HHS Public Access

Author manuscript

Nat Rev Microbiol. Author manuscript; available in PMC 2025 October 20.

Published in final edited form as:

Nat Rev Microbiol. 2023 April ; 21(4): 236–247. doi:10.1038/s41579-022-00805-x.

Bile acids and the gut microbiota: metabolic interactions and impacts on disease

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Abstract

Despite decades of bile acid research, diverse biological roles for bile acids have been discovered recently due to developments in understanding the human microbiota. As additional bacterial enzymes are characterized, and the tools used for identifying new bile acids become increasingly more sensitive, the repertoire of bile acids metabolized and/or synthesized by bacteria continues to grow. Additionally, bile acids impact microbiome community structure and function. In this Review, we highlight how the bile acid pool is manipulated by the gut microbiota, how it is dependent on the metabolic capacity of the bacterial community and how external factors, such as antibiotics and diet, shape bile acid composition. It is increasingly important to understand how bile acid signalling networks are affected in distinct organs where the bile acid composition differs, and how these networks impact infectious, metabolic and neoplastic diseases. These

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Author contributions

S.L.C. researched data for the article. All authors contributed to discussion of the content, and reviewed and edited the manuscript before submission. S.L.C., C.D.O., A.D.P. and J.G.S. wrote the article.

Competing interests

The authors declare no competing interests.

advances have enabled the development of therapeutics that target imbalances in microbiota-associated bile acid profiles.

In recent years, the focus of microbiota research has largely shifted from a compositional perspective (that is, 16S ribosomal RNA gene amplicon sequencing) to a functional perspective. The approximately 10^{13}–10^{14} bacteria composing the gut microbiota have the genetic potential to perform thousands more chemical reactions than humans, vastly expanding the metabolic capacity of the body[1]. One of the most important classes of gut microbiota metabolites is bile acids (BAs). BAs are amphipathic cholesterol metabolites that solubilize dietary lipids by forming micelles in the small intestine and facilitate their absorption or excretion. Additionally, they are hormones that regulate BA biosynthesis, lipid and glucose homeostasis, and immune signalling[2].

The BA pool consists of primary BAs, synthesized by hepatocytes and stored in the gall bladder, and secondary BAs, the products of bacterial metabolism (FIG. 1). BA biosynthesis from cholesterol is initiated by either cholesterol 7α-hydroxylase (CYP7A1) in the classic (neutral) pathway of hepatocytes or sterol 27-hydroxylase (CYP27A1) in the alternative (acidic) pathway found in extrahepatic tissues. The products are the primary BAs consisting of cholic acid (CA) and chenodeoxycholic acid (CDCA) in humans[3] and of CA and muricholic acid (MCA) in mice. Primary BAs are conjugated with glycine or taurine in humans, or predominantly taurine in mice, to form bile salts that are stored in the gall bladder. BAs are released into the duodenum when a meal is consumed, and along the gastrointestinal tract the gut microbiota metabolizes them[4]. Approximately 95% of BAs are reabsorbed (through both passive and active transport) before they reach the terminal ileum and are recycled via enterohepatic circulation[5]. The remaining BA pool enters the colon, where the majority of the gut microbiota population resides, facilitating the production of the major secondary BAs deoxycholic acid (DCA) and lithocholic acid (LCA) via dehydroxylation, and their passive reuptake[3].

The composition of the gut microbiota and the regulation of host BA transport and biosynthesis shape the BA pool (see BOX 1). BA compositions in mice are somewhat distinct from those in humans[6] because murine gut bacteria can produce more diverse secondary BAs than human gut bacteria[7]. Host BA biosynthesis differs substantially between mice and humans. In addition to the major human primary BAs CA and CDCA, mice also produce ursodeoxycholic acid (UDCA), and α-MCA and β-MCA from CDCA and UDCA, respectively[8]. Compared with humans, mice have a much larger proportion of primary BAs due to their expression of testosterone 7α-hydroxylase (CYP2A12), which converts DCA and LCA back to CA and CDCA, respectively[9]. In this Review, we examine how host–microbiota interactions affect the BA pool by bacterial transformation and community structure changes as well as signalling through host BA metabolic networks. We then discuss how these interactions impact human disease treatment and briefly discuss BA-targeted therapies.

Bacterial metabolism of BAs

Metabolism of primary BAs by the gut bacteria increases the diversity and overall hydrophobicity of the BA pool through a variety of modifications (TABLE 1 and FIG. 2). The first step in secondary BA metabolism is the hydrolysis of the amino acid moiety via bile salt hydrolase (BSH)[10]. BSHs are highly conserved across all major gut microbiota phyla (Bacteroidetes (also known as Bacteroidota), Firmicutes (also known as Bacillota) and Actinobacteria (also known as Actinomycetota))[4], but are distinct between bacteria because of their preferential activity towards either glycine-conjugated or taurine-conjugated BAs[11]. Bacterial BA deconjugation benefits the bacteria through the energy they harvest from the amino acid[12,13] and the host because it lowers BA toxicity[4]. However, there is some contention about whether harbouring a BSH provides a fitness benefit to bacteria[11,14].

Bacteria further dehydroxylate and epimerize hydroxy groups on the steroid backbone of deconjugated BAs. Dehydroxylation of the C7 hydroxy of CA and CDCA converts BAs to the major secondary BAs DCA and LCA, respectively. In mice, murideoxycholic acid, a 6β-hydroxylated BA, is also produced from α-MCA and β-MCA. The bacterial *bai* operon is responsible for BA dehydroxylation[15]. Recently, characterization of all eight *bai* gene products of *Clostridium scindens* was completed[16]. With use of single gene deletions and insertions, six enzymatic reactions were shown to be necessary and sufficient to confer DCA and LCA production in a non-producing *Clostridium sporogenes* strain[16]. Although *bai*-expressing *Extibacter muris* (in mice)[17] and *Clostridium* spp. are rare and dehydroxylate BAs exclusively in the caecum and colon[18], they produce all of the approximately 500 mg of DCA and LCA present in the body[3].

