Review

Farnesoid X receptor: From Structure to Function and Its Pharmacology in Liver Fibrosis

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ABSTRACT: The farnesoid X receptor (FXR), a ligand-activated transcription factor, plays a crucial role in regulating bile acid metabolism within the enterohepatic circulation. Beyond its involvement in metabolic disorders and immune imbalances affecting various tissues, FXR is implicated in microbiota modulation, gut-to-brain communication, and liver disease. The liver, as a pivotal metabolic and detoxification organ, is susceptible to damage from factors such as alcohol, viruses, drugs, and high-fat diets. Chronic or recurrent liver injury can culminate in liver fibrosis, which, if left untreated, may progress to cirrhosis and even liver cancer, posing significant health risks. However, therapeutic options for liver fibrosis remain limited in terms of FDA-approved drugs. Recent insights into the structure of FXR, coupled with animal and clinical investigations, have shed light on its potential pharmacological role in hepatic fibrosis. Progress has been achieved in both fundamental research and clinical applications. This review critically examines recent advancements in FXR research, highlighting challenges and potential mechanisms underlying its role in liver fibrosis treatment.

1. Introduction

Farnesoid X receptors (FXRs) belong to the nuclear receptor superfamily and are primarily expressed in the liver, small intestine, and kidneys [1]. Due to their roles in regulating the homeostasis of bile acids (BAs) and glucose lipids, FXRs are progressively becoming attractive targets for research and drug development [2]. Studies have demonstrated that FXRs consist of two members in mammals: FXRα (NR1H4) and FXRβ (NR1H5) [3]. Among these, FXRβ can perform receptor functions in certain species, such as rabbits, rats, dogs, and mice, while it encodes a pseudogene in primates and humans [4]. In contrast to FXRβ, the FXRα gene encodes four biologically active subtypes (α1, α2, α3, and α4), with their expression exhibiting tissue-dependent patterns [5]. FXR regulates the transcription process of target genes by binding to the FXR response element, either through the formation of FXR-RXR heterodimers in most cases or FXR monomers in rare cases [6, 7]. Microbiota, enterohepatic circulation, and liver illnesses represent only a few examples of metabolic and immunological diseases in which FXR, a transcription factor, can be activated by ligand binding [8, 9]. Notably, FXR also serves as a multifunctional cytoprotective agent and tumor inhibitor in the liver, holding significant importance for the amelioration of liver injuries [10-12]. Furthermore, liver fibrosis resulting from chronic liver injury poses a risk factor for cirrhosis or liver cancer, significantly endangering human health. However, the treatment of liver fibrosis encounters formidable challenges due to limitations in available therapeutic drugs. Characterized by the excessive deposition of extracellular matrix (ECM) and excessive proliferation,

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liver fibrosis refers to a group of clinical and pathological syndromes accompanied by abnormal liver structure and function [13]. Its underlying nature is a tissue compensatory response secondary to liver inflammation or injury [14]. During the course of chronic liver disease, hepatocytes undergo repetitive destruction and regeneration, leading to the manifestation of extracellular matrices marked by elevated expression of collagen, glycoproteins, and proteoglycans. These components become abnormally distributed within the liver, culminating in the formation of scars [15]. Numerous factors associated with prolonged chronic stimulation can trigger inflammation and necrosis of hepatocytes, thereby promoting the activation of hepatic stellate cells (HSCs) and resulting in hepatic fibrosis [16, 17]. For instance, liver fibrosis arises in the context of various conditions, including viral hepatitis, schistosomiasis infections, alcoholic or nonalcoholic fatty liver disease (NAFLD), Wilson's disease, drug-induced or toxic liver diseases, cholestasis, and autoimmune liver diseases [18, 19]. Common clinical manifestations observed in patients with hepatic fibrosis include fatigue, loss of appetite, abnormal stool, discomfort, swelling, pain in the liver area, and a dark complexion [15]. Some patients may also exhibit additional clinical manifestations that coincide with the

underlying disease [20]. Left untreated, hepatic fibrosis can progress to cirrhosis or even hepatocellular carcinoma (HCC). According to the 2020 Global Cancer Survey data, primary liver cancer-induced HCC accounts for up to 830,000 deaths, making it the third leading cause of cancer-related mortality. This reality has become a significant impediment to the well-being of individuals in numerous countries [21]. Research has demonstrated that the growth and progression of liver cancer are intimately linked with the microenvironment influenced by interstitial cells involved in liver fibrosis [22]. Consequently, there is an urgent need to explore therapeutic agents for liver fibrosis. Currently, FXR activation is implicated in various cellular molecular pathways, including hepatocyte protection and the inhibition of HSC activation, displaying a promising antifibrotic effect [23]. Importantly, obeticholic acid, an FXR agonist, has entered clinical trials as a potential antifibrosis drug [24, 25].

Building upon these findings, this article presents a comprehensive review of the structure, function, and pharmacology of FXR, with a particular focus on its pharmacological effects in liver fibrosis. Furthermore, the article offers strategies to enhance the prevention and treatment of liver fibrosis.
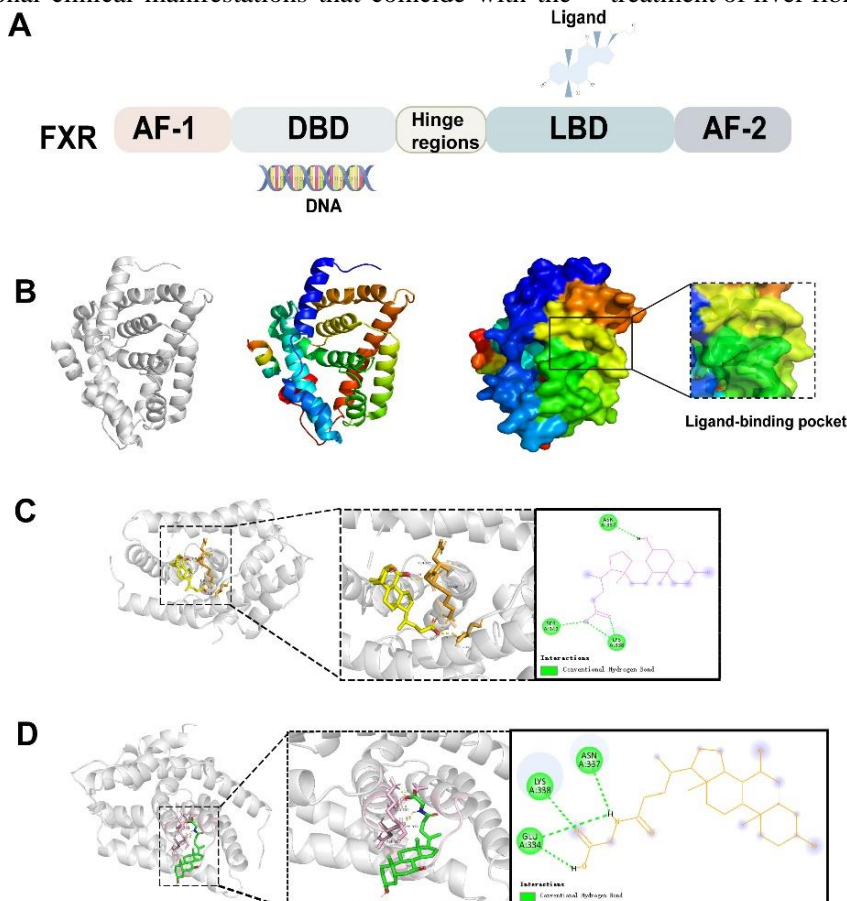

Figure 1. Three different crystal form structures known to FXR (PDB ID is 4QE6). **(A)** Common architecture of FXR. **(B)** The approximate location of the apo-FXR and its bonded pocket that employs different conformation according to the species of ligands. **(C)** Activated conformation of FXR combined with CDCA (agonist-FXR). **(D)** Antagonistic conformation of FXR binding to GUDCA (antagonist-FXR).

2. FXR structure and function

FXR, with a typical nuclear receptor structure, could regulate key metabolic and immune-related processes, such as BA homoeostasis, glucose lipid metabolism and energy consumption, as well as the inflammatory response, cellular proliferation and fibrosis [26], which are explained in detail as follows.

2.1. Structure of FXR and its crystalline structure with ligand complexes

FXR was initially identified and named in 1995 after the discovery of its activation by farnesol and its metabolites [27, 28]. Devarakonda and colleagues indicated that FXR comprises nonligand-dependent transcriptional activation domains (AF-1), DNA binding domains, hinge regions, ligand binding domains (LBD), and carboxyl terminals containing ligand-dependent activation domains (AF-2) [3] (Fig 1A). In fact, the structure of FXR's LBD closely resembles that of other members within the nuclear receptor family. As early as 2002, the X-ray crystal structure of HNF4α's LBD at high resolution unveiled the presence of fatty acids within the binding pocket, along with the AF2 helix adopting a conformation characteristic of a transcriptionally active nuclear receptor [29]. Subsequently, Sladek highlighted that the true ligand binds within a hydrophobic pocket of the LBD, prompting the repositioning of AF-2. This in turn induces conformational changes that activate co-suppressors and introduce coactivators [30]. Regarding FXR activation, ligands bind to the LBD region of FXR, inducing diverse dynamic conformational changes and orientational shifts of AF-2. These alterations collectively regulate downstream target gene transcription through FXR-RXR heterodimers or FXR monomers, thereby participating in metabolic homeostasis [31, 32]. Moreover, FXR features a flexible ligand-binding pocket within its LBD that adopts distinct conformations based on the ligand species [33]. Jiang and collaborators indicated that structures of FXR-ligand complexes in the PDB database can be broadly categorized into three types: FXR without ligand binding (apo-FXR) (Fig 1B), FXR bound to agonists (agonist-FXR) (Fig 1C), and FXR bound to antagonists (antagonist-FXR) (Fig 1D) [34]. Drawing upon the functional and structural aspects of FXR, numerous research laboratories worldwide, particularly within the pharmaceutical industry, have been dedicated to developing ligands targeting FXR. Recent studies have achieved some headway in seeking drugs that target FXR for the treatment of metabolic diseases. Notably, advancements have been made in both basic and clinical realms. However, given that the liver serves as the hub of human metabolism and that there are limited FDA-approved drugs for liver fibrosis therapy, we present an overview of recent advancements in the development of FXR regulators. This includes exploration of endogenous, exogenous, and naturally allosteric compounds as potential treatments for liver fibrosis. Our approach considers the structural and functional attributes of FXR.

