

Pathologic and therapeutic insights into cholestatic liver disease-associated depressive disorder

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ABSTRACT

The prevalence of depressive-like behavior is significantly higher in patients with cholestatic liver disease, leading to a notable reduction in the quality of life. This situation underscores the urgent need to investigate the mechanisms underlying the association between cholestasis and clinical depression. This review provides a comprehensive examination of how neuroendocrine disorders resulting from cholestasis influence the onset of depression through both direct and indirect mechanisms. First, how the accumulation of bile acids in the central nervous system (CNS) during cholestasis leads to damage to the blood-brain barrier, neuroinflammation, and neurodegeneration is discussed, highlighting the key roles of bile acid receptors, such as FXR and TGR5, in this process. Additionally, the gut-brain axis has been shown to be involved in the development of brain diseases in a variety of ways. Therefore, the indirect effects of bile acids *via* the gut-brain axis, which affect the composition of the gut microbiota, the integrity of the gut barrier, and the secretion of gut hormones are summarized, thereby regulating the development of depression. However, whether bile acids can directly enter the CNS and which targets are targetable within the gut-brain axis remain pivotal questions. Addressing these issues will open new avenues for developing more effective therapeutic strategies aimed at alleviating depressive symptoms experienced by patients with cholestasis.

Keywords: cholestatic liver disease, bile acids, depression, gut microbes, gut-brain axis

1. INTRODUCTION

Cholestasis, defined as an impairment in bile formation or flow, can be categorized into intra- and extra-hepatic forms based on the site of obstruction [1]. Intrahepatic cholestasis results from hepatocellular dysfunction or obstruction of canaliculi, ductules (diameter <15 µm [also known as Hering canals]), or interlobular bile ducts (diameter, 15–100 µm) [2–4]. Intrahepatic cholestasis commonly lacks major bile duct obstruction on imaging and can be triggered by various factors, including alcohol, drugs, viruses, and immune-mediated processes. In contrast, extrahepatic cholestasis involves obstruction of larger bile ducts, including septal ducts (diameter >100 µm), area ducts (diameter, 300–400 µm), segmental ducts (diameter, 400–800 µm), left and right hepatic ducts, and the common bile duct up to the ampulla of

Vater [4, 5]. Common causes of extrahepatic cholestasis include bile duct stones, pancreatic, biliary, and ampullary cancers, and benign bile duct strictures [6]. In brief, cholestatic liver diseases encompass a spectrum of conditions characterized by impaired bile flow, resulting in dramatically elevated serum bile acid levels. Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD) [7], intrahepatic cholestasis of pregnancy (ICP), progressive familial intrahepatic cholestasis (PFIC), drug-induced cholestasis, benign recurrent intrahepatic cholestasis (BRIC) are common forms of cholestasis in clinics [8, 9].

The biochemical imbalance resulting from cholestasis is prominently manifested as persistent pruritus, significantly impacting quality of life and presenting a challenge in drug development. In the PBC OCA International

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Study of Efficacy (POISE) trial involving obeticholic acid (OCA), 46% of patients developed pruritus with 10% discontinuing treatment due to intolerable symptoms [10, 11]. The ubiquity of this symptom across various cholestatic conditions underscores its importance as a therapeutic target and a key indicator of disease progression. Another hallmark of cholestatic disorders is profound fatigue, which is experienced by most patients. This debilitating symptom likely stems from neurologic alterations induced by the accumulation of toxic bile components [12, 13]. The precise mechanisms underlying this fatigue remain under investigation. However, emerging evidence suggests a complex interplay between bile acid signaling and central nervous system function.

Cholestatic liver diseases are increasingly associated with neuropsychiatric manifestations, especially depression. The prevalence of clinical depression in cholestatic patients significantly exceeds that of the general population. For example, several epidemiologic studies have reported that depression is a common and important problem in PBC patients, with studies finding that the prevalence of depression in PBC patients ranging from 44%–68% [14–17]. These findings unveil the vulnerability of patients with cholestatic liver disease to mental and psychological disorders, emphasizing the imperative for a heightened focus on their mental and psychological well-being. The increased incidence of depression in patients with cholestatic liver disease may not only exacerbate the physical symptoms but also affect the efficacy and prognosis of treatment. For example, in patients with chronic hepatitis C infection undergoing antiviral therapy, depression often leads to early discontinuation of treatment and poorer treatment outcomes [18]. Therefore, this issue urgently needs the attention of clinicians and researchers.

