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## **Bile acids and microbes in metabolic disease**

Sah DK *et al.* Biles and microbes in metabolic disease

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### **Abstract**

Bile acids (BAs) serve as physiological detergents that enable the intestinal absorption and transportation of nutrients, lipids, and vitamins. BAs are primarily produced by humans to catabolize cholesterol and play crucial roles in gut metabolism, microbiota habitat regulation, and cell signaling. BA-activated nuclear receptors regulate the enterohepatic circulation of BAs, which play a role in energy, lipid, glucose, and drug metabolism. The gut microbiota plays an essential role in the biotransformation of BAs and regulates BAs composition and metabolism. Therefore, altered gut microbial and BAs activity can affect human metabolism and thus result in the alteration of metabolic pathways and the occurrence of metabolic diseases/syndromes, such as diabetes mellitus, obesity/hypercholesterolemia, and cardiovascular diseases. BAs and their metabolites are used to treat altered gut microbiota and metabolic diseases. This review explores the increasing body of evidence that links alterations of gut microbial activity and BAs with the pathogenesis of metabolic diseases. Moreover, we summarize existing research on gut microbes and BAs in relation to intracellular pathways pertinent to metabolic disorders. Finally, we discuss how therapeutic interventions using BAs can facilitate microbiome functioning and ease metabolic diseases.

**Key Words:** Bile acids; Metabolic diseases; Gut microbe; Diabetic mellitus; Obesity; Hypercholesterolemia

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**Core Tip:** Bile acids (BAs) in enterohepatic circulation regulate metabolism through interorgan communication between the gut and liver microbiota. BAs secreted from the liver contribute to glucose and lipid metabolism. Disruption of the BA-gut microbiome link contributes to the occurrence of metabolic diseases, such as obesity, type 2 diabetic mellitus, and dyslipidemia. BAs and their metabolites can be used as potential therapeutics for treating metabolic diseases

## INTRODUCTION

<sup>2</sup> Bile acids (BAs) are unique amphipathic molecules that are primarily produced in the liver. They function as physiological detergents to facilitate bile flow and promote the transportation of nutrients, vitamins, and lipids *via* intestinal absorption<sup>[1]</sup>. Hepatic BA production accounts for a significant portion of the total cholesterol turnover in humans<sup>[2]</sup>. The principal constituents of bile are BAs, bilirubin, cholesterol, and phospholipids. BAs are mainly classified into primary and secondary types. Primary BAs (PBAs) include <sup>10</sup> cholic acid (CA) and chenodeoxycholic acid (CDCA). Their corresponding secondary BAs are deoxycholic acid (DCA) and lithocholic acid (LCA), which are produced by microbial enzymes in the colon *via* deconjugation and 7 $\alpha$ -dehydroxylation and are the most ubiquitous BAs in humans<sup>[3]</sup>. PBAs are formed by cholesterol in pericentral hepatocytes through a series of staged processes that are catalyzed by metabolic enzymes, particularly cytochrome P450 enzymes<sup>[4]</sup>.

BAs synthesis is predominantly mediated by classic and alternative pathways in the liver. <sup>5</sup> In the classic pathway, the rate-limiting enzyme CYP7A1 in the endoplasmic reticulum converts cholesterol into 7 $\alpha$ -hydroxycholesterol (HOC). The intermediate 7 $\alpha$ -hydroxy-4 cholesterin-3-one (C4) is <sup>19</sup> converted by the sterol 12 $\alpha$ -hydroxylase (CYP8B1) to 7 $\alpha$ , 12 $\alpha$ -dihydroxy-4-cholesterin-3-one, which results in the production of CA. Without the 12 $\alpha$ -hydroxylation of CYP8B1, C4 is ultimately transformed into CDCA. <sup>5</sup> Both CA and CDCA syntheses use the mitochondrial enzyme CYP27A1 to catalyze the oxidation of the steroid side chains. <sup>19</sup> In the alternative pathway, cholesterol is transformed by CYP27A1 into 27-HOC, which is in turn transformed into CDCA. <sup>3</sup> Bacterial 7-dehydroxylase eliminates a hydroxyl group at C-7 in the large intestine, which converts CA into DCA and CDCA into LCA. The secondary BAs hyocholic acid, murideoxycholic acid,  $\omega$ -muricholic acid ( $\omega$ -MCA), hyodeoxycholic acid (HDCA), and ursodeoxycholic acid (UDCA) <sup>3</sup> are produced by CYP3A1 and epimerases from CDCA. The majority of LCA and  $\omega$ -MCA are eliminated *via* feces<sup>[5]</sup>.

In addition to their involvement in the absorption of dietary lipids and cholesterol homeostasis, BAs play a versatile signaling role. Many signaling pathways <sup>38</sup> can be

activated by BAs. These include a wide range of metabolic pathways, such as those involved in glucose, lipid, drug, and energy metabolism<sup>[6]</sup>. During BAs metabolism, cholesterol is converted into BAs in the liver and is further metabolized by the gut microbiota. Moreover, dense populations of microorganisms inhabit the gut, making it one of the most complex ecosystems for health. For the past two decades, research has focused on the influence of the gut microbiome on health. BAs deconjugation occurs in the small intestine and is mediated by bile salt hydrolase (BSH)-active bacteria, resulting in the maintenance of normal circulating levels of deconjugated BAs and cholesterol. Through these bioconversions, BAs modulate diverse metabolic pathways in the host through signaling mediated by nuclear farnesoid X receptors (FXRs) and G-protein-coupled membrane receptors (GPCRs). Furthermore, BAs can influence the gut microbial composition both directly and indirectly by activating innate immune responses. Consequently, the host metabolism is affected by altered signaling *via* BA receptors (BARs) induced by microbial modification and by altered microbiota composition<sup>[7]</sup>. Therefore, the gut microbiota must be maintained for normal metabolic function and homeostasis. Altered gut microbiota composition may be related to metabolic diseases, such as diabetes mellitus (DM) and obesity<sup>[8]</sup>. Altered BAs synthesis and function are also associated with metabolic diseases. This review mainly focuses on the relationship between gut microbiota and BAs in metabolic diseases, emphasizing on the BA-mediated reversal of metabolic diseases (Figure 1).

