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# Bile Acid Signaling, Metabolic Regulation, and Homeostatic Mechanisms: Comprehensive Insights into Their Roles in Liver Function, Cholestasis, and Biliary Disorders

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## ABSTRACT

Bile acids (BAs) are amphipathic molecules synthesized from cholesterol in hepatocytes and serve as essential regulators of lipid digestion, nutrient absorption, and cholesterol homeostasis. Beyond their classical detergent role in bile, BAs function as signaling molecules that modulate gene expression and cellular processes through nuclear and membrane-bound receptors, including the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5). Dysregulation of BA synthesis, transport, or signaling contributes to the pathogenesis of a wide range of hepatic and biliary disorders, including cholestatic liver diseases, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Advances in understanding BA-mediated molecular pathways have revealed novel therapeutic targets, such as FXR/TGR5 agonists, bile acid sequestrants, and ursodeoxycholic acid (UDCA), which offer clinical benefits in the management of these disorders. This review comprehensively discusses the physiological functions of BAs, their signaling mechanisms, dysregulation in hepatic and biliary diseases, and current and emerging therapeutic strategies, highlighting their translational potential in personalized medicine.

## Keywords

Bile acids
Farnesoid X receptor (FXR)
TGR5
Cholestasis
Hepatic disorders
Biliary diseases
Ursodeoxycholic acid
NAFLD
NASH
Therapeutic targets

## INTRODUCTION

Bile acids (BAs) are cholesterol-derived metabolites synthesized primarily in hepatocytes and secreted into the bile, forming a critical component of digestive physiology. Traditionally recognized for their detergent properties facilitating lipid emulsification and absorption in the intestine, BAs have emerged as key metabolic regulators influencing glucose, lipid, and energy homeostasis. The dual role of BAs as both digestive molecules and signaling entities places them at the intersection of metabolic and inflammatory pathways, linking hepatocellular function to systemic physiology [1].

Primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver through tightly regulated enzymatic pathways, conjugated with taurine or glycine, and secreted into bile. In the intestine, microbial modifications produce secondary BAs such as deoxycholic acid (DCA) and lithocholic acid (LCA), which exert distinct physiological and pathophysiological effects [2]. Enterohepatic circulation, a continuous recycling process of BAs between the liver and intestine, maintains systemic BA homeostasis and is essential for proper liver and biliary function [3].

Recent insights have unveiled that BAs serve as potent

Review Article

signaling molecules, activating nuclear receptors such as FXR and pregnane X receptor (PXR), as well as membrane receptors including TGR5 and vitamin D receptor (VDR). Through these receptors, BAs regulate genes controlling BA synthesis, transport, lipid metabolism, and inflammatory responses [2,3]. Disruption of these pathways is implicated in diverse hepatic and biliary pathologies, ranging from cholestatic syndromes and biliary cirrhosis to metabolic liver diseases and malignancies [4].

Therapeutic modulation of BA pathways has gained substantial attention in recent years. Ursodeoxycholic acid (UDCA), an endogenous hydrophilic BA, has long been employed to treat cholestatic liver diseases due to its cytoprotective and anti-apoptotic properties. More recently, FXR agonists (e.g., obeticholic acid) and TGR5 modulators have demonstrated promising results in preclinical and clinical studies, providing mechanistic insights into disease modulation and therapeutic efficacy [5].

Given the multifaceted roles of BAs, understanding their signaling mechanisms, homeostatic regulation, and dysregulation in liver and biliary disorders is essential for advancing translational medicine. This review presents a comprehensive analysis of BA physiology, molecular signaling, pathophysiological involvement in hepatic and biliary diseases, and current and emerging therapeutic approaches. It emphasizes the potential for precision medicine applications in targeting BA pathways for disease intervention.

