*Egypt. J. Chem.* **Vol. 68**, No: SI: Z. M. Nofal, pp. 1349- 1355 (2025)

**Egyptian Journal of Chemistry**

**http://ejchem.journals.ekb.eg/**

# The Enterohepatic Circulatory System of Bile Acids: A Dynamic Endocrine Network Governing Metabolic and Inflammatory Balance

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**Abstract**

For centuries, bile acids (BAs) were primarily regarded as simple biological detergents, essential for the emulsification and absorption of dietary lipids and fat-soluble vitamins in the intestine. However, the last two decades have witnessed a paradigm shift in our understanding of these cholesterol-derived molecules. BAs are currently recognized as central signaling molecules responsible for orchestrating an intricate web of metabolic and inflammatory reactions in the body. This review synthesizes current research from 2020 to 2024 to describe the intricate biochemistry of BA synthesis from cholesterol that confers upon them their unique amphipathic nature. We review the molecular mechanisms by which BAs activate specific receptors, the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1 or TGR5), to regulate glucose, lipid, and energy homeostasis. We also review the increasing role of the gut-liver axis and the gut microbiota in the regulation of the BA pool, creating a dynamic endocrine loop. Dysregulation of BA signaling is intimately intertwined with the pathology of numerous diseases, including cholestatic liver disease, metabolic syndrome, NAFLD, and inflammatory diseases. The current review highlights how the recent understanding of BAs as hormonal integrators has paved the way for fresh therapeutic possibilities, such as FXR and TGR5 agonists, which can cure such widespread diseases. Through the addition of new findings, this review emphasizes the transformation of BAs from humble gut digestive surfactants to becoming central characters in systemic physiology and disease.

**Keywords:** bile acids, farnesoid X receptor, G protein-coupled bile acid receptor 1, gut-liver axis, metabolic syndrome.

## 1. Introduction

Bile acids, once mere passive end-products of cholesterol breakdown with one role in fat digestion, have been placed center stage in metabolic investigations. The discovery that they are endogenous ligands for nuclear receptors and G-protein-coupled receptors revolutionized our perception of their physiological significance (Chiang & Ferrell, 2018). This discovery put the BAs not only as absorptive facilitators but as bona fide hormones that integrate nutrient sensing with systemic metabolic control. BA synthesis is a closely regulated mechanism, one of the major routes of cholesterol clearance, and the organization of BAs, characterized by the availability of a steroid core with hydrophobic and hydrophilic faces, forms the platform for their dual function as surfactants and signaling molecules (de Aguiar Vallim et al., 2013).

BA biology is also made more complex by the gut microbiome, which significantly modifies the original BA pool to generate a heterogeneous collection of secondary BAs with individualized signaling profiles (Winston & Theriot, 2020). This microbial alteration generates a sophisticated crosstalk between the host and its commensal microbes and influences anything from gut barrier function to systemic inflammation. In this review, we will thoroughly explore the history of BAs, from their formation and biochemical properties, through their activity as potent signaling agonists, and finally to their role in disease causality and the design of targeted therapies. In focusing on the literature of the past five years, we aim to give a modern perspective on the multifaceted roles of these dynamic molecules.

### Bile Acid Synthesis and Enterohepatic Circulation Biochemistry

### Classical and Alternative Synthetic Pathways

BA synthesis from cholesterol occurs in the liver hepatocytes predominantly by two major routes, viz. the classical (neutral) and the alternative (acidic) pathways. The classical pathway is responsible for 90% of BA synthesis in healthy physiology and is initiated by the enzyme cholesterol 7α-hydroxylase (CYP7A1), which is the rate-determining step during the process (Chiang & Ferrell, 2018). CYP7A1 activity is under tight regulation by feedback mechanisms, most notably through the ileum-derived hormone fibroblast growth factor 19 (FGF19; FGF15 in mice), released following FXR activation in the ileum by BAs (Fu et al., 2016). The subsequent steps in the classical pathway are catalyzed by sterol 12α-hydroxylase (CYP8B1), which regulates the synthesis of cholic acid (CA) or chenodeoxycholic acid (CDCA), thereby influencing the hydrophobicity and detergent capacity of the whole BA pool (Zhou & Hylemon, 2023).