## **ROLE OF BILE ACIDS-GUT MICROBIOME INTERACTION IN METABOLIC REGULATION**

The term microbiome refers to the entire genome of the gut microbiota, which is two orders of magnitude larger than the human nuclear genome. Humans inherit the vaginal microbiome of their mothers at the time of birth. Eventually, a mutualistic relationship between this microbiota and the host is developed<sup>[9]</sup>. The human gastrointestinal system is colonized by numerous microorganisms, collectively known as the gut microbiota; these include bacteria, viruses, archaea, fungi, and protozoa. The human gut microbiota

contains up to 100 trillion microorganisms<sup>[10]</sup>. It plays an integral role in maintaining host health as it not only helps derive nutrients from food but also builds various metabolites that can regulate host metabolism<sup>[11]</sup>. One of these metabolites, BA, is produced in the liver through cholesterol and is additionally metabolized by the gut microbiota into secondary BAs<sup>[12]</sup>. A key physiological function of the gut microbiota is the modification of BAs composition. In addition to secondary BAs, different BAs species are produced in humans by the gut microbiota<sup>[13]</sup>. In the gut, branched-chain amino acids, short-chain fatty acids (SCFAs), indole, succinate, and imidazole are metabolites produced by gut microbes during anaerobic fermentation. These metabolites serve as key signaling components in the BA-gut microbe signaling pathways<sup>[14]</sup>. Various microbial genera produce these metabolites; these include *Akkermansia*, *Bacteroides*, *Clostridium*, *Coprococcus*, *Eubacterium*, *Faecalibacterium*, *Fusobacterium*, *Lactobacillus*, *Prevotella*, *Propionibacterium*, *Ruminococcus*, *Roseburia*, and *Streptococcus*<sup>[15]</sup>. The BAs composition is shaped by gut microbes that exhibit certain enzymatic activities, e.g., BSH or 7-dehydroxylation activity mediated by BA-inducible enzymatic reactions. BAs exert their effects by activating a class of receptors known as BARs. This receptor family comprises nuclear receptors, such as FXRs, vitamin D receptors, pregnane X receptor, and GPCRs (including GPBAR1)<sup>[13]</sup>. The gut microbiota modulates fibroblast growth factor 15 (FGF15) signaling through an FXR-dependent mechanism<sup>[16]</sup>. Recent research has linked gut microbe metabolism to the size of the BAs pool.

In germ-free (GF) and conventionally raised mice, the gut microbiota could not only regulates secondary BAs metabolism but also inhibit hepatic BA synthesis by suppressing FXR inhibition in the ileum<sup>[16]</sup>. Moreover, BAs can affect the gut bacterial composition by directly and indirectly activating genes associated with innate immunity in the small intestine<sup>[7]</sup>. Therefore, bacteria-induced changes in BAs may result in altered signaling of BARs and affect host metabolism. BAs and the gut microbiota can interact in various ways, and interruptions in these physiological interactions can cause several diseases. The composition of the intestinal microbiota and/or the intraluminal metabolome may be the cause or consequence of various disorders; however, their association remains



unknown. Various recent studies have reported the association of dyslipidemia, insulin resistance (IR), and DM with the dysregulation of BAs metabolism and alteration of the gut microbiota. This review mainly focuses on altered BA-gut microbiome interactions in metabolic diseases.

## **METABOLIC DISEASES CAUSED BY DISRUPTION OF BILE ACIDS-GUT MICROBIOME INTERACTIONS**

Research on BA has significantly enriched our understanding of BAs synthesis and metabolic syndrome over the last two decades. BAs play a crucial role in regulating glucose, lipid, and energy metabolism. Several metabolic diseases, including type 2 DM (T2DM), obesity, and nonalcoholic fatty liver disease (NAFLD), result from disrupted BA homeostasis<sup>[17]</sup>. The gut microbiota is a “metabolic organ” that regulates host metabolism<sup>[18]</sup>. Gut microbes, including *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterobacter*, and *Lactobacillus* species, play an important role in the synthesis, modification, and signaling of BAs<sup>[15]</sup>. The gut microbiota has recently been reported to play a role in obesity, in addition to other widely acknowledged major causes, which include an increased caloric intake and decreased energy expenditure. These factors are also linked to T2DM, metabolic syndrome, and CADs<sup>[19]</sup>. Diverse mechanisms have been proposed by which gut microbes can modulate metabolic diseases. Disrupted BA-gut microbiome interactions can cause metabolic disease (Table 1 and Figure 2).

## **OBESITY**

The global prevalence of various chronic diseases is increasing; obesity is the main cause and has been a serious concern for decades<sup>[20]</sup>. Obesity is linked to T2DM, NAFLD, hypertension, CAD, and cancer<sup>[21]</sup>. The prevalence of obesity is influenced by genetic and environmental factors, such as diet, culture, and socioeconomic status<sup>[22]</sup>. There is mounting evidence that the intestinal microbiota is inextricably related to general health, including obesity risk. Obesity-related metabolic diseases are defined by unique changes in the diversity and function of the human gut microbiome<sup>[23]</sup>. The human gut is home to

trillions of microbes, which break down otherwise indigestible foods<sup>[24]</sup>. A study revealed that transferring the gut microbiota from healthy mice to GF recipients could increase body fat without a significant increase in food consumption and suggested that the composition of gut microbial communities could affect how much energy is derived from food<sup>[25]</sup>. In particular, the gut-brain axis indirectly affects commensal organisms, intestinal permeability, motility, and secretion and modifies the levels of plasma peptides, particularly glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), by releasing signaling molecules into the gut lumen<sup>[26]</sup>.