2.1.1. Endogenous regulators

As we mentioned earlier, primary BAs are synthesized directly by hepatocytes and mainly include CA, CDCA, and taurocholate acid. Secondary BAs, on the other hand, are generated through the breakdown of intestinal bacteria and the intestine-liver circulation, predominantly including DCA, lithocholic acid (LCA), and GUDCA [35, 36]. CDCA stands out as the most potent ligand for FXR, succeeded by CA, DCA, and LCA, with their efficacy being closely tied to their structural features [37]. In the context of metabolic diseases, there is an upregulation of FXR antagonistic DCA in serum, coupled with a downregulation of CDCA (an FXR agonist) [38]. Specifically, DCA has the capacity to incite intestinal inflammation [39], while CDCA activates intestinal FXRs and ameliorates glucose metabolism associated with polycystic ovary syndrome [40]. However, the oral administration of CDCA does not restore plasma bile acid levels to normal levels; instead, it leads to elevated supraphysiological concentrations of endogenous CDCA and its derivatives [41]. Furthermore, FXR antagonists such as GUDCA and TUDCA exhibit the ability to mitigate metabolic disorders in obese mice [42, 43]. Intriguingly, LCA, an FXR antagonist possessing partial agonist activity, can induce cholestatic pruritus or reduce the expression of bile salt export pump (BSEP) under varying physiological conditions [44, 45]. Endogenous BAs display limited selectivity for FXR, which is a key reason for their limited usage in the treatment of liver diseases. Nonetheless, they offer a valuable framework for the synthesis of novel and selective FXR ligands, thereby serving as a promising scaffold for further research and development.

2.1.2. Synthetic regulators

Given FXR's pivotal role in metabolic diseases, high-throughput strategies and structure-oriented drug development have been employed to screen synthetic ligands. Clinical trials have demonstrated that compared to a placebo, obeticholic acid (OCA), a semisynthetic derivative of CDCA, effectively ameliorates the histological and biochemical characteristics of nonalcoholic steatohepatitis (NASH) without cirrhosis [46]. Additionally, OCA leads to a reduction in sodium+/taurocholate cotransporting polypeptide,

influencing BA circulation and subsequently lowering the expression of α-SMA in human HSCs, thereby attenuating liver fibrosis [47]. Among 141 patients treated with OCA, approximately 33 (23%) experienced pruritus (p < 0.0001). Further exploration is warranted to understand this phenomenon. As a full non-BA agonist of FXR, GW4064, notable for its high potency and selectivity, significantly decreases serum cholesterol and triglyceride levels in individuals with NAFLD. Unfortunately, it failed to progress beyond phase I clinical trials due to issues of instability [48]. Through structural modifications to GW4064, stable and pharmacologically viable FXR agonists have been developed, such as cilofexor and tropifexor. These compounds exhibit

therapeutic effects on liver fibrosis in NASH patients [49, 50]. Furthermore, research on partial agonists of FXR is in active progress. For instance, fexaramine, an intestinal FXR agonist, has shown promise in reducing systemic inflammation and improving metabolism in obese mice [51]. Nidufexor, a partial FXR agonist, has demonstrated marked effects in patients with NASH [52]. We have summarized partially synthesized FXR ligands to establish a foundation for subsequent investigations. The regulatory factors and related pharmacological activities of these partially synthesized FXR ligands have been consolidated in Table 1, contributing to the establishment of a framework for future studies.

Table 1. Partial FXR ligands.

	Types	Name	Outcomes	Refs.
Endogenous	Agonist	Androsterone	directly bind to purified hFXR ligand-binding domain (LBD) protein, recruit steroid receptor coactivator protein-1 (SRC-1) coactivator peptide	[235]
		CDCA	improve glucose metabolism and increase the mRNA expression of BSEP	[40, 44]
	Antagonist	TUDCA	improve glucose metabolism	[43]
		5Alpha-bile alcohols	modulate intestinal lipid absorption and expression of genes involved in the biosynthesis/catabolism of BAs	[236]
		T-βMCA	reduce the TCA-induced expression of *FGF 15 in* the ileum	[237]
		GUDCA	improve various metabolic endpoints in mice with obesity	[42]
		DCA	promote intestinal inflammation	[238]
	Selective modulators	progesterone metabolite, epiallopregnanolone sulfate	reduce FXR-mediated discharge of BAs and secretion of FGF19.	[239, 240]
		lithocholic acid (LCA)	a hydrophobic bile acid and strongly decrease BSEP	[44]
Synthetic	Agonist Agonist	GW4064	completely restores impaired BA way and metabolic syndrome in iron-fed mice.	[241]
		INT-767	relieves podocyte injury, mesangial expansion, collagen deposition and tubulointerstitial fibrosis	[214, 242]
		SU5	regulate lipid metabolism and triglyceride metabolism	[243]
		OCA	alleviated the histological and biochemical features of NASH without cirrhosis	[46]
		6α-ethyl-24-norcholanyl-23-amine	behave as full FXR agonist endowed with high binding affinity and efficacy	[43]
		fexaramine	reduces systemic inflammation and metabolic improvement in obese mice	[51]
		HEC96719	show higher FXR selectivity and more favorable tissue distribution dominantly in liver and intestine	[244]
		Nidufexor (LMB763)	regulates FXR-dependent gene in vitro and in vivo	[52]
		BAR502	reverses steatohepatitis and fibrosis caused by chronic exposure of mice to a high caloric diet	[245]
		tropifexor (LJN452)	reverses developed fibrosis, reduces non-alcoholic fatty liver disease activity scores and liver triglycerides	[246]

	Antagonist	3-(tert-Butyl)-4-hydroxyphenyl	obtain antagonistic activity of FXR	[247]
		4-({1-[5-({[1-tert-butyl-5-(4-fluorophenyl)-1H-pyrazol-4-yl]carbonyl}amino)-2-chlorobenzyl]piperidin-4-yl}oxy)benzoic acid	induce remarkable beneficial changes in both plasma non-HDL-cholesterol and HDL-cholesterol levels	[248]
		9,11-seco-cholesterol derivatives	display the best FXR antagonistic activity at the cellular level and decrease the target genes of FXR	[249]
		FLG249	controls the level of FXR target gene in mouse ileum	[250]
Natural	Agonist	Farnesol	stimulate growth of MCF-7 breast cancer cell	[251]
		20*S*-protopanaxatriol	ameliorated hepatic inflammation and fibrosis induced by TAA	[252]
		alisol A 23-acetate	antihyperglycemic	[253]
		alisol B 23-acetate	protects against ischemic acute kidney injury (AKI)	[254]
		altenusin	Attenuates NAFLD by reducing the body weight and fat mass	[255]
		Auraptene	Liver protection, anti-inflammatory and antioxidant activities	[243]
		berberine	reducing hepatic gluconeogenesis and lowering blood glucose	[256]
		Calycosin	improve liver steatosis and reduce liver fibrosis	[257]
		Hedragonic acid	protect mice from liver injury induced by acetaminophen overdose and decrease hepatic inflammatory responses	[258]
		dihydroartemisinin	attenuate portal hypertension by targeting HSC contraction	[259]
		hesperidin	Prevent cholestatic liver injury	[260]
		isotschimgine	alleviates nonalcoholic steatohepatitis and fibrosis	[261]
		schaftoside	could attenuate APAP-induced hepatotoxicity *by* regulating oxidative stress and inflammation	[262]
		Gypenosides	ameliorated NASH	[263]
		Swertiamarin	alleviate cholestasis	[264]
		conicasterol E	triggers BA detoxification	[265]
		cycloastragenol	Reduce fatty diet-induced liver lipid accumulation	[266]
		Ginsenoside Rc	Relieve inflammation and oxidative stress	[267]
		Cafestol	increased fat oxidation and energy expenditure	[268]
		coumestrol	exert beneficial effects on lipid and glucose metabolism	[269]
	Antagonist	Naringin	promoting BA synthesis from cholesterol by upregulating CYP7A1	[270]
		scalarane sesterterpenes	Inhibition of the interaction between FXR and SRC-1	[271]
		SIPI-7623	decreased the level of cholesterol and triglyceride	[272]
		Stigmasterol	contribute to BA-induced hepatocyte damage	[273]
		sulfated sterol	Inhibit a subset of FXR regulatory genes in hepatocytes	[274]
		guggulsterone	Reduced liver cholesterol in wild-type mice fed a high cholesterol diet, but not in FXR-deficient mice	[275]
	selective modulators	Oleanolic acid	reduce the biosynthesis of BAs and the cytotoxicity caused by the increase of BAs	[276]

2.1.3. Natural regulators

As the structural investigation of FXR agonists progresses, the presence of FXR regulators in natural products is gradually coming to light. These regulators encompass glycosides, flavonoids, and polyphenols. Salidroside, the primary active ingredient found in the plant Rhodiola rosea, exhibits the capacity to enhance NAFLD through the microbiota-BA-FXR axis and the AMPK-dependent TXNIP/NLRP3 pathway [53, 54]. Another natural isoflavone compound, formononetin, enhances liver/systemic BA metabolism and mitigates liver injury by modulating the SIRT1-FXR pathway [55]. Similarly, curcumin, a polyphenol, mitigates cholestasis

by affecting BA and inflammation, both of which are regulated by FXR [56]. Furthermore, epigallocatechin gallate, a polyphenol found in green tea, has the capability to activate FXR, with its effectiveness being concentration-dependent [57]. Numerous other compounds present in natural products also possess the ability to regulate FXR. Table 1 compiles a summary of these regulators and their associated pharmacological effects in certain natural products. The aim is to contribute to the clinical advancement of natural products with potential FXR-modulating properties.

2.2. Functions of FXR

FXR, functioning as a BA receptor, becomes activated by specific BA metabolites and operates as a transcription factor [2]. Its role is intricately linked to the regulation of diverse physiological processes, encompassing BA synthesis, enterohepatic circulation, glucose, and lipid metabolism [58]. In a study by Sun et al., the potential impact of FXR on rectal cancer, liver cancer, and other metabolic diseases were comprehensively summarized [58]. In this update, we will cover the latest advancements concerning FXR in the realms of BA and the intestine. Additionally, we will delve into its involvement in enterohepatic circulation and gut-to-brain communication, with a specific focus on its relevance in liver fibrosis and the potential for targeted drug development.
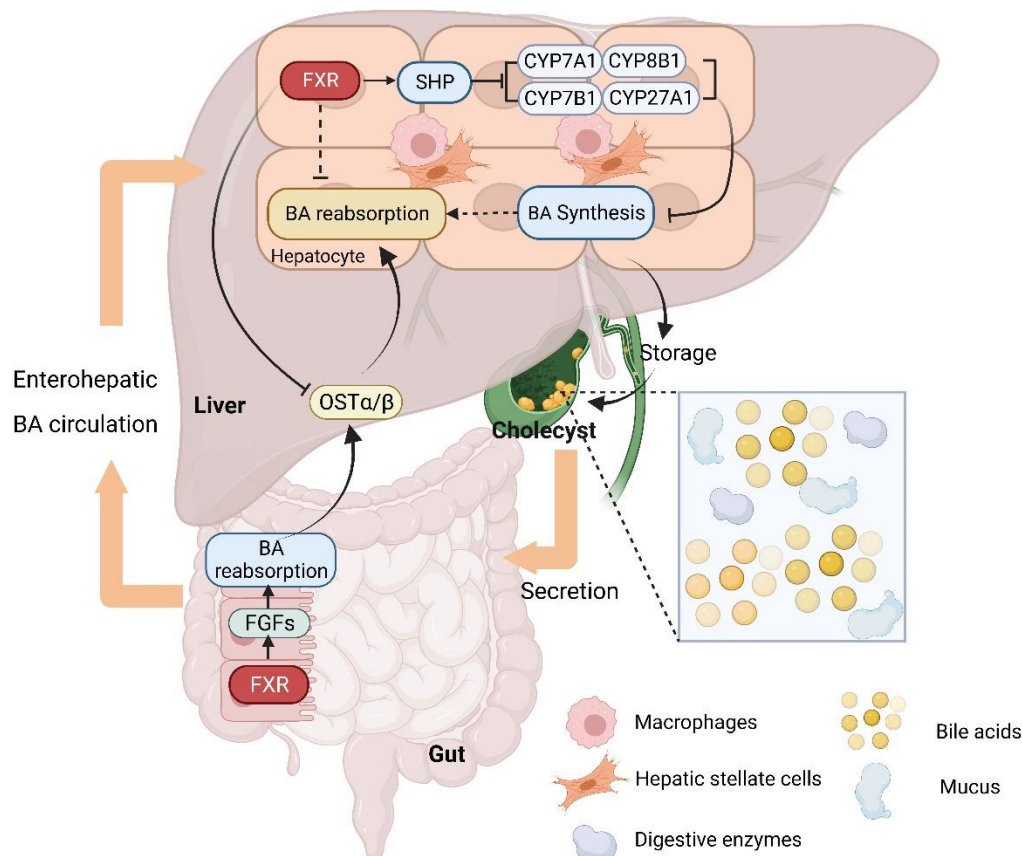

Figure 2. Relationship between FXR and BAs. BAs are mainly synthesized by hepatocytes via the classical pathway or alternative pathway, all of which are regulated by FXRs expression. Activated FXRs can reduce the expression of BA synthases through SHP or FGFs. The relationship between FXR and BAs is mainly established through hepatoenteric circulation.

