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Review Article

The functions of gut microbiota-mediated bile acid metabolism in intestinal immunity

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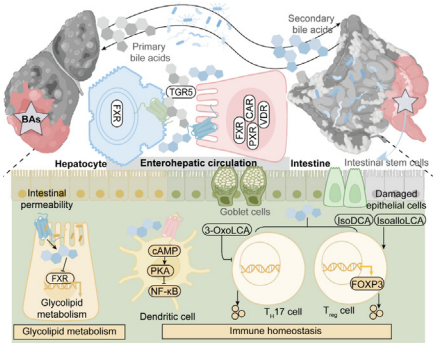
HIGHLIGHTS

- This review provided a comprehensive overview of bile acid (BA) synthesis, transport and metabolism.
- This review summarized the signaling and regulatory mechanisms by which BAs engage with their receptors.
- The factors affecting BA metabolism were reviewed.
- BA–microbiota interactions modulate host physiology and disease progression.
- Manipulating BA signaling could provide novel strategies to restore the host's health and the gastrointestinal ecosystem.

GRAPHICAL ABSTRACT



Abbreviations: AKR1D1, Aldo-keto reductase family 1, member D1; ApoCII, Apolipoprotein C-II; ASBT, Apical sodium-dependent BA transporter; BA, Bile acid; BAAT, Bile acid-CoA: amino acid N-acyltransferase; BACS, Bile acyl-CoA synthetase; BSEP, Bile salt export pump; BSH, Bile salt hydrolase; CA, Cholic acid; CAR, Constitutive androstane receptor; CD, Crohn's disease; CDCA, Chenodeoxycholic acid; *C. difficile*, *Clostridium difficile*; CDI, *Clostridium difficile* infection; CRC, Colorectal cancer; *C. scindens*, *Clostridium scindens*; CYP7A1, Cholesterol-7α-hydroxylase; CYP8B1, Sterol-12α-hydroxylase; CYP27A1, Sterol-27-hydroxylase; CYP450, Cytochrome P450; DCA, Deoxycholic acid; DCs, Dendritic cells; DSS, Dextran sodium sulfate; *EcN*, *Escherichia coli Nissle*; EMCA, 6alpha-ethyl-23(S)-methyl-cholic acid; FDA, Food and Drug Administration; FGF15, Fibroblast growth factor 15; FGFR4, Fibroblast growth factor receptor 4; FMT, Fecal microbiota transplantation; FXR, Farnesoid X receptor; GCA, Glycocholic acid; GCDCA, Glycochenodeoxycholic acid; GLP-1, Glucagon-like peptide-1; GPCRs, G protein-coupled receptors; GUDCA, Glycine-amidated ursodeoxycholic acid; HCA, Hyocholic acid; HCC, Hepatocellular carcinoma; HDCA, Hyodeoxycholic acid; HFD, High-fat diet; HSDH, Hydroxysteroid dehydrogenase; IBABP, Ileal BA-binding protein; IBD, Inflammatory bowel diseases; IBS, Irritable bowel syndrome; ICP, Intrahepatic cholestasis of pregnancy; IL-2, Interleukin-2; ISCs, Intestinal stem cells; IsoDCA, 3β-hydroxydeoxycholic acid; IUGR, Intrauterine growth restriction; LBW, Low-birth-weight; LCA, Lithocholic acid; LPL, Lipoprotein lipase; LPS, Lipopolysaccharide; MAFLD, Metabolic dysfunction-associated fatty liver disease; MCA, Muricholic acid; MCBAs, Microbially conjugated bile acids; MDR, Multidrug resistance; MRP3, Multidrug resistance-associated protein 3; NAFLD, Non-alcoholic fatty liver disease; NFAT, Nuclear factor of activated T; NKT, Natural killer T; NTCP, Sodium/taurocholate cotransporting polypeptide; NLRP3, NOD-like receptor protein 3; OA, Oleanolic acid; OATP2, Organic anion-transporting polypeptide 2; OCA, Obeticholic acid; OST, Organic solute transporter; PBA, Primary bile acid; PKA, Protein kinase A; PPARα, Peroxisome proliferator-activated receptor α; PXR, Pregnane X receptor; RXR, Retinoid X receptor; SBA, Secondary bile acid; SCFAs, Short-chain fatty acids; SHP, Small heterodimer partner; STAT1, Signal transducer and activator of transcription-1; SULTs, Sulfotransferases; T-α-MCA, Tauro-α-muricholic acid; TCA, Taurocholic acid; TCDCA, Taurochenodeoxycholic acid; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridylory)] benzene; TG, Triglycerides; TGR5, G protein-coupled bile acid receptor 1; TUDCA, Taurine-amidated ursodeoxycholic acid; UC, Ulcerative colitis; UDCA, Ursodeoxycholic acid; UGTs, UDP-glucuronosyltransferases; VDR, Vitamin D_3 receptor; 1, 25 $(OH)_2VD_3$, 1α,25-dihydroxy vitamin D3; 3-sucCA, 3-succinylated cholic acid; 7α-HSDs, 7α-hydroxysteroid dehydrogenases; 7-KLCA, 7-ketolithocholic acid; 12-KLCA, 12-ketolithocholic acid.

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ABSTRACT

Background: Bile acids, derived from cholesterol in the liver, consist a steroidal core. Primary bile acids and secondary bile acids metabolized by the gut microbiota make up the bile acid pool, which modulate nuclear hormone receptors to regulate immunity. Disruptions in the crosstalk between bile acids and the gut flora are intimately associated with the development and course of gastrointestinal inflammation.

Aim of review: This review provides an extensive summary of bile acid production, transport and metabolism. It also delves into the impact of bile acid metabolism on the body and explores the involvement of bile acid-microbiota interactions in various disease states. Furthermore, the potential of targeting bile acid signaling as a means to prevent and treat inflammatory bowel disease is proposed.

Key scientific concepts of review: In this review, we primarily address the functions of bile acid-microbiota crosstalk in diseases. Firstly, we summarize bile acid signalling and the factors influencing bile acid metabolism, with highlighting the immune function of microbially conjugated bile acids and the unique roles of different receptors. Subsequently, we emphasize the vital role of bile acids in maintaining a healthy gut microbiota and regulating the intestinal barrier function, energy metabolism and immunity. Finally, we explore differences of bile acid metabolism in different disease states, offering new perspectives on restoring the host's health and the gastrointestinal ecosystem by targeting the gut microbiota-bile acid-bile acid receptor axis.

Contents

Introduction

Common metabolic diseases, such as obesity, metabolic dysfunction-associated fatty liver disease (MAFLD), and diabetes, have become a global health burden and are facing great challenges [1]. Although there have been meaningful progress in the pharmacologic treatments of metabolic diseases, such as dulaglutide, exenatide, and semaglutide, the prevalence of metabolic diseases has increased in recent years, which reinforces the need for more effective treatments [2]. Notably, *Clostridium difficile* is an anaerobic toxigenic bacterium that can cause a severe infectious colitis [3]. Given the escalating global incidence and prevalence of *Clostridium difficile* infection (CDI) and inflammatory bowel diseases (IBD), there is a growing worldwide concern regarding their effective treatments [4]. Presently, IBD is primarily managed through immunosuppressive drug therapies. However, owing to

variations in individual responses to medications and the associated risks of infections and tumors, there is an urgent need for more universally applicable intervention strategies [5].

The human gut contains a wide variety of bacteria and microorganisms collectively referred to as the gut microbiota. This microbiota is pivotal for sustaining overall health and is also implicated in the pathogenesis of various diseases [6]. Despite the immense differences in pathologies of common metabolic disorders, they are related to the composition and function of the gut microbiota [7]. Notably, gut bacterial communities in stool specimens from individuals with IBD exhibit substantial variations compared to those of healthy controls [8]. Moreover, the combined influence of the host genome and its microbial community drives the synthesis of a diverse array of metabolic byproducts, such as bile acids (BAs), short-chain fatty acids (SCFAs), and compounds derived from tryptophan. These metabolites play a crucial role in immune regulation and intestinal homeostasis by facilitating interactions between the host and the gut bacteria.

Notably, BAs have garnered more attention than other metabolites that result from the co-metabolism of the host's intestinal flora owing to their distinctive immunomodulatory properties. Synthesized from cholesterol in the liver, BAs are subject to influence by the gut microbiota, which partakes in their synthesis and conversion, subsequently impacting microbiota composition [9]. BAs exert their effects through interacting with several nuclear hormone receptors, such as the farnesoid X receptor (FXR), G protein-coupled bile acid receptor 1 (TGR5), pregnane X receptor (PXR), vitamin D_3 receptor (VDR), and constitutive androstane receptor (CAR) [10]. The dynamic interactions among the gut microbiota, BAs, BA receptors and host significantly influences immune function and metabolic characteristics, establishing a critical link to the development of metabolic diseases and gastrointestinal inflammation.

The involvement of the BA-microbiota crosstalk in IBD has drawn more attention in recent years. This review delves into the metabolism of BAs, emphasizing the impact of BA-microbiota interactions and their involvement in disease. Furthermore, it is suggested that BA signaling may be targeted as a way to prevent and treat IBD.

BAs and BA metabolism

BA synthesis, transport and metabolism

BAs consist a steroidal core comparing three six-membered and one five-membered carbon ring [11]. This unique structure facilitates their solubility in water, crucial for fat digestion, absorption, and the removal of excessive cholesterol from the body. The hepatic production of BAs from cholesterol is coordinated by cytochrome P450 (CYPs) enzymes, involving two synthetic pathways: the classical and alternative pathways [12]. In the primary pathway, cholesterol-7α-hydroxylase (CYP7A1) initiates the process by converting cholesterol to 7α-hydroxyl cholesterol, a pivotal step in the entire reaction chain. Subsequent modification of the steroidal ring involves sterol-12α-hydroxylase (CYP8B1) and aldo–keto reductase family 1, member D1 (AKR1D1), followed by sterol-27-hydroxylase (CYP27A1)-mediated side chain oxidation, ultimately yielding cholic acid (CA) and chenodeoxycholic acid (CDCA). The secondary pathway involves the CYP27A1-catalyzed 27-hydroxylation of cholesterol, followed by further hydroxylation by CYP7B1, culminating in the synthesis of non-12-OH BAs, predominantly CDCA [13].

BAs can be broadly classified into primary bile acids (PBAs) and secondary bile acids (SBAs). PBAs are synthesized directly by hepatocytes and stored in bile, representing its predominant constituents, mainly including CA, CDCA, and their conjugates by combining with glycine (mainly in humans) or taurine (predominantly in mice) to generate glycocholic acid (GCA), glycochenodeoxycholic acid (GCDCA), taurocholic acid (TCA) and taurochenodeoxycholic acid (TCDCA). Upon secretion into the gut, PBAs are metabolized by the gut microbiota to produce SBAs, including deoxycholic acid (DCA), lithocholic acid (LCA) and their conjugates by combining with glycine or taurine [10]. Notably, the composition of BAs are species-specific, with humans predominantly featuring CA and CDCA, while rodents primarily exhibit CA and muricholic acid (MCA) [14,15]. α-MCA and β-MCA are formed by hydroxylation at C6, which are scarce in humans, though not absent [16]. CDCA, the main PBA in humans, is a potent agonist of the FXR [17]. In contrast, the mouse β-MCA derivative tauro-β-MCA is an FXR antagonist [18]. The ratio of PBAs to SBAs is lower in humans than in mice, largely due to the expression of CYP2A12 in mice, an enzyme that converts SBAs into PBAs [19]. Consequently, the different FXR responses from human and mouse BA pools have profound effects on signaling pathways and metabolic outcomes.

