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HARNESSING FARNESOID X RECEPTOR (FXR) ACTIVATION FOR LIVER PROTECTION: INSIGHTS FROM SYNTHETIC COMPOUNDS AND PLANT-DERIVED LIGANDS

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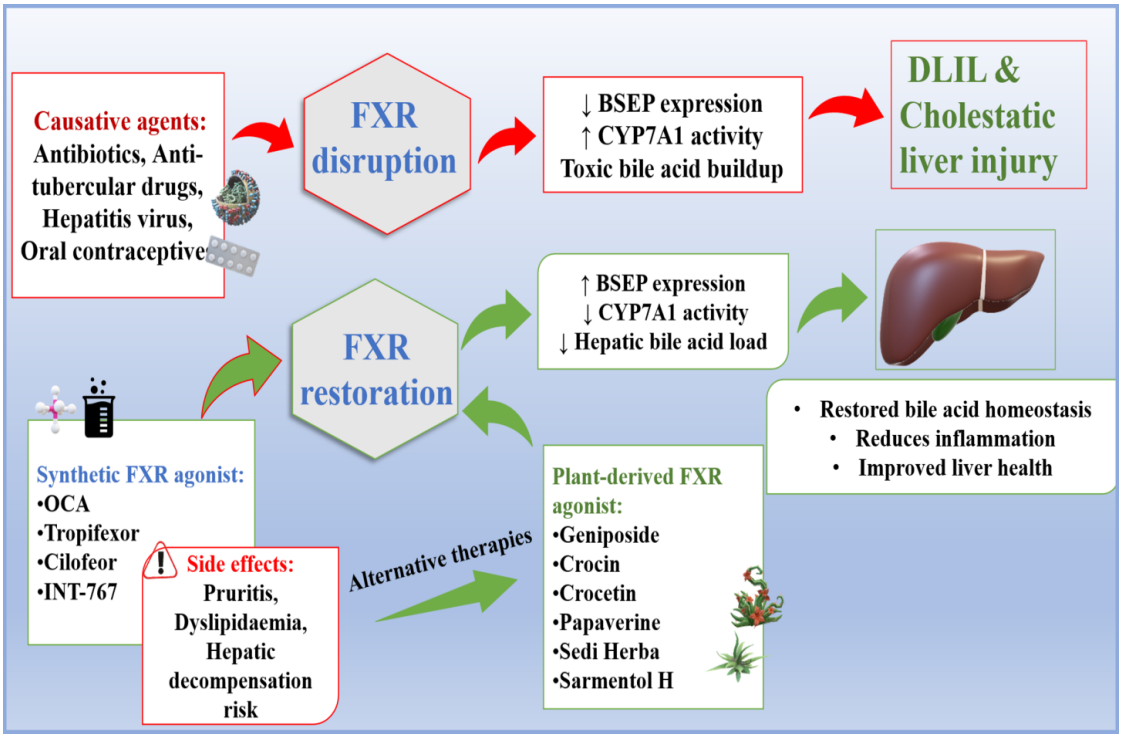
ABSTRACT

This review critically explores the therapeutic potential of both synthetic and phytochemical-based Farnesoid X Receptor (FXR) agonists in managing drug-induced liver injury (DILI) and cholestatic liver diseases. It compiles evidence from preclinical and clinical studies on synthetic agents such as obeticholic acid, tropifexor, cilofexor, INT-767, and fluorofenidone, alongside plant-derived modulators including Papaverine, 7,8-dihydroxy-4-methyl coumarin (DMC), Sarmentol H, *Gardenia jasminoides* extract, and Saffron constituents. These agents act through modulation of bile acid metabolism, FXR activation, and attenuation of inflammation and fibrosis. While synthetic FXR agonists are effective, they are often limited by adverse effects such as pruritus and dyslipidaemia. Conversely, phytochemical modulators offer anti-inflammatory, antioxidative, and hepatoprotective benefits, though concerns such as paradoxical hepatotoxicity, evident with Epimedii folium, highlight the need for cautious validation. Collectively, these insights support the growing potential of phytochemicals as viable FXR-targeted interventions, while emphasizing the importance of rigorous pharmacological profiling and clinical validation to ensure safe and effective therapeutic use.

KEYWORDS: Farnesoid X Receptor (FXR), Cholestasis, DILI, Synthetic FXR agonist, Phytochemical FXR modulators, Hepatoprotection.