2.2.1. The relationship between FXR and BAs

BAs are steroid compounds synthesized by hepatocytes from cholesterol and play a role in the digestion and absorption of lipids. Jia and colleagues have elucidated that BA synthesis in the liver follows two distinct

pathways: the classical pathway and the alternative pathway [59]. The classical pathway, which accounts for 75% of BA synthesis, is initiated by cholesterol 7α-hydroxylation through the catalysis of cholesterol 7-alpha hydroxylase (CYP7A1). Subsequently, the steroid nucleus undergoes transformation, and its side chain

undergoes oxidative cleavage, which is regulated by CYP8B1 [59]. On the other hand, the alternative pathway, known as the acidic pathway, is instigated by cholesterol 27-hydroxylation via CYP27A1. The resulting oxysterol products are then subjected to further hydroxylation via catalysis of oxysterol 7α-hydroxylase (CYP7B1) [59]. Research has indicated that non-20α-hydroxylated (chenodeoxycholic acid) synthesized via the alternative pathway exerts positive effects on lipid, cholesterol, and glucose metabolism. In cases where these processes become aberrant, the proportion of 12-hydroxy bile acid content synthesized through the classical pathway tends to increase, leading to a reduction in the control capacity over lipid homeostasis. This, in turn, can escalate inflammation and fibrosis within the liver [60, 61]. Clinical studies have demonstrated significantly elevated levels of serum and liver BAs in patients with liver fibrosis. Delving into BA-related signaling pathways might hold promise as a prospective avenue for liver disease treatment [62]. Recent findings have unveiled the involvement of several nuclear receptors in the metabolic

homeostasis of BAs, with FXR standing out as a crucial member [63-65], often referred to as a BA receptor [66]. FXR primarily regulates BAs by modulating their reabsorption through various mechanisms. For instance, FXR can reduce the expression of BA synthases through the regulation of the short heterodimer partner or fibroblast growth factor (FGF) pathways. Additionally, activated FXR can dampen the expression of BA uptake carriers, thereby inhibiting liver reabsorption. Furthermore, FXR can stimulate bile secretion and BA reabsorption by directly binding to the response element of BA secretion carriers or by regulating the expression of intestinal BA binding protein [67, 68]. Of notable importance is the fact that FXR is prominently distributed at sites where BAs exert their effects, with the highest concentration being in the liver, followed by the small intestine and kidneys [69]. As a result, the negative feedback regulatory influence of FXR on BAs predominantly operates through the intestinal and hepatic circulation (Fig. 2) [70].
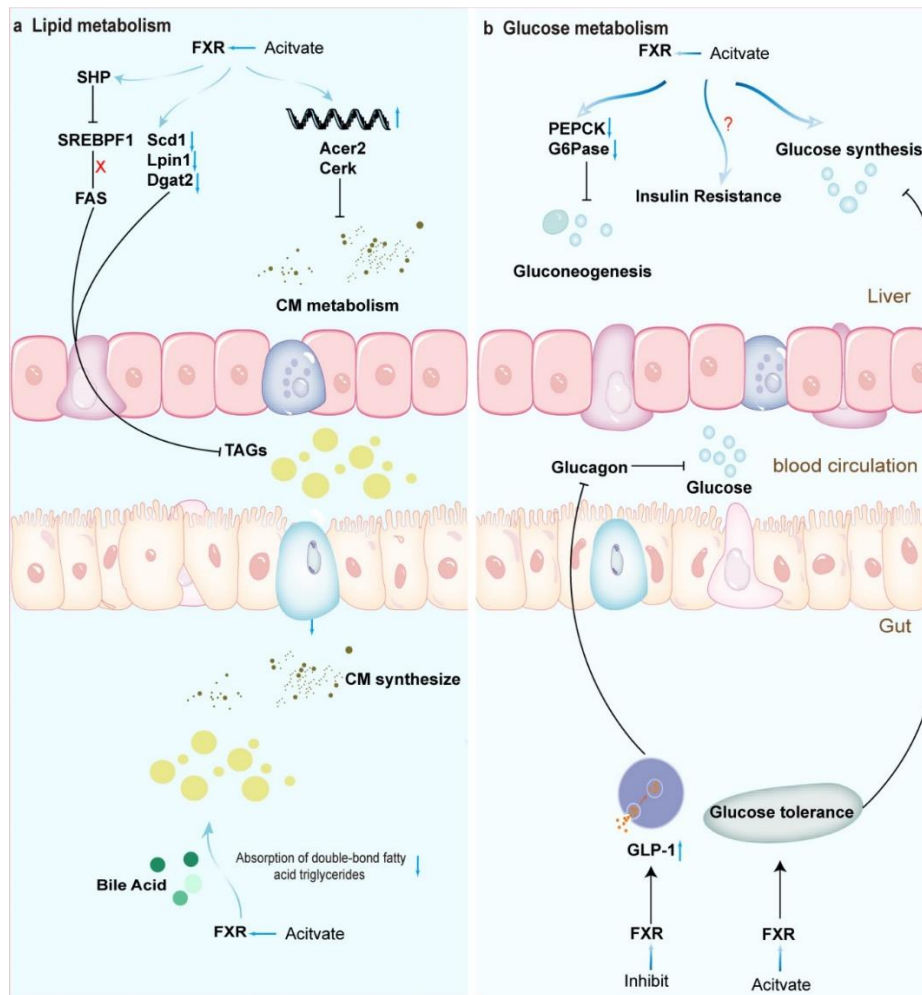

Figure 3. FXR in glucose lipid metabolism. In lipid metabolism, FXR reduces liver fat by inhibiting fat formation and promoting fatty acid oxidation; these functions are related to the expression of SREBP1 or PPARs, respectively; in glucose metabolism, FXR participates in glucose homeostasis through two pathways, namely, gluconeogenesis-related genes and glucagon-activated factors.

2.2.2. FXR in glucose lipid metabolism

FXR's influence extends beyond the realm of BA metabolism, encompassing the maintenance of the body's glucose and lipid metabolism homeostasis (Fig. 3). Watanabe and colleagues proposed that FXR diminishes de novo liver fat accumulation through the FXR-SHP-SREBP1c pathway, thus leading to a reduction in liver triglycerides [71]. A recent comprehensive lipid omics analysis revealed that FXR activation lowers hepatic levels of polyunsaturated and monounsaturated fatty acids (PUFAs and MUFAs) through two distinct pathways. These pathways involve the inhibition of lipogenesis gene expression and lipid absorption [72]. Specifically, FXR curtails MUFA levels by inhibiting Dgat2, Lpin1, and Scd1 expression. Notably, this effect operates independently of SHP and SREBP1. In contrast, FXR's effect on PUFA reduction is primarily mediated through the suppression of lipid absorption [72]. Further investigations have demonstrated that FXR is intricately involved in the transcriptional-level expression of miR-552-3p, which governs metabolic genes in glycolipid metabolic disorders through cis-binding [73]. In the context of glucose metabolism regulation, hepatic FXR positively modulates glucose production through two mechanisms. One mechanism entails protein kinase A-mediated FXR phosphorylation, contributing to the activation of gluconeogenic genes by activated FXR and cAMP-response element-binding protein. The second mechanism involves the suppression of FXR's anti-gluconeogenic function through FOXA2, which can be activated by glucagon. Particularly noteworthy is the physical interaction between FOXA2 and FXR. It is worth mentioning that low expression of Foxa2 does not affect the expression of gluconeogenic genes induced by glucagon. However, FXR agonists enhance the expression of gluconeogenic genes, indicating that the protein kinase A and FOXA2 pathways are involved in distinct FXR-mediated glucose metabolism pathways [74]. Moreover, bile transfer to the ileum enhances glucose homeostasis via the intestinal FXR-GLP-1 pathway. In particular, during fasting, BA signaling through intestinal FXR enhances intestinal GLP-1 production, which promotes intestinal glucose tolerance by augmenting insulin secretion [75]. In light of this, Zhang and colleagues injected taurocholate into the midjejunum of healthy men, resulting in increased expression of GLP-1 and insulin secretion, ultimately upregulating energy uptake by the large intestine [76]. Additionally, intestinal FXR exerts control over hepatic gluconeogenesis by influencing pyruvate carboxylase and mitochondrial acetyl-CoA levels [77]. FXR's influence on glycolipid metabolism does not solely rely on its pharmacological effects but is also intricately linked to the intestinal microbiota. FXR is involved in the metformin-regulated gut microbiome in the context of metabolic dysfunction, operating via the *B. fragilis*–glycoursodeoxycholic acid–intestinal FXR axis [42]. Given its multifaceted functions, current studies highlight the potential of targeted FXR activation as a more reliable approach compared to systemic therapies.

