

REVIEW ARTICLE

Bile Acid-Activated Receptors in Inflammatory Bowel Disease: Mechanisms, Dysregulation, and Therapeutic Potential

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ABSTRACT

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is characterized by immune dysregulation, epithelial barrier dysfunction, and gut microbiota imbalance. Beyond their classical role in lipid digestion, bile acids (BAs) are now recognized as key signaling molecules regulating immunity, metabolism, and epithelial integrity through nuclear and membrane receptors. Primary BAs synthesized from cholesterol in hepatocytes undergo microbial modification in the gut, forming a diverse BA pool with distinct signaling capacities. Receptors such as TGR5, farnesoid X receptor (FXR), pregnane X receptor (PXR), and vitamin D receptor (VDR) integrate BA signals to control BA synthesis, barrier homeostasis, and inflammatory responses. In IBD, disrupted receptor signaling—linked to dysbiosis, altered BA transport, and reduced secondary BA levels—exacerbates mucosal inflammation and diarrhea. Therapeutic strategies aiming to restore BA-receptor signaling include bile acid sequestrants, ursodeoxycholic acid, FXR agonists, PXR modulators, and experimental TGR5 agonists. While some are clinically employed for metabolic and hepatic disorders, others are under investigation for IBD. This review highlights current insights into BA metabolism, receptor signaling, and emerging therapeutic approaches targeting BA pathways to reestablish intestinal and hepatic homeostasis.

Keywords: Bile Acid-Activated Receptors; Immunomodulation; Bile acid metabolism; Dysbiosis

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INTRODUCTION

One of the worst health problems in the world, IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC), is becoming more common in both newly industrialized and Western countries. According to recent estimates, more than 6.8 million people worldwide suffer from high rates of morbidity and socioeconomic costs (1). Environmental stressors, immune dysregulation, gut microbiota, and host genetics all interact intricately in the multifactorial pathophysiology of IBD (2). Bile acids (BAs) have historically been thought of as molecules that aid in the digestion and absorption of lipids and have a detergent-like consistency. But because to developments in metabolomics and molecular biology, it is now acknowledged that BAs are strong signaling molecules that control liver metabolism, intestinal epithelial fitness, and immunological activity (3). The enterohepatic circulation keeps the size of the BA pool within a very narrow range, despite microbial modifications that alter the amount of BA and create ligands with varying degrees of receptor affinity (4). Nuclear receptors such as farnesoid X receptor (FXR), pregnane X receptor (PXR), and vitamin D receptor (VDR) as well as membrane-bound G-protein coupled receptors, including TGR5 (GPBAR1), are the receptors that mediate BA signaling. The receptors mediate immune modulation (TGR5-cAMP-NF-KB suppression), barrier function (VDR-dependent antimicrobial peptides), detoxification (PXR/CYP3A activation), and BA synthesis (FXR-FGF19 axis) (5). Significant changes in BA metabolism and signaling are linked to IBD. In order to deplete secondary BAs, including deoxycholic acid (DCA) and lithocholic acid (LCA), which are strong ligands of FXR, PXR, VDR, and TGR5, dysbiosis decreases microbial 7 α -dehydroxylation. In inflammatory intestinal tissue, bile

acid malabsorption and diarrhoea can also arise from the downregulation of some transporters, such as the apical sodium-dependent bile acid transporter (ASBT) (6). These alterations impair receptor-mediated protective signaling, increase mucosal inflammation, and impair barrier function. The therapeutic modification of BA signaling has gained interest as a result of these discoveries. Bile acid sequestrants (cholestyramine, colesevelam), ursodeoxycholic acid (UDCA, nor-UDCA), FXR agonists (obeticholic acid, cilofexor), PXR modulators (rifaximin), and synthetic TGR5 agonists are examples of current and experimental approaches. Some of these are already relevant to clinical practice in cases of cholestatic liver illness or bile acid diarrhoea, while others are still being studied in the context of IBD (7). Bile acid chemistry, biosynthesis, receptor signaling cascades, and their alterations in IBD are all thoroughly covered in the review. Additionally, the therapeutic possibility of addressing bile acid-receptor pathways to support intestinal and hepatic homeostasis is analyzed.