INTRODUCTION

Hepatotoxicity remains a major contributor to acute liver failure (ALF), accounting for approximately 32% of all drug withdrawals between 1975 and 2007 in Western countries.[1] Among the various forms of hepatotoxicity, drug-induced liver injury (DILI) and herbal and dietary supplement-induced liver injury (HILI) represent growing concerns in clinical hepatology and drug safety assessment. DILI refers to liver damage resulting from therapeutic drug exposure, characterized by hepatocellular, cholestatic, or mixed patterns of injury. The liver's pivotal role in metabolizing xenobiotics makes it especially susceptible to these adverse effects.[2]

DILI has been typically classified into intrinsic and idiosyncratic. Intrinsic DILI, such as that caused by acetaminophen overdose, occurs in a predictable, dose-related manner, whereas idiosyncratic DILI (iDILI) is rare, unpredictable, and not directly related to dose. It often arises from the complex interplay between drug properties, host susceptibility, and environmental factors.[3] Several key factors have been identified, among which elevated daily dose and hepatic metabolism via cytochrome P450 (CYP450) enzymes are prominent. A study analysing 254 orally administered drugs demonstrated that compounds metabolized by CYP450 enzymes are more likely to be associated with DILI. Furthermore, it was observed that CYP450 inhibitors increase DILI risk predominantly at higher doses, whereas CYP450 inducers did not show a significant correlation with DILI incidence.[4]

Clinically, DILI is classified into hepatocellular, cholestatic, and mixed injury patterns, based on serum transaminases, alkaline phosphatase (ALP), and bilirubin levels, and quantified using R-value. Marked elevations in ALT and AST characterize hepatocellular injury, while cholestatic injury is associated with raised ALP, γ-GT, and bilirubin levels. Mixed injury displays features of both. The R-value (ALT/ULN: ALP/ULN) helps classify injury types: Hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), and mixed ($2 \leq R \leq 5$).[5]

Cholestatic liver injury is a serious condition characterized by disrupted bile flow, leading to hepatocellular damage, inflammation, and progression to fibrosis. Clinically, it is often associated with elevated levels of liver function markers, including ALT, AST, ALP, γ-GT, TBA (total bile acid), and TBIL (total bilirubin).[6] Current treatment strategies are limited to symptomatic management and withdrawal of causative agents, underscoring the need for target therapies.

In recent years, the Farnesoid X Receptor (FXR), a bile acid-activated nuclear receptor predominantly expressed in the liver and intestine, has gained recognition as a key therapeutic target for managing cholestatic and DILI. FXR orchestrates the regulation of genes involved in bile acid synthesis (such as CYP7A1), transport (including BSEP and OSTα/β), lipid metabolism, inflammation, and fibrosis. Its activation plays a critical role in re-establishing bile acid balance, mitigating hepatic inflammation, and safeguarding against liver damage.[7]

Synthetic FXR agonists such as obeticholic acid have demonstrated efficacy in clinical trials for primary biliary cholangitis and are under investigation for broader hepatobiliary indications. Their hepatoprotective effects in experimental models and cholestasis suggest a potential disease-modifying role in these conditions.[8]

However, concerns over adverse effects and cost have accelerated interest in plant-derived FXR modulators. Natural products and phytochemicals with FXR-activating properties offer a safer, accessible, and structurally diverse alternative to synthetic ligands. These agents have demonstrated hepatoprotective effects in preclinical models of liver injury, including modulation of FXR signalling, antioxidant defense, and bile acid detoxification.

This review comprehensively analyses FXR agonists, encompassing both synthetic and plant-derived ligands. It examines their molecular mechanisms, therapeutic relevance in drug-

induced and cholestatic liver injury, preclinical and clinical evidence, associated challenges such as adverse effects, pharmacokinetics, enhancing clinical efficacy, and facilitating the translation of both synthetic and phytochemical FXR modulators. Emerging phytochemical agonists are highlighted as complementary or alternative strategies alongside synthetic agents to improve therapeutic outcomes in liver disease management.

Molecular basis of cholestatic dili

The development of drug-induced cholestasis (DIC) is characterized by intricate alterations in hepatic bile acid transport mechanisms and bile acid homeostasis. In normal hepatocytes, the uptake of physiological substances and xenobiotics from the portal bloodstream is predominantly facilitated by organic anion transporting polypeptides (OATPs). However, certain pharmaceuticals or their metabolites may inhibit these transporters, impairing bile acid elimination and causing intracellular accumulation, which can ultimately result in hepatocellular damage.