2.2.3. FXR with microbiota

Based on sequence analysis results, the human intestine is host to a range of 1000 to 1150 bacterial species, categorized into 7 bacterial phyla: Pachylobacteria, Bacteroides, Actinomycetes, Proteus, Clostridium, Wartymic microbacteria, and Cyanobacteria. Notably, Pachylobacteria and Bacteroides together constitute over 95% of this microbial community [78-80]. The equilibrium between the human body and the intestinal microbiota, which is essential for normal physiological functions such as immunity, metabolism, and inflammation, can be disrupted by various factors, including chronic diseases and medications [81-83]. A study by Jian et al. indicated that abdominal irradiation prompts alterations in gut microbiota composition, leading to decreased abundance and diversity [84]. They further elucidated the role of L. plantarum in activating the FXR-fibroblast growth factor 15 (FGF15) signaling pathway, which promotes DNA damage repair in intestinal epithelial cells [84]. It has been observed that intestinal FXR activation can curb aberrant bacterial proliferation and mitigate intestinal mucosal damage [85]. Building upon this, FXR activators have been employed to attenuate pathological bacterial translocation via the portal-venous route [86, 87]. Ava Parséus and colleagues challenged the conventional genetic notion by discovering that the microbiota influences adipose inflammation, steatosis, and obesity in an FXR-dependent manner. To substantiate this, they transplanted microbiota from FXR-deficient mice and FXR-competent mice into germ-free mice, demonstrating that the altered microbiome partially ameliorated the metabolic status of FXR-deficient mice [88]. Considering the intricate interplay between FXR and the microbiota, Shu and team found that berberine alleviates NASH by regulating the interplay between the gut microbiome-manifested through increased relative abundance of Clostridium, Lactobacillus, and Phytodermidae- and BA metabolism, along with activating gut FXR [89]. Additionally, the microbiota can influence the activation of FXR by binding amino acids to bile acids [90] (Fig 4). Investigations have demonstrated that Pu-erh tea confers hypolipidemic effects by suppressing microorganisms linked to bile salt hydrolase activity, thereby diminishing FXR-FGF15 signaling [91]. While the correlation between the gut microbiota and FXR warrants further exploration, targeting the

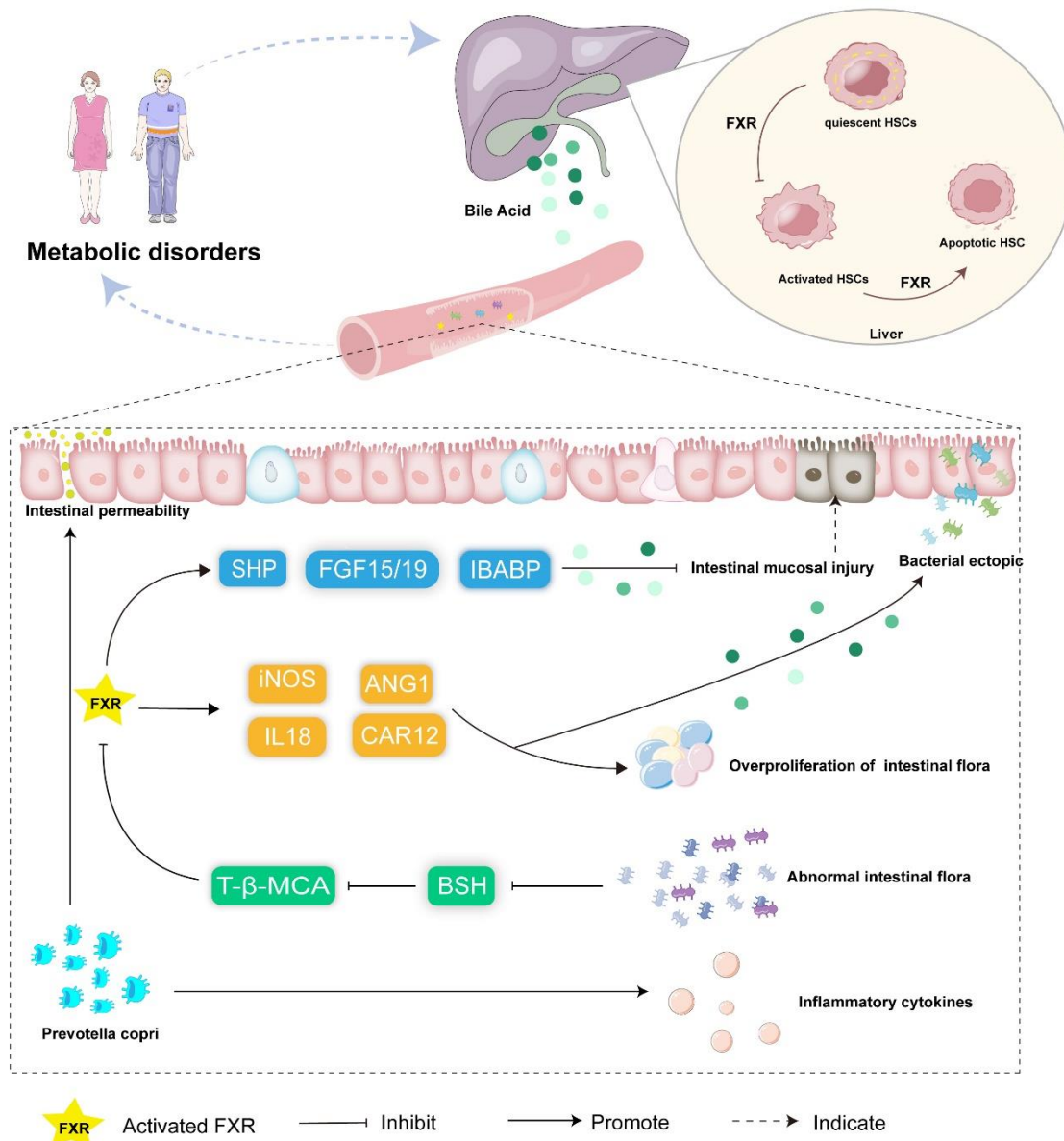microbiome is emerging as a promising therapeutic avenue for preventing and treating gut-related disorders.

Figure 4. Overview of FXRs' regulation of intestinal flora homeostasis and metabolic disorders. The imbalance between the body and the intestinal flora leads to the disturbance of normal physiological functions. The intestinal flora promotes fatty inflammation, steatosis, and obesity in an FXR-dependent manner. The activation of intestinal FXR can inhibit the abnormal proliferation of bacteria and reduce intestinal mucosal damage.

2.2.4. FXR in enterohepatic circulation

The intestinal microbiota exerts an influence on inflammation and immunity, a relationship closely intertwined with hepato-intestinal circulation [92]. According to the theory of the entero-liver axis, the liver and intestine establish a symbiotic relationship marked by the liver's profound processing of microbiota metabolites and the regulation of microbiota structure through the secretion of metabolic substances, such as BAs [93]. As previously mentioned, BAs are synthesized in the liver and stored in the bile duct or gallbladder. Upon food intake, they are released into the small intestine, where they undergo further metabolism by gut bacteria. Subsequently, BAs are transported back into the enterohepatic circulation, with approximately 95% being reabsorbed in the ileum and entering the portal vein of the liver. They then traverse liver sinusoids and are conveyed

to hepatic cells [94, 95]. Throughout these processes, liver FXR not only suppresses BA synthesis but also enhances the recirculation of BAs from the gut to the liver via the organic solute transporter alpha/beta (OSTα/β). Furthermore, it regulates bile acid intake through the portal vein circulation [96, 97]. Meanwhile, intestinal FXR activates downstream gene expression via the FGF 15/19 pathway, thereby curbing abnormal total BA elevation [98]. The relationship between BAs and the microbiota underscores FXR's role in liver-intestinal circulation, further demonstrated through its influence on

microbiota regulation. Degirolamo et al. demonstrated that probiotics induce microbiota regulation and enhance BA deconjugation, influencing variations in ileal BA assimilation and inhibiting the enterohepatic FXR-FGF15 axis [99]. FXR is also implicated in microbiota metabolism through flavin monooxygenases3, thereby affecting the occurrence of certain metabolic diseases such as atherosclerosis [100]. Consequently, the development of FXR agonists or antagonists targeting the gut flora-BA-gut FXR axis holds potential for treating related metabolic disorders.
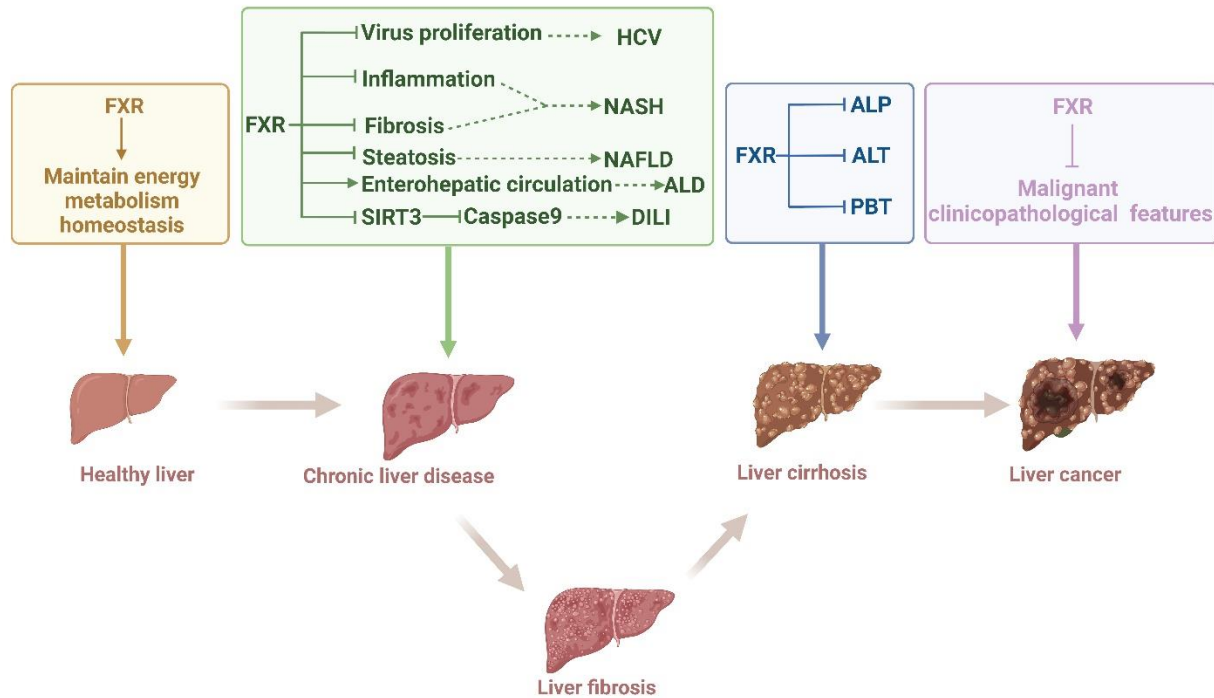

Figure 5. Role of FXRs in the liver. FXR activation is used in multiple liver diseases, such as liver injury, fibrosis, and even cancer, and the main mechanism is closely related to inflammation, steatosis, and apoptosis via related factors.