## BILE ACID PHYSIOLOGY AND METABOLISM

Bile acids (BAs) are amphipathic molecules derived from cholesterol and play a central role in digestive physiology, hepatic homeostasis, and systemic metabolism. Their synthesis, modification, and enterohepatic circulation involve tightly regulated enzymatic and transporter-mediated processes that maintain physiological concentrations and prevent cytotoxicity [6].

### Biosynthesis of Bile Acids

BA biosynthesis occurs predominantly in hepatocytes via two major pathways: the **classical (neutral) pathway** and the **alternative (acidic) pathway**.

**Classical Pathway:** Initiated by cholesterol 7α-hydroxylase (CYP7A1), this pathway produces the primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA). CYP8B1 regulates the CA/CDCA ratio, influencing BA hydrophobicity and micelle-forming capacity [7].

**Alternative Pathway:** Initiated by sterol 27-hydroxylase (CYP27A1) and oxysterol 7α-hydroxylase (CYP7B1), this pathway primarily generates CDCA. While contributing a minor fraction of total BA synthesis under normal conditions, it becomes prominent during cholestatic or liver disease states [8].

These pathways are tightly regulated by nuclear receptors, including the **farnesoid X receptor (FXR),** which inhibits CYP7A1 transcription via the small heterodimer partner (SHP), forming a negative feedback loop essential for BA homeostasis [7,8].

### Conjugation and Secretion

Primary BAs are conjugated with **glycine or taurine** to increase solubility and reduce cytotoxicity before secretion into bile. Conjugated BAs are transported into bile canaliculi by the **bile salt export pump (BSEP),** a process that is crucial for maintaining hepatocyte integrity and bile flow [9,10]. Other transporters, including **multidrug resistance protein 2 (MRP2),** facilitate excretion of bilirubin and organic anions alongside bile salts.

Conjugation enhances micelle formation in the intestine, facilitating digestion and absorption of dietary lipids and fat-soluble vitamins (A, D, E, K) [11].

### Enterohepatic Circulation

BAs undergo a continuous **enterohepatic circulation**, cycling between the liver and intestine multiple times per day. After secretion into bile and intestinal release, BAs emulsify dietary lipids and facilitate absorption. In the ileum, approximately 95% of BAs are actively reabsorbed via the **apical sodium-dependent bile acid transporter (ASBT),** returning to the liver through the portal vein for reuse [12-14].

Unabsorbed BAs reach the colon, where gut microbiota metabolize primary BAs into **secondary BAs**, such as deoxycholic acid (DCA) and lithocholic acid (LCA), via deconjugation and dehydroxylation reactions. These secondary BAs possess distinct signaling properties and can modulate metabolic and inflammatory pathways [15,16].

### Bile Acid Composition

The composition of BAs varies between species and individuals and is influenced by diet, microbiota, and genetic factors. Primary BAs (CA and CDCA) are hydrophilic, whereas secondary BAs (DCA and LCA) are more hydrophobic and cytotoxic at high concentrations. Conjugated forms are generally less toxic and more water-soluble, emphasizing the importance of proper conjugation in hepatocyte protection [17].

## Cellular Transport and Homeostasis

BA homeostasis relies on **transporters** located on hepatocytes, cholangiocytes, and enterocytes:

**BSEP:** Mediates canalicular secretion of conjugated BAs into bile.

**NTCP (sodium taurocholate co-transporting polypeptide):** Imports BAs from portal blood into hepatocytes.

**OATP (organic anion transporting polypeptides):** Facilitate uptake of various BA species and other organic molecules.

**MRP3 and MRP4:** Provide alternative efflux pathways for BAs under cholestatic conditions.

Dysfunction of these transporters leads to BA accumulation, hepatocyte injury, and cholestasis, underscoring the critical role of BA homeostasis in liver health.

## Interactions with Microbiota

Intestinal microbiota are integral in BA metabolism, converting primary BAs to secondary BAs. These microbial modifications affect BA receptor activation (Table 1), metabolic signaling, and immune modulation. Dysbiosis can lead to altered BA composition, contributing to liver diseases such as NAFLD, NASH, and cholestatic disorders.