Advancements of untargeted metabolomics have led to the discovery of microbially conjugated bile acids (MCBAs), a class of compounds formed by gut microbiota through the combination of BAs with non-traditional amino acids (such as those other than glycine or taurine) or other molecules via specific enzymes [20]. Some studies suggest that the bacterium *Enterocloster bolteae* is primarily responsible for their production [16]. These conjugates are found in high concentrations in the cecal and colonic contents of mice, as well as in their feces, where a significant presence of gut microbiota is observed [21]. They have also been shown to be accessible to the enterohepatic circulation. Quantitative studies of MCBAs in human fecal samples have revealed their concentrations to be equal to or higher than those of PBAs and SBAs. Furthermore, these concentrations were found to decrease after bariatric surgery, underscoring the significance of MCBAs as a pivotal component of BA pool, responsive to changes in gastrointestinal physiology [22]. Traditional BAs are typically conjugated with glycine or taurine at the C24 carboxyl site, while MCBAs include conjugation with other amino acids or esters at different positions, such as hydroxyls of the sterol backbone [23]. The exact mechanism of this microbially mediated conjugation has not been elucidated, but the addition of unique amino acid reactions alters the physicochemical and biological properties of BAs. Specifically, phenylalanine and leucine are hydrophobic amino acids, leading to an increase in the hydrophobicity of the BA itself, which may prevent binding to the receptors [16]. Recent studies suggest MCBAs can influence immune cell development and function. For example, in early-life cohorts, altered MCBA profiles were associated with the risk of developing islet autoimmunity and type 1 diabetes. These MCBAs were enriched in patients with inflammatory bowel disease or obesity [20]. Researchers are increasingly looking into how modulating gut microbiota could shape the MCBA pool and influence host health. Meanwhile, recent studies have demonstrated the existence of more BA modifications than previously recognized, with the discovery of polyamine biosynthesis pathway-derived metabolites that are amidated to BAs [24]. Studies have indicated that bile salt hydrolase (BSH) serves a dual function in the metabolism of BAs. Not only can it deconjugate amines from BAs, but it also acts as a bacterial N-acyltransferase, catalyzing the formation of amine-conjugated BAs with unconjugated BAs as the substrate [25]. Furthermore, the synthesis and modification of 3-O-acylated BAs have been revealed, especially 3-O-succinylated cholic acid (3-sucCA) and 3-acetylated cholic acid (3-acetyCA), modified by the gut microbiota *Bacteroides uniformis* and *Christensenella minuta*, respectively [26–28]. However, the 3-acylated BAs are limited to

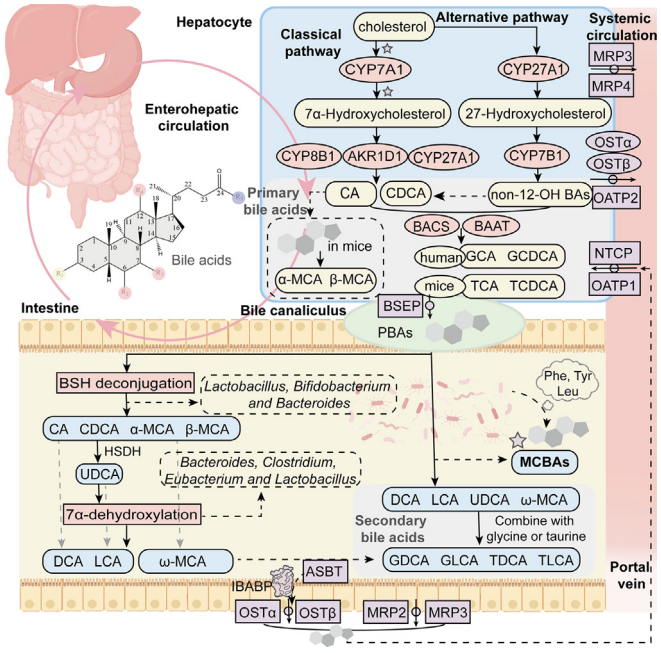

Fig. 1. Enterohepatic circulation of bile acids. The general structure of bile acids (BAs) consists a steroidal core. R_1-R_4 are sites of dehydroxylation, oxidation or amidation. Sites of esterification, amidation or deconjugation are indicated as R_5. BAs are produced via both the classical and alternative pathways [12]. The primary pathway, mainly mediated by cholesterol-7α-hydroxylase (CYP7A1), which serves as the pivotal step, also involves sterol-12α-hydroxylase (CYP8B1), aldo–keto reductase family 1, member D1 (AKR1D1), and sterol-27-hydroxylase (CYP27A1) to produce cholic acid (CA) and chenodeoxycholic acid (CDCA) [13]. The secondary pathway, mediated by CYP27A1, leads to the generation of non-12-OH BAs, predominantly CDCA, through the action of CYP7B1 [13]. CA, α-muricholic acid (α-MCA) and β-MCA are dominant in rodents [15]. CA and CDCA are conjugated to glycine or taurine by bile acyl-CoA synthetase (BACS) and bile acid-CoA:amino acid N-acyltransferase (BAAT), forming the primary bile acid (PBA) pool [29]. Excessive hepatic BAs are transported into the systemic circulation via multidrug resistance-associated protein 3 (MRP3), MRP4, and the organic solute transporter subunit alpha–beta (OSTα-OSTβ) complex [10,31]. In the intestine, gut microbiota metabolizes PBAs to SBAs using its own enzymes. Specifically, *Lactobacillus*, *Bifidobacterium* and *Bacteroides* deconjugates conjugated PBAs via BSH and anaerobic bacteria from the genera like *Bacteroides*, *Clostridium*, *Eubacterium* and *Lactobacillus* transform unconjugated PBAs into corresponding SBAs through 7α-dehydroxylation [34,141,142]. CDCA is converted into ursodeoxycholic acid (UDCA) via the hydroxysteroid dehydrogenase (HSDH) [263]. In addition, phenylalanine-, tyrosine- and leucine-conjugated CA derivatives, referred to as microbially conjugated bile acids (MCBAs), are generated in response to gut microbiotaactivity [20]. In the distal ileum, both conjugated and unconjugated BAs are reabsorbed via the apical sodium-dependent BA transporter (ASBT), bound to the ileal BA-binding protein (IBABP), and then delivered to the portal vein via transport proteins such as OSTα, OSTβ, MRP2 and MRP3 [31,38,39]. In the liver, ileal BAs are taken up by hepatocytes via the sodium/taurocholate cotransporting polypeptide (NTCP) and OATP1, completing the enterohepatic circulation [29]. ☆ indicates a key rate-limiting process and highlights a novel discovery. Solid black arrows indicate stepwise reaction processes, while dashed arrows represent cyclic processes. (Referenced from Jia W, et al. Nat Rev Gastroenterol Hepatol, 2018).

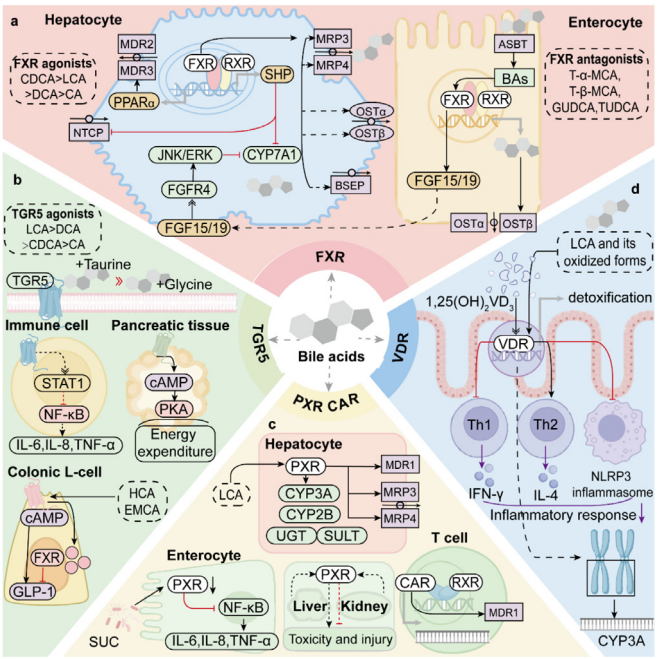

Fig. 2. BAs signaling and its regulatory mechanisms. (a) Interaction between BAs and FXR. FXR is primarily found in the liver and intestine, where is crucial in regulating BA biosynthesis. When FXR is activated in hepatocytes, it stimulates the expression of the small heterodimer partner (SHP), which in turn inhibits the transcription of CYP7A1, leading to a decrease in BA synthesis [42]. Additionally, FXR boosts the expression of peroxisome proliferator-activated receptor α (PPARα) and its downstream genes, enhancing bile excretion through upregulation of the multidrug resistance protein 2 (MDR2) and MDR3 transporters [44]. Additionally, FXR stimulates the expression of BSEP and other transporters including MRP3, MRP4, OSTα, and OSTβ, while inhibiting NTCP via SHP activation [43]. In the intestinal region, particularly the terminal ileum, FXR is triggered by BAs to stimulate the generation of fibroblast growth factor 15 (FGF15) in mice and its human counterpart FGF19 [45]. These growth factors travel to the liver, binding to fibroblast growth factor receptor 4 (FGFR4) and activating the JNK and ERK signaling pathways, which further suppress CYP7A1 transcription [45,46]. (b) BAs and TGR5. BAs function as natural activators for TGR5, a receptor that mitigates the pro-inflammatory NF-κB signaling pathway through the signal transducer and activator of transcription-1 (STAT1)-dependent mechanism, reducing the secretion of pro-inflammatory cytokines from immune cells [56,57]. However, this pathway is controversial (dashed arrow) [59]. In pancreatic tissue, stimulation of the TGR5-cAMP-protein kinase A (PKA) pathway by BAs regulate energy expenditure [56]. Additionally, hyocholic acid (HCA) can enhance the release of GLP-1 in the intestine by concurrently activating TGR5 and suppressing FXR [64]. Activation of TGR5 also promotes the regeneration of enterocytes [61]. (c) BAs, PXR and CAR. PXR can upregulate MDR1 and MRP to regulate BA excretion [70]. PXR also protects the host from microbial invasion by inducing the expression of CYP3A, CYP2B, sulfotransferases (SULTs), and UDP-glucuronosyltransferases (UGTs) [71,72]. PXR agonists suppressed the NF-κB signaling pathway and decreased cytokine production [76]. However, the therapeutic effects of PXR are conflicting depending on the tissue or model used and the different states. In the liver, activation of PXR induced hepatotoxicity, whereas activation of PXR in the kidney prevented acute injury [80,81]. CAR interacts with RXR to form heterodimers, regulating gene transcription related to BAs metabolism and detoxification [85]. (d) BAs and VDR. VDR primarily binds to 1α,25-dihydroxy vitamin D3 ($1,25(OH)_2VD_3$) [95]. Activation of VDR suppresses the inflammatory response by reducing Th1 cytokine production, and promoting Th2 cytokine production. It also inhibits the stimulation of NOD-like receptor protein 3 (NLRP3) inflammasome and other inflammation-related proteins [98–100]. Black single arrows indicate promotive processes, black double arrows represent binding interactions, red arrows denote inhibitory processes, and dashed arrows indicate controversial pathways. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

monocarboxylic acid, and the mechanism of their biosynthesis is unknown [27].