BILE ACIDS: CHEMISTRY, SYNTHESIS, AND ENTEROHEPATIC CIRCULATION

2.1 Structure and Classification of Bile Acids

Amphipathic steroid compounds known as bile acids (BAs) are created from cholesterol by oxidatively changing the steroid nucleus and shortening the side chain. Their hydrophilic hydroxyl groups and hydrophobic steroid backbone work together to make them natural detergents for lipid solubilization. While secondary BAs like deoxycholic acid (DCA) and lithocholic acid (LCA) are created by microbial metabolism, the two main primary BAs identified in humans are chenodeoxycholic acid (CDCA) and cholic acid (CA) (8). BAs come in conjugated and unconjugated forms. Conjugation with taurine or glycine enhances solubility and reduces toxicity in hepatocytes. The hydrophobic–hydrophilic balance of each BA determines its toxicity, detergent efficacy, and receptor affinity (9).

Hepatic Biosynthesis Pathways

Hepatocytes produce BAs through two broad enzymatic pathways that start with cholesterol:

Classic (neutral) pathway:

Cholesterol 7 α -hydroxylase (CYP7A1) starts this rate-limiting step in the production of BA. After cholesterol is converted to 7 α -hydroxycholesterol by CYP7A1, the metabolite is subsequently processed in a series of steps to yield CA and CDCA. Sterol 12 α -hydroxylase (CYP8B1) is the enzyme that determines the CA/CDCA ratio.

Alternative (acidic) pathway:

Oxysterol production was initiated by mitochondrial sterol 27-hydroxylase (CYP27A1) and subsequently hydroxylated by CYP7B1 to CDCA. Although it contributes less to the overall pool of BA, this route regulates the metabolism of cholesterol (10). It is estimated that around 90% of human BA synthesis occurs via the traditional method. One may argue that feedback inhibition is the mechanism by which FXR and other nuclear receptors strictly regulate the equilibrium between these two pathways.

Conjugation, Secretion, and Transporters

Following synthesis, primary BAs are changed into taurine or glycine by the bile acid-CoA: amino acid N-acyltransferase (BAAT) enzyme, which also increases their solubility and inhibits passive absorption in the proximal intestine. The bile salt export pump (BSEP; ABCB11) actively secretes conjugated BAs into bile canaliculi, while MRP2 and MDR3 enhance phospholipid secretion. After eating, the gallbladder stores and concentrates the bile before releasing it in reaction to cholecystokinin (CCK). The apical sodium-dependent bile acid transporter (ASBT; SLC10A2) in the intestine reabsorbs the conjugated BAs in the ileum. Ileal bile acid-binding protein (IBABP) carries them into cells, while organic solute transporter $\alpha/8$ (OST $\alpha/2$; SLC51A/B) carries them basolaterally to the portal vein. The majorities of organic anion transporting polypeptides (OATPs) and sodium-taurocholate co-transporting polypeptides (NTCP; SLC10A1) reabsorb them at the liver level (11). The benefit of enterohepatic cycling is that over 95% of the BA pool is recycled every day, with just about 5% being eliminated as feces and the remaining 5% being restored by de novo hepatic synthesis.

