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Biological functions and pharmacological behaviors of bile acids in metabolic diseases

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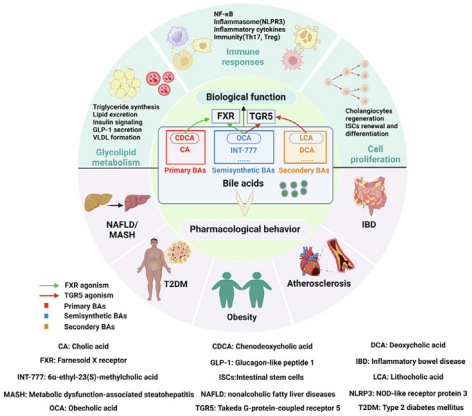
HIGHLIGHTS

- Functional bile acids (BAs) reveal diverse pharmacological activities attributed to their unique structural variations.
- BA receptors mediate essential signaling pathways to regulate glucose and lipid metabolism, and immune responses.
- BAs hold significant potential in safeguarding metabolic homeostasis and organ function through TGR5 and FXR signaling.
- BAs or BA analog-based medications offer promising approaches for addressing metabolic and gastrointestinal disorders.

GRAPHICAL ABSTRACT



Abbreviations: Allo-CA, Allocholic acid; APC, Adenomatous Polyposis Coli; ASBT, Apical sodium-dependent bile acid transporter; BAs, Bile acids; BAT, Brown adipose tissue; C-24 BAs, BAs containing 24 carbons; CA, Cholic acid; cAMP, Cyclic adenosine monophosphate; CD, Crohn's disease; CDCA, Chenodeoxycholic acid; CFTR, Cystic fibrosis transmembrane conductance regulator; CREB, cAMP response element binding protein; CYP7A1, Cytochrome P450 family 7 subfamily A member 1, also known as Cholesterol 7α-hydroxylase; CYP7B1, Cytochrome P450 family 7 subfamily B member 1, also known as Oxysterol 7α-hydroxylase; CYP8B1, Cytochrome P450 family 8 subfamily B member 1, also known as Sterol 12α-hydroxylase; DCA, Deoxycholic acid; DCs, Dendritic cells; Dehydro-DCA, Dehydrodeoxycholic acid; Dinor-DCA, dinorhyodeoxycholic acid; FAO, Fatty acid β-oxidation; FGF-15/19, Fibroblast growth factor 15/19; FXR, Farnesoid X receptor; G6P, Glucose 6-phosphatase; GDCA, glycodeoxycholic acid; Gly-β-MCA, Glycine-β-muricholic acid; GLP-1, Glucagon-like peptide-1; GPCRs, G protein-coupled receptors; HCA, Hyocholic acid; HCC, Hepatocellular carcinoma C; HFD, High-fat diet; HNF-4α, Hepatocyte nuclear factor 4α; HSCs, Hepatic stellate cells; IBABP, Ileal bile acid-binding protein; IBD, Inflammatory bowel disease; IDE, Insulin-degrading enzyme; IECs, Intestinal epithelial cells; ISCs, Intestinal stem cells; Iso-CA, Isocholic acid; Iso-CDCA, Iso-chenodeoxycholic acid; Keto-LCA, Ketolithocholic acid; KLB, Fibroblast growth factor receptor 4 (FGFR4)/β-klotho complex; LCA, Lithocholic acid; LPS, Lipopolysaccharide; LRH-1, Liver receptor homolog 1; MAPK, Mitogen–activated protein kinase; MCAs, Murine cholic acids; MDR-3, Multidrug resistance protein 3; MyD88, Myeloid differentiation factor 88; NALP3, NACHT, LRR, and PYD domain-containing protein 3; MASH, Metabolic dysfunction-associated steatohepatitis; NLRP3, NOD-like receptor protein 3; OCA, Obecholic acid; OS, Oxidative stress; 3-oxo-CA, 3-oxo-cholic acid; Oxo-DCA, Oxodeoxycholic acid; PEPCK, Phosphoenolpyruvate carboxykinase; PH, Partial hepatectomy; PKA, Protein kinase A; PPARα, peroxisome proliferator-activated receptor alpha; RAR, Retinoic acid receptor; RORγt, RAR-related orphan receptor γ; SCFA, Short-chain fatty acid; SHP, Small heterodimeric partner; SREBP-1c, Sterol-regulated binding protein 1c; T2DM, Type 2 diabetes mellitus; TCA, Taurocholic acid; TGF-β, Transforming growth factor β; TGR5, Takeda G-protein-coupled receptor 5, also known as G protein-coupled bile acid receptor 1 (GPBAR1); TJ, Tight junction; TLR-4, Toll–like receptor 4; Triketo-CA, Triketocholanic acid; TUDCA, Tauroursodeoxycholic acid; T-β-MCA, Tauro-β-muricholic acid; UC, Ulcerative colitis; UCP, Uncoupling protein; UDCA, Ursodeoxycholic acid; VDR, Vitamin D receptor; VLDL, Very-low-density lipoprotein; YAP1, Yes-associated protein 1.

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ABSTRACT

Background: Bile acids, synthesized endogenously from cholesterol, play a central role in metabolic regulation within the enterohepatic circulatory system. Traditionally known as emulsifying agents that facilitate the intestinal absorption of vitamins and lipids, recent research reveals their function as multifaceted signal modulators involved in various physiological processes. These molecules are now recognized as key regulators of chronic metabolic diseases and immune dysfunction. Despite progress in understanding their roles, their structural diversity and the specific functions of individual bile acids remain underexplored.

Aim of review: This study categorizes the bile acids based on their chemical structures and their roles as signaling molecules in physiological processes. It consolidates current knowledge and provides a comprehensive overview of the current research. The review also includes natural and semisynthetic variants that have demonstrated potential in regulating metabolic processes in animal models or clinical contexts.

Key scientific concepts of review: Bile acids circulate primarily within the enterohepatic circulation, where they help maintain a healthy digestive system. Disruptions in their balance are linked to metabolic disorders, hepatobiliary diseases and intestinal inflammation. Through receptor-mediated pathways, bile acids influence the progression of metabolic diseases by regulating glucose and lipid metabolism, immune function, and energy expenditure. This review aims to provide a comprehensive, systematic foundation to for understanding their physiological roles and supporting future therapeutic developments for metabolic and inflammatory diseases.

Contents

Introduction

Bile acids (BAs) are biosynthesized from cholesterol in the liver, and the biosynthesis and enterohepatic circulation of BAs are tightly regulated [1–3]. A growing body of evidence suggests that BAs act as hormones in regulating paracrine and endocrine signaling pathways in addition to their roles as natural detergents in the digestive system of the intestine [4]. BAs play a critical role in regulating lipid and glucose metabolism, as well as maintaining energy homeostasis [5,6]. Members of the BA family display diverse biochemical characteristics. Initially, BAs are synthesized in hepatocytes. They are then conjugated with either glycine or taurine to form amphiphilic BAs, which are stored in the gallbladder or secreted into the duodenum to facilitate lipid absorption [7,8]. Glycine-conjugated or taurine-conjugated BAs are converted to their corresponding secondary BAs through the action of enzymes derived from gut microbiota. Most BAs are reabsorbed in the terminal ileum through active transport [9,10]. Only a small amount of BAs released into the systemic circulation are absorbed by the kidney thereafter. Moreover, partially modified secondary BAs can generate various isomers regulated by gut bacteria in the ileum and colon. These isomers may potentially regulate immune, inflammatory, and endocrine homeostasis.

