0.2, 1.0, 10, 30, or 60 μmol/L for MCLS/PCLS and cell cultures[25,26,29,31]. Curiously, although the doses were quite different, the effects of elafibranor were similar in terms of reducing inflammation and improving lipid metabolism. Additionally, the great distinction in dosage, especially for MCLS/PCLS and cell cultures, reflects the strong tolerance of human, animal, and isolated cells to elafibranor. As a ligand, elafibranor binds to PPAR α/δ to function[34]. PPARα/δ, as receptors, are saturated when the level of elafibranor reaches a certain level. Therefore, the efficacy of elafibranor may be related to the expression levels of PPARα/δ in the liver, but research on this relationship is still lacking.

In clinical trials for the treatment of PBC, compared with the placebo group, the elafibranor group had higher rates of adverse events, including abdominal pain, diarrhea, nausea and vomiting[23,24]. Elafibranor, which is administered once daily, is well tolerated in children aged 8-17 years with NASH[5]. Hammoutene *et al*[29] reported that 10 μmol/L elafibranor had no toxic effect on PCLS derived from MAFLD patients. Therefore, elafibranor is generally safe although it may increase the rate of mild to moderate adverse events.

## PROSPECTS OF ELAFIBRANOR IN THE TREATMENT OF ALD

According to the World Health Organization's Global Status Report on alcohol and health, the incidence of ALD is much higher than that of PBC[35]. The pathogenic mechanism of ALD differs from that of nonalcoholic liver diseases such as MASLD and NASH, but ALD also involves abnormal fat metabolism and inflammation[14,36]. Alcohol absorption and metabolism disrupt liver metabolic homeostasis and form the basis for ALD through a multifaceted mechanism. Alcohol metabolism results in the production of large amounts of reductive NADH, which induces lipid synthesis in the liver[37]. Sterol regulatory element-binding protein-1c is the main regulatory factor that regulates fatty acid synthesis[38]. Excessive alcohol consumption enhances the activity of sterol regulatory element-binding protein-1c and thus promotes lipid synthesis. PPARα regulates fatty acid degradation, but excessive drinking inhibits PPARα activity. Consequently, heavy drinkers accumulate fat in the liver, which leads to the formation of alcohol-related fatty liver and then progresses to ALD[37]. PPARα prevents ALD progression through hepatic lipid metabolism pathways, including fatty acid oxidation, elongation, desaturation, and thyroglobulin synthesis and breakdown[38], while PPARδ functions in lipid metabolism through autophagy-mediated fatty acid oxidation[39].

Although the therapeutic effect of elafibranor on ALD cannot be confirmed at present because of the lack of clinical studies on the effects of elafibranor on ALD, the effects of elafibranor on the PPAR signaling pathway in some cell and mouse models have been reported. In alcohol-stimulated HepG2 cells, elafibranor promotes lipolysis and β-oxidation through the activation of PPARα, whereas in alcohol-stimulated Caco-2 cells, elafibranor protects the intestinal barrier through PPARδ[17]. In metabolic dysfunction-associated steatohepatitis mouse models, elafibranor elevated S100A4

expression by activating PPARβ/δ[3]. S100A4 is known to promote mitochondrial metabolism and maintain high levels of fatty acid β-oxidation in tumor-associated macrophages[40]. However, it is not clear whether the expression of S100A4 is also elevated in ALD. When NASH mice were treated with GFT505 (an alternative name for elafibranor), upregulated genes were enriched in the PPAR signaling pathway and fatty acid degradation pathway, and *Ehhadh* and *Acaa2* were two of the upregulated genes involved in fatty acid degradation[41].

Despite considerable efforts in the field of ALD research, the pathogenesis of ALD is still unclear, and no Food and Drug Administration-approved ALD drugs are available[37,42]. Given the effectiveness of elafibranor in nonalcoholic liver diseases and the shared symptoms between alcoholic and nonalcoholic liver diseases, the prospects of elafibranor in ALD treatment are promising. The positive effect of elafibranor on ALD mouse models reported by Koizumi *et al*[17] may support further exploration of the use of elafibranor in treating ALD. However, extensive experimental studies are needed to elucidate the mechanism of efficacy of elafibranor and the key to achieving optimal efficacy. Just as the level of ALP in PBC patients increased again after elafibranor was stopped, although elafibranor may have certain therapeutic effects on ALD, alcohol cessation may be the cornerstone for the treatment of ALD.