Other bacterial modifications include oxidation/epimerization, desulfation, esterification and conjugation. Bacterial hydroxysteroid dehydrogenases oxidize or reduce the steroid backbone of BAs to generate oxo-BAs and steroid backbone stereoisomers[19]. While some bacteria carry both oxidative and reductive stereospecific hydroxysteroid dehydrogenases, most require the cooperation of hydroxysteroid dehydrogenases from multiple bacteria to alter the stereochemistry of a backbone hydroxy group. In humans, UDCA and other stereoisomers are synthesized from the epimerization of CDCA. The function of bacterial epimerization may be in part to reduce BA toxicity (for example, DCA to isoDCA)[20]. Sulfate groups added by the host to facilitate excretion can be removed by bacteria expressing steroid 3-sulfatases[21], thereby reintroducing the BA to the BA pool. Esterified BAs have been reported to make up a large percentage (nearly 25%) of total faecal BAs in humans[22,23]. Although BA esters are depleted during antibiotic treatment[22], the bacterial enzymes responsible for their production are not known. Nonetheless, esterified versions of the major BAs (CA, CDCA, DCA and LCA) have all been reported[22].

Recent evidence suggests that bacteria can conjugate, rather than only deconjugate, amino acids at the C24 carbonyl. A comparison of intestinal metabolites from germ-free and conventional mice identified microbiota-dependent CA amidates with phenylalanine, tyrosine and leucine[24]. With use of an in silico tandem mass spectrometry fragmentation prediction workflow, 12 additional amino acid-conjugated BAs (AABAs) were identified in mouse faeces, including conjugates of cholenic acid, DCA and CDCA[25]. Dozens more

AABAs have been discovered in humans and mice from tandem mass spectrometry spectral matching of synthesized standards to compounds in spectrum databases[26,27]. Taxonomically diverse bacteria can conjugate amino acids to BAs in vitro, with the greatest producers being *Bifidobacterium*, *Bacteroides* and *Enterococcus* spp.[26,28]. Some AABAs may communicate with the host through modulation of FXR[24] or PXR[26] activity. Although no crystallographic structures of conjugated BAs with FXR or PXR have been reported, modelling predicts that conjugation at C24 enhances existing interactions with the loop linking helices H5 and H6 and introduces contacts with the loop linking H1 and H2 of the ligand-binding domain. Measuring the interaction of AABAs in the binding pockets of these and other BA receptors will be important to confirm their role as ligands. Additional transfers of saccharides or amino acid esters to BAs have been proposed, but the involvement of microorganisms is unknown. The continued expansion of known BAs suggests that other bacterial modifications of BAs may still be discovered.

Factors influencing bacterial BA metabolism

Alterations to the composition or activity of the gut microbiota due to antibiotics, exercise, diet or other dysbiotic states perturb BA metabolism (FIG. 3).

Antibiotics. Antibiotics have a dramatic impact on the BA pool. One of the metabolic pathways most disrupted in the host by antibiotic treatment is BA metabolism[29,30]. As bacteria are depleted, fewer BSHs are available to deconjugate host BAs, and secondary BAs are no longer generated. Therefore, elevated levels of conjugated BAs and a few secondary BAs are observed with use of antibiotics, including streptomycin[29], cefoperazone[31], vancomycin[32] and polymyxin B[33]. Other pharmaceuticals, such as the antidepressant drug paroxetine, can also perturb BA levels (including levels of AABAs) because of their unexpected antibiotic properties[34]. The loss of secondary BAs further exacerbates BA dysregulation because BA biosynthesis is upregulated, leading to a larger primary BA pool[33].

Physical activity. Several studies have linked exercise to differing BA profiles, but with conflicting results[35]. Rodent studies have found that moderate activity increases BA excretion, due to increased gastrointestinal motility and/or cholesterol uptake[36,37]. Surprisingly, however, BA synthesis and FXR–FGF15 signalling are not affected by exercise in these rodents[37]. In humans, increased duration and consistency of exercise leads to an overall decrease in serum and faecal BA pools[38]. This has disease implications for colorectal cancer (CRC) and non-alcoholic fatty liver disease (NAFLD), in which increased circulating BAs are associated with negative outcomes (see later). In addition, long-distance runners who have physiologic acclimation to exercise training have fewer mutagenic secondary BAs[39]. More research is needed to elucidate the impact of physical activity on the expression of FXR and GPBAR1 in the intestine and liver. Apart from host bile metabolism, physical activity reverses microbiota dysbiosis in patients with NAFLD, potentially contributing to differing secondary BA levels[40].

Diet. It has been long understood that diet, particularly fat and fibre intake, can dramatically alter the microbiota and BA metabolism. Intake of cholesterol raises overall BA levels in

humans, as cholesterol is the precursor for BAs and upregulates BA synthesis pathways[41]. The levels of secondary and unconjugated BAs are particularly elevated in people consuming a high-fat diet, due to the expansion of the population of 7α-dehydroxylase-expressing and BSH-expressing bacteria[41]. By contrast, fibre sequesters cholesterol and BAs in the intestine, leading to excretion of BAs and induction of BA biosynthesis[42,43]. The BA-expanding properties of a high-fat, low-fibre diet have been implicated in patients with colon cancer[44]. A recent article demonstrated that caloric restriction in mice reduces the total BA pool, including LCA and DCA, also reducing total microbiota content[45].

BAs shape the microbiota

BAs are important determinants of the abundance, diversity and metabolic activity of the microbiota. Increased primary BA concentrations (during newborn development) lead to enrichment of bacteria expressing BA metabolism genes in the small intestine[46,47]. BA-metabolizing enzymes are advantageous in bacteria because they provide tolerance to the toxic effects of BAs. The amphipathic structure of BAs, particularly of deconjugated and dihydroxylated BAs, facilitates insertion into and disruption of bacterial membranes[48,49]. Thus, Gram-negative bacteria resist BA toxicity[50] because of their second outer membrane[51]. BAs can also induce DNA damage, protein misfolding and oxidative stress, which lowers bacterial viability[50]. Individual bacterial strains differ in their tolerance to BAs due to their ability to express BA exporters[52] or enzymes[26]. However, BA toxicity with regard to microorganisms is also facilitated indirectly by activating FXR-mediated antimicrobial pathways (for example, inducible nitic oxide synthase and IL-18)[53,54].

Despite their toxic effects, BAs also support diversity in the microbiota. In humans, tauro-β-MCA and taurocholic acid (TCA) are central to the development of a diverse, adult-like microbiota[46]. Several studies have reported that microbiota diversity is reduced in patients with cholestasis[55], and in mice, bile duct ligation reduces microbial β-diversity[56]. Although a mechanism has not been demonstrated, the secretion of BAs may provide sufficient energy to support a large diversity of microorganisms[55]. In addition to compositional changes, BAs alter the functional capacity of the microbiota. For example, sublethal concentrations of DCA, TCA and tauroursodeoxycholic acid disrupt bacterial nucleotide and carbohydrate metabolism in mice[49]. However, more research is needed to understand how functional manipulation of the gut microbiota by the BA pool impacts host–microbiota communication.

