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MINIREVIEWS

Therapeutic potential of elafibranor in alcohol-associated liver disease: Insights into macrophage modulation and fibrosis reduction

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Abstract

Alcohol-associated liver disease (ALD) is a major global health concern, contributing to liver injury, morbidity, and mortality. Elafibranor (EFN), a dual peroxisome proliferator-activated receptor α/δ agonist, has shown promise as a therapeutic candidate in preclinical studies. EFN reduces liver fibrosis by inhibiting lipid accumulation, apoptosis, and inflammatory pathways (LPS/TLR4/NF-κB), while enhancing autophagy and antioxidant responses. It also improves intestinal barrier function and modulates gut microbiota, reducing endotoxin-producing bacteria and increasing beneficial species. By strengthening the intestinal barrier and suppressing pro-inflammatory mediators like tumor necrosis factor-alpha and interleukin-6, EFN mitigates hepatic stellate cell activation and fibrogenic signaling. Macrophages play a central role in ALD progression, and EFN's ability to modulate macrophage activity further highlights its anti-inflammatory properties. This review emphasizes EFN's dual-targeted approach, addressing both hepatic and intestinal dysfunctions, distinguishing it from conventional ALD treatments. While preclinical results are promising, EFN remains under clinical investigation, with ongoing trials evaluating its safety and efficacy. Future research should focus on elucidating EFN's molecular mechanisms and advancing its clinical application to establish its therapeutic potential in human populations. EFN represents a novel, comprehensive strategy for ALD management, targeting

both liver and gut pathologies.

Key Words: Alcohol-associated liver disease; Elafibranor; Peroxisome proliferator-activated receptor α/δ agonist; Macrophages; Liver fibrosis; Inflammatory responses

Core Tip: Macrophages play a central role in the progression of alcohol-associated liver disease (ALD), from initial liver injury to advanced stages like cirrhosis. Elafibranor (EFN), a dual peroxisome proliferator-activated receptor α/δ agonist, offers a promising therapeutic approach by reducing liver fibrosis, inhibiting macrophage activation, and suppressing TLR4/NF-κB inflammatory pathways. Additionally, EFN strengthens intestinal barrier function, addressing key drivers of ALD. With its dual anti-inflammatory and fibrosis-reducing effects, EFN holds potential for ALD and other liver diseases characterized by chronic inflammation and fibrosis. Further research is needed to validate its clinical applications.

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INTRODUCTION

Alcohol-associated liver disease (ALD) encompasses a spectrum of conditions induced by excessive alcohol consumption, ranging from hepatic steatosis to more severe stages such as alcoholic hepatitis (AH) and alcohol-associated cirrhosis[1]. ALD is a major global health challenge, contributing to approximately 2 million liver-related deaths annually, including those from cirrhosis and hepatocellular carcinoma (HCC). The prevalence of decompensated cirrhosis has notably increased, from 1.1 million cases in 1990 to 2.5 million in 2017[2]. Despite its widespread impact, no Food and Drug Administration (FDA)-approved therapies specifically target liver fibrosis in ALD[3]. The World Health Organization estimates that chronic alcohol consumption accounts for nearly 50% of liver-related deaths, with HCC being a major consequence of ALD progression. This highlights the urgent need for novel therapeutic strategies, as there are currently no FDA-approved treatments for ALD-related fibrosis or cirrhosis. ALD pathogenesis is driven by oxidative stress, lipid peroxidation, and chronic inflammation, which promote disease progression from steatosis to cirrhosis and HCC. Lipid peroxidation is particularly critical, generating reactive aldehydes that exacerbate hepatocyte injury and fibrosis[4]. Recent bibliometric analyses have emphasized the increasing research focus on lipid peroxidation in ALD and its therapeutic implications[5]. Moreover, the gut-liver axis and intestinal microbiota dysbiosis play central roles in ALD progression. Chronic alcohol consumption disrupts gut barrier integrity, allowing bacterial endotoxins to enter the liver and activate inflammation *via* the LPS/TLR4 pathway[6]. Modulating gut microbiota and inflammation has emerged as a promising therapeutic approach for ALD management[7].

