Bile acids and their receptors: Potential therapeutic targets in inflammatory bowel disease

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Abstract

Chronic and recurrent inflammatory disorders of the gastrointestinal tract caused by a complex interplay between genetics and intestinal dysbiosis are called inflammatory bowel disease. As a result of the interaction between the liver and the gut microbiota, bile acids are an atypical class of steroids produced in mammals and traditionally known for their function in food absorption. With the development of genomics and metabolomics, more and more data suggest that the pathophysiological mechanisms of inflammatory bowel disease are regulated by bile acids and their receptors. Bile acids operate as signalling molecules by activating a variety of bile acid receptors that impact intestinal flora, epithelial barrier function, and intestinal immunology. Inflammatory bowel disease can be treated in new ways by using these potential molecules. This paper mainly discusses the increasing function of bile acids and their receptors in inflammatory bowel disease and their prospective therapeutic applications. In addition, we explore bile acid metabolism and the interaction of bile acids and the gut microbiota.

Key Words: Bile acids; Inflammatory bowel disease; Intestinal immunology; Bile acid receptors; Bile acid metabolism; Gut microbiota

Core Tip: Chronic and recurrent inflammatory disorders of the gastrointestinal tract caused by a complex interplay between genetics and intestinal dysbiosis are called inflammatory bowel disease. With the development of genomics and meta-bolomics, more and more data suggest that bile acids operate as signalling molecules by activating a variety of bile acid receptors that regulate pathophysiological mechanisms of inflammatory bowel disease. Inflammatory bowel disease can be treated in new ways by using these potential molecules.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic and recurrent inflammatory diseases of the gastrointestinal tract, including two main subtypes: Ulcerative colitis (UC) and Crohn's disease (CD). Globally, the prevalence of IBD is increasing, especially in newly industrialized countries, with a prevalence of 0.5% in 2010, 0.75% in 2020, and a projected 1% in 2030, increasing the burden on health care systems around the world[1,2]. The etiology and pathogenesis of IBD are not well understood. However, it is generally accepted that IBD is a persistent and excessive immune inflammatory response in people with genetic susceptibility when exposed to environmental factors[3]. Immune homeostasis in the intestine involves the coordinated action of epithelial cells and innate and adaptive immune cells. As a result of impaired intestinal epithelial barrier function in IBD, commensal microorganisms translocate into the intestinal wall. The innate immune cells then take up the microbes and their mediators and respond, which activates immune cells and produces cytokines and chemokines. This process, in turn, upsets the homeostasis of the intestine, recruiting more immune cells to the intestinal wall and activating adaptive immunity[4,5]. IBD usually presents with chronic recurrent abdominal pain, diarrhea, mucus, and bloody stools and can also present with serious complications such as anal fistula, intestinal obstruction, and intestinal perforation[6]. Additionally, IBD patients frequently experience symptoms outside of the digestive system, such as joint, eye, or skin inflammation[7]. With the introduction of new biological and small molecule therapies, such as anti-TNF-α biologic agents, anti-interleukin (IL)-12/23 biologic agents, and anti-integrin biologic agents, significant progress has been made in the pharmacological treatment of IBD, but at a high financial and physical cost to patients. Moreover, these therapies can potentially produce life-threatening side effects and cannot cure IBD, and a significant proportion of patients still require surgical treatment. This underscores the need for new treatment strategies for IBD[8,9].

As a result of the interaction between the liver and gut bacteria, bile acids are a class of atypical steroids produced in mammals. Bile acid receptors are a type of cell membrane and nuclear receptor that is found in several digestive and immune system cells. Bile acids exert the majority of their biological effects by serving as ligands for specific bile acid receptors. In the past, bile acids were widely assumed to aid in intestinal nutrition absorption and biliary transport of lipids, toxic metabolites, and foreign substances. However, it is now well established that bile acids can act as multidirec-tional signaling metabolites, modulating physiopathological processes associated with a variety of digestive diseases *via* dynamic interactions with germline-encoded host receptors and microbiota[10-12]. In particular, in IBD, bile acids can modulate IBD pathophysiological pathways by acting on several bile acid receptors, including farnesol X receptor (FXR), retinoid-related orphan receptor γt (RORγt), G protein-coupled bile acid receptor 1 (GPABR1), vitamin D receptor (VDR), pregnane X receptor (PXR), constitutive androstane receptor (CAR), and sphingosine-1-phosphate receptor 2 (S1PR2)[13] (Table 1). This review primarily outlines the growing function of bile acids and their receptors in IBD, as well as their prospective therapeutic applications. Furthermore, we explore bile acid metabolism and the interaction of bile acids and microbiota to present fresh perspectives and molecular targets for diagnosing and treating IBD.

BILE ACID METABOLISM

Bile acids are the end product of cholesterol metabolism. Bile acids are composed mainly of cholesterol, and unlike other steroid hormones, bile acids are amphiphilic molecules with a hydrophobic (beta side) and a hydrophilic (alpha side) surface. They have detergent properties due to their amphiphilic nature, which helps to solubilize lipids in micelles, facilitating emulsification and absorption of dietary fatty acids and cholesterol[14,15]. Mammals have two main types of bile acids: Primary bile acids (PBAs) and secondary bile acids (SBAs). PBAs are formed by cholesterol catabolism in hepatocytes, whereas SBAs are derivatives of PBAs and are generated by the gut microbiome. The bile acid pool is maintained in balance by their hepatic synthesis, enterohepatic circulation, and microbial metabolism[16] (Figure 1).

Bile acid metabolism in the liver

In the liver, cholesterol is generated in the central hepatocyte in several steps to produce PBAs of 24 carbons. In humans, cholic acid (CA) and chenodeoxycholic acid (CDCA) are the most prevalent PBAs, while rats create the 6-hydroxylated

Table 1 Nuclear and membrane receptors of bile acids

| Bile acid receptor	Abbreviation	Type	Bile acid agonists	Main tissue distribution
Farnesol X receptor	FXR	Nuclear hormone receptor	CDCA > DCA > LCA > CA	Intestinal epithelial cells, hepatocytes
Retinoid-related orphan receptor γt	RORγt	Nuclear hormone receptor	3oxo-LCA, isoLCA	Th17 cells, ILC3 and γδT cells
G protein-coupled bile acid receptor 1	GPBAR1 or TGR5	Membrane-bound receptor	LCA > DCA > CDCA > UDCA > CA	Epithelial cells, immune cells, and intestinal nerves in the gut and biliary tract
Vitamin D receptor	VDR	Nuclear hormone receptor	LCA, 3-oxoLCA, and isoalloLCA	Intestinal epithelial cells
Pregnane X receptor	PXR	Nuclear hormone receptor	CDCA, LCA	Intestinal epithelial cells, hepatocytes
Costitutive androstane receptor	CAR	Nuclear hormone receptor	CDCA, LCA	Hepatocytes
Sphingosine-1-phosphate receptor 2	S1PR2	Membrane-bound receptor	GCA, TCA, GCDCA and TCDCA	Intestinal epithelial cells, hepatocytes

DCA: Deoxycholic acid; LCA: Lithocholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; isoLCA: Isolithocholic acid; isoalloLCA: Isoallolithocholic acid; 3-oxoLCA: 3-oxolithocholic acid; FXR: Farnesoid X receptor; GPABR1: G protein-coupled bile acid receptor 1; PXR: Pregnane X receptor; VDR: Vitamin D receptor; RORγt: Retinoid-related orphan receptor γt; CAR: Costitutive androstane receptor; S1PR2: Sphingosine-1-phosphate receptor 2; GCA: Glycocholic acid; TCA: Taurocholic acid; GCDCA: Glycochenodeoxycholic acid; TCDCA: Taurochenodeoxycholic acid.

versions of CA and CDCA, named muricholic acid (MCA)[17]. The conventional or alternative/acidic pathways are both possible for this process to take place in the human liver. The first limiting step in the conventional route is the 7-hydroxylation of cholesterol catalysed by cholesterol-7-hydroxylase (CYP7A1), which irreversibly transforms cholesterol to 7-hydroxycholesterol. This intermediate is then converted to 7α-hydroxy-4-cholesten-3-one by 3β-hydroxy-Δ5-C27-steroid oxidoreductase, which can be used for generating both CA and CDCA in the classic pathway. In contrast, the alternative/acidic pathway begins with the conversion of cholesterol by sterol 27-hydroxylase (CYP27A1) to 27-hydroxy-cholesterol, followed by B-ring hydroxylation and metabolic side chain modification by oxysterol 7-hydroxylase (CYP7B) to create CDCA. The alternate pathway generates solely CDCA, which accounts for 10% of the liver's total bile acids[18-20]. Subsequently, PBAs are converted to tauro-CA (TCA) and tauro-CDCA (TCDCA) and glyco-CA (GCA) and glyco-CDCA (GCDCA), respectively, by the actions of BA-CoA synthase and BA-CoA amino acid N-acetyltransferase. Conjugation turns bile acids into stronger acids and increases their aqueous solubility at acidic pH and the retention of their amphiphilic structure. This limits their passive reabsorption and is essential for their lipid emulsification activity in the acidic environment of the duodenum[21,22]. Notably, conjugation with glycine is common in the human liver, accounting for 90% of the bile acid pool. However, approximately 95% of PBAs in mice are taurine-conjugated[23]. Conjugated bile acids will be stored in the gallbladder, forming bile with phospholipids, cholesterol, and other components. Finally, the gallbladder releases bile acids into the duodenum after each meal[24].

Bile acid metabolism in the intestine

Upon release into the small intestine, bile acids form micelles with cholesterol and dietary fats to facilitate their dissolution and absorption[25,26]. However, conjugated bile acids are not absorbed and are instead retained in the small intestine. At the end of the ileum, approximately 95% of the conjugated bile acids are reabsorbed *via* the apical sodium-dependent bile acid transporter (ASBT) and enter the liver *via* the portal vein[27]. It is estimated that humans complete the enterohepatic circulation of bile acids between six and eight times a day, depending on their dietary habits. The bile acid pool in healthy persons remains between 4 and 6 g. In contrast, changes in the intestinal epithelium of individuals with IBD decrease the reabsorption of bile acids by ASBT and increase the number of bile acids discharged in the feces [28]. It is important to note that the bile acid pool that is returned from the ileum to the liver directly suppresses the production of new bile acids in hepatocytes through FXR, FXR-dependent transactivation of the small isomeric partner (SHP), and SHP-mediated suppression of CYP7A1 and CYP8B1 expression[17,29,30]. In addition, bile acid-activated FXR drives fibroblast growth factor (FGF-15/19; FGF-15 in mice and FGF-19 in humans) expression in intestinal epithelial cells (IECs). Subsequently, FGF-15/19 is secreted into the portal circulation, translocated to the liver, binds to heterodimeric receptors on hepatocytes, and reduces hepatic bile acid synthesis by inhibiting CYP7A1 expression[26,31].

The intestinal microbiota can be directly involved in the biotransformation of bile acids through microbial enzymes. The five known mechanisms of bile acid metabolism by the intestinal microbiota are dehydroxylation, dehydration, exo-embedding of the cholesterol backbone, depolymerization of amino acids (glycine or taurine), and amide conjugation of the bile acid backbone with the amino acids phenylalanine, tyrosine, and leucine. Many potential mechanisms still exist to be discovered and explored[32]. Approximately 5% of bile acids are retained in the intestinal lumen for further metabolism by the intestinal microbiota to generate SBAs *via* the aforementioned processes[33]. In particular, the depoly-merization reaction of bile acid metabolism is first carried out by the gut bacteria (enzymatic hydrolysis of the C-24N-
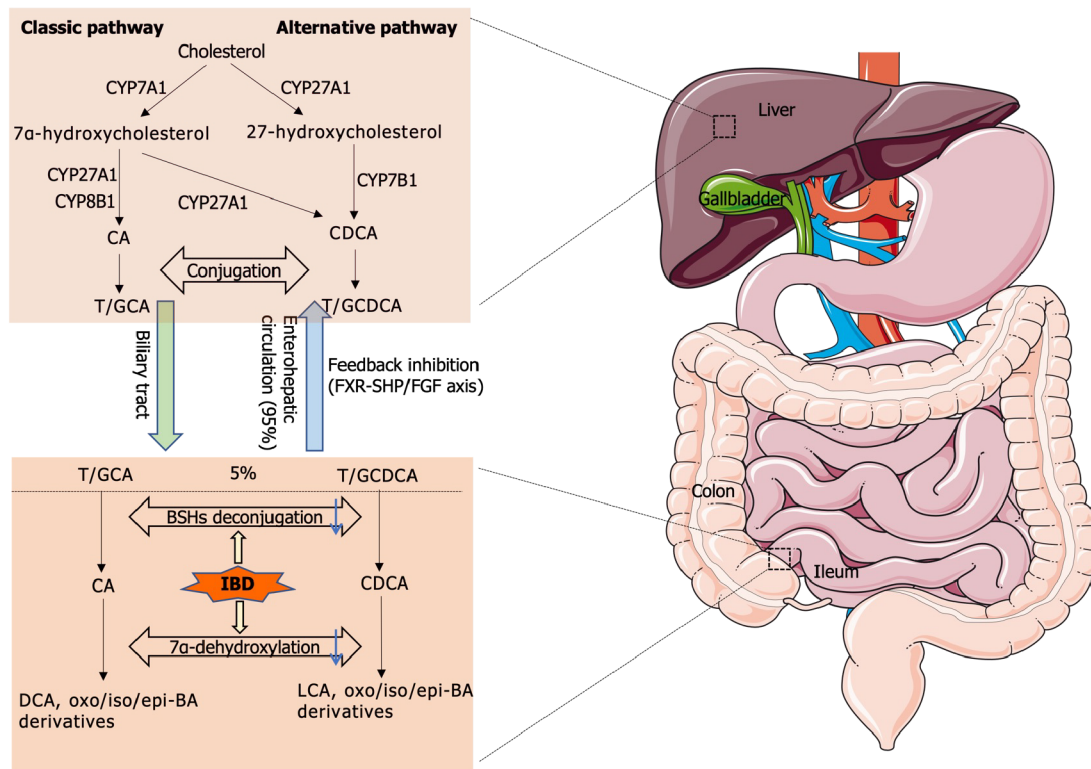
Figure 1 Synthesis, recirculation, and microbial modification of bile acids in the gut. Bile acids are synthesized from cholesterol in the liver. In the classical pathway, cholesterol-7α-hydroxylase converts cholesterol to 7α-hydroxycholesterol, which is then metabolized to cholic acid *via* mitochondrial sterol-27-hydroxylase (CYP27A1) or CYP8A1, or to chenodeoxycholic acid (CDCA) *via* CYP27A1. In the alternative pathway, CYP27A1 begins the conversion of cholesterol to 27-hydroxycholesterol, which is then metabolized to CDCA by oxysterol 7α-hydroxylase. These primary bile acids are then conjugated with taurine or glycine and then released into the bile for secretion into the duodenum. At the end of the ileum, 95% of the conjugated bile acids (BAs) are reabsorbed through the enterohepatic circulation, while the remaining 5% depolymerizes and enters the colon, where BAs undergo a series of chemical modifications by intestinal bacteria, including catabolism, desulfurization, dehydrogenation, dehydroxylation, and exo-embedding reactions to form secondary bile acids (mainly lithocholic acid and deoxycholic acid) and their oxidative, isomeric, and exo-derivatives. IBD: Inflammatory bowel disease; CA: Cholic acid; CDCA: Chenodeoxycholic acid; GCA: Glycocholic acid; TCA: Taurocholic acid; GCDCA: Glycochenodeoxycholic acid; TCDCA: Taurochenodeoxycholic acid; DCA: Deoxycholic acid; LCA: Lithocholic acid; BA: Bile acid; CYP7A1: Cholesterol-7α-hydroxylase; CYP27A1: Mitochondrial sterol-27-hydroxylase; CYP8B1: Sterol-12α-hydroxylase; CYP7B1: Oxysterol 7α-hydroxylase; BSHs: Bile salt hydrolases; FXR: Farnesol X receptor; FGF: Fibroblast growth factor; SHP: Small isomeric partner.

acylamide bond). Bile salt hydrolases (BSHs), which are extensively found in both Gram-positive and Gram-negative bacteria in the gut, including *Clostridium*, *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, and *Enterococcus*, mediate this process [34]. It eliminates the glycine or taurine conjugates and stops the small intestine's active reabsorption. The depolymerized PBAs are then converted to SBAs in the colon by dehydroxylation at the carbon-7 position. Bacteria that express 7-dehydroxylases, such as *Clostridium* and *Eubacterium*, play a major role in mediating this process. The two SBAs that are most frequently produced by these reactions are lithocholic acid (LCA from CDCA) and deoxycholic acid (DCA from CA). Additionally, a variety of oxo-, iso-, and epi-derivatives of bile acids can also arise in the colon as a result of different intestinal microbiota dehydrogenation and exo-embedding processes[35]. For example, in *Escherichia*, *Clostridium*, *Bacteroides*, and *Eubacerium*, C7β exochimerization of CDCA can occur to produce the 7β exochimer, 3α-,7β-dihydroxy-5β-cholic acid, also known as ursodeoxycholic acid (UDCA)[36]. The complete metabolic pathway for the conversion of PBAs (CA and CDCA) to the two major SBAs (DCA and LCA) has been identified[37]. It is still unclear how the gut microbiota converts PBAs into other bile acid derivatives. Moreover, it is not clear which exact bacterial species or strains are required for these processes. Furthermore, it is noteworthy that the gut microbiota can also regulate the hepatic enzymes CYP7A1 and CYP27A1, thus affecting the synthesis of bile acids in the liver[38].