CA and CDCA are produced from cholesterol in hepatocytes and subsequently conjugated with glycine or taurine by bile acyl-CoA synthetase (BACS) and bile acid-CoA: amino acid N-acyltransferase (BAAT), after which they are stored in the gallbladder [29,30]. In the postprandial state, PBAs are released from the liver into the bile canaliculus via the canalicular bile salt export pump (BSEP) [6]. Elevated levels of hepatic BAs and bilirubin are transported into the systemic circulation via multidrug resistance-associated protein 3 (MRP3), MRP4, organic anion-transporting polypeptide 2 (OATP2), and the organic solute transporter subunit alpha–beta (OSTα-OSTβ) complex, eventually entering the intestine through the bile together [31]. In the intestine, gut microbiota metabolizes PBAs into SBAs using its own enzymes. Specifically, the microbiota deconjugates conjugated PBAs via BSH and converts them into the predominant SBAs through 7α-dehydroxylation [11]. BSH enzymes are represented in various microbial species in most phyla, with *Bacteroides* spp. playing a

major role in the deconjugation of PBAs [32]. Gram-positive bacteria are capable of deconjugating conjugated BAs, such as *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Clostridium*, which are similar to Gram-negatives, like *Brucella* and *Bacteroides* [16,33–36]. Subsequently, only a few species of intestinal anaerobic bacteria can accomplish BA 7α-dehydroxylation, such as *Clostridium scindens*, *Clostridium hylemonae*, and *Peptacetobacter hiranonis* [32,37]. Both conjugated and unconjugated BAs are reabsorbed in the terminal ileum via the apical sodium-dependent BA transporter (ASBT), after which they attach to the ileal BA-binding protein (IBABP) and are carried to the basolateral membrane [38]. These conjugates are then delivered to the portal vein via OSTα, OSTβ, MRP2 and MRP3, returning to the liver with the bloodstream [31,39]. In the liver, ileal BAs are recycled back to hepatocytes through the sodium/taurocholate cotransporting polypeptide (NTCP) and OATP1, where they are re-secreted into the bile canaliculus by BSEP alongside newly generated BAs. The process is known as enterohepatic circulation, which occurs 4 to 12 times daily in humans (Fig. 1) [29,40].

Signalling by BAs

BAs act as signal molecules and can coordinate with various BA receptors to regulate metabolic and inflammatory processes, including FXR, PXR, CAR, VDR and TGR5 (Fig. 2) [13]. It is noteworthy that different BAs exhibit varying affinities for these receptors [41].

Bas and FXR

Farnesoid X receptor (FXR) plays a central role in regulating BA biosynthesis and intracellular homeostasis in both hepatic and intestinal tissues. Within hepatocytes, FXR triggers the expression of small heterodimer partner (SHP), consequently suppressing CYP7A1 transcription and thus BA production [42]. Additionally, FXR upregulates the expression of BSEP and other transporters such as MRP3, MRP4, OSTα and OSTβ, while inhibiting NTCP through activated SHP, thereby enhancing hepatic BA efflux [43]. Notably, FXR also contributes to controlling the detoxification process of BAs. Reduced transcriptional level of FXR results in lower expression of peroxisome proliferator-activated receptor α (PPARα) and its downstream genes, exacerbating cholestasis [44]. Apart from its direct impacts in the liver, FXR is triggered by BAs in the terminal ileum, leading to the induction of fibroblast growth factor 15 (FGF15) expression in mice and its equivalent FGF19 expression in humans [45]. Subsequently, FGF15/19 is transported to hepatic tissues and engages with fibroblast growth factor receptor 4 (FGFR4), activating the JNK 1/2 and ERK 1/2 signaling cascades, thereby inhibiting CYP7A1 transcription and BA synthesis [45,46]. Overall, FGF15/19 and SHP synergistically regulate BA synthesis in the enterohepatic circulation.

FXR's regulatory breadth is extensive, directly controlling more than 300 primary response genes and potentially thousands of additional ones through its interaction with the retinoid X receptor (RXR) [47]. Some studies indicate that BAs serve as endogenous FXR agonists, activating FXR at physiological concentrations [48]. The ability of BAs to activate FXR is ranked as CDCA, LCA, DCA and CA, with CDCA exhibiting the highest potential for activating FXR [48,49]. Notably, MCBAs show unique receptor affinities compared to traditional BAs, in which phenylalanocholic acid and tyrosocholic acid act as even stronger FXR agonists than CDCA (2-fold and 69-fold, respectively) [20,50]. Tauro-α-muricholic acid (T-α-MCA) and T-β-MCA are recognized as potent antagonists of FXR, while glycine-amidated ursodeoxycholic acid (GUDCA) and taurine-amidated ursodeoxycholic acid (TUDCA) have also been identified as FXR antagonists [18,51].

BAs and TGR5

BAs act as natural ligands for TGR5, which belongs to the rhodopsin-like subfamily of G protein-coupled receptors (GPCRs). TGR5 is widely expressed across various tissues, particularly in gallbladder epithelial cells, where it is most abundant [52]. The potency of unconjugated BAs in stimulating TGR5 follows this order: LCA, DCA, CDCA, CA [53]. Both conjugated and unconjugated BAs can activate TGR5, with taurine-conjugated BAs showing a stronger ability to activate TGR5 compared to glycine-conjugated BAs [54]. Notably, Leucine-conjugated chenodeoxycholic acid and Phenylalanine-conjugated chenodeoxycholic acid are able to act as activating ligands for TGR5 with similar efficacy as taurolithocholic acid, albeit with lower potency [55]. The activation of TGR5 leads to inhibition of the pro-inflammatory NF-κB signaling pathway through the signal transducer and activator of transcription-1 (STAT1)-dependent mechanism, thereby reducing the secretion of pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α in immune cells [56,57]. In a mouse model of mastitis caused by *Staphylococcus aureus*, DCA-mediated TGR5 activation alleviated symptoms by inhibiting the NF-κB and NLRP3 pathways [58]. However, activation of TGR5 enhanced the LPS-induced NF-κB signaling pathway and inflammatory responses in human monocytes, suggesting that TGR5 may have different regulatory roles in different cell types [59]. Overall, the anti-inflammation effects of TGR5 have been highlighted in past studies [60]. Moreover, the activation of TGR5 in intestinal stem cells aids in the regeneration of enterocytes [61]. BAs and their secondary metabolites can trigger the proliferation of intestinal organoids through TGR5, simultaneously increasing the number of cells that secrete glucagon-like peptide-1 (GLP-1) [62]. These studies emphasize the role of TGR5 in maintaining intestinal homeostasis, making it a critical mediator linking intestinal epithelial regeneration with metabolic regulation. Additionally, BAs can trigger the TGR5-cAMP-protein kinase A (PKA) pathway to modulate energy expenditure [56]. Cholic acid 7-sulfate, an apical activator of TGR5 expression specific to the gut, boosts the release of GLP-1, conferring anti-diabetic effects [61,63]. Hyocholic acid (HCA) enhances the production of GLP-1 in the intestine by concurrently stimulating TGR5 and suppressing FXR, thereby improving glucose regulation [64]. Furthermore, 6alpha-ethyl-23(S)-methyl-cholic acid (EMCA, INT-777) has been recognized as a specific TGR5 agonist, capable of inducing GLP-1 release [65]. Collectively, BA-mediated TGR5 activation promotes GLP-1 secretion, serving as a promising pharmacological target for metabolic disorders.

BAs, PXR and CAR

In addition to FXR and TGR5, nuclear receptors such as PXR, CAR, and VDR also play significant roles in BA-mediated immune regulation, although their contributions are less well characterized. Which BA receptor would be predominate in case of coexpression in a specific immune cell population remains unclear and might depend on the pathological context [66]. Specifically, FXR and TGR5 are activated at nonpathological concentrations, whereas PXR and CAR are also stimulated by BAs, but at higher concentrations [67].

Pregnane X receptor (PXR), belonging to the nuclear receptor superfamily, is a transcription factor activated by ligands, with high levels in both the liver and intestine. It is essential for regulating BA metabolism and the detoxification of exogenous drugs [68]. LCA and its 3-keto metabolite are capable of activating PXR [69], and subsequently upregulate the expression of MDR1 and MRP to regulate BA excretion [70]. Additionally, PXR protects the host from invasion by inducing the expression of various enzymes, including CYP2B, CYP3A, sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs) [71,72]. Oleanolic acid (OA) can

induce the expression of PXR target proteins, including CYP3A11, GSTM2, and UGT1A1, thereby promoting liver restoration [73]. Importantly, recent study has shown that macrophage PXR activation modulates macrophage polarization and attenuates endotoxin-induced liver injury [74]. Several reports have suggested a potential role for PXR in regulating intestinal inflammation, representing an interesting target in the IBD. Notably, in mice receiving severe ulcerative colitis-derived microbiota, the expression of PXR in the colon is reduced [75]. Studies have shown that PXR agonists alleviated experimental colitis induced by dextran sodium sulfate (DSS) by blocking the NF-κB signaling pathway and decreasing cytokine production [76–78]. In a mouse model of necrotizing enterocolitis, the disease severity was significantly increased by PXR knockout, whereas low doses of LCA reduced the intestinal expression of IL-6 and attenuated intestinal proinflammatory responses [79]. However, the therapeutic effects of PXR are conflicting depending on the tissue or model used and the different states. Rifampicin and isoniazid have been shown to mediate hepatotoxicity through PXR activation, although another report showed that PXR activation in the kidney protected against acute kidney injury [80,81]. Besides, xenobiotic clearance of PXR is essential for the prevention of tumorigenesis [82]. However, CYP3A4, the maker of activated PXR, affects pharmacokinetic drug–drug interactions, leading to decreased efficacy of anticancer drugs [83]. Therefore, the treatment of PXR antagonists may enhance the therapeutic effect by inhibiting CYP3A4 [84]. These discoveries suggest that PXR may be a regulatory center for tumorigenesis.

Constitutive androstane receptor (CAR) is recognized to form heterodimers with retinoid X receptor (RXR), which is involved in regulating gene transcription [85]. CAR is regarded as an indirect receptor for BAs, as it does not directly bind to major BAs, and it has been recognized as a major xenosensor of xenobiotic metabolism and disposition [86,87]. CAR activates the expression of several hydrolytic, conjugative drug transporters, and drug-metabolizing enzymes, thus contributing to drug elimination and toxicological processes [88]. It controls the expression of MDR1 in T cells, thereby protecting mice from BA toxicity [86,89]. The use of transgenic mouse models revealed that CAR was able to induce the expression of sulfotransferase and 3′-phosphoadenosine-5′-phosphosulfate synthetase 2, conferring resistance to LCA-mediated hepatotoxicity [90]. Moreover, 1,4-bis[2-(3,5-dichloropyridylory)] benzene (TCPOBOP)-mediated CAR activation significantly alleviated obesity, diabetes and fatty liver in mice fed with HFD [87]. There are several similarities between PXR and CAR. First, both receptors can be activated by exogenous substances and induce the expression of drug-metabolizing enzymes and transporters, such as the CYP3A family [91]. Second, both receptors are capable of participating in BA homeostasis and other pathophysiological processes. In contrast to PXR, there is no experimental evidence to suggest that BAs are direct ligands of CAR [92]. Both PXR and CAR can regulate BA toxicity, each exerting different protective properties by regulating distinct BA detoxification enzymes and transporters [66,89]. PXR is thought to activate the CYP3A promoter, whereas CAR regulates the expression of CYP2B, which has a smaller role in drug metabolism than CYP3A [93]. In conclusion, PXR and CAR have overlapping but differential roles in pathophysiology, and the crosstalk between the two receptors should be of concern.

BAs and VDR

In contrast to the anti-inflammatory functions of BA signaling through FXR and TGR5, BAs can damage cellular membranes and have potent cytotoxicity at high concentrations. Accordingly, the VDR acts as a low-affinity BA sensor to maintain homeostasis [92]. BAs can activate the VDR, which predominantly binds to 1α,25-dihydroxy vitamin D3 (1,25(OH)2VD3), the biologically active form of vitamin D. VDR is abundantly present in the gastrointestinal tract, where it exerts potent and specific immunomodulatory effects [94,95]. VDR binds to numerous genomic loci in a ligand-dependent fashion and regulates the expression of target genes by inducing local chromosome changes [96]. Apart from vitamin D and its analogues, LCA and its oxidized forms can also activate VDR [97]. VDR is recognized as an important regulator of both innate and adaptive immune cell function. Upon activation, VDR suppresses the inflammatory response by inhibiting the production of Th1 cytokine, promoting the production of Th2 cytokine, and reducing the expression of NOD-like receptor protein 3 (NLRP3) inflammasome and other inflammation-related proteins [98–100]. VDR can negatively regulate monocyte-derived macrophage activation, promote T_{reg} cell differentiation and inhibit pro-inflammatory Th1 and Th17 responses [101,102]. Furthermore, VDR activation induces the expression of CYP3A in vivo, thereby providing protection to the intestine from BA toxicity. Studies have shown $1,25(OH)_2VD_3$ inhibits the NLRP3 inflammasome via VDR, thereby alleviating ulcerative colitis induced by DSS [103].