Microbiota and BAs in disease

Clostridioides difficile infection. *Clostridioides difficile* is the cause of many health care-acquired infections, leading to severe diarrhoea, fever and death in severe cases. *C. difficile* infection (CDI) can arise when the normal microbiota is depleted by antibiotics. Antibiotic depletion of the resident microbiota reduces the population of antimicrobial peptide-secreting *Clostridium* spp., which typically control *C. difficile* populations[57], and also increases the availability of nutrients for *C. difficile* growth, such as primary sugars and germination-promoting TCA[31,58]. In addition, the conversion of primary BAs to secondary BAs by the native microbiota is essential for preventing CDI[59] (FIG. 4). Indeed, antibiotic-related elevations of primary BAs and reduced levels of secondary BAs are associated with recurring CDI[59,60].

The benefits of microbial BA metabolism regarding CDI are multifactorial. Certain primary BAs, including CA, TCA and GCA, induce *C. difficile* germination from spores to an active, toxin-producing state[61]. Conversely, DCA and LCA have been demonstrated to directly inhibit both *C. difficile* germination and *C. difficile* outgrowth[62]. This is in part why secondary BA production by *bai*-encoding *Clostridium* spp. such as *C. scindens* protects from CDI[63]. *C. scindens* and *Clostridium* also secrete antimicrobials against *C. difficile*, which are more effective in conjunction with DCA and LCA[64]. Secondary BAs also directly bind and sequester the *C. difficile* toxin TcdB to lower its toxicity[65]. The knowledge that bacterial BA metabolism is important for prevention of CDI may provide new treatment options. Faecal microbiota transfer as an alternative to antibiotics has demonstrated success in mitigating CDI by restoring secondary BAs[66]. If antibiotics are necessary, use of narrower-spectrum antibiotics, such as fidaxomicin[67] or ridinilazole, which have minimal impact on BA profiles, can limit susceptibility to CDI[68].

Inflammatory bowel disease. Inflammatory bowel disease (IBD) is a collection of chronic inflammatory conditions of the gastrointestinal tract, the most common being Crohn's disease and ulcerative colitis. Ulcerative colitis affects only the colon, whereas Crohn's disease can affect both the small intestine and the colon. During IBD flare-ups, the intestinal epithelium becomes inflamed and loses barrier integrity. Although the causes of IBD are incompletely understood, large-scale changes to the gut microbiota have been associated with both ulcerative colitis and Crohn's disease. Changes in microbiota diversity and loss of Firmicutes bacteria are consistently observed in IBD[69–71], especially loss of *Faecalibacterium prausnitzii*[72], which is thought to be protective against gut inflammation in IBD[73].

BA metabolism is markedly dysregulated in IBD, particularly when the microbiota is disrupted. Patients with active IBD have elevated levels of conjugated BAs and reduced levels of secondary BAs in their stool[69,72,74]. The levels of several novel AABAs also appear to be elevated in patients with Crohn's disease or ulcerative colitis compared with healthy individuals[24,26]. A study using computational predictions of the deconjugation and modification potential of the microbiota of patients with IBD and healthy individuals found that the BA metabolic potential of the microbiota of patients with IBD is perturbed[75]. However, several factors complicate the association between BAs, the microbiota and IBD. In particular, the increased intestinal transit rate of patients with active IBD reduces the total microbiota population and limits sufficient reaction time to metabolize BAs[74].

Elevated levels of primary BAs and reduced levels of secondary BAs, as seen in patients with IBD, induce a greater inflammatory response in Caco-2 cells compared with BAs from healthy individuals[72], potentially through the repression of NF-κB by the BA nuclear receptors FXR and PXR[76,77]. Activation of FXR by synthetic agonists attenuates inflammatory cytokine expression and intestinal permeability in chemically induced colitis mouse models[76,78]. Similarly, PXR agonists prevent inflammatory cytokine production and colon shortening in mouse models of colitis[79]. Although many of the BAs whose levels are elevated in IBD are FXR agonists with differing affinities (CDCA, CA, phenylalanocholic acid, tyrosocholic acid and leucocholic acid)[24], the collective plasma BA pool in patients with Crohn's disease reduces FXR and PXR activation[80]. FXR and PXR activation, in turn,

is reduced in patients with IBD[80]. This contradictory reduction in FXR and PXR activation may be due to the presence of uncharacterized antagonists or increased receptor turnover, although neither has been tested in humans.

Metabolic diseases, including obesity. Metabolic syndrome is identified in individuals with at least three of the following signs: hypertension, obesity, reduced blood HDL cholesterol level, elevated blood triglyceride levels, and elevated blood glucose level[81]. Individuals with metabolic syndrome are at risk of a variety of conditions, including diabetes mellitus, stroke, heart disease and CRCs. Genetics, diet and environment all play a role in metabolic disease[82], and this includes the microbiota and BA composition. Obesity[83,84] and insulin resistance[85,86] can be induced by transferring the gut microbiota of an obese mouse into a lean recipient. In addition, germ-free and antibiotic-treated animals fail to gain weight[50,84]. Gut microbiota dysbiosis in humans is associated with metabolic syndrome and obesity[85,87,88]. Initial studies found an association between obesity and a higher Firmicutes-to-Bacteroidetes ratio of the gut microbiota[83,89], but this relationship has been inconsistent across cohorts[90,91], and may represent an artefact of experimental design[92]. Nonetheless, the microbiota is essential for metabolic homeostasis by increasing dietary energy harvest[83], regulating appetite[93] and altering the BA pool. Antibiotic-associated reductions in the abundance of Firmicutes bacteria and subsequent depletion of secondary BAs coincide with decreased insulin sensitivity in patients with metabolic syndrome[32], whereas microbiota-dependent increases in the levels of secondary BAs are associated with NAFLD[94], underlining the importance of microbiota-related BA profiles for metabolic health.