The intestines of IBD patients have been found to have dysbiosis of the intestinal bacterial flora and a considerable loss in microbial diversity. Most importantly, the abundance of bacteria containing BSH and bile acid-inducible enzymes (BAIs), such as *Firmicutes, Ruminococcaceae, Lachnospiraceae*, and *Eubacterium*, was decreased. This alteration reduces depolymerization and 7α-dehydroxylation, strongly decreasing the conversion capacity of the microbiota, resulting in a decrease in SBAs (DCA and LCA) and an elevation in primary and conjugated bile acids (CA, CDCA, TCA, and GCA)[39-41]. Multiple risk factors (genetics, psychological factors, Western food, and antibiotics) may lead to intestinal flora dysbiosis and bile acid abnormalities, which are linked to the pathophysiology of IBD[42]. Notably, it has been reported that disturbances in bile acid metabolism will, in turn, exacerbate IBD damage, affect intestinal stem cell differentiation and renewal, and impair intestinal mucosal barrier function[30].

Notably, the composition of the microbiota is directly or indirectly affected by bile acids in several studies. It has been shown that bile acids inhibit bacteria by increasing cell membrane permeability and causing cell damage, as well as causing oxidative DNA damage in bacteria. Alternatively, bile acids can indirectly influence bacterial growth through FXR and VDR[40]. The overall number of bacteria in rats' feces decreased with increased CA concentration in their meal, as determined by DAPI staining, sequencing of 16S rRNA gene clone libraries, and FISH analysis. The proportion of *Bacteroidetes* and *Actinobacteria* decreased dramatically in the CA-fed group, whereas the proportion of Firmicutes increased significantly[43]. Considered together, bile acids and the gut microbiota have a bidirectional effect on each other, and this balance is critical for human health and disease.

IMPACT OF BILE ACIDS AND THEIR RECEPTORS IN IBD

FXR

FXR is a nuclear receptor belonging to a subclass of metabolic receptors, first described by Forman *et al*[44] in 1995. FXR is predominantly found in intestinal epithelial cells, hepatocytes, and some immune cells (such as macrophages and dendritic cells) of the colon and liver[45]. Its main endogenous ligand is bile acids, in the order of FXR activation potency: CDCA > DCA > LCA > CA. Numerous studies demonstrate that through modulating bile acid metabolism, FXR can improve the pathogenesis of IBD. The enzyme CYP8B1, which synthesises CA, was increased in the liver of mice with colitis. Chen *et al*[30] found that mucosal barrier repair was impaired in CYP8B1 overexpressing mice, which resulted in more severe colitis. The specific mechanism was shown that CA leads to impaired fatty acid oxidation (FAO) and LGR5+ intestinal stem cell (ISC) renewal through inhibition of peroxisome proliferator-activated receptor alpha (PPARα). Surprisingly, they found that activation of FXR inhibited hepatic CYP8B1 expression and ameliorated colitis in mice. FGF19-M52, an analog of FGF19, has been reported to inhibit bile acid synthesis, modulate bile acid pool composition, and inhibit intestinal inflammation in mice. The particular mechanisms underlying these processes are associated with maintaining intestinal epithelial barrier integrity, suppressing inflammatory immune responses, and controlling microbial composition. However, the FGF19-M52-induced anti-inflammatory effect was completely abolished in FXR-deficient animals[46]. In addition, in UC mouse models, dextran sodium sulfate (DSS)-induced colitis activates the intestinal PPARα-UDP-glucuronosyltransferases (UGTs) axis, which inhibits downstream FXR-FGF15 signaling, resulting in up-regulation of hepatic CYP7A1 and promotion of hepatic bile acids synthesis. Both inhibition of PPARα and stimulation of the FXR-FGF15 axis greatly decreased colitis induced by DSS[47]. As a result, intestinal FXR-FGF15 signaling may play a key role in controlling bile acid homeostasis and colitis development.

Mammalian innate lymphocyte type 3 (ILC3) is important in IBD, especially in innate intestinal immunity and mucosal barrier function[48]. Activation of FXR has been reported to block the production of IL-17A and IL-17F in ILC3, thereby eliminating ILC3-dependent intestinal inflammation and attenuating IBD injury. Interestingly, they also found that activation of FXR reduced characteristic transcription factors (including Batf3 and Tcf7)[49]. Transforming growth factor-beta (TGF-β) belongs to a family of multifunctional polypeptides produced by non-lymphoid cells and various lymphocytes. Previous studies have shown that TGF-β is essential for regulating immune cells and that TGF-β production is also associated with the pathogenesis of colitis. This implies that the pathological changes in UC may be caused by disorders of the TGF-β pathway[50]. A recent study revealed that a high-fat diet accelerated the course of DSS-induced UC and led to the down-regulation of FXR target genes (*FXR*, *Shp*, and *Ibabp*). The addition of the FXR agonist FexD repaired the high-fat diet-induced phenotype, whereas the TGF-β inhibitor SB431542 prevented FexD's restorative activity in DSS-induced UC mice[51]. This study showed that FXR alleviates inflammation in UC through a TGF-β-dependent pathway. In conclusion, these findings suggest that FXR can improve IBD by modulating intestinal immunity.

Western diets have high levels of fecal DCA, a substance that can cause inflammation in the intestines. The researchers discovered that mice fed a DCA-supplemented diet showed localised ileal and colonic inflammation, as well as changes in gut microbiota composition and faecal bile acid buildup. Dysregulation of gut microbiota homeostasis induced by DCA reduced bile acid depolymerization. This regulation was associated with the repressed expression of target genes in the FXR-FGF15 axis, leading to increased hepatic *de novo* bile acid synthesis. These results suggest that DCA-induced intestinal dysbiosis may be a key etiology of intestinal inflammation associated with disturbed bile acid metabolism and down-regulation of the FXR-FGF15 axis[52]. Subsequently, Xu *et al*[53] used the FXR agonist fexaramine to restore intestinal FXR activity. Activating FXR increased the abundance of bacteria producing short-chain fatty acids and normalized bile acid metabolism. DCA-induced intestinal inflammation can be reduced by targeting the FXR-gut microbiota signaling pathway.

In addition, FXR may ameliorate IBD through modifying the function of the intestinal mucosal barrier. By blocking lipopolysaccharide (LPS)-induced activation of the myosin light chain kinase (MLCK) pathway in an FXR-dependent manner, Song *et al*[54] showed that CDCA reversed LPS-induced decreases in intestinal permeability and tight junction protein expression and mitigated LPS-induced intestinal barrier breakdown. In another study, using the FXR agonist GW4064 to restore FXR activity, Liu *et al*[55] discovered that activation of FXR attenuates intestinal tight junction damage by inhibiting the LPS-induced TLR4/MyD88 signaling pathway. In summary, these recent findings suggest that FXR can influence the pathophysiological processes of IBD by regulating bile acid metabolism, intestinal immunity, intestinal flora, and intestinal mucosal barrier function (Figure 2). Activation of FXR may be considered a new therapeutic strategy for IBD.

RORγt

RORγ is one of three retinoid-related orphan nuclear receptors with two main isoforms: RORγ1 and RORγt (or RORγ2),
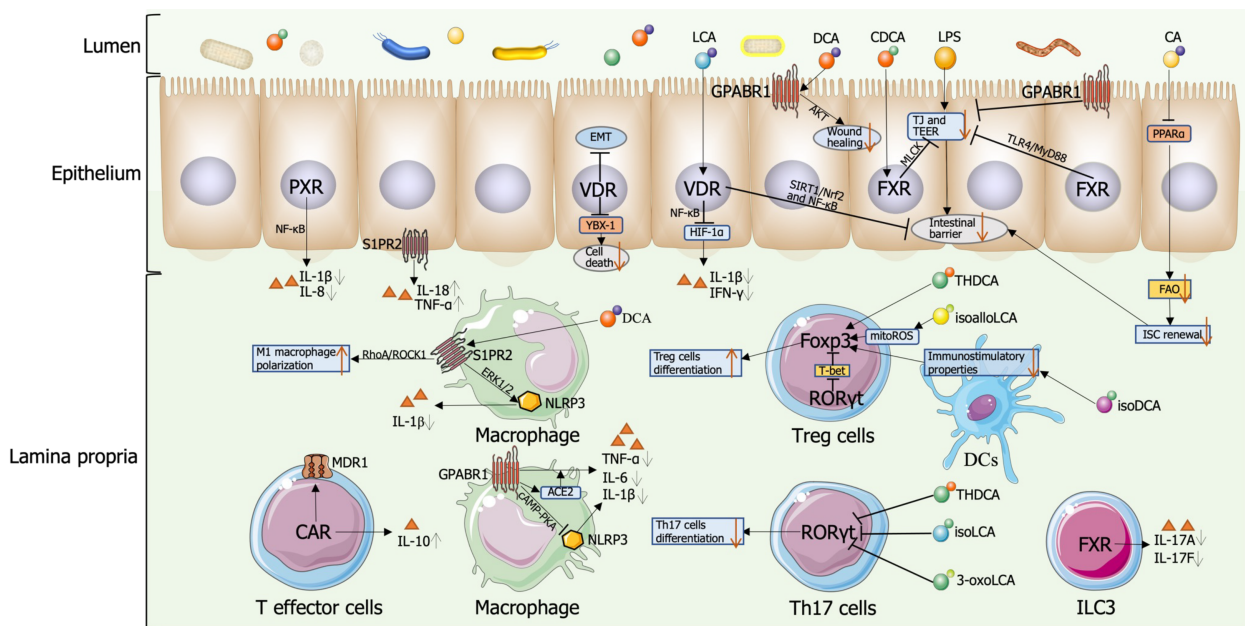
DOI: 10.3748/wjg.v29.i27.4252 **Copyright** ©The Author(s) 2023.

Figure 2 Emerging role of bile acids and their receptors. DCA: Deoxycholic acid; LCA: Lithocholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; isoLCA: Isolithocholic acid; isoalloLCA: Isoallolithocholic acid; 3-oxoLCA: 3-oxolithocholic acid; isoDCA: 3β-hydroxydeoxycholic acid; THDCA: Taurohyodeoxycholic acid; LPS: Lipopolysaccharide; FXR: Farnesoid X receptor; GPABR1: G protein-coupled bile acid receptor 1; PXR: Pregnane X receptor; VDR: Vitamin D receptor; RORγt: Retinoid-related orphan receptor γt; CAR: Costitutive androstane receptor; S1PR2: Sphingosine-1-phosphate receptor 2; Th17 cells: T helper 17 cells; Treg cells: Regulatory T cells; ILC3: Innate lymphocyte type 3; DCs: Dendritic cells; ISC: Intestinal stem cell; YBX-1: Y box binding protein 1; ACE2: Angiotensin-converting enzyme 2; NLRP3: The NACHT, LRR, and PYD domains-containing protein 3; mitoROS: Mitochondrial reactive oxygen species; EMT: Epithelial-mesenchymal transition; FAO: Fatty acid oxidation; PPARα: Peroxisome proliferator-activated receptor alpha; TLR4: Toll-like receptor 4; TJ: Tight junction; TEER: Trans-epithelial electrical resistance; TLR4: Toll-like receptor 4.

encoded by the *RORC* gene. RORγ1 is normally involved in the regulation of transcription of metabolic genes and some circadian rhythms in the liver and adipose tissue. However, the expression of RORγt is restricted to specific subpopulations of lymphoid spectrum immune cells, namely T helper 17 (Th17) cells, ILC3, and γδ T cells[19,56]. Recently, increasing attention has turned to RORγt, as it acts as a key transcription factor for Th17 cell and regulatory T(Treg) cell differentiation in IBD (Figure 2). Moreover, ROR-γt can depend on ILC3 to provide protective immunity[23,48]. Hang *et al* [57] discovered that 3-oxolithocholic acid (3-oxoLCA) decreased Th17 cell differentiation by directly interacting with the important transcription factor RORγt by giving mice 3-oxoLCA and isoallolithocholic acid (isoalloLCA). In contrast, isoalloLCA decreases intestinal inflammation by increasing Treg cell differentiation by generating mitochondrial reactive oxygen species (mitoROS), which enhances the expression of Forkhead box P3 (Foxp3). Interestingly, similar to 3-oxoLCA, isolithocholic acid (isoLCA) can also de-suppress Th17 cell differentiation by inhibiting RORγt[58]. In *in vivo* models, another study demonstrated that the secondary bile acid 3β-hydroxydeoxycholic acid (isoDCA) promotes Treg cell differentiation by increasing the induction of Foxp3 through its action on dendritic cells (DCs). Surprisingly, the researchers found that disruption of FXR in DCs enhanced Treg cell generation[59]. In addition, taurohyodeoxycholic acid (THDCA) was reported to not only inhibit RORγt-mediated Th17 cell differentiation, but also trigger Foxp3 expression and promote Treg cell differentiation[60]. These recent findings demonstrate the potential of bile acid derivatives to improve IBD prognosis by acting on RORγt. Kathania *et al*[61] identified a serine/threonine kinase, Pak2, directly associated with RORγt. Pak2 recognizes the conserved KRLS motif within RORγt and phosphorylates S-316 within this motif. Genetic deletion of Pak2 in Th17 cells decreases RORγt phosphorylation, increases IL-17 expression, and induces severe colitis after adoptive transfer to Rag1-/- mice. This suggests that other biological molecules *in vivo* can also regulate the developmental process of IBD by acting on RORγt and are potential targets for the treatment of IBD to be explored further.