In humans, the gut microbiota has been linked to body weight and weight loss following a lifestyle change. Gram-negative opportunistic pathogens in the gut may play a significant role in obesity<sup>[27]</sup>. The gut microbiota of ectomorphs has more *Bacteroidetes* species, whereas that of obese individuals has more *Firmicutes* species, particularly *Clostridium* clusters<sup>[23]</sup>. Thus, the bacterial composition could enhance the capacity of the host to absorb energy from their diet and retain it in adipose tissues<sup>[28]</sup>. In lean as well as obese pregnant subjects, an increase in *Bacteroides*, *Staphylococcus*<sup>[29]</sup>, and *Bifidobacterium* species was found to increase high-density lipoprotein cholesterol (HDL-C) and folic acid levels and reduce triglyceride (TG) levels<sup>[22]</sup>. On the other hand, the abundance of *Akkermansia muciniphila* (*A. muciniphila*), a mucoprotein-degrading bacterium present in the mucus layer<sup>[30]</sup>, was negatively correlated with body weight<sup>[22]</sup>. A decrease in the abundance of *A. muciniphila* was noted in obese and diabetic mice<sup>[31]</sup>. Feeding high-fat diets with viable *A. muciniphila* can hinder the development of metabolic disorders, such as obesity, low-grade inflammation, and metabolic endotoxemia<sup>[32]</sup>. A metatranscriptomic analysis revealed that mice receiving the microbiome of obese twins had higher expression levels of microbial genes associated with detoxification and oxidative stress, amino acid metabolism, cobalamin biosynthesis, and the pentose phosphate pathway<sup>[13]</sup>.

BA metabolism is altered in obese and diabetic individuals<sup>[33]</sup>. Patti *et al*<sup>[34]</sup> reported that patients who underwent Roux-en-Y gastric bypass (RYGB) had improved glucose and fat metabolism. This finding was attributed to the activation of GPCRs and



subsequent stimulation of GPBAR1 (TGR5, a membrane-bound BAR) and increase in deiodinase (a type II thyroid hormone) levels. Although recent research has revealed a link<sup>39</sup> between the gut microbiota and obesity, the precise molecular pathways remain unknown. In particular, the role of distinct gut microbial species and their metabolites in the regulation of obesity-related lipid metabolism and formation of the obese phenotype remains unknown.<sup>21</sup> Mechanisms linking the gut microbiota to obesity are being revealed through a collaborative approach of translation-focused human and animal studies. Increasing evidence indicates that the gut microbiota mediates the effects of diet on host metabolism<sup>11</sup>. In BA metabolism, TGR5 signaling is regulated by the microbiota by generating agonists<sup>36</sup>, whereas FXR signaling is regulated by metabolizing antagonists<sup>31</sup>. Both TGR5 and FXR have a significant influence on metabolism, and an altered microbiota may impact host physiology by modifying the signals transmitted through these receptors. The ability to metabolize TauroMCA, a naturally occurring FXR antagonist, is required for the microbiota to induce obesity, steatosis, and impaired glucose and insulin tolerance. An altered microbiota is responsible for these effects<sup>37</sup>. Taken together, these results indicate that targeting BAs, which function as microbiome-produced molecular regulators of energy homeostasis, can offer a substantial opportunity for treating obesity.

## DM

The prevalence of T2DM is increasing worldwide. By 2030, the incidence of T2DM is expected to be 360 million worldwide, with the estimated population being 8.5 billion<sup>38</sup>. BAs<sup>18</sup> are involved in the alteration of glucose metabolism associated with obesity and T2DM. By stimulating GLP1 synthesis in the small bowel and colon, BAs contribute to carbohydrate and fat metabolism. In addition to inducing IR and T2DM, BAs exhibit an insulin-sensitizing effect<sup>33</sup>. They control glucose homeostasis by directly acting on FXR and TGR5 in the liver, intestine, and pancreas and by indirectly stimulating FXR-dependent intestinal FGF15/19 production<sup>39</sup>. Both FXR and TGR5 are abundant in pancreatic b cells, where they favorably control insulin production and glucose-induced

insulin secretion. TGR5 activation in pancreatic  $\alpha$  cells promotes the expression of proconvertase-1, which shifts the synthesis of glucagon to GLP-1, thereby enhancing  $\beta$ -cell density and functioning in a paracrine manner. In patients with DM, BAs may promote FXR activation in L cells in the ileum. In an animal model of obesity, Cipriani *et al*<sup>[40]</sup> found that 6E-CDCA activated FXR, reversed IR, and restored lipid metabolism. Moreover, the microbiota could downregulate FXR with the maximum efficiency by converting PBAs into secondary BAs<sup>[16]</sup>.

External factors, such as diet, can alter the gut microbiota and cause dysregulation and secretory changes in intestinal microbial metabolites, triggering a series of possible mechanisms that lead to DM and insulin sensitivity<sup>[41]</sup>. In a metagenome-wide association study involving 345 Chinese participants with DM, gut microbial dysbiosis caused by opportunistic pathogens was moderate. Moreover, the reduction of butyrate-producing bacteria was associated with sulfate reduction and oxidative stress resistance<sup>[42]</sup>. Complex interactions between the immune system and gut microbiome have also been linked to both T1DM and T2DM. Aggarwal *et al*<sup>[43]</sup> reported that a combination of antidiabetic and antibiotic treatments reversed IR, hyperglycemia, and dyslipidemia and normalized blood glucose utilization in iNOS<sup>-/-</sup> mice. Duodenal-jejunal bypass liner (DJBL) replacement in obese patients with T2DM was found to increase unconjugated BA levels in a clinical study<sup>[44]</sup>. Fei *et al*<sup>[45]</sup> reported a high percentage of endobacteria (35%), pathogenic bacteria that produce endotoxin, in the gut microbiome of obese participants with hypertension, DM, and other severe metabolic complications. Patients with T2DM are particularly deficient in butyrate-producing microbes, such as *Clostridiales* species, *Ruminococcus* species, *Subdoligranulum* species, *Acetivibrio* species, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *R. inulinivorans*, and exhibit a high abundance of specific genera, such as *Abiotrophia*, *Blautia*, *Coprococcus*, *Collinsella*, *Parasutterella*, *Peptostreptococcus*, and *Sporobacter*<sup>[15]</sup>.