Although secondary BAs may help to mitigate metabolic syndrome[95], the mechanism is unclear. BA receptors such as FXR and TGR5 maintain lipid (cholesterol and triglyceride) homeostasis and glucose homeostasis, which are dysregulated in metabolic syndrome[96]. TGR5 activation by BAs increases insulin sensitivity by inducing secretion of the hormone GLP1 (REF.[95]). Although FXR activation also increases GLP1 secretion[97], its involvement in metabolic disease is convoluted and seemingly context specific. In some studies, FXR activation has a beneficial effect on cholesterol, triglyceride and glucose levels[96]. For example, hepatic FXR activation suppresses triglyceride production by inhibiting the SREBP1c lipogenic pathway[98]. According to this model, bacterial BSHs deconjugate the FXR antagonist tauro-β-MCA, permitting hepatic FXR to inhibit lipogenesis and cholesterol metabolism, thereby suppressing weight gain and lowering serum cholesterol and triglyceride levels[99]. *Cyp7a1* expression is also decreased in mice overexpressing BSH, supporting the role of FXR activation in mitigating metabolic disease[99]. FXR and gut microbiota shifts are associated with weight loss after bariatric surgery[100], which is attributed to FXR-associated appetite reduction[93,100]. Clinical trials of potent synthetic FXR agonists, including obeticholic acid, have shown increased weight loss in patients with NAFLD[101], possibly by stimulation of brown fat differentiation and metabolism[102]. However, there have been conflicting reports of the impact of obeticholic acid on insulin resistance in patients with NAFLD[103,104]. Furthermore, knocking out *Fxr* (also known as *Nr1h4*) in mice has similar effects as FXR activation (prevented weight gain and increased insulin sensitivity) in some studies[105], but not others[106]. The benefits seen in *Fxr*-knockout

mice are microbiota dependent as microbiota transfer from these mice into germ-free mice confers weight loss, lowered body fat percentage and insulin sensitivity[105]. Contradictory roles of FXR could be because of its tissue-specific functionality (hepatic versus intestinal). This effect is observed with the conflicting effects of the synthetic FXR agonist GW4064 on obese mice, depending on the route of administration. Whereas oral gavage of GW4064 exacerbated weight gain and insulin resistance in high-fat diet-fed mice[107], the opposite was seen with intraperitoneal injection[108]. Thus, intestinal and hepatic FXR activity should be carefully considered when examining the impact of BAs on obesity and metabolic diseases.

Inflammation and carcinogenesis. Gut microbiota-associated BAs contribute to gastrointestinal inflammation and tumour development (reviewed in[109]). As early as the 1930s, DCA was shown to cause injection site tumours in mice[110]. Particularly in conjunction with a high-fat diet, both of the major secondary BAs (DCA and LCA) have long been associated with gastrointestinal cancers, particularly CRC[111] and hepatocellular carcinomas (HCCs)[112]. The gut microbiota has separately been associated with cancer development. Mice treated with an antibiotic cocktail are protected from HCC progression because there are fewer bacterial membrane lipopolysaccharides that activate TLR4 to increase cell division and suppress apoptosis[113]. Conversely, high-fat diet-fed mice are prone to HCC development due, in part, to increased Gram-positive populations and their production of DCA by 7α-dehydroxylases[114]. Thus, the composition and BA synthesis potential of the microbiota are critical to the progression of inflammation and cancer.

Due to their hydrophobicity, secondary BAs such as DCA and LCA are more carcinogenic than primary BAs[115]. In both HCC and CRC, cancer acceleration by hydrophobic BAs is predicated on their ability to damage cells and induce inflammation[116]. Unconjugated and hydrophobic DCA and LCA more readily act as detergents to disrupt cellular membranes and induce cell damage responses[109]. DCA can trigger protein p53 degradation directly[117]. An alternative mechanism for the membrane damage-associated carcinogenicity of DCA and LCA is through the generation of reactive oxygen species. Activation of phospholipase A_2 from DCA-damaged cells frees arachidonic acid from the membrane to be metabolized into reactive oxygen species, which damages DNA and generates mutations[118,119].

Suppression of FXR activity further exacerbates the oncogenic potential of secondary BAs. Many studies have observed reduced FXR activation in human CRC[120,121], and *Fxr*-knockout mice are predisposed to developing colon and liver tumours[122,123]. In both humans and mice, the tumour-suppressing effects of FXR are caused by its inhibition of the Wnt–β-catenin pathway[120,124]. As a receptor for BAs, FXR is an important connection between lipid metabolism and the disrupted cell signalling events during cancer progression. Interestingly, inflammation, and specifically TNF and IL-1β secretion through NF-κB, reduces FXR activation[125]. Therefore, the aforementioned pro-inflammatory reaction of cells to DCA and LCA can suppress FXR to promote carcinogenesis. FXR inactivation also increases synthesis and reduces hepatocellular export of BAs, further exacerbating the damage and inflammation mediated by BA accumulation[109]. An additional mechanism has been proposed for the cancer-promoting effects of bacterially hydrolysed taurine-conjugated BAs. The taurine released from deconjugation is ultimately metabolized through sulfonic acid into H_2S, a potent carcinogen[126]. As deconjugation by the microbiota is ubiquitous,

a major risk factor for H_2S production in the colon is the intake of taurine-rich foods (for example, meat products, dairy and energy drinks), leading to increased taurine conjugation of BAs by the host[127,128].

Therapeutic options

Manipulation of microbial BA metabolism, either by modifying the composition of the microbiota or the ability of the microbiota to metabolize certain BAs or by administering secondary BAs, has the potential to provide health benefits. As research elucidates the precise health effects of specific BA profiles, treatments can move from more general microbiota-altering approaches (for example, faecal transplant, probiotics and prebiotics) to specifically target individual BAs.

Faecal microbiota transplantation. Faecal microbiota transplantation (FMT), the transfer of faecal microorganisms from a healthy donor to a recipient patient, was developed initially to restore the protective properties of the intact microbiota against CDI[129]. The success of FMT for CDI may be partially due to the restoration of BSH-dependent secondary BA production[66,130,131]. Although some primary BAs, such as TCA, promote *C. difficile* spore germination, microbial DCA and LCA inhibit both *C. difficile* growth and *C. difficile* spore germination, and their levels are elevated in CDI-resistant individuals[59]. Although FMT has shown mixed results for treatment of ulcerative colitis, restoration of microbial 3-oxo-LCA is associated with FMT success and suggests a role for secondary BAs in mitigating the disease[132]. FMTs can mitigate excessive secondary BA production associated with diarrhoea-predominant irritable bowel syndrome by reducing the population of BSH-active bacteria[133]. FMT has also been studied in mice to treat a variety of other conditions in which dysbiosis is observed (for example, ageing)[134]. However, the involvement of BAs in the benefits of FMT for these conditions is unknown. One of the major limitations to the widespread application of FMT is its lack of specificity in modulating the microbiota, which can lead to unexpected adverse effects. It remains challenging to design a successful FMT therapeutic when the complete bacterial community and its impact on human health is unknown, although this approach holds promise.