RORγt+ immune cells are generally thought to coordinate immunity, inflammation, or tolerance in the gut. In IBD, the function of RORγt+ immune cells can be significantly altered[62-64]. According to a recent study, ILC3 in intestinal draining lymph nodes expressed numerous significant class II histocompatibility complexes (MHCIIs). To increase microbiota-specific RORγt+ Treg cells and prevent them from proliferating into inflammatory Th17 cells, ILC3 is both essential and sufficient. AlphaV integrin, competing IL-2, and ILC3-mediated antigen presentation all contributes to this impact. Single cell analysis indicated that in IBD, the interaction between ILC3 and RORγt+ Treg cells was impaired[65]. It is interesting to note that Akagbosu *et al*[66] described a class of RORγt+ antigen-presenting cells dubbed Thetis cells. These cells had dendritic cell and medullary thymic epithelial cell (mTEC) transcriptional signatures. Colitis results from the loss of MHCII or ITGB8 by Thetis cells, which severely impairs peripheral Treg (pTreg) cell differentiation in the intestine. MHCII expression by RORγt+ ILC3 and classic dendritic cells, in contrast, is neither sufficient nor essential for pTreg cell formation. In a colitis model, Liu *et al*[67] demonstrated that *Akkermansia muciniphila* improves colitis by up-

regulating the RORγt+ Treg cell-mediated immune response, and this process is regulated by Toll-like receptor 4 (TLR4). RORγt is a main transcription factor for Th17 cells. However, in the intestine, RORγt is co-expressed in peripherally induced pTreg cells together with Foxp3. Surprisingly, Bhaumik *et al*[68] observed that RORγt-mediated T-bet inhibition is essential for regulating the immunosuppressive function of pTreg cells in inflammatory states, restoring Foxp3 expression, and preventing the onset of severe colitis. Despite these advancements, the full-spectrum cellular heterogeneity of RORγt+ immune cells, the potential for functional interactions between subpopulations, and the specific mechanisms influencing the pathophysiological processes of IBD in the context of complex microbiota remain unknown and require further investigation.

GPABR1

Kawamata *et al*[69] first described GPABR1 (TGR5 or M-BAR) in 2003 as a receptor for bile acids in the membrane. GPABR1 is mainly found in epithelial cells, immune cells, and intestinal nerves in the gut and biliary tract and belongs to the superfamily of G protein-coupled receptors. Bile acids agonistically affect GPABR1 in different ways: LCA > DCA > CDCA > UDCA > CA[20]. The adaptor apoptosis-associated speck-like protein containing a caspase recruitment domain, sensor NLRP3, and procaspase-1 form the cytosolic polyprotein complex NLRP3 inflammasome. The pathogenesis of IBD is closely linked to the NLRP3 inflammasome[70,71]. An *in vivo* experimental study showed that bile acids could inhibit NLRP3 inflammasome-dependent inflammation *via* the GPABR1-cAMP-PKA axis, suggesting GPABR1 as a potential target for alleviating intestinal inflammation in IBD[72]. Biagioli *et al*[73] found that activation of GPBAR1 can lower macrophage inflammatory gene expression (mRNA for TNF-α, IL-1, IL-6, and CCL2), hence reducing inflammation in animal models of IBD. Deletion of the anti-inflammatory gene angiotensin-converting enzyme 2 (*ACE2*) from mice with colitis resulted in worse inflammation[74]. Biagioli *et al*[75] further discovered that activation of GPBAR1 could regulate ACE2 colonic expression through a glucagon-promoting factor glucagon-like peptide (GLP)-1-dependent mechanism. Furthermore, the regulation of *ACE2* mRNA in the colitis setting may contribute to the anti-inflammatory effects of GPBAR1. A recent study showed that supplementation with LCA and DCA reduced intestinal inflammation in three mouse models of colitis. This anti-inflammatory effect partially depends on GPABR1[76].

AKT, a serine/threonine kinase, is crucial for the differentiation, proliferation, survival, and metabolism of cells. In a mouse model of DSS-induced colitis and the colonic epithelium of UC patients, Azuma *et al*[77] showed that DCA could slow wound healing in the colonic epithelial cell environment by acting as a ligand for GPABR1 to activate the AKT signaling pathway. Interestingly, another recent study showed that in a Caco-2 cell model, GPABR1 activation ameliorated LPS-induced reduction in trans-epithelial electrical resistance (TEER) and up-regulated tight junction protein expression, thereby enhancing mucosal barrier function to alleviate the progression of IBD[78]. However, inhibition of GPABR1 expression in the porcine jejunal epithelial cell line IPEC-J2 did not affect the function of the intestinal barrier [54]. This may be due to the different expression levels of GPABR1 in different intestinal slices. In conclusion, these findings suggest that GPABR1 plays different roles in the gastrointestinal tract of IBD (Figure 2). Moreover, the functions of GPABR1 may also differ due to differences in species and cell types. Therefore, the role of GPABR1 on the pathophysiological mechanisms of IBD deserves further investigation.

VDR

A nuclear receptor activated by 1,25-dihydroxyvitamin D is the VDR. The human metabolism, immunity, and cancer are all regulated by this receptor, which is widely expressed in a range of tissues. Additionally, the secondary bile acid LCA and its metabolites (3-oxoLCA and isoalloLCA) can activate VDR[79,80]. LCA was reported to ameliorate the TNF-α-induced decrease in the expression and distribution of tight junction proteins (ZO-1, occludin, and claudin-1) through activation of VDR. Furthermore, it significantly blocked TNF-α-mediated down-regulation of the oxidative stress-related genes silent information regulator 1 (*SIRT1*), nuclear factor erythroid 2-related factor 2 (*Nrf2*), and heme oxygenase-1. In addition, the TNF-α-induced increase in NF-κB p-p65 and p-IκB-α was significantly suppressed by LCA[81]. This study reveals that LCA strongly protects against TNF-α-induced intestinal barrier degradation *via* VDR. Activation of hypoxia-inducible factor 1α (HIF-1α) as a heterodimeric transcription factor has been shown in previous research to accelerate the course of DSS-induced colitis in mice[82,83]. However, the association of VDR signaling and HIF-1α in the development of IBD has been enigmatic. A recent study showed that in an animal model of colitis, VDR signaling suppressed the overexpression of HIF-1α in colonic epithelial cells by regulating the NF-κB pathway, thereby inhibiting the overproduction of interferon-gamma (IFN-γ) and IL-1β in these cells and attenuating the development of colitis in the animal model[84]. Another study showed that VDR could physically bind to Y box binding protein 1 (YBX-1), blocking its nuclear translocation, thus ameliorating the death of colonic epithelial cells in the presence of inflammation[85]. Furthermore, Fernández-Barral *et al*[86] demonstrated for the first time that activation of VDR can regulate stemness-related genes, including *LGR5, SMOC2, LRIG1, MSI1, PTK7*, and *MEXA*, and decrease cell proliferation in LGR5+ human colonic stem cells. This function is essential for maintaining colonic epithelial homeostasis in IBD.

Paneth cells, which are positioned at the base of small intestinal crypts, release α-defensins and play a crucial role in regulating intestinal flora and preserving intestinal homeostasis[87]. Paneth cells showed a significant decrease in lysozyme activity, a diminished inhibition of pathogenic bacterial growth, and a reduced autophagic response in a Paneth cell-specific VDR knockout mouse model, resulting in an increased inflammatory response. These findings suggest the importance of VDR on Paneth cells in IBD in preventing intestinal inflammation[88]. Claudin-2 is a linker protein that mediates water transport between epithelial cells, and elevated claudin-2 has been reported to be associated with active human IBD[89]. Another study showed that in a Salmonella colitis model and a DSS-induced colitis model, VDR deficiency may lead to claudin-2 hyperfunction and increased permeability in an inflammatory state, resulting in more severe intestinal leakage and intestinal inflammation in mice[90]. This study highlights the importance of VDR in intestinal mucosal barrier function. In addition, intestinal fibrosis is a common complication of CD. The epithelial-

mesenchymal transition (EMT) describes the process by which epithelial cells change from epithelial to mesenchymal cells, a crucial component of fibrogenesis. In addition to inhibiting fibroblast activation and epithelial mitochondria-mediated EMT, Yu *et al*[91] revealed that VDR activation attenuates intestinal fibrosis.

Several recent studies have shown that colonic mucosal VDR expression is reduced in patients with IBD and that VDR transcript expression negatively correlates with IBD inflammation[92,93]. Yang *et al*[94] found that dysbiosis of the gut microbiota and altered fecal bile acids could regulate the immune response in UC patients. VDR may alleviate intestinal inflammation by down-regulating NF-κB signaling and activating autophagy. These findings suggest that restoring intestinal VDR expression in IBD may be a viable therapeutic strategy. In conclusion, these findings contribute to a better understanding of the role of VDR in the etiology of IBD and serve as a significant reference for future research aimed at developing more effective therapeutic options (Figure 2).

PXR and CAR

PXR and CAR are members 2 and 3 of nuclear receptor subfamily 1, group I, NR1I2, and NR1I3, respectively. PXR was first described as a major regulator of CYP family 3 subfamily A (CYP3A) transcription by Kliewer *et al*[95] and Lehmann *et al*[96] in 1998. In contrast, CAR was first reported by Baes *et al*[97] in 1994 and was later found to be a transcriptional regulator of CYP2B6. PXR and CAR have the typical modular nuclear receptor structure, which consists of a hinge, a DNA-binding domain, a ligand-binding domain, activation function 1, and activation function 2. In addition to many endogenous and exogenous complex ligands, several subsequent studies have shown that PXR and CAR are hybrid receptors that can also accommodate LCA and CDCA and function as sensors for LCA and CDCA[98]. PXR and CAR are key transcription factors that regulate intestinal homeostasis. Uehara *et al*[99] demonstrated that PXR might reduce apoptosis in a mouse model of DSS-induced colitis by lowering the mRNA expression of pro-inflammatory cytokines (TNF-α and IL-1β). CAR inhibits apoptosis by inducing Gadd45b. Both of them protected mice from DSS-induced colitis. Interestingly, they also observed that the protective effect of FXR activation on CAR knockout mice and the protective effect of CAR activation on PXR knockout mice were reduced. CAR and PXR can synergistically ameliorate DSS-induced colitis. Another study showed that PXR and CAR deficiency synergistically increased the pro-inflammatory bacteria *Helicobacteraceae* and *Helicobacter* and the relative abundance of *Lactobacillus*. *Lactobacillus* has BSHs activity, corresponding to a decrease in primary taurine-bound bile acids in feces. This may lead to an increased internal burden of taurine and unbound bile acids, which are associated with inflammation, oxidative stress, and cytotoxicity[100].

The metabolism of tryptophan produces indole-3-propionic acid (IPA) in the intestine *via Clostridium perfringens*. Previous studies have shown that it can affect mucosal barrier function and inflammation through interaction with PXR [101]. Flannigan *et al*[102] found that PXR-deficient myofibroblasts overreact to stimuli and produce higher inflammatory mediators. In addition, biopsies from CD and UC patients revealed a correlation between decreased PXR expression and increased expression of fibrosis and innate immune genes. Intriguingly, they discovered that IPA decreased intestinal inflammation and fibrosis in mice with DSS-induced colitis *via* activating PXR, whereas microbiota removal increased intestinal inflammation and fibrosis[102]. These findings suggest that the interaction of the microbiota metabolite IPA with PXR may be an important determinant of the progression of fibrotic complications in IBD. In addition, Deuring *et al* [103] found a strict negative association between colonic epithelial PXR levels and NF-B target gene expression in CD patient colon biopsy tissue. During IBD, their findings show that PXR is a substantial and clinically relevant antagonist of NF-B activity in the intestinal epithelium[103].

MDR1 is a membrane-associated, ATP-dependent efflux pump preferentially expressed in intestinal and circulating human CD4+ effector T cells[104]. Chen *et al*[105] discovered CAR as a regulator of MDR1 expression in T cells that prevents bile acid toxicity and inflammation in the mouse small intestine. Activation of CAR induces not only the expression of detoxifying enzymes and transporters in CD4+ T effector cells in the lamina propria of the small intestine, but also the expression of the key anti-inflammatory cytokine IL-10. The activation of these programs provides an unexpected strategy for treating IBD and defines the subspecialization of lymphocytes in the small intestine.

S1PR2

S1PR2 is highly expressed in the ileum and colon, and it can be activated by the conjugated main bile acids GCA and TCA as well as GCDCA and TCA[23]. Vascular and immune dysfunction is thought to be involved in the pathogenesis of IBD, but the exact mechanisms of mucosal vascular endothelial barrier dysfunction and macrophage phenotypic transformation are not fully clarified. Wang *et al*[106] discovered that S1PR2 expression was considerably enhanced in intestinal mucosal vascular endothelial cells and macrophages from IBD patients and animals with DSS-induced colitis, as well as in vascular endothelial cells and macrophages treated with LPS *in vitro*. Knockdown or inhibition of S1PR2 expression significantly reduced the expression of RhoA and ROCK1 in vascular endothelial cells and macrophages. Furthermore, they discovered that inhibiting S1PR2 and ROCK1 reversed impaired vascular barrier function and M1 macrophage polarisation *in vivo* and *in vitro*, while decreasing endoplasmic reticulum stress and macrophage glycolysis in vascular endothelial cells, and reversing LPS-induced impairment of M1 macrophage polarisation and vascular endothelial cell barrier dysfunction. The results imply that the S1PR2/RhoA/ROCK1 signalling pathway, which regulates vascular endothelial cell barrier function and M1 macrophage polarisation, may have a role in the aetiology of IBD[106]. Chen *et al*[107] previously demonstrated that S1PR2 is abundantly expressed in intestinal epithelial cells and stimulates IEC proliferation and migration. However, the precise role of S1PR2 in UC is unknown. They recently discovered that S1PR2 may play a significant role in intestinal epithelial cell proliferation and barrier maintenance by influencing the expression levels of SphK2, HDAC1, HDAC2, and ERK1/2 signaling pathways. Surprisingly, they discovered that inhibiting S1PR2 in the UC mouse model might also reduce the severity of colonic pathological injury in mice, which was followed by a drop in TNF-α and IL-18 Levels in their serum[107]. These findings reveal that S1PR2, despite its beneficial effects on intestinal epithelial cell proliferation and barrier maintenance, may be a key pathogenic

factor in UC. In addition, researchers discovered that DCA dose-dependently increased S1PR2 expression in a mouse model of colitis. Meanwhile, at least in part, DCA-induced NLRP3 inflammasome activation was achieved by stimulating the ERK1/2 signaling pathway downstream of S1PR2 to promote cathepsin B release. S1PR2/ERK1/2/cathepsin B signaling is key in triggering DCA activation of inflammatory vesicles[108]. The results of this study suggest that S1PR2 should be investigated further as a possible treatment for IBD.