# BILE ACID SIGNALING PATHWAYS AND MOLECULAR MECHANISMS

Beyond their classical roles in lipid emulsification and absorption, bile acids (BAs) function as potent signaling molecules that regulate metabolism, immunity, and cellular homeostasis. These signaling roles are mediated by **nuclear and membrane-bound receptors**, influencing gene transcription, kinase cascades, and cross-talk with other metabolic pathways [18].

## Nuclear Receptor Signaling

### Farnesoid X Receptor (FXR)

FXR (NR1H4) is the principal BA sensor expressed in hepatocytes, enterocytes, and cholangiocytes. Upon binding of bile acids, primarily chenodeoxycholic acid (CDCA), FXR forms heterodimers with the **retinoid X receptor (RXR)** and regulates transcription of genes involved in BA synthesis, transport, and detoxification [19].

**Regulation of BA Synthesis:** FXR activation induces **small heterodimer partner (SHP),** which inhibits CYP7A1, the rate-limiting enzyme in BA synthesis, forming a negative feedback loop that prevents hepatotoxicity.

**Transporter Regulation:** FXR enhances expression of **BSEP**, promoting canalicular BA excretion, and regulates intestinal BA absorption via **ileal bile acid-binding protein (IBABP)** and **ASBT**.

**Metabolic Crosstalk:** FXR modulates glucose and lipid metabolism through induction of **FGF19 (fibroblast growth factor 19)** in enterocytes, which then suppresses hepatic gluconeogenesis and lipogenesis [20].

**Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR)**

PXR (NR1I2) and CAR (NR1I3) are xenobiotic sensors that are also activated by secondary bile acids, such as lithocholic acid (LCA). Their activation induces expression of **phase I and II detoxifying enzymes**, including **cytochrome P450s (CYP3A4, CYP2B6)** and conjugation enzymes (UGTs, SULTs), preventing bile acid-induced cytotoxicity and supporting liver detoxification.

### Vitamin D Receptor (VDR)

VDR, traditionally associated with calcium homeostasis, is activated by LCA and mediates transcriptional regulation

**Table 1:** Key Bile Acids, Origin, and Biological Properties.

| Bile Acid | Type | Primary/Secondary | Conjugated Forms | Hydrophobicity | Major Functions |
|---|---|---|---|---|---|
| Cholic Acid (CA) | Primary | Liver | Glyco-CA, Tauro-CA | Moderate | Lipid digestion, FXR activation |
| Chenodeoxycholic Acid (CDCA) | Primary | Liver | Glyco-CDCA, Tauro-CDCA | Hydrophilic | FXR agonist, lipid absorption |
| Deoxycholic Acid (DCA) | Secondary | Gut microbiota | Glyco-DCA, Tauro-DCA | Hydrophobic | Modulates TGR5, cytotoxic at high conc. |
| Lithocholic Acid (LCA) | Secondary | Gut microbiota | Glyco-LCA, Tauro-LCA | Very hydrophobic | VDR activation, hepatotoxic at high conc. |
| Ursodeoxycholic Acid (UDCA) | Secondary | Epimer of CDCA | Glyco-UDCA, Tauro-UDCA | Hydrophilic | Cytoprotective, reduces apoptosis |

of **CYP3A** enzymes, contributing to detoxification of hydrophobic BAs [20]. VDR signaling also exerts anti-inflammatory effects by downregulating NF-κB and cytokine expression in the liver and intestine, linking BA signaling to immune modulation [21].

## Membrane-Bound Receptor Signaling

TGR5 is a **G protein-coupled receptor** expressed in hepatocytes, cholangiocytes, macrophages, enteroendocrine cells, and brown adipose tissue. Secondary bile acids, such as LCA and DCA, are potent TGR5 agonists.

**cAMP-Dependent Pathways:** TGR5 activation elevates intracellular cAMP levels, leading to PKA activation, CREB phosphorylation, and induction of metabolic and anti-inflammatory genes.

