*Journal of Clinical and Translational Hepatology* **2025**
DOI: 10.14218/JCTH.2025.00212

Review Article

# Gut Microbiota: Implications in Pathogenesis and Potential Therapeutic Target in Primary Biliary Cholangitis

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**Received:** May 07, 2025 | **Revised:** July 06, 2025 | **Accepted:** July 21, 2025 | **Published online:** August 22, 2025

## Abstract

Primary biliary cholangitis (PBC) is a chronic progressive autoimmune disorder characterized by small non-purulent intrahepatic bile duct destruction (ductopenia) and cholestasis. While the etiology of PBC remains unclear, it is believed to involve genetic-environmental interactions. Emerging evidence highlights gut microbiota dysbiosis in PBC patients, with increased symbiotic bacteria and decreased pathogenic bacteria. Microbial alterations potentially influence disease pathogenesis through multiple mechanisms, including immune dysregulation, intestinal barrier damage, BA metabolic dysregulation, and cholestasis. These findings suggest that the gut microbiota can serve not only as a non-invasive biomarker for diagnosis and prognosis evaluation but also as a therapeutic target for the disease. In this review, we summarize changes in PBC patients' gut microbiota, explain how these changes affect disease occurrence and development, and discuss treatment methods with potential clinical value that intervene in gut microbiota.

**Citation of this article:** Nie Y, Shi Y, Yang Y. Gut Microbiota: Implications in Pathogenesis and Potential Therapeutic Target in Primary Biliary Cholangitis. J Clin Transl Hepatol 2025. doi: 10.14218/JCTH.2025.00212.

## Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic progressive autoimmune disorder predominantly affecting women aged 40–70 years, though recent epidemiological data have shown a gradual increase in male incidence.[1] PBC is characterized by immune-mediated destruction of small intrahepatic bile ducts, leading to chronic nonsuppurative cholangitis, ductopenia, and persistent cholestasis. Diagnostic hallmarks include sustained elevation of cholestatic liver enzymes (particularly alkaline phosphatase and γ-glutamyl transpeptidase) and the presence of pathognomonic autoantibodies such as anti-mitochondrial antibodies (AMA), anti-sp110, and anti-gp210.[2] The clinical presentation of early-stage PBC is often insidious, with nonspecific manifestations including pruritus, chronic fatigue, and the xerophthalmia-xerostomia complex. Without timely diagnosis and intervention, the disease typically progresses through stages of biliary fibrosis, ultimately culminating in cirrhosis and hepatic failure.[1] Ursodeoxycholic acid (UDCA) remains the first-line therapeutic agent, demonstrating significant improvement in long-term prognosis.[3] However, approximately 40% of patients exhibit a suboptimal biochemical response to UDCA monotherapy.[4]

The precise etiology of PBC remains incompletely elucidated, with current hypotheses proposing an intricate interplay between genetic predisposition and environmental triggers.[5,6] Genome-wide association studies have identified multiple susceptibility loci, primarily in immunomodulatory pathways, especially those linked to human leukocyte antigen Class II antigen presentation and interleukin (IL)-12 signaling. Studies exploring the relationship between genetic susceptibility and the microbiota reveal that human leukocyte antigen Class II genes may influence gut microbiota composition in PBC patients.[7] However, these genetic aberrations are not PBC-specific but common across various autoimmune diseases, suggesting that genetic factors primarily regulate disease susceptibility rather than directly initiating pathogenesis.[8–10] Environmental contributors include diverse exogenous agents such as cosmetic chemicals (hair dyes, perfumes, nail polish), tobacco smoke, xenobiotic estrogens, octynoic acid (a structural analog of lipoic acid found in mitochondrial enzymes),[11,12] and urinary tract infections.[6,13] The common conclusion of these studies is that environmental triggers may disrupt immune tolerance through molecular mimicry of the structure of the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) in biliary epithelial cells, ultimately leading to AMA-mediated destruction of small bile ducts.

The gut microbiota, a complex ecosystem comprising trillions of microorganisms, plays a pivotal role in maintaining host homeostasis. A well-balanced gut microbiota not only fosters the establishment of immune tolerance to commensal microorganisms during developmental stages but also serves as a biological barrier against exogenous and endogenous pathogens.[14,15] Moreover, the microbial community partici-

**Keywords:** Primary biliary cholangitis; PBC; Autoimmune liver disease; Cholestatic liver disease; Gut microbiota; Bile acid.
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**Table 1. Summary of studies about gut microbiota in PBC**

