Journal of Clinical and Translational Hepatology **2026**
DOI: 10.14218/JCTH.2026.00118

Review Article

Short-chain Fatty Acids and Bile Acids Signaling in Chronic Hepatitis B

Siqi Sun, Sisi Yang, Yihe Yu, Jiyang Chen, Jintao Ning, Yida Yang* and Hongyu Jia*

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Received: February 10, 2026 | **Revised:** March 24, 2026 | **Accepted:** April 13, 2026 | **Published online:** April 28, 2026

Abstract

Chronic hepatitis B (CHB) remains a major global public health challenge. Current therapies based on nucleos(t)ide analogues and interferon mainly achieve long-term viral suppression, whereas only a small proportion of patients attain a functional cure, defined as sustained hepatitis B surface antigen loss with hepatitis B virus (HBV) DNA below the limit of quantification for at least 24 weeks after treatment discontinuation, with or without anti-HBs seroconversion. Emerging evidence from the gut–liver axis indicates that gut microbiota–derived metabolites, particularly short-chain fatty acids (SCFAs) and bile acids (BAs), modulate the HBV life cycle and immune regulation in CHB, thereby offering therapeutic targets to overcome immune tolerance. This review summarizes the biological characteristics of SCFAs and BAs and their mechanistic roles across different stages of HBV infection, with emphasis on translational relevance. *In vitro* and animal studies suggest that butyrate and related SCFAs suppress HBV gene expression by inhibiting histone deacetylases and remodeling covalently closed circular DNA minichromatin. SCFAs may also enhance antiviral immunity, although they may reinforce immune tolerance in certain contexts. For BAs, the farnesoid X receptor, Takeda G protein–coupled receptor 5, and the HBV entry receptor sodium taurocholate cotransporting polypeptide form a key signaling hub with dual effects on viral replication and host responses. Early-phase studies suggest that farnesoid X receptor agonists, pegylated interferon-α, or nucleos(t)ide analogues are associated with hepatitis B surface antigen reductions, though larger trials are needed. This review proposes biomarker-guided stratification and multi-target combination strategies to improve functional cure rates in CHB.

Keywords: Chronic hepatitis B; CHB; Gut–liver axis; Short-chain fatty acids; SCFAs; Bile acids; Functional cure; Farnesoid X receptor; FXR; Sodium taurocholate cotransporting polypeptide; NTCP; Takeda G protein–coupled receptor 5; TGR5.

***Correspondence to:** Hongyu Jia and Yida Yang, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003, China. ORCID: https://orcid.org/0000-0002-9673-0969 (YY). Tel: +86-571-87236579, Fax: +86-571-87236755, E-mail: jiahongyu@zju.edu.cn (HJ) and yidayang65@zju.edu.cn (YY).

Citation of this article: Sun S, Yang S, Yu Y, Chen J, Ning J, Yang Y, *et al*. Short-chain Fatty Acids and Bile Acids Signaling in Chronic Hepatitis B. J Clin Transl Hepatol 2026. doi: 10.14218/JCTH.2026.00118.

Introduction

Chronic hepatitis B (CHB) is a major global public health challenge.[1] According to the 2022 World Health Organization report, an estimated 254 million people worldwide are living with hepatitis B virus (HBV) infection, with approximately 1.2 million new CHB cases each year. CHB-related cirrhosis and hepatocellular carcinoma account for nearly 1.1 million deaths annually.[2] A functional cure is generally defined as sustained hepatitis B surface antigen (HBsAg) loss with HBV DNA below the limit of quantification for at least 24 weeks after treatment discontinuation, with or without anti-HBs seroconversion. In contrast, reduction or silencing of covalently closed circular DNA (cccDNA) is more appropriately regarded as a mechanistic or virological research endpoint rather than part of the clinical definition of functional cure.[3–5]

Current first-line therapies, nucleos(t)ide analogues (NAs) and pegylated interferon-α (PegIFN-α), can effectively suppress HBV replication and reduce the risks of cirrhosis and hepatocellular carcinoma. However, they rarely achieve a functional cure.[6,7] Clinical studies have shown that among CHB patients receiving long-term NA therapy, the HBsAg clearance rate over 2–7 years is only approximately 1.4%–5.1%, whereas a single course of PegIFN-α results in HBsAg clearance in about 2.1%–20% of patients.[8] As a result, most patients require prolonged or even lifelong therapy and continue to face challenges related to treatment adherence, viral resistance, and progressive liver fibrosis. These limitations underscore the need to identify novel therapeutic targets, particularly those involving immune and metabolic regulation.[9]

The "gut–liver axis" is a bidirectional communication network linking the intestine and the liver through the portal venous system, enabling continuous exchange of nutrients, metabolites, and immune signals.[10] As the largest immune organ and microbial reservoir in the body, the gut plays a central role in maintaining the balance between hepatic immune tolerance and inflammation.[11] Increasing evidence

suggests that CHB progression is closely associated with gut microbiota dysbiosis. Patients with CHB often exhibit reduced gut microbial diversity, compositional alterations, and impaired intestinal barrier function, which facilitate the translocation of bacterial products (e.g., lipopolysaccharide) into the portal circulation and continuously activate liver immune cells. This process may lead to persistent activation of hepatic immune cells, thereby promoting chronic inflammation and fibrosis.[12–14]

Within this bidirectional network, gut microbiota-derived metabolites function as critical signaling molecules that regulate the HBV life cycle and shape the hepatic immune microenvironment.[11] Among these metabolites, short-chain fatty acids (SCFAs) and bile acids (BAs) have received increasing attention. SCFAs are primarily generated through the fermentation of dietary fiber by commensal gut bacteria, whereas BAs are synthesized in the liver and subsequently modified by the gut microbiota into a diverse array of secondary BAs. Both groups of metabolites return to the liver through the portal vein and exert broad effects on host immunity and metabolism.[15–19] Observational studies have reported altered SCFA levels and disrupted BA profiles in CHB patients, suggesting that gut–liver metabolic dysregulation may contribute directly to CHB pathophysiology.[20–22]

Against this background, targeting the SCFA- and BA-related components of the gut–liver metabolic axis may provide a promising therapeutic perspective beyond conventional suppression of viral replication.[23] In this review, we synthesize current basic, preclinical, and early translational evidence to systematically examine the mechanisms by which SCFAs and BAs influence different stages of HBV infection. We further evaluate their potential therapeutic relevance in CHB and discuss the strength of the available evidence, current limitations, and future research directions.

SCFAs in HBV infection: Roles and mechanisms

Generation and metabolism of SCFAs

SCFAs, predominantly acetate, propionate, and butyrate, are generated in the colon through anaerobic fermentation of dietary fiber. In this process, dietary fiber substrates are metabolized by commensal gut bacteria (mainly from the phyla *Firmicutes* and *Bacteroidetes*) into acetyl-CoA, which is subsequently converted through distinct metabolic pathways into acetate, propionate, and butyrate. Most SCFAs are rapidly absorbed by the intestinal epithelium. Among them, butyrate serves as the principal energy source for colonic epithelial cells and plays a key role in maintaining mucosal barrier integrity, whereas acetate and propionate are transported to the liver via the portal vein to participate in gluconeogenesis and lipid metabolism. Fractions that escape hepatic uptake may subsequently enter the systemic circulation and influence peripheral tissues.[19,24]

Beyond their nutritional functions, SCFAs also act as important signaling molecules. They regulate electrolyte absorption, mucosal immunity, and inflammatory responses primarily through two major mechanisms: activation of G-protein–coupled receptors (e.g., GPR41, GPR43, and GPR109A) and inhibition of histone deacetylases (HDACs).[24,25] Notably, SCFAs exhibit a marked concentration gradient from the intestinal lumen to the portal circulation and liver. For example, luminal butyrate concentrations in the colon can reach the millimolar range, whereas portal and hepatic concentrations are typically within the micromolar range.[25,26] This difference suggests that antiviral effects observed at high SCFA concentrations *in vitro* should be interpreted cautiously, particularly with respect to physiological exposure levels and *in vivo* delivery constraints. Current evidence further indicates that gut microbiota dysbiosis in CHB may alter SCFA production and composition. Consistent with this notion, several studies have reported reduced butyrate levels in the feces or blood of HBV-infected individuals, further supporting a potential link between SCFA imbalance and disease progression.[20,27]

Direct antiviral potential of SCFAs

Accumulating evidence from *in vitro* and animal studies suggests that SCFAs, particularly butyrate, may exert direct inhibitory effects on HBV replication. For example, in HBV-producing cell lines (e.g., HepG2.2.15), sodium butyrate treatment has been shown to significantly reduce HBV nucleic acid and protein levels. These antiviral effects appear to be closely linked to epigenetic regulation. As a broad-spectrum HDAC inhibitor, butyrate can modulate the epigenetic structure and transcriptional activity of the HBV cccDNA minichromosome. In addition, butyrate may inhibit deacetylases such as sirtuin 1 (SIRT1), thereby enhancing the acetylation and transcriptional activity of host restriction factors, including p53, which in turn suppresses HBV RNA, DNA, and antigen production.[28,29] Butyrate-induced histone acetylation and related epigenetic remodeling may also render host cells more permissive to antiviral responses.[30,31] Collectively, these findings provide mechanistic support for strategies aimed at increasing production or administering exogenous SCFAs to suppress HBV replication.