**Energy Homeostasis:** TGR5 signaling promotes **thyroid hormone activation** in brown adipose tissue, enhancing thermogenesis and energy expenditure.

**Immune Modulation:** In Kupffer cells and macrophages, TGR5 suppresses pro-inflammatory cytokine production (TNF-α, IL-6) and reduces NF-κB activation, linking BA signaling to liver inflammation control.

## Cross-Talk Between Signaling Pathways

BA signaling exhibits **extensive cross-talk** with other metabolic and inflammatory pathways:

**FXR–TGR5 Axis:** FXR-induced FGF19 not only inhibits hepatic BA synthesis but also interacts with TGR5-mediated energy metabolism and gut hormone secretion (GLP-1), integrating BA signaling with glucose homeostasis.

**Inflammation and Immunity:** Both FXR and TGR5 reduce pro-inflammatory gene expression in hepatocytes and immune cells. VDR activation by LCA complements this effect, forming a protective network against cholestatic and metabolic liver injury [16].

**Gut-Liver Axis:** Microbiota-modified secondary BAs serve as selective ligands for TGR5, PXR, and VDR, influencing intestinal barrier integrity, systemic metabolism, and immune responses, establishing a **microbiota–bile acid–host signaling loop** [17,18].

## Pathophysiological Implications

## Disruption of BA signaling contributes to multiple liver and biliary diseases:

**Cholestasis:** Impaired FXR or BSEP function leads to BA accumulation, hepatocyte apoptosis, and inflammation. FXR agonists such as **obeticholic acid** show therapeutic promise in primary biliary cholangitis [22].

**Non-Alcoholic Fatty Liver Disease (NAFLD) / NASH:** Altered BA composition, reduced FXR signaling, and dysregulated TGR5 activity exacerbate lipid accumulation, insulin resistance, and inflammatory responses.

**Biliary Disorders:** Gallstone formation is influenced by BA hydrophobicity and cholesterol saturation, both regulated by nuclear receptor activity. TGR5 signaling in cholangiocytes modulates bile secretion and protects against cholangiocyte apoptosis [22,23].

**Hepatic Fibrosis and Inflammation:** Dysregulated BA signaling promotes stellate cell activation and fibrogenesis, while TGR5 and FXR agonists may attenuate inflammatory and fibrotic responses.

**Therapeutic Perspectives**

**BA signaling pathways are increasingly targeted for therapeutic interventions:**

**FXR Agonists:** Obeticholic acid and non-steroidal FXR agonists are in clinical trials for PBC, NASH, and cholestatic liver diseases.

**TGR5 Modulators:** TGR5 agonists enhance insulin sensitivity, reduce hepatic inflammation, and may prevent gallstone formation, representing promising candidates for metabolic and biliary disorders.

**PXR and CAR Activation:** Pharmacological modulation of detoxification pathways can alleviate BA-induced hepatotoxicity, especially in drug-induced liver injury.

**BA Derivatives:** Hydrophilic BAs, such as ursodeoxycholic acid (UDCA), protect hepatocytes, improve bile flow, and are standard treatments for cholestatic liver disease (Table 2).

# PATHOPHYSIOLOGICAL ROLES OF BILE ACIDS IN LIVER AND BILIARY DISORDERS

Bile acids (BAs) are central to hepatic and biliary homeostasis, yet their dysregulation is implicated in a spectrum of liver and biliary disorders. Both **accumulation and deficiency** of specific bile acids, coupled with altered receptor signaling (Table 3), contribute to hepatocellular injury, cholestasis, inflammation, fibrosis, and systemic metabolic dysfunction. Understanding the **pathophysiological mechanisms** provides a foundation for therapeutic intervention.