The nuclear hormone receptor farnesoid X receptor (FXR), and membrane receptor takeda G-protein-coupled receptor 5 (TGR5) are key receptors involved in BA signaling [11]. FXR is a key nuclear receptor that regulates lipid and glucose metabolism by modulating plasma lipid clearance and intestinal cholesterol absorption. It

also plays roles in inflammatory and apoptotic pathways [12,13]. TGR5, a G protein-coupled receptor (GPCR), primarily regulates glucose transport, energy metabolism, immune responses, and cellular regeneration and proliferation [14–16]. The development of semisynthetic BA analogs has markedly enhanced the management of metabolic disorders by precisely adjusting BA levels in the intestine. BA-associated signaling pathways have thus emerged as promising targets for drug development in treating metabolic, hepatobiliary, and intestinal inflammatory diseases. Here, we provide an overview of structure-based BA classification, followed by an exploration of the mechanistic connections between BAs and metabolic processes through two crucial BA-sensing receptors, FXR and TGR5. Finally, we summarize therapeutic strategies for metabolic disorders and enterohepatic inflammatory diseases that utilize BAs or their analogs.

BA Classification

BAs are derivatives of cholesterol and encompass a blend of structurally and functionally similar compounds. Structurally, BAs can be classified as free BAs, such as cholic acid (CA), deoxycholic acid (DCA), chenodeoxycholic acid (CDCA), and lithocholic acid (LCA). Alternatively, free BAs may be conjugated with glycine or taurine to form glycocholic acid (GCA), taurocholic acid (TCA), glycochenodeoxycholic acid (GCDCA), and taurochenodeoxycholic acid (TCDCA), collectively known as conjugated BAs. Most naturally occurring BAs contain 24 carbons (C-24 BAs). The steroidal core of BAs constitutes a saturated cyclopentane phenanthrene nucleus comprising three six-membered and one five-membered ring, which forms the basis for their biosynthesis. BAs possess amphipathic properties due to a hydroxylated steroid nucleus and a hydrocarbon chain terminating in a carboxyl group. Variations in the positions of hydroxyl and carboxyl groups contribute to the production of diverse structural isomers of BAs.

Cholestane (24-carbon BA) free BAs

Free BAs, typically including CA, DCA, CDCA, and LCA, can be further classified into primary and secondary free BAs. There are two main biosynthesis pathways for free BAs: the classical and alternative pathways [17]. The classical pathway generally includes four major steps leading to the synthesis of primary BAs: initiation, ring structure modification, side chain oxidation, and conjugation [5]. Under physiological conditions, the first rate-limiting enzyme responsible for primary BA production in the classical pathway is cholesterol 7α-hydroxylase (CYP7A1), a cytochrome P450 enzyme that converts cholesterol to 7α-hydroxycholesterol. Subsequently, part of the reaction intermediate 7α-hydroxy-4-cholesten-3-one is finally converted to CDCA, while another part is converted to 7α,12α-dihydroxy-4-cholesten-3-one. This conversion is catalyzed by sterol 12α-hydroxylase (CYP8B1), which induces a hydroxyl group at position C-12 of the steroid nucleus, ultimately leading to the formation of CA. Therefore, the expression and activity of CYP8B1 affects the CA to CDCA ratio by promoting CA biosynthesis. In rodents, a substantial amount of CDCA is converted to murine cholic acids (MCAs) *via* 6β-hydroxylation in the liver.

The alternative pathway is initiated by sterol-27 hydroxylase (encoded by CYP27A1), and the intermediate 27-hydroxycholesterol then undergoes 7α-hydroxylation by oxysterol 7α-hydroxylase (CYP7B1). The product of 7α-hydroxylation, 4-cholesten-7α-3-one, can undergo further modification through steroid ring modifications and sidechain shortening, primarily resulting in the formation of CDCA. In contrast, the classical pathway produces both CA and CDCA.

These primary BAs are subsequently conjugated with taurine or glycine to yield the conjugated BAs, including TCA or GCA, TCDCA or GCDCA, tauro-α-muricholic acid (T-α-MCA) or G-α-MCA, and tauro-β-muricholic acid (T-β-MCA) or G-β-MCA, among others. The conjugated BAs are then excreted into the intestine, where they undergo deconjugation or dehydroxylation through the activity of intestinal microbiota. This process ultimately forms secondary free BAs such as DCA, LCA, ursodeoxycholic acid (UDCA), hyocholic acid (HCA), murideoxycholic acid (MDCA), ω-muricholic acid (ω-MCA), and hyodeoxycholic acid (HDCA). Notably, T-α-MCA and T-β-MCA are uncoupled through BSH, forming α-MCA and β-MCA. β-MCA is C-6 epimerized to form ω-MCA, and then ω-MCA is 7 α-dehydroxylated to form HDCA [18]. CDCA is converted to UDCA through hydroxysteroid dehydrogenase (HSDH) [19]. The participation of gut microbes results in considerable enrichment with a wide variety of free BAs [19,20]. In the gastrointestinal milieu, secondary metabolism by gut microbes (e.g., epimerization, hydroxyl group oxidation, dihydroxylation, and related biological reactions) can generate other secondary BAs such as isocholic acid (Iso-CA), *iso*-chenodeoxycholic acid (Iso-CDCA), allocholic acid (Allo-CA), oxodeoxycholic acid (Oxo-DCA), 3-oxocholic acid (3-oxo-CA), dehydrodeoxycholic acid (Dehydro-DCA), dinorhyodeoxycholic acid (Dinor-DCA), ketolithocholic acid (Keto-LCA), triketocholanic acid (Triketo-CA) (Fig. 1**A**).

Conjugated BAs

The conjugated BAs are mainly divided into primary and secondary conjugated BAs. The former group includes GCA, TCA, GCDCA, TCDCA, T-α-MCA, and T-β-MCA. In addition to aminoacyl bond formation with glycine or taurine, pathways such as glucuronidation, sulfation, and N-acetylglucosamine conjugation can generate several different types of BAs in humans. For instance, glycoursodeoxycholic acid-3-sulfate (Gly-UDCA-3-Sul), glycodeoxycholic acid-3-sulfate (Gly-DCA-3-Sul), taurocholic acid-3α-sulfate (Tau-CA-3α-Sul), and taurolithocholic acid-3α-sulfate (Tau-LCA-3α-Sul) are common products of these modifications. Fig. 1**A** provides an overview of the biotransformation pathways for several representative conjugated BAs.

Most naturally occurring BAs belong to the 5β series, characterized by hydroxyl groups in the A, B, and C rings of the steroid system [21,22]. These hydroxyl groups are typically α-oriented and are predominantly found at positions C-3, C-6, C-7, C-12, and C-23. In most BAs, the B/C and C/D ring junctions are in the *trans* configuration, while the A/B ring junction is in the *cis* (5β series) oriented. The A-ring commonly adopts a stable chair conformation rather than a less stable boat confirmation. Currently, there are five main known modifications of C-24 BAs: 1) N-acyl amidation with glycine or taurine, 2) sulfation, 3) ester glucuronidation at C-24, 4) ethereal conjugation at C-3, and 5) N-acetylglucose amination at C-7.