Macrophages, particularly pro-inflammatory M1 macrophages, are key mediators of ALD progression. Their persistent activation drives liver inflammation in early disease stages, highlighting the potential of macrophage-targeted therapies for ALD treatment[8,9]. Elafibranor (EFN), a dual peroxisome proliferator-activated receptor (PPAR)α/δ agonist, has demonstrated significant therapeutic potential in ALD by modulating key metabolic and inflammatory pathways[10,11]. EFN mitigates liver fibrosis by suppressing lipid accumulation and hepatocellular apoptosis while enhancing autophagic flux and antioxidant defense mechanisms[11]. Additionally, EFN downregulates the LPS/TLR4/NF-κB pathway and strengthens intestinal barrier integrity, thereby alleviating ALD progression[10,12]. It also induces autophagy in intestinal epithelial cells, reduces intestinal apoptosis, and modulates gut microbiota composition, contributing to gut-liver axis homeostasis[11,13]. These effects collectively support EFN's potential as a comprehensive treatment for ALD. Given the pivotal role of PPARs in hepatic metabolism and inflammation, comparative analyses with other PPAR modulators, such as pan-PPAR agonists (*e.g.*, lanifibranor) and selective PPARγ agonists (*e.g.*, pioglitazone), are warranted. Such studies could elucidate EFN's mechanistic advantages and provide a broader perspective on the clinical relevance of PPAR-targeted strategies in mitigating ALD pathogenesis (Figure 1) [12,14].

METHODOLOGY OF DATA COLLECTION

The data presented in this review were collected through a comprehensive search of peer-reviewed articles and preclinical studies using PubMed, Scopus, and Web of Science databases. Key search terms included "Elafibranor", "ALD", "PPAR agonists", "macrophage modulation" and "intestinal barrier". Only studies published in the last five years were prioritized to ensure up-to-date findings. Inclusion criteria focused on research examining the therapeutic potential of EFN in ALD and its mechanisms of action. The primary study for this review is "Elafibranor interrupts adipose