In the present review clinical and mechanistic research findings on the relationship between cholestatic liver disease and depression in recent years are summarized to provide new ideas for improving the mental health treatment of patients with cholestatic liver disease.

2. BILE ACID-MEDIATED NEUROENDOCRINE DISORDERS IN THE PATHOGENESIS OF DEPRESSION DURING CHOLESTASIS

The pathologic effects of cholestasis are not limited to the liver, but can be extended to extrahepatic tissues and organs, including the central nervous system (CNS). Bile acids (BAs), an essential component of bile, are also critical signaling molecules. Changes in BA levels in pathologic cholestasis may be an underappreciated cause of disorders, including nerve and internal system secretion, and therefore one of the main reasons for involvement in the pathogenesis of depression.

2.1 Accumulation of BAs in the CNS environment during cholestasis

2.1.1 Changes in BA level and composition are related to CNS disorders.

BAs are steroid acids primarily found

in mammalian bile that are synthesized from cholesterol in the liver. BAs have a crucial role in lipid digestion and absorption within the small intestine by facilitating emulsification of dietary fats. In addition to digestive functions, BAs act as signaling molecules that engage with nuclear receptors, such as farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), thereby influencing various neural and metabolic pathways. BAs are primarily synthesized in the liver, despite the primarily digestive functions. The two primary BAs synthesized in the liver are cholic acid (CA) and chenodeoxycholic acid (CDCA), which are then secreted into the bile as taurine- and glycine-conjugated BAs. Primary BAs can be further modified by intestinal bacteria to produce secondary BAs, such as deoxycholic acid (DCA) and lithocholic acid (LCA). Interestingly, BAs have been shown to exist in the CNS. Mano et al. [19] used liquid chromatography and mass spectrometry (LC-MS) to identify three unconjugated BAs (CA, CDCA, and DCA) in the rat brain. CDCA is the most abundant BA in the rat brain (30 times the concentration in serum). Moreover, no conjugated BAs were detected. Reinicke et al. [20] reported the presence of five free and five conjugated BAs in cerebrospinal fluid (CSF) using LC-ESI (+)-MS/MS. Zheng et al. [21] used LC-MS to detect and quantify 20 BAs in the rat brain, including 9 unconjugated BAs, 4 glycine-conjugated BAs, and 7 taurine-conjugated BAs. The concentrations of unbound and taurine-bound cholic acid are higher in the early developmental stages of the rat brain at weeks 7 and 12 (0.82–3 and 0.89–5 μM , respectively). The cholic acid levels stabilize as rats mature to adulthood but decrease slightly in older age (week 111) with the total cholic acid concentration ranging between 0.85–1.65 μM . These findings suggest that BAs may have an uncharacterized role in brain development and aging. The levels and composition of BAs in the blood, CSF, and brain are also altered in various neurologic diseases and brain disorders, including Alzheimer's disease (AD), Parkinson's disease, and hepatic encephalopathy (HE). There is a significant reduction in serum concentrations of primary cholic acids, such as cholic acid, in individuals with AD, while concentrations of secondary cholic acids, like deoxycholic acid, and the binding forms are increased. These alterations have a strong correlation with cognitive decline [22–24]. Furthermore, levels of highly toxic hydrophobic BAs, including DCA and LCA, are significantly elevated in patients with AD. These BAs may accelerate the progression of AD by disrupting the blood-brain barrier (BBB) and promoting the formation of beta-amyloid plaques [25]. In patients with PD, especially patients presenting with mild cognitive impairment, there is a significant reduction in levels of specific cholic acids, such as ursodeoxycholic acid (UDCA), CA, and CDCA [26–28]. Conjugated cholic acids, such as glycocholic acid (GCA), glycodeoxycholic acid (GDCA), taurine taurocholic acid (TCA), and taurochenodeoxycholic acid (TCDCA), are more prominent in patients with cirrhosis and HE; the proportion and absolute concentration of conjugated cholic acids are significantly increased. In

addition, the relative proportion of neuroprotective bile acids, including UDCA and tauroursodeoxycholic acid (TUDCA), are decreased in patients with HE [29, 30]. The alterations in cholic acid levels reported in various neurologic disorders are disease-specific and these changes may be intricately linked to the underlying mechanisms of disease progression yet to be identified.