Moreover, Lambeth *et al*<sup>[46]</sup> demonstrated that *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Pseudonocardiaceae*, *Verrucomicrobia*, and *Colorado* species were significantly more prevalent in the pre-DM stage, whereas *Enterobacteriaceae* and *Collinsella* species

were significantly more prevalent in patients with T2DM. Similarly, Larsen *et al*<sup>[47]</sup> reported a significant decrease in the prevalence of phylum *Firmicutes*, class Betaproteobacteria, and genus *Clostridium* in patients with T2DM. The *Bacteroidetes*: *Firmicutes* ratio and the *Bacteroides-Prevotella* group: *C. coccoides-E. rectale* group ratio showed a positive correlation and significantly increased the plasma glucose levels. During pregnancy, the abundance of the beneficial species *R. intestinalis* and *F. prausnitzii* decreases, whereas that of Proteobacteria and Actinobacteria phyla increases<sup>[48]</sup>. If these compositions are altered, pregnant women may experience an increase in adipose mass, blood sugar levels, IR, and circulating proinflammatory cytokines, resulting in gestational DM (GDM)<sup>[49]</sup>. In patients with GDM, obesity, and T2DM, the relative abundance of SCFA-producing bacteria belonging to the genera *Faecalibacterium*, *Rubinococcus*, *Roseburia*, *Coprococcus*, *Akkermansia*, *Phascolarctobacterium*, and *Eubacterium* was found to decrease<sup>[50]</sup>. Moreover, Liu *et al*<sup>[51]</sup> demonstrated increased hyperlipidemia and fasting blood glucose (FBG) levels and increased relative abundance of *Streptococcus*, *Faecalibacterium*, *Veillonella*, *Prevotella*, *Haemophilus*, and *Actinomyces* species in patients with GDM.

### **THERAPEUTIC INTERVENTIONS TARGETING BILE ACIDS-GUT MICROBIOME INTERACTIONS TO ALLEVIATE METABOLIC DISEASES**

BAs play an important role in signaling and metabolism, reigniting interest in these molecules as potential therapeutic targets. Studies have revealed that drugs used to treat metabolic diseases can alter the gut microbial environment. Similarly, antidiabetic medications may alter the composition of the gut microbiota, plasma, and fecal BAs, which may improve metabolic health. Notably, patients with T2DM had better glycemic control when taking medications for preventing BAs absorption from the small intestine or limiting enterohepatic circulation. Hence, experimental and clinical studies have focused on the therapeutic applications of BAs in metabolic diseases. Furthermore, microbiota targeting could open novel research avenues. Table 2 and Figure 3 depict BAs and their metabolites used for treating metabolic diseases.

## **BAS METABOLITES ALLEVIATE METABOLIC DISEASES**

### ***BA sequestrants***

For several years, BA sequestrants (BASs) have been utilized as therapeutics for patients with dyslipidemia and T2DM<sup>[52]</sup>. The BA-binding properties of BASs reduce the amount of BAs in enterohepatic circulation, thereby accelerating the conversion of cholesterol to BAs<sup>[53]</sup>. The effects of BASs on hyperglycemia have been demonstrated in both animal and clinical models of T2DM<sup>[54]</sup>. Furthermore, animal studies have revealed that BAs and BASs influence energy expenditure. A BAS molecule, also known as a resin, is a large, nonabsorbable polymeric molecule that binds negatively charged bile salts to the intestinal lining<sup>[55]</sup>. This promotes BA excretion through the feces by diverting the acids from the enterohepatic cycle. Consequently, BA synthesis increases and low-density lipoprotein (LDLR) receptors are upregulated. BASs can lower blood glucose as well as cholesterol levels, which may be beneficial for treating T2DM<sup>[54]</sup>.

BASs can exert their metabolic effects beyond cholesterol-lowering effects through several mechanisms, including GLP-1, the FXR-small heterodimer partner-liver X receptor pathway, and TGR5<sup>[56]</sup>. BAS reduces intestinal FXR activity by trapping BAs in the lumen, resulting in decreased expression levels of ileal *Shp* and *Fgf15*<sup>[57]</sup>. The resulting decrease in the hepatic accessibility of BA and FGF15/19 leads to the deactivation of hepatic FXR and the CYP7A1-mediated conversion of cholesterol to BA, reducing LDL cholesterol (LDL-C) levels. Consequently, lipogenesis is attenuated by FXR. BAS raises plasma TG levels and accumulates hepatic lipids, while lowering LDL-C levels<sup>[58]</sup>. However, the exact mechanism by which BASs exert their metabolic effects beyond cholesterol-lowering effects remains unknown. Rectal administration of taurocholic acid (TCA) was found to increase GLP-1 and PYY production in obese participants and those with T2DM<sup>[59]</sup>. Similarly, CDCA and colestevlam increased glycogen and GLP-1 levels and delayed stomach emptying in patients with T2DM<sup>[60]</sup>.