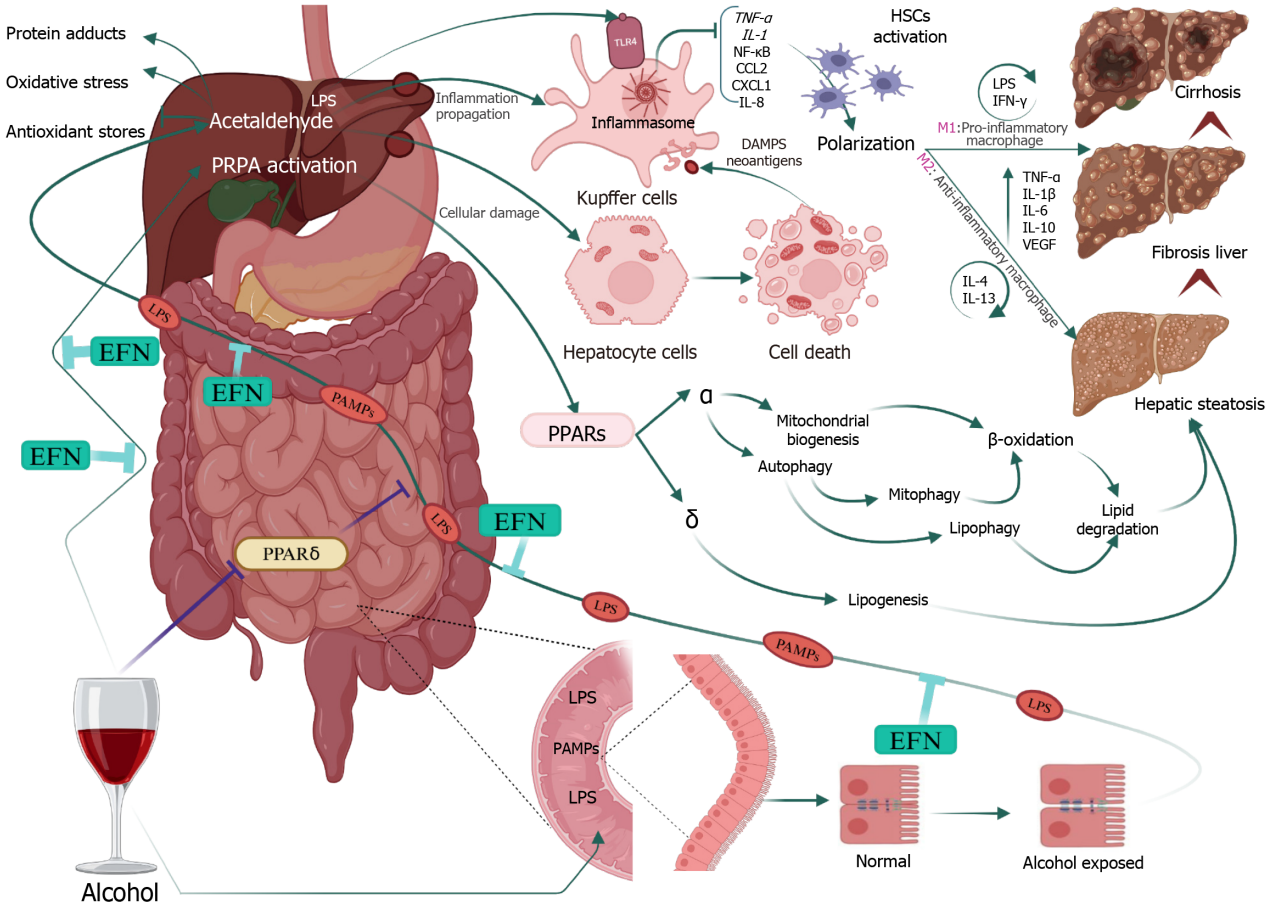

Figure 1 Mechanistic pathways of elafibranor in alcohol-associated liver disease. Elafibranor (EFN) exerts its therapeutic effects through dual activation of peroxisome proliferator-activated receptor (PPAR)α and PPARδ. PPARα activation reduces oxidative stress and inflammation by modulating Kupffer cell polarization and suppressing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Concurrently, PPARδ activation enhances mitochondrial biogenesis, β-oxidation, and lipid metabolism, counteracting hepatic steatosis. EFN also strengthens the gut barrier by limiting lipopolysaccharides and pathogen-associated molecular patterns translocation, thereby reducing systemic inflammation and liver injury. Moreover, EFN inhibits hepatic stellate cell activation, thereby attenuating fibrosis progression. These multifaceted actions position EFN as a promising therapeutic strategy for alcohol-associated liver disease, addressing both metabolic dysfunction and immune-mediated fibrosis. EFN: Elafibranor; ALD: Alcohol-associated liver disease; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; PPAR: Peroxisome proliferator-activated receptor; LPS: Lipopolysaccharides; HSC: Hepatic stellate cells.

dysfunction-mediated gut and liver injury in mice with alcoholic steatohepatitis".

CURRENT STATUS OF CLINICAL RESEARCH ON EFN

Despite promising preclinical findings, the clinical application of EFN in ALD remains under investigation. While its efficacy has been demonstrated in clinical trials for non-alcoholic steatohepatitis (NASH), data on its effects in ALD patients are still limited. Current research focuses on evaluating its ability to mitigate alcohol-induced hepatic fibrosis and inflammation, with early-phase studies assessing its safety and pharmacokinetics. Further randomized controlled trials are essential to establish its long-term benefits and determine optimal dosing regimens. Beyond its role in NASH, EFN has also shown potential in treating primary biliary cholangitis (PBC). A 2023 clinical study reported that EFN treatment led to significant biochemical improvements in cholestatic markers among PBC patients, reinforcing its broader therapeutic potential in liver diseases[15].

THE ROLE OF MACROPHAGES IN ALD PATHOGENESIS

Macrophages play a pivotal role in the progression of ALD, contributing to both inflammation and fibrosis at various stages of the disease, including AH and cirrhosis[16]. Macrophage polarization plays a critical role in determining the severity of ALD. The pro-inflammatory M1 phenotype secretes cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, which exacerbate hepatic injury and fibrogenesis. Conversely, the M2 phenotype is associated with the secretion of IL-10 and transforming growth factor-beta (TGF-β), promoting tissue repair and fibrosis resolution. However, an imbalance between these two phenotypes in ALD leads to chronic inflammation and progressive