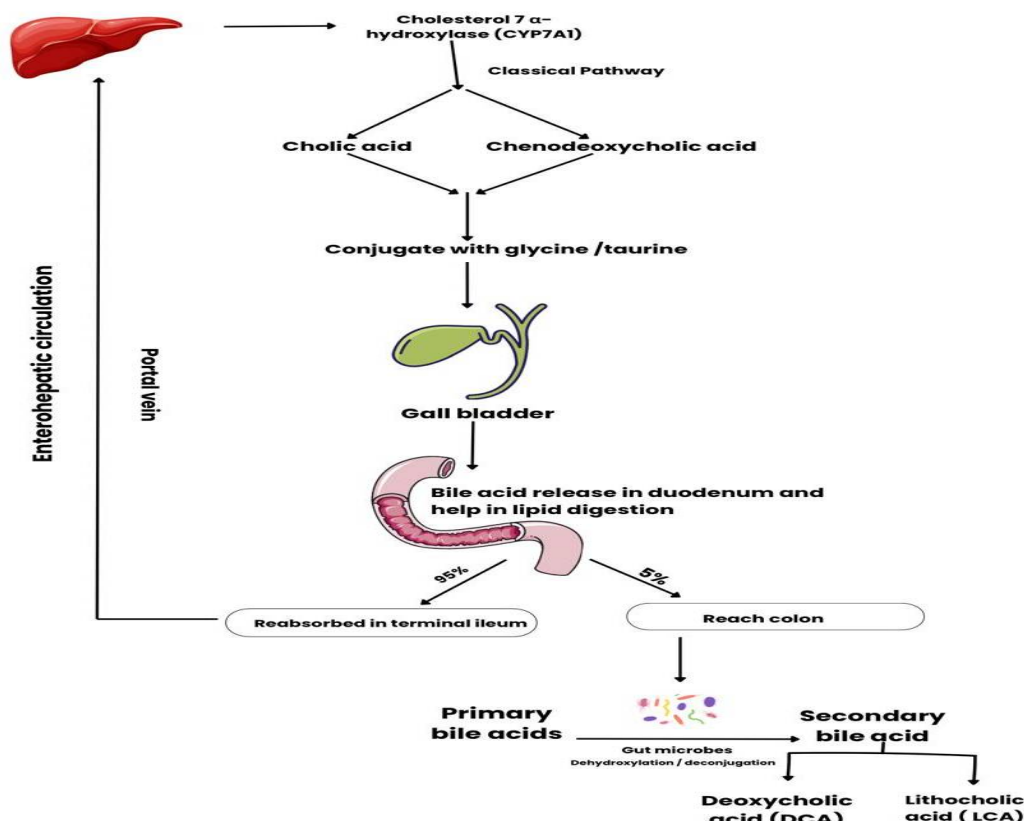


Figure1- Bile acid synthesis

Microbial Changes and the Second Bile Acid Pool

BA diversity is significantly influenced by the gut microbiome. Entroluminal bacteria like *Bacteroides*, *Clostridium*, and *Lactobacillus* express BSHs, which are deconjugated in the colon by taurine and glycine conjugated BAs. Then, CA is changed into DCA and CDCA into LCA by the *Clostridium scindens* and other 7 α -dehydroxylating bacteria (12). Secondary BAs with unique biological activity are produced by such microbial conversions. DCA and LCA are potent FXR, PXR, and TGR5 ligands that link host signaling to microbial action. By maintaining equilibrium in the hydrophobicity, microbial modification also lessens the toxicity of BA, avoiding undue damage to the epithelium. IBD disrupts the microbial composition, resulting in fewer 7 α -dehydroxylating taxa, which reduces secondary BAs and hinders receptor-mediated anti-inflammatory signaling (13).

BILE ACID RECEPTORS AND SIGNALING

Nuclear Receptors

Farnesoid X Receptor (FXR, NR1H4)

The master regulator of bile acid homeostasis in the liver, ileum, and immune cells is FXR. The strongest natural ligand is chenodeoxycholic acid (CDCA), which is followed by lithocholic acid (LCA) and deoxycholic acid (DCA) (14). When FXR binds to BA, it forms a heterodimer with the retinoid X receptor (RXR) and binds to FXR response elements (FXREs). These significant downstream effects include the induction of small heterodimer partner (SHP), a hepatocyte repressor of CYP7A1 (the rate-limiting enzyme of BA synthesis). To further decrease the synthesis of BA in ileal enterocytes, FXR-induced fibroblast growth factor 19 (FGF19) enters the portal circulation and binds to FGFR4/-Klotho in hepatocytes (15).

Additionally, FXR promotes BA efflux by increasing canalicular BA secretion, the bile salt export pump (BSEP/ABCB11), and OST α /Beta in the ileum. Additionally, FXR suppresses NF- κ B signaling, which lowers the amount of pro-inflammatory cytokines produced by enterocytes and macrophages (16).

Pregnane X Receptor (PXR, NR1I2)

The liver and intestines have high expression levels of the xenobiotic sensor PXR. Furthermore, LCA and its derivatives, as well as other medications like rifaximin and rifampicin, are natural ligands (17). PXR and RXR heterodimerize, triggering the production of detoxifying enzymes, CYP3A4, and multidrug resistance protein 1 (MDR1). By inhibiting the inflammatory transcription through NF- κ B-binding, it links

the control of inflammation to the metabolism of BA (18). In UC/CD patients and animals, Rifaximin reduces mucosal inflammation by activating intestinal PXR (19).