Probiotics. Live microorganisms with defined BA-metabolizing properties can be administered to alter the BA pool in dysbiosis and disease. Compared with FMT, probiotics are advantageous in that they are more targeted, with a defined mechanism of action. In an attempt to understand microbiota disruptions in CDI, *Clostridium* spp. with 7α-dehydroxylation activity, specifically *C. scindens*, were demonstrated to eliminate *C. difficile* due to their production of inhibitory secondary BAs[63,135]. By genetic engineering, the *bai* operon from bacteria with 7α-dehydroxylation activity has been transplanted to confer these benefits to a commensal *C. sporogenes* strain[16]. This approach can attribute BA synthesis to a variety of commensals and precisely generate BAs of interest.

Probiotic manipulation of the BA pool can regulate the activation of BA receptors such as FXR, PXR and VDR. Probiotic mixture VSL#3 was developed for the management of irritable bowel syndrome and ulcerative colitis (including pouchitis in patients who have undergone operative management with the creation of a J-pouch)[136], but also contains

BSH-expressing bacteria that increase BA deconjugation and excretion. Treatment with VSL#3 upregulates hepatic BA biosynthesis by suppressing the FXR–FGF15 pathway[137]. This effect may be beneficial to reduce circulating cholesterol levels. However, the same probiotic mixture may have the opposite effect of restoring FXR activation in patients with CRC[120,121]. Indeed, VSL#3 administration to chemically induced colitis rodent models prevents CRC-associated downregulation of FXR, PXR and VDR and reduces inflammation and tumour formation[138,139]. Another BSH-active probiotic, *Lactobacillus reuteri* NCIMB 30242, has similar anti-inflammatory and cholesterol-lowering effects in humans[140], suggesting that the beneficial actions of these bacteria are dependent on converting conjugated BAs to secondary BAs.

BAs as therapeutics. Rather than administering BA-producing bacteria, one can administer bioactive secondary BAs because these have similar desired effects. UDCA is primarily used as an anticholestatic agent, and is the primary therapeutic option for patients with autoimmune biliary disease such as primary biliary cholangitis, but also may suppress the progression of gastrointestinal cancers such as CRC and HCC[141–143]. The UDCA-dependent mitigation of CRC development is mediated by the BA membrane receptor TGR5 (REF.[144]), and is associated with alterations in the microbiota of men but not women, namely increased *F. prausnitzii* abundance and reduced *Ruminococcus gnavus* abundance[145]. BAs may also contribute to an anti-inflammatory phenotype in patients with colitis, which is characterized by an overactive immune response. Administration of LCA metabolites supports T cell differentiation into regulatory T cells rather than pro-inflammatory T helper 17 cells by regulating the transcription factor RORγt and by generating mitochondrial reactive oxygen species[146–148]. This secondary BA-mediated promotion of regulatory T cell differentiation reduces colitis severity[149], and is partially responsible for the benefits of treatment with a bacterial consortium for colitis in mice[150]. Both UDCA and LCA are FXR agonists and can attenuate metabolic syndrome through the FXR–FGF15 pathway. Obese mice have lowered cholesterol, plasma triglyceride and plasma fatty acid levels when treated with LCA and UDCA, due to FXR–FGF15 activation[151]. Thus, bacteria that produce these secondary BAs, such as *Parabacteroides distasonis*, contribute to reductions in hyperlipidaemia[151]. The synthetic FXR agonist obeticholic acid is an approved drug for treating primary biliary cholangitis[152], and has also demonstrated success against non-alcoholic steatohepatitis and obesity[104]. Although direct supplementation with BAs can produce beneficial outcomes against carcinogenesis, colitis and metabolic syndrome, these effects may last only for the duration of treatment. Conversely, modifying the microbiota to increase bile metabolism could facilitate prolonged effects.

Conclusions

Imbalance in the bacterial transformation of BAs is an important contributor to metabolic, inflammatory, infectious and neoplastic diseases, primarily through the dysregulation of BA receptors. Treatments targeting BAs and the microbiota have demonstrated success and facilitated a deeper understanding of how existing BA treatments (for example, UDCA) function. The composition of BAs at their predominant sites is dependent on host synthesis, the numerous bacterial enzymes, and their uptake and transport. More research is needed

to continue expanding the known repertoire of BAs and characterize the bacterial enzymes responsible for their synthesis. Interactions with host BA receptors impart functionality to BAs, dependent on the abundance and relative potency of BA ligands, receptor localization and pathways triggered by their activation. Research is still needed to resolve the impacts of hepatic and intestinal BA signalling by distinguishing FXR activity in the associated organs. Because of the many BA receptors expressed in tissues beyond the gastrointestinal tract (for example, brain, T cells and smooth muscle), additional studies measuring the impact of BAs in distant sites are merited.

Glossary

Amphipathic	Containing both hydrophilic (polar) and hydrophobic (nonpolar) regions
Micelles	A collection or aggregate of amphipathic molecules that self-assemble in aqueous solution so that the hydrophobic portions are shielded from water
Cholestasis	A liver disease characterized by blockage of or reduced bile flow
Brown fat	Adipose tissue containing high numbers of mitochondria, involved in metabolizing energy sources to produce heat
Pouchitis	Inflammation of the J-pouch in surgery for ulcerative colitis
J-pouch	A J-shaped surgical reformation of the ileum, connected directly to the anus after the removal of diseased colon in patients with ulcerative colitis