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Receive Date: 18 August 2025, Revise Date: 21 October 2025, Accept Date: 25 October 2025

DOI: 10.21608/ejchem.2025.415086.12208

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The alternative pathway, which is only 10% of total BA synthesis, is initiated by the enzyme sterol 27-hydroxylase (CYP27A1) in most tissues and subsequently oxysterol 7α-hydroxylase (CYP7B1) in the liver (Pikuleva, 2006). This pathway increases in significance in certain pathological conditions and is the principal source of CDCA. Both routes are completed by conjugation of the BA carboxyl group with glycine or taurine through a reaction catalyzed by the enzyme bile acid-CoA: amino acid N-acyltransferase (BAAT). Conjugation augments the solubility of BAs at acidic pH and their detergent nature, enhancing their emulsifying activity in the small intestine (Monte et al., 2009). The tight regulation of these synthetic pathways ensures stability of a well-balanced BA pool, which is critical for digestive and signaling functions.

**Amphipathic Nature of Bile Acids**

The unique biochemical feature of BAs that accounts for the dual function is their amphipathic nature. This structure arises from a rigid steroid nucleus, hydrophobic on one side and hydrophilic on the other. Hydrophilicity is conferred by hydroxyl groups and, in the case of conjugated BAs, by the polar amino acid side chain (Cai et al., 2022). This kind of molecular conformation allows BAs to act as biological surfactants. Above critical micellar concentration, they form micelles—aggregates in which the hydrophobic faces are buried inside and exposed to the aqueous phase are the hydrophilic faces. Micelles are needed for the solubilization of hydrophobic lipids like cholesterol and fatty acids so that they can be carried to the intestinal mucosa for absorption (Hofmann & Hagey, 2008). The quantity and orientation of hydroxyl groups determine the hydrophobicity index of a BA, which determines its toxicity, detergent activity, and agonist efficacy. For instance, the dihydroxy BA deoxycholic acid (DCA) is more hydrophobic and cytotoxic than the trihydroxy BA cholic acid (CA) (Jia et al., 2021).

**The Enterohepatic Circulation: A Delicately Tuned Circuit**

Enterohepatic circulation is a highly effective recycling mechanism that conserves BAs, with over 95% of intestinal BAs being reabsorbed and returned to the liver via the portal vein. This diminishes the need for de novo synthesis from cholesterol. Passive uptake occurs all along the intestine, but the majority of the BAs are actively reabsorbed by the terminal ileum through the apical sodium-dependent bile acid transporter (ASBT) (Dawson, 2010). Inside the enterocyte, BAs are bound to the ileal bile acid-binding protein (IBABP) and delivered to the basolateral membrane, from where they are effluxed into the portal circulation by the heterodimeric organic solute transporter OSTα/OSTβ (Li et al., 2004). The liver successfully sequesters BAs from portal blood primarily by the sodium-taurocholate cotransporting polypeptide (NTCP) and secondarily through organic anion-transporting polypeptides (OATPs). This exquisite cycle offers a readily-accessible reservoir of BAs that can be mobilized into bile following a meal, facilitating efficient lipid digestion and, concurrently, a steady release of signaling molecules that regulate their own production and a universe of additional metabolic processes (Slijepcevic & van de Graaf, 2017). Figure 1 illustrates the synthesis of bile acids from cholesterol in hepatocytes and their enterohepatic recirculation.