POTENTIAL THERAPEUTIC TARGETS OF BILE ACIDS AND THEIR RECEPTORS IN IBD

Bile acid receptor agonists or inhibitors

Based on growing knowledge and understanding of the mechanism of action of bile acid receptors, the development of medications targeting the bile acid receptor activity that changes considerably during the progression of IBD may give a more specific therapeutic effect. The development of bile acid receptor agonists or antagonists is widely recognized as a promising therapeutic avenue for treating IBD and is a hot area of research (Table 2). Recently, Miyazaki *et al*[109] showed that administration of the novel FXR agonist nelumal A induced the expression of FXR target genes and tight junction proteins in the intestine while decreasing the expression of hepatic bile acid synthesis genes, effectively reducing colitis and inhibiting colitis-related carcinogenesis. Another study found that the FXR agonist nigakinone alleviated DSS-induced experimental colitis *via* regulating bile acid profile and the FXR/NLRP3 signaling pathway. It inhibited inflammatory cytokine production by activating the FXR/NLRP3 signaling pathway and regulated bile acid metabolism by controlling cholesterol hydroxylase and FXR-mediated transporter proteins, reducing bile acid accumulation in the colon and thereby reducing colitis[110]. Although FXR agonists exhibit very positive effects, they are also commonly associated with many side effects. Its most common side effects are dose-dependent pruritus and an increased LDL:HDL ratio, which may increase the risk of atherosclerosis. Its long-term efficacy remains to be determined[111]. Qi *et al*[112] used structure-based virtual screening to identify 2',4'-dihydroxy-2,3-dimethoxychalcone (DDC). This is a chalcone derivative enriched in plants and food, located in the binding pocket of RORγt, which can target and inhibit RORγt activity, thereby indirectly stabilizing Foxp 3 expression, achieving regulation of Th17/Treg homeostasis, and improving Th17-mediated inflammation. In another study, Chen *et al*[113] proposed a dual-targeting approach for treating IBD using RORγt and dihydroorotic dehydrogenase (DHODH). Dual RORγt/DHODH inhibitors are expected to reduce RORγt-driven Th17 cell differentiation and attenuate T cell expansion and activation, which may enhance anti-inflammatory effects. They found that the 2-aminotetrahydrobenzothiazole compound 14d could act as a potent dual RORγt/DHODH inhibitor, exhibiting significant *in vivo* anti-inflammatory activity and dose-dependently reducing the severity of DSS-induced acute colitis in mice. Furthermore, by screening a large combinatorial library of 1,5-disubstituted acylated 2-amino-4,5-dihydroimidazoles and using a positional scanning library strategy to rapidly identify a novel class of RORγ inhibitors, Ortiz *et al*[113] found that compound 1295-273 had the highest activity against RORγ in this series, with almost twofold selectivity for this receptor isoenzyme. However, they did not further validate it *via in vivo* or *in vitro* experiments.

Genistein, a key isoflavone, stimulates GPABR1 receptors in a DSS-induced mouse colitis model, dramatically lowering inflammatory cell infiltration and generation of pro-inflammatory mediators in the blood and colon and reducing weight loss and increasing colon length in mice[114,115]. In another study, Nakhi *et al*[116] observed that the acid group of CDCA can be replaced by a wide range of chemical groups that can simultaneously maintain or significantly increase its agonistic potency against GPABR1. In particular, pyrrolidinamide 9 and 1,3,4-oxadiazole analog 23 were 10- and 70-fold more potent than CDCA. There is a slight loss of potency when the hydroxyl group at position 3 of the bile acid scaffold is methylated. Surprisingly, however, a more than 100-fold increase in potency was observed upon methylation of the 7-hydroxyl group of pyrrolidinamide 9. Based on these observations, they synthesized the 7-methylated oxadiazole analogue 17, which proved to be a highly potent agonist at the GPABR1 receptor. However, the specific efficacy has to be further de-validated in IBD models[116]. However, most of the GPABR1 agonists studied are unrestricted GPABR1 agonists, and the pharmacological application would be limited by the systemic targeting effect, with associated side effects such as gallbladder overfilling and gallbladder emptying block. Recently, researchers are exploring a series of intestinal-restricted GPABR1 agonists in an attempt to avoid these side effects. Dipeptidyl peptidase IV (DPP4) is a serine exopeptidase, and DPP4 inhibitors have been reported to reduce colitis *via* the GLP pathway after colonic administration in mice[117]. Recently, Han *et al*[118] identified a series of highly potent intestine-restricted GPABR1-DPP4 bifunctional molecules for the first time by integrating GPABR1 agonistic and DPP4 inhibitory efficacy into a single molecule. The effects of GPABR1 and DPP4 on UC were exploited and made to act locally in the gut to avoid unwanted systemic effects. In particular, racemic compound 15, a highly potent GPABR1-DPP4 bifunctional molecule, showed good intestinal distribution, efficacy, and gallbladder safety in a mouse model of colitis[118]. Chen *et al*[119] also described the discovery and optimization of a series of intestinal-restricted selective thiazolidine-type GPABR1 agonists that elicit a potent response with minimal effects on the gallbladder. In this series of drugs, they mainly explored compound No. 12, with minimal systemic availability, which stimulates prolonged and potent GLP-1 (7-36) amide (tGLP-1) secretion and may have significant therapeutic value in IBD[119].

Dvořák *et al*[120] proposed microbial metabolite mimicry as a new strategy for drug discovery based on the effect of microbial metabolites on PXR and reported the functionalized indole derivative lead compound Felix Kopp Kortagere 6 (FKK6) as the first class of non-cytotoxic PXR agonists as a proof of concept for microbial metabolite mimicry. In cells, human organs, and animals, FKK6 can directly bind PXR and stimulate PXR-specific target gene expression. In mice expressing human *PXR* genes, FKK6 dramatically suppressed the production of pro-inflammatory cytokines and prevented inflammation[120]. The development of FKK6 provided the first evidence that microbial metabolite mimicry is a viable drug discovery strategy and opened the door to an underutilized chemical space for IBD drug development.

Table 2 Potential applications of bile acids and their receptors in inflammatory bowel disease

Types	Ref.	Subjects	Treatment	Major findings
Bile acid receptor agonists or inhibitors	Miyazaki et al[109], 2021	Mice with AOM/DSS-induced colitis	Fed nelumal A for 15 wk	Nelumal A induced the expression of FXR target genes and tight junction proteins in the intestine; Nelumal A decreased the expression of hepatic bile acid synthesis genes
	Liu et al [110], 2023	Mice with DSS-induced colitis	Fed nigakinone for 9 d	Nigakinone inhibited inflammatory cytokine production by activating the FXR/NLRP3 signaling pathway; Nigakinone regulated bile acid metabolism by controlling cholesterol hydroxylase and FXR-mediated transporter proteins
	Qi et al [112], 2022	Mice with DSS-induced colitis	DDC gavage treatment for a week	DDC targeted and inhibited RORγt activity, thereby indirectly stabilizing Foxp 3 expression and achieving regulation of Th17/Treg homeostasis
	Chen et al [113], 2022	Mice with DSS-induced colitis	Fed compound 14d for 9 d	Compound 14d reduced RORγt-driven Th17 cell differentiation; Compound 14d attenuated T cell expansion and activation
	Chen et al [115], 2019	Mice with DSS-induced colitis	Fed genistein 14d for 9 d	Genistein lowered inflammatory cell infiltration and generation of pro-inflammatory mediators in the blood and colon; Genistein reduced weight loss and increased colon length in mice
	Han et al [118], 2022	Mice with DSS-induced colitis	Fed racemic compound 15 for 9 d	Racemic compound 15 showed good intestinal distribution and efficacy; Racemic compound 15 avoided unwanted systemic effects and showed better gallbladder safety
	Chen et al [119], 2018	Diet-induced obese mice	Fed compound 12 for 4, 8, 12, or 16 h	Compound 12 elicited a potent response with minimal effects on the gallbladder; Compound 12 stimulated prolonged and potent tGLP-1 secretion
	Dvořák et al [120], 2020	Mice with DSS-induced colitis	FKK6 oral gavage plus FKK6 intrarectal bolus for 10 d	FKK6 dramatically suppressed the production of pro-inflammatory cytokines and prevented inflammation; FKK6 provided the first evidence that microbial metabolite mimicry is a viable drug discovery strategy
Traditional Chinese medicine	Hua et al [122], 2021	Mice with DSS-induced colitis	Administrated with BTWT for 7 d	BTWT normalized the levels of some bile acids, especially CA and MCA; BTWT increased the expression of FXR and TGR5 in the liver; Relative species abundance and gut microbiota diversity were significantly higher in the BTWT-exposed group; BTWT significantly ameliorated colonic inflammation and clinical signs
	Su et al [123], 2022	Caco-2 cells treated with bile acids	Pre-incubated with GXD at subtoxic concentration for 24 h before treatment with BAs	GXD improved intestinal barrier dysfunction caused by abnormal bile acid metabolism in IBD by regulating tight junction protein expression levels, inhibiting oxidative stress, and reducing apoptosis
	Li et al [125], 2022	Mice with DSS-induced colitis	Fed SFE for 11 d	SFE regulated the transcriptional levels of RORγt and Foxp 3 in the colon and down-regulating the expression of the pro-inflammatory factor IL-17 A in colon tissue
	Shi et al [126], 2022	Mice with DSS-induced colitis	Fed LWE for a week	LWE inhibited the transcriptional activation of RORγT and IL-17A, thereby suppressing the differentiation of Th17 lymphocytes; LWE reduced inflammation and increased the protective action of the intestinal mucosal barrier via the TLR4/MyD88/NF-κB signal transduction pathway
	Xia et al [127], 2022	Mice with DSS-induced colitis	QCWZD gavage for a week	QCWZD inhibited the phosphorylation of JAK2-STAT3 pathway, reducing the transcriptional activation of RORγT and IL-17A
	Xiong et al [128], 2022	Mice with DSS-induced colitis	Fed HGT for 10 d	HGT inhibited DSS-induced necrotizing lesions in the colon through up-regulation VDR levels
	Zhang et al [129], 2020	Mice with DSS-induced colitis	PA administered intragastrically for 10 d	PA activated PXR signaling and inhibited NF-κB signaling, thereby ameliorating inflammation
	Yu et al [130], 2020	Mice with DSS-induced colitis	Fed Alpinetin for 9 d	Alpinetin activated PXR/NF-kB, thereby ameliorating inflammation

IBD: Inflammatory bowel disease; FXR: Farnesoid X receptor; PXR: Pregnane X receptor; VDR: Vitamin D receptor; RORγt: Retinoid-related orphan receptor γt; DSS: Dextran sodium sulfate; HGT: Huanglian Ganjiang Tang; QCWZD: Chingchang Wenzhong Decoction; LWE: Licorice water extraction; SFE: Sophora flavescens Aiton total flavonoids extracts; BTWT: Baitouweng Tang; GXD: Gualou Xiebai Decoctio; MCA: Muricholic acid.

In conclusion, the research and development of bile acid receptors and their agonist or inhibitor medicines is a viable treatment method for IBD. However, there are still numerous issues, such as the increased adverse effects of non-selective agonists and activators. Increasing the intestinal restriction of agonists by identifying modifications that block the active transport of ASBT while reducing passive absorption by increasing the compounds' size and polar surface area is a feasible solution to their side effects. However, the synthesis of existing intestinal restricted activators or inhibitors is very complex and expensive, and further research is needed to explore this.

Traditional Chinese medicine

Chinese medicine is garnering more attention as the global pharmaceutical industry develops, and herbal medicine has distinct advantages in treating IBD due to allopathic treatment[121]. Many academics have recently conducted basic research on traditional Chinese medicine for the treatment of IBD from various angles, and they discovered that traditional Chinese medicine may benefit the treatment of IBD by affecting bile acids and their receptors, which support intestinal mucosal barrier function, regulate intestinal immunity, and influence bile acid metabolism (Table 2). In China, Baitouweng Tang (BTWT) is a commonly prescribed drug for the treatment of UC. In a DSS-induced mouse model of UC, mice were given BTWT for 7 d. Surprisingly, the researchers found that BTWT treatment reduced the increased UDCA, HDCA, MCA, CA, and GLCA in UC and normalized the levels of some bile acids, especially CA and MCA. Moreover, BTWT increased the expression of FXR and GPBAR1 in the liver. In addition, they found that the relative species abundance and diversity of the gut microbiota were significantly higher in the BTWT-exposed group. BTWT significantly ameliorated colonic inflammation and clinical signs, such as histological damage and colonic shortening, in mice. This result may be achieved by affecting the intestinal microbiota and bile acid metabolism[122]. Gualou Xiebai Decoction (GXD) is a classic formula used in China for thousands of years to treat inflammatory diseases. A recent study showed that GXD significantly improved intestinal barrier dysfunction caused by abnormal bile acid metabolism in IBD by regulating tight junction protein expression levels, inhibiting oxidative stress, and reducing apoptosis[123].

"Kushen", the dried root of the *Sophora flavescens* Aiton, is a classical drug widely used in China to treat UC in ancient and modern times, with alkaloids and flavonoids as the main components. Previous studies have shown that *Sophora flavescens* Aiton total flavonoids extract (SFE) exhibits anti-UC effects by restoring the balance of the "host-microbe" co-metabolic network and modulating the intestinal microbial structure in UC mice[124]. A recent study further found that SFE, especially the flavonoid component represented by kurarinone, had a significant protective effect against UC by regulating the transcriptional levels of RORγt and Foxp 3 in the colon and down-regulating the expression of the pro-inflammatory factor IL-17A in colon tissue[125]. In addition, Chingchang Wenzhong Decoction (QCWZD) and licorice water extraction (LWE) also inhibited the transcriptional activation of RORγT and IL-17A, thereby suppressing the differentiation of Th17 Lymphocytes and reducing colonic inflammation[126,127]. Huanglian Ganjiang Tang (HGT) is the classic formula in Danxi Xinfa, used to relieve diarrhea, abdominal pain, and blood in the stool; it is currently used clinically for the treatment of UC with remarkable efficacy, but its mechanism of action needs to be further elucidated. Xiong *et al*[128] recently showed that HGT could reduce DSS-induced colitis in mice by inhibiting DSS-induced necrotizing lesions in the colon through up-regulation of VDR levels. Furthermore, in animal models of IBD, researchers found that patchouli alcohol (PA) and alpinetin from ginger plants could activate PXR signaling and inhibit NF-κB signaling, thereby ameliorating inflammation[129,130]. In conclusion, the results of these herbal studies provide new options for treating IBD and provide a theoretical basis for pharmacological studies of herbal medicines, which are beneficial for their application.

UDCA

UDCA is a secondary bile acid generated from CDCA, which is found in low concentrations in humans and was initially licensed by the FDA to treat cholestatic liver disease. However, several studies have shown that UDCA may play an important role in IBD by acting on bile acid receptors. For example, a previous study showed that DCA could inhibit the expression of CFTR Cl- channels by activating FXR, thereby delaying the repair of the intestinal mucosal barrier. Interestingly, UDCA inhibits this process and promotes epithelial cell migration and recovery[131]. In a recent study, UDCA was shown to reduce inflammatory cytokine production by activating FXR while inhibiting NF-κB activation in macrophages in a piglet model of intestinal inflammation[132]. These findings suggest a protective role for UDCA in IBD and support its use as a novel approach to treat IBD. In addition, UDCA can improve IBD injury through a few other potential mechanisms. MAdCAM-1 binds to integrin α4β7 on circulating T cells and recruits intestinal homing lymphocytes to intestinal damage sites during inflammation[133]. A recent study showed that by inhibiting NF-κB signaling, UDCA could directly attenuate the endothelial expression of MAdCAM-1 and other adhesion molecules, leading to a decrease in the accumulation of α4β7+ lymphocytes in the colon, thereby reducing the severity of colitis[134]. Another study showed that in a DSS-induced mouse model, UDCA and LCA prevented intestinal inflammation *in vivo*, at least in part by inhibiting epithelial cell apoptosis and promoting barrier function. Interestingly, LCA was more effective than UDCA in inhibiting epithelial cytokine release and preventing DSS-induced mucosal inflammation[135,136]. Mesalazine is the main drug used clinically for the treatment of UC and has been shown to induce remission of IBD and prevent IBD recurrence[137]. UDCA + mesalazine has been reported to have a better therapeutic effect than mesalazine alone, which may be related to the significant reduction of IL-23 and IL-17 and the altered distribution ratio of intestinal flora[138]. Tauroursodeoxycholic acid, a taurine conjugated UDCA, has been shown to reduce the accumulation of MPO activity, decrease colonic tissue levels of IL-1β, IFN-γ, and TNF-α, and also down-regulate nuclear receptor and bile acid transporter protein levels[139,140]. Hyodeoxycholic acid, glycine ursodeoxycholic acid, and taurocholate have similarly reduced colitis severity in in a mouse model of IBD[141-143]. However, it has also been shown that long-term use of high-dose UDCA increases the risk of colorectal neoplasia in patients with IBD, suggesting that we need to control the course and dose of the drug rationally[144]. In conclusion, secondary bile acids such as UDCA may be promising therapeutic agents for reducing ecological dysregulation and improving inflammation in human IBD and are attractive candidates for treating IBD.