Vitamin D Receptor (VDR, NR111)

Despite its common nomenclature, LCA and 3-keto-LCA derivatives are also recognized by the calcitriol receptor, VDR (20). VDR promotes the production of genes that maintain the integrity of epithelial junctions as well as antimicrobial peptidogens (defensins, cathelicidin). By inhibiting NF-KB signaling, it also has anti-inflammatory properties (21). VDR suppression in IBD is linked to worse outcomes for IBD patients and more severe colitis in mice, suggesting that LCA VDR signaling disruption may contribute to the disease's pathophysiology (22).

Membrane-Bound G-Protein–Coupled Receptors

TGR5 (GPBAR1)

TGR5 is a GPCR (plasma membrane) found on cholangiocytes, enteric neurons, immune cells, and enterodendocrine L-cells. Natural ligands are secondary BAs (LCA > DCA > CDCA). Through its interaction with Gs protein, TGR5 triggers adenylyl cyclase, which in turn activates cAMP and the protein kinase A (PKA) cascade. In immune cells, TGR5 activation reduces cytokine secretion and inhibits NF-KB signaling (23), in enteroendocrine L-cells, it stimulates GLP-1 release, improving glucose and barrier homeostasis (24), and in epithelial cells, it promotes tight junction proteins and mucin. IBD low luminal LCA/DCA reduces TGR5 activation and prefers continuous NF-KB-mediated inflammation.

Sphingosine-1-Phosphate Receptor 2 (S1PR2)

Taurocholic acid (TA) is one of the BAs that has the ability to activate S1PR2. Hepatocyte survival and proliferation are influenced by ERK1/2 and AKT signaling via BA-S1PR2 signaling. Even though it is most frequently researched in relation to cholestatic damage and cancer, its role in gut inflammation is still unknown, despite the fact that it is becoming recognized as a second BA-sensing route (26). Its significance in gut inflammation is unclear, despite the fact that it has been studied mostly in cholestatic damage and cancer. Nevertheless, it is emerging as another BA-sensing route.

Downstream Signaling Integration

A sophisticated regulatory system is synchronized by the combined action of nuclear and membrane BA receptors. Hepatic BA synthesis must be inhibited by the FXR-FGF19 axis. In immunological and epithelial cells, PXR/VDR inhibits NF-kB, and detoxifies harmful BAs (LCA). Through a cAMP signal, TGR5 sustains immunological tolerance, protective action, and gut-liver crosstalk. The preservation of gut-liver-immune homeostasis is strengthened and supported by the cross-linking between these receptors. Chronic inflammation, impaired detoxification, and unchecked BA buildup are the results of these pathways being disrupted in IBD (by dysbiosis, transporter anomalies, and receptor downregulation).

PHYSIOLOGICAL ROLES OF BILE ACID SIGNALING IN THE GUT–LIVER AXIS

Regulation of Bile Acid Homeostasis

Given the fundamental physiological roles of bile acid (BA) signaling, feedback inhibition is used to regulate the size and makeup of the BA pool. Induced by FXR in enterocytes, FGF19 (FGF15 in mice) signals to hepatocytes, where it activates FGFR4/8Klotho to prevent the creation of BA from scratch and CYP7A1 (15). Hepatocytes' CYP7A1 and CYP8B1 transcription is directly suppressed by FXR-SHP, which further reduces the synthesis of BA (27). Through the application of detergent, this dual procedure prevents the overabundance of BA, which would otherwise harm the liver and intestines.

Lipid and Glucose Metabolism

The relationship between metabolic control and BA signaling Through the stimulation of peroxisome proliferator-activated receptor alpha (PPAR α) and the inhibition of hepatic triglyceride synthesis, FXR activation promotes lipid catabolism (28). In muscle and brown adipose tissue, TGR5 activation increases energy expenditure by stimulating thyroid hormone through DIO2 in a cAMP-dependent manner (29). In enteroendocrine L-cells, TGR5 activation triggers the release of GLP-1, which improves insulin sensitivity and glucose regulation (30). As a result, systemic energy balance and digestion are linked by BA signaling.