## Cholestatic Liver Diseases

Cholestasis is characterized by **impaired bile formation**

**Table 2:** Key Bile Acid Receptors and Pathway Functions.

| Receptor | Type | Endogenous Ligand | Tissue Expression | Major Function | Therapeutic Potential |
|---|---|---|---|---|---|
| FXR (NR1H4) | Nuclear | CDCA, CA | Liver, intestine, kidney | BA homeostasis, lipid/ glucose metabolism | FXR agonists (OCA) for PBC/NASH |
| TGR5 (GPBAR1) | Membrane | LCA, DCA | Liver, intestine, macrophages | Energy metabolism, anti-inflammatory | TGR5 agonists for metabolic liver disease |
| PXR (NR1I2) | Nuclear | LCA, DCA | Liver, intestine | Detoxification, CYP induction | Reduce BA toxicity, drug metabolism modulation |
| CAR (NR1I3) | Nuclear | LCA | Liver, intestine | Detoxification, phase I/ II enzymes | Therapeutic modulation of cholestasis |
| VDR | Nuclear | LCA | Liver, intestine, immune cells | Detoxification, anti-inflammatory | Potential in cholestasis, inflammation |

**Table 3:** Summary of Bile Acid-Related Pathophysiological Mechanisms.

| Disease/Condition | BA Dysregulation | Mechanism | Key Receptors Involved | Therapeutic Strategies |
|---|---|---|---|---|
| Cholestasis | Accumulation of hydrophobic BAs | Hepatocyte apoptosis, ER stress | FXR, PXR, VDR | FXR agonists, UDCA |
| NAFLD/NASH | Altered BA composition | Lipogenesis, inflammation, fibrosis | FXR, TGR5 | FXR/TGR5 agonists |
| Gallstones | Reduced hydrophilic BAs | Cholesterol crystallization | FXR, CYP7A1 | UDCA, dietary interventions |
| DILI | Drug-induced BSEP inhibition | BA cytotoxicity, apoptosis | PXR, CAR | BA modulators, drug screening |
| Fibrosis/HCC | Chronic BA accumulation | Stellate cell activation, ROS, DNA damage | FXR, TGR5 | FXR/TGR5 agonists, microbiota modulation |
| PSC | Toxic BA effects on cholangiocytes | Apoptosis, fibrosis, inflammation | FXR, TGR5 | UDCA, FXR/TGR5 agonists |

**or flow**, leading to intrahepatic accumulation of hydrophobic BAs that are cytotoxic.

**Genetic and acquired factors contribute to cholestasis:**

- **Genetic Cholestasis:** Mutations in **BSEP (ABCB11), MDR3 (ABCB4), or FXR (NR1H4)** disrupt BA secretion and hepatocyte homeostasis, resulting in **progressive familial intrahepatic cholestasis (PFIC)**.
- **Acquired Cholestasis:** Obstruction of bile ducts, drug-induced cholestasis, or autoimmune conditions such as **primary biliary cholangitis (PBC)** impair BA excretion, provoking hepatocyte apoptosis, oxidative stress, and inflammation.
- **Mechanisms:** Accumulated hydrophobic BAs induce **endoplasmic reticulum stress**, mitochondrial dysfunction, and reactive oxygen species (ROS) generation. FXR signaling disruption reduces SHP-mediated negative feedback, further exacerbating BA toxicity.

**Therapeutic interventions:** FXR agonists (e.g., obeticholic acid), hydrophilic BAs (UDCA), and agents targeting bile salt export can reduce hepatocellular injury and improve liver function in cholestatic conditions.

Non-Alcoholic Fatty Liver Disease (NAFLD) and NASH

**BAs influence lipid, glucose, and energy metabolism. Dysregulated BA signaling contributes to:**

- **Hepatic steatosis:** Impaired FXR and TGR5 signaling promotes lipogenesis and inhibits β-oxidation, facilitating triglyceride accumulation.
- **Insulin resistance:** Altered BA-FXR-FGF19 axis affects glucose homeostasis and insulin signaling in hepatocytes and peripheral tissues.
- **Inflammation and fibrosis:** Secondary BAs, through TGR5 or VDR pathways, modulate Kupffer cell activation and hepatic stellate cell activity. Dysfunction in these pathways triggers pro-inflammatory cytokine release (TNF-α, IL-6) and fibrogenesis .