Factors influencing bile acid metabolism

Antibiotics

The type, duration, and route of administration of antibiotic treatment significantly affect BA composition by altering the gut microbiota. The use of antibiotics brings about significant alterations in both the composition and function of the gut microbiota [18,104–106]. Antibiotic-induced gut microbiota dysbiosis and regulation of the host transcriptome are closely linked to BA metabolism [107]. Specifically, broad-spectrum and narrow-spectrum antibiotics exhibit distinct effects. Broad-spectrum antibiotics, such as aminoglycosides and cephalosporins, dramatically reduce microbial diversity and deplete key anaerobic taxa like *Clostridium* spp., which are essential for the synthesis of SBAs via 7α-dehydroxylation pathways [108]. As a result, levels of SBAs such as DCA and LCA decreased significantly following broad-spectrum antibiotic treatment, while PBAs accumulated [109]. In contrast, narrow-spectrum antibiotics exert a more targeted effect, preserving overall microbial diversity and thus maintaining more stable BA profiles [110]. However, even narrow-spectrum agents can selectively affect specific bacterial populations involved in BSH activity, subtly modulating the composition of the BA pool [111]. Moreover, the effect of the duration of antibiotic administration on the hepatic BA profile was variable, for example, the expression of CYP3A11 decreased to 11.4 % after the 5-day treatment with vancomycin and polymyxin B and to 7.01 % after the 25-day treatment [112]. This suggests that the impact of antibiotic treatment on BAs and hepatic metabolizing enzymes varies over time. Notably, the alterations in the BA pool induced by antibiotics are influenced by the administration routes (Fig. 3). For example, treatment of rats with oral roxithromycin and vancomycin led to a reduction in PBAs levels, whereas parenteral roxithromycin administration increased the taurine conjugates of PBAs ($p < 0.05$) [113]. Furthermore, the decreases of SBAs after oral antibiotics were usually stronger than after parenteral treatment [113]. Different antibiotic treatments exhibit diverse effects on the composition of BAs. For instance, in rats treated with vancomycin and sparfloxacin, the separation of BAs in feces was more noticeable than in plasma, suggesting that antibiotics have a more significant impact on the metabolite profile in feces [114]. Additionally, other drugs such as ketoconazole and rifampicin can also interfere with BA metabolism [115].

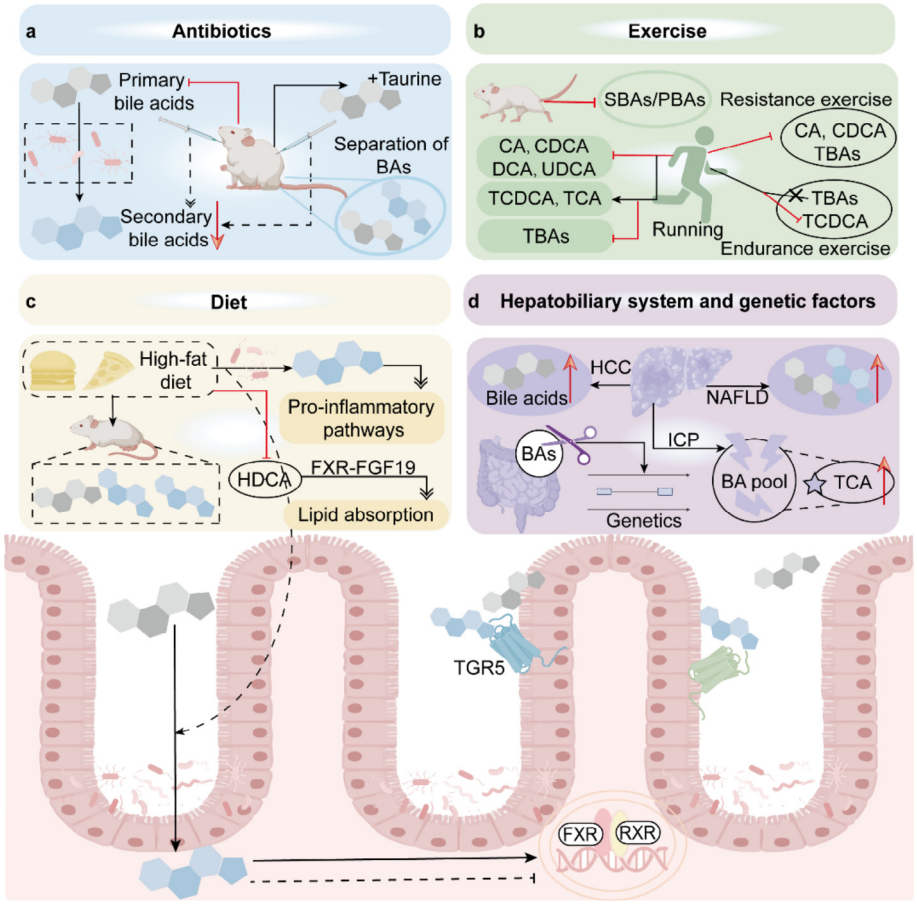

Fig. 3. Factors influencing bile acid metabolism. (a) Antibiotics. The administration of antibiotics changes the composition and function of the gut microbiota, leading to a reduction in SBAs. This change affects the makeup of BA pool, leading to rapid alternations within the gastrointestinal tract [18,104]. Notably, antibiotic-induced changes in the BA pool depend on the administration routes. For example, oral antibiotic treatment of rats reduced the levels of PBAs, while parenteral antibiotic administration increased the taurine conjugates of PBAs [113]. The decreases of SBAs after oral antibiotics were usually stronger than after parenteral treatment [113]. Additionally, the separation of BAs in stools was more evident than in plasma after antibiotic treatments [114]. (b) Exercise. Physical activity, such as wheel running in rats, has been shown to decrease the ratio of SBAs to PBAs in feces [117]. Significant reductions in serum levels of CA, DCA, CDCA, and UDCA have been observed following a moderate-distance running test in healthy, middle-aged recreational athletes, indicating that exercise might lead to a decrease in total BAs concentration [118]. Notably, various forms of exercises have distinct effects on BA composition. For example, resistance exercise decreased plasma concentration of total BA, CA and CDCA, while endurance exercise had no effect on total BA plasma concentration and decreased TCDCA [119]. (c) Diet. Dietary choices, particularly a high-fat diet (HFD), can markedly affect BA composition in the gastrointestinal tract. Consumption of HFDs resulted in the generation of SBAs by gut microbiota enriched with BSH, subsequently activating pro-inflammatory pathways in the host [126]. In mice fed a HFD, there is a notable decrease in the diversity of BA composition, accompanied by a substantial increase in the proportion of SBAs [127]. HFD led to reduced intestinal HDCA in the dyslipidemia mice and promoted lipid absorption via the intestinal FXR-FGF19 axis [129]. (d) Hepatobiliary system diseases and genetic factors. In individuals with hepatocellular carcinoma (HCC), a significant rise in BA levels has been closely linked to the advancement of the disease [132]. In patients with NAFLD, the serum levels of PBAs and SBAs were increased [133]. Additionally, genetic factors can influence BA metabolism, as evidenced by the loss of intestinal BAs in mice, which has been associated with specific genetic profiles [137]. Furthermore, an elevated percentage of TCA in total BAs emerges as a biomarker for predicting preterm delivery in Intrahepatic cholestasis of pregnancy (ICP) [136]. Black single arrows indicate positively induced processes, while red blunt arrows represent negatively inhibited processes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Exercise

Different types of exercise can affect BA levels in feces and blood, offering new insights into its therapeutic potential for metabolic and gastrointestinal diseases. Researches have indicated that exercise is essential in regulating the makeup of both the gut microbiota and BA pool in enterohepatic axis [116]. Physical exercise influences BAs levels in feces and blood. Research indicates that the proportion of SBAs to PBAs in feces decreased after wheel running exercise in rats, while the daily excretion of BA remained unchanged [117]. Studies on healthy, middle-aged recreational athletes undergoing a middle-distance running test revealed significant decreases in serum levels of CA, DCA, CDCA and UDCA, while the levels of TCDCA and TCA increased substantially (Fig. 3). This suggests that exercise, especially aerobic or endurance exercise, may reduce total BAs concentration, with potential implications for gastrointestinal cancers [118]. Interestingly, various forms of exercises (i.e., resistance or endurance exercise) have different effects on BA composition. For example, resistance exercise decreased plasma concentration of total BA, CA and CDCA, while endurance exercise did not impact the total BA plasma concentration and decreased TCDCA [119]. Moreover, in non-alcoholic fatty liver disease (NAFLD) patients after 12 weeks of intensive interval training, glyco-conjugated BAs decreased in adipose tissue and urine, which has beneficial ameliorating effects on NAFLD disease [120]. Human clinical data summarized in the study found that regulating BAs through exercise may be a promising therapeutic strategy for NAFLD [116]. An analysis of BA levels in 735 colorectal adenoma formers obtained from participants in the phase III UDCA chemoprevention trial found that exercise may be responsible for reducing the incidence of colon cancer by reducing colonic BA exposure [121]. In summary, exercise-mediated BA signaling holds significant promise for improving metabolic disorders within the body [116,122].

Table 1
Intestinal microbiota, bile acids and their crosstalk.

Microbes	Bile acids	Functions	References
Bacteroides, *Clostridium*, *Eubacterium* and *Lactobacillus*	DCA, LCA, ω-MCA, HDCA	– Increases intestinal permeability; – Reduces macrophage recruitment and inhibits NF-κB activation.	[142,148,149,171,172]
Bacteroides spp.	CDCA	– Increases expression levels of tight junction proteins.	[32,150]
Akkermansia	TUDCA	– Increases the number of goblet cells and the expression levels of Occludin and Claudin-1.	[151,152]
Clostridium AP sp000509125, *Bacteroides ovatus*, *Eubacterium limosum*	UDCA, LCA	– Inhibits epithelial cells apoptosis.	[156,222]
Clostridium scindens	UDCA	– Ameliorates metabolic disruptions and regulates energy metabolism; – Inhibits NF-κB activation and promotes M2 macrophage polarization	[159,170]
Christensenella minuta	3-O-acyl-CA	– Inhibits intestinal FXR and alleviates abnormal host glycolipid metabolism.	[28]
Dubosiella, *Colidextribacter*	CA, α-MCA, β-MCA	– Ameliorates glycolipid metabolism disorders.	[261]
Bacteroides vulgatus	GUDCA	– Activates TGR5 and attenuates diabetes.	[165]
Bacteroides fragilis, *Eggerthella lenta*	3-oxoLCA	– Curtails Th17 cell differentiation and restores colonic $ROR\gamma^{+}$ T_{reg} counts.	[50,175,176]
Clostridium scindens, *Clostridium hiranonis*, *and Bacteroides*	isoalloLCA, isoDCA	– Bolsters the induction of T_{reg} cells.	[177,262]

Diet

Dietary patterns have a major impact on modifying gut microbiota and BA metabolism, with different dietary patterns eliciting distinct alterations in BA profiles and associated host physiological responses (Fig. 3). Compared to African children eating a traditional rural diet (rich in starch and fiber), European children eating a typical Western diet had significantly higher concentrations of intestinal BAs [123]. Notably, significant reductions in faecal BAs occurred in overweight and obese subjects intervened with mediterranean diet compared with the regular diets [124]. Bacteria involved in 6α-hydroxylated BA production were enriched in mice fed with oligofructose [125]. Ingestion of lactose in rats has been shown to decrease SBAs-to-PBAs ratio and inhibit the production of hyodeoxycholic acid (HDCA) in feces [117]. The intake of high-fat diets (HFDs) leads to the formation of SBAs by gut microbiota abundant in BSH, which triggers the host pro-inflammatory pathways and increases risk of cancer incidence [126]. Research conducted on mice has shown that a HFD decreased the diversity of BA composition in the gut and substantially elevates the proportion of BAs modified by gut microbiota [127]. In mice fed a HFD, the intestinal levels of DCA were found to markedly elevated [128]. HFD led to reduced intestinal HDCA in the dyslipidemia mice and promoted lipid absorption via the intestinal FXR-FGF19 axis [129]. Healthy male volunteers who consumed a hypercaloric high fat diet had decreased circulating levels of each individual species of unconjugated BAs and increased levels of tauro- and glyco-conjugated BAs, which was associated with their healthy or unhealthy metabolic phenotypes [130]. Moreover, a recent study also found that a transient HFD disrupted BA tolerance, accelerating the process of colitis [131]. Human dietary studies have shown that animal-based diets resulted in elevated levels of faecal DCA and a reduction in Gram-positive Firmicutes [50], suggesting that diet is fundamental to driving variations in microbial and BA metabolism of mice. However, investigations of these mechanisms in the human host remain limited, underscoring the need for further human-centered research to validate and extend current findings.