Intestinal Barrier Integrity

Through receptor-mediated mechanisms including FXR activation, the BAs regulate the actions of the mucosal barrier by increasing tight junction proteins (occludin, claudin-1) and reducing bacterial translocation while preserving the integrity of the epithelium (16). VDR2-LCA signaling triggers antimicrobial peptides (e.g., cathelicidin) and can modify autophagy signaling to control microbiota composition in the lumen (20), while TGR5 signaling enhances epithelial repair and counteracts the effects of oxidative stress on the barrier (e.g., cathelicidin) and modifies autophagy signaling to control microbiota composition in the lumen (25). Together, these effects maintain gut immunological tolerance and limit intestinal permeability.

Immune Modulation

FXR reduces TNF- α , IL-1 β , and IL-6 production by blocking NF- κ B-mediated cytokine expression in macrophages (16). In Kupffer cells and dendritic cells, TGR5 activation increases cAMP levels, inhibits the synthesis of pro-inflammatory cytokines, and stimulates the production of IL-10 (4). PXR prevents NF- κ B signaling, which protects epithelial cells from inflammatory-induced apoptosis, and promotes toxic BA detoxication (31). Th1/Th17 cell differentiation is suppressed and Th15 Treg responses are increased by VDR signaling, an adaptive immune regulation mechanism (22). These interrelated mechanisms maintain immune-epithelial balance and stop the gut from becoming too inflamed.

Gut-Microbiota-BA Crosstalk

Through bile salt hydrolases (BSHs) and 7 α -dehydroxylating enzymes, the gut microbiota modifies BA pools, which in turn influences receptor activation. Because secondary BAs (like DCA and LCA) are antimicrobial agents that prevent the growth of Gram-positive bacteria, BAs in turn affect the composition of the microbiota (12). The FXR signal maintains the equilibrium of microorganisms and regulates the expression of antimicrobial peptides (32). As a result, intestinal homeostasis depends on BA signaling, which is a negative feedback mechanism between the host and bacteria.

DYSREGULATION OF BILE ACID SIGNALING IN INFLAMMATORY BOWEL DISEASE (IBD)

Altered Bile Acid Pool Composition

In IBD, the BA pool is drastically altered by microbial dysbiosis and persistent mucosal inflammation. Patients with Crohn's disease (CD) and ulcerative colitis (UC) have higher primary BAs (CA, CDCA) and lower secondary BAs (DCA, LCA) according to faecal BA study (33). The loss of bacteria that convert CA/CDCA into secondary BAs, such as *Clostridium scindens* and *Clostridium hiranonis*, is the cause of this (13). Depletion of LCA and its derivatives suppresses VDR and TGR5 activation, compromising antimicrobial peptide induction and epithelial barrier defence.

Impaired Enterohepatic Circulation

Ileal inflammation in Crohn's disease alters the expression of ASBT (SLC10A2), which results in diarrhoea, luminal BA levels, and malabsorption of BA. Intestinal inflammation also inhibits the absorption and recycling of BA (34). Uncontrolled CYP7A1 activity results from declining FGF19 inflammatory ileum secretion, which increases hepatic BA synthesis and exacerbates the imbalance of BA (35).

Dysregulated FXR Signaling

Compared to controls, IBD patients have lower levels of FXR expression in their colonic tissues (16). Loss of SHP/FGF19 feedback brought on by FXR impairment leads to an overabundance of BA and hepatointestinal injury. Bacterial translocation and compromised epithelial barrier integrity also aggravate inflammation by lowering FXR activity.

TGR5 Dysfunction

IBD impairs cAMPKA signaling by lowering TGR5 expression in colon macrophages and epithelial cells (25). This promotes chronic disease by impairing GLP-1 secretion, barrier repair, and NF- κ B-mediated inflammation inhibition.

VDR and PXR Downregulation

The colonic mucosa of IBD has a significantly reduced quantity of vitamin D receptor (VDR), which is linked to increased permeability and more severe inflammation (5). Inflamed mucosa has reduced PXR activity, which inhibits LCA and xenobiotic detoxification and increases hyper-irritative inflammatory signaling (19). Loss of VDR and PXR signaling together removes important checkpoints for NF- κ B activation.

