**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 77180

**Manuscript Type:** REVIEW

**New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease**

Zheng L. Interplay between intestinal flora and bile acids in IBD

Lie Zheng

**Lie Zheng,** Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, Xi’an 710003, Shaanxi Province, China

**Author contributions:** Zheng L reviewed the literature, prepared the manuscript, performed to the writing, revising of the manuscript, contributed to design this work, and performed overall supervision, wrote and revised the paper, approved the final manuscript.

**Supported by** General Research of Xi’an Science and Technology Planning Project, No. 2022JH-YBYJ-0265; Shaanxi Province Natural Science Basic Research Program-General Project, No. 2019JM-580; Project of Shaanxi Administration of Traditional Chinese Medicine, No. 2019-ZZ-JC010; and Shaanxi Provincial Hospital of Traditional Chinese Medicine, No. 2021-07 and No. 2018-04.

**Corresponding author: Lie Zheng, PhD,** Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, No. 4 Xihuamen, Xi’an 710003, Shaanxi Province, China. 492688049@qq.com

**Received:** April 18, 2022

**Revised:** June 8, 2022

**Accepted:** September 16, 2022

**Published online:** October 26, 2022

**Abstract**

Intestinal flora plays a key role in nutrient absorption, metabolism and immune defense, and is considered to be the cornerstone of maintaining the health of human hosts. Bile acids synthesized in the liver can not only promote the absorption of fat-soluble substances in the intestine, but also directly or indirectly affect the structure and function of intestinal flora. Under the action of intestinal flora, bile acids can be converted into secondary bile acids, which can be reabsorbed back to the liver through the enterohepatic circulation. The complex dialogue mechanism between intestinal flora and bile acids is involved in the development of intestinal inflammation such as inflammatory bowel disease (IBD). In this review, the effects of intestinal flora, bile acids and their interactions on IBD and the progress of treatment were reviewed.

**Key Words:** Intestinal flora; Bile acids; Inflammatory bowel disease; Fecal microbiota transplantation; Prebiotics

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Zheng L. New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease. *World J Clin Cases* 2022; 10(30): 10823-10839

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/10823.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.10823

**Core Tip:** With the increase of economic level and the improvement of people's living standard, the incidence of inflammatory bowel disease (IBD) in China is gradually increasing, causing a heavy burden to the society. The pathogenesis of IBD is related to genetics, environment, intestinal microecology and immunity, but the specific biological mechanism is still unclear. As an important part of intestinal microecology, intestinal flora can directly affect intestinal environmental homeostasis and participate in bile acid (BA) metabolism, while the abnormal BA metabolism also affects the quality and quantity of intestinal flora, and both of them are involved in the occurrence and development of intestinal inflammation.

**INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic relapsing disease, including Crohn's disease (CD) and ulcerative colitis (UC), which has become a public health problem worldwide. With changes in diet and lifestyle, the incidence of IBD is rising rapidly worldwide. The composition of intestinal flora is considered to be the main driver of intestinal immune dysfunction in IBD, but this concept has not been fully proven[1]. Bile acids (BAs) are steroid molecules produced by interaction between the host and gut flora. It is one of the largest bioactive substances found in mammals and acts on the G protein and nuclear receptor families[2]. In this review, we reviewed the effects of intestinal flora, BA receptors and their interactions on IBD and the progress of its treatment.

**INTESTINAL FLORA AND IBD**

IBD patients were found to have intestinal microbiota imbalance, which was mainly characterized by decreased intestinal microbiota diversity. The anti-inflammatory bacteria in feces of IBD patients, such as *Faecalibacterium prausnitzii* and *Roseburia*, have decreased. In the intestinal mucus layer, *Roseburia* can convert acetate to butyrate and produce secondary BAs, which may have anti-inflammatory effects[3]. The proportion of *Bacteroides Fragilis* in IBD patients also decreased significantly. The polysaccharide A produced by The bacterium induces the development of CD4+ T cells and the anti-inflammatory function of regulatory T cells (Treg)[4]. A recent study found that the use of short-term antibiotics at an early age increased the susceptibility of mice to colitis induced by Dextran sulfate sodium (DSS), suggesting that the imbalance of intestinal flora is closely related to the incidence of IBD[5].

The intestinal flora metabolizes to produce many bioactive molecules that interact with the host. The typical representatives are short chain fatty acids, which mainly include acetic acid, propionic acid and butyric acid. These bioactive molecules not only serve as energy for intestinal epithelial cells, but also increase the secretion of anti-inflammatory cytokines such as interleukin (IL-10) and the number of Treg cells by activating the G protein-coupled receptor 5 (TGR5) on intestinal cells and immune cells[6]. It can reduce tissue inflammation and maintain the stability of intestinal mucosal barrier function. Studies have shown that butyrate can promote the recovery of intestinal barrier function and accelerate the repair of intestinal epithelial cell injury through synaptopoptin, while the loss of bacterial flora blocks the expression of synaptopoptin and increases the sensitivity to colitis and intestinal permeability in mice[7].

Dietary tryptophan can be metabolized by intestinal flora into metabolites such as indoleacetic acid, indole3-acetaldehyde, indole3-aldehydes, indole3-acrylics and indole3-propionic acid, thus acting as ligands of aromatic hydrocarbon receptors, which are closely related to the pathogenesis of IBD[8].

Indoles, indoles propionic acid and indoles acrylic acid bind to progesterone X receptors, thereby reducing intestinal permeability and affecting mucosal homeostasis[9]. Indoleformaldehyde secretes IL-22 by activating aromatic hydrocarbon receptors on intestinal immune cells. Indole-3-propionic acid protects mice from DSS-induced colitis by binding to aromatic hydrocarbon receptors to produce IL-10[10]. Therefore, intestinal flora disorder can disrupt immune regulation and promote inflammation through its metabolites.

**BA METABOLISM**

BA is an important compound and structural component in human and animal Bile, and the liver is the main site of BA formation[11]. BA synthesis by the great influence of diet, the body from free cholic acid (CA), the primary BAs combined with secondary free CA and BA composition, type of free BA is by chenodeoxycholic acid (CDCA) and CA, primary BA combination type of cows sulfonated goose deoxycholic acid (DCA) and ammonia goose DCA, taurocholic acid as well as the composition of gca, Secondary free CA consists of CA and DCA[12]. BAs are a kind of important host-derived compounds, which have many important physiological functions and effects on the host and its intestinal flora. BAs are metabolites of cholesterol, and the transformation of BAs requires the help of intestinal microflora[13]. The classical pathway and the alternative pathway are two pathways of BA synthesis. It is regulated by cholesterol 7α-hydroxylase (CYP7A1), sterol 12α-hydroxylase (CYP8B1), cholesterol 27α-hydroxylase (CYP27A1) and other enzymes related to BA synthesis[14]. It has been confirmed that in the classical pathway of BA synthesis, cholesterol in human liver is catalyzed by CYP7A1 to produce 7α-hydroxyl cholesterol, and then is catalyzed by 3β-hydroxyl-δ 5-C27-steroid dehydrogenase (3β-HSD), CYP8B1 and CYP27A1. 7α-hydroxyl cholesterol is catalyzed to produce primary BAs, free CA and goose DCA (CDCA)[15].

In the alternative pathway, cholesterol is catalyzed by CYP27A1 to produce 27α-hydroxyl cholesterol, followed by DCA in response to CYP7B1[16]. The free CA then binds to glycine and taurine by its own amide bond to form conjugated BAs which enter the intestinal tract of the body[17]. Taurocholic acid forms DCA after hydroxy release by intestinal bacteria. In the metabolism of goose DCA, goose DCA is a combination of glycine and goose DCA[18]. The intestinal bacteria of the body hydrolyze goose DCA and dehydroxyl to form stone CA[19]. Goose DCA can also react with taurine to form taurocholic acid. CYP7A1 is a rate-limiting enzyme of BA synthesis in the body, and its activity can regulate the rate of BA synthesis in the process of BA synthesis, which has been proved in an experimental study[20]. Rats in the experimental group were fed BA, and the activity of 7α-hydroxylase was decreased and the rate of BA synthesis was also significantly decreased in the experimental group compared with normal rats[21]. After BA synthesis by bile salt export pump into the gall bladder stores, when the body after eating, in the gallbladder bile into the intestine to help the body absorb the lipid in food, the BA level in the body is not fixed, it is in the steady state environment, in the terminal ileum 95% BA enterohepatic circulation will be absorbed by weight, over 5% of conjugated BA eduction of excrement and urine, Limited BAs are reused through the enterohepatic circulatory system[22]. This process, called BA enterohepatic circulation, occurs about six times a day in the body. Most BAs are reabsorbed at the terminal ileum *via* the apical membrane sodium-dependent bile salt transporter (ASBT) of intestinal cells, where bile salts are transported from the intestinal epithelial cells to the basal outer membrane side into the blood with the help of intestinal BA proteins[23].

**BA AND IBD**

Repeated stimulation of intestinal epithelial cells with high concentration of BAs is an important risk factor for the pathogenesis of IBD, which will destroy host material metabolism and signal transduction[24]. In rats with colitis induced by Trinitrobenzenesulfonic acid, apical sodium-dependent BA transporter, ASBT expression decreased. When intestinal inflammation occurs, the intestinal barrier is damaged, which leads to the reduction of ASBT expression, and finally the destruction of enterohepatic circulation leads to the accumulation of BAs in the intestinal mucosa, and the intestinal inflammation is aggravated. In IBD patients, ileal inflammation blocks hepatoenteric circulation of BAs, leading to reduced ileal reabsorption, which may be due to inhibition of ASBT promoter expression by inflammatory cytokines, thus increasing fecal BAs[25].

Hepatic BA synthesis is regulated by the Farnesoid X receptor (FXR)-FGF15/19 signaling pathway. Activation of this signaling pathway reduces the expression of enzymes related to hepatic BA synthesis and reduces BA synthesis[26]. Activation of FXR can improve colon inflammation, protect intestinal inflammation, reduce intestinal permeability, and reduce goblet cell extinction. The activation of FXR can also inhibit the secretion of tumor necrosis factor-α (TNF-α), interferon (IFN)-γ, IL-17 and other inflammatory cytokines in the mucosal cells of IBD patients, and up-regulate the expression of anti-inflammatory factor IL-10 in the intestinal tract[27]. Therefore, compared with the healthy control group, the enterohepatic circulation of IBD patients is blocked, the negative regulatory pathway of intrahepatic BA synthesis is reduced, and the total amount of BAs in the intestinal lumen is increased, leading to intestinal inflammation[28].

**BA-ACTIVATED RECEPTORS IN IBD**

BA receptors mainly consist of TGR5, FXR, and pregnane X receptor (PXR), Constitutive Androstane receptor (CAR), Vitamin D receptor (VDR), PXR. It has the functions of regulating BA metabolism, glucose utilization, fatty acid synthesis and oxidation, energy homeostasis balance, immune cell function, nerve activity and so on.

***TGR5 and IBD***

TGR5 is a membrane receptor containing seven transmembrane regions. TGR5 mRNA expression was found in almost all human and rodent tissues, especially in gallbladder, ileum and colon[29]. Lithocholic acid (LCA) was the most effective in TGR5 stimulation. The rest were DCA, CDCA and CA. Activation of TGR5 can trigger the elevation of cyclic adenosine monophosphate (C-AMP) or epidermal factor growth. The activation of receptor (EGFR)-sarcoma (SRC) kinase affects the physiological state of cells[30].

IBD is caused by an overactive immune response to intestinal antigens. TGR5 deletion has been found to exacerbate intestinal inflammation in DSS-induced colitis mice[31]. There was no significant difference in TGR5 expression in colonic mucosa between patients with UC and the control group[32]. However, a recent study showed that TGR5 expression was significantly elevated in the colonic mucosa of children with UC, and was concentrated in lamina propria phagocytes[33]. TGR5-specific activation of macrophages isolated from the intestines of patients with CD significantly inhibited the production of TNF-α in macrophages, suggesting that the TGR5 signaling pathway may play an immunomodulatory role in IBD[34].