liver damage. "Macrophage Polarization in Liver Diseases: Mechanisms and Therapeutic Targets" Hepatology, 2024[17]. Among them, Kupffer cells, the resident liver macrophages, are particularly responsive to alcohol and its metabolites. Upon activation, they release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, intensifying hepatic inflammation and accelerating ALD progression[9,18,19]. Beyond their inflammatory function, macrophages also drive liver fibrosis, a hallmark of ALD. By secreting profibrotic mediators, they activate hepatic stellate cells (HSCs), promoting excessive extracellular matrix deposition, tissue scarring, and hepatic dysfunction[20,21]. Additionally, macrophages are key players in the gut-liver axis, a crucial pathway linking alcohol consumption to liver damage. Chronic alcohol intake compromises intestinal barrier integrity, allowing bacterial endotoxins like lipopolysaccharides (LPS) to translocate into the liver *via* the portal circulation. Upon recognizing these microbial components through pattern recognition receptors such as TLRs, macrophages trigger NF-κB signaling, amplifying cytokine and chemokine production, and exacerbating hepatic injury[18,22-24]. Given their central role in ALD pathogenesis, targeting macrophage activity represents a promising therapeutic approach. Emerging evidence suggests that EFN modulates macrophage activation by regulating the TLR4/NF-κB pathway, leading to reduced pro-inflammatory cytokine secretion. This immunoregulatory function positions EFN as a potential therapeutic agent in ALD, distinct from its established role in NASH[25].

EFN'S IMPACT ON MACROPHAGE ACTIVITY

EFN, a dual agonist of PPARα and PPARδ, exhibits potent anti-inflammatory properties that may be beneficial in the treatment of ALD. Unlike traditional fibrates, which primarily target lipid metabolism through PPARα activation, EFN also modulates inflammatory pathways *via* PPARδ activation. This positions EFN as a promising candidate for addressing both metabolic and inflammatory disturbances in ALD[5,10,12,26]. Recent studies have demonstrated that EFN significantly reduces macrophage activation in ALD models. Notably, the infiltration of F4/80□ macrophages, a marker of macrophage activation, was markedly diminished following EFN treatment. This reduction was accompanied by a decrease in hepatic mRNA expression of LPS binding protein, TLR4, and its co-receptor CD14 key components of the LPS recognition complex. Consequently, EFN suppressed TLR4-mediated inflammatory signaling, as evidenced by reduced IκBα degradation and diminished NF-κB phosphorylation[12,27-29]. Additionally, EFN treatment led to a notable decrease in hepatic pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and CCL2 key drivers of inflammation and fibrosis in ALD. These findings underscore EFN's ability to mitigate liver inflammation and its progression toward fibrosis. Unlike conventional ALD treatments, EFN exerts direct effects on macrophages and modulates inflammation at multiple levels. Furthermore, EFN enhances intestinal barrier integrity, a benefit rarely observed in other ALD treatments[12,19,30]. Emerging evidence highlights EFN's role in suppressing the LPS/TLR4/NF-κB signaling pathway, thereby reducing hepatic inflammation. A recent study demonstrated that EFN administration significantly reduced NF-κB activation and pro-inflammatory cytokine levels in a mouse model of ALD, reinforcing its potential as a macrophage-targeted therapy[12]. However, further clinical investigations are necessary to validate its efficacy and explore its broader applications in inflammatory liver diseases[12].