| Researchers (year, country) | Participant | Sample | Result |
|---|---|---|---|
| Kitahata *et al*.[27] (2021, Japan); Zhou *et al*.[35] (2023, China); Wang *et al*.[34] (2024, China); Abe *et al*.[36] (2018, Japan); Chen *et al*.[33] (2020, China); Furukawa *et al*.[37] (2020, Japan); Tang *et al*.[41] (2018, China); Wang *et al*.[34] (2024, China); Lv *et al*.[45] (2016, China) | PBC patients and HC | Small intestinal MAM, stool, Salivary | PBC vs. HC: Gut microbiota: Diversity, richness, and evenness↓. ↑: Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria, Acidimicrobita, Lactobacillales, Enterobacteriales and Enterobacteriaceae, Sphingomonadaceae, Yersiniaceae, Lachnospiracea_incertae_sedis, ucg_010, *Pseudomonas*, *Serratia*, *Escherichia*, *Bacteroides*, *Megamonas*, *Klebsiella*, *Haemophilus*, *Veillonella*, *Clostridium*, *Lactobacillus*, *Streptococcus*; ↓: Firmicutes, Clostridiales, *Ruminococcaceae*, Clostridia, Sutterellaceae, Oscillospiraceae, *Bacteroidetes* spp, Christensenellaceae, *Faecalibacterium*, *Parasutterella*, *Coprococcus*, *Sutterella*, *Oscillospira*. Oral microbe: ↑: *Eubacterium*, *Veillonella*. ↓: *Fusobacterium*. PBC patients with cirrhosis *vs.* HC: ↑: Proteobacteria, Enterobacteriaceae, Neisseriaceae, Spirochaetaceae, *Veillonella, Streptococcus, Klebsiella, Actinobacillus pleuropneumoniae, Anaeroglobus geminatus, Enterobacter asburiae, Haemophilus parainfluenzae, Megasphaera micronuciformis, Paraprevotella clara;* ↓: Firmicutes, Acidobacteria, *Faecalibacterium, Gemmiger, Streptococcus, Lachnobacterium, Bacteroides eggerthii, Ruminococcus bromii* |
| Lammert *et al*.[38] (2021, USA); Zhou *et al*.[35] (2023, China); Hegade *et al*.[40] (2019, UK); Shi *et al*.[39] (2024, China) | PBC patients | Stool | Patients with advanced fibrosis *vs.* Patients without fibrosis: Microbe: Diversity↓, ↑: *Weissella*. gp210-(+) *vs.* gp210-(-): ↓*: Oscillospiraceae.* Patients with pruritus *vs.* asymptomatic individuals: Gut microbiota: similar. (ALBI Grade 2 & Grade 3) *vs.* ALBI Grade 1: ↓*:* Clostridia, *β-* Proteobacteria, Erysipelotrichia, *Lachnospira.* ↑*:* Lactobacillales, *Streptococcus, Enterococcaceae.* |
| Chen *et al*.[33] (2020, China); Tang *et al*.[41] (2018, China); Wang *et al*.[34] (2024, China); Furukawa *et al*.[37] (2020, Japan); Han *et al*.[42] (2024, China); Han *et al*.[43] (2022, China); Liu *et al*.[44] (2024, China) | PBC patients with or without UDCA treatment | stool | After treatment *vs.* Before treatment: ↑: *Bilophila* spp (e.g., *Bilophila wadsworthia*), Bacteroidetes spp, *Sutterella* spp, *and Oscillospira* spp. ↓*: Haemophilus* spp, *Streptococcus* spp, *Pseudomonas* spp. Non-responder *vs.* Responder: Diversity: ↓. ↑: *Faecalibacterium*, *Ruminococcus, Gemmiger*, *Blautia*, *Anaerostipes*, *Coprococcus, Holdemania.* Clostridia-low microbiomes *vs.* Clostridia-high. UDCA non-response rate: ↑. |

PBC, Primary biliary cholangitis; HC, Health controls; MAM, Mucosa-associated microbiota; ALBI, Albumin Bilirubin; UDCA, Ursodeoxycholic acid; gp210-(+), Anti gp-210-positive; gp210-(-), Anti-gp210-negative; ↑, Increase; ↓, Decrease.

pates in the biosynthesis of essential nutrients such as vitamins, short-chain fatty acids (SCFAs), and amino acids.[16,17] Notably, gut microbiota-derived metabolites mediate communication by engaging specific host signaling receptors, thereby regulating systemic physiological functions.[18] Previous studies have shown that the gut microbiota is closely associated with liver diseases such as alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, and primary sclerosing cholangitis.[19–29] Gut dysbiosis contributes to or exacerbates liver injury through multiple mechanisms, including disruption of bile acid (BA) homeostasis,[30] immune dysregulation,[14,18] impairment of intestinal barrier integrity, and translocation of microbial metabolites.[31,32]

In this review, we describe how the gut microbiota affects the occurrence and development of PBC, which is of great significance for the treatment of this disease.

We conducted searches on both PubMed and Web of Science in February 2025 using the following search terms: primary biliary cholangitis OR primary biliary cirrhosis OR PBC OR autoimmune liver disease; gut microbiota OR intestinal microbiome OR intestinal microbiota; bile acid OR pathogenesis OR mechanism OR therapy OR treatment. Furthermore, we manually screened additional relevant articles from the bibliographies of retrieved articles.