### ***Colestyramine***

Cholestyramine is a polystyrene-based polymer that has been crosslinked with divinylbenzene and functionalized to quaternary ammonium units to produce a robust anion exchange resin and increase the secretion of the pancreatic exocrine hormone cholecystokinin (CCK)<sup>[61]</sup>. A study revealed that cholestyramine administration increases the expression levels of genes encoding HMGCoAR, LDLR, PCSK9, and SREBP2<sup>[62]</sup>. Cholestyramine stimulates hepatic BA synthesis from cholesterol, which activates SREBP2 by inhibiting BA absorption from the intestine. LDLR increases the transport of cholesterol from the plasma when SREBP2 is expressed. The upregulation of HMGCoAR compensates for the reduction in LDL-C levels in the plasma. In addition to activating SREBP2, PCSK9 gets upregulated, thereby degrading LDLR. By modulating PCSK9, cholestyramine-induced increases in LDLR expression can be modulated<sup>[58]</sup>. In addition to treatments using cholestyramine and inhibitors of ileal BA uptake, treatments aimed at reducing PCSK9 expression would be beneficial for reducing the enterohepatic circulation of BAs<sup>[63]</sup>.

Similarly, several clinical and experimental models have revealed that cholestyramine improves BA-gut microbiome interactions, thereby facilitating glucose and fat metabolism. In clinical models of primary biliary cholangitis (PBC), two SCFA-producing *Lachnospiraceae* species were found to be enriched in the microbiome of the superior remission group after cholestyramine treatment. SCFAs derived from dietary fibers are produced by the gut microbiota, and SCFA signaling has anti-inflammatory, antiobesity, and antidiabetic properties<sup>[52]</sup>. This denotes the favorable effects of cholestyramine in treating PBC by enhancing BA-gut microbiome interactions<sup>[64]</sup>. Newman *et al*<sup>[57]</sup> reported that cholestyramine reduced hyperglycemia by increasing the ileal expression of glucagon through an increase in the prevalence of *Acetatifactor Muris* and *Muribaculum intestinal*. In another study, cholestyramine-treated ZDF rats showed reduced glycosylated hemoglobin A1c (HbA1c) levels, serum glucose levels, and FXR activation and increased PYY levels, GLP-1 Levels, and insulin release<sup>[65]</sup>.

### ***Colesevelam***



Colesevelam hydrochloride (HCl) is a polyallylamine that has been crosslinked <sup>27</sup> with epichlorohydrin and alkylated with (6-bromohexyl)-trimethylammonium bromide and 1-bromodecane<sup>[66]</sup>. In clinical and animal studies on T2DM, obesity, and hyperlipidemia, colesevelam reduced blood glucose<sup>[67]</sup>, FBG<sup>[68]</sup>, mediator complex subunit 1, miR-182<sup>[69]</sup>, HbA1c<sup>[70]</sup>, hepatic TG, total LDL<sup>[71]</sup>, very-low-density lipoprotein (VLDL), chylomicron particle<sup>[72]</sup>, LDL-C<sup>[73]</sup>, non-HDL-C, ApoB, <sup>36</sup> TGR5/GLP-1-dependent glycogenolysis, FXR-dependent cholesterol, cytochrome P450, Cyp7a1<sup>[74]</sup>, FGF-19<sup>[75]</sup>, BA reabsorption<sup>[76]</sup>, high-sensitivity C-reactive protein<sup>[77]</sup>, and fructosamine levels<sup>[78-80]</sup> and increased glycolysis, postmeal glucose tolerance, insulin levels<sup>[81]</sup>, splanchnic sequestration of meal-derived glucose<sup>[82]</sup>, GLP-1/GIP levels<sup>[83]</sup>, total HDL particle levels, miR-96/182/183 expression levels,  $\beta$ -cell function [as revealed by homeostatic model assessment (HOMA)]<sup>[56]</sup>, BA synthesis, ApoA-1 levels<sup>[54]</sup>, and CCK levels<sup>[84]</sup>. As <sup>22</sup> a molecularly engineered, second-generation BA <sup>22</sup> sequestrant, colesevelam has been recommended for reducing LDL-C in patients with primary hypercholesterolemia by inhibiting b-hydroxymethylglutaryl coenzyme A reductase<sup>[85]</sup>. Colesevelam enhances glycemic control in patients with T2DM<sup>[86]</sup>. When metformin-based, sulfonylurea-based therapy fails to completely control T2DM, colesevelam can improve glycemic and lipid indices<sup>[54]</sup>. Moreover, colesevelam significantly alters BA metabolism. A non-absorbable complex of colesevelam in the gastrointestinal tract can stimulate the excretion of BAs through feces and their removal from enterohepatic circulation. Therefore, colesevelam treatment may reduce the total BA pool size<sup>[75]</sup>. Colesevelam reduces the influx of CDCA and DCA, two of the most potent FXR ligands, into ileal enterocytes. Therefore, plasma levels of FGF19 are likely to decrease when FXR is less activated<sup>[75]</sup>.

### *Colestimide*

Colestimide, an anion exchange resin, lowers serum cholesterol levels by binding to BAs in the intestinal tract<sup>[87]</sup>. Although colestimide is used to treat hyperlipidemia in Japanese patients, the mechanism by which it lowers blood glucose levels remains poorly understood<sup>[88]</sup>. CA reduces blood glucose levels and facilitates energy metabolism

through the type 2 iodothyronine deiodinase (D2) enzyme. Various clinical and experimental studies have revealed that colestimide treatment reduced blood glucose, FBG, postprandial blood glucose, HbA1c, IR, and serum LDL-C levels and increased serum 1,5-AG and postprandial plasma GLP-1 Levels in patients with T2DM<sup>[89-91]</sup>. Another study revealed that colestimide altered BA composition and CA ratios, thereby reducing blood glucose levels *via* the TGR5-Camp-D2 pathway<sup>[92]</sup>. Similarly, elobixibat induced colonic motility and secretion by inhibiting an ileal BA transporter in a highly selective manner<sup>[93]</sup>, reduced the LDL-C levels and LDL-C: HDL-C ratio, and increased the circulating GLP1 levels in a clinical study on dyslipidemia<sup>[94]</sup>. Colestilan is also a BAS that could reduce body weight and HbA1c, FBG, LDL-C, and total cholesterol levels and increase fecal lipid excretion in patients with T2DM<sup>[95]</sup>.