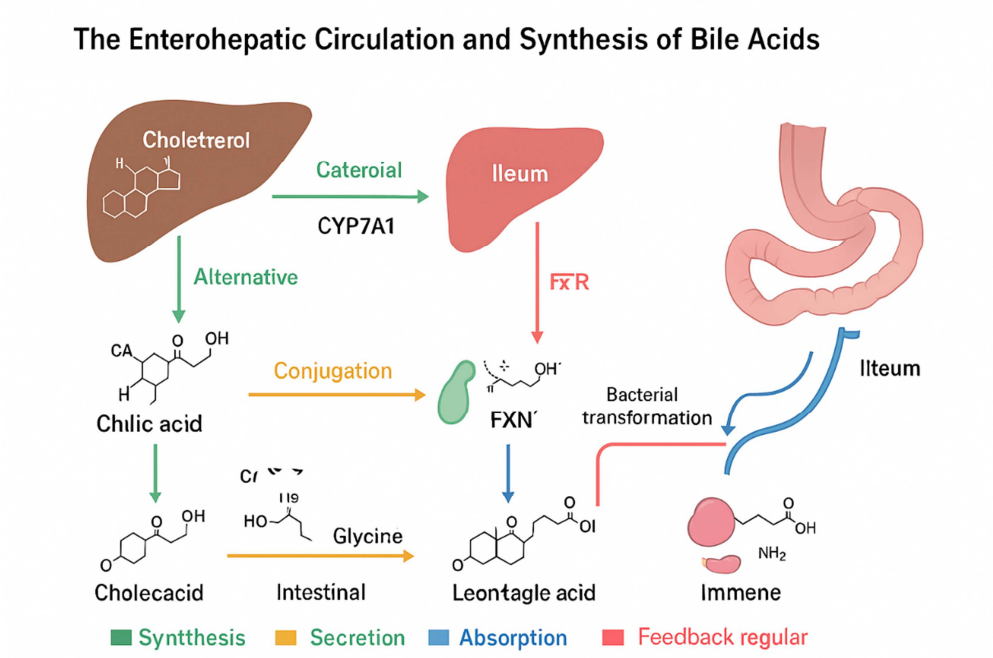


**Figure 1: The Enterohepatic Circulation and Synthesis of Bile Acids**

**Bile Acids as Signaling Molecules: The Receptor Network**

The key discovery that BAs are specific ligands to several receptors redesignated them as endocrine molecules. Through these receptors, BAs regulate their own synthesis and enterohepatic recirculation, and exert potent effects on glucose homeostasis, lipid metabolism, energy expenditure, and immune responses.

**The Farnesoid X Receptor (FXR)**

FXR (NR1H4) is a nuclear receptor highly expressed in the liver and intestine, and is considered the master regulator of BA homeostasis. When it binds to BAs, with the greatest affinity by CDCA and its conjugated derivatives being the most potent endogenous agonists, FXR undergoes conformational change, heterodimerizes with the retinoid X receptor (RXR), and translocates into the nucleus to regulate transcriptional activity of target genes (Jia et al., 2021). In the liver, FXR activation induces expression of the small heterodimer partner (SHP) and suppresses transcription of CYP7A1, thus providing a direct negative feedback mechanism to limit BA synthesis (Chiang & Ferrell, 2018). Besides, FXR activation enhances expression of the bile salt export pump (BSEP) for canalicular secretion of BAs and reduces NTCP to restrain BA uptake from the blood, and this preserves hepatocytes from BA overloading in the course of cholestasis (Meadows et al., 2021).

The intestinal FXR axis is equally critical. BA activation of ileal enterocyte FXR induces expression and release of FGF19/15. This hormone travels to the liver and attaches to its receptor FGFR4/β-Klotho complex, and activates downstream signaling pathways that potently suppress CYP7A1 transcription (Fu et al., 2016). This gut-liver endocrine axis represents an important mechanism for postprandial suppression of BA synthesis. Beyond BA homeostasis, FXR plays a broader metabolic function. It controls lipid metabolism through the inhibition of hepatic lipogenesis and activation of fatty acid β-oxidation, and controls glucose homeostasis through the repression of hepatic gluconeogenesis (Yu et al., 2023). The new studies have also discovered a role for FXR in controlling the gut microbiota and the intestinal barrier integrity, linking BA signaling to the control of systemic inflammation (Wang et al., 2022).