Canalicular excretion of bile acids into bile is driven by ATP-dependent transporters belonging to the multidrug resistance (MDR) and multidrug resistance-associated proteins (MRP) families, notably MDR1 (ABCB1), MDR3 (ABCB4), MRP2 (ABCC2), and the bile salt export pump (BSEP/ABCB11). Of these, BSEP is the principal transporter for bile acids. Pharmacological inhibition of BSEP by agents such as oral contraceptives, macrolide antibiotics, or psychotropic drugs can lead to bile acid retention and cholestasis, particularly in genetically predisposed individuals. For instance, variants in BSEP or MDR3 genes can increase the risk of cholestatic liver injury up to threefold.

Additional pathogenic mechanisms include cytoskeletal disruption, impaired vesicular trafficking, tight junction disintegration, and inhibition of ATPase activity, all of which compromise bile acid transport and hepatocyte integrity.[9]

The FXR serves as a key molecular regulator, acting as a bile acid sensor that controls their synthesis, transport, and detoxification. In cholestatic conditions, downregulation or impaired activation of FXR exacerbates hepatocellular injury by decreasing the expression of protective genes such as BSEP, SHP, and OSTα/β, while permitting unchecked bile acid synthesis via CYP7A1. Thus, FXR dysfunction contributes to the pathophysiological cascade in drug-induced cholestasis and represents a potential therapeutic target to restore bile acid homeostasis and hepatocellular function.[10]

Risk factors for cholestatic dili[9]

1. Chemical properties of drugs

Physiochemical properties significantly influence a drug's potential to cause liver injury, in addition to its pharmacological effects and potency. Lipophilicity, in particular, plays a critical role by affecting drug uptake and metabolism. Drugs exhibiting high lipophilicity (Log*P* ≥ 3) and prescribed at a daily dose of ≥ 100 mg exhibit a notable increased risk of DILI.

Additionally, drug-related factors that may influence susceptibility to DILI include the formation of reactive metabolites, mitochondrial toxicity, and inhibition of hepatic transporters. While reactive metabolites are typically associated with hepatotoxicity, drugs lacking known reactive metabolites, such as ambrisentan, flecainide, maraviroc, and bosentan, can still cause severe liver injury, as evidenced by their black box warnings for hepatotoxicity.

2. Age

Age influences the clinical presentation and susceptibility to DILI. Younger individuals predominantly exhibit hepatocellular injury, whereas cholestatic injury is more prevalent among older patients. One study reported that 61% of DILI cases in patients over 60 years were cholestatic compared to 39% in younger patients. Mixed injury patterns also occurred more frequently in older populations. The exact mechanisms underlying age-related susceptibility remain unclear but may involve reduced hepatocellular transporter expression or altered hepatic drug handling in older individuals.

3. Underlying liver disease

The role of preexisting liver conditions as risk factors for DILI remains uncertain. However, lower peak ALT and ALP elevations during DILI episodes have been observed in patients with underlying liver conditions such as chronic hepatitis C or non-alcoholic fatty liver disease. Certain liver conditions specifically increase susceptibility to cholestatic liver injury; for example, individuals with a history of intrahepatic cholestasis of pregnancy exhibit increased vulnerability to cholestatic injury from oral contraceptives or hormone replacement therapies. Additionally, rifampicin has shown a higher incidence of hepatotoxicity among patients with primary biliary cirrhosis. Nonetheless, multiple episodes of DILI in the same patient due to different drugs remain rare, occurring in only 1.2% of cases according to the Spanish Hepatotoxicity Registry.

4. Genetic determinants

Genetic factors significantly contribute to cholestatic DILI susceptibility, with specific human leukocyte antigen (HLA) haplotypes playing pivotal roles. For example, amoxicillin/clavulanate-induced cholestatic DILI, a commonly reported form of DILI, is linked to HLA haplotypes such as haplotypes HLA B1*1501-DRB5 0101-DQB10602, present in 57% of affected patients versus 12% of unaffected users. Additionally, significant associations have been identified with HLA DRB1*15 and HLADQB1*06 alleles, and an inverse association with DRB1*07 and DQB1*02 alleles.