TGR5 is highly expressed in mononuclear macrophages, and intestinal macrophages, as the main source of cytokines, play an important role in immune homeostasis[35]. Polarization of macrophages is generally divided into two types, M1, which promotes inflammation, and M2, which suppresses inflammation. Rather than inducing macrophage activation to either phenotype alone, BA-activated TGR5 induces "mixed phenotype" macrophages, where an elevated IL-10/IL-12 ratio indicates the dominance of the immunosuppressive M2 phenotype[36]. TGR5 specific activation can reduce the production of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α in THP1 cells, and TGR5 activation can inhibit the secretion of inflammatory cytokines in intestinal macrophages in a dose-dependent manner[37]. In terms of mechanism, TGR5 activates C-AMP and EGFR-SRC kinase pathways in response to BAs. On the one hand, BA-activated TGR5 mediated the activation of C-AMP, which further activated PKA, up-regulated the expression and activity of C-AMP binding element, and finally inhibited the translocation of NF-κB into the nucleus through a series of steps[38]. Meanwhile, the expression of anti-inflammatory factor IL-10 was significantly increased after the activation of C-AMP binding element[39]. On the other hand, in M1-type macrophages, TGR5-dependent EGFR trans-activated SRC kinase activation leads to NF-κB activation through downstream protein kinase C, and increased expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α[40]. In summary, BA-TGR5 signal transduction regulates a complex balance between pro-inflammatory and anti-inflammatory cytokines in the gut.

***FXR and IBD***

A nuclear receptor superfamily member, FXR, with BA ligand activity was first identified in a 1995 study of rat liver C DNA[41]. FXR mainly exists in the intestine, liver and kidney, especially in the ileum, colon and liver, and is involved in the regulation of a large number of physiological activities of the human body. In addition to regulating BA metabolism and transport, FXR also plays a key role in regulating lipid and glucose homeostasis, inflammatory response, and barrier function[42].

BAs can be classified according to their affinity for binding FXR in vitro. CDCA has the highest excitatory effect on FXR, followed by CA, DCA and LCA[43]. Compared with their natural forms, the sugar-taurosulfo-conjugated forms of CDCA, DCA and LCA are more effective agonists. Among the synthesized FXR agonists, GW4064 selectively excites FXR with high affinity, which is widely used in experimental studies[44].

FXR plays an important role in the development and progression of IBD. Early colon cell tests showed that FXR gene knockout mice were more likely to develop severe intestinal inflammation than wild-type mice, suggesting that intestinal FXR could reduce intestinal inflammation[45]. It has been found that activation of intestinal FXR can inhibit NF-κB activation and reduce intestinal inflammation through multiple pathways[46]. FXR attenuates the translocation of NF-κB subunit P65, thereby inhibiting NF-κB transcription, reducing the gene expression of pro-inflammatory factor IL-8, and alleviating intestinal inflammation[47]. Activation of intestinal FXR expression can inhibit intestinal toll-like receptor 4-myeloid differentiation factor 88 signaling pathway, thereby down-regulating NF-κB expression and alleviating intestinal inflammation[48]. In addition, activation of FXR can up-regulate the expression of IL-10, an anti-inflammatory factor in the intestinal tract, thus exerting an anti-inflammatory effect. It is concluded that activation of intestinal FXR can reduce intestinal inflammation and play a protective role in IBD intestine, and FXR is expected to become a drug target for IBD treatment[49]. It is important to note that FXR has different functions in different tissues, and currently there are no intestinal FXR specific agonists. Therefore, when FXR is used as a treatment for IBD, it may activate hepatic FXR and cause adverse reactions[50].

Intestinal BA accumulation can cause the proliferation and apoptosis of intestinal epithelial cells, leading to IBD. FXR can regulate BA synthesis and reabsorption to maintain intestinal BA homeostasis[51]. On the one hand, FXR can regulate the expression of fibroblast growth factor (FGF), thereby inhibiting the expression of CYP7A1 and reducing BA synthesis[52]. On the other hand, intestinal FXR also promotes the expression of organic solute transporter alpha-beta (OSTα/β), Inhibit the expression of ASBT in ileum, thus promoting the excretion of intestinal BA and alleviating the injury of intestinal BA[53]. Therefore, intestinal FXR has a protective effect on the intestinal tract of IBD and can be used as a therapeutic target for IBD. As a synthetic FXR agonist, GS-9674 alleviates cholestatic intestinal injury by activating FXR in intestinal epithelial cells to up-regulate FGF19 expression[54]. Based on 6-alpha-ethyl-chenodeoxycholic acid (6-ECDCA), which is mainly used for the treatment of cholestatic diseases, the 6-ECDCA can activate FXR, regulate the expression of OSTα/β and ASBT, and improve the intestinal cholestasis[55]. However, there is no clinical trial of 6-ECDCA as a treatment for IBD, but with the deepening of basic research, it is expected to become a treatment for IBD targeting FXR.

***PXR and IBD***

PXR is an important member of the nuclear receptor superfamily and is mainly expressed in colon and liver. Studies have shown that PXR plays an important role in maintaining intestinal homeostasis, and its gene deletion leads to an increased risk of IBD[56]. Moreover, PXR not only participates in intestinal immune response by regulating inflammatory signaling pathways, but also can receive endogenous signals to regulate intestinal homeostasis, so it is expected to become a new therapeutic target.

Excessive inflammatory response is the most prominent feature of IBD. NF-κB is the most classic inflammatory signaling pathway, and when activated, it releases a large number of inflammatory factors, exacerbating IBD[57]. The nuclear receptor PXR is an upstream regulatory factor of NF-κB, and can regulate NF-κB through PXR to reduce intestinal inflammation. We found that compared with wild-type mice, NF-κB was activated in the colon of PXR knockout mice, resulting in the release of a large number of inflammatory factors (such as TNF-α, IL-6, *etc.*), and increased intestinal inflammation[58]. It is speculated that PXR gene deletion may activate NF-κB pathway and increase intestinal inflammation. Activation of PXR receptor can inhibit NF-κB expression in the intestinal tract, thereby reducing the level of downstream inflammatory factors and reducing intestinal inflammation[59]. PXR protects the intestine by regulating NF-κB signaling. In addition, PXR also regulates non-classical inflammatory pathways, such as transforming growth factor (TGF-β1) expression, which plays a role in reducing intestinal inflammation. Therefore, PXR is considered as one of the most promising targets for IBD treatment[60].

Intestinal mucosal barrier is an important physical barrier to prevent toxic substances from invading the intestine, maintaining intestinal mucosal homeostasis and avoiding intestinal injury. When the intestinal permeability is increased, the intestinal mucosal barrier function is reduced, which can directly lead to the occurrence or exacerbation of IBD symptoms. Increased intestinal permeability in IBD patients is closely related to the abnormal expression of Myosin light-chain kinase (MLCK) and C-Jun n-terminal kinase 1/2 (JNK1/2)[61]. However, nuclear receptor PXR can reduce intestinal permeability by down-regulating the expression of MLCK and JNK1/2, and play a role in maintaining intestinal mucosal barrier function. It was found that MLCK expression and myosin Ⅱ light chain phosphorylation level in colon tissue of IBD patients were significantly increased, and intestinal permeability was increased[62]. Pregnenolone 16-alpha carbonitrile (PCN), a PXR agonist, can inhibit MLCK and myosin Ⅱ light chain phosphorylation, reduce the permeability of the intestinal barrier, and avoid intestinal injury. The up-regulation of JNK1/2 expression in intestinal cells of IBD patients increases intestinal permeability, while PCN can down-regulate intestinal JNK1/2 expression by inducing GADD45β protein transcription, reducing intestinal permeability and avoiding toxin invasion[63]. Therefore, PXR can maintain intestinal mucosal barrier function, and its ligand can be used to treat IBD. However, PXR receptor agonist PCN is only used in animal experimental studies, and has not been used for clinical treatment. The study of intestinal protective mechanism of PXR will promote the application of PXR agonists in clinical treatment[64].

In human body, metabolic enzymes and transporters are highly expressed in the intestine, among which metabolic enzymes are mainly involved in the detoxification process of intestinal toxic substances, such as CYP3A4 and CYP3A11[65]. Transporters are mainly involved in the excretion of intestinal cytotoxic substances, such as P-glycoprotein (P-GP)[66]. Studies have shown that the reduced expression of metabolic enzymes and transporters involved in the metabolism of heterogenic substances in the intestine of IBD patients leads to the accumulation of intestinal toxins, and PXR is an upstream regulatory factor of multiple metabolic enzymes and transporters, which can regulate their expression to play a detoxification role[67]. Activation of PXR can significantly up-regulate the expression of *CYP3A4* gene in wild-type mice, thus improving the symptoms of abdominal pain and diarrhea. The expression level of P-GP in colon tissues of IBD mice prepared by DSS was down-regulated, and the poison was accumulated in intestine. PXR could reduce the accumulation of poison by regulating the expression of P-GP[68]. PXR can up-regulate the expression of drug metabolism enzymes and transporters to eliminate intestinal toxicity, and has a protective effect on IBD intestinal tract. Tanshinone Ⅱ A, the active ingredient of Salvia miltiorrhiza in labiaceae, is A highly active PXR agonist, which mainly upregulates the expression of PXR to increase the expression of downstream metabolic enzymes and transporters, thereby promoting intestinal toxin metabolism and efflux, and improving the symptoms of IBD[69]. PXR agonists speed up the metabolism of other drugs in the body, reducing the potential for adverse reactions to these drugs. However, large-scale activation of PXR can up-regulate the expression of metabolic enzymes and transporters, and then affect the metabolism of other drugs, leading to decreased efficacy and even induced drug interactions, which may limit the clinical application of PXR agonists in the treatment of IBD[70]. It can be seen from the above that the protective effect of PXR on the intestinal tract of IBD has been preliminarily confirmed. Based on its protective mechanism, PXR can be used as a target for drug therapy of IBD, providing a new perspective for innovative drug research and IBD treatment.

***CAR and IBD***

CAR is a nuclear receptor for steroidal hormones, which is mostly expressed in intestinal epithelial cells. Although the protective mechanism of CAR against IBD is not fully understood, there is increasing evidence that it also plays a key role in regulating intestinal inflammation and protecting the intestinal mucosal barrier[71]. Biopsies of the intestinal mucosa of IBD patients showed that *CAR* gene expression was strongly associated with intestinal inflammation levels. In IBD mice, intestinal mucosal barrier was disrupted, and the activation of p38MAP kinase by CAR agonist CITCO enhanced IEC cell migration and accelerated intestinal mucosal healing[72]. In addition, CAR significantly regulates metabolic enzymes and transporters located in the intestine, and protects the intestine from toxic interference by inducing the expression of metabolic enzymes and transporters[73]. These results suggest that CAR, like PXR and FXR, can play a protective role in IBD by reducing intestinal inflammation and maintaining intestinal mucosal homeostasis, but the specific mechanism remains to be studied[74]. In conclusion, CAR is also a promising drug target for IBD treatment, and further study of its protective mechanism against IBD can provide reference for drug development targeting CAR.

***VDR and IBD***

VDR is a member of the nuclear hormone receptor superfamily, which exists in all the target tissues of vitamin D3, such as intestinal tract and liver[75]. VDR, as an important nuclear transcription factor, intervenes in many downstream genes through specific binding with ligands. Studies have confirmed that VDR gene polymorphism is associated with the risk of IBD, and there are differences in VDR genotypes among different genders and populations[76]. Human proteomics shows that VDR is highly expressed in the normal small intestine and colon, but reduced intestinal VDR expression and impaired VD/VDR signaling pathway were observed in patients with CD and UC[77]. Therefore, intestinal VDR plays an important role in the occurrence and development of IBD.