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Box 1 |

Bile acid signalling and networks

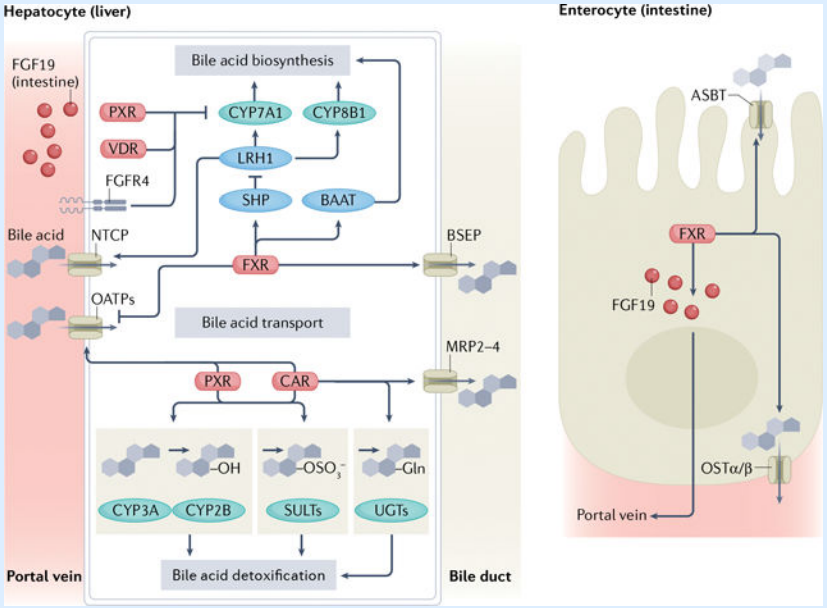
Human–microbiota communication relies in part on host receptor responses to microbial metabolites (see the figure). The microbiota regulates bile acid (BA) metabolism and transport by several key host BA receptors[155]. The nuclear receptors farnesoid X receptor (FXR), vitamin D receptor (VDR), pregnane X receptor (PXR) and constitutive androstane receptor (CAR) act as liaisons between BAs and nuclear receptor target genes involved in lipid and glucose homeostasis, xenobiotic metabolism, and immunoregulatory pathways[156,157]. Several G protein-coupled receptors (GPCRs) also bind to BAs and have mainly immunoregulatory functions[156].

FXR is the major BA receptor as its agonists include both free and conjugated cholic acid, chenodeoxycholic acid, lithocholic acid (LCA) and deoxycholic acid[158,159], whereas the conjugated BA murine tauro-β-muricholic acid is an antagonist[155]. In the ileum, activation of FXR induces secretion of fibroblast growth factor 15 (FGF15)/FGF19, which travels to the liver to suppress BA metabolism via FGF receptor (FGFR)[160,161]. Activation of hepatic FXR also reduces BA synthesis by upregulating the expression of the transcriptional repressor small heterodimer partner (SHP)[162,163]. Both FXR signalling pathways inhibit the expression of cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1), enzymes involved in the classic (neutral) BA biosynthetic pathway[160,164,165]. To alleviate BA toxicity, FXR induces BA-CoA:amino acid *N*-acyltransferase (BAAT) expression in the liver, thereby suppressing the accumulation of toxic unconjugated BAs[166]. FXR also eliminates hepatic BAs by increasing expression of the canalicular bile salt export pump (BSEP) and reducing the expression of hepatic transporters that take up bile (for example, organic anion-transporting polypeptide 1 (OATP1))[164]. In summary, an overabundance of toxic unconjugated BAs triggers FXR to lower biosynthesis of BAs and induce their export from the liver.

PXR, CAR and VDR are closely related nuclear receptors that play similar roles in BA detoxification and clearance. Although CAR does not have any known BA ligands[167,168], all three nuclear receptors promote the clearance of hepatotoxic LCA. LCA-activated PXR and VDR increase the expression of CYP3A and sulfotransferases (SULTs), which oxidize and sulfonate LCA[169,170]. They also facilitate the expression of the LCA exporters OATP2 and multidrug resistance protein 3 (MRP3)[171,172]. Additionally, PXR, CAR, and VDR contribute to BA homeostasis by inhibiting CYP7A1 through the FGF15/FGF19 pathway[173–175].

Response to BAs is also mediated by GPCRs (TGR5, S1PR2, M3 and MRGPRX4) expressed throughout the body. TGR5 agonists include both conjugated and unconjugated LCA, deoxycholic acid, chenodeoxycholic acid and cholic acid[176,177]. TGR5 is highly expressed in the spleen, lung and placenta, along with the liver, gall bladder and intestine, and has unique functions in each tissue. In monocytes, TGR5 suppresses NF-κB-mediated inflammation[178], while in gastric neurons, it regulates peristalsis[179], and in splenic B cells, it promotes energy consumption and insulin sensitivity[180,181].

Chronic itch in humans caused by bile cholestasis was originally thought to be mediated by TGR5, as it is in mice, but has now been linked to MRGPRX4 (REFS.[182,183]). Recent structural characterization of MRGPRX4 has identified residues necessary for receptor activation, for which synthetic antagonists may be designed to treat cholestatic itch[184]. The identification of GPCR BA receptors largely diversifies the potential regulatory functions of microbiota-associated BAs and the cell types they may act upon, further emphasizing the importance of tissue specificity when it comes to activation of host receptors for BA signalling.



ASBT, apical sodium–bile acid transporter; LRH1, liver receptor homologue 1; NTCP, sodium–taurocholate co-transporting polypeptide; OST, organic solute transporter; UGT, UDP-glucuronyltransferase.

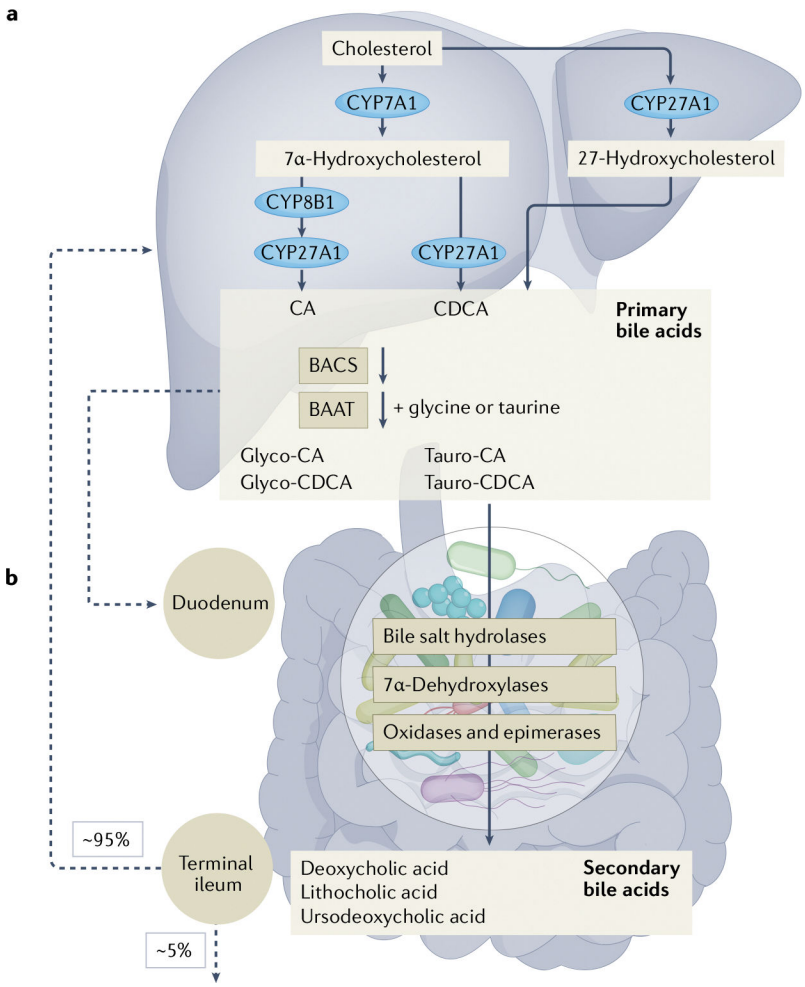


Fig. 1 |. Enterohepatic circulation of bile acids in humans.