**The G Protein-Coupled Bile Acid Receptor 1 (GPBAR1 or TGR5)**

TGR5 is a G protein-coupled receptor expressed widely among tissues, such as the gallbladder, intestine, BAT, skeletal muscle, and immune cells. Unlike FXR, TGR5 is primarily located on the plasma membrane and causes rapid, non-genomic signal responses. Secondary BAs, such as lithocholic acid (LCA) and deoxycholic acid (DCA), are potent TGR5 agonists (Duboc et al., 2014). One of the most potent metabolic functions of TGR5 is energy intake and glucose metabolism. In brown adipose tissue and skeletal muscle tissue, TGR5 activation leads to the formation of the active thyroid hormone T3 from its inactive form T4 through the induction of the type 2 iodothyronine deiodinase (DIO2). This peripheral increase in T3 activity enhances mitochondrial activity and thermogenesis, activating energy expenditure and an apparent therapeutic opportunity in obesity (van Nierop et al., 2019).

Within the gut, TGR5 activation of L-cells results in the release of GLP-1, an incretin hormone that enhances glucose-stimulated insulin secretion from pancreatic β-cells, suppresses glucagon release, and slows gastric emptying (Katsuma et al., 2005). This makes the TGR5-GLP-1 pathway a prime target for type 2 diabetes treatment. Secondly, TGR5 also has potent anti-inflammatory actions in innate immune cells, including macrophages and Kupffer cells. Activation of TGR5 inhibits the NF-κB signaling pathway, which results in reduced expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Guo et al., 2016). This immunomodulatory effect is especially crucial in the context of metabolic inflammation and liver disease.

**Other Molecular Targets**

Even though the most-well-studied BA receptors are FXR and TGR5, BAs do have other signaling molecules with which they interact. They are able to activate the pregnane X receptor (PXR) and the vitamin D receptor (VDR), particularly by toxic secondary BAs like LCA, as a detoxification mechanism (Staudinger et al., 2001). BAs are also known to modulate the sphingosine-1-phosphate receptor 2 (S1PR2), which is involved in hepatocyte proliferation, lipid metabolism, and liver regeneration (Liu et al., 2016). BAs can also exhibit receptor-independent actions, such as inducing oxidative stress and apoptosis of hepatocytes at high concentrations, which is attributed to their cytotoxic action in cholestatic disease (Perez & Briz, 2009). Table 1 summarizes the main bile acid receptors and their action.

**Table 1: Main Bile Acid Receptors and Their Action**

| Receptor | Type | Main Sites of Expression | Endogenous Agonists (Potency) | Key Functions |
|---|---|---|---|---|
| **FXR (NR1H4)** | Nuclear Receptor | Liver, Intestine (Ileum), Kidney | CDCA > DCA = LCA > CA | **Metabolic:** Regulates BA homeostasis (suppresses CYP7A1, induces BSEP), modulates lipid/glucose metabolism. **Anti-inflammatory:** Inhibits hepatic inflammation and fibrosis. |
| **TGR5 (GPBAR1)** | GPCR | Gallbladder, Intestine (L-cells), Brown Adipose Tissue, Immune Cells | LCA > DCA > CDCA > CA | **Metabolic:** Stimulates GLP-1 secretion, enhances energy expenditure via DIO2. **Anti-inflammatory:** Inhibits NF-κB in macrophages. |
| **PXR (NR1I2)** | Nuclear Receptor | Liver, Intestine | LCA, 3-keto-LCA | **Detoxification:** Induces xenobiotic metabolism and detoxification enzymes (CYP3A4). |
| **VDR (NR1I1)** | Nuclear Receptor | Intestine, Immune Cells | LCA (3-keto-LCA) | **Calcium Homeostasis:** Classical role. **Immunity/Inflammation:** Modulates immune responses in the gut. |
| **S1PR2** | GPCR | Liver, Heart, Adipose Tissue | Taurine-conjugated BAs (TCA, TCDCA) | **Cell Signaling:** Activates ERK and AKT pathways; regulates lipid metabolism, hepatocyte proliferation, and liver regeneration. |