Loss of VDR in intestinal epithelial cells leads to activation of NF-κB signaling, which promotes production of pro-inflammatory cytokines[78]. A genome-wide association analysis showed that VDR binds to 42 disease-associated single nucleotide polymorphisms, of which one-third significantly affect transcription factor NF-κB binding and gene regulation. Immunoprecipitation results suggested that VDR had a protein-protein interaction with IKKβ upstream of NF-κB[79]. VDR inhibited ser-177 phosphorylation of IKKβ by binding to IKKβ, thereby inhibiting NF-κB activation and IL-6 elevation induced by TNF-α, and improving intestinal inflammation[80].

A meta-analysis shows that variations in the VDR gene significantly affect the human gut microbiome[81]. It was found that the protective effect of probiotics on IBD depends on the epithelial VDR signaling pathway. In the normal intestinal flora of mice, the distribution and abundance of bacteria in the intestinal epithelium after VDR knockout were significantly changed, mainly manifested as increased abundance of Bacteroides fragilis in mice with VDR deletion[82]. In addition, intestinal epithelial VDR deletion exacerbated the intestinal inflammatory damage caused by sodium glucan sulfate modeling in mice, while the intestinal epithelial VDR deletion mice and wild-type control mice were reared in the same cage for modeling, this difference in intestinal inflammation caused by different genotypes disappeared[83]. This indicates that VDR deficiency causes intestinal flora disorder and aggravates the occurrence and development of IBD. Another study showed that defective VDR expression in intestinal Panth cells leads to reduced lysozyme secretion, impaired antimicrobial activity of pathogenic bacteria, and thus increased inflammatory response[84]. Other studies have found that lack of VD in the diet of mice can cause intestinal microflora disorder, mainly manifested in increased abundance of Helicobacter hepaticus and decreased abundance of probiotics Akkermansia Muciniphila[85]. Therefore, VDR genes may play an important role in homeostasis and signal transduction between the microbiome and host in intestinal inflammation.

Some studies have speculated that metabolites of intestinal flora regulate intestinal immune responses in a VDR dependent manner[86]. Butyrate is a short-chain fatty acid produced by intestinal microorganisms. 2% sodium butyrate in drinking water increased intestinal VDR expression and inhibited inflammation in mice with colitis[87]. In addition, secondary BAs and shicholic acids produced by intestinal flora metabolism inhibit Th cell immune response by activating VDR of CD4+Th cells, thereby reducing IFN-γ and IL-2 production in intestinal inflammation[88]. In conclusion, VDR related basic studies provide many new ideas and explanations for the mechanism of intestinal flora in IBD.

***Sphingosin1-phosphate receptor 2 and IBD***

Sphingosine-1 (S1P) is an active sphingosine-1 that participates in the regulation of various cell functions under physiological and pathological conditions[89]. S1P can function directly as intracellular signaling molecules or extracellular by activating 5 G protein-coupled receptors (GPCRs). S1P has been shown to be a key regulator of proliferation, migration, and survival of many cell types. The expression of 5 S1PRs was different in different tissues or organs. All five S1PRs were detected in the human intestine, but the expression levels of S1PRs were different[90]. It has been reported that S1P regulates the expression of e-cadherin by activating S1PR2 to enhance intestinal epithelial cell barrier function. It has also been reported that S1P reduces intestinal epithelial cell apoptosis through the Akt dependent pathway[91,92]. These studies suggest that S1P and its receptor can promote intestinal epithelial cell proliferation and enhance epithelial cell barrier function, and play a protective role in intestinal mucosal barrier.

***Retinoid-related orphan receptor gammar and IBD***

Retinoid-related orphan receptor gammar (RORγ T) is a specific transcription factor controlling Th17 cell differentiation. Treg cells are from the same source as Th17 cells, and they are closely related[93]. Treg cells play an important role in maintaining the body's immune tolerance state and the stability of internal environment, and preventing the occurrence of autoimmune diseases. Th17 cells, a new type of CD4+ cell subpopulation discovered in 2003, play a pro-inflammatory role mainly by secreting cytokines such as IL-17, IL-22 and IL-21[94]. RORγ T is a transcriptional activator that plays a key role in the differentiation of Th17 cells. Inhibition of RORγ T expression can inhibit the differentiation of non-sensitized T cells into Th17 cells[95]. It has been found that RORγ T directs the differentiation of proinflammatory Th17 cells and regulates the production of IL-17 in peripheral blood[96]. Therefore, it is reasonable to believe that RORγ T can be used as an important target for the treatment of autoimmune and inflammatory diseases. Treg cells are newly discovered T cell subsets that negatively regulate the body's immune response, and their immune regulatory function is closely related to the continuous expression of Foxp3[97]. Foxp3 is considered to be a key transcription factor and specific marker of Treg cells, which can regulate the expression and function of multiple genes after binding to chromosomes, thus controlling the development and function of Treg cells[98]. *In vitro* studies have shown that TGF-β can inhibit RORγt function and promote Treg differentiation by inducing Foxp3 expression, and the full-length Foxp3 subtype can bind to RORγ T to inhibit RORγ T function[99]. In the presence of pro-inflammatory cytokines, Foxp3 levels decreased and RORγ T levels increased, ultimately promoting Th17 cell differentiation. In a mouse model of colitis, RORγ T binding reduced IL-17 production and Th17 cell count and reduced intestinal inflammation[100]. Studies have shown that Th17 lymphocytes are involved in the pathogenesis of CD and UC. Increased IL-17 expression in mucosa and serum of IBD patients was associated with increased RORγ T expression and Th17 cell number[101]. Therefore, Th17 and Treg cells antagonize each other functionally and are closely related in differentiation. Under normal circumstances, they maintain a relative balance, which is beneficial to maintain the immune stability of the body[102]. At present, the relationship between Th17/Treg cell imbalance and disease occurrence and development has become the focus of people's attention.

**INTERACTION BETWEEN INTESTINAL FLORA AND BAS**

***Intestinal flora and BA synthesis***

Intestinal flora can further modify the synthetic BAs to form a series of intestinal BA metabolites. These metabolites can act as important signaling molecules to regulate cholesterol metabolism and energy balance of the host through BA receptors[103]. The involvement of intestinal flora in the synthesis of BAs increases the diversity of BAs and the hydrophobicity of BA pools, which is conducive to BA excretion[104]. The modification of BAs by intestinal flora mainly includes early uncoupling, dehydrogenation, dehydroxylation and differential isomerization of BAs. Bile salt-hydrolases (BSHs) produced by intestinal bacteria catalyze BSHs, and then uncouple bile c-24 with n-acetyl amino bonds bound to amino acids to form free BAs[105]. Studies have found that there are many bacteria in the intestinal tract of the organism that can produce BA salinase, such as bifidobacterium, Lactobacillus, Bacteroides, Listeria and Clostridium have BA salinase activity[106]. 7α-hydroxyl dehydrogenation occurs in free BAs under the catalytic action of Clostridium and Clostridium, and hydroxyl steroid dehydrogenase (HSDH) produced by intestinal microflora such as Clostridium, Eubacter, Ruminococcus, Bacteroidetes and Digestive streptococcus dehydrogenases at the positions of C-3, C-7 and C-12. Secondary BAs DCA and shicholic acid (LCA) were then produced, as shown in Figure 1. Increased LEVELS of DCA have been associated with obesity and cancer in mice, further supporting the important role of BA conversion in the intestinal flora in host metabolism[107].

Metabolome study found that in C57BL/6 mice, under the action of intestinal microflora on BA dehydroxylation and decoupling, the primary BA gradually decreased and the secondary BA gradually increased during the continuation process from small intestine to large intestine[108]. Compared with specific pathogen-free (SPF) mice fed a normal rich-diet diet, the changes of BA components in feces of SPF mice fed with minimal chemical diet and germ free (GF) mice fed with normal diet were detected by mass spectrometry. Levels of liver-derived taurine conjugated primary BAs in the intestinal tract of the minimal pathogen-free mice were significantly decreased compared with those in the RICH-diet SPF mice, while they were increased in the RICH-diet GF mice[109]. The results indicate that diet can directly control the hepatic synthesis of BAs, and the intestinal flora mainly controls the modification process of BAs in the intestine.

As a potential regulator of gut microbiota composition and host metabolism, microbial HSDH may open up new pathways for how the microbiota regulates signaling pathways in the host.

**THE EFFECT INTESTINAL FLORA ON BAS VIA FXR**

Study method of alcohol receptor in closely related to the metabolism of BA synthesis of highly expressed in the organs, such as the liver, small intestine, BA synthesis of organisms play a regulatory role of BA in the BA, goose DCA and LCA and DCA is liver alcohol receptor agonist, CYP7A1 is the promoter of BA synthesis[110]. In the liver, BA-activated FXR induces the expression of a small heterodimer partner (SHP) that binds to liver receptor homologous protein-1, thereby inhibiting *Cyp7a1* gene expression. In addition to local effects in the liver, FXR is also activated by BAs in the distal ileum. FXR induces expression of FGF15 (FGF19 in humans) in the ileum. So farnesol receptor-FGF15/19 signaling pathway plays an important role in BA synthesis. In the study of lactobacillus rhamnosus GG (LGG) on BDL mice, it was found that compared with the sham operation group, In BDL mice, the content of DCA (deoxycholic acid is a strong agonist of FXR) and the concentration of T-αMCA and T-βMCA (MCA is an antagonist of FXR) were decreased, and the mRNA expression of CYP7A1 and FGF15 in BDL mice were increased[111]. The BA content and the size of total BA pool in liver were significantly increased, and the BA content and total BA pool size were significantly decreased after LGG treatment. At the same time, it was found that the mRNA expression level of FXR target gene SHP and FGF15 were significantly decreased in the ileum of BDL mice, while LGG could inhibit the decrease of FGF15 protein level[112].

This confirms that in BDL mice, LGG treatment-mediated reduction in BA synthesis is achieved through upregulation of the intestinal FXR-FGF15 signaling pathway[113]. Other studies confirm the BA levels of traditional breeding mice, and the germ-free mice raised in BA levels, may be due to the traditional breeding mice intestinal microbial flora make mice reduced levels of MCA, activation of FXR, make FGF15 higher expression, thus inhibiting the activity of CYP7A1 to inhibit the synthesis of BA [114].

It was found that after fecal microbiota transplanta-tion (FMT) of sterile mice received FMT, the expression of FXR in intestinal epithelium was up-regulated, and FXR further induced the expression of FGF15, thereby inhibiting the activities of CYP7A1, CYP8B1 and other enzymes. Thus inhibiting the synthesis of BAs[115]. The expression of FGF15 in ileum was inhibited by antibiotics, and the expression level and activity of CYP7A1 in liver increased significantly, resulting in BA synthesis. *Parabacteroides distasonis* was used to treat obese mice. It was found that *Parabacteroides* *distasonis* can hydrolyse a variety of conjugated BAs, convert primary BAs into secondary BAs (LCA, UDCA, *etc.*), and produce a large amount of succinic acid[116]. LCA and other secondary CAs increased the level of FGF15 in serum and colon, and decreased the level of CYP7A1 in liver by activating the intestinal FXR signaling pathway. UDCA can repair intestinal wall integrity and succinic acid can improve host sugar metabolism disorder[117].

TGR5 can also be activated by intestinal flora to inhibit BA synthesis. TGR5 is a GPCR, and it has been found that compared with WT mice, the BA pool size of mice lacking the *TGR5* gene in a high-fat diet decreased by 21% to 25%, and body fat accumulation increased, and body mass increased[118]. Intestinal bacteria can also induce the expression of cardiac transcription factor 4 in intestinal epithelial cells by stimulating them continuously, and inhibit the expression of ABST, resulting in reduced BA reabsorption in the terminal ileum[119].