MOLECULAR MECHANISMS OF EFN ACTION

EFN is a dual agonist of peroxisome proliferator-activated receptors (PPARα and PPARδ) that shows promise as a therapeutic agent for ALD by targeting key metabolic, inflammatory, and cellular pathways. PPARs are nuclear receptors involved in lipid metabolism, inflammation regulation, glucose homeostasis, and cellular differentiation, making EFN's dual activation profile particularly effective against the complex pathology of ALD[12,31,32]. EFN activates PPARα enhances lipid metabolism by stimulating fatty acid oxidation (β-oxidation) and lipolysis, reducing hepatic lipid accumulation, a hallmark of ALD. Furthermore, PPARα activation promotes autophagy, a critical process for clearing damaged organelles and lipid droplets, thereby reducing oxidative stress and lipotoxicity. This effect is complemented by the upregulation of antioxidant enzymes such as superoxide dismutase and catalase, further mitigating oxidative damage and inflammation in the liver[32,33]. Beyond its role in lipid metabolism, EFN has been shown to modulate glucose homeostasis and hepatic inflammation. Activation of PPARα/δ by EFN not only enhances fatty acid oxidation but also suppresses hepatic glucose output by downregulating phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. This dual action prevents hyperglycemia-induced oxidative stress, a key factor in ALD progression. Furthermore, EFN inhibits NF-κB signaling, thereby reducing TNF-α and IL-6 expression, ultimately mitigating hepatic inflammation[13]. PPARδ activation by EFN contributes to maintaining intestinal barrier integrity, which plays a crucial role in reducing endotoxin translocation from the gut to the liver. EFN upregulates tight junction proteins such as occludin and claudin-1, which enhance intestinal barrier function, and reduces apoptosis in intestinal epithelial cells by modulating pro- and anti-apoptotic proteins. Additionally, EFN positively influences gut microbiota composition, reducing systemic inflammation and its impact on the liver[13,34]. EFN also exerts direct anti-inflammatory effects by modulating macrophage activity. It suppresses pro-inflammatory M1 macrophage markers (*e.g.*, TNF-α, IL-1β, NOS2) through inhibition of the TLR4/NF-κB pathway while promoting an anti-inflammatory M2 macrophage phenotype. This shift reduces hepatic inflammation and fibrosis by lowering pro-inflammatory cytokines (*e.g.*, TNF-α, IL-6, IL-1β) and increasing anti-inflammatory cytokines such as IL-10. EFN further suppresses Kupffer cell activation, limiting their contribution to liver inflammation and fibrosis[35,36]. Beyond its effects on macrophages, EFN inhibits HSC activation, thereby reducing extracellular matrix deposition and liver fibrosis. EFN further modulates extracellular matrix (ECM) remodeling by regulating the balance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), promoting ECM degradation and

reducing fibrogenesis[37,38]. By downregulating MMP-2 and MMP-9 activity, EFN facilitates the breakdown of excessive collagen deposition, thereby decreasing liver stiffness and improving hepatic architecture[39]. Additionally, EFN suppresses lysyl oxidase, an enzyme involved in ECM cross-linking, further contributing to fibrosis resolution[40]. These effects collectively highlight EFN's potential as a therapeutic agent in reversing fibrosis and restoring liver homeostasis. It modulates MMP and their inhibitors (TIMPs), playing a role in extracellular matrix remodeling. EFN also suppresses the expression of LPS binding protein and CD14, attenuating the LPS/TLR4 signaling pathway and reducing inflammatory responses in ALD[12,35,37,38]. In addition to macrophage modulation, EFN exerts anti-fibrotic effects by targeting HSCs. Activated HSCs are the primary source of ECM deposition, leading to hepatic fibrosis. EFN inhibits HSC activation by downregulating TGF-β1 and collagen I/III expression, thereby reducing ECM accumulation. Moreover, EFN induces apoptosis in activated HSCs, preventing the persistence of fibrogenic signaling in the liver[39]. Furthermore, PPARα activation induces fibroblast growth factor 21, a hormone with anti-inflammatory and metabolic regulatory properties, adding another layer to EFN's therapeutic effects. By integrating these mechanisms, EFN effectively addresses the metabolic, inflammatory, and fibrotic aspects of ALD[35,40]. In conclusion, EFN's dual activation of PPARα and PPARδ allows it to target multiple facets of ALD pathology. Its ability to enhance lipid metabolism, reduce oxidative stress, restore intestinal barrier function, modulate macrophage phenotypes, and inhibit fibrosis underscores its potential as a novel therapeutic strategy for ALD and other inflammatory liver disorders[13,31].

EFN modulates inflammatory cytokines such as TNF-α and IL-10, which play crucial roles in immune regulation. TNF-α, a pro-inflammatory cytokine, is downregulated through inhibition of the TLR4/NF-κB signaling pathway, reducing hepatic inflammation. Conversely, IL-10, an anti-inflammatory cytokine, is upregulated, promoting M2 macrophage polarization and tissue repair. These effects suggest a broader immunomodulatory role for EFN beyond ALD, particularly in cancer-associated inflammation. Recent studies have highlighted the tumor microenvironment's influence on T cell exhaustion, with novel CD8+ markers identified in breast cancer models[41]. Given EFN's impact on immune regulation, future studies should explore its potential in modulating T cell function in cancer settings (Table 1).