**4. The Gut Microbiome: A Master Modulator of the Bile Acid Pool**

The gut microbiota is a key metabolic organ that profoundly transforms the BA pool, which in turn regulates host physiology and disease susceptibility. Secretion of primary bile acids (CA and CDCA) into the intestine is under the control of a cascade of bacterial conversions. The most critical of these are the deconjugation of glycine/taurine by bacterial bile salt hydrolases (BSH), present in many bacterial genera, like Lactobacillus, Bifidobacterium, and Clostridium (Foley et al., 2019). The deconjugated primary BAs are further metabolized by bacterial 7α-dehydroxylase activity, an enzyme found in a few species like Clostridium scindens, which converts CA to DCA and CDCA to LCA (Ridlon et al., 2016). This generates a heterogeneous mix of secondary BAs with distinct signaling properties, e.g., DCA is a very potent TGR5 agonist but perhaps more cytotoxic, and LCA is a highly active FXR antagonist and VDR agonist.

The composition of the gut microbiome thus directly influences the composition of the intestinal BA pool. Dysbiosis, an imbalance of the microbial community, can lead to a disorganized BA pool and disrupt signaling through FXR, TGR5, and other receptors. For example, loss of bacteria with 7α-dehydroxylase activity can lead to a decrease in secondary BA production and interfere with TGR5-mediated GLP-1 release and thermogenesis and potentially correlate with obesity and insulin resistance (Janssen et al., 2017). Alternatively, the BA pool itself exerts strong selective pressure on the gut microbial community since BAs have innated antimicrobial activity. Hydrophobic BAs like DCA and LCA are more bactericidal in character, and hence the composition of the host's BAs can define its gut microbiota (Winston & Theriot, 2020). This reciprocating interaction establishes a critical homeostatic loop: the host secretes endogenous BAs that adapt the microbiome, and the microbiome secretes a BA metabolome of complexity that regulates host metabolism and immunity. Disruptions to this very tenuous balance are the cause of a wide range of pathologies.

**Bile Acids in Disease Pathophysiology**

**Cholestatic Liver Diseases**

Cholestasis, with defective bile flow and BA accumulation in the liver, leads to hepatocyte damage, inflammation, and fibrosis. Pathophysiology is inevitably linked to dysregulated BA signaling. In cholestasis, the hydrophobic, toxic BAs are accumulated, overburdening the protective FXR-mediated adaptive mechanisms. Even though FXR activation is initially protective via downregulation of CYP7A1 and NTCP and upregulation of BSEP, during advanced cholestasis, this feedback is often insufficient (Trauner et al., 2011). The resultant elevated intracellular BA levels lead to mitochondrial dysfunction, generate oxidative stress, and induce apoptosis and necrosis (Perez & Briz, 2009). Additionally, the pro-inflammatory effect of accumulated BAs, mediated by inhibition of TGR5 and FXR signaling in immune cells, is held responsible for the recruitment of inflammatory cells and activation of hepatic stellate cells, resulting in fibrosis (Lleo et al., 2020). The therapeutic potential of FXR agonists, such as obeticholic acid, in primary biliary cholangitis (PBC) underscores the central role of BA signaling in such conditions, as they reverse the deficiency of negative feedback on BA production and increase hepatoprotection (Kowdley et al., 2018).

**Metabolic Syndrome, NAFLD, and Type 2 Diabetes**

The role of BA signaling in metabolic disorders is one of the most interesting areas of research in contemporary science. A decompartmentalized pool of BAs is a common state in obesity, insulin resistance, and NAFLD. NAFLD patients would have an elevated primary BAs and reduced total, and secondary BAs discomposed BA pool, along with a blunted FXR-FGF19 axis (Jiao et al., 2018). This dysfunction results in the loss of feedback inhibition of CYP7A1, and as a result, increased BA synthesis that can further induce liver damage. The reduced TGR5 signaling, resulting from low secondary BA levels, can also impair GLP-1 secretion and energy expenditure and exacerbate hyperglycemia and obesity (van Nierop et al., 2019). Conversely, bariatric surgery, that is, Roux-en-Y gastric bypass, profoundly alters BA metabolism, resulting in increased total BA levels and a composition shift toward enhanced FXR and TGR5 signaling. This is now considered a key mechanism in the superb metabolic improvement and diabetes remission after such surgeries (Penney et al., 2015). Therefore, targeting BA receptors is an appropriate therapeutic strategy for metabolic syndrome. FXR agonists have been evaluated for their ability to increase insulin sensitivity and reduce hepatic steatosis, while TGR5 agonists are being targeted for glucose-lowering and energy-terminating actions (Bhimanwar & Mittal, 2022).