Noncholestane C-24 acidsNoncholestane C-24 acids can be generally classified into four categories based on the total number of carbon atoms, including nor-BAs (parent nucleus II), dinor-BAs (parent nucleus I), homo-BAs (parent nucleus III), and dihomo-BAs (parent nucleus IV) (Table 1, Fig. 1**B**). Nor-BAs are C-23 BAs or alcohols and their derivatives that differ from the natural C-24 BAs by having one less methylene group in the side chain. Decoupling, dehydrogenation, and hydroxylation reactions commonly occur at positions C-3, C-7, C-12, and C-23 of nor-BAs. Homo-BAs are C-25 BAs or alcohols and their derivatives. Dinor-BAs include C-22 BAs or alcohols and their derivatives, which are often hydroxylated, methylated, and decoupled. Dihomo-BAs refer to C-26 BAs or alcohols and their derivatives. In addition to the more common C-24 BAs, several BAs have been identified with a C-27 core structure. C-27 BAs typically form amide linkages with taurine, connect-

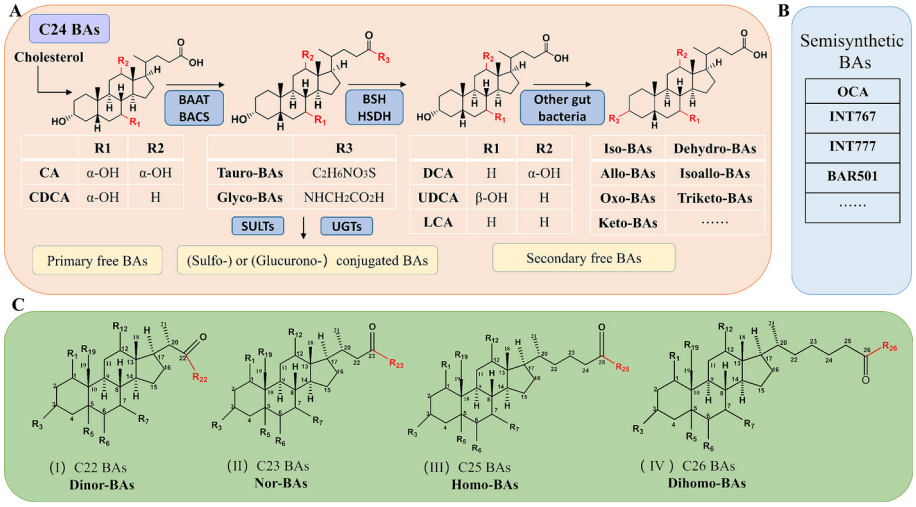

Fig. 1. Classifications of BAs based on the number of carbon atoms constituting the backbone structure. **A**) Schematic presentation of the main biochemical transformations during C-24 BA synthesis and its secondary metabolism. **B**) The structure of the non-C-24 parent nucleus of secondary BAs like dinor-BA, nor-BA, homo-BA, and dihomo-BA species. **C**) Partial semisynthetic non-C-24 parent nucleus of BAs that are derived from natural BAs through structural modifications.

Table 1
Specific categories of Nor-BAs, Homo-BAs, Dinor-BAs, and Dihomo-BAs.

Class	Blie Acids	Name	R3	R6	R7	R12	R24/23/25/22
Nor-BAs (II)	Noravi-CA	Noravicholic acid	α-OH	H	α-OH	H	OH
	Nor-DCA	Nordeoxycholic acid	α-OH	H	H	α-OH	OH
	Nor-α-MCA	Nor-α-muricholic acid	α-OH	β-OH	α-OH	H	OH
	Nor-β-MCA	Nor-β-muricholic acid	α-OH	β-OH	β-OH	H	OH
	Nor-w-MCA	Nor-w-muricholic acid	α-OH	α-OH	β-OH	H	OH
	Nor-MDCA	Normurideoxycholic acid	α-OH	β-OH	H	H	OH
	Nor-CDCA	Norchenodeoxycholic acid	α-OH	H	α-OH	H	OH
	Nor-UDCA	Norursodeoxycholic acid	α-OH	H	β-OH	H	OH
	Nor-HDCA	Norhyodeoxycholic acid	α-OH	α-OH	H	H	OH
	Nor-LCA	Norlithocholic acid	α-OH	H	H	H	OH
	Nor-DCA-Disul	Nordeoxycholic acid disulfate	α-HSO_4	H	H	α-HSO_4	OH
Homo-BAs (III)	Homo-CA	Homocholic acid	α-OH	H	α-OH	α-OH	OH
	Homoavi-CA	Homoavicholic acid	α-OH	H	α-OH	H	OH
	Homo-DCA	Homodeoxycholic acid	α-OH	H	H	α-OH	H
	Homo-α-MCA	Homo-α-muricholic acid	α-OH	β-OH	α-OH	H	OH
	Homo-β-MCA	Homo-β-muricholic acid	α-OH	β-OH	β-OH	H	OH
	Homo-ω-MCA	Homo-ω-muricholic acid	α-OH	α-OH	β-OH	H	OH
	Homo-MDCA	Homomurideoxycholic acid	α-OH	β-OH	H	H	OH
	Homo-CDCA	Homochenodeoxycholic acid	α-OH	H	α-OH	H	OH
	Homo-UDCA	Homoursodeoxycholic acid	α-OH	H	β-OH	H	OH
	Homo-HCA	Homohyocholic acid	α-OH	α-OH	α-OH	H	OH
	Homo-HDCA	Homohyodeoxycholic acid	α-OH	α-OH	H	H	OH
	Homo-LCA	Homolithocholic acid	α-OH	H	H	H	OH
Dinor-BAs (IV)	Dinor-α-MCA	Dinor-α-muricholic acid	α-OH	β-OH	α-OH	H	OH
	Dinor-β-MCA	Dinor-β-muricholic acid	α-OH	β-OH	β-OH	H	OH
	Dinor-MDCA	Dinormurideoxycholic acid	α-OH	β-OH	H	H	OH
	Dinor-CDCA	Dinorchenodeoxycholic acid	α-OH	H	α-OH	H	OH
	Dinor-UDCA	Dinorursodeoxycholic acid	α-OH	H	β-OH	H	OH
Dihomo −BAs (V)	Dihomoavi-CA	Dihomoavicholic acid	α-OH	H	α-OH	H	OH
	Dihomo-DCA	Dihomodeoxycholic acid	α-OH	H	H	α-OH	OH
	Dihomo-α-MCA	Dihomo-α-muricholic acid	α-OH	β-OH	α-OH	H	OH
	Dihomo-β-MCA	Dihomo-β-muricholic acid	α-OH	β-OH	β-OH	H	OH
	Dihomo-ω-MCA	Dihomo-ω-muricholic acid	α-OH	α-OH	β-OH	H	OH
	Dihomo-MDCA	Dihomomurideoxycholic acid	α-OH	β-OH	H	H	OH
	Dihomo-CDCA	Dihomochenodeoxycholic acid	α-OH	H	α-OH	H	OH
	Dihomo-UDCA	Dihomoursodeoxycholic acid	α-OH	H	β-OH	H	OH
	Dihomo-HCA	Dihomohyocholic acid	α-OH	α-OH	α-OH	H	OH
	Dihomo-HDCA	Dihomohyodeoxycholic acid	α-OH	α-OH	H	H	OH
	Dihomo-LCA	Dihomolithocholic acid	α-OH	H	H	H	OH

ing the BA-carboxyl to the taurine-amino group. In contrast, C-27 bile alcohols primarily interact with sulfates through esterification at C-27.