## Dysbiosis of gut microbiota in PBC

Table 1 summarizes recent studies on the gut microbiota in PBC.[27,33–45] Several studies from China and Japan have found significant differences in the composition of gut microbiota between PBC patients and healthy controls. Overall, the diversity and species abundance of gut microbiota in PBC patients were significantly decreased. Alterations in the intestinal flora of PBC patients are mainly characterized by reduced abundance of beneficial bacteria (e.g., *Faecalibacterium*, *Sutterella*, and *Oscillospira*) and increased proliferation of potential pathogens (e.g., *Veillonella*, *Streptococcus*, and *Klebsiella*).[27,33–37] In addition to comparisons between PBC patients and healthy controls, differences in gut microbiota have also been observed between PBC patients with different disease statuses. Lammert *et al*. found that the abundance of *Weissella* was significantly higher in patients with progressive liver fibrosis than in PBC patients without liver fibrosis.[38] Shi *et al*. reported that compared with PBC patients with mild liver function damage and Albumin-Bilirubin (ALBI) Grade 1, those with ALBI Grades 2 and 3 showed a significant increase in *Streptococcus* and *Enterococcaceae* abundance and a reduction in *Lachnospira*. The former are mostly pathogenic bacteria, while the latter is an intestinal commensal involved in dietary fiber decomposition.[39] Additionally, Zhou *et al*. compared the intestinal flora of anti-gp210-positive and anti-gp210-negative PBC patients. Anti-gp210-positive patients, who are associated with worse prognosis, showed a significant reduction in *Oscillospiraceae* abundance.[39] These findings suggest that gut microbiota changes in PBC patients are involved in disease progression.

However, alterations in the gut microbiota cannot explain pruritus in PBC patients; as a nonspecific clinical symptom, pruritus correlates positively with serum BA concentration and autotaxin levels.[40]

Conversely, PBC treatment can also affect gut microbiota composition. Chen, Tang, and colleagues conducted a 12-month trial of UDCA monotherapy in PBC patients. After treatment, the abundances of *Bilophila* spp., *Bacteroidetes* spp., *Sutterella* spp., and *Oscillospira* spp. significantly increased, while those of pathogenic microorganisms such as *Haemophilus* spp., *Streptococcus* spp., and *Pseudomonas* spp. significantly decreased.[33,41] Wang, Han, *et al*. evaluated biochemical responses to UDCA treatment and found that, compared with complete responders, patients with no or poor response had significantly higher abundances of *Faecalibacterium*, *Ruminococcus*, *Gemmiger*, *Blautia*, *Anaerostipes*, *Coprococcus*, and *Holdemania* in their gut.[42–43,46] In a prospective study, Liu *et al*. reported that PBC patients with lower baseline abundance of Clostridia had a higher rate of non-response to UDCA monotherapy, suggesting that gut microbial characteristics influence treatment outcomes. These findings demonstrate that gut microbiota has potential as a tool for evaluating drug efficacy.[44]

## Gut microbiota influences the onset and progression of PBC through effects on immune responses, intestinal barrier function, and BA circulation

Transplantation of fecal microbiota from PBC patients into mice induced PBC-like alterations in serum parameters and liver tissue, while administration of quadruple antibiotics reversed splenomegaly and liver inflammation in PBC-model mice,[47,48] indicating a direct role of gut microbiota in disease pathogenesis. Although human clinical trials on fecal microbiota transplantation (FMT) are lacking, numerous retrospective and prospective studies have identified distinct gut microbiota profiles between PBC patients and healthy individuals. Metabolomics analyses reveal that these intestinal flora changes correlate with dysregulation of secondary metabolites, including reduced levels of protective metabolites (e.g., secondary BAs and SCFAs) and accumulation of pro-inflammatory metabolites (e.g., primary BAs).[33,41,45] Regarding disease onset, gut microbial dysbiosis promotes the production of autoimmune antibodies, triggering immune dysfunction. During disease progression, gut microbiota dysbiosis impacts the host through intestinal barrier disruption, metabolite dysregulation, and bacterial translocation. Notably, gut microbiota dysbiosis is closely linked to BA metabolic dysregulation. These processes ultimately result in bile duct injury and cholestasis, leading to liver fibrosis.

In this paper, we describe how the gut microbiota contributes to disease pathogenesis through four mechanisms: immune dysregulation, intestinal barrier damage, BA metabolic dysregulation, and cholestasis.

### *Gut microbiota dysbiosis and immune disorders*

A characteristic diagnostic feature of PBC is the presence of AMA targeting the PDC-E2, which is widely expressed in mitochondria across various cell types. Intriguingly, strains of rough Enterobacteriaceae exhibit cross-reactivity with AMA. Subsequent studies have identified the cross-reactive epitope as the *Escherichia coli* 2-oxoglutarate dehydrogenase complex, which shares structural homology with human PDC-E2. This molecular mimicry implies a microbial role in PBC pathogenesis, whereby *E. coli* infection disrupts immune tolerance and promotes disease onset through autoantibody induction.[49–51] Epidemiological evidence supports this hypothesis: PBC patients demonstrate a higher incidence of refractory urinary tract infections, with urinary tract infection onset frequently preceding PBC diagnosis.[52,53] Experimental validation in *non-obese diabetic, B6 (Idd10/Idd18)* mice revealed that *E. coli* infection induces autoantibodies against murine PDC-E2 and promotes PBC-like histopathology, mechanistically linking enterobacterial infection to AMA production via molecular mimicry, ultimately driving autoimmune bile duct injury.[54] Jochen Mattner *et al*. infected mice with *Novosphingobium aromaticivorans* via intravenous injection to induce AMA and trigger chronic T cell-mediated autoimmunity against small bile ducts.[55] *Serratia, Yersiniaceae*, and *Escherichia coli* all belong to the order Enterobacteriales; they exhibit similar antigenic structures and are significantly enriched in the gut microbiota of PBC patients, with their abundance positively correlated with serum IgG levels.[34,35,41,45] Additionally, *Pseudomonas* overgrowth in the ileal mucosa has been linked to antigenic structures cross-reacting with AMA,[27] collectively supporting the "molecular mimicry" hypothesis. However, the changes in gut microbiota observed in these studies do not establish causal relationships. Whether alterations in gut microbiota contribute directly to autoantibody production remains to be confirmed by larger controlled trials.