Similarly, flucloxacillin-induced DILI has been strongly associated with the HLA-B*5701 allele, showing an odds ratio of 80.6. Moreover, an increased susceptibility to cholestatic liver injury due to oral contraceptives has been linked to the T-to-C polymorphism in the BSEP 1331 gene.[9] These genetic insights underscore the complex interplay between pharmacogenetics and clinical outcomes in cholestatic DILI, emphasizing the need for personalized therapeutic approaches and risk assessment.[9]

FXR: A master regulator of hepatic homeostasis

The FXR, often referred to as the "bile acid receptor," is a ligand-activated transcription factor belonging to the nuclear receptor superfamily. It plays a pivotal role in maintaining hepatic and intestinal homeostasis. FXR regulates bile acid synthesis, conjugation, transport, and detoxification, and its activation initiates a cascade of metabolic and anti-inflammatory responses. Beyond bile acid homeostasis, FXR also influences lipoprotein and glucose metabolism, hepatic regeneration, intestinal microbiota balance, and reactions to hepatotoxic insults. While the human and murine *FXRα* gene gives rise to multiple isoforms through alternative promoter usage and splicing, therapeutic research largely focuses on its functional capacity as a master regulator in hepatobiliary physiology and pathology.[11,12] The FXR, a member of the nuclear hormone receptor superfamily, operates as a ligand-activated transcription factor. Structurally, FXR comprises a DNA-binding domain (DBD), a ligand-binding domain (LBD), and activation function domains (AF-1 and AF-2). Upon activation by endogenous ligands, predominantly bile acids such as chenodeoxycholic acid (CDCA), FXR forms a heterodimer with the retinoid X receptor (RXR). This complex subsequently binds to specific FXR response elements (FXEs) within the promoters of target genes, thereby modulating their transcriptional activity.[13] FXR expression is highly tissue-specific, with the liver and ileum exhibiting the greatest levels. In hepatic tissue, FXR activation

suppresses bile acid synthesis by downregulating CYP7A1, the rate-limiting enzyme of the classical bile acid biosynthetic pathway. Concurrently, it upregulates genes responsible for bile acid transport and excretion, including BSEP, OSTα/OSTβ, and MRP2.[14] Upon activation in intestinal tissues, FXR induces the synthesis of fibroblast growth factor 19 (FGF19 in humans; FGF15 in mice), which circulates back to the liver and inhibits CYP7A1 expression, thereby completing a crucial feedback loop that regulates bile acid synthesis and maintains enterohepatic homeostasis.[15] Beyond bile acid regulation, FXR influences lipid and glucose metabolism. It downregulates lipogenesis by suppressing *SREBP-1c* and upregulates fatty acid oxidation through the induction of *PPARα*. FXR also reduces hepatic gluconeogenesis and improves insulin sensitivity, positioning it as a therapeutic target in diseases associated with metabolic dysfunction like non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus.[16]

Plant-derived fxr agonist

In recent years, increasing attention has been directed towards plant-derived and phytochemical-based FXR agonists as promising alternatives to synthetic compounds. These natural agents are increasingly recognized for their favourable safety profiles, accessibility, and structural diversity shaped by evolutionary processes. Phytochemicals often exhibit superior tolerability and lower toxicity, which are critical advantages in the management of chronic liver disorders. Moreover, their affordability, widespread availability, and historical use in traditional medicine further underscore their potential in the treatment of drug-induced and cholestatic liver injury.

1. Papaverine

Papaverine, a plant-derived isoquinoline alkaloid, has demonstrated hepatoprotective effects as an FXR agonist in alpha-naphthylisothiocyanate (ANIT)-induced cholestasis models. In a study by Atshan and Zalzala (2024), Wistar rats were assigned to control, ANIT-induced, and Papaverine-treated groups (200mg/kg for 7 days before 100 mg/kg ANIT). Papaverine markedly improved liver function by normalizing serum biomarkers (ALT, AST, ALP, GGT, bile acids), enhancing antioxidant defences (SOD, GSH) reducing lipid peroxidation (MDA) and suppressing inflammatory cytokines (TNF--α, IL-1β). Mechanistically, papaverine upregulated FXR and Nrf2 pathways and restored expression of bile acid transporters (BSEP, SHP). Histopathological analysis further confirmed amelioration of liver injury.

These findings highlight Papaverine's multifactorial protective role via FXR activation, antioxidant restoration, and anti-inflammatory action, positioning it as a promising candidate for managing cholestatic liver diseases.[17]

2. 7, 8-DIHYDROXY-4-METHYL COUMARIN (DMC)

DMC has emerged as a promising FXR agonist with therapeutic potential in cholestatic liver diseases. By modulating bile acid synthesis and transport, DMC activates FXR to suppress CYP7A1 expression and enhance efflux transporter activity, thereby restoring bile acid homeostasis.