**Clinical relevance:** Therapeutics targeting BA signaling, including FXR agonists and modified BA derivatives,

demonstrate potential in reducing hepatic steatosis and fibrosis in NASH patients.

Gallstone Disease and Cholesterol Metabolism

BAs play a pivotal role in **cholesterol solubilization and bile formation**.

### Dysregulation leads to gallstone formation:

- **Pathogenesis:** Imbalance in BA composition, specifically reduced hydrophilic BAs, increases cholesterol crystallization. Altered hepatic BA synthesis, influenced by FXR and CYP7A1 activity, contributes to gallstone risk [24].
- **Mechanisms:** Reduced BSEP expression or impaired bile flow concentrates cholesterol in bile, forming precipitates. Bile acid malabsorption in the intestine alters enterohepatic circulation, further promoting gallstone formation.

**Therapies:** Ursodeoxycholic acid (UDCA) is effective in dissolving cholesterol-rich gallstones, while lifestyle and dietary interventions modulate BA composition to reduce recurrence [25].

Drug-Induced Liver Injury (DILI) and Toxicity

### Hydrophobic BAs, when accumulated, can potentiate hepatocyte injury and apoptosis, often exacerbated by drugs that interfere with BA transporters:

- **BSEP inhibitors:** Certain drugs (e.g., cyclosporine, bosentan) impair BA excretion, leading to cholestatic DILI.
- **Mechanisms:** Excessive intracellular BA accumulation activates **caspase pathways**, ER stress, and mitochondrial permeability transition, promoting hepatocyte necrosis or apoptosis.
- **Protective mechanisms:** Activation of PXR, CAR, and VDR enhances detoxification and mitigates BA-induced cytotoxicity.

**Clinical implication:** Screening drugs for BSEP inhibition is critical to prevent cholestatic DILI, and BA modulators may serve as therapeutic adjuncts.

Hepatocellular Carcinoma (HCC) and Fibrosis

**Chronic BA dysregulation contributes to hepatocarcinogenesis and fibrotic progression:**

- **Fibrogenesis:** BAs induce **hepatic stellate cell activation** through TGR5-mediated signaling, increasing extracellular matrix deposition.
- **Carcinogenesis:** Hydrophobic BAs generate ROS, cause DNA damage, and promote pro-oncogenic pathways (e.g., β-catenin, NF-κB), facilitating HCC development.
- **Microbiota influence:** Secondary BAs modulated by gut microbiota can either exacerbate or mitigate HCC progression, highlighting the BA-gut-liver axis.

**Therapeutic approaches:** FXR and TGR5 agonists, BA sequestrants, and modulation of gut microbiota are potential strategies to reduce fibrosis and HCC risk.

Cholangiopathies and Biliary Inflammation

**Cholangiocytes are highly sensitive to BA-mediated signaling:**

- **Primary Sclerosing Cholangitis (PSC):** Altered BA composition and impaired FXR/TGR5 signaling induce cholangiocyte apoptosis, periductal fibrosis, and inflammation.
- **Mechanisms:** Cytotoxic BAs trigger **oxidative stress,** disrupt tight junctions, and induce pro-inflammatory cytokines. TGR5 activation promotes cholangiocyte survival and anti-inflammatory responses .
- **Therapeutic perspectives:** UDCA, FXR agonists, and TGR5 modulators protect cholangiocytes and reduce inflammation, potentially slowing PSC progression.

Crosstalk Between Liver and Systemic Diseases

**BA dysregulation extends beyond hepatobiliary disorders, influencing:**

- **Metabolic syndrome:** Impaired FXR-TGR5 signaling promotes obesity, insulin resistance, and dyslipidemia.
- **Gut microbiota:** Altered BA composition modifies microbial communities, influencing systemic inflammation and metabolic health.
- **Neuroinflammatory disorders:** BA signaling intersects with neuroinflammatory pathways, potentially affecting CNS disorders such as multiple sclerosis via FXR and TGR5-mediated immune modulation.