### ***Receptor-mediated therapeutics***

Since BAs were initially considered lipid solubilizers, they have evolved into complex metabolic integrators. BAs can modulate their energy expenditure through the stimulation of TGR5- and FXR-mediated signaling pathways<sup>[36]</sup>. The metabolism-related protein TGR5 may be a novel promising target for treating metabolic disorders associated with obesity. Recently, TGR5 expression has been reported in enteroendocrine L cells, including STC-1 cells, which secrete GLP-1 upon calorie intake<sup>[96]</sup>. In preclinical studies, INT-177 (a semisynthetic BA derivative) and nonsteroidal TGR5 agonists promoted glucose homeostasis<sup>[97]</sup>. The activation of TGR5 by BAs reduced diet-induced obesity by increasing energy expenditure in brown adipose tissues and muscles<sup>[97]</sup>. Moreover, TGR5-mediated release of GLP-1 modulated the ATP/ADP ratio and oxidative phosphorylation in the mitochondria by activating the  $K_{ATP}/C_{av}$  channels. Thus, the TGR-5-mediated pathway is therapeutically beneficial, considering that incretin-based therapies are effective in treating DM<sup>[98]</sup>. Moreover, FXR activation has not yet been associated with significant weight loss<sup>[99]</sup>. FXR activation reduces hepatic glucose and fatty acid outputs by increasing glycogen production and decreasing lipogenesis and VLDL production, thereby increasing insulin sensitivity<sup>[99]</sup>. Similarly, 6E-CDCA was

found to reduce blood glucose, insulin, TG, and plasma cholesterol levels and fatty acid synthesis and facilitate FXR activation in Zucker (fa/fa) obese rats with liver steatosis<sup>[40]</sup>. Moreover, tauroUDCA increased muscular and hepatic insulin signaling by phosphorylating the insulin receptor substrate Tyr and Akt at Ser473 in obese participants<sup>[100]</sup>. In summary, TGR5 agonists activate the TGR5 signaling pathway by increasing mitochondrial function and enteroendocrine cell function, ultimately leading to increased incretin release. This has various metabolic effects, including reduction of weight gain and hepatic steatosis, improvement of liver function, and maintenance of insulin sensitivity and glucose homeostasis.

### ***BAs metabolites and bariatric surgery***

CDCA (3 $\alpha$ ,7 $\alpha$ -dihydroxy-5 $\beta$ -cholan-24-oic acid) is a PBAs produced in the liver from cholesterol. CDCA is a potent inhibitor of CYP7A1, the enzyme responsible for BA synthesis. In addition to suppressing cholesterol synthesis, CDCA may inhibit HMGCoA reductase<sup>[101]</sup>. Mantovani *et al*<sup>[102]</sup> reported decreased plasma levels of CA and TCA but significantly increased plasma levels of TCDCA, TDCA, HDCA, GDCA, GLCA, and DCA in patients with T2DM. Moreover, Cariou *et al*<sup>[103]</sup> reported that plasma levels of CDCA, CA, and DCA were negatively correlated with insulin sensitivity in patients with T2DM. CDCA may inhibit high-fat diet (HFD)-induced obesity and hyperglycemia through the activation of TGR5 and inhibition of PPAR $\gamma$  transcriptional activity<sup>[104]</sup>. Another study revealed that CDCA increased GLP-1 and glucagon secretion and delayed gastric emptying by activating GPBAR1 in patients with T2DM<sup>[60]</sup>. The activation of FXR and TGR5 through CDCA and DCA mimicked and suppressed SPX promoter activity induced by CDCA and DCA. SPX promoter activity was significantly increased by adenylate cyclase (AC)/cAMP activators and reduced by CDCA, DCA, and PKA pathway inhibitors. Through FXR- and TGR5-mediated AC/cAMP/PKA and MAPK cascades, CDCA and DCA could promote SPX expression at the hepatic level<sup>[105]</sup>.

Obeticholic acid (OCA, 6E-CDCA) is a semisynthetic BAs with a 30-fold higher potency than that of CDCA for activating FXR. OCA-mediated inhibition of BAs

synthesis increased the abundance of *Firmicutes* species and reduced nonalcoholic steatohepatitis in humans<sup>[106]</sup>. UDCA is commonly used for treating liver dysfunction. UDCA treatment reduced hyperinsulinemia and fasting hyperglycemia in a mouse model of T2DM with hepatic steatosis<sup>[107]</sup>. Moreover, Osorio *et al*<sup>[108]</sup> reported that UDCA inhibited sodium–glucose co-transporter overexpression, thereby reducing oxidative stress in mice with streptozotocin (STZ)-induced DM. A recent meta-analysis revealed that UDCA significantly reduced fasting plasma glucose, HbA1c, and insulin levels, indicating a positive impact on glucose homeostasis<sup>[109]</sup>. Another clinical trial demonstrated that UDCA treatment reduced HbA1c levels and increased early-phase GLP-1 secretion<sup>[110]</sup>.