A large number of lymphocytes infiltrate the portal vein area around damaged bile ducts in PBC patients, suggesting that after antigen exposure, autoimmune responses contribute to disease progression.[56] Antigen-presenting cells (such as dendritic cells) present autoantigens and induce $CD4^+$ and $CD8^+$ T cells to target the immunodominant epitope of PDC-E2 on biliary epithelial cells, triggering an autoimmune response.[55,57,58] Among these, $CD103^+$ tissue-resident memory T cells are the predominant reactive $CD8^+$ T cells and play a key pathogenic role in PBC.[59] Additionally, plasma cells secrete AMA that specifically targets the lipid acyl domain of PDC-E2 in bile duct epithelial cells (BECs), forming immune complexes that stimulate liver macrophage aggregation and amplify duct damage.[60]

Gut-colonizing bacteria such as *Bacteroides*, *Ruminococcus*, *Faecalibacterium*, *Clostridium,* and *Anaerostipes* break down dietary fiber or complex carbohydrates to produce SCFAs such as acetate, propionate, and butyrate. These microbial metabolites exhibit immunomodulatory and anti-inflammatory properties through multiple pathways. As endogenous ligands for free fatty acid receptors 2/3 expressed on immune cells, SCFAs mediate systemic immune regulation. Acting as signal transduction molecules, SCFAs bind to various cognate G-protein coupled receptors and regulate immune cells such as neutrophils, macrophages, dendritic cells, mast cells, and lymphocytes.[61] In the liver, butyrate attenuates inflammation by suppressing nuclear factor kappa B activation in Kupffer cells, thereby reducing tumor necrosis factor-α, IL-5, and myeloperoxidase production. Furthermore, propionate and butyrate regulate T cell and dendritic cell functions through histone deacetylase (HDAC) inhibition.[62–64]

Many studies have consistently demonstrated reduced abundance of SCFA-producing taxa in PBC patients and UDCA non-responders.[34–37,39,41,44,45] However, these investigations primarily established correlative relationships without elucidating the underlying molecular mechanisms. Notably, Wang *et al*. demonstrated that butyrate enhances the immunosuppression of myeloid-derived suppressor cells via the HDAC pathway and alleviates bile duct injury in PBC mice.[46] Nevertheless, the immunomodulatory roles of other SCFAs (e.g., acetate and propionate) in PBC pathogenesis remain to be experimentally validated.

### *Gut microbiota dysbiosis and intestinal barrier destruction*

Alterations in gut microbiota composition and their metabolites impact the liver by disrupting the first line of defense in the gut-liver axis—intestinal barrier integrity. Kitahata *et al*. revealed ileal mucosa-associated microbiota dysbiosis in PBC patients, characterized by overgrowth of *Sphingomonadaceae* and *Pseudomonas*, alongside reduced abundance of the TM7 phylum and *Leptotrichia* genera. Notably, *Sphingomonadaceae* enrichment was undetectable in fecal microbiota, suggesting that ileal mucosal sampling may provide more direct insights into barrier-disrupting taxa than fecal microbiota analysis. However, methodological challenges in ileal mucosal biopsy limited validation across broader populations.[27] Functional analyses of enriched gut microbiota in PBC patients revealed aberrant activation of the "bacterial invasion of epithelial cells" pathway, correlating with proliferation of Enterobacteriaceae and Klebsiaceae. These bacteria can translocate to mesenteric lymph nodes and the liver, directly triggering infections and exacerbating barrier permeability.[41] Studies by Wang *et al*. and Lv *et al*. identified significantly elevated levels of *Enterobacteriaceae* and *Klebsiaceae* in PBC patients. Notably, the abundance of *Klebsiella* was positively correlated with cytokine IL-2, implicating its pro-inflammatory potential.[34,45]

Under physiological conditions, the host establishes gradients of oxygen and nitrate concentrations, allowing the small and large intestines to be predominantly colonized by aerobic and anaerobic bacteria, respectively, which govern energy metabolism.[65] UDCA non-responsive PBC patients exhibit a respiratory mode shift: downregulation of anaerobic fermentation pathways (e.g., butyrate and methane production) and upregulation of aerobic pathways (e.g., nitrate respiration and oxidative phosphorylation).[44] Disruption of this respiratory mode transition not only signifies intestinal barrier damage but also drives shifts in microbial composition and metabolite profiles.