In conclusion, intestinal flora not only participates in the processes of BA decoupling, dehydrogenation and dehydroxylation, but also negatively regulates BA synthesis through the FXR-FGF15/19 pathway.

**INTESTINAL FLORA PARTICIPATES IN THE REGULATION OF NORMAL METABOLISM OF BAS**

The metabolism of BAs in the body is mediated by intestinal flora. The whole metabolic process of BAs synthesized in liver cells is regulated by intestinal flora. The intestinal flora in patients with gallstones is unbalanced and the metabolism of BAs is also in disorder, which may be because the imbalance of intestinal flora in the body affects the hepatoenteric circulation of BAs in the body and causes the metabolic disorder of BAs and cholesterol. BSHs produced by *bifidobacterium*, *Clostridium*, *Lactobacillus*, *Listeria*, *enterococcus*, *bacteroidetes* and other bacteria in the intestinal tract of the body can reduce the production of cholesterol in serum[120]. BSHs is mainly involved in the uncoupling of conjugated BAs to form free BAs in the body. When intestinal flora in the body is unbalanced, BSH activity increases and free BA content increases, which then activates the NEGATIVE feedback regulation system of FXR-FGF15/19 BA, resulting in reduced BA synthesis content and over-saturated cholesterol[121]. If it is not dissolved effectively by BAs, it will remain as a deposit, slowly turning into a stone state. In addition, lactobacillus and bifidobacterium in intestinal flora also has the ability of removing cholesterol, mainly through the intake to the cholesterol assimilation or binding to the cell or and BA form coprecipitation[122], some intestinal bacteria also can produce cholesterol reductase, catalytic cholesterol into insoluble prostaglandins, and turn it into the feces. Other studies have confirmed that intestinal flora mediates normal metabolism of BAs. In the study of liver cancer, antibiotics can increase the Natural kilkR T cell (NKT) in mouse liver, and CXCL16, a chemokine expressed by hepatic sinusoid endothelial cells, can inhibit the growth of liver tumors by regulating hepatic NKT cells[123]. The primary BAs in liver can promote the expression of CXCL16, while the secondary BAs can inhibit the expression of CXCL16. When mice were treated with vancomycin (an antibiotic), vancomycin eliminated gram-positive bacteria (including those involved in primary BA conversion) from their intestines and induced the accumulation of hepatic NKT cells, thereby inhibiting the development of liver cancer[124]. At the same time, vancomycin-treated mice were fed with secondary BAs or clostridium bacteria that colonized and transformed primary BAs, and the accumulation of NKT cells in the liver was reduced and the anti-tumor effect was reduced[125].

Studies have shown that in patients with UC, the levels of secondary BAs (deoxycholic acid and stone CA) in the intestinal tract are reduced, and rumen bacteria and other bacteria that convert primary BAs into secondary BAs are also reduced[126]. Supplementation of secondary BAs with G-protein-coupled receptor for BAs (TGR5) improved intestinal inflammation in mice with colitis.In the enterohepatic circulation with normal enteral nutrition, BAs activate the enterofarnicol receptor (FXR), triggering the release of FGF19 into the portal vein circulation[127]. FGF19 regulates the synthesis of intrahepatic BAs through enteral nutrition. This signaling pathway is impaired in patients with total venous nutrition (TPN), and studies have shown a decrease in serum FGF19 levels in subjects receiving TPN. Due to intestinal dysfunction, the intestinal microbiota in TPN patients is severely altered. Changes in intestinal flora can affect patients' immune response and promote endotoxin secretion, thus negatively affecting liver function, suggesting that intestinal flora affects the related BA signaling pathway in the treatment of TPN[128].

**BAS AFFECT THE COMPOSITION OF INTESTINAL FLORA**

The regulation between intestinal flora and BA metabolism is bidirectional, intestinal flora can participate in the synthesis and normal metabolism of BA, and BA can in turn regulate the composition of intestinal flora. The effects of BAs on intestinal flora include damage to bacterial cell membrane, destruction of bacterial amino acids, nucleotides and carbohydrate metabolism, activation of innate immune genes in the small intestine to change the composition of intestinal flora and affect body metabolism[129]. The size and diversity of BA pools can affect the intestinal flora of the body. Studies on colorectal cancer (CRC) patients found higher concentrations of Clostridium 7α-dehydroxy in feces, which can promote the production of secondary BAs. High levels of clostridium 7α-dehydroxy increase the content of secondary BAs in the intestinal tract, leading to an imbalance of intestinal microflora that promotes the development of CRC[130]. High-fat diet can cause the imbalance of intestinal flora in mice. When adding ursodeoxycholic acid into the diet of high-fat diet mice, it was found that the intestinal flora in mice restored to the similar level as normal mice (for example, the contents of *Faecalis* and *Ackmanniella* increased, while the contents of *Spironella* and *ruminococcus* decreased)[131]. The effects of BAs on the composition of intestinal flora can also be mediated by FXR. When mice were fed a high-fat diet, the levels of T-βMCA in FXR deficient mice increased and the abundance of *Firmicutes* increased while the abundance of *Bacteroidetes* decreased compared with the control mice. It is possible that the FXR-mediated high-fat diet altered the BA pool in mice, leading to changes in gut microbiota[132].

BAs can also change the composition of intestinal flora by inhibiting the growth of intestinal bacteria, and the antimicrobial activity of non-conjugated BAs is stronger than conjugated BAs, and the sensitivity of gram-positive bacteria to BAs is stronger than gram-negative bacteria[133]. It was found that the synthesis of BA in rats with liver cirrhosis was lower than that in healthy rats, and the total bacterial content in ileum and bacterial translocation rate were increased[134]. After BA injection, the bacterial quantity in ileum of cirrhotic rats returned to healthy level and the bacterial translocation rate decreased. Obeccholic acid (OCA) is a BA derivative that activates FXR to inhibit endogenous BA synthesis. When healthy subjects were given doses of OCA, they found increased levels of gram-positive bacteria in their small intestines, such as *Lactococcus lactis*, *Lactobacillus casei* and *Streptococcus thermophilus*, while normal levels of BA inhibited the growth of these bacteria. When healthy mice were fed OCA, the BA content in their small intestine decreased, while the content of firmicide bacteria, mainly gram-positive bacteria, increased, suggesting that OCA can inhibit BA synthesis through activation of FXR and thus alter the intestinal microflora[135-137].

**INTESTINAL FLORA, BA METABOLISM AND IBD**

***Probiotics and prebiotics***

Exogenous supplementation of probiotics to regulate BAs to prevent or treat diseases has been demonstrated in metabolic diseases, such as hypercholesterolemia or obesity[138]. Probiotics can relieve the clinical symptoms of IBD patients to different degrees. Probiotic mixture VSL#3 can significantly reduce cryptitis, and *Clostridium butyricum* MIYAIRI is also better than placebo in clinical efficacy, but its exact efficacy needs to be further studied[139]. BAs levels are reduced in IBD patients and experimental enteritis animals[130]. However, the improvement of enteritis symptoms by exogenous *Clostridium scindens* supplementation has only been demonstrated in animals, and clinical studies on strains that regulate BSH or 7α dehydroxylase in a targeted way are lacking[140].

***Fecal microbiota transplantion***

FMT is a process in which feces from healthy people are transferred to patients, and it was first used to treat patients with recurrent *Clostridium difficile* infection. Recent studies have shown that FMT can significantly improve the composition of BAs in the gut of patients with *C. difficile*, increase the content of secondary BAs and prevent *C. difficile* colonization[141]. Because of its apparent efficacy in treating recurrent C. difficile infection, it has been applied to other intestinal diseases, such as IBD, IBS, and pancreatitis. In IBD studies, FMT has shown significant efficacy in inducing remission of UC. A study of UC in children showed that the gut microbiota and metabolome of FMT responders were significantly more similar to those of healthy people[141].

***Antibiotics***

Studies have found that antibiotics on DCA induced inflammation of the intestinal protective, may significantly reduced intestinal flora diversity and broad-spectrum antibiotics, reduced intestinal tract has 7 alpha to hydroxylation enzyme bacteria, lead to waste source of primary BA dominate in the host, and the source of intestinal flora secondary BA decreased[140]. However, the choice of antibiotics is also important. In a 12-wk clinical study, the nonabsorbable antibiotic rifaximin showed higher remission rates in patients with active CD. Given that different antibiotics have different effects on BA concentration and composition as well as IBD, antibiotic and patient selection will be important in evaluating antibiotic efficacy against IBD in the future[141].

**CONCLUSION**

Changes in lifestyle and diet have contributed to the increasing incidence of IBD. High fat diet not only changes the characteristics of intestinal flora, but also affects the metabolism of BAs in intestinal lumen. Therefore, studies focusing on BAs and gut microbiota have attracted much attention in digestive diseases. Characteristic changes in the gut microbiota in IBD patients affect the composition of the BA pool. Secondary BAs, as anti-inflammatory factors, may be non-invasive biomarkers in mucosal healing. The emergence of novel metabolomics has revealed the bacterial species that transform BAs and the mechanism of signaling pathways that regulate the development of IBD disease. The interaction between gut microbiota and BAs represents a promising new therapeutic approach for IBD. Some animal studies have shown the important value of the gut microbial-BA axis. However, there is no clear evidence of a similar effect in clinical practice, and further clinical studies are needed to verify it.

**REFERENCES**

1 **Franzosa EA**, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, Vatanen T, Hall AB, Mallick H, McIver LJ, Sauk JS, Wilson RG, Stevens BW, Scott JM, Pierce K, Deik AA, Bullock K, Imhann F, Porter JA, Zhernakova A, Fu J, Weersma RK, Wijmenga C, Clish CB, Vlamakis H, Huttenhower C, Xavier RJ. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat Microbiol* 2019; **4**: 293-305 [PMID: 30531976 DOI: 10.1038/s41564-018-0306-4]

2 **Lavelle A**, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 223-237 [PMID: 32076145 DOI: 10.1038/s41575-019-0258-z]

3 **Lloyd-Price J**, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, Andrews E, Ajami NJ, Bonham KS, Brislawn CJ, Casero D, Courtney H, Gonzalez A, Graeber TG, Hall AB, Lake K, Landers CJ, Mallick H, Plichta DR, Prasad M, Rahnavard G, Sauk J, Shungin D, Vázquez-Baeza Y, White RA 3rd; IBDMDB Investigators, Braun J, Denson LA, Jansson JK, Knight R, Kugathasan S, McGovern DPB, Petrosino JF, Stappenbeck TS, Winter HS, Clish CB, Franzosa EA, Vlamakis H, Xavier RJ, Huttenhower C. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019; **569**: 655-662 [PMID: 31142855 DOI: 10.1038/s41586-019-1237-9]

4 **Yan JB**, Luo MM, Chen ZY, He BH. The Function and Role of the Th17/Treg Cell Balance in Inflammatory Bowel Disease. *J Immunol Res* 2020; **2020**: 8813558 [PMID: 33381606 DOI: 10.1155/2020/8813558]

5 **Tang WHW**, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol* 2019; **16**: 137-154 [PMID: 30410105 DOI: 10.1038/s41569-018-0108-7]

6 **Weng YJ**, Gan HY, Li X, Huang Y, Li ZC, Deng HM, Chen SZ, Zhou Y, Wang LS, Han YP, Tan YF, Song YJ, Du ZM, Liu YY, Wang Y, Qin N, Bai Y, Yang RF, Bi YJ, Zhi FC. Correlation of diet, microbiota and metabolite networks in inflammatory bowel disease. *J Dig Dis* 2019; **20**: 447-459 [PMID: 31240835 DOI: 10.1111/1751-2980.12795]