Nevertheless, this evidence is derived almost exclusively from *in vitro* and animal models, and robust prospective clinical data in CHB patients remain lacking. Moreover, the butyrate concentrations required to achieve anti-HBV effects *in vitro* are often in the millimolar range, whereas physiological SCFA concentrations in the portal circulation and liver are typically several orders of magnitude lower, generally within the micromolar range.[25–27,29] Therefore, clinical translation will require optimization of delivery strategies to enhance local hepatic SCFA exposure, together with well-designed clinical studies to evaluate antiviral efficacy and safety. At present, the therapeutic potential of SCFA-based interventions remains supported primarily by preclinical evidence.

Immunomodulatory functions of SCFAs: A double-edged sword

Promotion of antiviral immunity: SCFAs exert broad immunomodulatory effects and may thereby indirectly influence the course of HBV infection.[32] At moderate concentrations, SCFAs generally favor the activation of antiviral immune responses. On the one hand, SCFAs function as ligands for GPR41/43 and GPR109A, thereby modulating the activity of T cells, dendritic cells, macrophages, and natural killer (NK) cells. For example, activation of GPR43 by SCFAs promotes the differentiation of naïve T cells into regulatory T cells (Tregs), accompanied by upregulation of forkhead box P3 (FoxP3) expression. In mouse models, GPR43 signaling has been shown to increase mucosal Treg abundance and interleukin-10 (IL-10) production, thereby limiting excessive inflammation.[33] In macrophages and neutrophils, GPR43/41 also regulates the secretion of chemokines and inflammatory cytokines.[34] Meanwhile, activation of GPR109A mediates the anti-inflammatory effects of butyrate on dendritic cells and macrophages, enhancing their capacity to induce Tregs.[35]

On the other hand, SCFAs also influence the hepatic immune microenvironment. Acetate, butyrate, and related SCFAs can activate the AMP-activated protein kinase/peroxisome proliferator-activated receptor-γ (AMPK/PPARγ) signaling axis in hepatic stellate cells and inhibit transforming

growth factor-β (TGF-β)-related and nuclear factor-κB (NF-κB) inflammatory pathways, thereby attenuating fibrosis-associated inflammation.[36,37] In an HBV-susceptible mouse model, butyrate supplementation was also reported to reduce the incidence of hepatocellular carcinoma, an effect attributed to its suppression of chronic inflammation and pro-oncogenic signaling pathways, including HBx-mediated phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling.[38] Taken together, moderate enhancement of SCFA signaling may help preserve gut–liver homeostasis while enhancing host immune control of HBV infection.

Inducing immune tolerance: Potential risks: Despite their potential benefits, SCFAs may also promote immune-tolerant effects. In immune contexts characterized by low-grade inflammation or a pre-existing tolerogenic bias, SCFAs such as butyrate may reinforce peripheral tolerance and attenuate HBV-specific T-cell responses by promoting Treg differentiation and upregulating anti-inflammatory mediators, including FoxP3, IL-10, and TGF-β.[39–41] This possibility is of particular concern during the immune-tolerant phase of CHB, which is characterized by high viral loads and normal alanine aminotransferase (ALT) levels, when antiviral immune responses remain limited. *In vitro* studies indicate that SCFAs can influence the differentiation of both effector T cells and Tregs in a cytokine milieu-dependent manner. In the presence of strong co-stimulatory and pro-inflammatory signals, SCFAs tend to promote the expansion of effector subsets such as T helper 1 and 17 cells.[33,42] By contrast, under conditions of persistent antigen exposure and insufficient co-stimulation, SCFAs may preferentially amplify Treg-mediated tolerance.[43]

Accordingly, the effects of SCFA-based interventions are likely to depend on disease stage and the host immune status. During phases of active viral replication accompanied by minimal inflammation (e.g., the immune-tolerant phase), indiscriminate augmentation of SCFA levels may further skew immune responses toward tolerance, thereby hindering viral clearance. In contrast, in patients in whom viral replication is at least partially controlled but inflammation and immune-mediated liver injury are evident, the anti-inflammatory properties of SCFAs may help limit hepatic damage and improve clinical outcomes. Future studies should incorporate stratified animal models and carefully designed clinical investigations to define the net effects of SCFAs across different doses, delivery routes, and immune contexts, with the goal of balancing enhancement of antiviral immunity against maintenance of immune homeostasis and prevention of excessive inflammation.

BAs and derivatives in HBV infection: Roles and mechanisms

Physiological and metabolic overview of BAs

BAs are steroid metabolites generated through the hepatic conversion of cholesterol. Primary BAs are synthesized in hepatocytes from cholesterol via the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1), after which they are conjugated with glycine or taurine and stored in the gallbladder. Following food intake, bile is released into the intestine, where most primary BAs are actively reabsorbed in the terminal ileum and returned to the liver through the portal circulation, thereby completing the enterohepatic cycle.[44,45] A small proportion of primary BAs escapes and reaches the colon, where microbiota enzymes (e.g., bile salt hydrolases and 7α-dehydroxylases) deconjugate and convert them into a variety of secondary BAs, such as deoxycholic acid and lithocholic acid (LCA). Accordingly, the composition of the gut microbiota has a major influence on the BA pool. For example, 7α-dehydroxylating bacteria, particularly members of the order Clostridiales, can substantially affect LCA production.[46–48]

Beyond their classical role in dietary lipid digestion and absorption, BAs also function as signaling molecules by engaging specific host receptors that regulate metabolic and immune processes. The two principal BA receptors are the nuclear farnesoid X receptor (FXR) and the membrane G-protein–coupled BA receptor 1 (TGR5, also known as GPBAR1).[49] Different BA species display distinct receptor affinities. Hydrophilic conjugated primary BAs (e.g., taurochenodeoxycholic acid) are potent FXR agonists, whereas some hydrophobic secondary BAs (e.g., LCA) preferentially activate TGR5 signaling.[50] FXR is highly expressed in both the liver and intestine. Upon ligand binding, for example by the endogenous BA chenodeoxycholic acid, FXR initiates a transcriptional program that includes induction of small heterodimer partner (SHP, encoded by NR0B2) and fibroblast growth factor 19 (FGF19; FGF15 in mice). This feedback pathway suppresses CYP7A1 expression, thereby limiting BA synthesis, while also upregulating the bile salt export pump and the basolateral transporters organic solute transporter α/β to promote BA efflux from hepatocytes and transport from portal blood, thus maintaining BA homeostasis.[51] In contrast, TGR5 is broadly expressed in hepatic non-parenchymal cells and immune cells. Its activation increases intracellular cyclic adenosine monophosphate (cAMP), promotes anti-inflammatory signaling such as IL-10 production, and modulates energy expenditure and glucose homeostasis.[52,53]

Interactions between BA receptor pathways and HBV infection

FXR: A hijacked "double-edged sword": BA metabolism and the HBV life cycle intersect at multiple levels, with FXR emerging as a key regulator in HBV transcription. Studies have identified FXR response elements within the HBV cccDNA minichromosome. Under physiological conditions, activation of FXR by endogenous BAs enables FXR to bind HBV promoters and enhancer regions, thereby enhancing HBV mRNA transcription and antigen production.[54,55] In HBV-infected cell models, exposure to exogenous BAs that activate FXR has been shown to increase levels of HBV pregenomic RNA (pgRNA) and core protein, further supporting the notion that FXR can function as a proviral host factor in HBV infection.[56] Conversely, pharmacological inhibition or genetic ablation of FXR reduces HBV gene expression and replication. For example, in FXRα-knockout mouse hepatocyte models, HBsAg secretion and cccDNA levels are markedly reduced, suggesting that FXR inhibition may contribute to suppression of HBV replication.[55]

Interestingly, sustained and high-intensity pharmacological activation of FXR may produce the opposite effect. In an HBV-infected cell model, Radreau *et al*. (2016) reported that prolonged high-dose FXR activation triggered a negative-feedback response characterized by marked downregulation of cellular FXR protein levels, accompanied by significant reductions in HBV pgRNA, cccDNA copy number, and HBsAg/hepatitis B e antigen (HBeAg) secretion. This phenomenon may reflect excessive activation of FXR leading to overexpression of downstream repressors such as SHP, or alternatively, FXR conformational changes that alter its interaction with the HBV genome.[57] In addition, FXR activation can downregulate the hepatocyte BA transporter sodium taurocholate cotransporting polypeptide (NTCP), which also serves as the HBV entry receptor, thereby potentially reducing susceptibility to de novo infection.[58] Taken together, these findings indicate that, depending on the pattern and intensity of

BA or pharmacological stimulation, FXR may either be "hijacked" by HBV to support replication or be reprogrammed toward an antiviral state, making it a prototypical double-edged regulator in HBV infection.