**Gut Health and Inflammation**

Immunomodulatory effects of BAs, particularly through TGR5 and FXR, link them to intestinal and systemic inflammation. In the intestine, BAs also play roles in homeostasis by promoting FXR-mediated expression of protective mucosal barrier genes and antimicrobial effects. Dysbiosis with concomitant change in the BA pool could impair this homeostasis. For instance, intestinal FXR deficiency has been linked with elevated intestinal permeability, bacterial translocation, and induction of experimental colitis (Wang et al., 2022). Similarly, TGR5's anti-inflammatory action on macrophages is critical in the suppression of hyperactive immune responses. For example, inflammatory bowel disease (IBD) patients are likely to present with abnormalities within the BA pool and receptor levels, reflecting the pathogenic involvement (Duboc et al., 2014). Furthermore, the BA-VDR pathway, activated by LCA, may also play a role in regulating colonic inflammation as well as immune cell behavior (Staudinger et al., 2001). The interaction among BAs, microbiome, and host immune system forms a crucial triad determining gut health status and its relevance to systemic inflammation (Table 2). Figure 2 shows how bile acids act as signaling molecules across organs.

**Table 2: Dysregulation of Bile Acid Signaling in Selected Diseases**

| Disease | Key Alterations in BA Pool/Composition | Dysregulated Signaling Pathways | Pathophysiological Consequences |
|---|---|---|---|
| **Cholestasis (e.g., PBC, PSC)** | ↑ Total BA concentration in liver; ↑ hydrophobic BAs (CDCA, DCA). | Impaired FXR signaling (overwhelmed); Reduced TGR5 signaling. | BA-induced hepatotoxicity, oxidative stress, inflammation, and fibrosis. Pruritus. |
| **Non-Alcoholic Fatty Liver Disease (NAFLD/NASH)** | ↑ Total BA pool size; ↑ primary BAs (CA, CDCA); ↓ secondary BAs (DCA, LCA). | Blunted FXR-FGF19 axis; Reduced TGR5 signaling. | Loss of feedback inhibition on BA synthesis, increased hepatic lipogenesis, reduced energy expenditure, and impaired GLP-1 secretion. |
| **Type 2 Diabetes & Obesity** | Often similar to NAFLD; Altered after bariatric surgery (↑ total BAs, ↑ secondary BAs). | Impaired TGR5-GLP-1 axis; Dysregulated FXR signaling. | Contributes to insulin resistance, hyperglycemia, and weight gain. Post-surgery changes improve metabolism. |
| **Inflammatory Bowel Disease (IBD)** | ↓ Total BA levels, ↓ secondary BAs, and altered conjugation patterns. | Reduced FXR and TGR5 signaling in the gut. | Impaired gut barrier function, dysbiosis, and uncontrolled inflammation. |