Probiotics and fecal microbiota transplantation

Probiotic therapy introduces specific bacteria that have a recognized advantage in competitively suppressing pathogens and normalizing intestinal microbiota composition. Probiotics are classified by the World Health Organization as live

microorganisms that, when consumed in sufficient quantities, can help the host's health. The probiotics *Bifidobacterium*, *Lactobacillus*, and *Lactococcus* are the most frequently utilized. As an adjuvant therapy for addressing the functional symptoms of IBD, probiotics have shown promise in numerous human and animal studies[145-147]. Wong *et al*[148] recently demonstrated that *Lactobacillus casei* strain Shirota (LcS) not only increased beneficial bacterial species but also modified the circulating bile acid profile in a mouse model of DSS-induced acute colitis. Furthermore, LcS treatment increased mucin-2 and occludin expression in the colon while improving intestinal integrity. It was also shown that LcS therapy decreased the expression of pro-inflammatory mediators IFN-γ and NO and raised the expression of anti-inflammatory mediators in colonic tissue, possibly due to an altered bile acid profile[148]. Another study showed that probiotic mixtures containing *Lactobacillus rhamnosus* and *Lactococcus lactis* reduced the expression levels of IFN-γ, IL-17F, IL-1α, and IL-25, as well as the levels of the main NLRP3 inflammasome components (NLRP3, ASC, caspase-1, and IL-1β) and NOD2 in IBD mice. Probiotics have also increased FXR, GPABR1, vitamin D, and CAR expression in IBD mice[149]. Furthermore, the probiotic *Lactobacillus* has anti-inflammatory activity and induces cellular autophagy, and these effects are achieved by increasing VDR expression[150]. Recently, Zhou *et al*[151] designed a bile acid consortium (BAC) composed of three species of *Bacteroides ovatus*, *Clostridium* AP sp000509125, and *Eubacterium limosum*. They observed that BAC restored secondary bile acid metabolism in DSS-treated mice, thereby increasing the levels of UDCA and LCA, which induced activation of GPABR1 to improve the integrity of the intestinal barrier and reduce inflammation[151]. In addition, the probiotic strain *Bifidobacterium longum* CECT 7894 could improve the efficacy of infliximab against DSS-induced colitis by modulating intestinal flora composition and bile acid metabolism[152]. Probiotics may increase the risk of bacteremia, adverse effects, and the spread of antibiotic resistance in IBD patients because of their bioactivity and other characteristics. In addition, probiotics used for adjuvant therapy may be unsuccessful in some patients due to strain specificity or individual differences, in which case they should be discontinued. Therefore, the duration of probiotics should be dependent on various therapeutic benefits, objectives, and practical circumstances. Future clinical and animal investigations are required to study the direct effects and specific mechanisms of probiotics on bile acids and their receptors in IBD patients.

Fecal microbiota transplantation (FMT) is a novel and appropriate route to modify the microbial ecosystem in the host gastrointestinal tract. In recent decades, FMT has improved diseases such as *Clostridioides difficile* infections, IBD, and irritable bowel syndrome. However, the exact mechanisms still need to be better understood[153,154]. Several recent studies have found that FMT may improve IBD by acting on bile acids and their receptors. Lima *et al*[155] showed that FMT induced the production of RORγt+ regulatory T cells, IL-10, and short-chain fatty acids by macrogenomic analysis and strain tracing in 60 donor and recipient samples of active UC treated by FMT, thus protecting patients from colitis [155]. Another study showed that the long-term *Faecalibaterium* colonization following FMT could reduce intestinal inflammation by regulating the expression of RORγt and Foxp3 in UC, thereby ameliorating the imbalance in Th 17/Treg levels[156]. In addition, a mouse model of colitis was shown to be significantly inhibited by the intestinal fungus *C. metapsilosis* M2006 B, which was isolated from human feces. Moreover, the researchers identified two acyclic sesquiterpenoids (F4 and F5) as the main active metabolites of M2006 B. Surprisingly, in an animal model, these metabolites were able to effectively ameliorate colitis by selectively activating FXR. These findings suggest that M2006 B in human feces may be a beneficial intestinal fungus for treating and preventing IBD[157]. Interestingly, another recent study found that administering antibiotic pretreatment to IBD patients contributed to microbial implantation and possible clinical effectiveness[158]. In conclusion, these findings support the use of FMT in treating IBD, but the safety and efficacy of FMT remain to be investigated.

Bile acid sequestrants

A bile acid sequestrant is a positively charged indigestible resin that binds to bile acids in the intestine and forms insoluble compounds in the feces. They are mainly used in treating primary hypercholesterolemia and hypercholesterolemia with mild hypertriglyceridemia[159,160]. Currently, there are three major medications available for purchase: Cholestyramine, colestipol, and, more recently, colesevelam. Bile acid malabsorption (BAM), also known as bile acid diarrhea (BAD), is a prevalent, underappreciated, and frequently missed indicator of IBD. Clinically relevant BAM is most commonly seen in patients with IBD, especially in ileal resected CD patients.

In most cases, BAM in IBD is caused by impaired reabsorption of conjugated bile acids[161]. CD patients with BAM treated with bile acid sequestrants achieved a good response in 72.2% of cases. Researchers also analyzed the relationship between the degree of BAM (moderate or severe), intestinal surgery, and response to bile acid chelation therapy, but unfortunately, this was not statistically significant[162]. Another study showed a significant improvement in the quality of life of CD patients after terminal ileal resection when molecular treatment was given to them[163]. Although some research progress has been made, the specific mechanisms of bile acid chelators in treating BAM caused by IBD need to be further explained.

CONCLUSION

The data suggest that bile acid metabolism and receptor signaling play a key role in regulating dysregulated gut homeostasis in IBD. Changing bile acid metabolism and bile acid receptor signalling has been found to influence the pathogenesis of IBD *via* modulation of immunology, intestinal epithelial barrier function, and the gut microbiome. It is an attractive and highly promising therapeutic target for IBD. Many therapeutic strategies have shown positive effects, such as bile acid receptor agonists or inhibitors, traditional Chinese medicine, UDCA, probiotics, FMT, and bile acid sequestrants. However, due to the differences between species and cell types (IBD is exclusively a human disease),

valuable preclinical mechanistic studies must be performed to elucidate the function of bile acids and their receptors in human intestinal models. In this regard, human organoid technologies and bioinformatics approaches may be good tools to address this issue. In addition, the current therapeutic strategies described above have yet to be widely validated in clinical trials in patients with IBD, despite the promising results documented in cellular and animal studies. Future research efforts should focus on clinical trial data collection in IBD patients.

FOOTNOTES

REFERENCES

1   **Buie MJ**, Quan J, Windsor JW, Coward S, Hansen TM, King JA, Kotze PG, Gearry RB, Ng SC, Mak JWY, Abreu MT, Rubin DT, Bernstein CN, Banerjee R, Yamamoto-Furusho JK, Panaccione R, Seow CH, Ma C, Underwood FE, Ahuja V, Panaccione N, Shaheen AA, Holroyd-Leduc J, Kaplan GG; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group, Balderramo D, Chong VH, Juliao-Baños F, Dutta U, Simadibrata M, Kaibullayeva J, Sun Y, Hilmi I, Raja Ali RA, Paudel MS, Altuwaijri M, Hartono JL, Wei SC, Limsrivilai J, El Ouali S, Vergara BI, Dao VH, Kelly P, Hodges P, Miao Y, Li M. Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review With Temporal Analyses. *Clin Gastroenterol Hepatol* 2022 [PMID: 35863682 DOI: 10.1016/j.cgh.2022.06.030]

2   **Kaplan GG**, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 56-66 [PMID: 33033392 DOI: 10.1038/s41575-020-00360-x]

3   **Krela-Kaźmierczak I**, Zakerska-Banaszak O, Skrzypczak-Zielińska M, Łykowska-Szuber L, Szymczak-Tomczak A, Zawada A, Rychter AM, Ratajczak AE, Skoracka K, Skrzypczak D, Marcinkowska E, Słomski R, Dobrowolska A. Where Do We Stand in the Behavioral Pathogenesis of Inflammatory Bowel Disease? The Western Dietary Pattern and Microbiota-A Narrative Review. *Nutrients* 2022; **14** [PMID: 35745251 DOI: 10.3390/nu14122520]

4   **Neurath MF**. Targeting immune cell circuits and trafficking in inflammatory bowel disease. *Nat Immunol* 2019; **20**: 970-979 [PMID: 31235952 DOI: 10.1038/s41590-019-0415-0]

5   **Khor B**, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011; **474**: 307-317 [PMID: 21677747 DOI: 10.1038/nature10209]

6   **Flynn S**, Eisenstein S. Inflammatory Bowel Disease Presentation and Diagnosis. *Surg Clin North Am* 2019; **99**: 1051-1062 [PMID: 31676047 DOI: 10.1016/j.suc.2019.08.001]

7   **Rogler G**, Singh A, Kavanaugh A, Rubin DT. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology* 2021; **161**: 1118-1132 [PMID: 34358489 DOI: 10.1053/j.gastro.2021.07.042]

8   **Lowe SC**, Sauk JS, Limketkai BN, Kwaan MR. Declining Rates of Surgery for Inflammatory Bowel Disease in the Era of Biologic Therapy. *J Gastrointest Surg* 2021; **25**: 211-219 [PMID: 33140318 DOI: 10.1007/s11605-020-04832-y]

9   **Baumgart DC**, Le Berre C. Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease. *N Engl J Med* 2021; **385**: 1302-1315 [PMID: 34587387 DOI: 10.1056/NEJMra1907607]

10   **Brandl K**, Hartmann P, Jih LJ, Pizzo DP, Argemi J, Ventura-Cots M, Coulter S, Liddle C, Ling L, Rossi SJ, DePaoli AM, Loomba R, Mehal WZ, Fouts DE, Lucey MR, Bosques-Padilla F, Mathurin P, Louvet A, Garcia-Tsao G, Verna EC, Abraldes JG, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross D, Stärkel P, Ho SB, Bataller R, Schnabl B. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. *J Hepatol* 2018; **69**: 396-405 [PMID: 29654817 DOI: 10.1016/j.jhep.2018.03.031]

11   **Hu Y**, Chau T, Liu HX, Liao D, Keane R, Nie Y, Yang H, Wan YJ. Bile acids regulate nuclear receptor (Nur77) expression and intracellular location to control proliferation and apoptosis. *Mol Cancer Res* 2015; **13**: 281-292 [PMID: 25232032 DOI: 10.1158/1541-7786.MCR-14-0230]

12   **Bertolini A**, Fiorotto R, Strazzabosco M. Bile acids and their receptors: modulators and therapeutic targets in liver inflammation. *Semin Immunopathol* 2022; **44**: 547-564 [PMID: 35415765 DOI: 10.1007/s00281-022-00935-7]

13   **Fuchs CD**, Trauner M. Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 432-450 [PMID: 35165436 DOI: 10.1038/s41575-021-00566-7]

14   **Hofmann AF**. Bile Acids: The Good, the Bad, and the Ugly. *News Physiol Sci* 1999; **14**: 24-29 [PMID: 11390813 DOI: 10.1152/physiologyonline.1999.14.1.24]

15   **Westergaard H**, Dietschy JM. The mechanism whereby bile acid micelles increase the rate of fatty acid and cholesterol uptake into the intestinal mucosal cell. *J Clin Invest* 1976; **58**: 97-108 [PMID: 932213 DOI: 10.1172/jci108465]

16   **Tiratterra E**, Franco P, Porru E, Katsanos KH, Christodoulou DK, Roda G. Role of bile acids in inflammatory bowel disease. *Ann Gastroenterol* 2018; **31**: 266-272 [PMID: 29720851 DOI: 10.20524/aog.2018.0239]

17   **Chiang JY**. Bile acids: regulation of synthesis. *J Lipid Res* 2009; **50**: 1955-1966 [PMID: 19346330 DOI: 10.1194/jlr.R900010-JLR200]

18   **Goodwin B**, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM, Kliewer SA. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. *Mol Cell* 2000; **6**: 517-526 [PMID: 11030332 DOI: 10.1016/s1097-2765(00)00051-4]

19   **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]

20   **Fiorucci S**, Distrutti E. The Pharmacology of Bile Acids and Their Receptors. *Handb Exp Pharmacol* 2019; **256**: 3-18 [PMID: 31201555 DOI: 10.1007/164_2019_238]

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   **Monte MJ**, Marin JJ, Antelo A, Vazquez-Tato J. Bile acids: chemistry, physiology, and pathophysiology. *World J Gastroenterol* 2009; **15**: 804-816 [PMID: 19230041 DOI: 10.3748/wjg.15.804]

23   **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]

24   **de Aguiar Vallim TQ**, Tarling EJ, Edwards PA. Pleiotropic roles of bile acids in metabolism. *Cell Metab* 2013; **17**: 657-669 [PMID: 23602448 DOI: 10.1016/j.cmet.2013.03.013]

25   **Chandra R**, Liddle RA. Cholecystokinin. *Curr Opin Endocrinol Diabetes Obes* 2007; **14**: 63-67 [PMID: 17940422 DOI: 10.1097/MED.0b013e3280122850]

26   **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]

27   **Wang C**, Zhu C, Shao L, Ye J, Shen Y, Ren Y. Role of Bile Acids in Dysbiosis and Treatment of Nonalcoholic Fatty Liver Disease. *Mediators Inflamm* 2019; **2019**: 7659509 [PMID: 31341422 DOI: 10.1155/2019/7659509]

28   **Jahnel J**, Fickert P, Hauer AC, Högenauer C, Avian A, Trauner M. Inflammatory bowel disease alters intestinal bile acid transporter expression. *Drug Metab Dispos* 2014; **42**: 1423-1431 [PMID: 24965812 DOI: 10.1124/dmd.114.058065]

29   **Lu TT**, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J, Mangelsdorf DJ. Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Mol Cell* 2000; **6**: 507-515 [PMID: 11030331 DOI: 10.1016/s1097-2765(00)00050-2]

30   **Chen L**, Jiao T, Liu W, Luo Y, Wang J, Guo X, Tong X, Lin Z, Sun C, Wang K, He Y, Zhang Y, Xu H, Zuo J, Ding Q, He S, Gonzalez FJ, Xie C. Hepatic cytochrome P450 8B1 and cholic acid potentiate intestinal epithelial injury in colitis by suppressing intestinal stem cell renewal. *Cell Stem Cell* 2022; **29**: 1366-1381.e9 [PMID: 36055192 DOI: 10.1016/j.stem.2022.08.008]

31   **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]