This context-dependent duality provides the mechanistic basis for considering FXR a potential therapeutic target, whether through precisely designed agonists, antagonists, or temporally controlled activation strategies. At the same time, it highlights the need for caution in clinical manipulation of FXR, as inappropriate timing, intensity, or duration of activation could inadvertently enhance rather than suppress HBV replication. Further studies in humanized HBV infection models, together with well-designed clinical investigations, are needed to clarify the dynamic interplay between FXR signaling and HBV under different biological and therapeutic conditions.

TGR5 and immunometabolism: In contrast to FXR, TGR5 functions primarily as a regulator of host inflammation and metabolism. TGR5 is predominantly expressed in Kupffer cells, cholangiocytes, intestinal epithelial cells, and brown adipose tissue.[59] In the context of HBV infection, there is currently no evidence that TGR5 activation directly modulates viral replication. However, TGR5 signaling can influence the hepatic immune microenvironment. Specifically, activation of TGR5 stimulates the cAMP–protein kinase A pathway, which suppresses NF-κB activity and prompts Kupffer cells to secrete higher levels of IL-10 and other anti-inflammatory cytokines, thereby reducing the production of pro-inflammatory mediators.[60,61] In models of cholestatic and metabolic liver diseases, TGR5 activation has been shown to alleviate inflammatory injury in the bile ducts and parenchyma.[62]

Although TGR5-specific agonists have not yet been evaluated in CHB, one representative compound is INT-767, a dual FXR/TGR5 agonist that has demonstrated marked anti-inflammatory and metabolic regulatory effects in animal models of nonalcoholic steatohepatitis.[63,64] Notably, recent research has shown that INT-767 can bind directly to the HBV envelope protein preS1, thereby blocking its interaction with NTCP and inhibiting HBV entry into hepatocytes.[65] This observation suggests that certain BA analogues may possess both immunometabolic regulatory activity and direct antiviral potential.

NTCP: An intersection between viral entry and BA transport: NTCP is the major BA uptake transporter located on the basolateral membrane of hepatocytes and also serves as the essential receptor for HBV entry.[66,67] The identification of NTCP as an HBV receptor established a direct mechanistic link between HBV infection and BA metabolism. HBV uses its preS1 domain to bind NTCP, thereby competitively interfering with its physiological role in BA uptake. This interaction may contribute to intrahepatic BA accumulation and compensatory alterations in BA synthesis. For example, in HBV-infected humanized mouse models, hepatic activity of CYP7A1, the rate-limiting enzyme in BA synthesis, is significantly increased, whereas the FXR–SHP feedback pathway is suppressed, consistent with disruption of the normal feedback regulation of BA homeostasis by HBV. In parallel, HBV infection and the associated liver injury may downregulate NTCP expression, further impairing BA clearance. Together, these effects help explain the elevated serum BA levels observed in patients with CHB and HBV-related cirrhosis.[68]

Because NTCP functions both as the gateway for HBV entry and as a key regulator of BA transport, it represents an attractive therapeutic target. A phase III clinical trial of an NTCP competitive inhibitor (Bulevirtide) has shown that blockade of NTCP can effectively prevent viral entry in patients with HBV/hepatitis D virus coinfection.[69] However, therapies targeting NTCP are also likely to perturb BA metabolism and may increase the risk of cholestasis injury. Therefore, BA-related strategies for CHB should carefully balance antiviral efficacy against preservation of BA homeostasis in order to minimize the risk of treatment-related cholestatic liver injury.

Overall, HBV infection not only disrupts BA synthesis, transport, and signaling pathways, but BAs and their receptors may also exert antiviral effects under specific conditions. A central challenge for future therapeutic development will be to determine how FXR, TGR5, and NTCP pathways act according disease stage and biological context.

SCFA-BA pathway synergies and therapeutic strategies

Synergy at the level of gut microbial metabolism

A close bidirectional relationship exists among the gut microbiota, SCFAs, and BAs, and this interplay may collectively influence the course of CHB. On one hand, alterations in BA composition can reshape the ecological niche of SCFA-producing bacteria. BAs, particularly conjugated primary BAs, possess antimicrobial activity and can inhibit certain Gram-positive anaerobes. In patients with CHB, especially those with liver dysfunction associated with increased intraintestinal BA accumulation, excessive BA exposure may suppress butyrate-producing bacteria and further reduce SCFA levels.[70–72] As disease progresses, key butyrate-producing genera such as *Faecalibacterium* and *Butyrivibrio* decline markedly during advanced fibrosis and cirrhosis, and these changes correlate with the severity of inflammation and fibrosis.[14,73] Meanwhile, some anaerobic taxa (e.g., *Megasphaera*) have been reported to increase in abundance in patients with CHB and elevated ALT levels, with their abundance showing a positive correlation with serum ALT.[74]

On the other hand, SCFAs may, in turn, regulate BA metabolism. Propionate, butyrate, and related SCFAs can indirectly contribute to the suppression of CYP7A1 and to negative-feedback regulation of BA synthesis by modulating the gut microbiota and the intestinal FXR–FGF19 axis.[75,76] In addition, SCFAs strengthen the intestinal barrier and reduce endotoxin translocation, which may mitigate inflammation-driven disturbances in BA metabolism.[77] In the setting of CHB, these interactions may form a self-reinforcing cycle, characterized by BA dysregulation, gut microbiota imbalance, and reduced SCFA availability, each of which may further exacerbate the others. Interrupting this cycle provides an important theoretical basis for combined metabolic and microbiota-targeted strategies.

Cross-talk between SCFA and BA receptor signaling

Within the hepatic microenvironment, SCFA- and BA-associated signaling pathways are closely interconnected and jointly influence HBV entry, viral transcription, immune regulation, and liver injury (Fig. 1). As illustrated, gut microbiota-derived SCFAs and BA metabolites are delivered to the liver through the portal circulation, where they engage distinct but functionally overlapping receptor and signaling networks.

SCFA pathway: Through HDAC inhibition and modulation of the SIRT1–p53 axis, SCFAs can directly influence the epigenetic structure of cccDNA and viral gene transcription. In parallel, via receptors GPR41/43 and GPR109A, SCFAs act on T cells, NK cells, and macrophages to enhance antiviral immunity (though in specific contexts this immune stimulation may be attenuated, as discussed earlier).