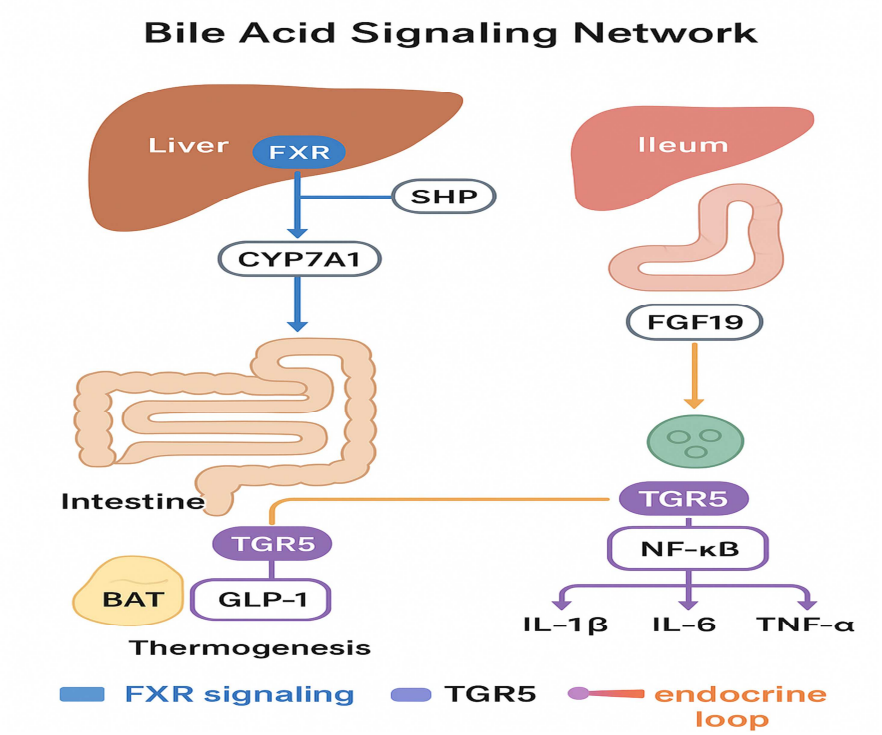


**Figure 2: Bile Acid Signaling Network — FXR–FGF19–TGR5 Axis**

**Therapeutic Implications and Future Directions**

The discovery of BAs as signaling molecules has dawned a new era in pharmacology. BA receptor agonists and analogs are already in various stages of clinical development. Obeticholic acid (OCA), a potent FXR agonist, is approved for PBC treatment and has been in development for NASH, though its application is tempered by pruritus and dyslipidemia side effects (Younossi et al., 2019). Non-bile acid FXR agonists (e.g., cilofexor, tropifexor) and tissue-selective FXR modulators are under study to have therapeutic effects with improved safety (Schattenberg, 2020). Similarly, highly selective and high-efficacy TGR5 agonists are being explored for type 2 diabetes and NASH, with a main research focus on the development of gut-restricted agonists to avoid systemic side effects, above all, gallbladder distension (Bhimanwar & Mittal, 2022).

Besides single-receptor targeting, combination therapy and microbiome-targeting therapy are in the pipeline. Co-administration with other agents, such as a fibroblast growth factor receptor 1c (FGFR1c) agonist to mimic FGF21 activity, is being explored to enhance metabolic efficacy in NASH (Harrison et al., 2021). Manipulation of the gut microbiome to alter the BA pool for therapeutic benefit is another new strategy. This may be achieved using probiotics (such as high BSH activity strains), prebiotics, or fecal microbiota transplantation (FMT) to engraft a BA-producing community with an improved BA metabolome (Janssen et al., 2017). Finally, ASBT inhibitors that block ileal BA reabsorption and increase BA loss into the feces are being researched for different disorders. By depleting the BA pool, they repress ileal FXR signaling, paradoxically

augmenting CYP7A1-mediated hepatic BA synthesis, leading to cholesterol utilization and lowering of plasma LDL-cholesterol; thus, they are sought after for hypercholesterolemia and type 2 diabetes therapies (Li et al., 2023).

**Conclusion**

The development of bile acids from modest digestive surfactants to multifunctional endocrine and paracrine signal molecules is an incredible tale of physiological discovery. Their in vivo biosynthesis from cholesterol is a biochemical marvel, and their amphipathic nature is the key to their flexibility. As ligands for FXR, TGR5, and other receptors, BAs stand at the intersection of metabolism and inflammation, bridging signals from diet and gut microbiome to coordinate systemic responses. The gut-liver axis, mediated by BAs and FGF19, is the ultimate example of such an advanced communication system. The BA-signaling dysregulation represents a pathogenic foundation for cholestatic, metabolic, and inflammatory diseases, revealing these pathways as therapeutic targets of great value. The challenge in the future will be to turn this molecular information into safe and effective therapies that can harness the therapeutic power of the BA-signaling network without disrupting its fine-tuned balance. Future research will indeed continue to untangle the complexity of this system, challenging tissue-specific activities, functions for less-well-defined BA species, and intricate crosstalk with other hormonal systems, solidifying the status of bile acids as central regulators of human disease and health.

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