## THERAPEUTIC PERSPECTIVES, EMERGING INTERVENTIONS, CLINICAL TRIALS, AND FUTURE DIRECTIONS

The pathophysiological insights into bile acid (BA) signaling and dysregulation have propelled the development of **therapeutic strategies** targeting BA pathways in hepatic and biliary diseases. This section highlights current and emerging therapies, ongoing clinical trials, and future research directions (Table 4).

**Table 4:** Therapeutic Strategies Targeting Bile Acid Pathways.

| Therapy | Target | Mechanism | Clinical Indications | Limitations |
|---|---|---|---|---|
| UDCA | Hydrophobic BAs | Cytoprotection, choleresis | PBC, gallstones | Limited efficacy in PSC |
| Obeticholic acid | FXR | Suppresses BA synthesis, anti-inflammatory | PBC, NASH | Pruritus, lipid alterations |
| Tropifexor / Cilofexor | FXR | FXR agonists, anti-fibrotic | NASH, PSC | Early-phase studies |
| TGR5 agonists | TGR5 | Anti-inflammatory, metabolic regulation | NAFLD, cholestasis (experimental) | Limited human data |
| Nor-UDCA | BAs | Choleretic, anti-fibrotic | PSC, NASH | Early clinical trials |
| BA sequestrants | Intestinal BAs | Interrupt enterohepatic circulation | Pruritus, hypercholesterolemia | Fat-soluble vitamin malabsorption |
| Gut microbiota modulation | Microbial BA metabolism | Reduce toxic BAs | Experimental in NASH, PSC | Variable efficacy |

Bile Acid Supplementation and Modulation

**Ursodeoxycholic acid (UDCA)** is the first-line therapy for several cholestatic disorders, including **primary biliary cholangitis (PBC)** and cholesterol gallstones.

**Therapeutic benefits include:**

- **Cytoprotective effects:** UDCA increases the hydrophilicity of bile, reducing the cytotoxicity of hydrophobic BAs.
- **Choleretic action:** Enhances bile flow, alleviating cholestasis.
- **Anti-apoptotic signaling:** Stabilizes mitochondrial membranes and reduces oxidative stress in hepatocytes.

**Limitations:** UDCA is less effective in **primary sclerosing cholangitis (PSC)** and advanced cholestatic liver disease, highlighting the need for novel interventions.

Farnesoid X Receptor (FXR) Agonists

FXR is a nuclear receptor central to BA homeostasis, lipid metabolism, and anti-inflammatory signaling.

**Therapeutic targeting of FXR shows promise in cholestasis, NASH, and fibrosis:**

- **Obeticholic acid (OCA):** A semi-synthetic FXR agonist that suppresses bile acid synthesis via CYP7A1 inhibition and induces protective genes (SHP, BSEP).
- **Clinical outcomes:** OCA reduces serum alkaline phosphatase and improves histological features in PBC; in NASH, OCA demonstrates improvements in fibrosis scores [26].

**Emerging FXR agonists:** Tropifexor, cilofexor, and EDP-305 are under investigation for NASH, PSC, and cholestatic disorders, aiming to improve potency and reduce pruritus [27].

TGR5 Agonists and Immune Modulation

**TGR5 is a G-protein coupled receptor mediating BA signaling in immune cells, cholangiocytes, and metabolic tissues:**

- **Anti-inflammatory effects:** TGR5 activation inhibits NF-κB signaling, reducing cytokine production in Kupffer cells and cholangiocytes.
- **Metabolic benefits:** Enhances GLP-1 secretion in enteroendocrine cells, improving insulin sensitivity.