IMPLICATIONS FOR ALD TREATMENT

EFN, a dual agonist of PPARα and PPARδ, has emerged as a promising therapeutic option for ALD by modulating macrophage activity. Through the activation of PPARs, EFN inhibits the TLR4/NF-κB signaling pathway, which plays a critical role in hepatic and intestinal inflammation. This inhibition reduces the overall inflammatory response in both the liver and gut, helping to prevent liver fibrosis progression and promote liver regeneration. Additionally, the combined effects of EFN on both the liver and intestinal barrier function underscore its potential as a holistic treatment for ALD, addressing multiple disease mechanisms and offering a comprehensive therapeutic approach[11,38,42].

HYPOTHESIS ON THE ROLE OF EFN IN ALD TREATMENT

Recent evidence suggests that EFN, as a dual PPARα/δ agonist, may exert therapeutic effects in ALD beyond its metabolic benefits. Emerging hypotheses indicate that EFN could modulate the hepatic immune response by influencing macrophage polarization and reducing pro-inflammatory cytokine secretion. Moreover, its impact on gut barrier integrity suggests a potential role in mitigating endotoxemia-induced liver injury. These insights open promising avenues for investigating EFN as a broad-spectrum therapeutic strategy in ALD.

FUTURE DIRECTIONS

The current study highlights the therapeutic potential of EFN in treating ALD, particularly through its modulation of macrophage activity. However, further research is necessary to elucidate its precise molecular mechanisms and long-term effects. Key directions for future studies include.

Macrophage and HSC interactions

Investigating the direct effects of EFN on isolated macrophages and HSC will help clarify its impact on fibrotic pathways in ALD.

Bile acid metabolism and liver-gut axis

Understanding how EFN influences bile acid metabolism and its crosstalk with the gut microbiome could provide insights into its broader metabolic benefits.

Comparative efficacy across ALD subtypes

Since ALD presents with heterogeneity in disease progression, it is crucial to study EFN's differential effects in various ALD subgroups (*e.g.*, early-stage steatosis vs. advanced fibrosis).

Table 1 Mechanisms of elafibranor in alcohol-associated liver disease

Mechanism	Target/effect	Benefit in ALD	Translational implications
PPARα activation	Stimulates fatty acid breakdown (lipolysis) and β-oxidation	Reduces hepatic steatosis	Potential target for reducing liver fat accumulation in ALD patients
	Promotes autophagy	Mitigates oxidative stress	Enhances cellular repair mechanisms in ALD-related damage
	Upregulates antioxidant genes	Maintains cellular homeostasis	May prevent disease progression and hepatocyte injury
		Reduces hepatic injury and inflammation	Could serve as a therapeutic strategy to limit liver damage
PPARδ activation	Enhances tight junction protein expression (intestinal barrier integrity)	Reduces intestinal permeability	Prevents endotoxin leakage, reducing inflammation in ALD
	Promotes intestinal epithelial cell autophagy	Prevents endotoxin translocation	Protects gut-liver axis and limits systemic inflammation
	Reduces intestinal apoptosis	Maintains intestinal barrier function	Prevents gut-derived inflammation in ALD pathogenesis
		Reduces inflammation and systemic effects	Could lower systemic complications associated with ALD
Macrophage activity	Reduces M1 macrophage markers (pro-inflammatory)	Suppresses TLR4/NF-κB signaling	Decreases inflammation-driven liver damage
	Promotes M2 macrophage marker (anti-inflammatory)	Shifts macrophage phenotype to anti-inflammatory state	Could be harnessed for immunomodulation in ALD therapy
	Reduces hepatic pro-inflammatory cytokine expression	Attenuates liver fibrosis	Potential strategy to prevent fibrosis progression
Other mechanisms	Decreases LPS binding protein and CD14 expression (reduces LPS signaling)	Reduces inflammation	Targets gut-derived inflammation, a key factor in ALD
	Influences bile acid metabolism	Potentially reduces hepatic lipid accumulation	May improve metabolic balance in ALD patients
	Regulates Kupffer cell activity	Mitigates liver damage and fibrosis	Modulating Kupffer cells could be a therapeutic approach for ALD
	Induces fibroblast growth factor 21 expression (anti-inflammatory and metabolic regulation)	Further modulates inflammatory responses and metabolic processes	Could be explored for systemic metabolic benefits in ALD

ALD: Alcohol-associated liver disease; LPS: Lipopolysaccharides; PPAR: Peroxisome proliferator-activated receptor.

Clinical validation and translational research

Future clinical trials should focus on validating the efficacy of EFN in ALD patients with advanced fibrosis.