32   **Quinn RA**, Melnik AV, Vrbanac A, Fu T, Patras KA, Christy MP, Bodai Z, Belda-Ferre P, Tripathi A, Chung LK, Downes M, Welch RD, Quinn M, Humphrey G, Panitchpakdi M, Weldon KC, Aksenov A, da Silva R, Avila-Pacheco J, Clish C, Bae S, Mallick H, Franzosa EA, Lloyd-Price J, Bussell R, Thron T, Nelson AT, Wang M, Leszczynski E, Vargas F, Gauglitz JM, Meehan MJ, Gentry E, Arthur TD, Komor AC, Poulsen O, Boland BS, Chang JT, Sandborn WJ, Lim M, Garg N, Lumeng JC, Xavier RJ, Kazmierczak BI, Jain R, Egan M, Rhee KE, Ferguson D, Raffatellu M, Vlamakis H, Haddad GG, Siegel D, Huttenhower C, Mazmanian SK, Evans RM, Nizet V, Knight R, Dorrestein PC. Global chemical effects of the microbiome include new bile-acid conjugations. *Nature* 2020; **579**: 123-129 [PMID: 32103176 DOI: 10.1038/s41586-020-2047-9]

33   **Pavlidis P**, Powell N, Vincent RP, Ehrlich D, Bjarnason I, Hayee B. Systematic review: bile acids and intestinal inflammation-luminal aggressors or regulators of mucosal defence? *Aliment Pharmacol Ther* 2015; **42**: 802-817 [PMID: 26223936 DOI: 10.1111/apt.13333]

34   **Ridlon JM**, Harris SC, Bhowmik S, Kang DJ, Hylemon PB. Consequences of bile salt biotransformations by intestinal bacteria. *Gut Microbes* 2016; **7**: 22-39 [PMID: 26939849 DOI: 10.1080/19490976.2015.1127483]

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

36   **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]

37   **Funabashi M**, Grove TL, Wang M, Varma Y, McFadden ME, Brown LC, Guo C, Higginbottom S, Almo SC, Fischbach MA. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. *Nature* 2020; **582**: 566-570 [PMID: 32555455 DOI: 10.1038/s41586-020-2396-4]

38   **Sayin SI**, Wahlström A, Felin J, Jäntti S, Marschall HU, Bamberg K, Angelin B, Hyötyläinen T, Orešič M, Bäckhed F. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab* 2013; **17**: 225-235 [PMID: 23395169 DOI: 10.1016/j.cmet.2013.01.003]

39   **Lavelle A**, Nancey S, Reimund JM, Laharie D, Marteau P, Treton X, Allez M, Roblin X, Malamut G, Oeuvray C, Rolhion N, Dray X, Rainteau D, Lamaziere A, Gauliard E, Kirchgesner J, Beaugerie L, Seksik P, Peyrin-Biroulet L, Sokol H. Fecal microbiota and bile acids in IBD patients undergoing screening for colorectal cancer. *Gut Microbes* 2022; **14**: 2078620 [PMID: 35638103 DOI: 10.1080/19490976.2022.2078620]

40   **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]

41   **Duboc H**, Rajca S, Rainteau D, Benarous D, Maubert MA, Quervain E, Thomas G, Barbu V, Humbert L, Despras G, Bridonneau C, Dumetz F, Grill JP, Masliah J, Beaugerie L, Cosnes J, Chazouillères O, Poupon R, Wolf C, Mallet JM, Langella P, Trugnan G, Sokol H, Seksik P. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut* 2013; **62**: 531-539 [PMID: 22993202 DOI: 10.1136/gutjnl-2012-302578]

42   **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]

43   **Islam KB**, Fukiya S, Hagio M, Fujii N, Ishizuka S, Ooka T, Ogura Y, Hayashi T, Yokota A. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology* 2011; **141**: 1773-1781 [PMID: 21839040 DOI: 10.1053/j.gastro.2011.07.046]

44   **Forman BM**, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM, Weinberger C. Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell* 1995; **81**: 687-693 [PMID: 7774010 DOI: 10.1016/0092-8674(95)90530-8]

45   **Fiorucci S**, Biagioli M, Zampella A, Distrutti E. Bile Acids Activated Receptors Regulate Innate Immunity. *Front Immunol* 2018; **9**: 1853 [PMID: 30150987 DOI: 10.3389/fimmu.2018.01853]

46   **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]

47   **Zhou X**, Cao L, Jiang C, Xie Y, Cheng X, Krausz KW, Qi Y, Sun L, Shah YM, Gonzalez FJ, Wang G, Hao H. PPARα-UGT axis activation represses intestinal FXR-FGF15 feedback signalling and exacerbates experimental colitis. *Nat Commun* 2014; **5**: 4573 [PMID: 25183423 DOI: 10.1038/ncomms5573]

48   **Schroeder JH**, Howard JK, Lord GM. Transcription factor-driven regulation of ILC1 and ILC3. *Trends Immunol* 2022; **43**: 564-579 [PMID: 35618586 DOI: 10.1016/j.it.2022.04.009]

49   **Fu T**, Li Y, Oh TG, Cayabyab F, He N, Tang Q, Coulter S, Truitt M, Medina P, He M, Yu RT, Atkins A, Zheng Y, Liddle C, Downes M, Evans RM. FXR mediates ILC-intrinsic responses to intestinal inflammation. *Proc Natl Acad Sci U S A* 2022; **119**: e2213041119 [PMID: 36508655 DOI: 10.1073/pnas.2213041119]

50   **Del Zotto B**, Mumolo G, Pronio AM, Montesani C, Tersigni R, Boirivant M. TGF-beta1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. *Clin Exp Immunol* 2003; **134**: 120-126 [PMID: 12974764 DOI: 10.1046/j.1365-2249.2003.02250.x]

51   **Zhao D**, Cai C, Chen Q, Jin S, Yang B, Li N. High-Fat Diet Promotes DSS-Induced Ulcerative Colitis by Downregulated FXR Expression through the TGFB Pathway. *Biomed Res Int* 2020; **2020**: 3516128 [PMID: 33029504 DOI: 10.1155/2020/3516128]

52   **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]

53   **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]

54   **Song M**, Ye J, Zhang F, Su H, Yang X, He H, Liu F, Zhu X, Wang L, Gao P, Shu G, Jiang Q, Wang S. Chenodeoxycholic Acid (CDCA) Protects against the Lipopolysaccharide-Induced Impairment of the Intestinal Epithelial Barrier Function *via* the FXR-MLCK Pathway. *J Agric Food Chem* 2019; **67**: 8868-8874 [PMID: 31319027 DOI: 10.1021/acs.jafc.9b03173]

55   **Liu HM**, Liao JF, Lee TY. Farnesoid X receptor agonist GW4064 ameliorates lipopolysaccharide-induced ileocolitis through TLR4/MyD88 pathway related mitochondrial dysfunction in mice. *Biochem Biophys Res Commun* 2017; **490**: 841-848 [PMID: 28647362 DOI: 10.1016/j.bbrc.2017.06.129]

56   **Mickael ME**, Bhaumik S, Basu R. Retinoid-Related Orphan Receptor RORγt in CD4(+) T-Cell-Mediated Intestinal Homeostasis and Inflammation. *Am J Pathol* 2020; **190**: 1984-1999 [PMID: 32735890 DOI: 10.1016/j.ajpath.2020.07.010]

57   **Hang S**, Paik D, Yao L, Kim E, Trinath J, Lu J, Ha S, Nelson BN, Kelly SP, Wu L, Zheng Y, Longman RS, Rastinejad F, Devlin AS, Krout MR, Fischbach MA, Littman DR, Huh JR. Bile acid metabolites control T(H)17 and T(reg) cell differentiation. *Nature* 2019; **576**: 143-148 [PMID: 31776512 DOI: 10.1038/s41586-019-1785-z]

58   **Paik D**, Yao L, Zhang Y, Bae S, D'Agostino GD, Zhang M, Kim E, Franzosa EA, Avila-Pacheco J, Bisanz JE, Rakowski CK, Vlamakis H, Xavier RJ, Turnbaugh PJ, Longman RS, Krout MR, Clish CB, Rastinejad F, Huttenhower C, Huh JR, Devlin AS. Human gut bacteria produce T(H)17-modulating bile acid metabolites. *Nature* 2022; **603**: 907-912 [PMID: 35296854 DOI: 10.1038/s41586-022-04480-z]

59   **Campbell C**, McKenney PT, Konstantinovsky D, Isaeva OI, Schizas M, Verter J, Mai C, Jin WB, Guo CJ, Violante S, Ramos RJ, Cross JR, Kadaveru K, Hambor J, Rudensky AY. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. *Nature* 2020; **581**: 475-479 [PMID: 32461639 DOI: 10.1038/s41586-020-2193-0]

60   **Lv L**, Chen Z, Bai W, Hao J, Heng Z, Meng C, Wang L, Luo X, Wang X, Cao Y, He J. Taurohyodeoxycholic acid alleviates trinitrobenzene sulfonic acid induced ulcerative colitis *via* regulating Th1/Th2 and Th17/Treg cells balance. *Life Sci* 2023; **318**: 121501 [PMID: 36801213 DOI: 10.1016/j.lfs.2023.121501]

61   **Kathania M**, Kumar R, Lenou ET, Basrur V, Theiss AL, Chernoff J, Venuprasad K. Pak2-mediated phosphorylation promotes RORγt ubiquitination and inhibits colonic inflammation. *Cell Rep* 2022; **40**: 111345 [PMID: 36103814 DOI: 10.1016/j.celrep.2022.111345]

62   **Ohnmacht C**, Park JH, Cording S, Wing JB, Atarashi K, Obata Y, Gaboriau-Routhiau V, Marques R, Dulauroy S, Fedoseeva M, Busslinger M, Cerf-Bensussan N, Boneca IG, Voehringer D, Hase K, Honda K, Sakaguchi S, Eberl G. MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORγt⁺ T cells. *Science* 2015; **349**: 989-993 [PMID: 26160380 DOI: 10.1126/science.aac4263]

63   **Sefik E**, Geva-Zatorsky N, Oh S, Konnikova L, Zemmour D, McGuire AM, Burzyn D, Ortiz-Lopez A, Lobera M, Yang J, Ghosh S, Earl A, Snapper SB, Jupp R, Kasper D, Mathis D, Benoist C. MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of RORγ⁺ regulatory T cells. *Science* 2015; **349**: 993-997 [PMID: 26272906 DOI: 10.1126/science.aaa9420]

64   **Maloy KJ**, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* 2011; **474**: 298-306 [PMID: 21677746 DOI: 10.1038/nature10208]

65   **Lyu M**, Suzuki H, Kang L, Gaspal F, Zhou W, Goc J, Zhou L, Zhou J, Zhang W; JRI Live Cell Bank, Shen Z, Fox JG, Sockolow RE, Laufer TM, Fan Y, Eberl G, Withers DR, Sonnenberg GF. ILC3s select microbiota-specific regulatory T cells to establish tolerance in the gut. *Nature* 2022; **610**: 744-751 [PMID: 36071169 DOI: 10.1038/s41586-022-05141-x]

66   **Akagbosu B**, Tayyebi Z, Shibu G, Paucar Iza YA, Deep D, Parisotto YF, Fisher L, Pasolli HA, Thevin V, Elmentaite R, Knott M, Hemmers S, Jahn L, Friedrich C, Verter J, Wang ZM, van den Brink M, Gasteiger G, Grünewald TGP, Marie JC, Leslie C, Rudensky AY, Brown CC. Novel antigen-presenting cell imparts T(reg)-dependent tolerance to gut microbiota. *Nature* 2022; **610**: 752-760 [PMID: 36070798 DOI: 10.1038/s41586-022-05309-5]

67   **Liu Y**, Yang M, Tang L, Wang F, Huang S, Liu S, Lei Y, Wang S, Xie Z, Wang W, Zhao X, Tang B, Yang S. TLR4 regulates RORγt(+) regulatory T-cell responses and susceptibility to colon inflammation through interaction with Akkermansia muciniphila. *Microbiome* 2022; **10**:

98 [PMID: 35761415 DOI: 10.1186/s40168-022-01296-x]

68   **Bhaumik S**, Mickael ME, Moran M, Spell M, Basu R. RORγt Promotes Foxp3 Expression by Antagonizing the Effector Program in Colonic Regulatory T Cells. *J Immunol* 2021; **207**: 2027-2038 [PMID: 34518282 DOI: 10.4049/jimmunol.2100175]

69   **Kawamata Y**, Fujii R, Hosoya M, Harada M, Yoshida H, Miwa M, Fukusumi S, Habata Y, Itoh T, Shintani Y, Hinuma S, Fujisawa Y, Fujino M. A G protein-coupled receptor responsive to bile acids. *J Biol Chem* 2003; **278**: 9435-9440 [PMID: 12524422 DOI: 10.1074/jbc.M209706200]

70   **Schroder K**, Tschopp J. The inflammasomes. *Cell* 2010; **140**: 821-832 [PMID: 20303873 DOI: 10.1016/j.cell.2010.01.040]

71   **Zhen Y**, Zhang H. NLRP3 Inflammasome and Inflammatory Bowel Disease. *Front Immunol* 2019; **10**: 276 [PMID: 30873162 DOI: 10.3389/fimmu.2019.00276]

72   **Guo C**, Xie S, Chi Z, Zhang J, Liu Y, Zhang L, Zheng M, Zhang X, Xia D, Ke Y, Lu L, Wang D. Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome. *Immunity* 2016; **45**: 802-816 [PMID: 27692610 DOI: 10.1016/j.immuni.2016.09.008]

73   **Biagioli M**, Carino A, Cipriani S, Francisci D, Marchianò S, Scarpelli P, Sorcini D, Zampella A, Fiorucci S. The Bile Acid Receptor GPBAR1 Regulates the M1/M2 Phenotype of Intestinal Macrophages and Activation of GPBAR1 Rescues Mice from Murine Colitis. *J Immunol* 2017; **199**: 718-733 [PMID: 28607110 DOI: 10.4049/jimmunol.1700183]

74   **Khajah MA**, Fateel MM, Ananthalakshmi KV, Luqmani YA. Anti-Inflammatory Action of Angiotensin 1-7 in Experimental Colitis. *PLoS One* 2016; **11**: e0150861 [PMID: 26963721 DOI: 10.1371/journal.pone.0150861]

75   **Biagioli M**, Marchianò S, Roselli R, Di Giorgio C, Bellini R, Bordoni M, Distrutti E, Catalanotti B, Zampella A, Graziosi L, Donini A, Fiorucci S. GLP-1 Mediates Regulation of Colonic ACE2 Expression by the Bile Acid Receptor GPBAR1 in Inflammation. *Cells* 2022; **11** [PMID: 35406751 DOI: 10.3390/cells11071187]

76   **Sinha SR**, Haileselassie Y, Nguyen LP, Tropini C, Wang M, Becker LS, Sim D, Jarr K, Spear ET, Singh G, Namkoong H, Bittinger K, Fischbach MA, Sonnenburg JL, Habtezion A. Dysbiosis-Induced Secondary Bile Acid Deficiency Promotes Intestinal Inflammation. *Cell Host Microbe* 2020; **27**: 659-670.e5 [PMID: 32101703 DOI: 10.1016/j.chom.2020.01.021]

77   **Azuma Y**, Uchiyama K, Sugaya T, Yasuda T, Hashimoto H, Kajiwara-Kubota M, Sugino S, Kitae H, Torii T, Mizushima K, Doi T, Inoue K, Dohi O, Yoshida N, Kamada K, Ishikawa T, Takagi T, Konishi H, Naito Y, Itoh Y. Deoxycholic acid delays the wound healing of colonic epithelial cells *via* transmembrane G-protein-coupled receptor 5. *J Gastroenterol Hepatol* 2022; **37**: 134-143 [PMID: 34477242 DOI: 10.1111/jgh.15676]