a | Primary bile acids (BAs) are synthesized from cholesterol in the liver by the classic (cholesterol 7α-hydroxylase (CYP7A1)-mediated) pathway or the alternative (sterol 27-hydroxylase (CYP27A1)-mediated) pathway. BA-CoA synthetase (BACS) and BA-CoA:amino acid *N*-acyltransferase (BAAT) then catalyse BA amidation (conjugation) with glycine or taurine to form bile salts. **b** | The gut microbiota metabolizes BAs secreted into the duodenum into secondary BAs. Reabsorption of approximately 95% of the BAs that reach the terminal ileum permits their recycling by the liver. CA, cholic acid; CDCA, chenodeoxycholic acid; CYP8B1, sterol 12α-hydroxylase.

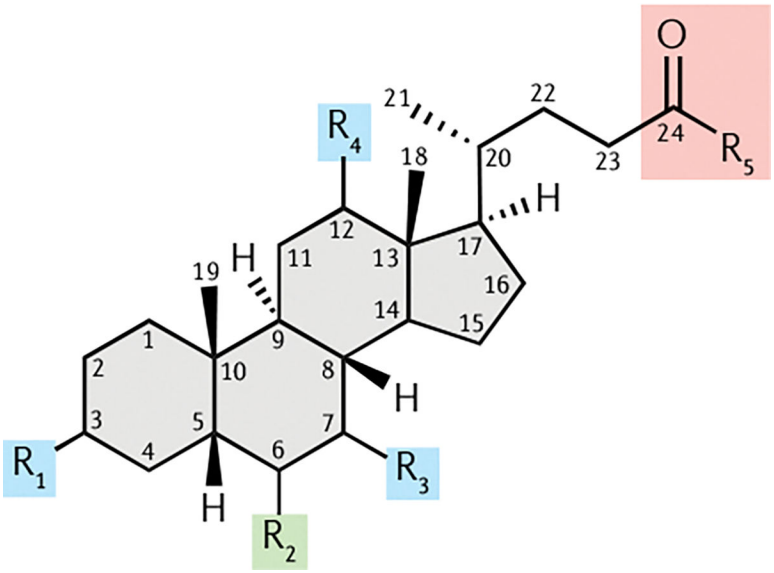


Fig. 2 |. General bile acid structure.

Sites of dehydroxylation or oxidation (–H, –OH or =O) are indicated as R_1–R_4. Esterification and amidation or deconjugation occur at R_5.

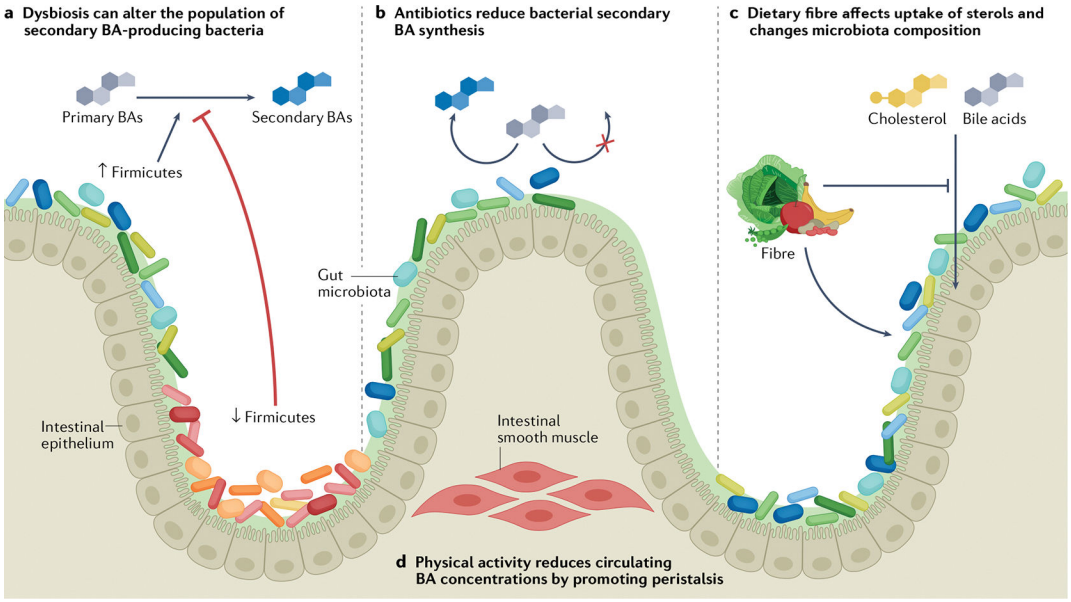


Fig. 3 |. Factors affecting bacterial transformation of bile acids.

a | Dysbiosis or **b** | antibiotics reduce populations of 7α-dehydroxylating Firmicutes, and thereby perturb secondary bile acid (BA) levels. **c** | Dietary consumption of cholesterol increases total BA pools, but insoluble fibre can bind and sequester cholesterol and BAs in the intestinal lumen. Prebiotic fibre and other dietary components also modulate the microbiota composition. **d** | Exercise-associated shortened intestinal transit time reduces the concentrations of secondary BAs and reabsorption of BAs because they are excreted faster.