## CONCLUSION

Due to its ability to improve lipid metabolism, inflammatory responses, and hepatic fibrosis, elafibranor is a promising drug that may play an essential role in treating ALD. PPAR is a transcription factor and elafibranor binds to PPARα/δ to function. Nevertheless, the amount of elafibranor needed to effectively activate PPARα/δ to initiate downstream gene expression, as well as the expression levels of PPARα/δ in patients with liver disease, deserves further research. In addition, the differences in reactions to elafibranor between patients and animal/cell models are also key factors that need to be fully considered when elucidating the mechanisms of ALD and evaluating drug efficacy and safety.

## FOOTNOTES

**Author contributions:** Cui WT designed the research study; Xue HR and Wang K contributed to the search and analysis of the literatures; Cui WT and Xue HR drafted the manuscript, they contributed equally to this manuscript and as co-first authors; Wei DF and Feng XY helped in reviewing and editing of the manuscript; and all the authors have read and approved the final manuscript.

**Supported by** Natural Science Foundation of Shandong Province, China, No. ZR2019PC053; and the Projects of Medical and Health Technology Development Program in Shandong Province, China, No. 202202020837 and No. 202301040472.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



**Country of origin:** China

**ORCID number:** Wei-Tong Cui 0000-0001-9083-0494; Hua-Ru Xue 0009-0001-1267-7217; Kai Wang 0000-0002-3798-060X.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Zheng XM

## REFERENCES

1 **Wang Y**, Nakajima T, Gonzalez FJ, Tanaka N. PPARs as Metabolic Regulators in the Liver: Lessons from Liver-Specific PPAR-Null Mice. *Int J Mol Sci* 2020; **21**: 2061 [PMID: 32192216 DOI: 10.3390/ijms21062061]

2 **Blair HA**. Elafibranor: First Approval. *Drugs* 2024; **84**: 1143-1148 [PMID: 39110316 DOI: 10.1007/s40265-024-02075-8]

3 **Zhang M**, Barroso E, Ruart M, Peña L, Peyman M, Aguilar-Recarte D, Montori-Grau M, Rada P, Cugat C, Montironi C, Zarei M, Jurado-Aguilar J, Camins A, Balsinde J, Valverde ÁM, Wahli W, Palomer X, Vázquez-Carrera M. Elafibranor upregulates the EMT-inducer S100A4 *via* PPARβ/δ. *Biomed Pharmacother* 2023; **167**: 115623 [PMID: 37783154 DOI: 10.1016/j.biopha.2023.115623]

4 **Perakakis N**, Stefanakis K, Feigh M, Veidal SS, Mantzoros CS. Elafibranor and liraglutide improve differentially liver health and metabolism in a mouse model of non-alcoholic steatohepatitis. *Liver Int* 2021; **41**: 1853-1866 [PMID: 33788377 DOI: 10.1111/liv.14888]

5 **Goyal NP**, Mencin A, Newton KP, Durelle J, Carrier C, Ugalde-Nicalo P, Noel B, Mouton J, Vargas D, Magrez D, Tadde B, Birman P, Best BM, Addy C, Schwimmer JB. An Open Label, Randomized, Multicenter Study of Elafibranor in Children With Nonalcoholic Steatohepatitis. *J Pediatr Gastroenterol Nutr* 2023; **77**: 160-165 [PMID: 37084342 DOI: 10.1097/MPG.0000000000003796]

6 **van den Hoek AM**, Verschuren L, Caspers MPM, Worms N, Menke AL, Princen HMG. Beneficial effects of elafibranor on NASH in E3L.CETP mice and differences between mice and men. *Sci Rep* 2021; **11**: 5050 [PMID: 33658534 DOI: 10.1038/s41598-021-83974-8]

7 **Briand F**, Maupoint J, Brousseau E, Breyner N, Bouchet M, Costard C, Leste-Lasserre T, Petitjean M, Chen L, Chabrat A, Richard V, Burcelin R, Dubroca C, Sulpice T. Elafibranor improves diet-induced nonalcoholic steatohepatitis associated with heart failure with preserved ejection fraction in Golden Syrian hamsters. *Metabolism* 2021; **117**: 154707 [PMID: 33444606 DOI: 10.1016/j.metabol.2021.154707]

8 **Hakeem AN**, Kamal MM, Tawfiq RA, Abdelrahman BA, Hammam OA, Elmazar MM, El-Khatib AS, Attia YM. Elafibranor modulates ileal macrophage polarization to restore intestinal integrity in NASH: Potential crosstalk between ileal IL-10/STAT3 and hepatic TLR4/NF-κB axes. *Biomed Pharmacother* 2023; **157**: 114050 [PMID: 36462310 DOI: 10.1016/j.biopha.2022.114050]