Molecular docking confirmed its strong affinity for the FXR ligand binding domain. In vitro studies using HepaRG cells showed that DMC significantly reduced cholestatic markers (ALT, AST, ALP) and improved bile acid transport. *In vivo*, DMC attenuated ANIT-induced cholestasis in mice, reducing bile accumulation, hepatocellular necrosis, and liver enlargement. Histological analysis confirmed restoration of hepatic architecture, while western blotting demonstrated upregulation of FXR and downregulation of bile acid synthesis enzymes.

These findings position DMC as a potent, dose-dependent FXR agonist with superior efficacy and mechanistic clarity, offering a novel avenue for targeted intervention in cholestatic liver disorders.[18]

3. Sedi herba (Sedum sarmentosum) and Sarmentol h

Sedi Herba, derived from Sedum sarmentosum, has shown promising hepatoprotective effects in cholestasis through its activation of FXR. In an ANIT-induced rat model, the ethyl acetate extract (SDEAE) significantly improved liver function markers (ALT, AST, ALP) and improved bile acid profiles. SDEAE upregulated FXR and its downstream target genes such as SHP, BSEP, and UGT2B4, while suppressing CYP7A1 and NTCP, enhancing bile acid metabolism and transport. Screening of 23 compounds identified Sarmentol H as the strongest FXR activator, with further validation through molecular docking and FXR-knockdown cell studies confirming its potent FXR-mediated effects.[19]

Similarly, Sarmentol H, a nor-sesquiterpenoid isolated from *S. sarmentosum Bunge*, was shown to target FXR in ANIT-induced cholestasis directly. It significantly reduced liver damage markers (ALT, AST, ALP) and improved liver histopathology, including reduced

inflammation and bile duct damage. Mechanistic studies demonstrated its high binding affinity to the FXR-ligand binding domain (KD = 2.55 μmol/L), as confirmed by CETSA, ITC, and DARTS assays, and recruits the coactivator SRC1, and activates key FXR signalling pathways, such as BSEP, SHP, and UGT2B4, while downregulating CYP7A1 and NTCP to restore bile acid homeostasis. In FXR knockdown mice, these therapeutic effects were abolished, confirming its FXR-dependent mechanism. Compared to UDCA, it demonstrated superior efficacy in alleviating liver damage and bile acid accumulation, making it a promising natural FXR agonist for cholestatic liver diseases.[20]

Both Sedi Herba and Sarmentol H illustrate the therapeutic potential of the Sedum sarmentosum species in targeting FXR to regulate bile acid metabolism, mitigate liver damage, and offer an alternative to conventional bile acid-based therapies.

4. Jiagasongtang (Jgst)

JGST, a traditional Tibetan formulation, demonstrates hepatoprotective effects in chronic cholestasis via FXR-mediated bile acid regulation. In an ANIT-induced mouse model, JGST significantly lowered liver injury markers (ALT, AST, ALP), improved histopathological outcomes (reduced necrosis, inflammation, and fibrosis), and enhanced bile acid detoxification.

JGST upregulated FXR and its efflux transporters (BSEP, MRP2), while suppressing uptake transporters (NTCP, ASBT), promoting BA excretion and reducing toxic BA accumulation, including deoxycholic acid. Faecal analysis supported enhanced BA elimination. The primary active compound, 6-gingerol, was identified as a direct FXR agonist through docking, SPR, and luciferase assays. *In vitro*, 6-gingerol mitigated BA-induced hepatic and intestinal damage, reduced fibrosis, and restored epithelial integrity.

The therapeutic efficacy of JGST and 6-gingerol was abolished by FXR inhibition, confirming an FXR-dependent mechanism. These findings underscore JGST and 6-gingerol as promising candidates for managing cholestatic liver diseases via modulation of FXR pathways.[21]

Non-Classical fxr pathways: Role of phytochemicals

While not classical FXR agonists, certain plant-derived agents exert therapeutic benefits in cholestatic liver disorders by indirectly modulating FXR expression and related signalling

pathways. Through enhancement of bile acid metabolism and restoration of enterohepatic circulation, these compounds offer mechanistic complementarity to direct FXR-targeted therapies.

1. *Gardeniae jasminoides* extract (GE)

Gardeniae jasminoides extract (GE), rich in iridoid glycosides such as geniposide, has shown promising hepatoprotective effects in intrahepatic cholestasis. In an ANIT-induced rat model, GE administration (21 and 42 mg/kg) significantly reduced liver injury markers, including TBA, TBIL, DBIL, ALP, and GGT, in a dose-dependent manner. Histopathological analysis revealed reduced bile duct proliferation and inflammatory infiltration.