BA pathway: Through FXR binding to HBV enhancer/

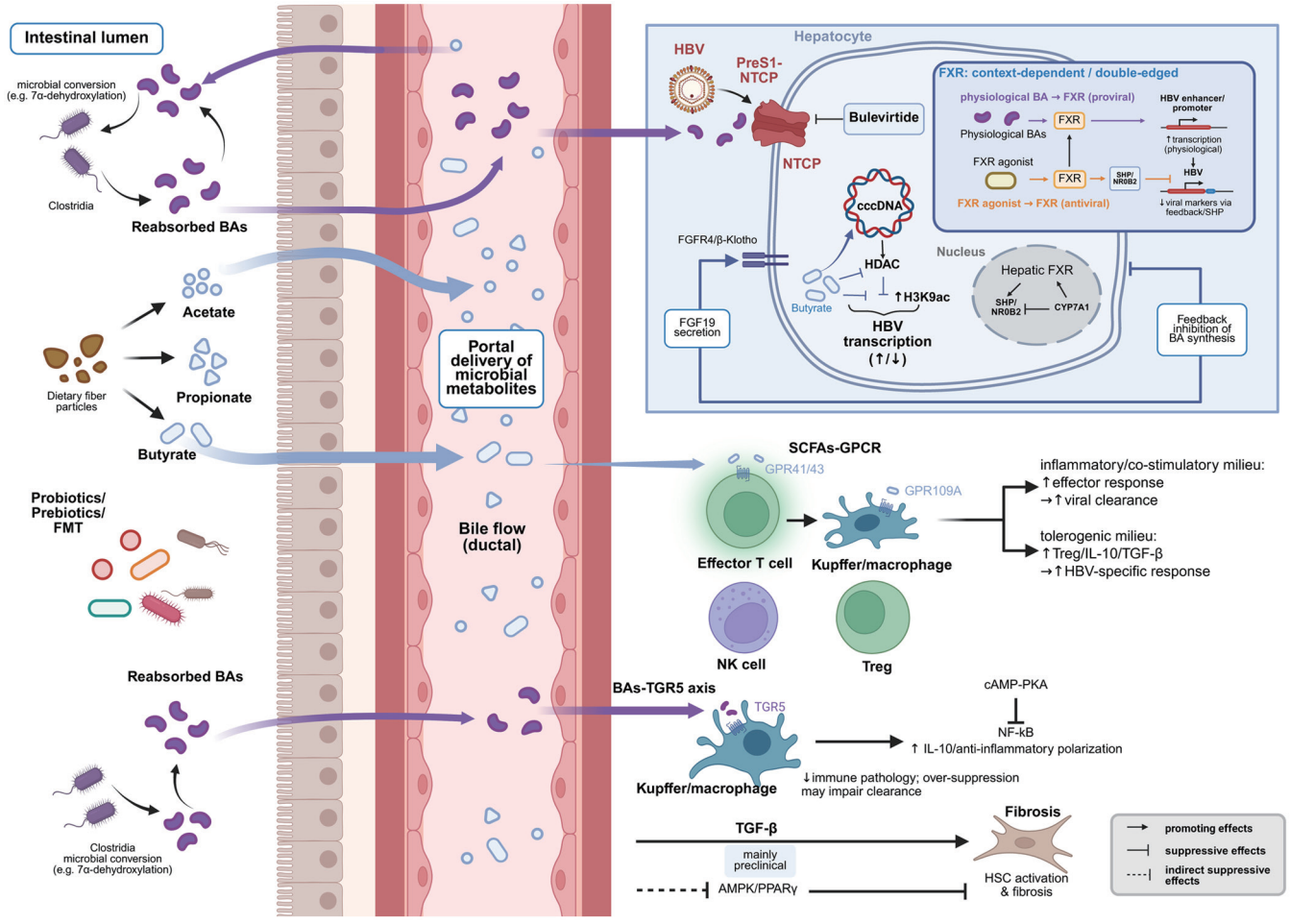

Fig. 1. SCFAs and bile acid derivatives in CHB therapy: A gut–liver axis map of mechanisms and translational targets. BAs, bile acids; SCFAs, short chain fatty acids; FMT, fecal microbiota transplantation; HBV, hepatitis B virus; CHB, chronic hepatitis B; NTCP, sodium taurocholate cotransporting polypeptide; FXR, farnesoid X receptor; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; HDAC, histone deacetylase; H3K9ac, histone H3 lysine 9 acetylation; GPCR, G protein-coupled receptor; GPR41/43, G protein-coupled receptor 41/43; GPR109A, G protein-coupled receptor 109A; TGR5, Takeda G protein-coupled receptor 5; Treg, regulatory T cell; NK cell, natural killer cell; NF-κB, nuclear factor kappa B; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; TGF-β, transforming growth factor beta; AMPK, AMP-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor gamma; HSC, hepatic stellate cell; SHP, small heterodimer partner; CYP7A1, cholesterol 7 alpha-hydroxylase; ↑, increased; ↓, decreased. Created with BioRender.com.

promoter regions, BAs can modulate viral transcription. Through regulation of NTCP, they can influence HBV hepatocyte entry. Via TGR5–cAMP–PKA signaling in macrophages, BAs affect macrophage polarization and inflammatory responses—potentially reducing immune-mediated liver damage, but if inflammation is overly suppressed, it may hinder viral clearance.

Taken together, these findings indicate that SCFA and BA signaling pathways converge on a shared immune-metabolic framework that shapes the balance among antiviral activity, inflammatory injury, and tissue repair in CHB. Accordingly, an effective therapeutic strategy may need to integrate the beneficial components of both pathways. SCFA-based interventions may help restore gut–liver metabolic homeostasis and improve HBV-specific immune function, FXR/TGR5-targeted modulators may help rebalance BA signaling and inflammatory responses, and NTCP inhibitors may block de novo viral entry. By combining direct antiviral approaches with correction of immune-metabolic dysregulation, such multi-target strategies may offer greater potential to improve disease control and promote functional cure in CHB.

Therapeutic strategies centered on SCFA and BA pathways

SCFA supplementation and microbiota interventions: Given the frequent depletion of SCFA-producing bacteria in CHB, therapeutic strategies aimed at increasing SCFA availability, either directly or indirectly, represent a biologically plausible therapeutic approach. Direct supplementation includes oral or targeted delivery of SCFA formulations, such as butyrate salts. Current experience with these approaches is derived largely from other disease settings, particularly inflammatory bowel disease.[78] In HBV transgenic mouse models, SCFA-enriched diets have been reported to reduce hepatic inflammation and tumor incidence, although the translatability of dosing regimens and the long-term safety of this strategy remain uncertain.[38]

Indirect approaches seek to restore endogenous SCFA production through modulation of the gut microbiota. These strategies include prebiotics, such as fermentable fibers; probiotics containing SCFA- or butyrate-producing bacterial strains; and fecal microbiota transplantation (FMT), all of which are intended to replenish beneficial microbial popu-

lations, strengthen intestinal barrier integrity, and reduce endotoxemia.[79–81] In the context of CHB, such interventions may have the potential to enhance antiviral immune responses while simultaneously mitigating inflammatory liver injury. However, caution is warranted because these approaches may, under certain immunological conditions, also skew host responses toward immune tolerance, and live microbial interventions may carry a risk of infection or other safety concerns.[82,83] To date, randomized controlled trials (RCTs) evaluating SCFA supplementation or broad microbiota-directed interventions in patients with CHB remain extremely limited, and these strategies are still largely at a conceptual or early translational stage.[27]

FXR agonists and BA modulators: Given the dual involvement of FXR in HBV replication and BA homeostasis, several selective FXR agonists (e.g., vonafexor, ASC42) have entered clinical evaluation for CHB.[84] Early studies suggest that, in patients with HBeAg-negative CHB, combination therapy with an FXR agonist and PegIFN-α may induce a greater decline in HBsAg levels than PegIFN-α alone, thereby providing preliminary clinical support for FXR-targeted therapy as a potential enhancer of antiviral and immunomodulatory treatment.[56] Novel agents such as ASC42 are also being investigated in combination with NAs and PegIFN-α, with proposed mechanisms including suppression of cccDNA transcription and restoration of BA homeostasis.[85,86] Nevertheless, recent developments suggest that progress in this field remains limited and somewhat heterogeneous. Although vonafexor continues to support the mechanistic and translational rationale for FXR-targeted strategies, robust new late-stage clinical evidence in CHB is still lacking, and recent studies have provided mainly additional experimental and mechanistic support rather than definitive clinical advances.[87,88]

By contrast, traditional BA-based agents such as ursodeoxycholic acid appear to have little direct effect on HBV replication. Current international guidelines do not recommend ursodeoxycholic acid as an antiviral therapy for CHB and instead restrict its use to the adjunctive management of cholestasis or other specific indications.[4]

Looking ahead, several therapeutic directions warrant further investigation.

One promising approach is the development of intestine-targeted FXR agonists designed to preferentially modulate the intestinal FXR–FGF19 axis, thereby reducing systemic exposure and potential adverse effects. A second strategy is the selective short-term use of FXR antagonists in carefully defined patient subgroups or disease phases to counterbalance the proviral effects of FXR. A third direction involves dual FXR/TGR5 modulators, including BA-derived compounds capable of activating TGR5 while fine-tuning FXR signaling, with the aim of harnessing metabolic and anti-inflammatory benefits while also influencing HBV infection-related pathways.[89,90]

Metabolic–immune combination therapy: Synergy with existing antiviral and immunotherapeutic approaches: Ultimately, interventions targeting SCFAs or FXR/TGR5 are intended to reshape the host immune-metabolic milieu in a manner that favors immune-mediated control and clearance of HBV. Accordingly, combining metabolic interventions with existing antiviral and immunotherapeutic approaches represents one of the most promising translational directions. For example, several studies have explored the addition of probiotics or microbial metabolites to interferon-based therapy. In one report, probiotics enhanced HBV-specific interferon-γ^+ $CD4^+$ T-cell responses in patients with CHB, suggesting that microbiota-directed interventions may exert synergistic effects when combined with immunostimulatory treatment.[91] Similarly, the previously mentioned phase I study showed that an FXR agonist combined with PegIFN-α produced greater reductions in HBsAg than either agent alone.[56] Looking ahead, future therapeutic regimens may involve triple-combination strategies (e.g., an "SCFA prodrug + NA + immunotherapy"), with the goal of targeting multiple pathogenic mechanisms simultaneously.[92] In such a framework, NAs would maintain suppression of viral replication, SCFA- or BA-directed agents would help optimize the immune-metabolic microenvironment, and immunotherapy would directly enhance antiviral T- and B-cell responses, potentially overcoming the current plateau in functional cure rates.