9 **Kamata S**, Honda A, Ishikawa R, Akahane M, Fujita A, Kaneko C, Miyawaki S, Habu Y, Shiiyama Y, Uchii K, Machida Y, Oyama T, Ishii I. Functional and Structural Insights into the Human PPARα/δ/γ Targeting Preferences of Anti-NASH Investigational Drugs, Lanifibranor, Seladelpar, and Elafibranor. *Antioxidants (Basel)* 2023; **12**: 1523 [PMID: 37627519 DOI: 10.3390/antiox12081523]

10 **Zivko C**, Witt F, Koeberle A, Fuhrmann G, Luciani P. Formulating elafibranor and obeticholic acid with phospholipids decreases drug-induced association of SPARC to extracellular vesicles from LX-2 human hepatic stellate cells. *Eur J Pharm Biopharm* 2023; **182**: 32-40 [PMID: 36470521 DOI: 10.1016/j.ejpb.2022.11.025]

11 **Huang DQ**, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 37-49 [PMID: 36258033 DOI: 10.1038/s41575-022-00688-6]

12 **Malhi H**, Gores GJ. Alcohol-associated liver disease: The time to act is now. *Hepatology* 2024 [PMID: 39018554 DOI: 10.1097/HEP.0000000000001022]

13 **Sengupta S**, Gill V, Mellinger JL. Alcohol-associated liver disease and public health policies. *Hepatology* 2024 [PMID: 38950410 DOI: 10.1097/HEP.0000000000000989]

14 **Bi G**, Zhang X, Li W, Lu X, He X, Li Y, Bai R, Zhang H. Modeling alcohol-associated liver disease in humans using adipose stromal or stem cell-derived organoids. *Cell Rep Methods* 2024; **4**: 100778 [PMID: 38749443 DOI: 10.1016/j.crmeth.2024.100778]

15 **Lee BP**, Witkiewitz K, Mellinger J, Anania FA, Bataller R, Cotter TG, Curtis B, Dasarathy S, DeMartini KS, Diamond I, Diazgranados N, DiMartini AF, Falk DE, Fernandez AC, German MN, Kamath PS, Kidwell KM, Leggio L, Litten R, Louvet A, Lucey MR, McCaul ME, Sanyal AJ, Singal AK, Sussman NL, Terrault NA, Thursz MR, Verna EC, Radaeva S, Nagy LE, Mitchell MC. Designing clinical trials to address alcohol use and alcohol-associated liver disease: an expert panel Consensus Statement. *Nat Rev Gastroenterol Hepatol* 2024; **21**: 626-645 [PMID: 38849555 DOI: 10.1038/s41575-024-00936-x]

16 **Li TH**, Yang YY, Huang CC, Liu CW, Tsai HC, Lin MW, Tsai CY, Huang SF, Wang YW, Lee TY, Huang YH, Hou MC, Lin HC. Elafibranor interrupts adipose dysfunction-mediated gut and liver injury in mice with alcoholic steatohepatitis. *Clin Sci (Lond)* 2019; **133**: 531-544 [PMID: 30602573 DOI: 10.1042/CS20180873]

17 **Koizumi A**, Kaji K, Nishimura N, Asada S, Matsuda T, Tanaka M, Yorioka N, Tsuji Y, Kitagawa K, Sato S, Namisaki T, Akahane T, Yoshiji H. Effects of elafibranor on liver fibrosis and gut barrier function in a mouse model of alcohol-associated liver disease. *World J Gastroenterol* 2024; **30**: 3428-3446 [PMID: 39091710 DOI: 10.3748/wjg.v30.i28.3428]

18 **Inoue I**, Goto S, Matsunaga T, Nakajima T, Awata T, Hokari S, Komoda T, Katayama S. The ligands/activators for peroxisome proliferator-activated receptor alpha (PPARalpha) and PPARgamma increase Cu2+,Zn2+-superoxide dismutase and decrease p22phox message expressions in primary endothelial cells. *Metabolism* 2001; **50**: 3-11 [PMID: 11172467 DOI: 10.1053/meta.2001.19415]

19 **Kong L**, Ren W, Li W, Zhao S, Mi H, Wang R, Zhang Y, Wu W, Nan Y, Yu J. Activation of peroxisome proliferator activated receptor alpha ameliorates ethanol induced steatohepatitis in mice. *Lipids Health Dis* 2011; **10**: 246 [PMID: 22208561 DOI: 10.1186/1476-511X-10-246]