7 **Fiorucci S**, Carino A, Baldoni M, Santucci L, Costanzi E, Graziosi L, Distrutti E, Biagioli M. Bile Acid Signaling in Inflammatory Bowel Diseases. *Dig Dis Sci* 2021; **66**: 674-693 [PMID: 33289902 DOI: 10.1007/s10620-020-06715-3]

8 **Moszak M**, Szulińska M, Bogdański P. You Are What You Eat-The Relationship between Diet, Microbiota, and Metabolic Disorders-A Review. *Nutrients* 2020; **12** [PMID: 32326604 DOI: 10.3390/nu12041096]

9 **Long SL**, Gahan CGM, Joyce SA. Interactions between gut bacteria and bile in health and disease. *Mol Aspects Med* 2017; **56**: 54-65 [PMID: 28602676 DOI: 10.1016/j.mam.2017.06.002]

10 **Michaudel C**, Sokol H. The Gut Microbiota at the Service of Immunometabolism. *Cell Metab* 2020; **32**: 514-523 [PMID: 32946809 DOI: 10.1016/j.cmet.2020.09.004]

11 **Rohr MW**, Narasimhulu CA, Rudeski-Rohr TA, Parthasarathy S. Negative Effects of a High-Fat Diet on Intestinal Permeability: A Review. *Adv Nutr* 2020; **11**: 77-91 [PMID: 31268137 DOI: 10.1093/advances/nmz061]

12 **Guzior DV**, Quinn RA. Review: microbial transformations of human bile acids. *Microbiome* 2021; **9**: 140 [PMID: 34127070 DOI: 10.1186/s40168-021-01101-1]

13 **Little R**, Wine E, Kamath BM, Griffiths AM, Ricciuto A. Gut microbiome in primary sclerosing cholangitis: A review. *World J Gastroenterol* 2020; **26**: 2768-2780 [PMID: 32550753 DOI: 10.3748/wjg.v26.i21.2768]

14 **Gallagher K**, Catesson A, Griffin JL, Holmes E, Williams HRT. Metabolomic Analysis in Inflammatory Bowel Disease: A Systematic Review. *J Crohns Colitis* 2021; **15**: 813-826 [PMID: 33175138 DOI: 10.1093/ecco-jcc/jjaa227]

15 **Lee JWJ**, Plichta D, Hogstrom L, Borren NZ, Lau H, Gregory SM, Tan W, Khalili H, Clish C, Vlamakis H, Xavier RJ, Ananthakrishnan AN. Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. *Cell Host Microbe* 2021; **29**: 1294-1304.e4 [PMID: 34297922 DOI: 10.1016/j.chom.2021.06.019]

16 **Yang Y**, Jobin C. Novel insights into microbiome in colitis and colorectal cancer. *Curr Opin Gastroenterol* 2017; **33**: 422-427 [PMID: 28877044 DOI: 10.1097/MOG.0000000000000399]

17 **Biagioli M**, Marchianò S, Carino A, Di Giorgio C, Santucci L, Distrutti E, Fiorucci S. Bile Acids Activated Receptors in Inflammatory Bowel Disease. *Cells* 2021; **10** [PMID: 34064187 DOI: 10.3390/cells10061281]

18 **Hosseinkhani F**, Heinken A, Thiele I, Lindenburg PW, Harms AC, Hankemeier T. The contribution of gut bacterial metabolites in the human immune signaling pathway of non-communicable diseases. *Gut Microbes* 2021; **13**: 1-22 [PMID: 33590776 DOI: 10.1080/19490976.2021.1882927]

19 **Fang Y**, Yan C, Zhao Q, Xu J, Liu Z, Gao J, Zhu H, Dai Z, Wang D, Tang D. The roles of microbial products in the development of colorectal cancer: a review. *Bioengineered* 2021; **12**: 720-735 [PMID: 33618627 DOI: 10.1080/21655979.2021.1889109]

20 **Magri V**, Boltri M, Cai T, Colombo R, Cuzzocrea S, De Visschere P, Giuberti R, Granatieri CM, Latino MA, Larganà G, Leli C, Maierna G, Marchese V, Massa E, Matteelli A, Montanari E, Morgia G, Naber KG, Papadouli V, Perletti G, Rekleiti N, Russo GI, Sensini A, Stamatiou K, Trinchieri A, Wagenlehner FME. Multidisciplinary approach to prostatitis. *Arch Ital Urol Androl* 2019; **90**: 227-248 [PMID: 30655633 DOI: 10.4081/aiua.2018.4.227]

21 **Bromke MA**, Krzystek-Korpacka M. Bile Acid Signaling in Inflammatory Bowel Disease. *Int J Mol Sci* 2021; **22** [PMID: 34445800 DOI: 10.3390/ijms22169096]

22 **Banfi D**, Moro E, Bosi A, Bistoletti M, Cerantola S, Crema F, Maggi F, Giron MC, Giaroni C, Baj A. Impact of Microbial Metabolites on Microbiota-Gut-Brain Axis in Inflammatory Bowel Disease. *Int J Mol Sci* 2021; **22** [PMID: 33562721 DOI: 10.3390/ijms22041623]

23 **Gasaly N**, de Vos P, Hermoso MA. Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation. *Front Immunol* 2021; **12**: 658354 [PMID: 34122415 DOI: 10.3389/fimmu.2021.658354]

24 **Li N**, Zhan S, Tian Z, Liu C, Xie Z, Zhang S, Chen M, Zeng Z, Zhuang X. Alterations in Bile Acid Metabolism Associated With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; **27**: 1525-1540 [PMID: 33399195 DOI: 10.1093/ibd/izaa342]

25 **Yang M**, Gu Y, Li L, Liu T, Song X, Sun Y, Cao X, Wang B, Jiang K, Cao H. Bile Acid-Gut Microbiota Axis in Inflammatory Bowel Disease: From Bench to Bedside. *Nutrients* 2021; **13** [PMID: 34579027 DOI: 10.3390/nu13093143]

26 **Liu Z**, Wang H. Probiotics alleviate inflammatory bowel disease in mice by regulating intestinal microorganisms-bile acid-NLRP3 inflammasome pathway. *Acta Biochim Pol* 2021; **68**: 687-693 [PMID: 34648252 DOI: 10.18388/abp.2020\_5597]

27 **Wellman AS**, Metukuri MR, Kazgan N, Xu X, Xu Q, Ren NSX, Czopik A, Shanahan MT, Kang A, Chen W, Azcarate-Peril MA, Gulati AS, Fargo DC, Guarente L, Li X. Intestinal Epithelial Sirtuin 1 Regulates Intestinal Inflammation During Aging in Mice by Altering the Intestinal Microbiota. *Gastroenterology* 2017; **153**: 772-786 [PMID: 28552621 DOI: 10.1053/j.gastro.2017.05.022]

28 **Foley SE**, Tuohy C, Dunford M, Grey MJ, De Luca H, Cawley C, Szabady RL, Maldonado-Contreras A, Houghton JM, Ward DV, Mrsny RJ, McCormick BA. Gut microbiota regulation of P-glycoprotein in the intestinal epithelium in maintenance of homeostasis. *Microbiome* 2021; **9**: 183 [PMID: 34493329 DOI: 10.1186/s40168-021-01137-3]

29 **Paramsothy S**, Nielsen S, Kamm MA, Deshpande NP, Faith JJ, Clemente JC, Paramsothy R, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Lin E, Borody TJ, Wilkins MR, Colombel JF, Mitchell HM, Kaakoush NO. Specific Bacteria and Metabolites Associated With Response to Fecal Microbiota Transplantation in Patients With Ulcerative Colitis. *Gastroenterology* 2019; **156**: 1440-1454.e2 [PMID: 30529583 DOI: 10.1053/j.gastro.2018.12.001]

30 **Sitkin S**, Pokrotnieks J. Bad "Good" Bile Acids and Gut Microbiota Dysbiosis in Inflammatory Bowel Disease: Mice and Humans Are Not the Same. *Dig Dis Sci* 2021; **66**: 925-927 [PMID: 33063190 DOI: 10.1007/s10620-020-06650-3]

31 **Camilleri M**. Ten Reasons to Think About Bile Acids in Managing Inflammatory Bowel Disease. *J Crohns Colitis* 2021; **15**: 511-515 [PMID: 32866248 DOI: 10.1093/ecco-jcc/jjaa175]

32 **Hu J**, Huang H, Che Y, Ding C, Zhang L, Wang Y, Hao H, Shen H, Cao L. Qingchang Huashi Formula attenuates DSS-induced colitis in mice by restoring gut microbiota-metabolism homeostasis and goblet cell function. *J Ethnopharmacol* 2021; **266**: 113394 [PMID: 32941971 DOI: 10.1016/j.jep.2020.113394]

33 **Liu TC**, Kern JT, Jain U, Sonnek NM, Xiong S, Simpson KF, VanDussen KL, Winkler ES, Haritunians T, Malique A, Lu Q, Sasaki Y, Storer C, Diamond MS, Head RD, McGovern DPB, Stappenbeck TS. Western diet induces Paneth cell defects through microbiome alterations and farnesoid X receptor and type I interferon activation. *Cell Host Microbe* 2021; **29**: 988-1001.e6 [PMID: 34010595 DOI: 10.1016/j.chom.2021.04.004]

34 **Baumgartner M**, Lang M, Holley H, Crepaz D, Hausmann B, Pjevac P, Moser D, Haller F, Hof F, Beer A, Orgler E, Frick A, Khare V, Evstatiev R, Strohmaier S, Primas C, Dolak W, Köcher T, Klavins K, Rath T, Neurath MF, Berry D, Makristathis A, Muttenthaler M, Gasche C. Mucosal Biofilms Are an Endoscopic Feature of Irritable Bowel Syndrome and Ulcerative Colitis. *Gastroenterology* 2021; **161**: 1245-1256.e20 [PMID: 34146566 DOI: 10.1053/j.gastro.2021.06.024]

35 **Xu M**, Shen Y, Cen M, Zhu Y, Cheng F, Tang L, Zheng X, Kim JJ, Dai N, Hu W. Modulation of the Gut Microbiota-farnesoid X Receptor Axis Improves Deoxycholic Acid-induced Intestinal Inflammation in Mice. *J Crohns Colitis* 2021; **15**: 1197-1210 [PMID: 33417675 DOI: 10.1093/ecco-jcc/jjab003]

36 **Connors J**, Dunn KA, Allott J, Bandsma R, Rashid M, Otley AR, Bielawski JP, Van Limbergen J. The relationship between fecal bile acids and microbiome community structure in pediatric Crohn's disease. *ISME J* 2020; **14**: 702-713 [PMID: 31796936 DOI: 10.1038/s41396-019-0560-3]

37 **Yang ZH**, Liu F, Zhu XR, Suo FY, Jia ZJ, Yao SK. Altered profiles of fecal bile acids correlate with gut microbiota and inflammatory responses in patients with ulcerative colitis. *World J Gastroenterol* 2021; **27**: 3609-3629 [PMID: 34239273 DOI: 10.3748/wjg.v27.i24.3609]

38 **Panek-Jeziorna M**, Mulak A. The role of bile acids in the pathogenesis of bowel diseases. *Postepy Hig Med Dosw (Online)* 2017; **71**: 737-746 [PMID: 28894048 DOI: 10.5604/01.3001.0010.3852]

39 **Hernández-Rocha C**, Borowski K, Turpin W, Filice M, Nayeri S, Raygoza Garay JA, Stempak JM, Silverberg MS. Integrative Analysis of Colonic Biopsies from Inflammatory Bowel Disease Patients Identifies an Interaction Between Microbial Bile Acid-inducible Gene Abundance and Human Angiopoietin-like 4 Gene Expression. *J Crohns Colitis* 2021; **15**: 2078-2087 [PMID: 34077506 DOI: 10.1093/ecco-jcc/jjab096]

40 **Chen ML**, Takeda K, Sundrud MS. Emerging roles of bile acids in mucosal immunity and inflammation. *Mucosal Immunol* 2019; **12**: 851-861 [PMID: 30952999 DOI: 10.1038/s41385-019-0162-4]