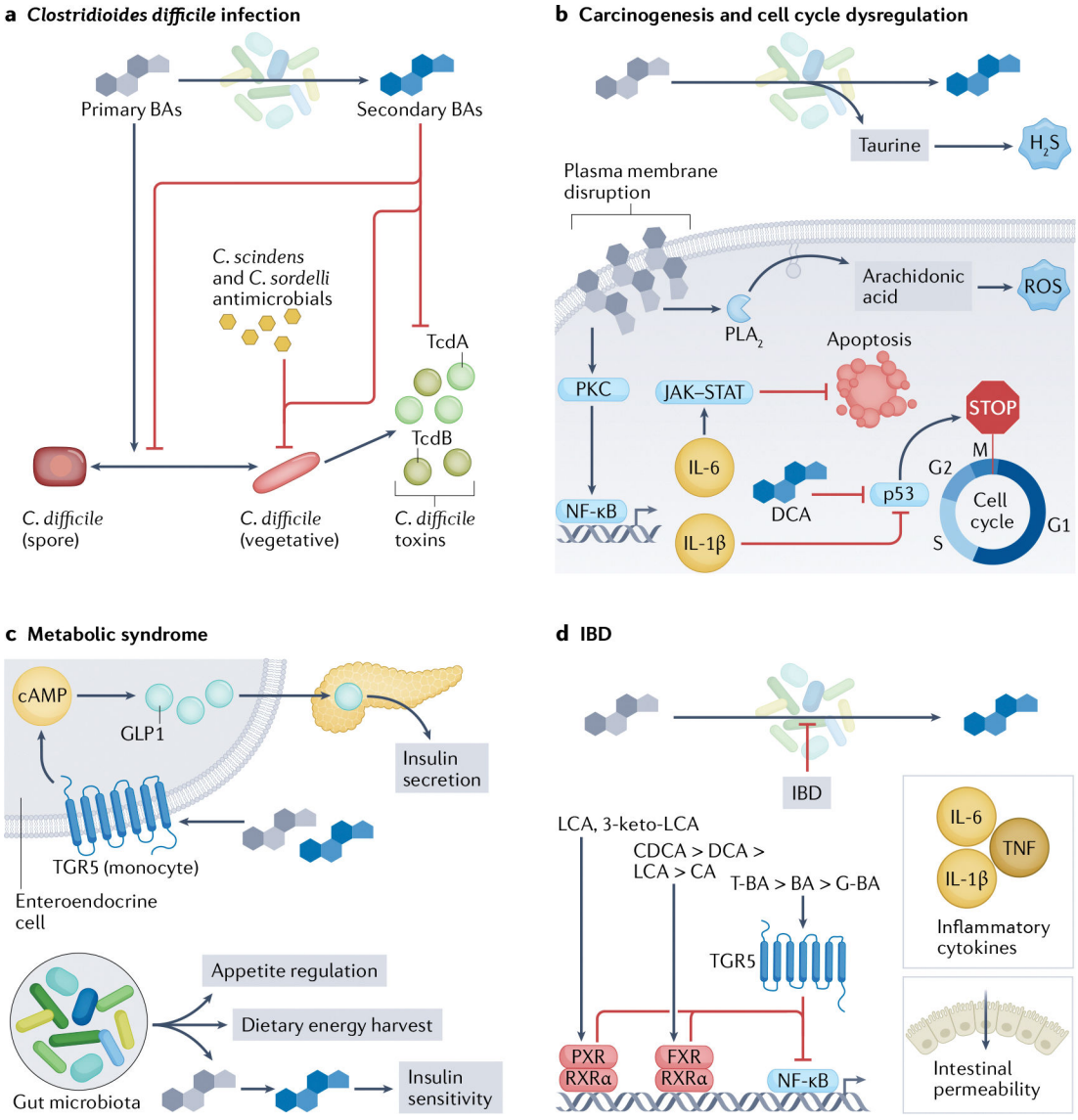


Fig. 4 |. Host and microbiota-dependent bile acid contributions to human disease.

a | Primary bile acids (BAs) promote *Clostridioides* germination, whereas secondary BAs inhibit it. Secondary BAs increase the efficacy of antimicrobials against *C. difficile* and sequester *C. difficile* toxins. **b** | Secondary BAs are associated with carcinogenesis through several mechanisms. Bacterially deconjugated taurine is further metabolized into carcinogenic hydrogen sulfide (H_2S). The insertion of secondary BAs into the plasma membrane triggers phospholipase A_2 (PLA_2) metabolism of phospholipids into arachidonic acid, ultimately leading to the release of DNA-damaging reactive oxygen species (ROS). Nuclear factor κB (NF-κB)-mediated expression of the pro-inflammatory cytokines IL-6 and IL-1β suppresses apoptosis through the JAK–STAT pathway and inhibits cell cycle arrest by p53, respectively. **c** | In enteroendocrine cells, TGR5 agonist BAs trigger synthesis of glucagon-like peptide 1 (GLP1), which circulates to pancreatic β-cells to induce insulin secretion. The presence of the gut microbiota has been separately associated with appetite regulation, energy harvest and insulin sensitivity. **d** | BA activation of PXR, FXR and

monocyte TGR5 reduces inflammatory cytokine production and intestinal permeability by inhibiting NF-κB. CA, cholic acid; CDCA, chenodeoxycholic acid; *C. scindens*, *Clostridium scindens*; *C. sordelli*, *Clostridium sordelli*; DCA, deoxycholic acid; G-BA, glycine-conjugated bile acid; IBD, inflammatory bowel disease; LCA, lithocholic acid; PKC, protein kinase C; T-BA, taurine-conjugated bile acid.

Table 1 |

Chemical transformations of bile acids by the gut microbiota

Modification	Enzyme	Bacteria	Reaction	Sites	Products	Refs.
Hydrolysis (deconjugation)	Bile salt hydrolase	Bacteroides, Firmicutes and Actinobacteria	-CONH-R → COOH	C24/R_5	Unconjugated BAs (from glycine/taurine conjugates)	4
Dehydroxylation	bai operon proteins (BaiA2 and BaiB-I)	Firmicutes (*Clostridium* and *Extibacter* spp.)	-OH → -H	C7	DCA LCA MDCA (mice)	16,17
Oxidation and epimerization	Hydroxysteroid dehydrogenase	Actinobacteria, Proteobacteria, Firmicutes and Bacteroidetes	α/β-OH =O	C3, C6, C7 or C12	UDCA *w*-MCA (mice) Iso/allo BAs Oxo BAs	19,20
Desulfation	Sulfatase	*Clostridium, Peptococcus, Fusobacterium, Proteobacterium* and *Pseudomonas* spp.	-SO_3H_2 → -OH	C3	LCA/CDCA/CA (from 3-sulfates)	153,154
Esterification	Unknown	Unknown	-OH → -COOR	C3 C24/R_5	3-Ethyl esters 24-carbonyl esters PolyDCA	23
Amidation (conjugation)	Unknown	*Bacteroides, Bifidobacterium, Enterococcus* and *Enterocloster*	-COOH → -CONH-R	C24/R_5	AABAs	24,26,28

AABA, amino acid-conjugated bile acid; BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; MCA, muricholic acid; MDCA, murideoxycholic acid; UCDA, ursodeoxycholic acid.