2.2.5. FXR in liver disease

As a pivotal factor in metabolic regulation, FXR plays a crucial role in various liver diseases, including alcoholic liver disease (ALD), NAFLD, viral hepatitis, and drug-induced liver injury (Fig. 5) [101, 102]. Particularly noteworthy is the work of Hartmann and colleagues, who have shown that alcohol leads to alterations in the BA profile due to the reduced activity of FXR [103]. Throughout these processes, FXR upregulates the expression of FGF15 and the BSEP, while concurrently suppressing the expression of CYP8B1 and CYP7A1, all of which collectively contribute to the inhibition of BA synthesis [104]. Furthermore, exposure to alcohol disrupts the interaction between RXRα and FXR, facilitated by the acetylation of FXR, ultimately resulting in the inactivation of FXR [105]. Additionally, the expression of FXR is modulated by proteins whose expressions undergo

changes in liver disease, such as sirtuin 1 [66], liver X receptors, PPARs, and others [106, 107]. Much like its role in ALD, studies by Clifford et al. have demonstrated that hepatic FXR controls the expression of genes implicated in adipogenesis, while intestinal FXR regulates lipid absorption [72]. Moreover, FXR agonists, like GSK2324, are employed in the treatment of NAFLD due to their role in decreasing fatty acid absorption and selectively reducing fatty acid synthesis [72]. Additionally, in individuals with HCV infection, FXR participates in lipid oxidation and ketogenesis. Notably, the activation of PPARα and FXR during HCV infection hampers the viral life cycle and potentially forms part of the host's metabolic antiviral response to the infection [108, 109]. Furthermore, antagonism toward FXR might underlie certain occurrences, such as how indomethacin can induce STAT3 phosphorylation, subsequently promoting caspase 9 activation and contributing to drug-

induced liver injury [110]. Building upon these insights, our prior research has also delved into the regulatory function of FXR in lipid metabolism induced by alcohol and a high-fat diet. Our findings suggest that traditional Chinese medicine can modulate FXR, thereby ameliorating ALD and NAFLD. Examples of such medicinal agents include *Araliaceae* and *Allium victorialis L* [111, 112]. Beyond the scope of liver injury, FXR also exerts regulatory influence over liver fibrosis. OCA, the pioneering drug targeting FXR, effectively lowers BA levels and impedes the activation of HSCs, thus mitigating fibrosis progression without compromising hepatocyte apoptosis [25]. Significantly, the discovery of OCA dates back to 2002 as 6ECDCA [113]. Initial research unveiled that 6ECDCA, a semisynthetic bile acid derivative, prompts the upregulation of SHP and BSEP, coupled with

downregulation of cyp7a1, cyp8b1, and NTCP at the mRNA level [114]. Furthermore, 6-ECDCA enhances insulin-induced differentiation of preadipocytes by modulating the expression of adipocyte-related genes [115], underscoring the potential of exploiting FXR ligands as a promising avenue for addressing cholestatic disorders and fibrosis improvement.

Importantly, the expression of hepatic FXR demonstrates an inverse correlation with various malignant clinical and pathological features of liver cancer. These features encompass outcomes of liver disease, such as tumor size, clinical classification of liver cancer, cancer cell differentiation, and tumor tissue encapsulation [58]. Given the paucity of clinically approved drugs for liver fibrosis, targeting FXR regulation holds promise as a potential breakthrough avenue.
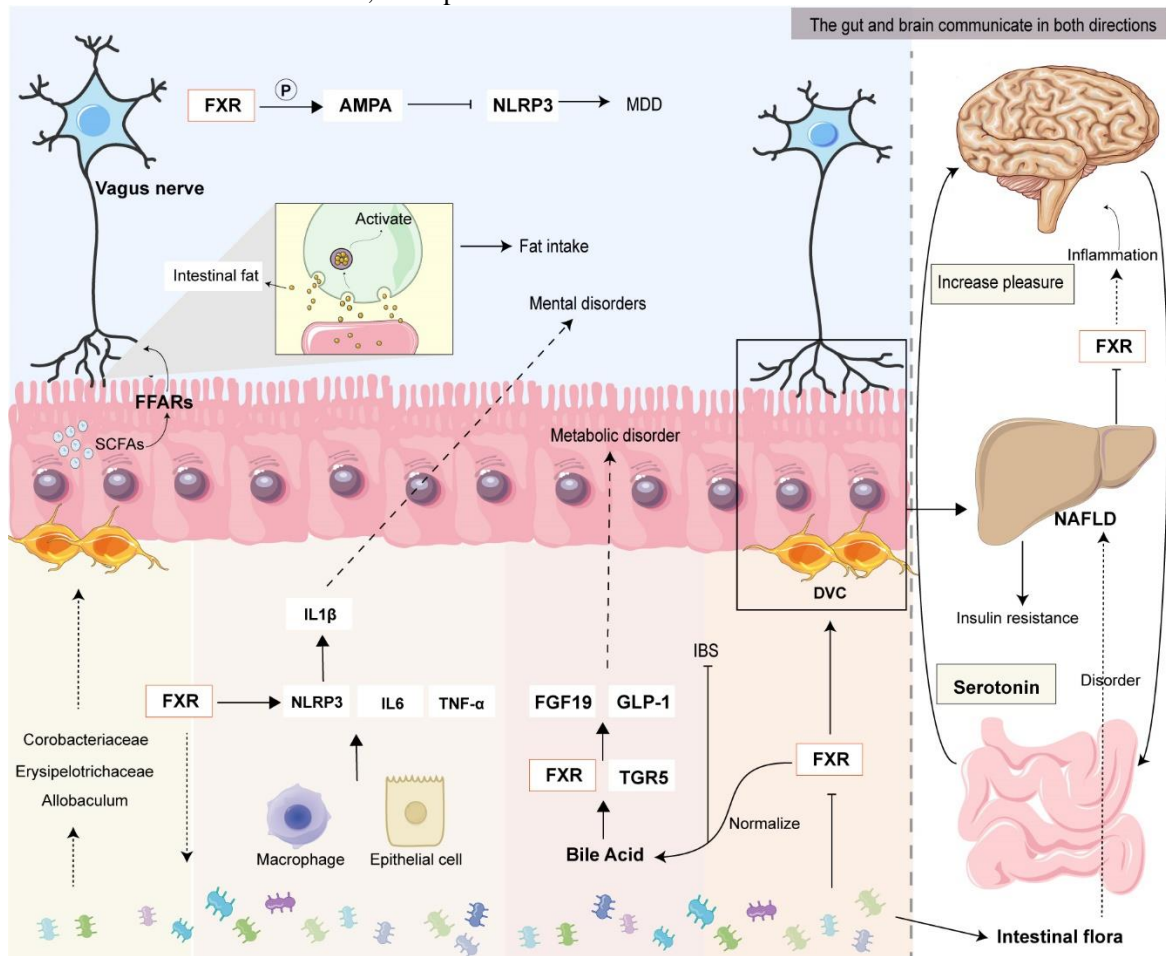

Figure 6. FXR in the gut-brain axis. FXRs interact and work together by regulating inflammatory responses, BAs, and the intestinal microbiome involved in entero-brain circulation.

2.2.6. FXR in gut-brain Axis

Apart from its involvement in intestinal-hepatic circulation, the significance of FXR in the intestinal-brain

axis should not be underestimated (as illustrated in Fig. 6). The gut-brain axis constitutes a bidirectional communication network connecting the brain and the intestine, encompassing neural pathways, endocrine

pathways, immune pathways, and the gut microbiota [116]. Research has highlighted that neuron within the vagus nerve, which connects the intestine and the brain, become activated in response to intestinal fat. These neurons transmit information from the intestine to the brain. In instances where the activity of fat-sensing endothelial cells on the inner wall of the intestine is impeded, signal transmission can be halted, leading to a reduction in mice's appetite for fat [117]. This mechanism has emerged as a significant target for addressing NASH and obesity. Additionally, it has been observed that human mood can affect microbiota composition. Notably, gastrointestinal disorders regulated by intestinal neurons often co-occur with fatty liver disease [118]. This phenomenon arises primarily due to chronic psychological stress inducing shifts in intestinal flora diversity and an increase in intestinal permeability. These changes are accompanied by the release of lipopolysaccharides (LPS) from the intestine into the liver, triggering the activation of the Toll-like receptor 4 (TLR4) signaling pathway, all of which collectively contribute to liver injury [119]. Likewise, alterations in the microbiota can reciprocally influence the body's emotional state [120]. This is due to the gut flora's capacity to synthesize corresponding neurotransmitters that facilitate communication between the gut and the brain. Furthermore, pathogenic microorganisms and bacterial metabolites can stimulate the secretion of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α. These cytokines not only influence macrophage recruitment within the liver but also directly affect brain function, thereby participating in the emergence of neurological disorders [121]. Of paramount importance is the role of BAs in transmitting signals to the central nervous system through two distinct pathways: a direct central FXR-TGR5 signal and an indirect pathway involving the activation of intestinal FXR and TGR5, leading to the induction of FGF19 and GLP-1 [122-124]. FXR is not confined to the gut and liver; it is also expressed in the brain, indicating its potential circulatory effect. This circulatory effect can be categorized into three key aspects: 1) disruption of the release of proinflammatory cytokines and alleviation of intestinal inflammation; 2) modulation of the body's lipid and energy metabolism through BA regulation; and 3) enhancement of the composition of the gut microbiome. Drawing from these insights, Bao et al. discovered that ganoderic acid A curtailed NLRP3 inflammasome activity and heightened the expression of AMPA receptors in the prefrontal cortex of mice by regulating FXR. As a result, encephalitis activity was suppressed, ultimately ameliorating major depressive disorder [125]. These findings underscore FXR's propensity to interact synergistically with the aforementioned three areas within

the gut-brain circulation, thereby assuming a pivotal role in liver fibrosis.

3. Pharmacology of FXR in liver fibrosis

In fact, systemic FXR deficiency in mice leads to Indeed, the absence of systemic FXR in mice results in elevated liver BA levels and ensuing liver damage, encompassing hepatic steatosis, inflammation, and fibrosis. The emergence of liver fibrosis is contingent not only upon the activation of HSCs but also on the intimate involvement of hepatocyte injury, immune cell activation, and the modulation of the liver microenvironment, among other factors. Consequently, in the pursuit of preventing and managing liver fibrosis, it becomes imperative to comprehensively grasp the underlying pathogenesis of liver fibrosis and the intricate regulatory role that FXR plays within distinct cell types that contribute to the fibrotic process.