Recently, research attention has focused on semisynthetic BAs due to their potent agonist/antagonist effects towards BA receptors [23,24]. For example, selective TGR5 agonists like INT777 and BAR501 are analogues of CA and UDCA, respectively. INT767, a semisynthetic 23-sulfate derivative of obecholic acid (OCA), demonstrates dual agonism of both TGR5 and FXR. In addition, OCA, also known as 6-ethylchenodeoxycholic acid, is a CDCA

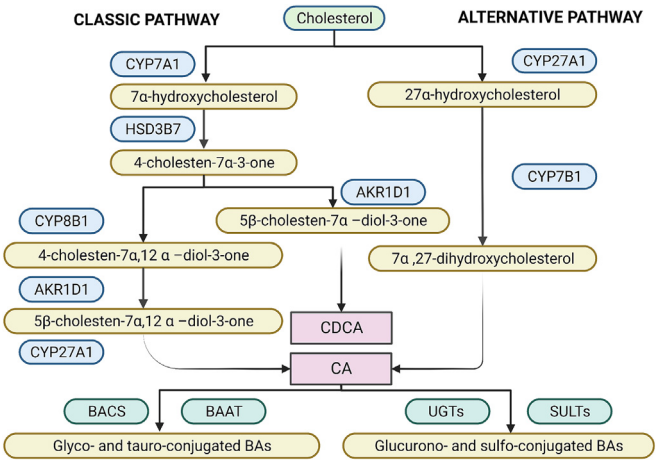

Fig. 2. Simplified scheme of classical and alternative pathways for the synthesis of primary bile acidsBAs The conversion of cholesterol into BAs occurs in hepatocytes mainly through two different approaches: the classical and alternative pathways. Primarily, cholesterol 7α- Hydroxylase (encoded by CYP7A1) is a key rate limiting enzyme in the classical pathway, sterol 12α- Hydroxylase (encoded by CYP8B1) introduces hydroxyl at the 12th position of steroid nucleus, which is responsible for the production of CA. CYP7A1 determines the size of the BA pool, while CYP8B1 is critical to the proportion of CA: CDCA. Sterol-27 hydroxylase is the first enzyme in the alternative pathway. The classical pathway produces CA and CDCA through the action of CYP8B1 and CYP27A1, while the alternative pathway yields CDCA *via* CYP7B1. Furthermore, the newly synthesized free BAs will be widely combined to form a variety of conjugated BAs and enter the intestinal lumen for metabolic circulation.

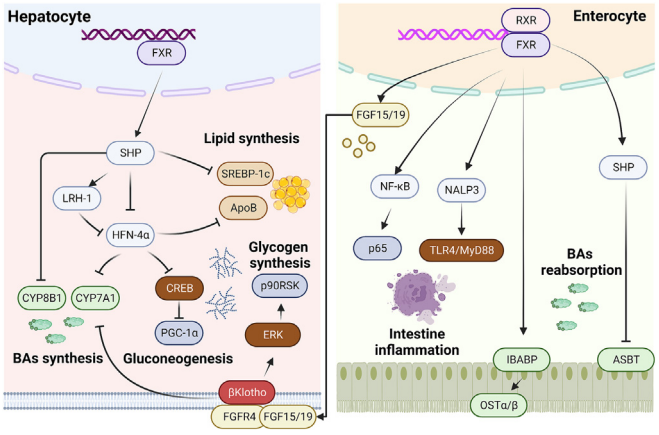

Fig. 3. Schematic illustration depicting enterohepatic FXR-mediated BAs signaling in physiological metabolic processes. BA-mediated FXR signaling activation regulates BAs synthesis *via* facilitating SHP-LRH-1 signaling in the liver and affects BA reabsorption in intestine. BAs inhibit the secretion of GLP-1 by activating FXR in L-cells to maintain glucose homeostasis, and regulate hepatic gluconeogenesis and glycogen synthesis. BAs also regulate hepatic lipid metabolism by activating FXR-SHP axis to inhibit liver adipogenesis regulator SREBP-1c. Furthermore, the activation of FXR-SHP signaling decrease the production of VLDL and lipoprotein synthesis *via* suppressing HNF-4 gene expression. In addition, FXR plays an important role in the improvement of liver inflammation, especially liver fibrosis, and intestinal inflammation.

derivative with strong agonist activity towards FXR, utilized in clinical settings. Examples of semisynthetic BAs with skeletons larger than C-24 are shown in Fig. 1**C**.

BA receptor-mediated signaling pathways in metabolic homeostasis

BAs regulate physiological mechanisms through interactions with two main BA receptors, FXR and TGR5. Generally, FXR is highly expressed in the liver, intestine, kidneys, and adrenal tissues, and its function is closely linked to the regulation of gut inflammation, cholestasis, dyslipidemia, and hepatitis (Fig. 2). In contrast, TGR5-mediated BA signaling is involved in multiple physiological metabolic programs such as glucose and lipid metabolism, as well as energy balance, which is related to its high expression levels in the gallbladder, lung, intestine, placenta, and spleen (Fig. 3). Collectively, BA receptor-mediated signaling pathways play indispensable roles in maintaining metabolic homeostasis.

Regulation of BA metabolism

Over the past two decades, FXR has been characterized as a BA sensor that regulates the enterohepatic circulation of BAs. In the liver, FXR activates small heterodimeric partner (SHP), which subsequently suppresses the expression of downstream transcription factors, including liver receptor homolog 1 (LRH-1) [25], and the CYP7A1 transcriptional activator hepatocyte nuclear factor 4α (HNF-4α) [26,27]. This cascade leads to the inhibition of CYP7A1 expression and a reduction in BA biosynthesis [28]. In the gut, BAs bind to the FXR ligand binding domain, activating FXR transcriptional activity. This activation reduces the expression of fibroblast growth factor 15/19 (FGF-15/19) in intestinal epithelial cells. FGF-15/19, in turn, activates FGFR-4 and initiates β-Klotho-mediated inhibition of CYP7A1, thereby blocking the synthesis of BAs [29,30]. FXR also activates ileal SHP to downregulate the expression of the retinoic acid receptor (RAR)-dependent apical sodium-dependent BA transporter (ASBT) [31], thereby reducing intestinal BA uptake. Additionally, the increased BA flux through reabsorption leads to upregulation of ileal bile acid-binding protein (IBABP) in cytosol enterocytes, which facilities the transport of BAs to the basolateral membrane for secretion [32]. Meanwhile, BA stimulates FXR binding with response elements in the OSTα/β, thereby *trans*-activating these two genes responsible for transporting BAs from basolateral membrane of enterocytes to the portal vein [32]. Moreover, FXR activation drives BA detoxification by upregulating the expression of CYP3A4, SULT2A1, and UGT2B4. It also stimulates the excretion of bile phospholipid through multidrug resistance protein 3 (MDR-3) [33,34]. Additionally, the vitamin D receptor (VDR), another intestinal BA sensor, participates in signal transduction induced by the secondary BA, LCA, to promote the expression of CYP3A and SULT2A1, along with other immunomodulatory factors, in response to BA toxicity in the gut [35,36]. Overall, FXR-mediated multiple signal transduction plays an important role in regulating BAs metabolism in conjunction with downstream regulatory factors.

Compared to FXR, the expression levels of *Tgr5* mRNA in the liver are markedly lower in the liver due to tissue-specific constraints that make direct regulation of BA biosynthesis less favorable. However, administration of the TGR5 agonist, INT777, in healthy mice downregulates the expression of hepatic CYP8B1, thereby inhibiting the production of 12-α-hydroxy BAs [37]. In contrast to the liver, TGR5 is highly expressed in cholangiocytes, where it promotes chloride secretion through cAMP-regulated cystic fibrosis transmembrane conductance regulator (CFTR). Knockout of *Tgr5* or inhibition of CFTR abolishes this effect [38], indicating that TGR5-mediated chloride secretion is dependent on CFTR activation [16]. These findings underscore the critical role of TGR5 in regulating bile secretion.