Hepatobiliary system diseases and genetic factors

Both pathological conditions of the hepatobiliary system and host genetic variations play critical roles in shaping BA metabolism and influencing disease susceptibility. Hepatobiliary system disorders, including fatty liver disease and gallbladder disease, can impact the generation and metabolism of BAs. It was found that intrahepatic BA metabolic fractions in patients with hepatocellular carcinoma (HCC) were significantly different compared to healthy individuals. Notably, abnormally high levels of BA were closely linked to the development of HCC [132]. Additionally, patients with NAFLD exhibited higher serum levels of PBAs and SBAs [133]. In mice with cholestatic liver disease induced by bile duct ligation, a significant rise in both hepatic BA level and the overall BA pool size was observed ($p < 0.05$), while hepatic CDCA levels were decreased ($p < 0.01$) [134]. Furthermore, elevated maternal serum total BA concentrations were linked to a higher risk of low birth weight and intrauterine growth restriction (IUGR) [135]. Intrahepatic cholestasis of pregnancy (ICP) is marked by disturbed BA metabolism, with an elevated percentage of TCA in total BAs emerging as a biomarker for predicting preterm delivery in ICP [136]. Research has demonstrated a relationship between the loss of intestinal BAs in mice and host genetics [137]. In humans, genetic variations in *NTCP* result in abnormally increased serum BA concentrations, while the overall BA levels tend to decline with advancing age [138]. CYP7A1 is the rate-limiting enzyme of the classical BA synthesis pathway, and polymorphisms of its gene significantly affect the rate of BA generation. It has been shown that the alternative BA pathway was upregulated by a homozygous deletion mutation in CYP7A1, which resulted in hyperlipidemia [139]. Similarly, BSEP deficiency led to several different genetic forms of cholestasis [140]. These illustrate that host genetic variations significantly affect BA metabolism and disease susceptibility by regulating key enzymes and transporters involved in the BA circulation.

Effects of microbiota-BA interactions

Within the gut, the microbiota is instrumental in the metabolism of BA. Bacterial species possessing bile salt hydrolase (BSH) activity, like *Lactobacillus*, *Bifidobacterium* and *Bacteroides*, deconjugates conjugated PBAs into unconjugated forms [34,141]. Subsequently, anaerobic bacteria including *Bacteroides*, *Clostridium*, *Eubacterium*, and *Lactobacillus* transform the unconjugated PBAs into corresponding SBAs through 7α-dehydroxylation [142]. Additionally, the gut microbiota generates phenylalanine-, tyrosine- and leucine-conjugated CA derivatives, serving as FXR agonists [20]. The microbial processing of BAs not only diversifies the BA pool but also increases its hydrophobicity, thereby facilitating the excretion of BAs. Notably, the host metabolite BA-methylcysteamine is regulated by microbiota-derived free BA levels and, in turn, functions as an FXR antagonist to feedback-

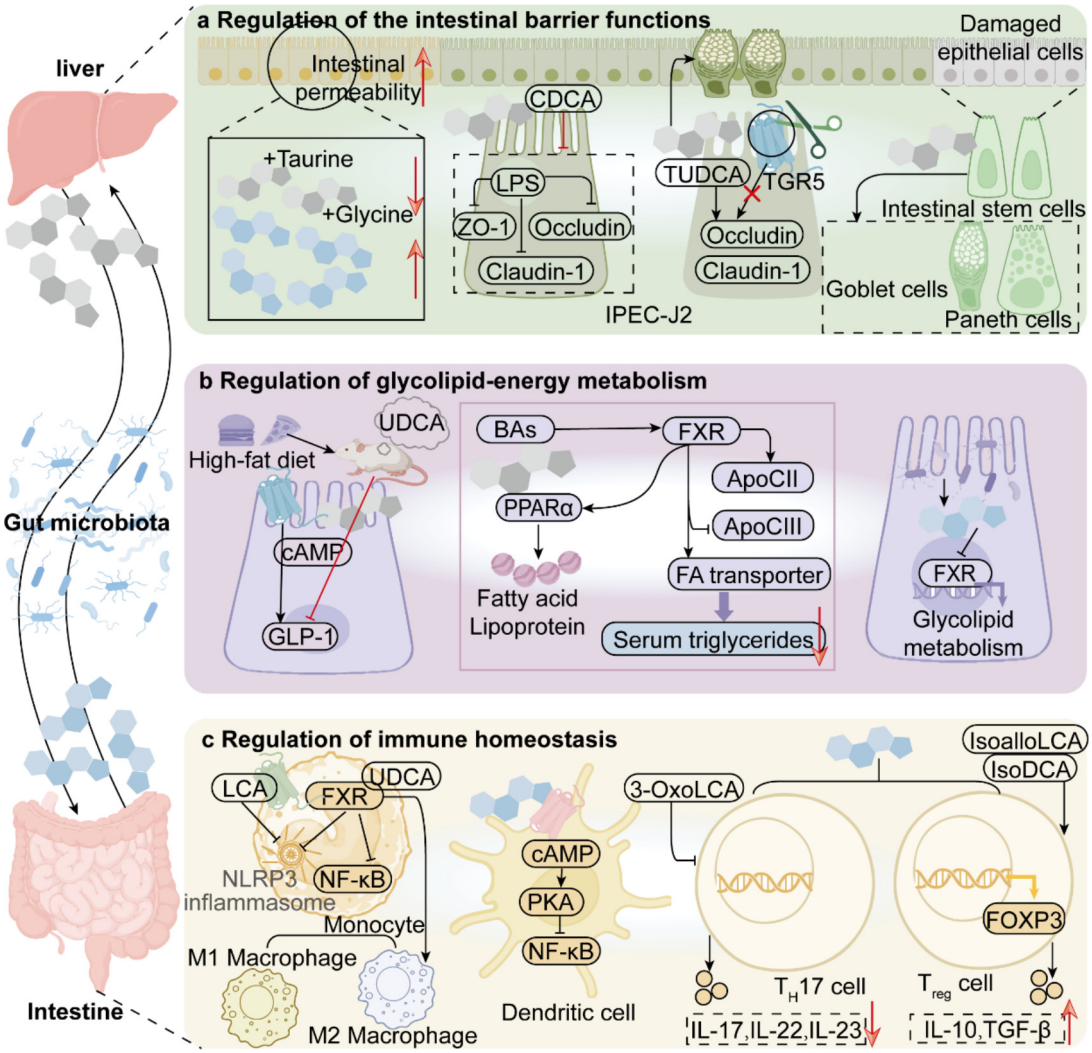

Fig. 4. Effects of microbiota-BA interactions. (a) Regulation of the intestinal barrier functions. The enhanced intestinal permeability was linked to reduced levels of host-produced conjugated BAs and elevated levels of SBAs in the large intestine in mice and rats fed a high fat diet [148,149]. Treatment with CDCA restored the levels of tight junction proteins, which were reduced by lipopolysaccharide (LPS) in IPEC-J2 porcine intestinal epithelial cells [150]. Similarly, supplementation of TUDCA increased the count of goblet cells and the expression levels of Occludin and Claudin-1 in jejunum and ileum of weaned piglets, while the knockout of TGR5 eliminated the ameliorative effect of TUDCA on IPEC-J2 [151]. BAs also promoted the proliferation of $Lgr5^{+}$ intestinal stem cells (ISCs) to replenish damaged epithelial cells [155]. (b) Regulation of glycolipid-energy metabolism. The dysregulation of BA profiles in HFD-fed obese mice was accompanied by reduced GLP-1 levels, and treatment with UDCA ameliorated these metabolic disruptions [159]. BAs influenced fatty acid and lipoprotein metabolism by triggering the expression of PPARα by activating FXR [160]. FXR reduced serum TG by promoting the expression of ApoCII, an activator of lipoprotein lipase (LPL), and inhibiting the expression of the LPL inhibitor ApoCIII [161–163]. The gut commensal bacteria regulated host glycolipid metabolism by producing SBAs that specifically inhibited intestinal FXR [28]. (c) Regulation of immune homeostasis. FXR in macrophages functions as a negative regulator of the NLRP3 inflammasome [168]. UDCA combined with FXR to inhibit NF-κB activation and promote M2 macrophage polarization [170]. It has been shown that LCA inhibited NLRP3 inflammasome activation via the TGR5-cAMP-PKA axis [167]. In dendritic cells (DCs), SBAs inhibited NF-κB activation through the TGR5-cAMP-PKA pathway [172]. BAs directly modulate host immunity through regulating the balance of Th17 and T_{reg} cells [174,175]. Specifically, 3-oxoLCA curtails Th17 cell differentiation, while isoalloLCA and 3-β-hydroxydeoxycholic acid (isoDCA) bolster the induction of T_{reg} cells [176,177].

regulate the BA biosynthetic pathway [143]. The relationship between BAs and gut microbiota is reciprocal. Gut microbiota also suppresses BA synthesis in the liver by reducing the suppression of FXR in the ileum [18]. In turn, BAs can influence the makeup and functional capacity of the microbiota [11]. BAs promote or inhibit the growth and multiplication of intestinal bacteria. BAs are commonly used as antimicrobial compounds that disrupt bacterial membranes, cause oxidative damage to DNA, and modulate the expression of genes involved in host immunity [144]. BAs can alter membrane lipid composition and disrupt membranes in a dose-dependent manner [145]. Similarly, BAs act as detergents in the gut, leading to increased membrane permeability [16]. In addition to membrane damage, BAs pose an adaptive challenge to gut microbes by interfering with RNA secondary structures and chelating metal ions such as calcium and magnesium, which are required for cellular life activities [109]. In the distal ileum, BAs exert their antimicrobial effects indirectly by inducing the production of antimicrobial peptides mainly through FXR [146]. However, bacterial species adapted to the mammalian gut are able to tolerate the antimicrobial activity of BAs through a variety of physiological adjustments, including activation of the stress response and remodeling of the cell envelope [144]. These interactions between BAs and the microbiota are essential for regulating gut barrier function, glycolipid-energy metabolism, and immune homeostasis (refer to Table 1 and Fig. 4).