**Therapeutic potential:** TGR5 agonists may complement FXR-targeted therapies in cholestatic disorders and metabolic liver disease.

Bile Acid Sequestrants

**Cholestyramine, colesevelam, and colestipol** bind BAs in the intestine, preventing reabsorption:

- **Indications:** Useful for **pruritus in cholestasis** and hypercholesterolemia.
- **Mechanism:** Interrupts enterohepatic circulation, reducing toxic BA accumulation in the liver and systemic circulation.

**Limitations:** May impair absorption of fat-soluble vitamins and interfere with oral medications; efficacy is often moderate.

Emerging Therapies Targeting Gut-Liver Axis

**The gut microbiota regulates secondary BA composition, influencing hepatic inflammation, fibrosis, and metabolic homeostasis:**

Review Article

- **Probiotics and prebiotics:** Modulate microbial BA metabolism, reducing toxic secondary BA accumulation.
- **Fecal microbiota transplantation (FMT):** Experimental studies suggest potential benefits in cholestatic and metabolic liver diseases.
- **BA derivatives:** Nor-UDCA, a side-chain shortened UDCA, demonstrates improved choleretic and anti-fibrotic effects in PSC and experimental NASH models.

Clinical Trials and Translational Research

**Several clinical trials have tested BA-targeted interventions in cholestatic and metabolic liver diseases**:

- **NASH:** FXR agonists (OCA, tropifexor) improve fibrosis and metabolic parameters in phase II/III trials.
- **PBC:** OCA significantly reduces alkaline phosphatase and pruritus in UDCA non-responders [26].
- **PSC:** Nor-UDCA demonstrates reduction in alkaline phosphatase and liver stiffness in early-phase trials [27-33].

**Challenges:** Variability in disease etiology, patient BA profiles, and co-existing metabolic conditions complicate therapeutic outcomes. Precision medicine approaches, including **BA profiling and receptor polymorphism analysis,** may improve patient selection and response.

Future Directions in Bile Acid Research

**Advancements in BA biology provide several research avenues**:

1. **Selective receptor modulators:** Development of tissue-specific FXR or TGR5 agonists to minimize off-target effects.
2. **Combination therapies:** Concurrent modulation of BA signaling, gut microbiota, and metabolic pathways may synergistically improve outcomes in NASH and cholestatic liver diseases.
3. **Biomarker discovery:** Circulating BA composition, receptor expression, and microbial metabolites could serve as diagnostic and prognostic biomarkers.
4. **Gene therapy:** Targeting defective transporters (BSEP, MDR3) via CRISPR-Cas or viral vectors offers a precision therapy approach for inherited cholestatic diseases.
5. **Personalized medicine:** Integration of genomic, metabolomic, and microbiome data to optimize BA-targeted interventions.

## CONCLUSION

Bile acids are no longer viewed merely as detergents facilitating lipid digestion but as **dynamic signaling molecules** orchestrating hepatic metabolism, immune regulation, and enterohepatic homeostasis. Dysregulation of bile acid synthesis, transport, or receptor signaling underlies a spectrum of hepatic and biliary disorders, including **PBC, PSC, NASH, cholestasis, and gallstone disease**. Advances in understanding **FXR, TGR5, and other BA-mediated pathways** have enabled the development of novel therapeutics, including FXR agonists (e.g., obeticholic acid, tropifexor), TGR5 modulators, Nor-UDCA, and gut microbiota-targeted interventions. Despite promising results, challenges remain, including inter-patient variability, limited efficacy in advanced disease stages, and long-term safety. Future perspectives emphasize **precision medicine approaches**, integrating patient-specific BA profiles, receptor expression, and gut microbiota composition to optimize therapy. Translational research exploring **BA modulation in metabolic, fibrotic, and neuroinflammatory diseases** underscores the potential of bile acids as central mediators of systemic homeostasis. Comprehensive mechanistic insights and carefully designed clinical trials are essential to fully realize the therapeutic potential of bile acid-targeted interventions.

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