As mentioned earlier, gut microbiota-derived metabolites such as butyrate act as anti-inflammatory agents by binding to free fatty acid receptors 2 to enhance regulatory T cell function and inhibit HDAC6/9 activity, thereby promoting anti-inflammatory mediators (e.g., IL-10 and Foxp3).[66,67] Butyrate deficiency impairs mucosal repair, and fecal metagenomic/metabolomic analyses of anti-gp210-positive PBC patients with poor clinical prognosis demonstrate significantly reduced abundance of butyrate-producing *Faecalibacterium* compared to gp210-negative patients, indicating exacerbated intestinal barrier injury.[41] Other protective metabolites, including tryptophan derivatives (e.g., indole-3-propionic acid and indole-3-aldehyde) and B vitamins (e.g., biotin and pyridoxal), maintain epithelial tight junctions. Multiple controlled studies report diminished abundance of protective metabolite-producing genera (e.g., *Clostridium*) in PBC patients.[34,44] Intestinal barrier dysfunction and increased permeability facilitate entry of pro-inflammatory metabolites and bacteria into the bloodstream and liver via circulation, causing damage to the liver and bile ducts.

### *Gut microbiota dysbiosis, BA dysregulation, and cholestasis*

Under normal circumstances, BECs are in a quiescent state and form a protective alkaline bicarbonate "umbrella" through anion exchanger 2.[68] When anion exchanger 2 is deficient or the alkaline bicarbonate umbrella is damaged, BECs can be stimulated by exogenous or endogenous factors, leading to a series of phenotypic changes. They actively proliferate and release chemokines (such as ICAM-1, tumor necrosis factor-α, CCL2, CXCL9, CXCL10, etc.) that recruit various inflammatory cells, including natural killer cells, natural killer T cells, liver-resident Th1-like cells, mucosa-associated invariant T cells, and hepatic stellate cells, amplifying local inflammation.[69] This response represents a self-protective mechanism by which BECs coordinate proliferation and apoptosis to repair damage and remodel the biliary tract. However, if the stimulating factors persist, chronic inflammation leads to destruction and disappearance of small bile ducts, eventually progressing to liver fibrosis.[67,70] In a mouse model of drug-induced autoimmune cholangitis, alterations in intestinal flora induce BECs to recruit $CD8^+$ T cells and produce inflammatory damage by secreting chemokines via the Toll-like receptor 2 pathway.[71] In another study, PBC mice fed p-Cresol sulfate, a metabolite produced by *Clostridium* metabolism of tyrosine, showed that p-Cresol sulfate inhibits Kupffer cell immune responses by polarizing Kupffer cells and alleviating bile duct inflammation.[72] This illustrates that gut dysbiosis and its metabolites can enter the liver via the mesenteric circulation, stimulate BECs, and induce their phenotypic changes.[73]

BAs are bioactive molecules regulating metabolic and immune functions. Figure 1 illustrates the enterohepatic circulation. Primary BAs (cholic acid, chenodeoxycholic acid) are synthesized in hepatocytes from cholesterol by the rate-limiting enzyme cholesterol 7α-hydroxylase, which maintains cholesterol homeostasis and protects against hepatic inflammation and fibrosis.[74] Free BAs are conjugated with glycine or taurine to form conjugated BAs (e.g., glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid) and secreted into the intestine, where they facilitate lipid and fat-soluble vitamin absorption, modulate fatty acid metabolism, mediate cholesterol excretion, and regulate gut microbiota to maintain immune balance and intestinal barrier integrity. Approximately 95% of BAs are reabsorbed in the ileum via the apical sodium-dependent bile acid transporter and enter the portal circulation. They are ultimately reabsorbed into hepatocytes via sodium taurocholate co-transporting polypeptide and organic anion-transporting polypeptide 1/4, completing enterohepatic circulation.[75–77] Unabsorbed BAs are metabolized by gut microbiota (e.g., Lachnospiraceae, Ruminococcaceae, and *Blautia*) through 7α-dehydroxylation to generate secondary BAs such as deoxycholic acid and lithocholic acid, enhancing BA pool diversity and hydrophobicity to promote fecal excretion.[30,75,78,79]

BAs interact with receptors such as farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5, pregnane X receptor, and vitamin D receptor to regulate BA synthesis. For instance, secondary BAs activate ileal FXR, suppressing cholesterol 7α-hydroxylase expression and downregulating hepatic BA production via negative feedback.[26,78] Thus, intact BA cycling depends on microbiota-host equilibrium. Impaired microbial generation of secondary BAs or inhibited FXR signaling disrupts enterohepatic circulation, leading to accumulation of hydrophobic and toxic BAs (e.g., deoxycholic acid). Elevated BA concentrations damage cholangiocyte barriers, induce mitochondrial swelling and apoptosis, and ultimately cause bile duct injury and cholestasis.[26,31,80] Notably, PBC patients with low *Clostridium* abundance exhibit marked reductions in secondary BAs.[44] Kyoto Encyclopedia of Genes and Genomes pathway analysis confirms dysregulated microbial secondary BA synthesis in PBC, strongly associated with altered BA hydrophobicity and toxic accumulation.[35]

Dysbiosis not only aggravates cholestasis but is also exacerbated by cholestatic conditions. In patients with advanced liver fibrosis, gut microbiota displays reduced biodiversity