Regulation of glucose and lipid homeostasis

BAs are the crucial postprandial mediators responsible for maintaining glucose metabolism homeostasis. Activation of hepatic FXR generally enhances insulin effects by inducing SHP, which

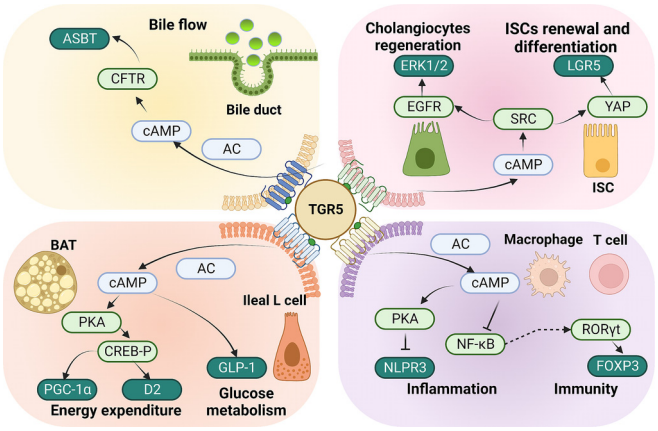

Fig. 4. Illustration of TGR5-mediated BA signaling pathways in different physiological metabolic processes. BA-mediated TGR5 signaling activation regulates BA flow *via* facilitating cAMP-induced CFTR potentiation in the gallbladder. BAs stimulate the secretion of GLP-1 by activating TGR5 in L-cells of the terminal ileum and maintains glucose homeostasis. BAs also promote thermogenesis and energy consumption *via* targeting the TGR5 signaling in muscles and brown adipose tissues. Additionally, BAs activate tyrosine-protein kinase Src promoting regeneration of cholangiocytes as well as intestinal stem cell renewal and differentiation by acting on the TGR5 in the bile duct and intestinal epithelium, respectively. TGR5 signaling cascade regulates the downstream NF-κB signaling pathway to improve the inflammatory responses and facilitates the differentiation of T_{reg} and T_H17 cells to participate in immune regulation.

inhibit gluconeogenesis while stimulating glycogen synthesis (Fig. 4). By targeting the hepatic FGFR4/β-Klotho (KLB) signaling cascade, BA can affect the Ras-ERK-p90RSK pathway to regulate glycogen synthesis independently of insulin signaling [39]. In addition, FXR-SHP-mediated inhibition of gluconeogenesis is largely dependent on the suppression of cAMP response element binding protein (CREB) phosphorylation and downregulating the transcription of PGC-1α and its target genes encoding glucose 6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK) [40]. Activation of hepatic FXR inhibits L-type pyruvate kinase (LPK) transcription, thereby promoting the diversion of glucose metabolites from glycolysis to hepatic glycogen synthesis [41]. In line with these discoveries, FXR deficiency results in insulin resistance and overt hyperglycemia [42]. Paradoxically, activating intestinal FXR significantly reduces GLP-1 secretion, probably by interfering with signal transduction through the short-chain fatty acid (SCFA) receptor, FFAR2, on intestinal endocrine L-cells [43,44]. However, despite the inhibition of GLP-1 release, administration of FXR agonists does not lead to hyperglycemia. Further investigation is needed to understand the underlying mechanism of this intriguing phenomenon.

The regulatory effects of BAs on lipids and cholesterol metabolism also partially depend on FXR signaling. The beneficial remodeling of lipid metabolism is coordinated by FXR-SHP signaling, which inhibits sterol-regulated binding protein 1c (SREBP-1c), a main regulator of liver adipogenesis, and interferes with the binding of ChREBP and liver pyruvate kinase (LPK) promoter through FXR-dependent interference [45]. In hepatocytes, the FXR-SHP axis participates in downregulating the secretion of very-low-density lipoprotein (VLDL) through suppressing HNF-4α expression [46]. Interestingly, FXR activation has been shown to decrease intestinal lipid absorption and liver triglyceride levels independent of SHP and SREBP-1c. Instead, three adipogenic factors, stearoyl-CoA desaturase 1 (Scd1), lipin 1 (Lpin1), and diacylglycerol O-acyltransferase 2 (Dgat2), play pivotal roles in repressing lipid absorption following FXR activation. These findings suggest novel avenues for exploring the role of FXR in lipid metabolism [47].

BA-mediated TGR5 signaling has emerged as a crucial pathway for regulating glucose metabolism and energy expenditure. Stimulation of TGR5 by BAs leads to the release of Gαs and a concurrent increase in cAMP levels [48,49]. Dietary supplementation with CA or TCA activates the TGR5-cAMP signaling in brown adipose tissues and skeletal muscles, which results in significantly reducing body weight in high-fat diet (HFD) fed mice [50,51]. CDCA activates TGR5 to promote thermogenesis by enhancing the expression of uncoupling protein (UCP) [52]. Moreover, BA-mediated TGR5 activation enhances insulin sensitivity by stimulating incretin secretion, thereby efficiently maintaining glucose homeostasis. TGR5 agonism by BAs in terminal ileum L-cells promotes GLP-1 secretion, a process abolished in TGR5 knockout mice [53]. In addition, administering dietary supplements containing BAs or specific TGR5 agonists restores energy metabolism capacity by activating the sympathetic nervous system in rodents, thereby inhibiting weight gain [54]. These findings suggest that BAs engage a bidirectional brain-periphery regulatory mechanism to control metabolic responses through TGR5 signaling. Interestingly, numerous studies have demonstrated that BA can activate both FXR and TGR5 simultaneously, suggesting potential synergistic role in regulating glucose homeostasis and lipogenesis in combined therapeutic strategies [55–57].

S1PR2, a subtype of GPCRs, exhibits functional redundancy with TGR5 activation and is widely expressed in hepatocytes and immune system [58]. Conjugated BAs can activate the ERK1/2 and AKT signaling pathways, which in turn activate S1PR2 in rodents [59]. Previous studies have demonstrated that the S1PR2/AKT pathway potentially regulates hepatic glucose and lipid metabolisms by inhibiting GSK3β expression and activating glycogen synthase, thereby stimulating glyconeogenesis [60]. Tauroursodeoxycholic acid (TUDCA) significantly increases the expression of insulin-degrading enzyme (IDE) in HepG2 cells through a S1PR2-IR-PI3K-AKT pathway-dependent mechanism, improving islet β-cell function and glucose metabolism [61,62]. Moreover, S1PR2-deficient mice rapidly develop fatty livers when fed a HFD, indicating the importance of conjugated BAs and S1PR2 in regulating hepatic lipid metabolism in obese mice [63].

Regulation of the immune responses

Necrotic liver parenchyma cells release a variety of pro-inflammatory factors that stimulate the activation of interstitial cells, particularly hepatic stellate cells (HSCs), exacerbating fibrosis [64]. FXR agonist GW4064 can significantly suppress the release of pro-inflammatory factors by liver macrophages, mitigating inflammation partially through the toll like receptor 4 (TLR-4) mediated p38 and mitogen activated protein kinase (TLR4/p38-MAPK) signaling pathways [65,66]. FXR activation also inhibits the transforming growth factor β (TGF-β)-SMAD3-JunD activator protein−1 pathway, conferring both preventive and therapeutic effects on liver fibrosis [67]. In addition, OCA inhibits p53 activation and significantly improves hepatic inflammatory response in metabolic dysfunction-associated steatohepatitis (MASH) model mice [68].

Intestinal inflammatory signaling pathways regulated by FXR have been extensively studied in the context of metabolic disorders. Specifically, activation of FXR by OCA significantly inhibits TLR4-mediated pro-inflammatory cytokines in intestinal epithelial cells (IECs) [69], consistent with findings in cultured human $CD14^+$ monocytes. FXR activation also impedes nuclear translocation of the NF-κB subunit p65, thereby attenuating intestinal inflammation by preventing the activation of NF-κB target genes [70]. In an animal model of lipopolysaccharide (LPS)-induced colitis, administration of GW4064 significantly inhibits the formation of inflammasomes and downregulates intestinal TLR4-myeloid differentiation factor 88 (MyD88)-mediated signaling [71].