Bariatric surgery is effective in treating obesity, DM, and related complications. However, this surgery is not the only factor responsible for treating obesity. Bariatric surgery alters gut microbiota profiles and induces gut microbes to synthesize SCFAs. Gut microbes are crucial for improving the outcomes of bariatric surgery. Gut microbes are also important for reducing weight and lowering adverse events after bariatric surgery. Therefore, prebiotics, probiotics, and postbiotics are recommended for patients who have undergone bariatric surgery in order to improve their clinical outcomes<sup>[111]</sup>. Bariatric surgery causes changes in the gut microbiota because of a malabsorptive status and changes in BA metabolism, gastric pH, and hormone metabolism<sup>[112]</sup>. It may also change the levels of hormones, such as leptin and ghrelin. Changes in hormones have been reported as a result of energy metabolism and the microbiota. Prebiotics modulate the intestinal microbiota and reduce the levels of ghrelin in the blood; however, the relationship between the two is not fully understood<sup>[113]</sup>. Similarly, postsurgical microbiomes were more different from lean microbiomes than obese microbiomes, whereas postsurgical microbiomes were less different from lean microbiomes than obese microbiomes. Body mass index loss following bariatric surgery could be predicted based on the presurgical microbiome. After surgery, the relative abundance of Proteobacteria and Fusobacteria increased, whereas that of *Firmicutes* decreased<sup>[114]</sup>. On the other hand, in patients with mild obesity, RYGB is an effective treatment option. It can also improve



the metabolic and inflammatory status. Lau *et al*<sup>[115]</sup> reported that RYGB altered 29 rich bacterial genera in the gut microbiota of patients with T2DM. To better understand the weight-independent antidiabetic mechanisms of RYGB, researchers have developed DJB surgery. Han *et al*<sup>[116]</sup> demonstrated that DJB increased intraduodenal BAs levels and upregulated duodenal SIRT1 expression in rats with HFD- and STZ-induced DM. Patients with T2DM reported significant and long-lasting glycemic improvements after undergoing duodenal mucosal resurfacing, an endoscopic technique that involves circumferential hydrothermal ablation and subsequent regeneration of the duodenal mucosa<sup>[117]</sup>.

### *Gut microbe-mediated alleviation of metabolic diseases*

Studies have revealed that obesity alters microbial composition and nature<sup>[23,28]</sup>. The development of metabolic illnesses, such as obesity and T2DM, has recently been linked to the gut microbiota. Increasing attention has been paid to altering the gut microbiota for treating metabolic diseases. Numerous microbial compositions (probiotics, symbiotics, and antibiotics) have been used to treat illnesses. Probiotics are live microorganisms that have positive effects on host health when administered in adequate concentrations<sup>[118]</sup>.

### **PROBIOTICS**

The use of probiotic bacteria as prophylactics and therapeutics is receiving attention because of the potential effects of gut microbes in lowering IR and lipid levels. Increasing evidence suggests using probiotics to prevent metabolic diseases<sup>[119]</sup>. Probiotics are live microbes that provide the host with health benefits when administered in optimal concentrations<sup>[120]</sup>. Probiotic administration may lower TG and VLDL cholesterol (VLDL-C) levels by inhibiting the NF- $\kappa$ B pathway and the gut microbiota-SCFA-hormone axis<sup>[121]</sup>. Moreover, a substantial decrease in lipid levels was noted in healthy pregnant women without GDM after the administration of a two-strain probiotic containing *L. acidophilus* LA5 and *B. animalis* BB12 for 9 wk<sup>[122]</sup>. Probiotics can also increase the  $\beta$ -



oxidation of long-chain fatty acids in muscle and liver tissues, modifying the energy pathways for fatty acid oxidation, lowering the formation of new TGs, and eventually reducing serum TG and VLDL-C levels<sup>[123]</sup>. Furthermore, probiotic consumption can increase the number of natural killer T cells in the liver<sup>[124]</sup>, reduce inflammatory signaling, increase adiponectin levels, reduce inflammation, and prevent GLUT4 inhibition to improve glucose homeostasis. Probiotic dosages can also trigger enteroendocrine L cells to release GLP-1, thereby improving glucose metabolism, reducing glucotoxicity, and improving insulin sensitivity in the target tissue<sup>[125]</sup>.

Recently, there have been many discussions on fecal microbiota transplantation. Vrieze *et al*<sup>[126]</sup> reported that participants with metabolic syndrome showed enhanced peripheral and hepatic insulin sensitivity in response to modest intestinal transfusions of fecal microbiota from allogenic lean donors, together with an upsurge of the gut microbiome. Various microbes are used as probiotics. Our review mainly focuses on *A. muciniphila* and *Bifidobacterium* species, which are closely associated with metabolic diseases.

### *A. muciniphila*

In recent years, *A. muciniphila*, a commensal bacterium found in the intestine, has attracted increasing interest because of its health-promoting effects<sup>[127]</sup>. Interestingly, various clinical disorders in humans, including obesity, T2DM<sup>[128]</sup>, inflammatory bowel disorder, hypertension, and liver disease, decrease the abundance of *A. muciniphila*<sup>[129]</sup>. Animal studies have demonstrated that *A. muciniphila* can alleviate obesity and related illnesses, such as steatosis, gut permeability, glucose intolerance, and IR<sup>[130,131]</sup>. Moreover, in one study, animals treated with live *A. muciniphila* did not exhibit IR or inflammatory cell (CD11c) infiltration in adipose tissues, which are crucial for the development of obesity, because of low inflammation<sup>[32]</sup>. *A. muciniphila* and *F. prausnitzii* can protect against the development of T2DM<sup>[132]</sup>. By activating tight junction proteins (occludin, claudin-3, and ZO-1) and preventing the accumulation of lipopolysaccharides (LPSs) and occurrence of metabolic endotoxemia, *A. muciniphila* can restore the thickness of the

mucus layer<sup>[127]</sup>. Furthermore, *A. muciniphila* exhibits antibacterial and anti-inflammatory effects when administered endogenously and influences the endogenous synthesis of GLP-1 and GLP-2<sup>[133]</sup>. Notably, all these findings have now received backing from different firms and have been used for treating various disorders, including metabolic diseases, such as DM<sup>[134]</sup>, obesity<sup>[135]</sup>, atherosclerosis, hepatic inflammation, and hypercholesterolemia<sup>[136]</sup>.