20 **Yue R**, Chen GY, Xie G, Hao L, Guo W, Sun X, Jia W, Zhang Q, Zhou Z, Zhong W. Activation of PPARα-catalase pathway reverses alcoholic liver injury *via* upregulating NAD synthesis and accelerating alcohol clearance. *Free Radic Biol Med* 2021; **174**: 249-263 [PMID: 34390780 DOI: 10.1016/j.freeradbiomed.2021.08.005]

21 **Wang Y**, Chen Y, Xiao X, Deng S, Kuang J, Li Y. HRD1-mediated ubiquitination of HDAC2 regulates PPARα-mediated autophagy and alleviates metabolic-associated fatty liver disease. *Biochim Biophys Acta Mol Cell Res* 2024; **1871**: 119765 [PMID: 38815686 DOI: 10.1016/j.bbamcr.2024.119765]

22 **Chu H**, Jiang L, Gao B, Gautam N, Alamoudi JA, Lang S, Wang Y, Duan Y, Alnouti Y, Cable EE, Schnabl B. The selective PPAR-delta agonist seladelpar reduces ethanol-induced liver disease by restoring gut barrier function and bile acid homeostasis in mice. *Transl Res* 2021; **227**: 1-14 [PMID: 32553670 DOI: 10.1016/j.trsl.2020.06.006]

23 **Kowdley KV**, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, Arrese M, Corpechot C, Francque SM, Heneghan MA, Invernizzi P, Jones D, Kruger FC, Lawitz E, Mayo MJ, Shiffman ML, Swain MG, Valera JM, Vargas V, Vierling JM, Villamil A, Addy C, Dietrich J, Germain JM, Mazain S, Rafailovic D, Taddé B, Miller B, Shu J, Zein CO, Schattenberg JM; ELATIVE Study Investigators' Group; ELATIVE Study Investigators' Group. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. *N Engl J Med* 2024; **390**: 795-805 [PMID: 37962077 DOI: 10.1056/NEJMoa2306185]

24 **Schattenberg JM**, Pares A, Kowdley KV, Heneghan MA, Caldwell S, Pratt D, Bonder A, Hirschfield GM, Levy C, Vierling J, Jones D, Tailleux A, Staels B, Megnien S, Hanf R, Magrez D, Birman P, Luketic V. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol* 2021; **74**: 1344-1354 [PMID: 33484775 DOI: 10.1016/j.jhep.2021.01.013]

25 **Boeckmans J**, Gatzios A, Heymans A, Rombaut M, Rogiers V, De Kock J, Vanhaecke T, Rodrigues RM. Transcriptomics Reveals Discordant Lipid Metabolism Effects between In Vitro Models Exposed to Elafibranor and Liver Samples of NAFLD Patients after Bariatric Surgery. *Cells* 2022; **11**: 893 [PMID: 35269515 DOI: 10.3390/cells11050893]

26 **van Os EA**, Cools L, Eysackers N, Szafranska K, Smout A, Verhulst S, Reynaert H, McCourt P, Mannaerts I, van Grunsven LA. Modelling fatty liver disease with mouse liver-derived multicellular spheroids. *Biomaterials* 2022; **290**: 121817 [PMID: 36208587 DOI: 10.1016/j.biomaterials.2022.121817]

27 **Baandrup Kristiansen MN**, Veidal SS, Christoffersen C, Feigh M, Vrang N, Roth JD, Erickson M, Adorini L, Jelsing J. Validity of biopsy-based drug effects in a diet-induced obese mouse model of biopsy-confirmed NASH. *BMC Gastroenterol* 2019; **19**: 228 [PMID: 31883514 DOI: 10.1186/s12876-019-1149-z]

28 **Briand F**, Heymes C, Bonada L, Angles T, Charpentier J, Branchereau M, Brousseau E, Quinsat M, Fazilleau N, Burcelin R, Sulpice T. A 3-week nonalcoholic steatohepatitis mouse model shows elafibranor benefits on hepatic inflammation and cell death. *Clin Transl Sci* 2020; **13**: 529-538 [PMID: 31981449 DOI: 10.1111/cts.12735]

29 **Hammoutene A**, Laouirem S, Albuquerque M, Colnot N, Brzustowski A, Valla D, Provost N, Delerive P, Paradis V; QUID-NASH Research Group. A new NRF2 activator for the treatment of human metabolic dysfunction-associated fatty liver disease. *JHEP Rep* 2023; **5**: 100845 [PMID: 37663119 DOI: 10.1016/j.jhepr.2023.100845]