Bile acid profiling demonstrated that GE modulated the composition and distribution and bile acids across hepatic, systemic, and faecal compartments. It decreased hepatotoxic taurine-conjugated bile acids and restored glycine-conjugated and unconjugated bile acids. GE also promoted faecal excretion of bile acids while reducing urinary loss, thereby enhancing enterohepatic circulation.

Mechanistically, GE upregulated key genes related to bile acid biosynthesis (CYP7A1, CYP8B1, CYP27A1) and transport (FXR, OATP1), as confirmed by transcriptomic and qRT-PCR analysis. Compared to obeticholic acid, GE exhibited comparable efficacy in restoring bile acid homeostasis. These findings underscore the therapeutic potential of *Gardenia jasminoides* extract as a multi-target natural agent for managing intrahepatic cholestasis. By modulating bile acid metabolism and circulation, GE offers a holistic approach to restoring bile acid homeostasis, showing comparable efficacy to obeticholic acid.[22]

2. Saffron

Recent studies have underscored the hepatoprotective potential of saffron, particularly its bioactive constituents, Crocin and Crocetin. These compounds exert a multifaceted mechanism of action, primarily through the inhibition of ERK phosphorylation, a crucial pathway in bile acid-induced hepatotoxicity. In both *In vivo* (bile duct ligation model) and *In vitro* (HepaRG cell line) studies, Crocin and Crocetin demonstrated significant hepatoprotective effects by downregulating CYP7A1, a key enzyme in bile acid synthesis, while upregulating PPARα, which negatively regulated CYP7A1 transcription. Furthermore, these compounds enhanced the expression of bile acid efflux transporters Mrp3 and Mrp4, promoting bile acid excretion and alleviating intrahepatic bile acid accumulation.

Consequently, these actions led to a marked reduction in liver injury, inflammation (IL-1β, IL-6, TNF-α), and fibrosis markers (Col-I, Col-III). Notably, the therapeutic effects of Crocin and Crocetin were reversed upon the administration of the ERK agonist Ro 67–7476, confirming ERK as the critical target of Saffron's action. These findings suggest Saffron as a promising multi-target phototherapeutic for the management of cholestasis-induced liver disorders.[6]

Epimedii Folium (EF): A paradox in fxr modulation

While FXR activation is generally hepatoprotective, certain phytochemicals may paradoxically disrupt bile acid (BA) homeostasis and contribute to cholestasis. Epimedii Folium (EF), traditionally used in Chinese medicine for bone and endocrine health, has recently been implicated in herb-induced liver injury (HILI). In a 14-week oral toxicity study, water extract of EF(WEF) administered at 5x and 15x clinical doses resulted in dose-dependent liver injury in mice, evidenced by elevated ALT, ALP, and DBIL levels, along with histological findings of hepatocyte necrosis, steatosis, and periportal fibrosis.

Mechanistic investigations revealed that WEF significantly altered BA transport by upregulating NTCP (enhancing hepatic BA uptake) while downregulating key efflux transporters such as BSEP, MDR1, MRP2, and MRP3, thus impairing BA clearance and causing intrahepatic accumulation. Interestingly, although FXR expression was upregulated, presumably as a compensatory response, its downstream targets (BSEP, CYP8B1) were suppressed, indicating disrupted FXR signalling. This uncoupling suggests that EF may disrupt the FXR signalling, possibly due to bile acid overload or interference with transcriptional regulation.

Phytochemical analysis identified flavonoid glycosides A/B, baohuoside I, and 2"-O-rhamnosylicariside II as candidate hepatotoxic constituents. These compounds have demonstrated oxidative and pro-apoptotic effects in preclinical models. Taken together, EF-induced cholestasis appears multifactorial, arising from transporter dysfunction, FXR pathway disruption, and possible phytochemical toxicity, underscoring the need for critical evaluation of herbal agents modulating the FXR-BA axis in the context of DILI.[23]

Synthetic fxr agonist: Clinical Applications and Challenges

The therapeutic landscape for chronic liver diseases has seen significant advancements with the development of FXR agonists, including Obeticholic acid (OCA), Tropifexor,

Fexaramine (Efx-7), Cilofexor (GS-9674), and INT-767. Each agent exhibits distinct pharmacodynamic properties, clinical utilities, and safety considerations.