3.1 Liver fibrosis: an overview

The development of hepatic fibrosis primarily arises from a sequence of disruptions to liver tissue structure caused by the imbalance between ECM synthesis and degradation [126]. Serving as the initial phase of liver fibrosis, diverse pathogenic factors, such as alcohol, high-fat diets, drugs, and viruses, can induce liver damage. However, when the extent of damage surpasses the liver's inherent repair capacity [127], the liver's elasticity wanes, progressively culminating in liver fibrosis [128]. At this juncture, patients often present with clinical symptoms such as fatigue, appetite loss, altered stool patterns, liver discomfort, and a pallid complexion. If left undiagnosed and untreated, liver fibrosis can advance to cirrhosis and even liver cancer, profoundly impacting quality of life. Clinical investigations have underscored the significance of certain serum markers in relation to the intensity of the inflammatory response and fibrosis. Parameters such as red blood cells, blood platelets, N-terminal procollagen III (PIII NP), and aspartate aminotransferase (AST) exhibit meaningful correlations with the extent of inflammation. Additionally, albumin, the albumin/globulin ratio [129], and PGA and PGAA levels have been linked to inflammation and fibrosis [130]. Notably, hyaluronic acid serves as a precise variable for evaluating inflammation and fibrosis severity in the liver [131]. Hence, the synergistic application of serum markers has the potential to enhance the accuracy of fibrosis diagnosis [132, 133]. With the continual advancement of molecular biology techniques and the pressing need for effective treatments, the intricate mechanisms underpinning liver fibrosis have been gradually unveiled [19]. Broadly, cells exerting pivotal roles in liver fibrosis can be broadly classified into

three categories. The first group comprises fibroblasts, including HSCs and epithelial cells, which, upon liver injury, undergo activation and transform into myofibroblasts (MFs) [134, 135]. The second category encompasses signaling cells, such as hepatocytes, hepatic sinus endothelial cells, and bile duct cells, that modulate MF activation and trigger profibrotic pathways [14]. The third class encompasses regulatory cells or immune cells, such as Kupffer cells, natural killer cells, macrophages, and mast cells. These cells can dynamically adapt their roles in response to the onset and regression of liver fibrosis [136, 137]. Throughout chronic liver injury, hepatocytes sustain damage and even undergo apoptosis,

releasing damage-related molecular patterns. This triggers a persistent inflammatory milieu characterized by macrophage and immune cell infiltration, accompanied by the release of profibrotic cytokines such as TGF-β, TNF-α, and PDGF. Within this continuum, HSCs become activated and differentiate into MF, identifiable by the expression of α-smooth muscle actin (α-SMA) and collagen I—an ECM component—ultimately driving the onset of liver fibrosis [138-140] (Fig 7). Hence, a comprehensive exploration of FXR's roles within distinct cell types is pivotal for a deeper comprehension of its mechanisms in liver fibrosis.
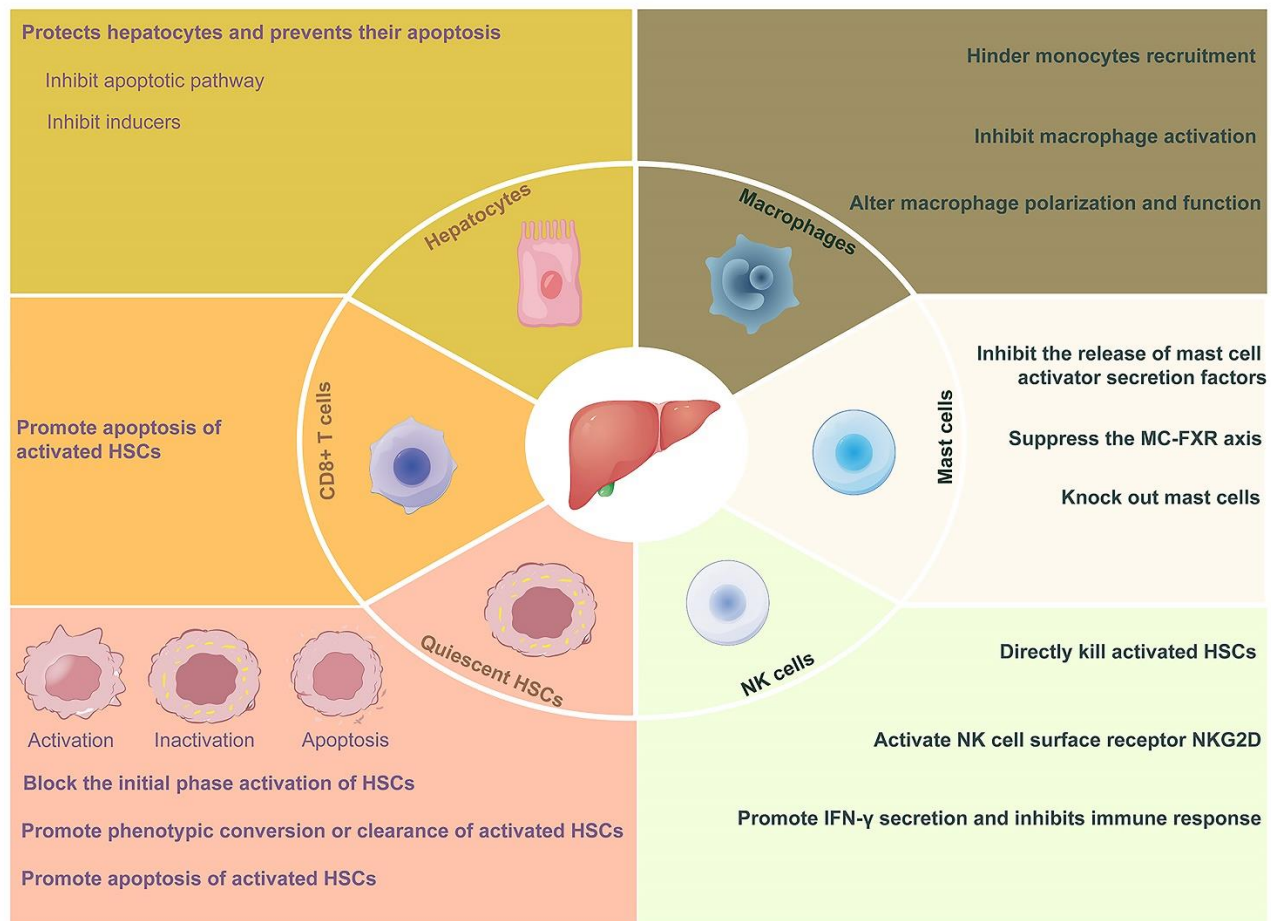

Figure 7. Anti-fibrosis therapy in liver fibrosis. According to the pathogenesis, the treatment of liver fibrosis can be started from the cells involved in liver fibrosis. The main methods are inhibiting the damage and apoptosis of liver cells, promoting the type of transformation of immune cells, inhibiting the activation of HSCs, and promoting the apoptosis of activated HSCs.

3.2. FXR with liver fibrosis

Systemic FXR deficiency in mice leads to elevated liver BA levels and subsequent liver disorders, including liver steatosis, inflammation, and fibrosis. The development of liver fibrosis involves not only the activation of HSCs but also close interactions with hepatocyte injury, immune cell activation, and alterations in the liver

microenvironment. Currently, the range of therapeutic drugs approved by the FDA remains limited, predominantly due to the constraints of existing methodologies for assessing fibrosis. While ultrasound, elastography, MRI, and CT serve as primary tools for diagnosing liver disease [141], the endorsement and clinical evaluation of novel liver fibrosis drugs necessitate invasive liver biopsies. This approach is susceptible to

variations between samples and observers and scaling it up to accommodate the approximately 1 billion affected individuals worldwide proves challenging [142]. In contrast, noninvasive tests using biomarkers assume a pivotal role in fibrosis diagnosis, staging, and continuous monitoring [143]. Presently, widely used noninvasive methods such as the FIB-4 index, and liver stiffness measurement carry a notable risk of false positives and outcome uncertainty [144]. Thus, delving into the distinctive roles of FXRs within various cell types emerges as highly significant for advancing the prevention and treatment of liver fibrosis (Fig. 8).

3.2.1. FXR in hepatocytes

In a healthy liver, hepatocytes constitute approximately 70% of the total cell population and primarily oversee

metabolic processes crucial to liver functions, including complement factor regulation, bile acid synthesis, and gluconeogenesis [145]. FXRs, not confined solely to bile acid metabolism, contribute to the reduction of de novo liver fat via the FXR-SHP-SREBP1c pathway, thereby curbing liver triglyceride accumulation [71]. Recent comprehensive lipidomics analysis has revealed that FXR activation diminishes the levels of PUFAs and MUFAs in the liver. This effect hinges on two distinct pathways: inhibition of lipogenesis gene expression and lipid absorption [72]. Additionally, FXRs participate in transcriptional-level regulation of miR-552-3p-controlled metabolic genes in glycolipid metabolic disorders through cis-binding [73]. Concerning the modulation of glucose metabolism, FXRs oversee liver glucose production through the activation of gluconeogenic-related genes and glucagon-triggered FOXA2 [74].
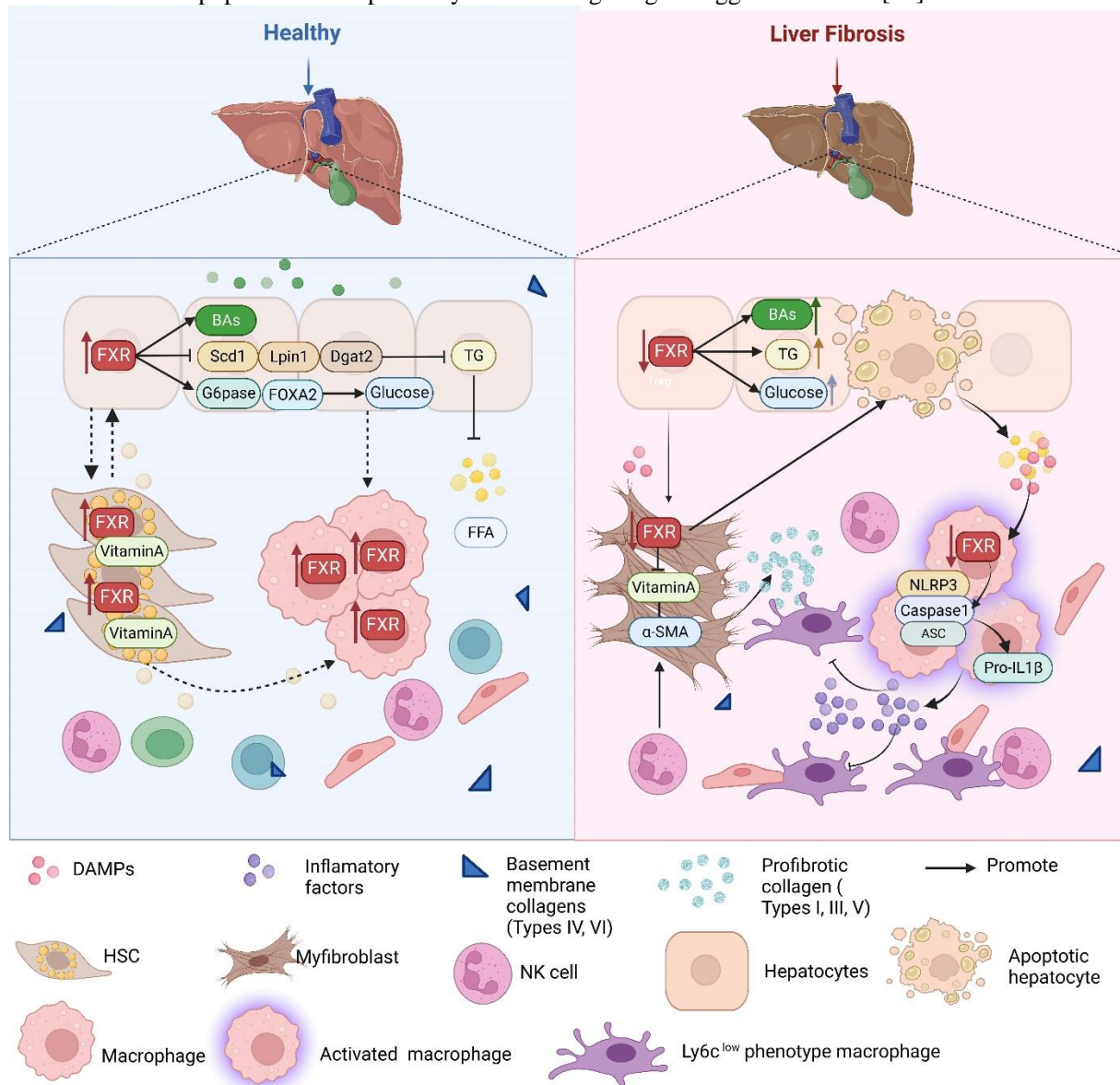
Figure 8. Summary of the role of FXR in key cells in liver fibrosis. In the normal liver, hepatocytes provide energy and nutrients to nonparenchymal cells. Vitamin A stored in HSCs promotes the growth and proliferation of hepatocytes and macrophages, effectively maintaining homeostasis in the liver microenvironment. After liver injury, FXR was decreased significantly, accompanied by apoptosis of hepatocytes as well as the release of increased DAMPs and FFA content, resulting in macrophage activation. During this process, HSCs lose the storage function of vitamin A and contribute to the deposition of ECM, leading to liver fibrosis.