TGR5 is expressed in both monocytes and macrophages. Activation of the classical TGR5-cAMP pathway reduces NF-κB-dependent inflammatory responses and suppresses the release of secretory inflammatory factors, conferring anti-inflammatory effects that alleviate the pathological development of certain diseases. TGR5 activation significantly blocks phosphorylation of nuclear factor of kappa light polypeptide gene enhancer α (IκBα), nuclear translocation of p65, as well as NF-κB pathway. TGR5 knockout mice present more severe liver necroses compared to wild-type mice [72]. Meanwhile, LCA inhibits NOD-like receptor protein 3 (NLRP3) inflammasome-dependent inflammation by interacting with the phosphorylation and ubiquitination of NLRP3 protein through the TGR5-cAMP-PKA dependent pathway [73]. Moreover, INT777 reduces oxidative stress (OS) as well as inflammatory response in bone marrow-derived macrophages, mitigating hepatic ischemia/reperfusion injury through regulation of the KEAP1-NRF2 pathway [74]. In addition to the classical TGR5-mediated anti-inflammatory immune response signaling, the BA-induced TGR5-GRK-β-arrestin-SRC signaling axis promotes the activation of various natural antiviral signaling components and enhances the antiviral immune response [75]. These studies suggest that TGR5 signaling pathway is widely involved in the process immune responses.

Regulation of cellular regeneration and proliferation

Studies in a variety of intestinal cell lineages have shown that TGR5 participates in BA-associated proliferation and regeneration, including cholangiocyte proliferation, and hepatocyte and intestinal epithelial cell regeneration. Treatment with taurolithocholic acid (TLCA) leads to significantly higher levels of ERK1/2 phosphorylation in mouse cholangiocytes. Importantly, BA-induced cholangiocytes proliferation requires activation of the cSrc-EGFR-ERK signaling cascade, independent of adenylate cyclase activation [76]. Furthermore, cholangiocytes are protected from receptor-mediated apoptosis *via* TGR5-dependent serine phosphorylation on the CD95 receptor [77]. The protective effects of TGR5 on hepatic cells have been revealed through a partial hepatectomy (PH) mice, in which TGR5 activation leads to positive effects on the process of liver regeneration [78]. The main mechanism underlying this phenomenon might be correlated with the clearance of BAs in the urine, which protects the liver from hepatotoxicity due to BA-overload and maintains a balanced control of cytokine secretion following potential of hydrogen.

In recent years, the effects of BA-induced TGR5 activation on IEC regeneration have been explored in depth. BAs and TGR5 agonists have been shown to promote the growth of intestinal organoids. INT777 has been found to facilitate activation of yes-associated protein 1 (YAP1) and its regulator Src in intestinal stem cells (ISCs), thus accelerating the regeneration of intestinal epithelium, and *Tgr5*$^{ISC-/-}$ mice develop severe colitis due to the loss of these protective effects conferred by epithelial cell regeneration [79]. Further investigations revealed that DCA delays tissue repair in colonic epithelial cells by activating AKT signaling in ulcerative colitis (UC) mice, while downregulation of *Tgr5* can significantly inhibit this effect. This suggests that aberrant TGR5 signaling may play a role in the regeneration of UC epithelial cells [80]. While TGR5-mediated regeneration of IECs is closely related to cellular BA levels, the mechanism responsible for these effects remain unclear.

Pharmacological behavior of BAs in metabolic diseases

BA-related signaling pathways have emerged as promising therapeutic targets for treating a wide spectrum of metabolic diseases. Administering BAs or their analogues can effectively modulate the composition of BA pools, agonize or antagonize BA receptor signaling, and potentially impact microbial abundance and diversity in the gut (Table 2). These interventions show considerable potential value for protecting metabolic homeostasis and organ function.

Chronic metabolic diseases

The role of BAs in nonalcoholic fatty liver diseases (NAFLD) and MASH

NAFLD is a clinicopathological syndrome characterized by steatosis, infiltration of hepatic macrophages and inflammatory factors, and accumulation of fat in liver parenchymal cells, occurring in the absence of excessive alcohol consumption [86,87]. Studies in NAFLD mice suggest that TUDCA can attenuate hepatic inflammation and fibrosis, as well as improve insulin resistance [81]. Moreover, TUDCA has been shown to alleviate intestinal inflammatory responses, restore intestinal barrier function by increasing tight junction (TJ) protein levels, and by modulating gut microbiota composition, which collectively deter the progression of HFD-induced NAFLD [82]. Another *in vivo* study demonstrated that in the absence of hepatocyte NF-κB, BA metabolism contributes to the progression of MASH through mechanisms involving DR5-mediated apoptosis and hepatic fibrosis, whereas NorUDCA exhibited remarkable therapeutic efficacy in alleviating the progression of MASH [88]. In addition, the uptake of OCA, a potent and highly selective FXR agonist, can restore insulin resistance, reduce hepatic triglyceride contents in genetic or diet-induced obese animals, and inhibit hepatic lipid synthesis in NAFLD patients by activating FXR signaling [83,89]. Interestingly, recent studies have uncovered a new mechanism of FXR activation that modulates NAFLD progression in HFD-fed mice. OCA blocks hepatic triglyceride accumulation by inhibiting hepatic FATP5-mediated uptake of long chain fatty acids [84]. Recent studies indicate that hyodeoxycholic acid (HDCA) in pigs is negatively correlated with the severity of NAFLD. HDCA treatment has been shown to alleviate NAFLD in various mouse models by inhibiting the intestinal FXR and upregulating hepatic CYP7B1 [85]. Additionally, other research suggests that HDCA significantly facilitates lipid metabolism through fatty acid-hepatic peroxisome proliferator-activated receptor alpha (PPARα) signaling, without activating FXR [90]. These findings suggest that HDCA has multiple targets for the treatment of NAFLD.

MASH is a critical stage in the progression of NAFLD that can lead to liver cirrhosis and even hepatocellular carcinoma (HCC). The CDCA analogue OCA treatment can enhance insulin sensitivity and reverse hepatic adipose degeneration, alleviate inflammatory responses, and attenuate liver fibrosis. In the phase III clinical trials of OCA for MASH treatment, no worsening trend was observed in the progression of fibrosis, and the rate of 2-point reduction in MASH score was significantly higher in the OCA treatment group [91,92]. In addition to the FXR signaling pathway, the mechanism of action for OCA in ameliorating MASH involves direct inhibition of NLRP3 inflammatory corpuscles in macrophages, thereby suppressing inflammasome activation-elicited hepatic lipid accumulation [93]. Norursodeoxycholic acid (norUDCA) is the C23 (C24-nor) homolog of UDCA. Nor-UDCA treatment has been shown to improve liver injury and fibrosis in MASH mice by significantly reducing serum alanine aminotransferase levels and rescuing serum insulin and leptin levels, collectively contributing to glucose homeostasis [94]. Nor-UDCA exhibits superior curative effects in ameliorating MASH compared to its homologs UDCA and dinor-UDCA [95]. Administration of INT767, a CDCA analogue that acts as a dual agonist for FXR and TGR5, significantly alleviates lipid accumulation in visceral adipose tissues, improve insulin sensitivity, and restore the levels of pro-inflammatory factors in MASH rabbits [96].

Table 2
Bile acids serves as treatment drugs for chronic metabolic disease, biliary tract diseases and inflammatory diseases.