1. Obeticholic acid (OCA)

OCA, a semisynthetic bile acid derivative, is the first FXR agonist approved for second-line primary biliary cholangitis (PBC) treatment in patients refractory to UDCA therapy.[23] Mechanistically, application is frequently complicated by pruritic and dyslipidaemia, particularly elevations in low-density lipoprotein cholesterol. Despite demonstrated efficacy in biochemical and histological improvements, concerns regarding hepatic decompensation in patients with advanced cirrhosis have restricted its broader use.[25]

2. Tropifexor

Tropifexor, a potent non-bile acid FXR agonist developed by Novartis, has demonstrated marked improvements in liver steatosis and cholestatic parameters in non-alcoholic steatohepatitis (NASH) and PBC populations. Nevertheless, dose-dependent pruritus remains a major adverse event, driving exploration of optimized dosing strategies and combination therapies to mitigate this limitation.[26,27]

3. Celofexor (GS-9674)

Celofexor is another non-steroidal FXR agonist developed for NASH and PSC. Clinical and animal studies show, it lowers liver fat and fibrosis biomarkers, similarly to Tropifexor. In a PSC trial, it also produced modest alkaline phosphatase reductions. Like other FXR agonists, Cilofexor use was associated with pruritic and slight LCL elevations.[28,29]

4. INT-767

Preclinical studies have demonstrated that INT-767, a dual agonist of the FXR and bile acid receptor TGRS (Takeda G-protein-coupled receptor 5), can effectively reduce liver steatosis, inflammation, and fibrosis in a rat model of NASH and cholestatic liver disease, highlighting its therapeutic potential. However, its clinical application remains limited, as it has not yet advanced beyond early-phase investigations. Further clinical trials are needed to establish its safety, efficacy, and long-term outcomes in human populations.[30]

5. Fluorofenidone (AKF-PD)

Fluorofenidone (AKF-PD), a novel pyridine-based anti-fibrotic agent, has demonstrated promising hepatoprotective activity in cholestasis-associated liver injury. In the DDC-

induced mouse model of intrahepatic cholestasis and fibrosis, AKF-PD significantly attenuated liver injury by lowering serum ALT, AST, ALP, and total bile acids, while improving histopathological features such as bile duct proliferation, inflammation, and fibrosis. Mechanistic investigations revealed that AKF-PD downregulated key bile acid synthesis enzymes (CYP7A1, CYP27A1) and upregulated detoxification-related genes (UGT1A1, CYP2B10, SULT2A1/2), enhancing bile acid clearance. Notably, it promoted FXR nuclear translocation, suggesting a potential FXR agonist-like effect contributing to improved bile acid homeostasis. Additionally, AFK-PD potently inhibited the ERK/Ege-1 signalling cascade, reducing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CCL2, CCL5, CXCL10), and hepatic macrophage infiltration. Its anti-fibrotic activity was further supported by suppression of the TGF-β1/Smad axis, leading to downregulation of fibrogenic markers (α-SMA, COL1A1, MMP2/9) and prevention of epithelial-mesenchymal transition (EMT). Overall, these findings highlight AKF-PD as a multi-target therapeutic candidate with the potential to address both the inflammation and fibrotic components of cholestatic liver disease, offering hope for a more effective treatment approach.[31]

CONCLUSION AND FUTURE PERSPECTIVES

Despite significant progress, DILI and cholestasis remain formidable clinical challenges, driven by complex pathogenic mechanisms and heterogeneous clinical presentations. The FXR, a master regulator of bile acid metabolism, has emerged as a pivotal therapeutic target in these disorders. Among FXR-targeted therapies, synthetic agonists such as OCA have demonstrated clinical benefits in improving cholestasis, reducing hepatic inflammation, and attenuating fibrosis. However, their broader adoption is tempered by limitations, including pruritic, dyslipidaemia, high treatment costs, and concerns regarding hepatic safety in advanced disease.

While synthetic FXR agonists like tropifexor, cilofexor, and INT-767 continue to hold therapeutic promise, their adverse event profiles necessitate careful dose optimization, patient selection, and exploration of combination strategies to maximize efficacy while minimizing toxicity. Importantly, the incomplete therapeutic window offered by current FXR modulators underscores the need for complementary or alternative strategies.

In this context, natural compounds and phytochemical-based FXR modulators are gaining increased attention. Agents such as Papaverine, DMC, Sarmentol H, JGST, and extracts from *Gardenia jasminoides* and Saffron have demonstrated hepatoprotective effects through

modulation of FXR signalling, along with anti-inflammatory, antioxidative, and antifibrotic properties. These findings suggest that plant-derived FXR modulators could serve either as adjunctive therapies to synthetic agonists or as safer alternatives in selected populations.