Regulation of the intestinal barrier functions

BAs are regarded as crucial compounds in preserving the integrity of the intestinal barrier. Different BAs exert varying impacts on

the intestinal barrier. Unconjugated BAs, except for LCA, have been found to interfere with or have no impact on gut barrier function, as demonstrated in both vivo models of intestinal inflammation and vitro studies of intestinal epithelial cells [147]. Studies in mice and rats fed a HFD have associated increased intestinal permeability with reduced abundance of host-produced conjugated BAs and elevated levels of SBAs in the large intestine [148,149]. These SBAs like DCA and LCA can be cytotoxic, disrupt epithelial cell membranes, and further compromise barrier function. Treatment with CDCA restored the levels of tight junction proteins, including ZO-1, Occludin, and Claudin-1, which were reduced by lipopolysaccharide (LPS) treatment in IPEC-J2 porcine intestinal epithelial cells [150]. Similarly, supplementation of TUDCA resulted in an elevation in the number of goblet cells and elevated the expression levels of Occludin and Claudin-1 in jejunum and ileum of weaned piglets, while the knockout of TGR5 eliminated the ameliorative effect of TUDCA on IPEC-J2 [151]. Another study has indicated that TUDCA influenced the dysbiosis in mice with colitis, particularly leading to a significant increase in *Akkermansia*, thereby protecting intestinal barrier integrity [152]. These findings suggest that specific BAs, such as CDCA and TUDCA, enhance barrier function by upregulating the expression of tight junction proteins through distinct receptors, or increasing the abundance of beneficial gut microbiota. Consistent with this, intestinal FXR deactivation has been associated with increased intestinal permeability in a rat model of cholestatic liver damage [153]. Conversely, obeticholic acid (OCA), a potent FXR agonist, improved intestinal barrier function by reducing intestinal inflammation [153]. These findings underscore the pivotal role of intestinal FXR signaling in maintaining epithelial barrier integrity. Additionally, BAs have been found to regulate the formation of the intestinal mucus layer [154]. $Lgr5^+$ intestinal stem cells (ISCs) replenished injured epithelial cells and generated progenitors of goblet and Paneth cells, thereby preserving the integrity of the intestinal mucus layer [155]. UDCA and LCA inhibited epithelial cells apoptosis to protect against intestinal inflammation [156]. These observations reveal that BAs contribute to intestinal homeostasis by modulating the mucus layer and stem cell stemness. Overall, BAs regulate intestinal barrier function by activating receptors, mitigating inflammation, and enhancing tight junctions.

Regulation of glycolipid-energy metabolism

BAs could regulate glycolipid and energy metabolism through their interactions with specific receptors. BAs and their secondary metabolites are able to enhance GLP-1 secretion by activating TGR5, thereby improving insulin resistance [62,64,157]. Furthermore, hepatic BA-FXR signaling controls glucose levels by reducing gluconeogenesis and influencing glycogen synthesis [158]. It has been reported that the disturbances in BA profiles in HFD-fed obese mice led to reduced GLP-1 levels and energy expenditure, and treatment with UDCA and *Clostridium scindens* (*C. scindens*) ameliorated these metabolic disruptions [159]. Interestingly, *C. scindens* exhibited a strong positive correlation with UDCA. Additionally, BAs facilitate the breakdown of fat globules into finer particles via emulsification, increasing their surface area for interaction with digestive enzymes and thus enhancing fat digestion efficiency [61]. BAs are also known to decrease serum triglycerides (TG) and affect lipogenesis through various mechanisms [41]. It has been shown that BAs influenced fatty acid and lipoprotein metabolism via inducing the expression of peroxisome proliferator-activated receptor alpha (PPARα) through FXR activation [160]. FXR further regulated the expression of key genes associated with TG metabolism, such as microsomal triglyceride transfer protein, very low density lipoprotein receptor, FA transporter, apolipoprotein C-II (ApoCII) and ApoCIII. Here, FXR reduced serum TG by promoting the expression of ApoCII, which activates lipoprotein lipase (LPL), while inhibiting the expression of ApoCIII, an LPL inhibitor [161–163]. Moreover, T-β-MCA, an inhibitor of intestinal FXR, contributes to reducing hepatic steatosis [164]. Administration of TGR5 agonists to HFD mice has been found to enhance energy expenditure and reduce steatosis [65]. The gut commensal *Christensenella minuta* could alleviate abnormal host glycolipid metabolism by producing a novel group of SBAs with 3-O-acylation substitutions, which specifically inhibited intestinal FXR [28]. It has been shown that GUDCA resulted in elevated abundance of *Bacteroides vulgatus* and activation of TGR5 to attenuate diabetes [165]. In general, BAs are integral in regulating their own synthesis, along with metabolism of glucose, fatty acids, lipids, and lipoproteins, underscoring their pivotal roles in metabolic process [13].

Regulation of immune homeostasis

BAs modulate both innate and adaptive immunity through interacting with various immune cells and cytokines. BAs and their receptors, particularly TGR5 and FXR, have emerged as pivotal regulators of innate immunity through their modulation of the NLRP3 inflammasome. Deubiquitination of NLRP3 is required for NLRP3 inflammasome activation [166]. It has been shown that LCA induced NLRP3 ubiquitination and inhibited NLRP3 inflammasome activation via the TGR5-cAMP-PKA axis [167]. BAs are capable of activating the NLRP3 inflammasome in inflammatory macrophages, while FXR within macrophages acts as an inhibitor of the NLRP3 inflammasome, significantly impacting the management of cholestasis [168]. Similarly, FXR inhibited NLRP3 activity by suppressing phosphorylation of NLRP3, and knockdown of NLRP3 may alleviate the onset of hepatic fibrosis [169]. In low-birth-weight (LBW) piglets, UDCA preserved intestinal immune homeostasis by collaborating with FXR to inhibit NF-κB activation, diminish inflammatory cytokine production, and promote M2 macrophage polarization [170]. Similarly, SBAs such as LCA and DCA might also ameliorate colitis by reducing macrophage recruitment [171]. It has been demonstrated that SBAs inhibited NF-κB activation in dendritic cells (DCs) via the TGR5-cAMP-PKA signaling pathway [172]. Additionally, gut microbiota-mediated BA metabolism contributes to the accumulation of natural killer T (NKT) cells through the regulation of CXCL16 expression in liver sinusoidal endothelial cells [173]. Beyond macrophages, DCs, and innate T lymphocytes, BAs influence the stability of the intestinal immune barrier by regulating effector T cells. BAs directly modulate host immunity through influencing the balance between Th17 and regulatory T (T_{reg}) cells, as well as regulating intestinal $ROR\gamma^+$ T_{reg} cells [174,175]. Specifically, 3-oxoLCA curtails Th17 cell differentiation, evidenced by decreased levels of the pro-inflammatory cytokines such as IL-17, IL-22, and IL-23 [176,177]. Conversely, isoalloLCA and 3β-hydroxydeoxycholic acid (isoDCA) bolster the induction of T_{reg} cells, enhancing the levels of Foxp3 and the anti-inflammatory cytokines IL-10 and TGF-β [61,176,177]. Notably, isoDCA could influence DCs, leading to a reduction in their immunostimulatory properties [176]. Further studies found that the addition of isoDCA produced a higher frequency of $Foxp3^+$ T_{reg} cells at baseline in DCs lacking FXR, suggesting that isoDCA acts on DCs via FXR to enhance the T_{reg} cells induction [176]. Similarly, transplantation of *Bacteroides* species into germ-free mice induced colonic $ROR\gamma^+$ T_{reg} cells by VDR and FXR [175]. These results suggest that BA receptors mediate the regulatory effects of BAs on T_{reg} cell populations. Studies have shown that the numbers of colonic $ROR\gamma^+$ T_{reg} cells and total $Foxp3^+$ T_{reg} cells remained unaffected by isolated administration of either individual primary or secondary BAs. However, combinations of specific murine PBAs, along with a blend of LCA/3-oxoLCA, were found to restore the counts of

Table 2
Gut microbes, bile acids, and their involvement in disease.

Microbes	Bile acids	Roles in Disease	References
Parabacteroides distasonis	LCA, UDCA	Alleviates obesity and metabolic dysfunction by activating the FXR pathway and repairing gut barrier integrity	[188]
Salmonella typhimurium	CDCA	Exerts anti-infective effects by inhibiting the function of HilD and preventing invasion of epithelial cells	[189]
Akkermansia muciniphila, *Bifidobacterium* spp.	OCA, 3-sucCA	Alleviates MAFLD by promoting the growth of *Akkermansia muciniphila* or enriching bacteria encoding 7alpha-hydroxysteroid dehydrogenase	[27,195]
Bacteroides vulgatus	GUDCA	Attenuates diabetes via elevating TLCA levels and regulating the composition of the gut microbiota	[165]
Clostridium scindens	DCA, LCA	Enhances resistance to CDI in an SBA-dependent manner	[202]
Bacteroides, *Clostridium*, and *Eubacterium*	LCA, DCA	Enhances gut-barrier integrity via TGR5 activation to mitigate IBD	[208,222]
Bacteroides, *Alistipes*	12-KLCA	Prevents acute exacerbation of UC via suppressing the secretion of IL-17A by colonic group 3 innate lymphoid cells	[75]
Parabacteroides goldsteinii	7-KLCA	Lessens intestinal injury by promoting Wnt signaling and self-renewal of intestinal stem cells	[224]

colonic RORγ^+ T_{reg} cells [175]. This increase was seen in germ-free murine models mono-associated with either *Bacteroides thetaiotaomicron* or *Bacteroides fragilis*. Conversely, animals colonized with *Bacteroides* lacking BSH demonstrated marked depletion of colonic RORγt^+ T_{reg} cells, implicating the significance of microbial BSH activity in regulating colonic T_{reg} cells [50,175]. Moreover, SBAs enhanced the activation of $CD8^+$ T cells through the TGR5, mTOR, and oxidative phosphorylation pathways, while DCA suppressed $CD8^+$ T cell responses by blocking Ca^{2+}-nuclear factor of activated T cells (NFAT) 2 signaling in patients with colorectal cancer (CRC) [178,179].

The role of microbiota and BAs in disease

Metabolic diseases

BAs coordinately regulate metabolic diseases like obesity, metabolic dysfunction-associated fatty liver disease (MAFLD), and diabetes through BA receptors [180]. Notably, mice with gut-specific FXR knockout exhibited resistance to obesity, insulin resistance, and NAFLD induced by a HFD, highlighting the critical function of intestinal FXR in these metabolic disorders [181]. In line with this, UDCA, an FXR antagonist that has received approval from the Food and Drug Administration (FDA), is used in the therapy of primary biliary cirrhosis and NAFLD [182,183]. However, studies suggest that levels of LCA might increase during UDCA administration, potentially limiting its therapeutic benefits [109,184]. In addition, the gut microbiota plays a crucial role in metabolic diseases. Elevated levels of the genera *Lactobacillus* and increased BSH activity in the HFD-induced mouse model led to reduced levels of tauro-β-MCA, which resulted in exacerbated adverse metabolic phenotypes [181]. In patients with metabolic dysfunction-associated steatotic liver disease, the abundance of the phylum Bacteroidetes and *Bifidobacterium* increased with the progression of liver disease [185,186].