41 **Li Q**, Cui Y, Xu B, Wang Y, Lv F, Li Z, Li H, Chen X, Peng X, Chen Y, Wu E, Qu D, Jian Y, Si H. Main active components of Jiawei Gegen Qinlian decoction protects against ulcerative colitis under different dietary environments in a gut microbiota-dependent manner. *Pharmacol Res* 2021; **170**: 105694 [PMID: 34087350 DOI: 10.1016/j.phrs.2021.105694]

42 **Grüner N**, Mattner J. Bile Acids and Microbiota: Multifaceted and Versatile Regulators of the Liver-Gut Axis. *Int J Mol Sci* 2021; **22** [PMID: 33573273 DOI: 10.3390/ijms22031397]

43 **Quraishi MN**, Acharjee A, Beggs AD, Horniblow R, Tselepis C, Gkoutos G, Ghosh S, Rossiter AE, Loman N, van Schaik W, Withers D, Walters JRF, Hirschfield GM, Iqbal TH. A Pilot Integrative Analysis of Colonic Gene Expression, Gut Microbiota, and Immune Infiltration in Primary Sclerosing Cholangitis-Inflammatory Bowel Disease: Association of Disease With Bile Acid Pathways. *J Crohns Colitis* 2020; **14**: 935-947 [PMID: 32016358 DOI: 10.1093/ecco-jcc/jjaa021]

44 **Cai J**, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. *Cell Host Microbe* 2022; **30**: 289-300 [PMID: 35271802 DOI: 10.1016/j.chom.2022.02.004]

45 **Kriaa A**, Mariaule V, Jablaoui A, Rhimi S, Mkaouar H, Hernandez J, Korkmaz B, Lesner A, Maguin E, Aghdassi A, Rhimi M. Bile Acids: Key Players in Inflammatory Bowel Diseases? *Cells* 2022; **11** [PMID: 35269523 DOI: 10.3390/cells11050901]

46 **Jin LH**, Fang ZP, Fan MJ, Huang WD. Bile-ology: from bench to bedside. *J Zhejiang Univ Sci B* 2019; **20**: 414-427 [PMID: 31090267 DOI: 10.1631/jzus.B1900158]

47 **Ke J**, Li Y, Han C, He R, Lin R, Qian W, Hou X. Fucose Ameliorate Intestinal Inflammation Through Modulating the Crosstalk Between Bile Acids and Gut Microbiota in a Chronic Colitis Murine Model. *Inflamm Bowel Dis* 2020; **26**: 863-873 [PMID: 32010956 DOI: 10.1093/ibd/izaa007]

48 **Walker A**, Schmitt-Kopplin P. The role of fecal sulfur metabolome in inflammatory bowel diseases. *Int J Med Microbiol* 2021; **311**: 151513 [PMID: 34147944 DOI: 10.1016/j.ijmm.2021.151513]

49 **Jin WB**, Li TT, Huo D, Qu S, Li XV, Arifuzzaman M, Lima SF, Shi HQ, Wang A, Putzel GG, Longman RS, Artis D, Guo CJ. Genetic manipulation of gut microbes enables single-gene interrogation in a complex microbiome. *Cell* 2022; **185**: 547-562.e22 [PMID: 35051369 DOI: 10.1016/j.cell.2021.12.035]

50 **Thomas JP**, Modos D, Rushbrook SM, Powell N, Korcsmaros T. The Emerging Role of Bile Acids in the Pathogenesis of Inflammatory Bowel Disease. *Front Immunol* 2022; **13**: 829525 [PMID: 35185922 DOI: 10.3389/fimmu.2022.829525]

51 **Ke J**, He R, Hou X. Reply to the Letter: Gut Microbiota-mediated Pleiotropic Effects of Fucose Can Improve Inflammatory Bowel Disease by Modulating Bile Acid Metabolism and Enhancing Propionate Production. *Inflamm Bowel Dis* 2021; **27**: e12 [PMID: 33051685 DOI: 10.1093/ibd/izaa234]

52 **Chen ML**, Sundrud MS. Xenobiotic and endobiotic handling by the mucosal immune system. *Curr Opin Gastroenterol* 2018; **34**: 404-412 [PMID: 30299289 DOI: 10.1097/MOG.0000000000000478]

53 **Heinken A**, Ravcheev DA, Baldini F, Heirendt L, Fleming RMT, Thiele I. Systematic assessment of secondary bile acid metabolism in gut microbes reveals distinct metabolic capabilities in inflammatory bowel disease. *Microbiome* 2019; **7**: 75 [PMID: 31092280 DOI: 10.1186/s40168-019-0689-3]

54 **Sitkin S**, Vakhitov T, Kononova S, Skalinskaya M, Pokrotnieks J. Gut Microbiota-Mediated Pleiotropic Effects of Fucose Can Improve Inflammatory Bowel Disease by Modulating Bile Acid Metabolism and Enhancing Propionate Production. *Inflamm Bowel Dis* 2021; **27**: e10-e11 [PMID: 32879958 DOI: 10.1093/ibd/izaa233]

55 **Debnath N**, Kumar R, Kumar A, Mehta PK, Yadav AK. Gut-microbiota derived bioactive metabolites and their functions in host physiology. *Biotechnol Genet Eng Rev* 2021; **37**: 105-153 [PMID: 34678130 DOI: 10.1080/02648725.2021.1989847]

56 **Bozward AG**, Ronca V, Osei-Bordom D, Oo YH. Gut-Liver Immune Traffic: Deciphering Immune-Pathogenesis to Underpin Translational Therapy. *Front Immunol* 2021; **12**: 711217 [PMID: 34512631 DOI: 10.3389/fimmu.2021.711217]

57 **Wang Y**, Gao X, Zhang X, Xiao F, Hu H, Li X, Dong F, Sun M, Xiao Y, Ge T, Li D, Yu G, Liu Z, Zhang T. Microbial and metabolic features associated with outcome of infliximab therapy in pediatric Crohn's disease. *Gut Microbes* 2021; **13**: 1-18 [PMID: 33430702 DOI: 10.1080/19490976.2020.1865708]

58 **Liu M**, Nazzal L. Enteric hyperoxaluria: role of microbiota and antibiotics. *Curr Opin Nephrol Hypertens* 2019; **28**: 352-359 [PMID: 31145706 DOI: 10.1097/MNH.0000000000000518]

59 **Bi C**, Xiao G, Liu C, Yan J, Chen J, Si W, Zhang J, Liu Z. Molecular Immune Mechanism of Intestinal Microbiota and Their Metabolites in the Occurrence and Development of Liver Cancer. *Front Cell Dev Biol* 2021; **9**: 702414 [PMID: 34957088 DOI: 10.3389/fcell.2021.702414]

60 **Özdirik B**, Müller T, Wree A, Tacke F, Sigal M. The Role of Microbiota in Primary Sclerosing Cholangitis and Related Biliary Malignancies. *Int J Mol Sci* 2021; **22** [PMID: 34203536 DOI: 10.3390/ijms22136975]

61 **Xu M**, Cen M, Shen Y, Zhu Y, Cheng F, Tang L, Hu W, Dai N. Deoxycholic Acid-Induced Gut Dysbiosis Disrupts Bile Acid Enterohepatic Circulation and Promotes Intestinal Inflammation. *Dig Dis Sci* 2021; **66**: 568-576 [PMID: 32198567 DOI: 10.1007/s10620-020-06208-3]

62 **Sittipo P**, Shim JW, Lee YK. Microbial Metabolites Determine Host Health and the Status of Some Diseases. *Int J Mol Sci* 2019; **20** [PMID: 31653062 DOI: 10.3390/ijms20215296]

63 **Maroni L**, Ninfole E, Pinto C, Benedetti A, Marzioni M. Gut-Liver Axis and Inflammasome Activation in Cholangiocyte Pathophysiology. *Cells* 2020; **9** [PMID: 32192118 DOI: 10.3390/cells9030736]

64 **Choi S**, Snider AJ. Diet, lipids and colon cancer. *Int Rev Cell Mol Biol* 2019; **347**: 105-144 [PMID: 31451212 DOI: 10.1016/bs.ircmb.2019.07.001]

65 **Kumar A**, Al-Hassi HO, Steed H, Phipps O, Brookes MJ. Bile Acids and the Microbiome: Making Sense of This Dynamic Relationship in Their Role and Management in Crohn's Disease. *Can J Gastroenterol Hepatol* 2022; **2022**: 8416578 [PMID: 35360442 DOI: 10.1155/2022/8416578]

66 **Kummen M**, Hov JR. The gut microbial influence on cholestatic liver disease. *Liver Int* 2019; **39**: 1186-1196 [PMID: 31125502 DOI: 10.1111/liv.14153]

67 **Li S**, Zhuge A, Wang K, Lv L, Bian X, Yang L, Xia J, Jiang X, Wu W, Wang S, Wang Q, Li L. Ketogenic diet aggravates colitis, impairs intestinal barrier and alters gut microbiota and metabolism in DSS-induced mice. *Food Funct* 2021; **12**: 10210-10225 [PMID: 34542110 DOI: 10.1039/d1fo02288a]

68 **Wang Z**, Chen WD, Wang YD. Nuclear receptors: a bridge linking the gut microbiome and the host. *Mol Med* 2021; **27**: 144 [PMID: 34740314 DOI: 10.1186/s10020-021-00407-y]

69 **Gadaleta RM**, Garcia-Irigoyen O, Cariello M, Scialpi N, Peres C, Vetrano S, Fiorino G, Danese S, Ko B, Luo J, Porru E, Roda A, Sabbà C, Moschetta A. Fibroblast Growth Factor 19 modulates intestinal microbiota and inflammation in presence of Farnesoid X Receptor. *EBioMedicine* 2020; **54**: 102719 [PMID: 32259714 DOI: 10.1016/j.ebiom.2020.102719]

70 **Hua YL**, Jia YQ, Zhang XS, Yuan ZW, Ji P, Hu JJ, Wei YM. Baitouweng Tang ameliorates DSS-induced ulcerative colitis through the regulation of the gut microbiota and bile acids *via* pathways involving FXR and TGR5. *Biomed Pharmacother* 2021; **137**: 111320 [PMID: 33578232 DOI: 10.1016/j.biopha.2021.111320]

71 **Ward JBJ**, Lajczak NK, Kelly OB, O'Dwyer AM, Giddam AK, Ní Gabhann J, Franco P, Tambuwala MM, Jefferies CA, Keely S, Roda A, Keely SJ. Ursodeoxycholic acid and lithocholic acid exert anti-inflammatory actions in the colon. *Am J Physiol Gastrointest Liver Physiol* 2017; **312**: G550-G558 [PMID: 28360029 DOI: 10.1152/ajpgi.00256.2016]

72 **Liao HY**, Wang CY, Lee CH, Kao HL, Wu WK, Kuo CH. Development of an Efficient and Sensitive Chemical Derivatization-Based LC-MS/MS Method for Quantifying Gut Microbiota-Derived Metabolites in Human Plasma and Its Application in Studying Cardiovascular Disease. *J Proteome Res* 2021; **20**: 3508-3518 [PMID: 34053222 DOI: 10.1021/acs.jproteome.1c00147]

73 **Bogatyrev SR**, Rolando JC, Ismagilov RF. Self-reinoculation with fecal flora changes microbiota density and composition leading to an altered bile-acid profile in the mouse small intestine. *Microbiome* 2020; **8**: 19 [PMID: 32051033 DOI: 10.1186/s40168-020-0785-4]

74 **Tian M**, Li D, Ma C, Feng Y, Hu X, Chen F. Barley Leaf Insoluble Dietary Fiber Alleviated Dextran Sulfate Sodium-Induced Mice Colitis by Modulating Gut Microbiota. *Nutrients* 2021; **13** [PMID: 33807544 DOI: 10.3390/nu13030846]