Microbiota-BA-Immune Axis Breakdown

FXR, TGR5, and VDR signaling are disrupted when dysbiosis reduces the production of secondary BA (36). Additional inflammation is caused by the expansion of pathobionts (such as *Escherichia coli* and *Enterococcus faecalis*) as a result of secondary BAs' diminished antimicrobial action (37). Inflammation, dysbiosis, altered BA metabolism, compromised receptor signaling, and increased inflammation create a vicious cycle.

Clinical Implications

When FXR, TGR5, VDR, and PXR signaling are all cross-inhibited at the same time, unchecked BA synthesis, barrier failure, immunological hyperactivation, and gut microbiota alterations result. The high prevalence of cholestasis, malabsorption, and BA diarrhea in IBD patients can be explained by these alterations. Crucially, rather than being a result of persistent intestinal inflammation, BA receptor dysfunction may be the cause of it.

THERAPEUTIC TARGETING OF BILE ACIDS AND THEIR RECEPTORS IN IBD

FXR Agonists

FXR agonist proteins are the new therapeutics that are proving to be effective in the treatment of IBD because these have the ability to restore the homeostasis of BA, enhance barrier strength, and inhibit the inflammation.

Obeticholic acid (OCA, INT-747)

Semi-synthetic derivative of BA which is an excellent FXR agonist. OCA suppressed colonic inflammation, as well as enhanced mucosal integrity under DSS induced colitis conditions (16). Approved in primary biliary cholangitis (PBC), and in non-alcoholic steatohepatitis (NASH) under investigation. Therapeutic benefit has been hinted at by small pilot studies in IBD but larger trials are expected (38).

INT-767

Dual FXR/TGR5 agonist that has increased anti-inflammatory properties. It also lessened colitis in murine IBD models and recovered barrier function (39).

Tropifexor (LJN452)

An improved FXR agonist, next-generation, non-steroidal with a superior tolerability profile, which is in clinical development in metabolic and cholestatic liver diseases (40). IBD potential use is being investigated.

6.2 TGR5 Agonists

TGR5 activation promotes immune suppression, GLP-1 secretion, and epithelial repair.

INT-777: A selective TGR5 agonist shown to reduce pro-inflammatory cytokine release and improve intestinal barrier integrity in preclinical colitis models (41).

6.3 PXR Ligands

PXR activation reverses inflammation mediated by NF- κ B and increases detoxification.

Rifaximin is incompletely absorbed antibiotic which is also a PXR agonist. Lessened colitis in mice by suppression of NF- κ B signaling. Rifaximin has demonstrated efficacy in mild-to-moderate IBD, but higher-order efficacy is observed in hepatic encephalopathy and IBS-D (42). Other drugs such as rifampicin can also stimulate PXR, although the systemic effect of the drug restricts its use in the IBD.

VDR Modulators

Vitamin D supplementation boosts VDR signaling, which recovers the integrity of epithelial barriers and immune tolerance. Clinical trials reveal that vitamin D deficiency is associated with poor outcomes of IBD, and their supplementation can lower relapse rates. Another therapeutic approach that is under development is the secondary BA -VDR signaling (i.e., through probiotics that amplify LCA derivatives) (43).

Bile Acid Transport Modulators and Sequestrants

Bile acid sequestrants (e.g., cholestyramine, colestevlam) are beneficial in IBD patients having BA diarrhoea, specifically in Crohn's disease with ileal resection. They attach luminal BAs and lessen irritation and diarrhoea (44).

ASBT inhibitors (e.g., elobixibat): ileal BA reuptake blocker, promoting colonic BA concentrations, and GLP-1 release. Nonetheless, inhibition of ASBT can exacerbate diarrhea in IBD and thus it is not used clinically (45).

FGF19 Analogues and FXR-FGF19 Axis Restoration

NGM282 (Aldafermin): A protease-resistant analogue of FGF19 which is under development in NASH. It reduces BA production by inhibiting CYP7A1 and could have therapeutic applications in IBD in which FGF19 signaling is impaired (46).

Microbiota-Based Interventions

Probiotics and microbiota transplantation should replace BA-transforming bacteria (*Clostridium scindens*, *Bacteroides*) to raise secondary BA levels and re-open FXR/TGR5/VDR signaling (47). Prebiotics and dietary intervention: High-fiber diets stimulate microbial primary to secondary BA conversion to improve receptor signaling.