BAs are typically elevated in the fasting circulation of obese individuals, while their post-prandial increase appears to be minimal [187]. BAs modulate obesity and associated metabolic disorders via three main pathways: 1) Bacteria related BA receptor signaling. In HFD-fed mice, *Parabacteroides distasonis* alleviated obesity and metabolic dysfunction by producing SBAs and activating the FXR pathway [188]. 2) Antibacterial action of BAs on the intestinal microbiota. Beyond modulating host immunity, BAs function as molecular messengers that maintain homeostasis within the gut microbiota. Evidence from studies suggests that BAs can cause bacterial DNA damage [145]. Additionally, the anti-infective effects of CDCA against *Salmonella typhimurium* have been demonstrated to occur through molecular targeting of the *HilD* transcriptional regulator, effectively suppressing its virulence-associated gene expression [189]. 3) Hydrophobic toxicity BAs. Hydrophobic BAs exhibit cytotoxic, triggering apoptotic cascades in hepatic parenchymal cells by activating Fas-associated death signaling in a ligand-dependent manner [190]. Together, these distinct yet interconnected pathways illustrate the multifaceted role of BAs in metabolic regulation. Microbiota-mediated BA receptor signaling not only modulates host metabolism directly but also influences the microbial community composition, thereby indirectly shaping downstream immune and metabolic responses [45,191]. Concurrently, the antimicrobial properties of BAs help maintain intestinal microbiota balance, which is essential for preserving gut barrier integrity [192]. Moreover, while the cytotoxic potential of hydrophobic BAs may appear detrimental, it may serve as a mechanism for removing dysfunctional cells in controlled contexts, thereby contributing to tissue remodeling during metabolic stress [193]. Collectively, these mechanisms highlight a complex network in which BAs function as metabolic integrators at the interface of host, microbiota, and immune system, underscoring their central role in the pathogenesis and potential treatment of obesity and related metabolic disorders.

Among semi-synthetic BA derivatives, OCA is the first drug approved as an FXR agonist for clinical application, specifically targeting primary biliary cholangitis [194]. Furthermore, studies have revealed that OCA can alleviate NAFLD in mice by enhancing the growth of bacteria encoding 7α-hydroxysteroid dehydrogenases (7α-HSDs) [195]. NAFLD, a liver manifestation of metabolic dysfunction, has been addressed using HDCA, which alleviate NAFLD by inhibiting intestinal FXR [196]. Reflecting the complexity of the etiology and diagnostic criteria, the American Gastroenterological Association endorsed renaming NAFLD to MAFLD [197]. Similarly, it has been demonstrated that microbially derived 3-succinylated cholic acid (3-sucCA) can alleviate MAFLD via selective enrichment of *Akkermansia muciniphila* [27]. In addition, clinical observations have shown that plasma levels of HCA were reduced in diabetic patients, which was associated with suppressed GLP-1 secretion and elevated blood glucose levels [64]. GUDCA modulated BA levels via activating TGR5, thereby attenuating diabetes [165]. In summary, BAs are considered a prospective therapeutic target for mitigating the risk of metabolic diseases (refer to Table 2).

Clostridium difficile infection

Clostridium difficile is an anaerobic, spore-producing intestinal pathogen that triggers severe diarrhea and has the potential to be fatal [198]. *Clostridium difficile* infection (CDI) ranks among the most prevalent infectious diseases globally [3]. The severity of CDI depends on the virulence of the strain, the makeup and action

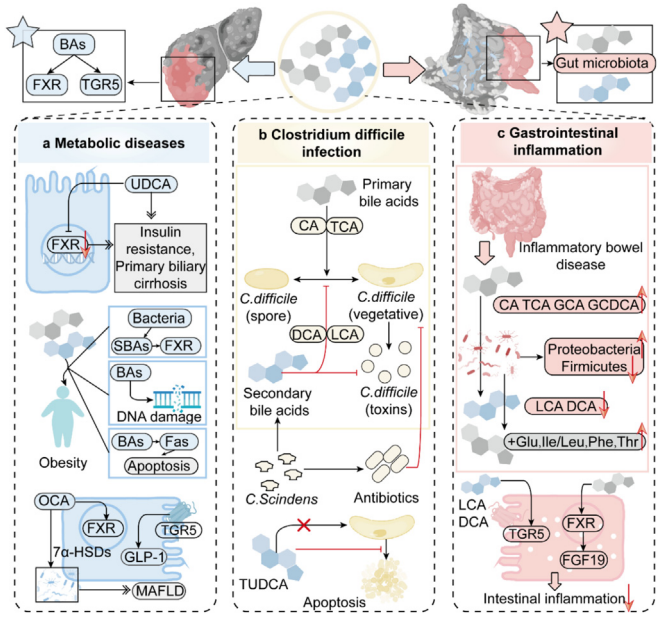

Fig. 5. The role of microbiota and BAs in disease. (a) Metabolic diseases. UDCA, an FXR antagonist, is utilized to treat primary biliary cirrhosis [182]. BAs modulate obesity and associated metabolic disorders via three main pathways: 1) Bacteria related BA receptor signaling [188]. 2) BAs could induce bacterial DNA damage [145]. 3) Hydrophobic toxicity BAs induce hepatocyte apoptosis by activation of Fas-associated death signaling in a ligand-dependent manner [190]. OCA alleviated MAFLD by activating FXR and enriching bacteria encoding 7α-hydroxysteroid dehydrogenases (7α-HSDs) [195]. (b) *Clostridium difficile* infection. *Clostridium difficile* is an anaerobic intestinal pathogen that produces spores [198]. PBAs can promote the proliferation of *C. difficile* and produce toxins, whereas SBAs inhibit the growth of *C. difficile* [198,201]. *C. scindens* could secrete antibiotics that inhibit *C. difficile*, acting synergistically with SBAs produced through its metabolism [203]. TUDCA could inhibit *C. difficile* toxin-induced apoptosis without affecting the growth of the bacteria itself [205]. (c) Gastrointestinal inflammation. In patients with active IBD, PBAs such as CA, TCA and GCA were significantly elevated, while SBAs like LCA and DCA were markedly reduced [208]. Other conjugated BAs were also associated with IBD, with increased levels of CA conjugated with amino acids such as glutamate, isoleucine/leucine, phenylalanine [210]. Microbial composition was typically manifested as a rise in Proteobacteria and a decline in Firmicutes [214]. BAs alleviate intestinal inflammation through activating the receptors [218,219]. Black single arrows indicate inductive processes, red blunt arrows represent inhibitory processes, and black double arrows indicate the resulting outcomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of gut microbiota, and the immune response of the host [199]. The gut microbiota influences the growth of *C. difficile* through BA metabolism (Fig. 5). Notably, exposure of *C. difficile* to PBAs in the gut, coupled with a lack of colonization resistance from the usual microbiota, leads to the germinates, colonization of the colon, and toxin produced by this bacterium [198]. CA and TCA are primary germinators of *C. difficile* spores [200]. In contrast, SBAs such as DCA, LCA, UDCA and HDCA can inhibit the growth of *C. difficile* [201]. Research has revealed that *C. scindens*, a BA 7α-dehydroxylating intestinal bacterium, enhanced resistance to CDI in an SBA-dependent manner [202]. *C. scindens* could also secrete antibiotics that inhibit *C. difficile*, acting synergistically with SBAs produced through its metabolism [203]. Moreover, researches have shown that administration of UDCA can suppress the growth of *C. difficile* and may modulate the innate immune response by stimulating FXR and TGR5 [204]. TUDCA has been found to block *C. difficile* toxin-induced apoptosis without affecting the growth of the bacteria itself [205]. In summary, targeting BAs presents a multifaceted approach to combatting CDI through various mechanisms (refer to Table 2).

Gastrointestinal inflammation

Inflammatory bowel disease (IBD) encompasses a set of non-specific chronic inflammatory conditions of the gastrointestinal tract, which includes Crohn's disease (CD) and ulcerative colitis (UC) [206]. CD can affect both the small intestine and the colon, whereas UC only affects the colon [11]. IBD is driven by both the gut microbiome and the immune system within the intestines, with BAs serving as a crucial signaling factor. Recent researches have highlighted a link between IBD and BAs, proposing that BAs could serve as both a signature predictor and a potential therapeutic target for IBD (Fig. 5). It has been demonstrated that BA metabolism was disturbed in IBD, with significantly elevated levels of CA detected in individuals with active IBD as well as in colitis mouse models [207]. Pathologically high concentrations of CA were shown to inhibit the proliferation of $Lgr5^{+}$ ISCs, potentially exacerbating intestinal epithelial injury [207]. In addition to CA, PBAs such as TCA, GCA and GCDCA were notably higher in CD patients [208]. Conversely, SBAs like LCA and DCA were markedly reduced, indicating a decrease in SBA-producing bacteria populations in IBD patients [208]. A similar trend in BA alterations has also been observed in the feces of patients with UC [209]. Concurrently, the colonic mucosa of UC patients exhibited elevated expression of TGR5 and downregulated expression of the VDR [209]. Other conjugated BAs have also been linked to IBD, with increased levels of CA conjugated with amino acids such as glutamate, isoleucine/leucine, phenylalanine, threonine, tryptophan, or tyrosine observed in CD patients [210]. These alternations may affect the disease process by modulating PXR signaling. In addition, recent studies suggest that changes in the BA pool may also be associated with therapeutic response. Specifically, CD patients who responded to anti-TNF therapy had higher serum SBA levels ($p < 0.05$), whereas those who did not respond had higher levels of serum unconjugated PBAs ($p < 0.01$) [211]. Pre-clinical studies have shown that supplementation with UDCA and TUDCA reduced inflammation in mouse models of colitis, indicating potential therapeutic significance in this setting [212,213]. Furthermore, in patients with IBD, abnormal microbial compositions have been observed, typically marked by an elevation in Proteobacteria and a decline in Firmicutes [214]. Since most BSH-expressing bacteria belong to Firmicutes phylum, changes of microbial composition can impact BA metabolism, contributing to the pathogenesis of IBD [215]. Previous clinical studies have demonstrated the numbers of *Bifidobacterium* and *Lactobacillus* reduced in the gut microbiota of IBD patients [216]. However, there is still much controversy regarding reports on changes in the abundance of *Bifidobacterium* and *Lactobacillus* in patients with IBD. One study illustrated that the levels of *Bifidobacterium* and *Lactobacillus* were significantly elevated in the biopsy specimens of active UC patients by quantitative real-time PCR targeting the 16S rRNA gene [217]. These seemingly contradictory results may be attributed to individual differences and variations in disease stages.

BAs not only serve as predictors for the onset of IBD through their interactions with ISCs and BA receptors, but also mitigate the disease's impact by activating these receptors and modulating metabolism processes. It has been demonstrated that stimulating FXR can alleviate intestinal inflammation and lower the release of pro-inflammatory cytokines, thereby helping to maintain intestinal barrier function [218]. For example, in colitis mice, treatment with the potent semi-synthetic FXR ligand OCA reversed the severity of colitis, but not in $FXR^{-/-}$ mice [219]. In the presence of FXR, the downstream factor FGF19 has been shown to lessen intestinal inflammation in a mouse model of colitis, aligning with the observed decrease in FGF19 levels in patients with CD [220]. Conversely, the removal of FXR and TGR5 receptors triggers inflammatory polarization of

intestinal T cells and macrophages [219]. Although FXR deficiency has been associated with an increased susceptibility to inflammation in both mice and humans, its therapeutic potential in clinical settings remains underexplored [221]. The administration of UDCA, DCA, and LCA has been proven to enhance gut-barrier integrity via TGR5 activation, thus alleviating symptoms of colitis [213,222,223]. Additionally, a metabolite produced by gut microbiota, 12-ketolithocholic acid (12-KLCA), has been found to suppress the secretion of IL-17A by colonic group 3 innate lymphoid cells, preventing acute worsening of UC [75]. Moreover, *Parabacteroides goldsteinii* and its metabolite 7-ketolithocholic acid (7-KLCA) had demonstrated a protective effect against intestinal damage induced by aspirin [224]. The use of rifaximin in clinical settings has successfully treated human IBD through local activation of PXR in the gut, providing a clinical proof-of-concept for targeting BA signaling in the intestine [225,226]. This highlights the therapeutic potential of targeting BA pathways and microbiota-derived metabolites in managing and potentially preventing complications in IBD (refer to Table 2).