Diseases	Drugs	Source	Targets/Receptors	*In vivo*/*In vitro*	Reference
NAFLD	TUDCA	Natural	NFATc1	*In vivo*	[81]
NAFLD	TUDCA	Natural	Gut microbiota	*In vivo*	[82]
NAFLD	OCA	Semisynthetic	FXR	*In vivo*	[83]
NAFLD	OCA	Semisynthetic	FATP5	*In vivo*	[84]
NAFLD	HDCA	Natural	FXR	*In vivo*	[85]
MASH	OCA	Semisynthetic	FXR	*In vivo*	[91]
MASH	INT767	Semisynthetic	TGR5/FXR	*In vivo*	[92]
MASH	OCA	Semisynthetic	NLPR3	*In vivo*	[93]
MASH	NorUDCA	Natural		*In vivo*	[94]
Obesity	CA	Natural	TGR5	*In vivo*	[97]
Obesity	BAR501	Semisynthetic	TGR5	*In vivo*	[98]
Obesity	CDCA	Natural	TGR5	*In vivo*	[99]
Obesity	UDCA	Natural	FXR	*In vivo*	[100]
Obesity	Gly-MCA	Natural	FXR	*In vivo*	[101]
T2DM	HCA	Natural	TGR5/FXR	*In vivo*	[55]
T2DM	JTE-013	Semisynthetic	S1PR2	*In vivo*	[60]
T2DM	CA7S	Natural	TGR5	*In vivo*	[102]
T2DM	INT777	Semisynthetic	TGR5	*In vivo*	[103]
T2DM	INT777	Semisynthetic	TGR5	*In vivo*	[104]
T2DM	INT767	Semisynthetic	TGR5/FXR	*In vivo*	[105]
Atherosclerosis	CA	Natural	ApoA-I	*In vivo*	[106]
Atherosclerosis	UDCA	Natural	XBP-1, CHOP	*In vitro*	[107]
Atherosclerosis	INT767	Semisynthetic	TGR5/FXR	*In vivo*	[108,109]
Atherosclerosis	INT777	Semisynthetic	TGR5	*In vivo*	[110]
Cholestasis	OCA	Semisynthetic	FXR	*In vivo*	[111]
Cholestasis	UDCA	Natural	TMEM16A	*In vitro*	[112]
Cholestasis	NorUDCA	Natural	FXR	*In vivo*	[113]
Cholestasis	TUDCA	Natural	PKC-α	*In vivo*	[114]
Cholelithiasis	CDCA	Natural		*In vivo*	[117]
Colitis	OCA	Semisynthetic	FXR	*In vivo*	[69]
CD	LCA, DCA	Natural	TGR5	*In vitro*	[120]
CD	LCA, DCA	Natural	TGR5	*In vivo*	[121]
CD	OxoLCA, IsoalloLCA	Natural	RORγt	*In vivo*	[122]

The roles of BAs in obesity and type 2 diabetes mellitus (T2DM)

Obesity commonly refers to excessive consumption of high-calorie foods or abrupt changes in metabolism that result in over-accumulation of adipocytes, oxidative stress (OS) and elevated systemic inflammation. Dietary supplementation with CA or TCA can activate the TGR5-cAMP-D2 regulatory pathway in brown adipose tissues (BAT) and skeletal muscles, thereby controlling body weight gain in HFD-induced obese mice [97]. Likewise, TGR5 activation with its selective agonist, BAR501, can also inhibit body weight gain in obese mice by increasing UCP-1 and PGC-1α expression to promote the browning of white adipose tissue [98]. In clinical trials, CDCA oral supplements promote energy consumption, metabolism in BAT, and thermogenesis [99]. In morbidly obese patients, UDCA administration lead to FXR antagonism and accelerating the production of BAs, which leads to a high level of UDCA in the noncholestatic liver. These effects ultimately lead to the depletion of liver cholesterol and improved liver function in obese individuals [100]. In addition, glycine-β-muricholic acid (Gly-β-MCA) is identified as a high-affinity, selective FXR inhibitor that can block FXR signaling in an intestine-specific manner, thus improving metabolic parameters in obese animals [101].

The pathogenesis of T2DM is associated with changes in circulating BA profile. The endogenous TGR5 agonist, CA7S, increases the level of glucose tolerance in a TGR5-dependent manner in T2DM mice. Notably, CA7S-mediated glucose regulation is confined to the gut, and it remains gut-restricted, minimizing off-target effects previously observed for TGR5 agonists absorbed into circulation [102]. The TGR5 agonist INT777 stimulates GLP-1 release in enteroendocrine cells, which could be beneficial for improving dysfunction in glycogen metabolism and enhancing glucose tolerance in T2DM mice [103]. Furthermore, INT777 treatment is shown to reduce proteinuria, mesangial expansion, fibrosis, and intrarenal $CD68^+$ macrophage infiltration in diabetic nephropathy mice. These effects are potentially related to the induction of mitochondrial biosynthesis and increased fatty acid β-oxidation (FAO) [104]. Additionally, the FXR/TGR5 dual agonist, INT767, can prevent renal mitochondrial dysfunction and OS from modulating the progression of nephropathy in T2DM mice [105]. Studies in a porcine model of diabetes show that HCA inhibits GLP-1 secretion and maintains blood glucose levels while synergistically activating TGR5 and inhibiting FXR signaling, which could explain the low susceptibility to diabetes in pigs [55].

Roles of BA in atherosclerosis

Atherosclerosis is typically caused by deposition of excess cholesterol and lipids accumulation in the intima of large and medium arteries. As important signal molecules in lipid digestion, absorption, and transport, BAs show benefits on the improvement of atherosclerosis, especially in lipid metabolism. Dietary CA supplement has been shown to inhibit apolipoprotein A-I (apoA-I) transcription, subsequently reducing plasma levels of apoA-I and HDL in atherosclerosis model mice [106]. UDCA can also effectively reduce endoplasmic reticulum (ER)-related stress by decreasing the expression of X-box binding protein 1 (XBP-1) and CEBP homologous protein (CHOP) in endothelial cells. These inhibitory effects lead to suppression of plasma adhesion molecules that exert anti-atherosclerotic effects on disturbances in blood flow [107]. INT767 regulates target genes by activating both TGR5 and FXR signaling, which rescues serum cholesterol and triglyceride levels, inhibits liver CYP8B1 expression, downregulates serum CA and DCA levels, and reduces the risk of atherosclerosis [108,109]. Activation of TGR5 by INT777 prevents macrophage secretion of pro-inflammatory cytokines through cAMP signaling, which attenuates atherosclerosis in mice by decreasing intraplaque

inflammation and reducing macrophage infiltration [110]. Taken together, these studies cumulatively support the therapeutic potential of BAs for treating atherosclerosis.

Roles of BA in hepatic cholestasis diseases

Cholestatic liver diseases initially manifest pathological hallmarks in hepatocytes and/or biliary ducts, later progressing to aberrant BA synthesis, secretion, and excretion, and ultimately leading to the excessive accumulation of bile components such as BAs, cholesterol, and bilirubin in the liver and serum. As the first FDA-approved drugs for clinical application in chronic cholestasis patients, both OCA and UDCA have shown substantial improvements in the hepatocytes, along with the improved level of alkaline phosphatase, indexes of hepatocyte necrosis, and a decline in necro-inflammatory activity [111]. UDCA exhibits immunomodulatory properties and can stimulate bicarbonate secretion from hepatocytes and cholangiocytes, thus exerting protective effects on the liver [112]. However, some patients are prone to developing UDCA tolerance, while others may be intolerant to UDCA treatment [115,116]. Recent studies have reported that nor-UDCA, rather than UDCA itself, may serve as a more effective therapeutic drug for counteracting cholestatic liver diseases [113]. Furthermore, TUDCA significantly alleviates cholestasis and tubular injury *via* the PKCα-ezrin pathway. In TUDCA-treated rats with liver ischemia–reperfusion injury-induced cholestasis, less damage was observed in the microvilli and bile duct areas of the liver than that in sham controls [114].

Roles of BA in cholelithiasis

Cholelithiasis is generally recognized as a digestive system disorder, in which cholesterol precipitates from bile and crystallizes. Most cholesterol deposition-related stones are found in the gallbladder. In recent years, the incidence of cholelithiasis has shown a significant upward trend along with societal changes in diet and lifestyle. CDCA, being more hydrophilic than secondary BAs, can reduce the efficiency of cholesterol crystallization in the gallbladder. Moreover, as a FXR agonist, CDCA increases bile flow and secretion through the FXR pathway [117,118]. At the same time, other studies have indicated that the combination of CDCA and UDCA may significantly reduce the severity and promote the dissolution of gallstones [119]. However, the mechanism by which this combination treatment synergistically promotes litholysis is still poorly understood, necessitating further evaluation of drug toxicity and optimal dosing.