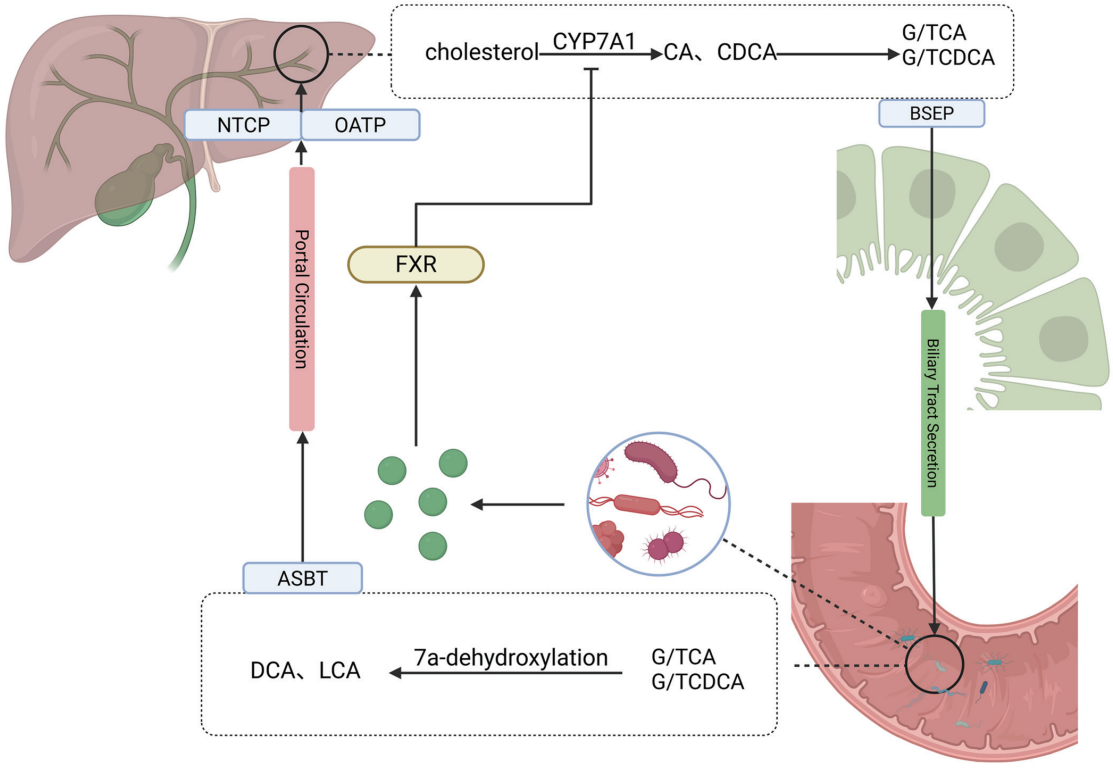


**Fig. 1. The enterohepatic circulation of bile acids.** Created with BioRender. CYP7A1,Cholesterol 7α-hydroxylase; CA, Cholic Acid; CDCA, Chenodeoxycholic Acid; GCA, Glycocholic acid; TCA, Taurocholic acid; GCDCA, Glycochenodeoxycholic acid; TCDCA, Taurochenodeoxycholic acid; DCA, Deoxycholic acid; LCA, Lithocholic acid; BSEP, Bile salt export protein ; ASBT, Apical sodium-dependent bile acids transporter; NTCP, Sodium taurocholate co-transporting polypeptide; OATP, Organic anion-transporters; FXR, Farnesoid X Receptor.

and diminished capacity to convert primary BAs into secondary forms, correlating with altered abundance of key genera (e.g., *Weissella*).[38,81] Abundance of protective metabolite-producing genera (e.g., *Clostridium*) is also decreased in PBC patients.[82] In bile duct ligation-induced cholestatic mice, gut microbial diversity is significantly reduced, accompanied by depletion of hepatoprotective metabolites (e.g., biotin, spermidine, arginine, and ornithine), which negatively correlate with pro-inflammatory cytokines (IL-6, IL-23, MCP-1). These functional losses are linked to depletion of beneficial genera (*Anaeroplasma*, Cyanobacteria, *Eubacterium*, *Lachnoclostridium*) and expansion of pathogens (*Escherichia*, *Enterococcus*).[83]

## Gut microbiota as biomarkers in PBC: Diagnostic, prognostic, and therapeutic implications

The gut microbiota has emerged as a promising non-invasive biomarker system in PBC, offering insights into diagnosis, disease stratification, treatment response prediction, and prognosis. For example, fecal microbiota sequencing suggests that enrichment or deletion of specific bacterial genera could serve as a non-invasive diagnostic tool for PBC. Zhou *et al*. identified four significantly enriched and eight significantly depleted bacterial genera in the intestinal flora of PBC patients. Moreover, the gut microbiota of PBC patients positive for anti-gp210 differs from those who are negative, notably exhibiting reduced levels of Oscillospiraceae.[35,84–86] In disease severity assessment, specific microbiota signatures correlate with clinical progression. For example, elevated *Gemmiger* and *Streptococcus* abundances predict cirrhosis risk, while variations in *Lachnospira* abundance differentiate ALBI grades, reflecting liver function damage severity.[34,39] Additionally, combined microbiome and metabolome models improve prognostic accuracy.[42] Furukawa *et al*. and Liu *et al*. compared fecal microbiota characteristics in PBC patients with complete and incomplete UDCA responses and found that *Clostridium* and *Faecalibacterium* abundance associate with UDCA response.[37,44] After 12 months of UDCA treatment, patients with normalized serum markers had lower intestinal *Gemmiger*, *Blautia*, *Anaerostipes,* and *Coprococcus* levels, supporting the evaluative value of intestinal flora changes for UDCA efficacy.[43] These findings may help clinicians identify patients at risk of poor response or prognosis early, enabling timely initiation of second-line therapies.