PROPOSED CLINICAL TRIALS AND EXPERIMENTAL APPROACHES FOR EFN VALIDATION

To establish the clinical efficacy and safety of EFN, we propose the following experimental setups

Randomized controlled trial: A multicenter, double-blind, placebo-controlled randomized controlled trial enrolling ALD patient at different disease stages to assess EFN's impact on fibrosis regression, inflammatory cytokine levels (*e.g.*, TNF-α, IL-6), and intestinal barrier integrity over 12 to 24 months.

Patient-derived xenograft models: These models can provide a more physiologically relevant platform to evaluate EFN's effects on liver fibrosis and macrophage polarization, bridging the gap between preclinical and clinical research. High-throughput single-cell RNA sequencing (scRNA-seq) can be used to gain deeper insights into EFN's cellular effects.

Combination therapy studies: Investigating the synergistic effects of EFN with farnesoid X receptor (FXR) agonists or other anti-fibrotic agents to determine potential combination treatments that enhance fibrosis resolution and hepatic homeostasis.

Biomarker-based response assessment: Implementing transcriptomic and metabolomic analyses to track PPARα/δ target genes, oxidative stress markers, bile acid metabolism, and gut microbiota composition, providing insights into EFN's mechanisms of action and personalized treatment strategies.

These studies will contribute to defining EFN's clinical relevance, optimizing its therapeutic application, and addressing current knowledge gaps regarding its long-term safety and efficacy in ALD patients.

A major limitation in current research is the lack of patient-derived xenograft (PDX) models that accurately mimic human ALD pathology. Although preclinical studies have demonstrated EFN's therapeutic potential, significant limitations exist in translating these findings to human pathology. Murine models of ALD exhibit fundamental differences in hepatic metabolism, immune system responses, and fibrosis progression compared to humans, which may affect EFN's observed efficacy. For instance, differences in HSC activation and inflammatory cytokine signaling can influence the extent of fibrosis resolution.

To overcome these limitations, PDX models offer a promising alternative by preserving human-like liver architecture, stromal interactions, and disease-specific genetic alterations. PDX models have been widely used in oncology and other liver diseases to evaluate drug efficacy under human-relevant conditions. Previous studies, such as "Comparing volatile and intravenous anesthetics in a mouse model of breast cancer metastasis, 2018" have demonstrated the advantages of xenograft models in mimicking human disease progression and drug responses. Incorporating PDX models in future EFN research could enhance our understanding of its therapeutic effects on human hepatic fibrosis and inflammation, leading to more reliable translational outcomes. Additionally, implementing high-throughput scRNA-seq in these models will provide deeper insights into cellular heterogeneity and EFN's specific effects on immune and hepatic cell populations.

Further studies should also explore combining EFN with anti-fibrotic agents such as FXR agonists, which may offer synergistic benefits in reducing liver fibrosis[43,44].

Beyond ALD

Potential applications in other liver diseases: Given its efficacy in NASH and PBC, EFN may also offer therapeutic value in other metabolic liver diseases, including cholestatic disorders and fibrosis-related conditions, warranting further investigation[11,20,27].

LONG-TERM SAFETY AND EFFICACY OF EFN

Despite promising preclinical and clinical findings, concerns regarding the long-term safety of EFN remain. Chronic activation of PPARα/δ signaling pathways may lead to unintended metabolic consequences, necessitating further research into its prolonged effects on lipid metabolism, insulin sensitivity, and cardiovascular health. Additionally, interindividual variability in response to EFN suggests personalized treatment approaches are needed. Future research should prioritize large-scale, multi-center clinical trials with extended follow-up periods to establish a robust safety profile and optimize patient selection criteria.

CONCLUSION

EFN represents a promising therapeutic candidate for ALD due to its dual action on hepatic inflammation and gut barrier function. By inhibiting macrophage activation and the TLR4/NF-κB signaling pathway, EFN effectively reduces hepatic inflammation and fibrosis. Additionally, its role in strengthening gut barrier integrity helps prevent endotoxin translocation, a critical factor in ALD progression. Beyond ALD, EFN has demonstrated efficacy in other liver disorders such as NASH and PBC, highlighting its broader therapeutic potential. However, further research is essential to fully characterize its molecular mechanisms, evaluate its long-term safety, and determine its clinical applicability across different subtypes of liver disease.

FOOTNOTES

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