30 **Malik A**, Nadeem M, Malik MI. Efficacy of elafibranor in patients with liver abnormalities especially non-alcoholic steatohepatitis: a systematic review and meta-analysis. *Clin J Gastroenterol* 2021; **14**: 1579-1586 [PMID: 34370218 DOI: 10.1007/s12328-021-01491-7]

31 **Gore E**, Bigaeva E, Oldenburger A, Jansen YJM, Schuppan D, Boersema M, Rippmann JF, Broermann A, Olinga P. Investigating fibrosis and inflammation in an ex vivo NASH murine model. *Am J Physiol Gastrointest Liver Physiol* 2020; **318**: G336-G351 [PMID: 31905025 DOI: 10.1152/ajpgi.00209.2019]

32 **Rakhshandehroo M**, Hooiveld G, Müller M, Kersten S. Comparative analysis of gene regulation by the transcription factor PPARalpha between mouse and human. *PLoS One* 2009; **4**: e6796 [PMID: 19710929 DOI: 10.1371/journal.pone.0006796]

33 **Rakhshandehroo M**, Sanderson LM, Matilainen M, Stienstra R, Carlberg C, de Groot PJ, Müller M, Kersten S. Comprehensive analysis of PPARalpha-dependent regulation of hepatic lipid metabolism by expression profiling. *PPAR Res* 2007; **2007**: 26839 [PMID: 18288265 DOI: 10.1155/2007/26839]

34 **Colapietro F**, Gershwin ME, Lleo A. PPAR agonists for the treatment of primary biliary cholangitis: Old and new tales. *J Transl Autoimmun* 2023; **6**: 100188 [PMID: 36684809 DOI: 10.1016/j.jtauto.2023.100188]

35 **Peacock A**, Leung J, Larney S, Colledge S, Hickman M, Rehm J, Giovino GA, West R, Hall W, Griffiths P, Ali R, Gowing L, Marsden J, Ferrari AJ, Grebely J, Farrell M, Degenhardt L. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction* 2018; **113**: 1905-1926 [PMID: 29749059 DOI: 10.1111/add.14234]

36 **Mullish BH**, Thursz MR. Alcohol-associated liver disease: Emerging therapeutic strategies. *Hepatology* 2024 [PMID: 38922808 DOI: 10.1097/HEP.0000000000000986]

37 **Wu X**, Fan X, Miyata T, Kim A, Cajigas-Du Ross CK, Ray S, Huang E, Taiwo M, Arya R, Wu J, Nagy LE. Recent Advances in Understanding of Pathogenesis of Alcohol-Associated Liver Disease. *Annu Rev Pathol* 2023; **18**: 411-438 [PMID: 36270295 DOI: 10.1146/annurev-pathmechdis-031521-030435]

38 **Meng FG**, Zhang XN, Liu SX, Wang YR, Zeng T. Roles of peroxisome proliferator-activated receptor α in the pathogenesis of ethanol-induced liver disease. *Chem Biol Interact* 2020; **327**: 109176 [PMID: 32534989 DOI: 10.1016/j.cbi.2020.109176]

39 **Tong L**, Wang L, Yao S, Jin L, Yang J, Zhang Y, Ning G, Zhang Z. PPARδ attenuates hepatic steatosis through autophagy-mediated fatty acid oxidation. *Cell Death Dis* 2019; **10**: 197 [PMID: 30814493 DOI: 10.1038/s41419-019-1458-8]

40 **Liu S**, Zhang H, Li Y, Zhang Y, Bian Y, Zeng Y, Yao X, Wan J, Chen X, Li J, Wang Z, Qin Z. S100A4 enhances protumor macrophage polarization by control of PPAR-γ-dependent induction of fatty acid oxidation. *J Immunother Cancer* 2021; **9** [PMID: 34145030 DOI: 10.1136/jitc-2021-002548]

41 **Liu L**, Liu C, Zhao M, Zhang Q, Lu Y, Liu P, Yang H, Yang J, Chen X, Yao Y. The pharmacodynamic and differential gene expression analysis of PPAR α/δ agonist GFT505 in CDAHFD-induced NASH model. *PLoS One* 2020; **15**: e0243911 [PMID: 33326461 DOI: 10.1371/journal.pone.0243911]

42 **Mackowiak B**, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. *J Clin Invest* 2024; **134**: e176345 [PMID: 38299591 DOI: 10.1172/JCI176345]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** office@baishideng.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com