75 **Xourgia E**, Papazafiropoulou A, Papanas N, Melidonis A. Anti-diabetic treatment leads to changes in gut microbiome. *Front Biosci (Landmark Ed)* 2019; **24**: 688-699 [PMID: 30844705 DOI: 10.2741/4743]

76 **Shah A**, Macdonald GA, Morrison M, Holtmann G. Targeting the Gut Microbiome as a Treatment for Primary Sclerosing Cholangitis: A Conceptional Framework. *Am J Gastroenterol* 2020; **115**: 814-822 [PMID: 32250997 DOI: 10.14309/ajg.0000000000000604]

77 **Wang S**, Martins R, Sullivan MC, Friedman ES, Misic AM, El-Fahmawi A, De Martinis ECP, O'Brien K, Chen Y, Bradley C, Zhang G, Berry ASF, Hunter CA, Baldassano RN, Rondeau MP, Beiting DP. Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids. *Microbiome* 2019; **7**: 126 [PMID: 31472697 DOI: 10.1186/s40168-019-0740-4]

78 **Thibaut MM**, Bindels LB. Crosstalk between bile acid-activated receptors and microbiome in entero-hepatic inflammation. *Trends Mol Med* 2022; **28**: 223-236 [PMID: 35074252 DOI: 10.1016/j.molmed.2021.12.006]

79 **Dilmore AH**, McDonald D, Nguyen TT, Adams JB, Krajmalnik-Brown R, Elijah E, Dorrestein PC, Knight R. The Fecal Microbiome and Metabolome of Pitt Hopkins Syndrome, a Severe Autism Spectrum Disorder. *mSystems* 2021; **6**: e0100621 [PMID: 34846164 DOI: 10.1128/mSystems.01006-21]

80 **Diederen K**, Li JV, Donachie GE, de Meij TG, de Waart DR, Hakvoort TBM, Kindermann A, Wagner J, Auyeung V, Te Velde AA, Heinsbroek SEM, Benninga MA, Kinross J, Walker AW, de Jonge WJ, Seppen J. Exclusive enteral nutrition mediates gut microbial and metabolic changes that are associated with remission in children with Crohn's disease. *Sci Rep* 2020; **10**: 18879 [PMID: 33144591 DOI: 10.1038/s41598-020-75306-z]

81 **Zhang C**, Zhao Y, Jiang J, Yu L, Tian F, Zhao J, Zhang H, Chen W, Zhai Q. Identification of the key characteristics of *Bifidobacterium longum* strains for the alleviation of ulcerative colitis. *Food Funct* 2021; **12**: 3476-3492 [PMID: 33900330 DOI: 10.1039/d1fo00017a]

82 **Das P**, Marcišauskas S, Ji B, Nielsen J. Metagenomic analysis of bile salt biotransformation in the human gut microbiome. *BMC Genomics* 2019; **20**: 517 [PMID: 31234773 DOI: 10.1186/s12864-019-5899-3]

83 **Zhu T**, Xue Q, Liu Y, Xu Y, Xiong C, Lu J, Yang H, Zhang Q, Huang Y. Analysis of Intestinal Microflora and Metabolites From Mice With DSS-Induced IBD Treated With *Schistosoma* Soluble Egg Antigen. *Front Cell Dev Biol* 2021; **9**: 777218 [PMID: 34858992 DOI: 10.3389/fcell.2021.777218]

84 **Tao F**, Xing X, Wu J, Jiang R. Enteral nutrition modulation with n-3 PUFAs directs microbiome and lipid metabolism in mice. *PLoS One* 2021; **16**: e0248482 [PMID: 33764993 DOI: 10.1371/journal.pone.0248482]

85 **Sidebottom AM**, Chang EB. IBD Microbial Metabolome: The Good, Bad, and Unknown. *Trends Endocrinol Metab* 2020; **31**: 807-809 [PMID: 32456844 DOI: 10.1016/j.tem.2020.05.001]

86 **Wan Y**, Tong W, Zhou R, Li J, Yuan J, Wang F, Li D. Habitual animal fat consumption in shaping gut microbiota and microbial metabolites. *Food Funct* 2019; **10**: 7973-7982 [PMID: 31776537 DOI: 10.1039/c9fo01490j]

87 **Mohammed AD**, Mohammed Z, Roland MM, Chatzistamou I, Jolly A, Schoettmer LM, Arroyo M, Kakar K, Tian Y, Patterson A, Nagarkatti M, Nagarkatti P, Kubinak JL. Defective humoral immunity disrupts bile acid homeostasis which promotes inflammatory disease of the small bowel. *Nat Commun* 2022; **13**: 525 [PMID: 35082296 DOI: 10.1038/s41467-022-28126-w]

88 **Montrose DC**, Nishiguchi R, Basu S, Staab HA, Zhou XK, Wang H, Meng L, Johncilla M, Cubillos-Ruiz JR, Morales DK, Wells MT, Simpson KW, Zhang S, Dogan B, Jiao C, Fei Z, Oka A, Herzog JW, Sartor RB, Dannenberg AJ. Dietary Fructose Alters the Composition, Localization, and Metabolism of Gut Microbiota in Association With Worsening Colitis. *Cell Mol Gastroenterol Hepatol* 2021; **11**: 525-550 [PMID: 32961355 DOI: 10.1016/j.jcmgh.2020.09.008]

89 **Halmos T**, Suba I. Non-alcoholic fatty liver disease, as a component of the metabolic syndrome, and its causal correlations with other extrahepatic diseases. *Orv Hetil* 2017; **158**: 2051-2061 [PMID: 29285942 DOI: 10.1556/650.2017.30936]

90 **Burkhardt W**, Rausch T, Klopfleisch R, Blaut M, Braune A. Impact of dietary sulfolipid-derived sulfoquinovose on gut microbiota composition and inflammatory status of colitis-prone interleukin-10-deficient mice. *Int J Med Microbiol* 2021; **311**: 151494 [PMID: 33711649 DOI: 10.1016/j.ijmm.2021.151494]

91 **Wang Z**, Chen J, Chen Z, Xie L, Wang W. Clinical effects of ursodeoxycholic acid on patients with ulcerative colitis may improve *via* the regulation of IL-23-IL-17 axis and the changes of the proportion of intestinal microflora. *Saudi J Gastroenterol* 2021; **27**: 149-157 [PMID: 33835051 DOI: 10.4103/sjg.SJG\_462\_20]

92 **Liu F**, Wang X, Li D, Cui Y, Li X. Apple polyphenols extract alleviated dextran sulfate sodium-induced ulcerative colitis in C57BL/6 male mice by restoring bile acid metabolism disorder and gut microbiota dysbiosis. *Phytother Res* 2021; **35**: 1468-1485 [PMID: 33215776 DOI: 10.1002/ptr.6910]

93 **Delmas J**, Gibold L, Faïs T, Batista S, Leremboure M, Sinel C, Vazeille E, Cattoir V, Buisson A, Barnich N, Dalmasso G, Bonnet R. Metabolic adaptation of adherent-invasive Escherichia coli to exposure to bile salts. *Sci Rep* 2019; **9**: 2175 [PMID: 30778122 DOI: 10.1038/s41598-019-38628-1]

94 **Feng L**, Zhou N, Li Z, Fu D, Guo Y, Gao X, Liu X. Co-occurrence of gut microbiota dysbiosis and bile acid metabolism alteration is associated with psychological disorders in Crohn's disease. *FASEB J* 2022; **36**: e22100 [PMID: 34939244 DOI: 10.1096/fj.202101088RRR]

95 **Martin FP**, Su MM, Xie GX, Guiraud SP, Kussmann M, Godin JP, Jia W, Nydegger A. Urinary metabolic insights into host-gut microbial interactions in healthy and IBD children. *World J Gastroenterol* 2017; **23**: 3643-3654 [PMID: 28611517 DOI: 10.3748/wjg.v23.i20.3643]

96 **Fobofou SA**, Savidge T. Microbial metabolites: cause or consequence in gastrointestinal disease? *Am J Physiol Gastrointest Liver Physiol* 2022; **322**: G535-G552 [PMID: 35271353 DOI: 10.1152/ajpgi.00008.2022]

97 **Jia YQ**, Yuan ZW, Zhang XS, Dong JQ, Liu XN, Peng XT, Yao WL, Ji P, Wei YM, Hua YL. Total alkaloids of Sophora alopecuroides L. ameliorated murine colitis by regulating bile acid metabolism and gut microbiota. *J Ethnopharmacol* 2020; **255**: 112775 [PMID: 32205259 DOI: 10.1016/j.jep.2020.112775]

98 **Jia B**, Park D, Hahn Y, Jeon CO. Metagenomic analysis of the human microbiome reveals the association between the abundance of gut bile salt hydrolases and host health. *Gut Microbes* 2020; **11**: 1300-1313 [PMID: 32329665 DOI: 10.1080/19490976.2020.1748261]

99 **Li Y**, Xie Z, Gao T, Li L, Chen Y, Xiao D, Liu W, Zou B, Lu B, Tian X, Han B, Guo Y, Zhang S, Lin L, Wang M, Li P, Liao Q. A holistic view of gallic acid-induced attenuation in colitis based on microbiome-metabolomics analysis. *Food Funct* 2019; **10**: 4046-4061 [PMID: 31225554 DOI: 10.1039/c9fo00213h]

100 **Yang L**, Lin Q, Han L, Wang Z, Luo M, Kang W, Liu J, Wang J, Ma T, Liu H. Soy hull dietary fiber alleviates inflammation in BALB/C mice by modulating the gut microbiota and suppressing the TLR-4/NF-κB signaling pathway. *Food Funct* 2020; **11**: 5965-5975 [PMID: 32662806 DOI: 10.1039/d0fo01102a]

101 **Feng W**, Liu J, Tan Y, Ao H, Wang J, Peng C. Polysaccharides from Atractylodes macrocephala Koidz. Ameliorate ulcerative colitis *via* extensive modification of gut microbiota and host metabolism. *Food Res Int* 2020; **138**: 109777 [PMID: 33288163 DOI: 10.1016/j.foodres.2020.109777]

102 **Li L**, Zhang X, Ning Z, Mayne J, Moore JI, Butcher J, Chiang CK, Mack D, Stintzi A, Figeys D. Evaluating in Vitro Culture Medium of Gut Microbiome with Orthogonal Experimental Design and a Metaproteomics Approach. *J Proteome Res* 2018; **17**: 154-163 [PMID: 29130306 DOI: 10.1021/acs.jproteome.7b00461]

103 **Singhal S**, Rani V. Study to Explore Plant-Derived Trimethylamine Lyase Enzyme Inhibitors to Address Gut Dysbiosis. *Appl Biochem Biotechnol* 2022; **194**: 99-123 [PMID: 34822060 DOI: 10.1007/s12010-021-03747-x]

104 **Murakami M**, Iwamoto J, Honda A, Tsuji T, Tamamushi M, Ueda H, Monma T, Konishi N, Yara S, Hirayama T, Miyazaki T, Saito Y, Ikegami T, Matsuzaki Y. Detection of Gut Dysbiosis due to Reduced Clostridium Subcluster XIVa Using the Fecal or Serum Bile Acid Profile. *Inflamm Bowel Dis* 2018; **24**: 1035-1044 [PMID: 29688473 DOI: 10.1093/ibd/izy022]

105 **Feng P**, Li Q, Liu L, Wang S, Wu Z, Tao Y, Huang P, Wang P. Crocetin Prolongs Recovery Period of DSS-Induced Colitis *via* Altering Intestinal Microbiome and Increasing Intestinal Permeability. *Int J Mol Sci* 2022; **23** [PMID: 35409192 DOI: 10.3390/ijms23073832]