Upon encountering stimuli, hepatocytes undergo changes in their secretion profiles and the gene expression of specific proinflammatory factors. These alterations bear an inverse relationship with FXR expression in the liver [146]. Furthermore, cystathionine γ-lyase (CSE) and its resultant product hydrogen sulfide (H_2S) generated in hepatocytes, which demonstrate decreased levels in NAFLD mice or hepatocyte models, can trigger posttranslational FXR modification at the Cys138/141 site. This mechanism can function as an FXR activator, modulating glycolipid metabolism and fibrosis [147, 148]. Similarly, FXR can bind to shared sites in the Sox9 promoter to boost glycolysis and ATP production. Consequently, this facilitates the regeneration of Sox9+ hepatocytes that assume the role of bidirectional progenitor cells following liver injury. These cells can give rise to hepatocytes or bile duct cells, contributing to liver repair and regeneration [149, 150]. Furthermore, specific FXR knockout in hepatocytes significantly delays the initiation signal of growth factors, hampering liver regeneration [151].

At present, several drugs targeting FXR have been developed to address various stages of liver cell damage. For instance, EDP-305, an oral synthetic FXR agonist, has demonstrated efficacy in reducing liver fat content and serum ALT levels in phase II trials. This supports the need for extended trials evaluating histological endpoints in NASH [152]. Vonafexor, another FXR agonist, has exhibited the ability to decrease HBV surface antigen levels in CHB within a short timeframe and has demonstrated certain safety parameters. This implies its potential role in preventing hepatocyte injury, although extensive trials are required to assess its therapeutic viability [153]. Nevertheless, Wang et al. highlighted that FXR overexpression, rather than its ligands, enhances its interaction with CASP8, thereby suppressing hepatocyte apoptosis in hepatic fibrosis [12]. Consequently, gaining a comprehensive understanding of FXR's roles within hepatocytes is pivotal for the development of FXR-targeting drugs and the treatment of liver fibrosis.

3.2.2. FXR in immune cells

Positioned at the junction of the immune system and antigens from the gastrointestinal tract, the liver is primarily endowed with innate immunocytes [154-156], which encompass Kupffer cells (a subtype of macrophages) [157, 158], natural killer (NK) cells, neutrophils, NK T (NKT) cells, monocytes, and dendritic cells [159]. This attribute designates the liver as an immune organ [160]. Research has illuminated that FXR's scope extends beyond hepatocyte metabolism and injury; it also influences immune cell activation. Specifically, FXR is expressed within immune cells and exerts regulatory effects on them [161]. For instance, the expression of FXR in KCs surpasses that in bone marrow-derived macrophages. Pretreatment of KCs with GW4064, rather than bone marrow-derived macrophages, inhibits TNF-α and elevates IL-10 levels upon TLR stimulation. Notably, SHP, an intrinsic negative factor in TLR-triggered inflammatory responses, plays a pivotal role in FXR's immune regulation in KCs [162]. Broadly speaking, FXR activation in KCs can dampen proinflammatory responses in the liver through heightened SHP expression [163]. Additionally, activated FXR fosters the generation of anti-inflammatory macrophages, enhances IL-10 secretion, and curbs T-cell responses. This phenomenon has been validated in human monocytes from both healthy controls and multiple sclerosis patients [164]. Furthermore, FXR physically interacts with NLRP3 and caspase 1, thereby exerting a negative regulatory influence on NLRP3 inflammasome activation in macrophages [165]. Notably, recent clinical trials utilizing OCA for NASH therapy have indicated a potential modulation of the NLRP3 inflammasome, hinting at the potential immunological mechanisms underlying OCA's effects [166, 167]. Moreover, the transformation of macrophages into an anti-inflammatory phenotype is intertwined with the production and elimination of osteopontin by NKT cells [168]. Activated FXR, in turn, can inhibit osteopontin production by engaging with its promoter in NKT cells through SHP [169]. These findings collectively underscore FXR's role in modulating NKT cell activation within the liver. Additionally, bile acid metabolism affects the aggregation of NKT cells by regulating the expression of CXCL16 in hepatic sinusoidal endothelial cells. This selective role plays a part in tumor suppression, a notion that has recently been corroborated by human HCC single-cell RNA-seq data. Building upon this foundation, Gou et al. observed that OCA combined with a TGR5 antagonist demonstrates certain antitumor activity [171]. This finding provides groundwork and potential strategy for NKT cell-based immunotherapy for HCC. Somewhat distinct from NKT cells, clinical investigations have unveiled that the number of mast cells and the expression

of FXR in the biliary tract are elevated in patients with liver injury compared to control subjects. In this context, mast cells can regulate intestinal inflammation and bile duct responses triggered by cholestasis via the FXR signaling pathway [172]. While preclinical FXR activation trials deliver negative regulatory signals that mitigate immune dysfunction in various liver diseases driven by inflammation, the clinical implications of these mechanisms in FXR-related conditions remain uncertain [173]. This underscores the ongoing endeavor to explore the clinical modulation of FXR and its agonists on immune cells.

3.2.3. FXR in HSCs

HSCs, constituting 15% of the hepatocyte population, reside in the Disse cavity in close proximity to sinusoidal endothelial cells and hepatocytes. These cells, primarily acting as fibroblasts, play a pivotal role in the progression of hepatic fibrosis [146]. Under normal conditions, HSCs are typically quiescent, primarily serving as reservoirs for storing vitamin A [174]. Notably, vitamin A directly influences bile acid synthesis and transport through nuclear receptors, including FXR [175]. Similarly, FXR-deficient mice exhibit reduced vitamin A storage capacity, a phenomenon ameliorated upon FXR reintroduction into the hepatic system [176]. As early as 2004, Fiorucci et al. reported that FXR is also present in HSCs and serves as a negative regulatory factor, extending its influence beyond bile acid metabolism [177]. FXR expression in primary HSCs and the HSC-T6 rat immortalized cell line [178] effectively inhibits collagen I mRNA expression and collagen synthesis [177]. Nevertheless, FXR activation does not hinder HSC proliferation or their transition into myofibroblast-like states, seemingly in contrast with FXR's purported antifibrotic effects. In reality, FXR exerts its influence by modulating the transcription of target genes, notably SHP [179, 180]. Studies have demonstrated that FXR ligands upregulate SHP expression at the mRNA level in HSCs, analogous to hepatocytes [181]. Importantly, the FXR-SHP-mediated regulatory cascade contributes to collagen remodeling induced by FXR ligands. Interestingly, manipulating SHP expression, whether through silencing or overexpression, nullifies the regulatory impact of FXR ligands on the expression of 1(I) collagen at the mRNA level, all of which showed that the. These observations underscore the SHP-dependent nature of FXR's regulatory mechanism in HSCs. Concurrently, FXR knockdown leads to an increase in tissue inhibitor of metalloproteinase 1 (TIMP1), a key participant in ECM formation within HSCs [182]. Upon activation by inflammatory mediators, such as TGF-β, quiescent HSCs transition to an activated state, participating in ECM deposition [183]. In this context, a selective FXR agonist (BAR704) can obstruct TGF-β promoter binding to p-SMAD3 through SHP-mediated transcription, consequently impeding HSC transdifferentiation and attenuating liver fibrosis [184]. Furthermore, activated FXR can influence HSC contraction through either sphingosine-1-phosphate receptor 2-mediated Ca^{2+} sensitization or Ca^{2+} dependent mechanisms [185]. Drawing from these insights, the exploration of FXR-targeting drugs for inhibiting HSC activation presents a promising avenue in the treatment of liver fibrosis.

3.2.4. FXR in enterohepatic circulation

In addition to primary liver cells, liver fibrosis is intricately linked to hepatoenteric circulation [186]. This connection predominantly arises from bacterial and microbiome derivatives, bile acids, physiological function, and intestinal barrier integrity [187]. For instance, in children with NAFLD, a decline in biodiversity and significant enrichment of genes involved in LPS synthesis were observed. This phenomenon might contribute to increased intestinal permeability and the promotion of a proinflammatory state, which is positively associated with liver fibrosis [188-190]. LPS-induced dysregulation of intestinal immunity and the microbiome is intertwined with changes in bile acid metabolism [191]. As a receptor for LPS, TLR4 is inhibited by activated FXR, regulating the expression of proteins linked to the TLR4/NF-κB signaling pathway, such as MyD88, p-p65, and p-IκBα. This mechanism shields the liver from enterogenic hepatitis [192]. Furthermore, research by Jiang et al. highlighted a significant reduction in the abundance of intestinal Prevotella copri in primary sclerosing cholangitis. However, treatment with Prevotella copri was shown to enhance hepatic fibrosis by activating the FXR pathway [193]. Similarly, intestinal Prevotella copri was found to restore glucose homeostasis by enhancing bile acid metabolism and FXR expression [194]. Additionally, the degradation of tight junction and adherens junction proteins in the intestinal tract accelerates apoptosis and nitrification of enterocytes. This process contributes to ALD-induced intestinal leakage and endotoxemia, triggering an inflammatory response in the liver [195]. Subsequent studies identified that occludin deficiency heightened the sensitivity of mice to ethanol-induced liver damage [196]. However, activated FXR can counteract intestinal epithelial barrier injury induced by LPS through the regulation of transepithelial resistance and tight junction proteins [197]. Central to this context is the hepatoenteric circulation, which governs the uptake of bile acids and other steroids metabolized or produced in the liver. These compounds are then secreted into the enteric canal, with a subsequent reabsorption back into

circulation before returning to the liver. This process underscores the crucial role of FXR in hepatoenteric circulation [95]. Presently, the probiotic Lactobacillus rhamnosus GG has been shown to reduce the liver concentration of the FXR antagonist T-βMCA and increase the FXR agonist chenodeoxycholic acid. This results in elevated serum and ileal FGF15 levels, ultimately ameliorating BDL-induced hepatic fibrosis in mice [198]. Moreover, the FXR novel antagonist glycine-β-muricholic acid, which is retained in the gut, has the potential to enhance glycolipid metabolism in obesity and NAFLD [199]. Consequently, FXR agonists or inhibitors targeting enterohepatic circulation might hold promise for therapeutic interventions in hepatic fibrosis.