78   **Zhai Z**, Niu KM, Liu Y, Lin C, Wu X. The Gut Microbiota-Bile Acids-TGR5 Axis Mediates Eucommia ulmoides Leaf Extract Alleviation of Injury to Colonic Epithelium Integrity. *Front Microbiol* 2021; **12**: 727681 [PMID: 34489916 DOI: 10.3389/fmicb.2021.727681]

79   **Kellermann L**, Jensen KB, Bergenheim F, Gubatan J, Chou ND, Moss A, Nielsen OH. Mucosal vitamin D signaling in inflammatory bowel disease. *Autoimmun Rev* 2020; **19**: 102672 [PMID: 32942038 DOI: 10.1016/j.autrev.2020.102672]

80   **Makishima M**, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, Mangelsdorf DJ. Vitamin D receptor as an intestinal bile acid sensor. *Science* 2002; **296**: 1313-1316 [PMID: 12016314 DOI: 10.1126/science.1070477]

81   **Yao B**, He J, Yin X, Shi Y, Wan J, Tian Z. The protective effect of lithocholic acid on the intestinal epithelial barrier is mediated by the vitamin D receptor *via* a SIRT1/Nrf2 and NF-κB dependent mechanism in Caco-2 cells. *Toxicol Lett* 2019; **316**: 109-118 [PMID: 31472180 DOI: 10.1016/j.toxlet.2019.08.024]

82   **Bäcker V**, Cheung FY, Siveke JT, Fandrey J, Winning S. Knockdown of myeloid cell hypoxia-inducible factor-1α ameliorates the acute pathology in DSS-induced colitis. *PLoS One* 2017; **12**: e0190074 [PMID: 29261815 DOI: 10.1371/journal.pone.0190074]

83   **Kim YE**, Lee M, Gu H, Kim J, Jeong S, Yeo S, Lee YJ, Im SH, Sung YC, Kim HJ, Weissman IL, Ahn GO. HIF-1α activation in myeloid cells accelerates dextran sodium sulfate-induced colitis progression in mice. *Dis Model Mech* 2018; **11** [PMID: 29967068 DOI: 10.1242/dmm.033241]

84   **Xue G**, Gao R, Liu Z, Xu N, Cao Y, Zhao B, Du J. Vitamin D/VDR signaling inhibits colitis by suppressing HIF-1α activation in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2021; **320**: G837-G846 [PMID: 33759562 DOI: 10.1152/ajpgi.00061.2021]

85   **Wang X**, Ge X, Liao W, Cao Y, Li R, Zhang F, Zhao B, Du J. ZFP36 promotes VDR mRNA degradation to facilitate cell death in oral and colonic epithelial cells. *Cell Commun Signal* 2021; **19**: 85 [PMID: 34380509 DOI: 10.1186/s12964-021-00765-4]

86   **Fernández-Barral A**, Costales-Carrera A, Buira SP, Jung P, Ferrer-Mayorga G, Larriba MJ, Bustamante-Madrid P, Domínguez O, Real FX, Guerra-Pastrián L, Lafarga M, García-Olmo D, Cantero R, Del Peso L, Batlle E, Rojo F, Muñoz A, Barbáchano A. Vitamin D differentially regulates colon stem cells in patient-derived normal and tumor organoids. *FEBS J* 2020; **287**: 53-72 [PMID: 31306552 DOI: 10.1111/febs.14998]

87   **Yang E**, Shen J. The roles and functions of Paneth cells in Crohn's disease: A critical review. *Cell Prolif* 2021; **54**: e12958 [PMID: 33174662 DOI: 10.1111/cpr.12958]

88   **Lu R**, Zhang YG, Xia Y, Zhang J, Kaser A, Blumberg R, Sun J. Paneth Cell Alertness to Pathogens Maintained by Vitamin D Receptors. *Gastroenterology* 2021; **160**: 1269-1283 [PMID: 33217447 DOI: 10.1053/j.gastro.2020.11.015]

89   **Luettig J**, Rosenthal R, Barmeyer C, Schulzke JD. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. *Tissue Barriers* 2015; **3**: e977176 [PMID: 25838982 DOI: 10.4161/21688370.2014.977176]

90   **Zhang YG**, Lu R, Xia Y, Zhou D, Petrof E, Claud EC, Sun J. Lack of Vitamin D Receptor Leads to Hyperfunction of Claudin-2 in Intestinal Inflammatory Responses. *Inflamm Bowel Dis* 2019; **25**: 97-110 [PMID: 30289450 DOI: 10.1093/ibd/izy292]

91   **Yu M**, Wu H, Wang J, Chen X, Pan J, Liu P, Zhang J, Chen Y, Zhu W, Tang C, Jin Q, Li C, Lu C, Zeng H, Yu C, Sun J. Vitamin D receptor inhibits EMT *via* regulation of the epithelial mitochondrial function in intestinal fibrosis. *J Biol Chem* 2021; **296**: 100531 [PMID: 33713706 DOI: 10.1016/j.jbc.2021.100531]

92   **Garg M**, Royce SG, Tikellis C, Shallue C, Sluka P, Wardan H, Hosking P, Monagle S, Thomas M, Lubel JS, Gibson PR. The intestinal vitamin D receptor in inflammatory bowel disease: inverse correlation with inflammation but no relationship with circulating vitamin D status. *Therap Adv Gastroenterol* 2019; **12**: 1756284818822566 [PMID: 30719077 DOI: 10.1177/1756284818822566]

93   **Huang J**, Chen T, Liu Y, Lyu L, Li X, Yue W. How would serum 25(OH)D level change in patients with inflammatory bowel disease depending on intestinal mucosa vitamin D receptor (VDR) and vitamin D1-α hydroxylase (CYP27B1)? *Turk J Gastroenterol* 2019; **30**: 132-138 [PMID: 30429108 DOI: 10.5152/tjg.2018.17828]

94   **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]

95   **Kliewer SA**, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterström RH, Perlmann T,

Lehmann JM. An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* 1998; **92**: 73-82 [PMID: 9489701 DOI: 10.1016/s0092-8674(00)80900-9]

96   Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* 1998; **102**: 1016-1023 [PMID: 9727070 DOI: 10.1172/jci3703]

97   Baes M, Gulick T, Choi HS, Martinoli MG, Simha D, Moore DD. A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Mol Cell Biol* 1994; **14**: 1544-1552 [PMID: 8114692 DOI: 10.1128/mcb.14.3.1544-1552.1994]

98   Poudel S, Huber AD, Chen T. Regulation of Nuclear Receptors PXR and CAR by Small Molecules and Signal Crosstalk: Roles in Drug Metabolism and Beyond. *Drug Metab Dispos* 2023; **51**: 228-236 [PMID: 36116789 DOI: 10.1124/dmd.122.000858]

99   Uehara D, Tojima H, Kakizaki S, Yamazaki Y, Horiguchi N, Takizawa D, Sato K, Yamada M, Uraoka T. Constitutive androstane receptor and pregnane X receptor cooperatively ameliorate DSS-induced colitis. *Dig Liver Dis* 2019; **51**: 226-235 [PMID: 30442521 DOI: 10.1016/j.dld.2018.10.008]

100   Little M, Dutta M, Li H, Matson A, Shi X, Mascarinas G, Molla B, Weigel K, Gu H, Mani S, Cui JY. Understanding the physiological functions of the host xenobiotic-sensing nuclear receptors PXR and CAR on the gut microbiome using genetically modified mice. *Acta Pharm Sin B* 2022; **12**: 801-820 [PMID: 35256948 DOI: 10.1016/j.apsb.2021.07.022]

101   Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benechet AP, Qiu Z, Maher L, Redinbo MR, Phillips RS, Fleet JC, Kortagere S, Mukherjee P, Fasano A, Le Ven J, Nicholson JK, Dumas ME, Khanna KM, Mani S. Symbiotic bacterial metabolites regulate gastrointestinal barrier function *via* the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity* 2014; **41**: 296-310 [PMID: 25065623 DOI: 10.1016/j.immuni.2014.06.014]

102   Flannigan KL, Nieves KM, Szczepanski HE, Serra A, Lee JW, Alston LA, Ramay H, Mani S, Hirota SA. The Pregnane X Receptor and Indole-3-Propionic Acid Shape the Intestinal Mesenchyme to Restrain Inflammation and Fibrosis. *Cell Mol Gastroenterol Hepatol* 2023; **15**: 765-795 [PMID: 36309199 DOI: 10.1016/j.jcmgh.2022.10.014]

103   Deuring JJ, Li M, Cao W, Chen S, Wang W, de Haar C, van der Woude CJ, Peppelenbosch M. Pregnane X receptor activation constrains mucosal NF-κB activity in active inflammatory bowel disease. *PLoS One* 2019; **14**: e0221924 [PMID: 31581194 DOI: 10.1371/journal.pone.0221924]

104   Ramesh R, Kozhaya L, McKevitt K, Djuretic IM, Carlson TJ, Quintero MA, McCauley JL, Abreu MT, Unutmaz D, Sundrud MS. Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. *J Exp Med* 2014; **211**: 89-104 [PMID: 24395888 DOI: 10.1084/jem.20130301]

105   Chen ML, Huang X, Wang H, Hegner C, Liu Y, Shang J, Eliason A, Diao H, Park H, Frey B, Wang G, Mosure SA, Solt LA, Kojetin DJ, Rodriguez-Palacios A, Schady DA, Weaver CT, Pipkin ME, Moore DD, Sundrud MS. CAR directs T cell adaptation to bile acids in the small intestine. *Nature* 2021; **593**: 147-151 [PMID: 33828301 DOI: 10.1038/s41586-021-03421-6]

106   Wang X, Chen S, Xiang H, Wang X, Xiao J, Zhao S, Shu Z, Ouyang J, Liang Z, Deng M, Chen X, Zhang J, Liu H, Quan Q, Gao P, Fan J, Chen AF, Lu H. S1PR2/RhoA/ROCK1 pathway promotes inflammatory bowel disease by inducing intestinal vascular endothelial barrier damage and M1 macrophage polarization. *Biochem Pharmacol* 2022; **201**: 115077 [PMID: 35537530 DOI: 10.1016/j.bcp.2022.115077]

107   Chen T, Gu K, Lin R, Liu Y, Shan Y. The function of Sphingosine-1-phosphate receptor 2 (S1PR2) in maintaining intestinal barrier and inducing ulcerative colitis. *Bioengineered* 2022; **13**: 13703-13717 [PMID: 35707833 DOI: 10.1080/21655979.2022.2076500]

108   Zhao S, Gong Z, Du X, Tian C, Wang L, Zhou J, Xu C, Chen Y, Cai W, Wu J. Deoxycholic Acid-Mediated Sphingosine-1-Phosphate Receptor 2 Signaling Exacerbates DSS-Induced Colitis through Promoting Cathepsin B Release. *J Immunol Res* 2018; **2018**: 2481418 [PMID: 29854830 DOI: 10.1155/2018/2481418]

109   Miyazaki T, Shirakami Y, Mizutani T, Maruta A, Ideta T, Kubota M, Sakai H, Ibuka T, Genovese S, Fiorito S, Taddeo VA, Epifano F, Tanaka T, Shimizu M. Novel FXR agonist nelumal A suppresses colitis and inflammation-related colorectal carcinogenesis. *Sci Rep* 2021; **11**: 492 [PMID: 33436792 DOI: 10.1038/s41598-020-79916-5]

110   Liu F, Yao Y, Wang Q, Zhang F, Wang M, Zhu C, Lin C. Nigakinone alleviates DSS-induced experimental colitis *via* regulating bile acid profile and FXR/NLRP3 signaling pathways. *Phytother Res* 2023; **37**: 15-34 [PMID: 36054406 DOI: 10.1002/ptr.7588]

111   Zhou M, Wang D, Li X, Cao Y, Yi C, Wiredu Ocansey DK, Zhou Y, Mao F. Farnesoid-X receptor as a therapeutic target for inflammatory bowel disease and colorectal cancer. *Front Pharmacol* 2022; **13**: 1016836 [PMID: 36278234 DOI: 10.3389/fphar.2022.1016836]

112   Qi WH, Zhang YY, Xing K, Hao DX, Zhang F, Wang RN, Bao MY, Tian MY, Yang YN, Li X, Zhang Y. 2', 4'-Dihydroxy-2,3-dimethoxychalcone: A pharmacological inverse agonist of RORγt ameliorating Th17-driven inflammatory diseases by regulating Th17/Treg. *Int Immunopharmacol* 2022; **108**: 108769 [PMID: 35453073 DOI: 10.1016/j.intimp.2022.108769]

113   Chen JA, Ma H, Liu Z, Tian J, Lu S, Fang W, Ze S, Lu W, Xie Q, Huang J, Wang Y. Discovery of Orally Available Retinoic Acid Receptor-Related Orphan Receptor γ-t/Dihydroorotate Dehydrogenase Dual Inhibitors for the Treatment of Refractory Inflammatory Bowel Disease. *J Med Chem* 2022; **65**: 592-615 [PMID: 34957834 DOI: 10.1021/acs.jmedchem.1c01746]

114   Ortiz MA, Piedrafita FJ, Nefzi A. 1,5-Disubstituted Acylated 2-Amino-4,5-dihydroimidazoles as a New Class of Retinoic Acid Receptor-Related Orphan Receptor (ROR) Inhibitors. *Int J Mol Sci* 2022; **23** [PMID: 35457251 DOI: 10.3390/ijms23084433]

115   Chen Y, Le TH, Du Q, Zhao Z, Liu Y, Zou J, Hua W, Liu C, Zhu Y. Genistein protects against DSS-induced colitis by inhibiting NLRP3 inflammasome *via* TGR5-cAMP signaling. *Int Immunopharmacol* 2019; **71**: 144-154 [PMID: 30901677 DOI: 10.1016/j.intimp.2019.01.021]

116   Nakhi A, McDermott CM, Stoltz KL, John K, Hawkinson JE, Ambrose EA, Khoruts A, Sadowsky MJ, Dosa PI. 7-Methylation of Chenodeoxycholic Acid Derivatives Yields a Substantial Increase in TGR5 Receptor Potency. *J Med Chem* 2019; **62**: 6824-6830 [PMID: 31268316 DOI: 10.1021/acs.jmedchem.9b00770]

117   Salaga M, Binienda A, Draczkowski P, Kosson P, Kordek R, Jozwiak K, Fichna J. Novel peptide inhibitor of dipeptidyl peptidase IV (Tyr-Pro-D-Ala-NH(2)) with anti-inflammatory activity in the mouse models of colitis. *Peptides* 2018; **108**: 34-45 [PMID: 30179653 DOI: 10.1016/j.peptides.2018.08.011]

118   Han F, Ning M, Wang K, Gu Y, Qu H, Leng Y, Shen J. Design and exploration of gut-restricted bifunctional molecule with TGR5 agonistic and DPP4 inhibitory effects for treating ulcerative colitis. *Eur J Med Chem* 2022; **242**: 114697 [PMID: 36029562 DOI: 10.1016/j.ejmech.2022.114697]

119   Chen T, Reich NW, Bell N, Finn PD, Rodriguez D, Kohler J, Kozuka K, He L, Spencer AG, Charmot D, Navre M, Carreras CW, Koo-McCoy S, Tabora J, Caldwell JS, Jacobs JW, Lewis JG. Design of Gut-Restricted Thiazolidine Agonists of G Protein-Coupled Bile Acid Receptor 1 (GPBAR1, TGR5). *J Med Chem* 2018; **61**: 7589-7613 [PMID: 30141927 DOI: 10.1021/acs.jmedchem.8b00308]