Nonetheless, challenges persist in translating these natural candidates to clinical application. Paradoxical hepatotoxicity, exemplified by Epimedium folium, highlights the critical need for rigorous preclinical toxicology studies, standardized extraction methods, and comprehensive pharmacological characterization. Furthermore, genetic susceptibility, drug interactions, and pre-existing liver disease must be accounted for to optimize safety and efficacy.

Looking ahead, future research should focus on robust structure-activity relationship investigations, advanced pharmacokinetic modelling, and well-designed clinical trials. Additionally, innovative drug delivery systems capable of enhancing tissue targeting and minimizing systemic side effects could substantially advance the field. Through a multipronged strategy encompassing synthetic innovations and phytochemical discoveries, FXR-targeted therapies have the potential to transform the management of cholestatic and metabolic liver diseases, ultimately leading to improved patient outcomes and quality of life.

Table I: Comparative Overview of Synthetic and Plant-based FXR agonists.

FXR Agonist	Source	Mechanism of Action	Target Conditions	Key Benefits	Limitations / Concerns
Obeticholic acid (OCA)	Synthetic	Potent FXR agonist; ↓ CYP7A1, ↑ BSEP, SHP	PBC, NASH	Clinically approved; improves fibrosis and bile acid regulation	Pruritus, ↑ LDL, risk in advanced cirrhosis
Tropifexor	Synthetic	Highly potent FXR agonist; ↓ liver fat, ↓ ALT	NASH, PBC (investigational)	Reduces liver enzymes and fat	Dose-dependent pruritus, under trial
Cilofexor (GS-9674)	Synthetic	FXR activation; ↓ ALP, ↑ FGF19	NASH, PSC	Mild side effect profile, ↓ liver fat	Modest efficacy, mild pruritus
INT-767	Synthetic	Dual FXR/TGR5 activation; ↓ fibrosis, ↓ inflammation	Preclinical (NASH, cholestasis)	Multifunctional; effective in models	Not yet advanced clinically

Papaverine	Phytochemical	Activates FXR and Nrf2; ↑ BSEP, ↓ TNF-α	Cholestasis (preclinical)	Antioxidant, anti-inflammatory	No clinical data yet
7,8-Dihydroxy-4-methyl coumarin (DMC)	Phytochemical	FXR activation; ↓ CYP7A1, ↑ Bile acid transporters	ANIT-induced cholestasis	FXR-selective, potent in vitro and in vivo	No toxicity or PK data yet
Sarmentol H	Phytochemical	High-affinity FXR agonist; recruits SRC1 coactivator	Cholestasis (preclinical)	Strong FXR binding, bile acid detox	Preclinical only
Gardenia jasminoides extract (GE)	Plant extract	Indirect FXR modulation; ↑ bile acid excretion	Intrahepatic cholestasis	Comparable to OCA in some models	Crude extract, complex composition
Saffron (Crocin/Crocetin)	Phytochemical	Modulates FXR and ERK; ↓ CYP7A1, ↑ MRP3/4	Cholestasis, inflammation	Multi-pathway effect, safe	No clinical FXR data
Fluorofenidone (AKF-PD)	Synthetic phytomimetic	FXR translocation; ↓ TGF-β1/Smad, ↓ bile acids	Fibrosis + cholestasis	Anti-inflammatory + anti-fibrotic	Investigational; no FXR selectivity confirmed

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Abbreviations used

Abbreviations	Full forms
FXR	Farnesoid X Receptor
DILI	Drug-Induced Liver Injury
CDCA	Chenodeoxycholic Acid
RXR	Retinoid X Receptor

FXREs	FXR Response Elements
CYP7A1	Cholesterol 7 alpha-hydroxylase
BSEP	Bile Salt Export Pump
OSTα/OSTβ	Organic Solute Transporter alpha and beta
MRP2	Multidrug Resistance-associated Protein 2
FGF19	Fibroblast Growth Factor 19
PBC	Primary Biliary Cholangitis
UDCA	Ursodeoxycholic Acid
OCA	Obeticholic Acid
NASH	Non-Alcoholic Steatohepatitis
LCL	Low-Density Lipoprotein Cholesterol
PSC	Primary Sclerosing Cholangitis
INT-767	FXR/TGR5 Dual Agonist
TGR5	Takeda G-protein-coupled Receptor 5
DMC	7,8-Dihydroxy-4-methyl Coumarin
JGST	JiaGaSongTang

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