Other inflammatory diseases

Inflammatory bowel disease (IBD) is a chronic intestinal disease that primarily includes ulcerative colitis (UC), and Crohn's disease (CD). Symptoms of epithelial permeability, rectal bleeding, and infiltration of immune-activated cells were significantly reduced following intervention with the FXR agonist, OCA, in colitis mice [69]. In addition, FXR activation in differentiated intestinal cells was shown to suppress the level of key pro-inflammatory cytokines and protect epithelial barrier function. Likewise, OCA strongly reduces TNF-α secretion and the abundance of monocytes in lamina propria in IBD patients. Both DCA and LCA can activate the TGR5-cAMP signaling, inducing phosphorylation of c-Fos to mediate the activation of NF-κB p65, and inhibiting LPS-stimulated production of TNF-α. These findings reveal that the TGR5 signaling can potentially modulate the immune response in Crohn's disease patients [120]. In murine colitis models, administration of exogenous secondary BAs, such as DCA and LCA, could prevent the hyperactivation of inflammatory markers in wild-type, but not *Tgr5*-deficient mice, further supporting the TGR5-dependent protective effects of secondary BAs [121]. These findings suggest that secondary BAs may act as anti-inflammatory factors and might serve as reliable indirect biomarkers of the intestinal mucosal healing process.

Microbe-derived secondary BA metabolites have recently drawn considerable research attention for their influence on intestinal inflammation *via* regulation of T_H17 and T_{reg} cell differentiation [123]. In particular, 3-Oxo-LCA and *iso*-alloLCA can directly bind to the ligand-binding domain of RAR-related orphan receptor γ (RORγt) to promote T_H17 differentiation, which is negatively associated with Crohn's disease development [122]. Functional genetic screens revealed that 3-Oxo-LCA and *iso*-alloLCA can relieve IBD symptoms *via* IL-17 signaling in T_H17 cells. Additionally, isoDCA induces Foxp3 expression by diminishing the immunostimulatory properties of dendritic cells (DCs) and potentiating differentiation in peripherally induced T_{reg} cells. This activity can improve immune balance and alleviate inflammatory responses in the intestinal cells modulated by FXR signaling [124]. Further understanding of the BA-associated intracellular mechanisms underpinning immune regulation will greatly facilitate delineation of their roles in inflammation.

Conclusion and perspectives

BAs are mainly present in enterohepatic circulation, where they play protective roles in maintaining a healthy digestive system. Currently, more than 200 BA species have been identified and biochemically characterized, with several showing promise as diagnostic biomarkers. For example, in two independent cohorts of hepatic sinusoidal obstruction syndrome patients [125]. CA, TCA, and GCA were confirmed as diagnostic markers [126]. The ratio of primary to secondary BAs also emerged as a novel index with excellent diagnostic performance in children with inflammatory bowel disease (IBD) [127]. Furthermore, the accumulation of GDCA in non-survivors of acute liver failure suggests it can predict patient outcomes [128]. These findings underscore the significant potential of BAs not only for early disease detection but also for guiding personalized therapies. As research advances, the use of BAs as diagnostic biomarkers and therapeutic tools is likely to expand, further enhancing the field of personalized medicine. In addition to numerous natural BA compounds that are biosynthesized, biotransformed, or metabolized by gut bacteria in animals, semisynthetic BAs with targeted structural modifications have also attracted much attention in recent years due to their potent agonist or antagonist activity on BA receptors. The dedicated BA receptors, FXR and TGR5, are prime targets for drug development. Obeticholic acid (INT-747) is an FXR agonist, while INT-777 is a selective TGR5 agonist. INT-767 interacts with both receptors [129–131]. Notably, modifications to the side chain, such as the addition of a methyl group, can convert obeticholic acid into the potent and selective TGR5 agonist INT-777. This highlights the potential for developing BAs as semisynthetic drugs. Given that FXR and TGR5 agonists have been explored as next-generation treatments for metabolic diseases and cholestatic liver disease [132–134]. These drugs undergo enterohepatic circulation, making them most effective in the liver and intestines. With continued structural modifications, semisynthetic BAs are anticipated to emerge as promising therapies for hypercholesterolemia, cholestatic liver disease, and T2DM.

Under physiological conditions, BAs can activate or inhibit downstream effector molecules by selectively binding to their receptors. Biological signaling pathways regulated by nuclear and membrane BA receptors play essential roles in maintaining metabolic homeostasis and regulating inflammation, cell differentiation, apoptosis, and other physiological processes. Dysregulation of BA homeostasis has been associated with hepatobiliary metabolic

disturbances, chronic metabolic diseases and intestinal inflammation. Although the exact mechanism or molecular targets of BAs or BA analogues in improving these diseases are still poorly understood, their involvement in the pathogenesis of metabolic disorders is well-recognized.

The properties and functions of BAs have been studied for more than one hundred years. For a long time, BAs were considered as emulsifiers to promote lipid absorption. Only within the past two decades have BAs been recognized as signal molecules that can affect downstream regulatory cascades. More recently, several studies have identified numerous BA species in animals with uncharacterized functions, and the relevance of their structure and function in various signaling pathways and biological processes warrants exploration. The relationship between the dynamic changes in BA types and levels with the occurrence and progression of various diseases is also worthy of extensive investigation. It therefore seems that overlooking the dynamics of their temporal and spatial distribution, as well as their various functions, hinders a comprehensive understanding of their physiological and pathological roles in biological systems or organs. BA expression profiles vary across different diseases and stages. Secondary BAs, such as DCA and LCA, are distributed throughout the gastrointestinal system and are closely linked to tumorigenesis in these organs. Research has demonstrated that elevated levels of DCA and LCA in the colon activate Wnt/β-catenin and NF-κB signaling pathways, promoting oxidative DNA damage and increased mitotic activity [135,136], which contribute to tumor development. BAs also function as danger-associated molecular patterns (DAMPs), activating the NLRP3 inflammasome in inflammatory macrophages and exacerbating sepsis [137]. Monitoring BA concentrations at different disease stages and within various cell populations is essential to better understand their involvement in disease progression. Furthermore, disruptions in circadian rhythms can destabilize BA homeostasis, potentially leading to metabolic disorders [138]. A combination of dietary factors (e.g., high-fat diets) and dysregulated WNT signaling (e.g., adenomatous polyposis coli (APC) mutations) can further alter the BA profile. This imbalance promotes the malignant transformation of $Lgr5^{+}$ cancer stem cells, accelerating the progression from adenomas to adenocarcinomas [139]. Since BA receptors are widely expressed in different cell types, their functions are worthy of further exploration and may help elucidate previously unrecognized cellular functions or processes. In conclusion, the activities of different BA types towards their receptors and their functions in regulating related disease deserves further explore. The dissection of functional differences among various BAs will facilitate the development of BA- or BA analog-based drugs for treating a range of metabolic and gastrointestinal disorders.

CRediT authorship contribution statement

Tongxi Zhuang: Writing – original draft. **Xunjiang Wang:** Validation. **Zixuan Wang:** Writing – original draft. **Lihua Gu:** Writing – original draft. **Dawei Yue:** Validation. **Zhengtao Wang:** Validation. **Xiaohua Li:** Visualization, Writing – review & editing. **Li Yang:** Visualization, Writing – review & editing. **Wendong Huang:** Revision and Writing – review. **Lili Ding:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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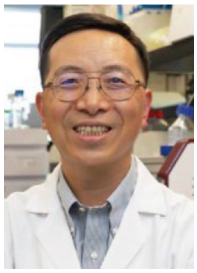

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