120 **Dvořák Z**, Kopp F, Costello CM, Kemp JS, Li H, Vrzalová A, Štěpánková M, Bartoňková I, Jiskrová E, Poulíková K, Vyhlídalová B, Nordstroem LU, Karunaratne CV, Ranhotra HS, Mun KS, Naren AP, Murray IA, Perdew GH, Brtko J, Toporova L, Schön A, Wallace BD, Walton WG, Redinbo MR, Sun K, Beck A, Kortagere S, Neary MC, Chandran A, Vishveshwara S, Cavalluzzi MM, Lentini G, Cui JY, Gu H, March JC, Chatterjee S, Matson A, Wright D, Flannigan KL, Hirota SA, Sartor RB, Mani S. Targeting the pregnane X receptor using microbial metabolite mimicry. *EMBO Mol Med* 2020; **12**: e11621 [PMID: 32153125 DOI: 10.15252/emmm.201911621]

121 **Yuan S**, Wang Q, Li J, Xue JC, Li Y, Meng H, Hou XT, Nan JX, Zhang QG. Inflammatory bowel disease: an overview of Chinese herbal medicine formula-based treatment. *Chin Med* 2022; **17**: 74 [PMID: 35717380 DOI: 10.1186/s13020-022-00633-4]

122 **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]

123 **Su J**, He Z, Yu Y, Lu M, Wu Z, Zhang D. Gualou Xiebai Decoction ameliorates increased Caco-2 monolayer permeability induced by bile acids *via* tight junction regulation, oxidative stress suppression and apoptosis reduction. *J Bioenerg Biomembr* 2022; **54**: 45-57 [PMID: 34718922 DOI: 10.1007/s10863-021-09927-y]

124 **Chen L**, Shao J, Luo Y, Zhao L, Zhao K, Gao Y, Wang S, Liu Y. An integrated metabolism in vivo analysis and network pharmacology in UC rats reveal anti-ulcerative colitis effects from Sophora flavescens EtOAc extract. *J Pharm Biomed Anal* 2020; **186**: 113306 [PMID: 32371325 DOI: 10.1016/j.jpba.2020.113306]

125 **Li Z**, Lin M, Li Y, Shao J, Huang R, Qiu Y, Liu Y, Chen L. Total flavonoids of Sophora flavescens and kurarinone ameliorated ulcerative colitis by regulating Th17/Treg cell homeostasis. *J Ethnopharmacol* 2022; **297**: 115500 [PMID: 35863614 DOI: 10.1016/j.jep.2022.115500]

126 **Shi G**, Kong J, Wang Y, Xuan Z, Xu F. Glycyrrhiza uralensis Fisch. alleviates dextran sulfate sodium-induced colitis in mice through inhibiting of NF-κB signaling pathways and modulating intestinal microbiota. *J Ethnopharmacol* 2022; **298**: 115640 [PMID: 36030029 DOI: 10.1016/j.jep.2022.115640]

127 **Xia S**, Chen L, Li Z, Li Y, Zhou Y, Sun S, Su Y, Xu X, Shao J, Zhang Z, Kong D, Zhang F, Zheng S. Qingchang Wenzhong Decoction reduce ulcerative colitis in mice by inhibiting Th17 lymphocyte differentiation. *Phytomedicine* 2022; **107**: 154460 [PMID: 36182798 DOI: 10.1016/j.phymed.2022.154460]

128 **Xiong X**, Cheng Z, Zhou Y, Wu F, Xie L, Lawless L, Dong R, Zhao Y, Yu L, Chen G. HuanglianGanjiang Tang alleviates DSS-induced colitis in mice by inhibiting necroptosis through vitamin D receptor. *J Ethnopharmacol* 2022; **298**: 115655 [PMID: 35988837 DOI: 10.1016/j.jep.2022.115655]

129 **Zhang G**, Liu M, Song M, Wang J, Cai J, Lin C, Li Y, Jin X, Shen C, Chen Z, Cai D, Gao Y, Zhu C, Liu C. Patchouli alcohol activates PXR and suppresses the NF-κB-mediated intestinal inflammatory. *J Ethnopharmacol* 2020; **248**: 112302 [PMID: 31614203 DOI: 10.1016/j.jep.2019.112302]

130 **Yu Z**, Yue B, Ding L, Luo X, Ren Y, Zhang J, Mani S, Wang Z, Dou W. Activation of PXR by Alpinetin Contributes to Abrogate Chemically Induced Inflammatory Bowel Disease. *Front Pharmacol* 2020; **11**: 474 [PMID: 32372959 DOI: 10.3389/fphar.2020.00474]

131 **Mroz MS**, Lajczak NK, Goggins BJ, Keely S, Keely SJ. The bile acids, deoxycholic acid and ursodeoxycholic acid, regulate colonic epithelial wound healing. *Am J Physiol Gastrointest Liver Physiol* 2018; **314**: G378-G387 [PMID: 29351391 DOI: 10.1152/ajpgi.00435.2016]

132 **Pi Y**, Wu Y, Zhang X, Lu D, Han D, Zhao J, Zheng X, Zhang S, Ye H, Lian S, Bai Y, Wang Z, Tao S, Ni D, Zou X, Jia W, Zhang G, Li D, Wang J. Gut microbiota-derived ursodeoxycholic acid alleviates low birth weight-induced colonic inflammation by enhancing M2 macrophage polarization. *Microbiome* 2023; **11**: 19 [PMID: 36721210 DOI: 10.1186/s40168-022-01458-x]

133 **Streeter PR**, Berg EL, Rouse BT, Bargatze RF, Butcher EC. A tissue-specific endothelial cell molecule involved in lymphocyte homing. *Nature* 1988; **331**: 41-46 [PMID: 3340147 DOI: 10.1038/331041a0]

134 **Gao RY**, Shearn CT, Orlicky DJ, Battista KD, Alexeev EE, Cartwright IM, Lanis JM, Kostelecky RE, Ju C, Colgan SP, Fennimore BP. Bile acids modulate colonic MAdCAM-1 expression in a murine model of combined cholestasis and colitis. *Mucosal Immunol* 2021; **14**: 479-490 [PMID: 33004979 DOI: 10.1038/s41385-020-00347-6]

135 **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]

136 **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]

137 **Barberio B**, Segal JP, Quraishi MN, Black CJ, Savarino EV, Ford AC. Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-analysis. *J Crohns Colitis* 2021; **15**: 1184-1196 [PMID: 33433562 DOI: 10.1093/ecco-jcc/jjab010]

138 **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]

139 **Van den Bossche L**, Borsboom D, Devriese S, Van Welden S, Holvoet T, Devisscher L, Hindryckx P, De Vos M, Laukens D. Tauroursodeoxycholic acid protects bile acid homeostasis under inflammatory conditions and dampens Crohn's disease-like ileitis. *Lab Invest* 2017; **97**: 519-529 [PMID: 28165466 DOI: 10.1038/labinvest.2017.6]

140 **Yang Y**, He J, Suo Y, Zheng Z, Wang J, Lv L, Huo C, Wang Z, Li J, Sun W, Zhang Y. Tauroursodeoxycholate improves 2,4,6-trinitrobenzenesulfonic acid-induced experimental acute ulcerative colitis in mice. *Int Immunopharmacol* 2016; **36**: 271-276 [PMID: 27179450 DOI: 10.1016/j.intimp.2016.04.037]

141 **Van den Bossche L**, Hindryckx P, Devisscher L, Devriese S, Van Welden S, Holvoet T, Vilchez-Vargas R, Vital M, Pieper DH, Vanden Bussche J, Vanhaecke L, Van de Wiele T, De Vos M, Laukens D. Ursodeoxycholic Acid and Its Taurine- or Glycine-Conjugated Species Reduce Colitogenic Dysbiosis and Equally Suppress Experimental Colitis in Mice. *Appl Environ Microbiol* 2017; **83** [PMID: 28115375 DOI: 10.1128/AEM.02766-16]

142 **Yang Y**, He J, Suo Y, Lv L, Wang J, Huo C, Zheng Z, Wang Z, Li J, Sun W, Zhang Y. Anti-inflammatory effect of taurocholate on TNBS-induced ulcerative colitis in mice. *Biomed Pharmacother* 2016; **81**: 424-430 [PMID: 27261622 DOI: 10.1016/j.biopha.2016.04.037]

143 **Watanabe S**, Chen Z, Fujita K, Nishikawa M, Ueda H, Iguchi Y, Une M, Nishida T, Imura J. Hyodeoxycholic Acid (HDCA) Prevents Development of Dextran Sulfate Sodium (DSS)-Induced Colitis in Mice: Possible Role of Synergism between DSS and HDCA in Increasing Fecal Bile Acid Levels. *Biol Pharm Bull* 2022; **45**: 1503-1509 [PMID: 36184509 DOI: 10.1248/bpb.b22-00373]

144   **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]

145   **Li L**, Liu T, Gu Y, Wang X, Xie R, Sun Y, Wang B, Cao H. Regulation of gut microbiota-bile acids axis by probiotics in inflammatory bowel disease. *Front Immunol* 2022; **13**: 974305 [PMID: 36211363 DOI: 10.3389/fimmu.2022.974305]

146   **Jakubczyk D**, Leszczyńska K, Górska S. The Effectiveness of Probiotics in the Treatment of Inflammatory Bowel Disease (IBD)-A Critical Review. *Nutrients* 2020; **12** [PMID: 32630805 DOI: 10.3390/nu12071973]

147   **Binda S**, Hill C, Johansen E, Obis D, Pot B, Sanders ME, Tremblay A, Ouwehand AC. Criteria to Qualify Microorganisms as "Probiotic" in Foods and Dietary Supplements. *Front Microbiol* 2020; **11**: 1662 [PMID: 32793153 DOI: 10.3389/fmicb.2020.01662]

148   **Wong WY**, Chan BD, Sham TT, Lee MM, Chan CO, Chau CT, Mok DK, Kwan YW, Tai WC. Lactobacillus casei Strain Shirota Ameliorates Dextran Sulfate Sodium-Induced Colitis in Mice by Increasing Taurine-Conjugated Bile Acids and Inhibiting NF-κB Signaling *via* Stabilization of IκBα. *Front Nutr* 2022; **9**: 816836 [PMID: 35529468 DOI: 10.3389/fnut.2022.816836]

149   **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]

150   **Lu R**, Shang M, Zhang YG, Jiao Y, Xia Y, Garrett S, Bakke D, Bäuerl C, Martinez GP, Kim CH, Kang SM, Sun J. Lactic Acid Bacteria Isolated From Korean Kimchi Activate the Vitamin D Receptor-autophagy Signaling Pathways. *Inflamm Bowel Dis* 2020; **26**: 1199-1211 [PMID: 32170938 DOI: 10.1093/ibd/izaa049]

151   **Zhou C**, Wang Y, Li C, Xie Z, Dai L. Amelioration of Colitis by a Gut Bacterial Consortium Producing Anti-Inflammatory Secondary Bile Acids. *Microbiol Spectr* 2023; **11**: e0333022 [PMID: 36943054 DOI: 10.1128/spectrum.03330-22]

152   **Xiao F**, Dong F, Li X, Li Y, Yu G, Liu Z, Wang Y, Zhang T. Bifidobacterium longum CECT 7894 Improves the Efficacy of Infliximab for DSS-Induced Colitis *via* Regulating the Gut Microbiota and Bile Acid Metabolism. *Front Pharmacol* 2022; **13**: 902337 [PMID: 35979230 DOI: 10.3389/fphar.2022.902337]

153   **Costello SP**, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, Katsikeros R, Makanyanga J, Campaniello MA, Mavrangelos C, Rosewarne CP, Bickley C, Peters C, Schoeman MN, Conlon MA, Roberts-Thomson IC, Andrews JM. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA* 2019; **321**: 156-164 [PMID: 30644982 DOI: 10.1001/jama.2018.20046]

154   **Kelly CR**, Yen EF, Grinspan AM, Kahn SA, Atreja A, Lewis JD, Moore TA, Rubin DT, Kim AM, Serra S, Nersesova Y, Fredell L, Hunsicker D, McDonald D, Knight R, Allegretti JR, Pekow J, Absah I, Hsu R, Vincent J, Khanna S, Tangen L, Crawford CV, Mattar MC, Chen LA, Fischer M, Arsenescu RI, Feuerstadt P, Goldstein J, Kerman D, Ehrlich AC, Wu GD, Laine L. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. *Gastroenterology* 2021; **160**: 183-192.e3 [PMID: 33011173 DOI: 10.1053/j.gastro.2020.09.038]

155   **Lima SF**, Gogokhia L, Viladomiu M, Chou L, Putzel G, Jin WB, Pires S, Guo CJ, Gerardin Y, Crawford CV, Jacob V, Scherl E, Brown SE, Hambor J, Longman RS. Transferable Immunoglobulin A-Coated Odoribacter splanchnicus in Responders to Fecal Microbiota Transplantation for Ulcerative Colitis Limits Colonic Inflammation. *Gastroenterology* 2022; **162**: 166-178 [PMID: 34606847 DOI: 10.1053/j.gastro.2021.09.061]

156   **Huang C**, Mei Q, Lou L, Huang Z, Fu Y, Fan J, Wang J, Yin N, Zheng Y, Lu Y, Zeng Y. Ulcerative Colitis in Response to Fecal Microbiota Transplantation *via* Modulation of Gut Microbiota and Th17/Treg Cell Balance. *Cells* 2022; **11** [PMID: 35681546 DOI: 10.3390/cells11111851]

157   **Huo X**, Li D, Wu F, Li S, Qiao Y, Wang C, Wang Y, Zhou C, Sun L, Luan Z, Yan Q, Wang J, Zhang Y, Zhao T, An Y, Zhang B, Tian X, Yu Z, Ma X. Cultivated human intestinal fungus Candida metapsilosis M2006B attenuates colitis by secreting acyclic sesquiterpenoids as FXR agonists. *Gut* 2022; **71**: 2205-2217 [PMID: 35173042 DOI: 10.1136/gutjnl-2021-325413]

158   **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]

159   **Staels B**, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; **67**: 1383-1392 [PMID: 17600387 DOI: 10.2165/00003495-200767100-00001]

160   **Islam MS**, Sharif A, Kwan N, Tam KC. Bile Acid Sequestrants for Hypercholesterolemia Treatment Using Sustainable Biopolymers: Recent Advances and Future Perspectives. *Mol Pharm* 2022; **19**: 1248-1272 [PMID: 35333534 DOI: 10.1021/acs.molpharmaceut.2c00007]

161   **Vítek L**. Bile acid malabsorption in inflammatory bowel disease. *Inflamm Bowel Dis* 2015; **21**: 476-483 [PMID: 25248001 DOI: 10.1097/MIB.0000000000000193]

162   **Mena Bares LMª**, Benítez Cantero JM, Iglesias Flores E, Gros Alcalde B, Moreno Ortega E, Maza Muret FR, Carmona Asenjo E, García Sánchez MªV, Vallejo Casas JA. Bile acid malabsorption in patients with chronic diarrhea and Crohn's disease. *Rev Esp Enferm Dig* 2019; **111**: 40-45 [PMID: 30284903 DOI: 10.17235/reed.2018.5376/2017]

163   **Kumar A**, Galbraith N, Al-Hassi HO, Jain M, Phipps O, Butterworth J, Steed H, McLaughlin J, Brookes MJ. The impact of treatment with bile acid sequestrants on quality of life in patients with bile acid diarrhoea. *BMC Gastroenterol* 2022; **22**: 325 [PMID: 35778677 DOI: 10.1186/s12876-022-02404-9]

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