At the same time, successful multi-target combinations will require careful attention to mechanistic compatibility among the individual components. SCFA- or BA–based interventions should not compromise the efficacy of immunotherapy, whereas excessive immune activation should not negate the metabolic or hepatoprotective benefits of these agents. Accordingly, treatment sequencing, timing, and dosing are likely to be critical determinants of efficacy. One potential strategy would be to achieve stable viral suppression first with NAs, then introduce a metabolic modulator for a defined period to reduce antigen burden and hepatic inflammation, followed by immunotherapy aimed at eliminating residual infected cells. Such combination regimens remain conceptually attractive but will require further optimization and rigorous validation in clinical trials.

Patient stratification and personalized treatment: Therapeutic strategies targeting SCFA and BA pathways are unlikely to be uniformly effective across all patients with CHB. Gut microbiota composition, metabolic profiles, and immune status vary substantially among individuals, and different disease phases, including the immune-tolerant, immune-active, inactive carrier, and reactivation phases, are characterized by distinct pathophysiological features.[4,5,93] Accordingly, biomarker-guided patient stratification will be essential to identify those most likely to benefit from these interventions. For example, in the immune-tolerant phase, which is characterized by high HBV DNA levels and normal ALT, interventions with predominantly anti-inflammatory or tolerogenic effects should be applied cautiously, as the primary therapeutic goal in this setting is to overcome immune tolerance and restore antiviral immune responsiveness. In the immune-active phase, where elevated ALT levels and active inflammation or fibrosis are evident, SCFA- or TGR5-directed interventions may be considered on a background of antiviral therapy to reduce immune-mediated liver injury without compromising immune clearance. In addition, in patients with severe gut dysbiosis, such as marked depletion of butyrate-producing bacteria or profoundly disturbed BA profiles, priority may be given to microbiota-directed approaches, including probiotics or FMT, or to FXR/TGR5-targeted strategies aimed at correcting these specific metabolic disturbances.

Emerging multi-omics approaches, including metagenomics, metabolomics, and immunomics, are likely to facilitate the development of integrated biomarker panels encompassing the gut microbiota–SCFA–BA–immune axis.[94,95] Such biomarker frameworks may not only individualize therapeutic strategies but also provide tools for monitoring treatment responses, thereby representing an important direction for future research and clinical translation in this field.

Limitations and risks

Despite the strong theoretical rationale for targeting SCFA and BA pathways in CHB, several important limitations and

potential risks must be carefully considered before these strategies can be translated into clinical implementation.

Low overall level of evidence

At present, the evidence supporting the anti-HBV effects of SCFAs and BAs remains derived predominantly from preclinical studies, including *in vitro* experiments and animal models. Clinical studies are limited in number and are generally characterized by small sample sizes and short follow-up durations. Another important limitation is the lack of standardized methodologies for measuring SCFAs and BAs across studies. Variability in specimen type, sampling conditions, analytical platforms, and normalization strategies substantially hampers cross-study comparability and poses a major challenge for biomarker development. In addition, clinical trials of FXR agonists have thus far been largely confined to early-phase studies, with limited standardization of endpoints and insufficient long-term outcome data. RCTs evaluating SCFA supplementation, probiotics, or FMT in CHB remain extremely scarce. Therefore, before these approaches can be incorporated into clinical practice guidelines, more rigorous RCTs and well-designed longitudinal cohort studies will be required to strengthen the overall level of evidence.

Gaps in dosing and exposure

The effective concentrations of SCFAs, BAs, or related analogues observed *in vitro* often substantially exceed their physiological levels in humans. In addition, experimental exposure durations and routes of administration may not adequately reflect clinical conditions. Species-specific differences in BA composition and gut microbiota further limit the direct extrapolation of findings from rodent models to human disease.[25–27,29] Future research should therefore integrate pharmacokinetic and pharmacodynamic investigations to support the development of liver-targeted or gut-targeted delivery systems (e.g., microencapsulation, prodrugs, nanoparticles) that can achieve sufficient local concentrations while minimizing systemic adverse effects.

Drug–drug interactions and combination therapy safety

FXR agonists, BA modulators, and live biotherapeutic products, including probiotics, may interact with existing antiviral agents or with other medications commonly used by patients with CHB. For example, certain FXR agonists may influence hepatic transport activity and thereby alter exposure to statins or other concomitant medications.[96,97] Probiotics, through modification of the intestinal microenvironment, may also affect the absorption of orally administered drugs.[98] Accordingly, when designing combination regimens, potential drug–drug interactions should be systematically evaluated, particularly in older patients receiving multiple medications and in those with impaired liver function.

Adverse effects and long-term safety

A range of adverse effects and safety concerns should be considered for these emerging therapeutic approaches. For FXR agonists, reported adverse effects include pruritus and dyslipidemia, and excessive modulation of BA signaling may lead to cholestatic liver injury or worsening hepatic dysfunction if not carefully monitored.[99] SCFA supplementation, whether administered orally or rectally, may cause gastrointestinal adverse effects such as bloating and diarrhea. In addition, excessive dosing or inappropriate use of SCFAs may skew host immune responses toward tolerance and potentially attenuate antiviral immunity.[100] Microbiota-directed interventions, including probiotics and FMT, may also carry infectious risks, particularly in immunocompromised patients or those with advanced liver disease, in whom bacteremia and other serious infections are potential concerns.[83] With respect to TGR5, although its activation has anti-inflammatory properties, chronic or excessive stimulation could theoretically affect cholangiocyte function or influence carcinogenic processes, although these long-term effects remain insufficiently defined.[97]

Accordingly, comprehensive safety assessments and long-term surveillance will be essential as these herapeutic strategies advance through clinical development.

Uncertain long-term outcomes and viral adaptation

Metabolic–immune combination therapies may impose novel selective pressures on HBV. At present, it remains unclear whether such interventions could contribute to viral adaptation, altered viral fitness, or resistance-related phenomena. Moreover, even if HBsAg clearance is achieved, it is unclear whether therapy-induced changes in the gut microbiota and host metabolic state will be durable or reversible after treatment withdrawal, and whether any residual virus may subsequently reactivate. These uncertainties underscore the need for prolonged follow-up and real-world studies to evaluate the durability of treatment responses and to monitor for delayed or late-emerging adverse outcomes.

Conclusion and outlook

As our understanding of the mechanisms underlying persistent HBV infection continues to evolve, the gut–liver axis has emerged as an important regulatory framework in CHB. SCFAs and BAs, as products of the dynamic metabolic interplay between the gut microbiota and the liver, appear to influence multiple stages of the HBV life cycle as well as host immune and metabolic responses. The evidence reviewed in this article suggests that targeting SCFA and BA pathways may provide novel perspectives and potential therapeutic opportunities to overcome the current limitations of CHB treatment. On the one hand, SCFAs may exert dual effects on HBV through epigenetic suppression of viral transcription and modulation of antiviral immunity. On the other hand, rational targeting of FXR-, TGR5-, and NTCP-mediated BA pathways may help balance viral suppression, inflammatory control, and blockade of viral entry. Moreover, these two metabolic axes appear to be complementary at both the immunological and metabolic levels, thereby providing a conceptual basis for multi-target combination strategies aimed at functional cure.

Nevertheless, this field remains at an early stage, and most conclusions are derived from preclinical studies with limited clinical validation. Future research should focus on several key priorities.

First, multi-omics profiling approaches, including metagenomics, metabolomics, and immunomics, should be used to better characterize the gut microbiota–SCFA–BA–immune axis in patients with CHB and to identify biomarker combinations that may guide treatment selection and response monitoring. Second, more humanized and physiologically relevant experimental models are needed to evaluate the antiviral and immunomodulatory effects of SCFA- and BA-targeted interventions across different doses and exposure patterns, with the aim of defining safe and effective therapeutic windows. Third, rigorous RCTs should be designed, initially on a background of stable NA therapies, to assess the incremental value of SCFA supplementation, microbiota-directed interventions, and FXR/TGR5

modulation. Relevant endpoints may include HBsAg loss, changes in cccDNA activity or burden, and improvement in liver histology. Fourth, next-generation therapeutics and delivery platforms, such as liver- or gut-targeted SCFA prodrugs, selective FXR modulators, and bifunctional FXR/TGR5-active compounds, warrant further development to maximize efficacy while minimizing adverse effects. Finally, long-term follow-up and real-world studies will be essential to determine how metabolic–immune combination strategies influence fibrosis regression, hepatocellular carcinoma risk, and patient quality of life over time.

In summary, targeting SCFA and BA pathways represents a promising frontier in CHB therapy. However, translation of these mechanistic insights into effective clinical strategies will require substantial further investigation. Through rigorous, evidence-based research and careful clinical development, metabolic–immune combination strategies may ultimately improve functional cure rates in CHB and provide meaningful long-term benefits for patients.