### ***Bifidobacterium species***

Probiotics, which are a component of the gut microbiome, successfully regulate the intestinal microbiota and have potential antidiabetic applications<sup>[137]</sup>. *Bifidobacterium*, one of the most significant probiotics found in the mammalian gut, exhibits positive effects on health<sup>[138]</sup>. Numerous studies have demonstrated that *Bifidobacterium* species improved insulin sensitivity in patients with T2DM<sup>[139,140]</sup>. In HFD-fed rats with T2DM, the administration of *B. animalis* 01 reduced food and water intake, blood glucose levels, HbA1c levels, and hepatic injuries and increased the antioxidant status, HOMA-IR, and lipid levels by affecting the IRS/PI3K/AKT and Keap1/Nrf2 signaling pathways<sup>[141]</sup>. Similarly, Le *et al*<sup>[142]</sup> reported that STZ-induced C57BL/6J mice treated with *Bifidobacterium* species exhibited significantly reduced blood glucose levels and significantly increased IR, IRS1, Akt/PKB, IKK $\alpha$ , and I $\kappa$ B $\alpha$  levels. Moreover, increased extracellular signal-regulated kinase 2 and <sup>24</sup>adiponectin expression levels and decreased macrophage chemoattractant protein-1 and interleukin-6 expression levels were noted following the administration of *Bifidobacterium* species. Furthermore, in obese and DM models, treatment with *B. animalis* subsp. *lactis* GCL2505 reduced visceral fat accumulation, increased GLP-1 and acetate levels, and enhanced glucose tolerance<sup>[143]</sup>.

*Bifidobacterium*, one of the most significant gut bacteria, diminishes intestinal endotoxin concentrations and enhances mucosal barrier function<sup>[144]</sup>. Recently, HFD-induced models verified an increase in intestinal inflammation. By lowering the levels of metabolic endotoxins and reducing intestinal inflammation, *Bifidobacterium* species may benefit patients with metabolic syndrome<sup>[145]</sup>. In an HFD-fed mouse model,

*Bifidobacterium* species dramatically improved glucose-induced insulin secretion, increased glucose tolerance, and reduced endotoxemia and proinflammatory cytokine levels<sup>[146]</sup> by altering GLP-2 levels<sup>[147]</sup>. Thus, by lowering metabolic endotoxin levels and intestinal inflammation and increasing the expression level of intestinal Reg I, a growth factor regulator<sup>[148]</sup>, *Bifidobacterium* supplementation could alleviate HFD-induced metabolic syndrome. Specific strategies for altering the gut microbiota in favor of *Bifidobacterium* species may be beneficial for mitigating the effect of HFD on the occurrence of metabolic syndrome.

In summary, *A. muciniphila* and *Bifidobacterium* species are highly viable and proliferative probiotics that can alleviate metabolic syndrome through increased glucose tolerance and reduced visceral fat accumulation by altering the overall bacterial composition of the gut microbiota. Moreover, they can increase the levels of SCFAs, which can activate several signaling pathways, including the AKT/PKB/IRS/ERK/Nrf2 pathways.

### **LIMITATIONS AND FUTURE PERSPECTIVES**

Research on the synthesis of BAs and the pathogenesis of liver diseases and metabolic diseases has made significant progress in the last two decades. BAs exert several metabolic functions, and their physicochemical properties can affect their metabolic activities. Gut microbes can be modified by various factors, such as age, diseases, diet, and drugs. BAs play a significant role in regulating gut microbes. Moreover, the size of the BA pool has been shown to be affected by microbial metabolism in the intestines; however, most of these studies have been conducted on experimental animals. Therefore, further research is warranted to identify novel therapeutic targets for maintaining human intestinal health. Importantly, while increasing experimental evidence is available, clinical research on the importance of the human microbiota in relation to rodent metabolic functions is still in its inception. For example, BAS is not recommended for individuals who have a bowel obstruction or are pregnant. Cholestyramine and

colestipol are <sup>42</sup>classified as pregnancy category C, while colestevlam HCl <sup>is</sup> classified as pregnancy category B<sup>[149]</sup>.

Clinical research has mainly been epidemiological in nature and has therefore failed to determine whether modifications in the intestinal microbiota play a molecular role in metabolic diseases. <sup>37</sup>A better understanding of these aspects <sup>is required to</sup> determine whether BA-gut microbiota axes can promote human health and how these pathways can be used to design novel therapeutic interventions for <sup>8</sup>metabolic diseases, such as obesity, DM, and hyperlipidemia, and CADs using BAs and its metabolites, probiotics, and microbial transplantation.

## CONCLUSION

<sup>4</sup>The major objective of this review was to assess the functional implications of gut microbes and BAs for metabolic diseases. In the past, the gut microbiota was considered a bystander in the intestinal tract. The role of these microbes in supporting intestinal function has become more widely recognized in recent years. BAs and the gut microbiota interact in a mutually beneficial manner. When the gut microbiota is disturbed in metabolic illnesses, inflammation occurs and the gut barrier is compromised. Modulating receptor-mediated transport, energy balance, gut permeability, and serum LPSs can impact BAs metabolism. <sup>25</sup>The gut microbiota composition and the specific mechanisms in which the gut microbiota and BAs interact to alter the metabolism and functioning of the host-gut barrier remain somewhat unclear. Understanding the significance of the BAs-gut microbiota relationship in metabolic health could lead to revolutionary advances in the treatment of metabolic illnesses in the future.

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