Therapeutics targeting BA signaling

The metabolic and immunological properties of BAs present novel opportunities for restoring host and gastrointestinal ecosystem health by modulating the gut microbiota-BA-host axis in various disease states.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is an innovative therapeutic strategy aimed at treating intestinal microbiota dysbiosis. This procedure involves the effective transfer of functional microorganisms from the processed stool of a healthy donor to the recipient individual. Successful outcomes from FMT have been linked to greater biodiversity of the microbiome and the presence of bacteria that produce short-chain fatty acid in the donor's gut microbiome [227]. Gut dysbiosis is a prominent suspected trigger of IBD [44]. FMT has been demonstrated to increase the α-diversity of gut microbiota in patients with CD, leading to disease remission [228,229]. It has been reported that FMT effectively managed experimentally induced UC by correcting imbalances between Th1/Th2 and Th17/T_{reg} via the modulation of gut microbiota [230]. Notably, the effectiveness of FMT in treating IBD has shown variability, largely because of the lack of standardized procedures and specificity in its application. Nevertheless, it is evident that the success of FMT is often associated with the production of SBAs, particularly dehydrolithocholate [231]. Additionally, FMT has been effective in mitigating intestinal inflammatory diarrhea by reducing the levels of gut microbiota-derived lipopolysaccharide [232]. This underscores the potential of FMT not only as a means to rebalance gut microbiota but also as an essential intervention in managing gastrointestinal inflammatory conditions. However, its broader application in BA-related metabolic and inflammatory diseases remains limited due to several key challenges. Along with the success of FMT, several adverse events have been reported with FMT. Most commonly, patients develop mild symptoms such as abdominal pain, constipation, and nausea after FMT [233]. In addition, improper standardization of donor screening, like donor colonization with Shiga toxin-producing *Escherichia coli*, can lead to adverse events in FMT [234]. Specifically, the significant inter-individual variability of the microbiome, its temporal dynamics, and the lack of a clear definition of a "healthy microbiome" make FMT particularly challenging [235]. In the future, the availability of standardized microbiome-based therapies will help to reduce the risks of FMT.

Probiotics

While FMT presents promising therapeutic outcomes, it also carries potential drawbacks, such as the risk of transferring antibiotic resistance functions [222]. As an alternative, the strategic selection of probiotics offers an effective means to address ecological dysbiosis. *Bifidobacterium bifidum* has been found to ameliorate colitis induced by DSS through targeting alternations in the gut microbiota [236]. *Christensenella minuta* administration has demonstrated potential in alleviating lipometabolic disorders and reducing inflammation in both the liver and colon of obese mice via acylated SBAs [28]. Multispecies probiotics complexes, including strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus,* have improved BAs and gut microbiota metabolism status [237]. A combination consisting of *Clostridium AP sp000509125*, *Eubacterium limosum*, and *Bacteroides ovatus*, attenuated colitis by normalizing dysregulated BA metabolism [222]. The VSL#3 probiotic mixtures has shown effectiveness in delaying the progression of diseases such as colitis and amyotrophic lateral sclerosis [238,239]. In studies involving patients with irritable bowel syndrome (IBS), both probiotics and FMT have been shown to effectively alleviate overall IBS symptoms [240]. In network *meta*-analyses, probiotics, particularly *Bifidobacterium* and *Lactobacillus*, have demonstrated the most favorable therapeutic outcomes. However, due to the heterogeneity between the gut microbiota of donors, the feasibility of personalized FMT strategies require further evaluation [241]. Notably, despite their promising therapeutic potential, the widespread clinical application of probiotics in diseases faces several critical challenges. A major limitation is the poor colonization capacity of many probiotic strains within the gastrointestinal tract, especially under conditions of antibiotic exposure, bile salt stress, or microbial competition [242]. Host-specific factors, including individual microbiota composition and immune status, further complicate the standardization of probiotic therapy [243]. Therefore, there is an urgent need for large-scale clinical data to validate the efficacy and safety of probiotic interventions, taking into account not only differences in disease states but also inter-individual variations in BA metabolism.

Meanwhile, the development of genetically engineered probiotics marks a new frontier in therapeutic strategies. For instance, the oral probiotic *Escherichia coli Nissle 1917* (*EcN*) has been genetically modified to produce and secrete interleukin-2 (IL-2), offering a novel approach to treating IBD [244]. To overcome the challenge of limited intestinal colonization of probiotics, it has established a bacteria-microalgae symbiosis system (*EcN*-SP) as a natural carrier for *EcN*, effectively treating IBD by regulating gut microbiota balance [245]. Microencapsulation methods have also been employed to boost the bioavailability and intestinal colonization of probiotics, further optimizing their therapeutic potiential [246]. Recent studies have also investigated the synergistic effects of engineered probiotics and BA metabolism on immune modulation. It has been shown that the development of engineered *Bacteroides* strain can produce isoDCA and further increase the number of colonic T_{reg} cells [176]. Koh et al. designed a sialic acid-sensing BSH Cbh gene circuit by using engineered probiotics, which hydrolyzed taurocholate into free BAs, thereby restoring intestinal BA metabolism disrupted by antibiotic treatment [247]. Currently, BSH-active bacteria in probiotic preparations are also being aggressively researched for the treatment of IBD [248]. These studies highlight the therapeutic potential of engineered bacteria in treating IBD, but further clinical trials are needed to validate their safety.

Administration of BAs and related drugs

In various disease states, abnormal BA metabolism is often observed, and the direct administration of BAs has shown promise in delaying disease progression. It has been demonstrated the potential of targeting CDCA and its receptor FXR for treating pancreatic necrosis through BA metabolomics [249]. UDCA has received FDA approval for treating cholesterol cholelithiasis and hepatobiliary diseases [250,251]. Although LCA has demonstrated efficacy in preventing colitis, the associated weight loss is a concern and is related to BA's ability to increase energy expenditure [213,252,253]. This highlights the need to take into account the dual impact of BAs on metabolism and inflammation when developing therapeutic agents for IBD. Therefore, targeted colonic or rectal delivery of BAs, which prevent systemic metabolic effects, may be the optimal approach for IBD treatments. Additionally, it has been shown that derivatives of DCA and LCA can effectively prevent the progression of cancer [254]. Recent studies have found that 3-sucCA attenuated MASH by promoting the growth of Akkermansia muciniphila [27]. Similarly, 3-O-acyl-cholic acids modulated the characterization of metabolic diseases in HFD-induced obese mice by inhibiting the intestinal FXR [28].

The development of FXR agonists is beneficial for reducing liver and serum triglyceride levels in disorders like metabolic syndrome, while also preventing intestinal bacteria overgrowth [10]. Both UDCA and LCA, acting as FXR agonists, help to alleviate metabolic syndrome via the FXR-FGF15 signaling pathway [11]. Despite promising preclinical outcomes, clinical trials targeting FXR agonists have faced significant setbacks due to adverse effects and limited efficacy in humans. For example, OCA, a potent FXR agonist, has been demonstrated therapeutic potential for primary biliary cholangitis and NAFLD [195,255]. However, long-term trials revealed notable side effects such as pruritus, dyslipidemia, and even hepatotoxicity at higher doses [256–258]. Notably, almost all currently available synthetic FXR ligands cause pruritus in a dose-dependent manner [259]. TGR5 agonists, such as INT-777, hold potential for treating diabetes and IBD, but to date, no clinical trials have been initiated to assess its safety and efficacy in humans [260]. This limitation restricts its immediate clinical applicability and underscores the need for further research to translate preclinical results into clinical settings. Furthermore, any alteration in the activity of any molecule within the BA signaling pathway can impact the immune response of the host. Intriguingly, inhibitors of the ASBT, which inhibit the reabsorption of BAs in the ileum and increase BA synthesis, have been used to achieve cholesterol-lowering effect [10]. These studies underscore the therapeutic potential of targeting BA receptors in disease treatment; however, species-specific differences in BA receptor biology must also be carefully considered. Rodents and humans differ in BA composition, FXR ligand specificity, and receptor distribution. For instance, tauro-β-MCA in mice acts as an FXR antagonist, while CDCA is a potent agonist in humans [17,18]. Furthermore, variations in downstream signaling pathways and microbiota-dependent BA metabolism complicate the extrapolation of findings from animal models to human disease. Therefore, there is an urgent need for human-centered approaches in the development of BA-targeted therapeutics, including the incorporation of human organoid systems and stratified clinical trial designs that account for interindividual variability in BA profiles and receptor expression.

Conclusions

Past research has illuminated how BA-microbiota crosstalk sustains host gut health through various BA receptors and cell signaling pathways. However, the immunological functions of MCBAs, the differential receptor interactions, recently discovered metabolic pathways *in vivo*, and precise mechanisms underlying novel therapeutic strategies remain to be elucidated. This review summarizes the generation and transport of BAs, highlighting the significant role of newly identified MCBAs within BA pool. BAs engage with signaling receptors such as FXR, PXR, CAR, VDR, and TGR5 to regulate metabolic and inflammatory processes, with each receptor playing a distinct and non-redundant role. However, factors like medications, exercise, diet, or other adverse biological states can interfere with BA metabolism. This disruption impacts the ability of BAs to regulate the intestinal barrier, glycolipid-energy metabolism, and immune homeostasis. Additionally, BAs play roles in metabolic diseases, *Clostridium difficile* infection, and gastrointestinal inflammation, which have inspired a variety of therapeutic approaches including FMT, the administration of probiotics, and direct BAs treatment. These strategies underscore the potential of BAs and their receptors as therapeutic targets. Building on these insights, several critical challenges remain in the field of BA-microbiota crosstalk. Firstly, the precise mechanisms by which specific BAs and microbial metabolites interact to influence host receptors and downstream signaling pathways are not fully understood. The functional roles of newly identified BA derivatives, such as MCBAs, require further clarification, particularly in human systems. Secondly, the variability of gut microbiota composition among individuals presents a major obstacle in translating microbiota-targeted therapies into consistent clinical outcomes. Thirdly, while therapeutic strategies such as FMT, probiotics, and BA receptor agonists show promise, their long-term safety, specificity, and efficacy need rigorous validation in clinical trials. Future research should prioritize integrative approaches that combine metagenomics, metabolomics, and host transcriptomics to unravel host-microbiota-BA interactions.

Currently, our understanding of BA diversity and function is still evolving. With the advent of new scientific methodologies and technologies, novel BAs are continuously being discovered. There is a need to further characterize these novel BAs to uncover their functions and to construct innovative BA metabolic networks. Specifically, the receptor specificity, signaling dynamics, and tissue-specific effects of novel BAs should be prioritized. The multifaceted impacts of BAs on the host make the microbiota-BA-BA receptor axis a promising therapeutic target for treating inflammatory diseases. Because of the many BA receptors expressed in tissues beyond the gastrointestinal tract, elucidating how BAs transmit signals across these organs and how dysregulation contributes to metabolic and inflammatory disorders is essential. Additionally, understanding individual variability in BA metabolism, such as shaped by genetics, microbiota composition, and environmental factors, will be critical for developing personalized interventions. Studies on BAs will persist in delving into the systemic crosstalk between BAs and other organs across homeostasis and disease states, offering new possibilities for the progression of targeted therapies for metabolic diseases and IBD.

Compliance with ethics requirement

This article does not contain any studies with human or animal subjects.

CRediT authorship contribution statement

Yanmin He: Conceptualization, Writing – original draft, Writing – review & editing. **Weike Shaoyong:** Writing – review & editing, Visualization. **Yanli Chen:** Conceptualization, Validation. **Menglin Li:** Validation. **Yujie Gan:** Conceptualization. **Lu Sun:** Visualization.

Yalin Liu: Methodology. **Yizhen Wang:** Supervision. **Mingliang Jin:** Conceptualization, Supervision, Writing – review & editing.

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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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