3.2.5 Exploration of FXR-related pathways and mechanisms in liver fibrosis

As previously highlighted, while FXR serves as a pivotal target, it seldom operates in isolation within disease contexts, often entwined with other pathways. When considering the induction of liver fibrosis formation, FXR-related pathways can be classified into various facets, the foremost being its involvement in fat synthesis. FXR plays a role in modulating lipid homeostasis through its influence on de novo lipogenesis, HDL formation, hepatic uptake of HDL, and β-oxidation of fatty acids. This regulatory impact stems from its control over the expression of key players, including SREBP1, PLTP, SCARB1, and PPARα [200-202]. Regarding inflammation, FXR activation exhibits the ability to curtail the production of proinflammatory cytokines, such as IL1β and NOS$_2$. This effect primarily stems from the trans-repression of TLR4 and the modulation of NLRP3 inflammasome assembly [203]. Moreover, oxidative stress and other contributing factors further underscore FXR's connections with AMPK, SIRT6, and NRF2 [204-206]. Hence, delving into the intricate interactions between FXR and other pathways holds paramount importance in surmounting the therapeutic challenges surrounding FXR and devising more effective treatments for liver fibrosis.

3.2.6. Interactions between FXR and other molecular targets

As a nuclear receptor, RXR typically forms heterodimers with other nuclear receptors, such as FXR/RXR, LXR/RXR, and PPAR/RXR, thereby orchestrating the expression of downstream target genes [207]. This underscores FXR's capacity to interact with other receptors or signaling pathways within physiological contexts. Our previous research revealed that FXR knockdown leads to a downregulation of PPARα and

LXRα expression, subsequently fostering SREBP1 expression and lipid accumulation [112]. In the realm of maintaining liver energy metabolism homeostasis, PPARα and FXR work synergistically to curb lipid production [208]. Therapies targeting PPARα and FXR agonists have been employed for the treatment of NAFLD [209]. Diverging slightly from the role of PPARα, FXR and PPARγ exert counterregulatory functions on HSCs, thereby hindering the progression of liver fibrosis in rodent models. To elucidate, transdifferentiation of HSCs involves the inhibition of PPARγ mRNA expression, while FXR ligand treatment augments PPARγ expression and suppresses type I collagen accumulation induced by TGFβ, amplifying the antifibrotic potential of PPARγ [210]. Furthermore, the heterodimer formed by FXR and RXR binding enhances FXR's ligand-binding capability, with this effect being linked to the augmentation of RXRα ligands [211]. Correspondingly, Jenniskens et al. demonstrated that FXR/RXR heterodimers effectively curtail bile acid synthetic feedback, thus mitigating intrahepatic cholestasis and ameliorating liver fibrosis-related symptoms [212]. Additionally, chenodeoxycholic acid can bolster GLP-1 production and secretion in enteral endocrine cells by simultaneously activating TGR5 and inhibiting FXRs. This interplay leads to improved glucose homeostasis, indicating a prospective anti-hepatic fibrosis effect [213]. Notably, FXR and TGR5 not only harmonize in regulating bile acids but also contribute to microbiota regulation [172]. Consequently, the FXR/TGR5 dual receptor agonist INT-767 has been employed for conditions linked to glucose-lipid metabolism imbalances [214]. While the synergistic interplay between FXR and other factors or ligands holds promise for metabolic disease treatment, it simultaneously poses challenges in developing highly selective FXR modulators.

4. Clinical significance of FXR regulators in liver fibrosis

Currently, several FXR regulators are being investigated for the treatment of chronic liver diseases in clinical research stages, offering valuable insights for clinical approaches to liver fibrosis treatment. For instance, OCA, an FXR agonist developed by Intercept, shows promise in treating various liver conditions and may enhance survival rates [24]. Specifically, a phase 3 randomized, double-blind, multicenter, placebo-controlled international trial focused on NASH without cirrhosis patients revealed that OCA significantly alleviates fibrosis in NASH patients [215]. However, patients treated with OCA experienced pruritus and impaired quality of life [215, 216]. Furthermore, a randomized controlled trial demonstrated that OCA treatment during liver disease management led to elevated cholesterol

levels, correlated with an increase in small and large LDL particles, as well as a decrease in HDL particles at week 12, which improved after discontinuation of the drug for 24 weeks [216]. In response, Pockros et al. proposed combining OCA and atorvastatin. In this approach, patients took atorvastatin (10 mg/day) after four weeks of OCA administration. The results showed that atorvastatin reduced LDLc and LDLpc levels induced by OCA by week 8, indicating that this combination is well tolerated and generally safe [217]. Similarly, EDP-305, an oral synthetic FXR agonist, underwent double-blind phase II research on fibrotic NASH patients (without cirrhosis). Patients were randomly assigned to receive EDP-305 or placebo for 12 weeks. The findings demonstrated that EDP-305 decreases liver fat content and serum ALT levels, supporting the need for longer trials assessing histological endpoints in NASH. Notably, adverse events, including pruritus, vomiting, nausea, diarrhea, dizziness, and headache, were reported by patients (≥5%) [152].

Other FXR agonists in phase II clinical trials include tropifexor, vonafexor, and cilofexor. Initially, the safety, tolerability, and pharmacokinetics of tropifexor were evaluated in healthy volunteers, indicating its acceptability in terms of safety and tolerability, with minimal pruritus and transient increases in serum ALT [218]. Subsequent studies by Camilleri et al. found that a once-daily dose of 60 μg tropifexor was well tolerated and safe [219]. However, recent clinical data evaluating the efficacy and safety of tropifexor in NASH patients over 48 weeks revealed that tropifexor could inhibit ALT and HFF up to week 48, but it did not improve AST at week 12. Additionally, patients randomized to receive tropifexor frequently reported dose-related pruritus, aligning with observations from previous FXR agonist trials [220]. Compared to tropifexor monotherapy, the safety profile of tropifexor combined with CVC demonstrated a similar trend, with no new safety signals or deaths and notably lower rates of adverse events such as itching, nausea, and fatigue [221]. It is important to note that this study did not display a synergistic effect on ALT, weight, or histological endpoints, but the possibility of such an effect in other combinations should not be ruled out.

Similarly, Vonafexor led to decreased HBV surface antigen levels in CHB within a few weeks of administration and demonstrated certain safety [153]. Recent research also found that vonafexor was safe and had the potential to suppress liver fat production, improve liver enzymes, and inhibit weight loss while causing a certain percentage of generalized pruritus [222]. Meanwhile, although cilofexor showed little significant difference in its effects compared to placebo on NASH-induced advanced fibrosis (F3-F4) patients, the proportion of patients experiencing pruritus induced by cilofexor was higher than that of placebo. However, combining cilofexor with firsocostat effectively alleviated steatosis and inflammation and lowered ALT, AST, and TBIL, thus improving the fibrosis score (≤F2) [223]. The latest study revealed that the FXR agonist HPG1860 displayed promising antifibrotic effects in clinical treatment for NASH, with reduced pruritus, and the notable finding was that there was no significant elevation of LDL-C within 16 weeks [224]. Other FXR regulators undergoing clinical trials, as listed on *ClinicalTrials.gov* (https://clinicaltrials.gov/), are outlined in Table 2.

Hence, combining drugs and restructuring FXR agonists may provide avenues to overcome challenges in translating FXR research into clinical practice. However, the development of clinical FXR agonists encompasses various etiologies of liver fibrosis, necessitating consideration of both their efficacy and side effects [130].

Table 2. Summary of partial FXR ligands entering clinical trials in liver disease.

Type	Ingredients	Study	Conditions	Status
Agonists	OCA	Phase 2 Study on Lipoprotein Metabolism	Primary Biliary Cirrhosis	Completed
Agonists	OCA	Evaluation of Pharmacokinetics and Safety	Liver Cirrhosis	Terminated
Agonists	Tropifexor (LJN452)	Safety and Tolerability.	Liver Disease	Completed
Agonists	Tropifexor (LJN452)	Study of Safety, Tolerability, and Efficacy of a Combination Treatment of LJN452 and CVC	NASH and liver fibrosis	Completed
Agonists	Tropifexor (LJN452)	Evaluation of the Pharmacokinetics	NAFLD	Completed
Agonists	EYP001a	Food Effect Study in Subjects	Hepatitis B, Chronic	Completed
Agonists	EYP001a	Safety, Tolerability, Pharmacokinetics and Pharmacodynamics	NASH	Completed
Agonists	ASC41	Evaluate the Safety, Tolerability, and Efficacy	NAFLD and NASH	Recruiting
Agonists	ASC41	Evaluate the Safety and Efficacy	Obesity and NAFLD	Completed
Agonists	EYP001a	Safety, Tolerability, Pharmacokinetics and Pharmacodynamics	NASH	Completed

Agonists	EYP001a	Evaluation of the Safety and Pharmacology	Hepatitis B, Chronic	Completed
Agonists	Px-104	Safety Pilot Study	NAFLD	Completed
Agonists	TQA3526	Study in the Treatment	Primary Biliary Cirrhosis	Unknown
Agonists	MET409	Study to Evaluate Alone or Combination	NASH	Active, not recruiting
Agonists	TERN-501	Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics	NASH	Recruiting
Agonists	TERN-101	Safety, Tolerability, Efficacy, and Pharmacokinetics Study	NASH	Completed
Agonists	BAR502	Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics	NAFLD	Not yet recruiting
Antagonist	Guggulsterone	Role in Hepatitis C Virus Replication	Chronic Hepatitis C	Terminated

5. Concluding Remarks and Future Perspectives

While targeting FXR for the treatment of liver fibrosis encompasses various aspects, its application requires careful selection due to potential concerns. Doubts still exist concerning the research on FXR ligand drugs. For instance, certain studies have questioned whether the timing of FXR agonist administration aligns with the clinical context, yielding less than satisfactory results [152]. Notably, FXR agonist administration is in part aimed at preventing the onset of liver fibrosis. However, findings from clinical trials indicate that liver fibrosis symptoms may have already manifested at the time of treatment initiation, necessitating attention [225]. The efficacy of FXR in regulating hepatic fibrosis is acknowledged, but its underlying mechanism warrants further exploration and refinement.

Furthermore, the potential side effects stemming from FXR activation raise concerns. Pruritus and dyslipidemia are recognized side effects that cannot be entirely circumvented. Current research endeavors seek to mitigate these issues by reducing dosages for symptomatic relief and exploring combinations with other drugs such as statins, CCR2 inhibitors, and ACC inhibitors to mitigate side effects [226]. Despite pruritus-related challenges, OCA has gained FDA approval as a treatment for NASH, with side effects managed through statin use and pruritus-alleviating medications [227]. Presently, the development of clinical drugs targeting FXR ligands primarily focuses on continuous structural optimization, aiming to alleviate side effects, akin to searching for a needle in a haystack. Encouragingly, there have been promising outcomes. Harrison et al. identified MET409, a structurally optimized compound, in clinical trials. MET409 reduces fat content in NASH patients with mild side effects, offering hope in terms of structural optimization of FXR regulators [228].

Although the study of side effects progresses at a relatively gradual pace, it is understandable due to the inherent difficulty in finding suitable models that accurately mimic human responses to side effects [229].

Another reason behind FXR's significance lies in its multifaceted potential for therapeutic applications, which could extend beyond liver fibrosis treatment.

Declaration of interests

The authors declare that there is no competition of interest.

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