Table-1 Therapeutic Targets of Bile Acids and Their Receptors

S. No.	Receptor Target	Type
1.	FXR Agonists	Obeticholic acid, INT-767, Tropifexor
2.	TGR5 Agonists	INT-777
3.	PXR Ligands	Rifaximin, rifampicin
4.	VDR Modulators	Vitamin D supplementation
5.	Bile Acid Transport Modulators and Sequestrants	Cholestyramine, Colesevelam
6.	FGF19 Analogues	Aldafermin
7.	Microbiota-Based Interventions	Probiotics

RECENT PROBLEMS AND OUTLOOK

Translational gaps and safety issues

Although it is a promising therapeutic target, several interferences exist in converting preclinical models to human IBD. Elements of mucosal inflammation are recapitulated in animal colitis models (DSS, TNBS, IL-10^{-/-}), which do not fully recapitulate the genetic and microbial heterogeneity of human IBD; dose selection and safety prediction of FXR/TGR5/PXR modulators is more challenging due to differences in receptor expression, BA pool composition, and microbiome-BA interactions species-specifically. Alternatively, gut-restricted/cell-type selective methods are more desirable since systemic FXR or TGR5 stimulation may cause off-target effects (including pruritus or lipid effects/gallbladder stasis).

Precision biology need bile acid phenotyping

IBD is a multifaceted illness. Precision phenotyping that includes a combination of ileal transporter expression (e.g., ASBT), receptor expression (FXR, TGR5, PXR, VDR), microbiota composition, and faecal/serum BA profile may be required for successful translation into therapeutic practice. This will help identify patient subgroups that are more likely to respond to particular therapies, such as those with an FXR-low phenotype or BA-malabsorption dominating. The topic of causality vs consequence can be clarified by longitudinal sampling of flares and remissions.

Directed approaches using microbiomes & metabolite therapeutics

Administering certain, less toxic analogues of DCA/LCA or VDR/TGR5-selective metabolites, such as 7 α -dehydroxylating *Clostridium*, is one of the more attractive approaches to physiological receptor tone restoration that does not include systemic receptor agonism. It is necessary to conduct extensive testing on manufactured probiotics that produce protective BA species or postbiotics (microbial metabolites) that are logically designed.

Invention of intestinal restricted agonists and prodrugs

In order to reduce systemic exposure, FXR/TGR5 agonists or prodrugs that are gut-restricted by colonic bacteria may also avoid hepatic or biliary adverse effects and concentrate activity where necessary (ileum/colon). Similar to this, therapeutic windows can be enhanced by biased agonists that preserve the benefits of the gallbladder while only activating anti-inflammatory signaling pathways (such as TGR5, cAMP, and IL-10).

Combination-therapies and multimodal

The success of combination therapies (such as microbiome restoration + receptor agonist; ASBT modulation + sequestrant in post-resection BAM) over their monotherapy may depend on the interplay between BAs, microbiota, and immune cells. The safety and synergy of integration with small molecules (anti-integrin, anti-TNF, and JAK inhibitors) or with an existing biologic will be assessed by mechanistic analysis.

Biomarkers and clinical trial design

To show target engagement and help de-risk bigger efficacy studies, early-phase trials should incorporate robust and mechanistically informative biomarkers (faecal BA ratios, blood FGF19, ileal ASBT expression, and receptor phosphorylation status). Adaptive trial designs that focus on biomarker-enriched subpopulations help expedite the development process.

CONCLUSION

The network Bile acids centrally modulate intestinal physiology and immunology by directly activating a network of nuclear receptors (FXR, PXR, VDR) and membrane GPCRs (TGR5, S1PR2). Microbial dysbiosis, transporter dysregulation, and loss of secondary BA species all work together to disrupt BA-receptor signaling in IBD, which encourages barrier dysfunction and persistent inflammation. The gut-liver equilibrium may be restored and symptoms like bile-acid diarrhoea may be lessened by therapeutically modulating the BA axis using sequestrants, receptor agonists/antagonists, microbiota alteration, or synthetic metabolites. It will take gut-restricted, pathway-selective drug design, microbiome-based therapeutic integration, and biomarker-guided clinical trials to realize this potential precision phenotyping. BA-directed treatments may thus prove to be beneficial additions to currently available IBD medications.

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