## Gut microbiota and treatment progress of PBC

### *Microbiome-targeted therapies*

**Probiotics and protective metabolites:** Probiotics are live microorganisms that can reshape the gut microbiota and improve microbiome composition under pathological conditions, demonstrating promising therapeutic potential in various diseases such as colorectal cancer and inflammatory bowel disease.[87] In a mouse model, probiotic supplementation with *Lactobacillus rhamnosus* GG reduced cholestasis and liver fibrosis in bile duct-ligated mice by increasing secondary BA production, activating gut FXR-FGF15 signaling, and negatively regulating BA synthesis.[88] Another study showed that *Lactobacillus plantarum* inhibits lipopolysaccharide-induced inflammatory pathway activation, oxidative damage, and ap-

optosis via the TLR-4/MAPK/nuclear factor kappa B and Nrf2-HO-1/CYP2E1 pathways, indicating its potential to alleviate liver injury.[89] These mouse studies demonstrate the therapeutic potential of oral probiotics. However, clinical evidence on oral probiotic therapy in PBC patients is currently lacking, and its efficacy remains unclear. Similarly, supplementation with oral protective metabolites such as SCFAs, produced by microbial metabolism, offers therapeutic potential. For example, administration of butyrate or transplantation of myeloid-derived suppressor cells treated with butyrate significantly alleviated liver injury in a mouse model of cholangitis.[46] This more direct therapy represents a promising direction for future microbial intervention strategies.

**FMT:** FMT, in which gut microbiota from a healthy donor is transferred into a patient, can modify gut microbial composition and enhance probiotic abundance. The efficacy and safety of FMT have been well established in diseases such as irritable bowel syndrome and inflammatory bowel disease. Transplanting feces from PBC patients into mice induces PBC-like lesions in the serum and liver,[47] indirectly supporting the potential of FMT, transferring healthy feces into PBC patients, to alleviate disease symptoms. Clinical studies of FMT in PBC patients may therefore be a worthwhile area for future research.

**Antibiotics:** Antibiotics aim to restore gut microbiota balance by reducing pathogenic bacteria abundance. This approach has been tested in mouse models of PBC and PSC. For instance, administration of a quadruple antibiotic mixture (ampicillin, vancomycin, metronidazole, and neomycin) alleviated liver injury and splenomegaly in PBC mice.[48] Similarly, spontaneous cholangitis in NOD.c3c4 mice was significantly alleviated by antibiotic treatment.[90] However, antibiotic type and timing are critical; inappropriate use may eliminate beneficial bacteria and lead to adverse effects such as antibiotic-associated diarrhea and *Clostridioides difficile* infection, common in clinical practice.[91] Therefore, rigorous human trials are necessary to assess the efficacy and safety of antibiotic therapies in PBC.

**Bacteriophage therapy:** Bacteriophages are viruses that specifically infect and lyse bacteria by recognizing receptors on bacterial surfaces (e.g., lipopolysaccharides, teichoic acids, membrane proteins, and flagella). This specificity allows bacteriophages to target particular bacteria without disrupting the overall gut microbial ecology.[92–95] Recently, bacteriophage therapy has gained clinical traction, initially to combat infections caused by antibiotic-resistant bacteria such as *Salmonella*, *Clostridioides difficile*, and *Escherichia coli*.[96,97] As gut microbiome research advances, bacteriophage therapy is increasingly applied to modulate the gut microbiota. For example, bacteriophages targeting *Klebsiella* have alleviated colitis in mice, with human trials confirming safety.[98] Beyond intestinal infections and inflammatory bowel diseases, bacteriophage therapy has been explored for liver diseases. Oral administration of bacteriophages targeting lytic *Enterococcus faecalis* improves alcoholic fatty liver disease,[99,100] while phages against *Klebsiella* alleviate non-alcoholic fatty liver disease.[101] *Klebsiella pneumoniae* exacerbates liver injury in primary sclerosing cholangitis by activating IL-17–secreting $CD4^+$ T cells and promoting bacterial translocation; a bacteriophage cocktail targeting K. *pneumoniae* reduces bacterial load and hepatic inflammation in mice.[102] Although bacteriophage therapy has not yet been applied to PBC, successful precedents suggest its feasibility, and it may become a promising future strategy for gut microbiota intervention in PBC.