106 **Smith BJ**, Piceno Y, Zydek M, Zhang B, Syriani LA, Terdiman JP, Kassam Z, Ma A, Lynch SV, Pollard KS, El-Nachef N. Strain-resolved analysis in a randomized trial of antibiotic pretreatment and maintenance dose delivery mode with fecal microbiota transplant for ulcerative colitis. *Sci Rep* 2022; **12**: 5517 [PMID: 35365713 DOI: 10.1038/s41598-022-09307-5]

107 **van Best N**, Rolle-Kampczyk U, Schaap FG, Basic M, Olde Damink SWM, Bleich A, Savelkoul PHM, von Bergen M, Penders J, Hornef MW. Bile acids drive the newborn's gut microbiota maturation. *Nat Commun* 2020; **11**: 3692 [PMID: 32703946 DOI: 10.1038/s41467-020-17183-8]

108 **Huber RM**, Murphy K, Miao B, Link JR, Cunningham MR, Rupar MJ, Gunyuzlu PL, Haws TF, Kassam A, Powell F, Hollis GF, Young PR, Mukherjee R, Burn TC. Generation of multiple farnesoid-X-receptor isoforms through the use of alternative promoters. *Gene* 2002; **290**: 35-43 [PMID: 12062799 DOI: 10.1016/s0378-1119(02)00557-7]

109 **Inagaki T**, Moschetta A, Lee YK, Peng L, Zhao G, Downes M, Yu RT, Shelton JM, Richardson JA, Repa JJ, Mangelsdorf DJ, Kliewer SA. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci U S A* 2006; **103**: 3920-3925 [PMID: 16473946 DOI: 10.1073/pnas.0509592103]

110 **Rapozo DC**, Bernardazzi C, de Souza HS. Diet and microbiota in inflammatory bowel disease: The gut in disharmony. *World J Gastroenterol* 2017; **23**: 2124-2140 [PMID: 28405140 DOI: 10.3748/wjg.v23.i12.2124]

111 **Ridlon JM**, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res* 2006; **47**: 241-259 [PMID: 16299351 DOI: 10.1194/jlr.R500013-JLR200]

112 **Ni J**, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol* 2017; **14**: 573-584 [PMID: 28743984 DOI: 10.1038/nrgastro.2017.88]

113 **Zhang Y**, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, Edwards PA. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proc Natl Acad Sci U S A* 2006; **103**: 1006-1011 [PMID: 16410358 DOI: 10.1073/pnas.0506982103]

114 **Winston JA**, Theriot CM. Diversification of host bile acids by members of the gut microbiota. *Gut Microbes* 2020; **11**: 158-171 [PMID: 31595814 DOI: 10.1080/19490976.2019.1674124]

115 **Han CY**. Update on FXR Biology: Promising Therapeutic Target? *Int J Mol Sci* 2018; **19** [PMID: 30013008 DOI: 10.3390/ijms19072069]

116 **Jia W**, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 111-128 [PMID: 29018272 DOI: 10.1038/nrgastro.2017.119]

117 **Cao H**, Xu M, Dong W, Deng B, Wang S, Zhang Y, Wang S, Luo S, Wang W, Qi Y, Gao J, Cao X, Yan F, Wang B. Secondary bile acid-induced dysbiosis promotes intestinal carcinogenesis. *Int J Cancer* 2017; **140**: 2545-2556 [PMID: 28187526 DOI: 10.1002/ijc.30643]

118 **Martinez-Medina M**, Denizot J, Dreux N, Robin F, Billard E, Bonnet R, Darfeuille-Michaud A, Barnich N. Western diet induces dysbiosis with increased E coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. *Gut* 2014; **63**: 116-124 [PMID: 23598352 DOI: 10.1136/gutjnl-2012-304119]

119 **Rossi O**, van Berkel LA, Chain F, Tanweer Khan M, Taverne N, Sokol H, Duncan SH, Flint HJ, Harmsen HJ, Langella P, Samsom JN, Wells JM. Faecalibacterium prausnitzii A2-165 has a high capacity to induce IL-10 in human and murine dendritic cells and modulates T cell responses. *Sci Rep* 2016; **6**: 18507 [PMID: 26725514 DOI: 10.1038/srep18507]

120 **Vich Vila A**, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z, Kurilshikov A, Bonder MJ, Jiang X, Tigchelaar EF, Dekens J, Peters V, Voskuil MD, Visschedijk MC, van Dullemen HM, Keszthelyi D, Swertz MA, Franke L, Alberts R, Festen EAM, Dijkstra G, Masclee AAM, Hofker MH, Xavier RJ, Alm EJ, Fu J, Wijmenga C, Jonkers DMAE, Zhernakova A, Weersma RK. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. *Sci Transl Med* 2018; **10** [PMID: 30567928 DOI: 10.1126/scitranslmed.aap8914]

121 **Blandford LE**, Johnston EL, Sanderson JD, Wade WG, Lax AJ. Promoter orientation of the immunomodulatory *Bacteroides fragilis* capsular polysaccharide A (PSA) is off in individuals with inflammatory bowel disease (IBD). *Gut Microbes* 2019; **10**: 569-577 [PMID: 30732524 DOI: 10.1080/19490976.2018.1560755]

122 **Round JL**, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science* 2011; **332**: 974-977 [PMID: 21512004 DOI: 10.1126/science.1206095]

123 **Ozkul C**, Ruiz VE, Battaglia T, Xu J, Roubaud-Baudron C, Cadwell K, Perez-Perez GI, Blaser MJ. A single early-in-life antibiotic course increases susceptibility to DSS-induced colitis. *Genome Med* 2020; **12**: 65 [PMID: 32711559 DOI: 10.1186/s13073-020-00764-z]

124 **Kim MH**, Kang SG, Park JH, Yanagisawa M, Kim CH. Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology* 2013; **145**: 396-406.e1-10 [PMID: 23665276 DOI: 10.1053/j.gastro.2013.04.056]

125 **Wang RX**, Lee JS, Campbell EL, Colgan SP. Microbiota-derived butyrate dynamically regulates intestinal homeostasis through regulation of actin-associated protein synaptopodin. *Proc Natl Acad Sci U S A* 2020; **117**: 11648-11657 [PMID: 32398370 DOI: 10.1073/pnas.1917597117]

126 **Alexeev EE**, Lanis JM, Kao DJ, Campbell EL, Kelly CJ, Battista KD, Gerich ME, Jenkins BR, Walk ST, Kominsky DJ, Colgan SP. Microbiota-Derived Indole Metabolites Promote Human and Murine Intestinal Homeostasis through Regulation of Interleukin-10 Receptor. *Am J Pathol* 2018; **188**: 1183-1194 [PMID: 29454749 DOI: 10.1016/j.ajpath.2018.01.011]

127 **Jones ML**, Martoni CJ, Prakash S. Letter to the editor regarding the report of Duboc *et al*: Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut* 2013; **4**: 531-539

128 **Coccia M**, Harrison OJ, Schiering C, Asquith MJ, Becher B, Powrie F, Maloy KJ. IL-1β mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. *J Exp Med* 2012; **209**: 1595-1609 [PMID: 22891275 DOI: 10.1084/jem.20111453]

129 **Fitzpatrick LR**, Jenabzadeh P. IBD and Bile Acid Absorption: Focus on Pre-clinical and Clinical Observations. *Front Physiol* 2020; **11**: 564 [PMID: 32595517 DOI: 10.3389/fphys.2020.00564]

130 **Uchiyama K**, Kishi H, Komatsu W, Nagao M, Ohhira S, Kobashi G. Lipid and Bile Acid Dysmetabolism in Crohn's Disease. *J Immunol Res* 2018; **2018**: 7270486 [PMID: 30402511 DOI: 10.1155/2018/7270486]

131 **Song X**, Sun X, Oh SF, Wu M, Zhang Y, Zheng W, Geva-Zatorsky N, Jupp R, Mathis D, Benoist C, Kasper DL. Microbial bile acid metabolites modulate gut RORγ+ regulatory T cell homeostasis. *Nature* 2020; **577**: 410-415 [PMID: 31875848 DOI: 10.1038/s41586-019-1865-0]

132 **Wang W**, Zhao J, Gui W, Sun D, Dai H, Xiao L, Chu H, Du F, Zhu Q, Schnabl B, Huang K, Yang L, Hou X. Tauroursodeoxycholic acid inhibits intestinal inflammation and barrier disruption in mice with non-alcoholic fatty liver disease. *Br J Pharmacol* 2018; **175**: 469-484 [PMID: 29139555 DOI: 10.1111/bph.14095]

133 **Lajczak-McGinley NK**, Porru E, Fallon CM, Smyth J, Curley C, McCarron PA, Tambuwala MM, Roda A, Keely SJ. The secondary bile acids, ursodeoxycholic acid and lithocholic acid, protect against intestinal inflammation by inhibition of epithelial apoptosis. *Physiol Rep* 2020; **8**: e14456 [PMID: 32562381 DOI: 10.14814/phy2.14456]

134 **Eaton JE**, Silveira MG, Pardi DS, Sinakos E, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Lindor KD. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Am J Gastroenterol* 2011; **106**: 1638-1645 [PMID: 21556038 DOI: 10.1038/ajg.2011.156]

135 **Ajouz H**, Mukherji D, Shamseddine A. Secondary bile acids: an underrecognized cause of colon cancer. *World J Surg Oncol* 2014; **12**: 164 [PMID: 24884764 DOI: 10.1186/1477-7819-12-164]

136 **Ansaldo E**, Slayden LC, Ching KL, Koch MA, Wolf NK, Plichta DR, Brown EM, Graham DB, Xavier RJ, Moon JJ, Barton GM. *Akkermansia muciniphila* induces intestinal adaptive immune responses during homeostasis. *Science* 2019; **364**: 1179-1184 [PMID: 31221858 DOI: 10.1126/science.aaw7479]

137 **Sokol H**, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, Bourrier A, Le Gall G, Lalande V, De Rougemont A, Kirchgesner J, Daguenel A, Cachanado M, Rousseau A, Drouet É, Rosenzwajg M, Hagege H, Dray X, Klatzman D, Marteau P; Saint-Antoine IBD Network, Beaugerie L, Simon T. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. *Microbiome* 2020; **8**: 12 [PMID: 32014035 DOI: 10.1186/s40168-020-0792-5]

138 **Zhang Y**, Limaye PB, Renaud HJ, Klaassen CD. Effect of various antibiotics on modulation of intestinal microbiota and bile acid profile in mice. *Toxicol Appl Pharmacol* 2014; **277**: 138-145 [PMID: 24657338 DOI: 10.1016/j.taap.2014.03.009]

139 **Prantera C**, Lochs H, Campieri M, Scribano ML, Sturniolo GC, Castiglione F, Cottone M. Antibiotic treatment of Crohn's disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment Pharmacol Ther* 2006; **23**: 1117-1125 [PMID: 16611272 DOI: 10.1111/j.1365-2036.2006.02879.x]

140 **Zheng L**, Wen XL, Duan SL. Role of metabolites derived from gut microbiota in inflammatory bowel disease. *World J Clin Cases* 2022; **10**: 2660-2677 [PMID: 35434116 DOI: 10.12998/wjcc.v10.i9.2660]

141 **Zheng L**, Ji YY, Wen XL, Duan SL. Fecal microbiota transplantation in the metabolic diseases: Current status and perspectives. *World J Gastroenterol* 2022; **28**: 2546-2560 [PMID: 35949351 DOI: 10.3748/wjg.v28.i23.2546]

**Footnotes**

**Conflict-of-interest statement:** All theauthors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** April 18, 2022

**First decision:** June 2, 2022

**Article in press:** September 16, 2022

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Dhaliwal A, United States; Šarenac TM, Serbia **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Fan JR

**Figure Legends**



**Figure 1 Synthesis and metabolism of bile acids.** DCA: Deoxycholic acid; LCA: Lithocholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**