Funding

This work was supported by the National Key R&D Program of China (2022YFC2304500, 2023YFC2306800), the Ningbo Science and Technology 2035 Plan Project (Grant No. 2025Z186), the Key Project of the Beilun District Health Science and Technology Plan (Project ID 2024BLWSZD001), and the Ningbo Natural Science Foundation (Project ID 2023J195).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception (HJ), literature search, drafting of the manuscript, preparation for figures and tables (SS, SY), preparation of the article, and revision of the manuscript (SS, SY, YhY, JC, JN, YdY, HJ). All authors have read and approved the final version and publication of the manuscript.

References

[1] Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet 2023;401 (10381):1039–1052. doi:10.1016/S0140-6736(22)01468-4, PMID:36774930.
[2] Hepatitis B [Internet]. [cited 2025 May 4]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
[3] Ghany MG, Buti M, Lampertico P, Lee HM, 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference Faculty. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. J Hepatol 2023;79(5):1254–1269. doi:10.1016/j.jhep.2023.06.002, PMID:37377088.
[4] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–398. doi:10.1016/j.jhep.2017.03.021, PMID:28427875.
[5] Wu D, Kao JH, Piratvisuth T, Wang X, Kennedy PTF, Otsuka M, *et al*. Update on the treatment navigation for functional cure of chronic hepatitis B: Expert consensus 2.0. Clin Mol Hepatol 2025;31(Suppl):S134–S164. doi:10.3350/cmh.2024.0780, PMID:39838828.
[6] Wang X, Liu X, Dang Z, Yu L, Jiang Y, Wang X, *et al*. Nucleos(t)ide Analogues for Reducing Hepatocellular Carcinoma in Chronic Hepatitis B Patients: A Systematic Review and Meta-Analysis. Gut Liver 2020;14(2):232–247. doi:10.5009/gnl18546, PMID:31158948.
[7] Wu WJ, Liu WJ, Lin CL, Liu CJ, Huang YW, Hu JT, *et al*. Impact of tenofovir vs. entecavir treatment on progression of chronic hepatitis B: A nationwide cohort study. JHEP Rep 2025;7(10):101511. doi:10.1016/j.jhepr.2025.101511, PMID:40919078.
[8] Song A, Lin X, Chen X. Functional cure for chronic hepatitis B: accessibility, durability, and prognosis. Virol J 2021;18(1):114. doi:10.1186/s12985-021-01589-x, PMID:34082765.
[9] Block PD, Lim JK. Unmet needs in the clinical management of chronic hepatitis B infection. J Formos Med Assoc 2025;124(6):502–507. doi:10.1016/j.jfma.2024.08.020, PMID:39155176.
[10] Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. Cell Metab 2022;34(11):1700–1718. doi:10.1016/j.cmet.2022.09.017, PMID:36208625.
[11] Wang R, Tang R, Li B, Ma X, Schnabl B, Tilg H. Gut microbiome, liver immunology, and liver diseases. Cell Mol Immunol 2021;18(1):4–17. doi:10.1038/s41423-020-00592-6, PMID:33318628.
[12] Zhou W, Luo J, Xie X, Yang S, Zhu D, Huang H, *et al*. Gut Microbiota Dysbiosis Strengthens Kupffer Cell-mediated Hepatitis B Virus Persistence through Inducing Endotoxemia in Mice. J Clin Transl Hepatol 2022;10(1):17–25. doi:10.14218/JCTH.2020.00161, PMID:35233369.
[13] Płóciennikowska A, Hromada-Judycka A, Borzęcka K, Kwiatkowska K. Co-operation of TLR4 and raft proteins in LPS-induced pro-inflammatory signaling. Cell Mol Life Sci 2015;72(3):557–581. doi:10.1007/s00018-014-1762-5, PMID:25332099.
[14] Wang K, Zhang Z, Mo ZS, Yang XH, Lin BL, Peng L, *et al*. Gut microbiota as prognosis markers for patients with HBV-related acute-on-chronic liver failure. Gut Microbes 2021;13(1):1–15. doi:10.1080/19490976.2021.1921925, PMID:34006193.
[15] Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol 2014;30(3):332–338. doi:10.1097/MOG.0000000000000057, PMID:24625896.
[16] Sabahat SE, Saqib M, Talib M, Shaikh TG, Khan T, Kailash SJ. Bile acid modulation by gut microbiota: a bridge to understanding cognitive health. Ann Med Surg (Lond) 2024;86(9):5410–5415. doi:10.1097/MS9.0000000000002433, PMID:39239005.
[17] Fleishman JS, Kumar S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. Signal Transduct Target Ther 2024;9(1):97. doi:10.1038/s41392-024-01811-6, PMID:38664391.
[18] Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol 2024;24(8):577–595. doi:10.1038/s41577-024-01014-8, PMID:38565643.
[19] Facchin S, Bertin L, Bonazzi E, Lorenzon G, De Barba C, Barberio B, *et al*. Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implications. Life (Basel) 2024;14(5):559. doi:10.3390/life14050559, PMID:38792581.
[20] Zhang W, Wu Y, Cheng M, Wei H, Sun R, Peng H, *et al*. Chronic hepatitis B virus infection imbalances short-chain fatty acids and amino acids in the liver and gut via microbiota modulation. Gut Pathog 2025;17(1):18. doi:10.1186/s13099-025-00695-3, PMID:40188120.
[21] Wang J, Xu H, Liu Z, Cao Y, Chen S, Hou R, *et al*. Bile acid-microbiota crosstalk in hepatitis B virus infection. J Gastroenterol Hepatol 2024;39(8):1509–1516. doi:10.1111/jgh.16604, PMID:38721685.
[22] Sun Z, Huang C, Shi Y, Wang R, Fan J, Yu Y, *et al*. Distinct Bile Acid Profiles in Patients With Chronic Hepatitis B Virus Infection Reveal Metabolic Interplay Between Host, Virus and Gut Microbiome. Front Med (Lausanne) 2021;8:708495. doi:10.3389/fmed.2021.708495, PMID:34671614.
[23] Faure-Dupuy S, Baumert TF. Targeting immuno-metabolism and anti-viral immune responses in chronic hepatitis B. Hepatol Int 2023;17(5):1075–1078. doi:10.1007/s12072-023-10546-5, PMID:37369910.
[24] Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell 2016;165(6):1332–1345. doi:10.1016/j.cell.2016.05.041, PMID:27259147.
[25] den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013;54(9):2325–2340. doi:10.1194/jlr.R036012, PMID:23821742.
[26] Boets E, Gomand SV, Deroover L, Preston T, Vermeulen K, De Preter V, *et al*. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. J Physiol 2017;595(2):541–555. doi:10.1113/JP272613, PMID:27510655.
[27] Honda T, Ishigami M, Ishizu Y, Imai N, Ito T, Yamamoto K, *et al*. Gut microbes associated with functional cure of chronic hepatitis B. Hepatol Int 2025;19(3):519–528. doi:10.1007/s12072-025-10776-9, PMID:39869245.
[28] Wei ZQ, Zhang YH, Ke CZ, Chen HX, Ren P, He YL, *et al*. Curcumin inhibits hepatitis B virus infection by down-regulating cccDNA-bound histone acetylation. World J Gastroenterol 2017;23(34):6252–6260. doi:10.3748/wjg.v23.i34.6252, PMID:28974891.
[29] Pant K, Mishra AK, Pradhan SM, Nayak B, Das P, Shalimar D, *et al*. Butyrate inhibits HBV replication and HBV-induced hepatoma cell proliferation via modulating SIRT-1/Ac-p53 regulatory axis. Mol Carcinog 2019;58(4):524–532. doi:10.1002/mc.22946, PMID:30501014.
[30] Watt R, Parkin K, Martino D. The Potential Effects of Short-Chain Fatty Acids on the Epigenetic Regulation of Innate Immune Memory. Challenges 2020;11(2):25. doi:10.3390/challe11020025.
[31] Xu Z, Wang T, Wang Y, Li Y, Sun Y, Qiu HJ. Short-chain fatty acids: key antiviral mediators of gut microbiota. Front Immunol 2025;16:1614879. doi:10.3389/fimmu.2025.1614879, PMID:40787446.
[32] Kim CH. Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. Cell Mol Immunol 2023;20(4):341–350. doi:10.1038/s41423-023-00987-1, PMID:36854801.
[33] Park J, Kim M, Kang SG, Jannasch AH, Cooper B, Patterson J, *et al*. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. Mucosal Immunol 2015;8(1):80–93. doi:10.1038/mi.2014.44, PMID:24917457.
[34] Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, *et al*. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor

GPR43. Nature 2009;461(7268):1282–1286. doi:10.1038/nature08530, PMID:19865172.
[35] Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, *et al*. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity 2014;40(1):128–139. doi:10.1016/j.immuni.2013.12.007, PMID:24412617.
[36] Li W, Deng M, Gong J, Zhang X, Ge S, Zhao L. Sodium Acetate Inhibit TGF-β1-Induced Activation of Hepatic Stellate Cells by Restoring AMPK or c-Jun Signaling. Front Nutr 2021;8:729583. doi:10.3389/fnut.2021.729583, PMID:34660662.
[37] Gart E, van Duyvenvoorde W, Toet K, Caspers MPM, Verschuren L, Nielsen MJ, *et al*. Butyrate Protects against Diet-Induced NASH and Liver Fibrosis and Suppresses Specific Non-Canonical TGF-β Signaling Pathways in Human Hepatic Stellate Cells. Biomedicines 2021;9(12):1954. doi:10.3390/biomedicines9121954, PMID:34944770.
[38] McBrearty N, Arzumanyan A, Bichenkov E, Merali S, Merali C, Feitelson M. Short chain fatty acids delay the development of hepatocellular carcinoma in HBx transgenic mice. Neoplasia 2021;23(5):529–538. doi:10.1016/j.neo.2021.04.004, PMID:33945993.
[39] Kilany MM, Sonneveld MJ, Feld JJ, Janssen HLA. Management of immune-tolerant chronic hepatitis B. Hepatology 2025. doi:10.1097/HEP.0000000000001407, PMID:40392125.
[40] Hu M, Alashkar Alhamwe B, Santner-Nanan B, Miethe S, Harb H, Renz H, *et al*. Short-Chain Fatty Acids Augment Differentiation and Function of Human Induced Regulatory T Cells. Int J Mol Sci 2022;23(10):5740. doi:10.3390/ijms23105740, PMID:35628549.
[41] Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, *et al*. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504(7480):446–450. doi:10.1038/nature12721, PMID:24226770.
[42] Sun M, Wu W, Liu Z, Cong Y. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. J Gastroenterol 2017;52(1):1–8. doi:10.1007/s00535-016-1242-9, PMID:27448578.
[43] Rangan P, Mondino A. Microbial short-chain fatty acids: a strategy to tune adoptive T cell therapy. J Immunother Cancer 2022;10(7):e004147. doi:10.1136/jitc-2021-004147, PMID:35882448.
[44] Chiang JYL, Ferrell JM. Bile Acid Biology, Pathophysiology, and Therapeutics. Clin Liver Dis (Hoboken) 2020;15(3):91–94. doi:10.1002/cld.861, PMID:32257118.
[45] Jones H, Alpini G, Francis H. Bile acid signaling and biliary functions. Acta Pharm Sin B 2015;5(2):123–128. doi:10.1016/j.apsb.2015.01.009, PMID:26579437.
[46] Ridlon JM, Devendran S, Alves JM, Doden H, Wolf PG, Pereira GV, *et al*. The 'in vivo lifestyle' of bile acid 7α-dehydroxylating bacteria: comparative genomics, metatranscriptomic, and bile acid metabolomics analysis of a defined microbial community in gnotobiotic mice. Gut Microbes 2020;11(3):381–404. doi:10.1080/19490976.2019.1618173, PMID:31177942.
[47] Wise JL, Cummings BP. The 7-α-dehydroxylation pathway: An integral component of gut bacterial bile acid metabolism and potential therapeutic target. Front Microbiol 2022;13:1093420. doi:10.3389/fmicb.2022.1093420, PMID:36699589.
[48] Mullish BH, Allegretti JR. The contribution of bile acid metabolism to the pathogenesis of Clostridioides difficile infection. Ther Adv Gastroenterol 2021;14:17562848211017725. doi:10.1177/17562848211017725, PMID:34104212.
[49] Chiang JYL, Ferrell JM. Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy. Am J Physiol Gastrointest Liver Physiol 2020;318(3):G554–G573. doi:10.1152/ajpgi.00223.2019, PMID:31984784.
[50] Zangerolamo L, Carvalho M, Barbosa HCL. The Critical Role of the Bile Acid Receptor TGR5 in Energy Homeostasis: Insights into Physiology and Therapeutic Potential. Int J Mol Sci 2025;26(14):6547. doi:10.3390/ijms26146547, PMID:40724796.
[51] Liu J, Lu H, Lu YF, Lei X, Cui JY, Ellis E, *et al*. Potency of individual bile acids to regulate bile acid synthesis and transport genes in primary human hepatocyte cultures. Toxicol Sci 2014;141(2):538–546. doi:10.1093/toxsci/kfu151, PMID:25055961.
[52] Ye D, He J, He X. The role of bile acid receptor TGR5 in regulating inflammatory signalling. Scand J Immunol 2024;99(4):e13361. doi:10.1111/sji.13361, PMID:38307496.
[53] Wammers M, Schupp AK, Bode JG, Ehlting C, Wolf S, Deenen R, *et al*. Reprogramming of pro-inflammatory human macrophages to an anti-inflammatory phenotype by bile acids. Sci Rep 2018;8(1):255. doi:10.1038/s41598-017-18305-x, PMID:29321478.
[54] Ramière C, Scholtès C, Diaz O, Icard V, Perrin-Cocon L, Trabaud MA, *et al*. Transactivation of the hepatitis B virus core promoter by the nuclear receptor FXRalpha. J Virol 2008;82(21):10832–10840. doi:10.1128/JVI.00883-08, PMID:18768987.
[55] Mouzannar K, Fusil F, Lacombe B, Ollivier A, Ménard C, Lotteau V, *et al*. Farnesoid X receptor-α is a proviral host factor for hepatitis B virus that is inhibited by ligands in vitro and in vivo. FASEB J 2019;33(2):2472–2483. doi:10.1096/fj.201801181R, PMID:30307769.
[56] Erken R, Andre P, Roy E, Kootstra N, Barzic N, Girma H, *et al*. Farnesoid X receptor agonist for the treatment of chronic hepatitis B: A safety study. J Viral Hepat 2021;28(12):1690–1698. doi:10.1111/jvh.13608, PMID:34467593.
[57] Radreau P, Porcherot M, Ramière C, Mouzannar K, Lotteau V, André P. Reciprocal regulation of farnesoid X receptor α activity and hepatitis B virus replication in differentiated HepaRG cells and primary human hepatocytes. FASEB J 2016;30(9):3146–3154. doi:10.1096/fj.201500134, PMID:27251172.
[58] Matsubara T, Li F, Gonzalez FJ. FXR signaling in the enterohepatic system. Mol Cell Endocrinol 2013;368(1-2):17–29. doi:10.1016/j.mce.2012.05.004, PMID:22609541.
[59] Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J Hepatol 2011;54(6):1263–1272. doi:10.1016/j.jhep.2010.12.004, PMID:21145931.
[60] Guo C, Xie S, Chi Z, Zhang J, Liu Y, Zhang L, *et al*. Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome. Immunity 2016;45(4):802–816. doi:10.1016/j.immuni.2016.09.008, PMID:27692610.
[61] Yoneno K, Hisamatsu T, Shimamura K, Kamada N, Ichikawa R, Kitazume MT, *et al*. TGR5 signalling inhibits the production of pro-inflammatory cytokines by in vitro differentiated inflammatory and intestinal macrophages in Crohn's disease. Immunology 2013;139(1):19–29. doi:10.1111/imm.12045, PMID:23566200.
[62] Zhang F, Xiao X, Li Y, Wu H, Deng X, Jiang Y, *et al*. Therapeutic Opportunities of GPBAR1 in Cholestatic Diseases. Front Pharmacol 2021;12:805269. doi:10.3389/fphar.2021.805269, PMID:35095513.
[63] Wang XX, Xie C, Libby AE, Ranjit S, Levi J, Myakala K, *et al*. The role of FXR and TGR5 in reversing and preventing progression of Western diet-induced hepatic steatosis, inflammation, and fibrosis in mice. J Biol Chem 2022;298(11):102530. doi:10.1016/j.jbc.2022.102530, PMID:36209823.
[64] Hu YB, Liu XY, Zhan W. Farnesoid X receptor agonist INT-767 attenuates liver steatosis and inflammation in rat model of nonalcoholic steatohepatitis. Drug Des Devel Ther 2018;12:2213–2221. doi:10.2147/DDDT.S170518, PMID:30038487.
[65] Okumura A, Muraki Y, Arai J, Nishimura S, Inden N, Sakamoto K, *et al*. Molecular mechanisms of hepatitis B virus entry inhibition by a bile acid derivative INT-767 binding to the preS1 region. Antiviral Res 2025;240:106213. doi:10.1016/j.antiviral.2025.106213, PMID:40513783.
[66] Ni Y, Lempp FA, Mehrle S, Nkongolo S, Kaufman C, Fälth M, *et al*. Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. Gastroenterology 2014;146(4):1070–1083. doi:10.1053/j.gastro.2013.12.024, PMID:24361467.
[67] Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, *et al*. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012;1:e00049. doi:10.7554/eLife.00049, PMID:23150796.
[68] Oehler N, Volz T, Bhadra OD, Kah J, Allweiss L, Giersch K, *et al*. Binding of hepatitis B virus to its cellular receptor alters the expression profile of genes of bile acid metabolism. Hepatology 2014;60(5):1483–1493. doi:10.1002/hep.27159, PMID:24711282.
[69] Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, *et al*. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med 2023;389(1):22–32. doi:10.1056/NEJMoa2213429, PMID:37345876.
[70] Zhang YL, Li ZJ, Gou HZ, Song XJ, Zhang L. The gut microbiota-bile acid axis: A potential therapeutic target for liver fibrosis. Front Cell Infect Microbiol 2022;12:945368. doi:10.3389/fcimb.2022.945368, PMID:36189347.
[71] Lv D, Han N, Liu H, Tang H. Hepatitis B Virus-Related Liver Disease and Gut Microbiota: An Updated Review. Microorganisms 2025;13(11):2445. doi:10.3390/microorganisms13112445, PMID:41304131.
[72] Visekruna A, Luu M. The Role of Short-Chain Fatty Acids and Bile Acids in Intestinal and Liver Function, Inflammation, and Carcinogenesis. Front Cell Dev Biol 2021;9:703218. doi:10.3389/fcell.2021.703218, PMID:34381785.
[73] Zeng Y, Chen S, Fu Y, Wu W, Chen T, Chen J, *et al*. Gut microbiota dysbiosis in patients with hepatitis B virus-induced chronic liver disease covering chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. J Viral Hepat 2020;27(2):143–155. doi:10.1111/jvh.13216, PMID:31600845.
[74] Yun Y, Chang Y, Kim HN, Ryu S, Kwon MJ, Cho YK, *et al*. Alterations of the Gut Microbiome in Chronic Hepatitis B Virus Infection Associated with Alanine Aminotransferase Level. J Clin Med 2019;8(2):173. doi:10.3390/jcm8020173, PMID:30717396.
[75] Demigné C, Morand C, Levrat MA, Besson C, Moundras C, Rémésy C. Effect of propionate on fatty acid and cholesterol synthesis and on acetate metabolism in isolated rat hepatocytes. Br J Nutr 1995;74(2):209–219. doi:10.1079/bjn19950124, PMID:7547838.
[76] Lu D, Liu Y, Luo Y, Zhao J, Feng C, Xue L, *et al*. Intestinal farnesoid X receptor signaling controls hepatic fatty acid oxidation. Biochim Biophys Acta Mol Cell Biol Lipids 2022;1867(2):159089. doi:10.1016/j.bbalip.2021.159089, PMID:34856412.
[77] Wang LY, He LH, Xu LJ, Li SB. Short-chain fatty acids: bridges between diet, gut microbiota, and health. J Gastroenterol Hepatol 2024;39(9):1728–1736. doi:10.1111/jgh.16619, PMID:38780349.
[78] Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, *et al*. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. Front Immunol 2019;10:277. doi:10.3389/fimmu.2019.00277, PMID:30915065.
[79] Chauhan A, Kumar R, Sharma S, Mahanta M, Vayuuru SK, Nayak B, *et al*. Fecal Microbiota Transplantation in Hepatitis B e Antigen-Positive Chronic Hepatitis B Patients: A Pilot Study. Dig Dis Sci 2021;66(3):873–880. doi:10.1007/s10620-020-06246-x, PMID:32279172.
[80] Ren YD, Ye ZS, Yang LZ, Jin LX, Wei WJ, Deng YY, *et al*. Fecal microbiota transplantation induces hepatitis B virus e-antigen (HBeAg) clearance in patients with positive HBeAg after long-term antiviral therapy. Hepatology 2017;65(5):1765–1768. doi:10.1002/hep.29008, PMID:28027582.