### *First-line therapy: UDCA*

UDCA, a secondary BA metabolized by intestinal bacteria, is widely used in various cholestatic diseases and is the first-line treatment for PBC. UDCA significantly prolongs transplantation-free survival by altering the hydrophobicity of the BA pool, stimulating hepatic BA excretion, and protecting BECs from BA-induced apoptosis.[3] In addition, UDCA modulates the gut microbiota. Although it does not fully restore gut microbial biodiversity in PBC patients, UDCA partially rebalances the microbiome by reducing the abundance of Firmicutes genera (e.g., *Streptococcus* and *Haemophilus*) and promoting recovery of *Bacteroidetes*.[41,44]

Importantly, a prospective study indicated that baseline gut microbiota characteristics may influence the therapeutic response to UDCA, with reduced Clostridia abundance strongly associated with poor UDCA response. Does altering Clostridia abundance improve UDCA efficacy? Recent clinical trials investigating probiotic supplementation alongside UDCA for poor responders (NCT03521297) are ongoing, with efficacy yet to be determined. Future research should focus on therapeutic strategies combining UDCA with targeted gut microbiota interventions.[44]

### *Second-line therapies*

**FXR agonists:** Obeticholic acid (OCA), an FXR agonist, represents the principal second-line therapy for PBC. Its mechanism involves activation of FXR signaling to suppress BA synthesis and enhance excretion, thereby alleviating cholestasis.[59] Compared to UDCA-treated cohorts over five to six years, OCA demonstrates superior transplant-free and decompensation-free survival rates.[103–105] However, clinical use is limited by higher risks of adverse effects (e.g., severe pruritus) and potential hepatic dysfunction, especially in advanced cirrhosis.[106] Development of novel non-BA FXR agonists (e.g., Tofenixicor) offers a promising strategy to mitigate these side effects. Besides FXR activation, these agents also regulate BA metabolism through inhibition of apical sodium-dependent bile acid transporter and sodium taurocholate co-transporting polypeptide.[107,108]

**Peroxisome proliferator-activated receptor (PPAR) agonists:** PPARs are nuclear receptors activated by diverse ligands that regulate transcriptional programs of BA metabolism via three major isoforms: PPARα, PPARδ, and PPARγ. PPARα agonists (e.g., fenofibrate and pemafibrate) improve cholestasis by enhancing BA glucuronidation.[109] Other agonists such as seladelpar, elafibranor, saroglitazar, and bezafibrate have demonstrated significant cholestasis alleviation in clinical trials. Fibrates also provide superior pruritus relief compared to OCA, potentially improving patient adherence. Furthermore, combination therapy with fenofibrate and UDCA significantly improves transplant-free survival and reduces decompensation rates, expanding therapeutic options.[105] Additionally, the natural compound formononetin shows experimental efficacy in cholestasis management through SIRT1-mediated PPARα activation. While not yet in clinical trials, it provides a foundation for novel drug development.[110]

### *Novel immunomodulatory approaches*

Current evidence does not support conventional immunosuppression for PBC due to disease pathogenesis centered on BA-mediated biliary damage. However, emerging strategies utilizing antigen-coated nanoparticles to selectively inhibit autoreactive T cells show therapeutic promise in preclinical models.[111,112]

### *Symptomatic management: Pruritus-targeted therapy*

Pruritus in PBC correlates with elevated serum total BAs, par-

ticularly glycocholic and glycochenodeoxycholic acids. Ileal bile acid transporter inhibitors alleviate pruritus by reducing serum conjugated BAs and enhancing fecal excretion, accompanied by gut microbiota alterations, specifically increased Firmicutes and decreased Bacteroidetes.[40] Cholestyramine, a BA sequestrant, reduces serum BAs by intestinal binding and enriches SCFA-producing microbiota (e.g., Ruminococcaceae), modulating microbial metabolic functions.[113]

### *Emerging anti-fibrotic strategies*

Hepatic fibrosis and cirrhosis are common clinical outcomes across liver diseases. Current therapies predominantly focus on liver transplantation and managing complications from decompensated liver function. For PBC-related hepatic fibrosis, specific therapeutic strategies remain investigational, with most research concentrating on modulation of BA metabolism and inflammatory pathways. Future advancements require integrating gut microbiota–liver axis mechanisms to develop multi-target combination therapies aimed at overcoming current limitations in anti-fibrotic treatment.

## Conclusions

PBC is a chronic autoimmune liver disease. In recent years, gut microbiota dysbiosis has emerged as a key research focus in PBC. This review summarizes how gut microbiota contributes to PBC progression through immune dysregulation, intestinal barrier disruption, and BA metabolism disorders. These processes activate inflammatory signaling pathways in BECs, accelerating bile duct injury and ultimately leading to cholestasis and hepatic fibrosis. With advances in microbiomics and metabolomics, the gut microbiome analyzed via fecal samples as a non-invasive biomarker can assess disease severity and prognosis and predict responses to drug therapy. This helps clinicians initiate comprehensive treatments early. Meanwhile, therapies targeting microbial composition are becoming a highly promising research direction. Whether via oral probiotics, bacteriophage therapy, or FMT, clinical trials are needed to validate efficacy and safety. It is hoped that gut microbiota-targeted therapies will soon play a unique role in both monotherapy and combination treatments.

## Funding

This work was supported by the Key R&D Program of Zhejiang (No. 2025C02131), the National Key R&D Program of China (No. 2022YFC2304500), and the National Natural Science Foundation of China (No. 82300690).

## Conflict of interest

YS has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication.

## Author contributions

Conception (YY), literature search, drafting of the manuscript, preparation for figures and tables (YN), preparation for the article, and revision of the manuscript (YN, YS, YY). All authors have read and approved the final version and publication of the manuscript.

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