[81] Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, *et al*. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology 2014;147(6):1327–37.e3. doi:10.1053/j.gastro.2014.08.031, PMID:25450083.
[82] Suk KT, Koh H. New perspective on fecal microbiota transplantation in liver diseases. J Gastroenterol Hepatol 2022;37(1):24–33. doi:10.1111/jgh.15729, PMID:34734433.
[83] DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, *et al*. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med 2019;381(21):2043–2050. doi:10.1056/NEJMoa1910437, PMID:31665575.
[84] Mak LY, Seto WK, Yuen MF. Novel Antivirals in Clinical Development for Chronic Hepatitis B Infection. Viruses 2021;13(6):1169. doi:10.3390/v13061169, PMID:34207458.
[85] Study to Evaluate Safety and Efficacy of ASC42 Combined With ETV and PEG-IFN α-2a in Subjects With HBV. [cited 2025 Dec 12] Available from: https://ctv.veeva.com/study/study-to-evaluate-safety-and-efficacy-of-asc42-combined-with-etv-and-peg-ifn-a-2a-in-subjects-with-h.
[86] He H, Wu JJ. Human Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASC42, a Novel Farnesoid X Receptor Agonist. Drugs R D 2023;23(4):453–464. doi:10.1007/s40268-023-00444-4, PMID:37919483.
[87] Fouillé R, Verrier ER, De Meyer A, Verhoye L, Michelet M, Barnault R, *et al*. A novel in vitro system for simultaneous infections with hepatitis B, C, D and E viruses. JHEP Rep 2025;7(5):101383. doi:10.1016/j.jhepr.2025.101383, PMID:40242313.
[88] Pan B, Chen S, Zhang Z, Ye D, Zhang X, Yao Y, *et al*. New mechanistic understanding of FXR agonist Vonafexor: inducing sublethal damage of HBV-positive liver cancer cells via promoting anti-tumor immunity. Br J Cancer 2025;133(5):697–708. doi:10.1038/s41416-025-03089-z, PMID:40588513.
[89] Henry Z, Meadows V, Guo GL. FXR and NASH: an avenue for tissue-specific regulation. Hepatol Commun 2023;7(5):e0127. doi:10.1097/HC9.0000000000000127, PMID:37058105.
[90] Fiorucci S, Biagioli M, Sepe V, Zampella A, Distrutti E. Bile acid modulators for the treatment of nonalcoholic steatohepatitis (NASH). Expert Opin Investig Drugs 2020;29(6):623–632. doi:10.1080/13543784.2020.1763302, PMID:32552182.
[91] Wang T, Fan Y, Tan S, Wang Z, Li M, Guo X, *et al*. Probiotics and their metabolite spermidine enhance IFN-γ(+)CD4(+) T cell immunity to inhibit hepatitis B virus. Cell Rep Med 2024;5(11):101822. doi:10.1016/j.xcrm.2024.101822, PMID:39536754.
[92] Ray G. Functional cure of chronic hepatitis B-hope or hype? World J Hepatol 2024;16(9):1199–1205. doi:10.4254/wjh.v16.i9.1199, PMID:39351521.
[93] Shen Y, Wu SD, Chen Y, Li XY, Zhu Q, Nakayama K, *et al*. Alterations in gut microbiome and metabolomics in chronic hepatitis B infection-associated liver disease and their impact on peripheral immune response. Gut Microbes 2023;15(1):2155018. doi:10.1080/19490976.2022.2155018, PMID:36519342.
[94] Yu X, Tian W, Bao X, Li Z, Tu H, Xu X, *et al*. Dissecting the liver inflammation ecosystem identifies annexin A1 as a pro-resolving target for liver failure. Hepatology 2026;83(5):1174–1191. doi:10.1097/HEP.0000000000001427, PMID:40560812.
[95] Xu X, Chen J, Yu X, Li Z, Chen J, Fang D, *et al*. Single-cell analysis identifies RETN(+) monocyte-derived Resistin as a therapeutic target in hepatitis B virus-related acute-on-chronic liver failure. Gut 2026;75:605–619. doi:10.1136/gutjnl-2025-335998, PMID:41052916.
[96] Fiorucci S, Distrutti E, Carino A, Zampella A, Biagioli M. Bile acids and their receptors in metabolic disorders. Prog Lipid Res 2021;82:101094. doi:10.1016/j.plipres.2021.101094, PMID:33636214.
[97] Guo C, Chen WD, Wang YD. TGR5, Not Only a Metabolic Regulator. Front Physiol 2016;7:646. doi:10.3389/fphys.2016.00646, PMID:28082913.
[98] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature 2019;570(7762):462–467. doi:10.1038/s41586-019-1291-3, PMID:31158845.
[99] Commissioner O of the. Ocaliva (obeticholic acid) by Intercept Pharmaceuticals: Drug Safety Communication - Serious Liver Injury Being Observed in Patients without Cirrhosis. FDA. [cited 2025 Dec 14]. Available from: https://www.fda.gov/safety/medical-product-safety-information/ocaliva-obeticholic-acid-intercept-pharmaceuticals-drug-safety-communication-serious-liver-injury.
[100] van der Beek CM, Dejong CHC, Troost FJ, Masclee AAM, Lenaerts K. Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. Nutr Rev 2017;75(4):286–305. doi:10.1093/nutrit/nuw067, PMID:28402523.