BA levels in clinically depressed patients, especially in stool samples, show significant changes with reductions in cholic acid (CA, DCA, and CDCA) and recovery of DCA following fluoxetine treatment [31]. DCA was significantly decreased in depressed mice and significantly increased after fluoxetine treatment, suggesting that DCA may be related to depression [32]. The findings of another study indicated that UDCA and TUDCA may have a potential therapeutic effect on depression, as manifested by reducing neuroinflammation and oxidative stress after corresponding treatment [33]. By combining these findings, it can be inferred that the accumulation of BAs, especially secondary BAs like DCA, may be implicated in neurologic dysfunction associated with depression. However, studies that systematically characterize BA profiles in the CNS of patients or depressed mouse models are lacking. This gap in research makes determining if the significantly altered BA levels in depression exert direct effects within the brain or contribute to the progression of depression through indirect pathways outside the CNS challenging.

Although several studies have elucidated the association between BAs and neurologic disorders, a comprehensive understanding of the origins of these BAs in the brain remains elusive. Studies have suggested an independent BA synthesis mechanism in the brain, especially in astrocytes and neurons, involving cytochrome enzymes, such as cytochrome P450 8B1 (CYP8B1), cytochrome P450 27A1 (CYP27A1), and cytochrome P450 7B1 (CYP7B1) [34]. Ogundare et al. [35] confirmed the presence of intermediates in BA biosynthesis in human CSF. A critical step for BAs synthesis is the oxidation of cholesterol to 24(S)-hydroxycholesterol and 25(S)-hydroxycholesterols by cholesterol 24-hydroxylase (cytochrome P46A1), which is primarily expressed in the brain [36, 37]. Lund et al. [38] reported 24(S)-hydroxycholesterol synthesis deficiency in mice with brain-specific knockout of cytochrome P46A1, which is associated with neurodegenerative disorders, including reduced learning abilities [38, 39]. Cognitive impairment in humans is also associated with cytochrome P46A1 polymorphisms [40], underscoring the involvement of dysregulated brain cholesterol and BA metabolism in cognitive impairment during aging [41–43]. Another study suggested that the accumulation of BAs in the brain is closely associated with BA levels in the circulation. LC-MS was used to measure 3 unconjugated BAs (CA, CDCA, and DCA) in rat brain tissue. The average concentrations of these BAs in normal rat brains were 58.7 ng/g for CA, 14.2 ng/g for CDCA, and 13.2 ng/g for DCA. It was hypothesized that these BAs primarily originate from peripheral sources. A comparison of the levels of BAs in the brain and serum

revealed strong correlations with consistently lower levels observed in the brain. BAs with higher lipophilicity exhibited higher ratios of brain than serum concentrations. Additionally, the administration of deuterium-labeled CA and CDCA to rats resulted in detection in the brain as well. These findings suggest that most of the BAs in the brain are derived from peripheral sources through passive diffusion across the BBB.

2.1.2 Accumulated BAs contribute to BBB impairment during cholestasis. The BBB, which is composed of endothelial cells, a basement membrane, and astrocytes, functions as a vital protective mechanism by effectively segregating brain tissue from circulating substances in the vasculature and safeguarding the brain against the penetration of large molecules or potentially harmful metabolites, such as BAs. In some cases BAs can enter the brain by diffusion or active transport across the BBB via BA transporters in the somatic circulation, which are specifically expressed on the BBB and highly selective for BA transport [44]. Sodium-taurocholate co-transporting polypeptide (NTCP) and organic anion-transporting polypeptides (OATPs) have been identified in the CNS. NTCP is expressed at low levels in the choroid plexus, as evidenced by bDNA probe studies, although the functional role and precise subcellular localization (e.g., apical or basolateral orientation) of NTCP have not been established. OATPs have been detected in brain capillary endothelial cells and potentially participate in BA transport across the BBB, although the specific transport directions (e.g., brain-to-blood or blood-to-brain) warrant further investigation. The bile salt export pump (BSEP), which is expressed on the canalicular membrane of hepatocytes, has not been conclusively shown to have functional expression in the CNS and the presence of a BSEP in the BBB is speculative. Additionally, the apical sodium-dependent BA transporter (ASBT) is primarily expressed in the hypothalamus, suggesting potential region-specific functions in BA regulation within the brain. However, further studies are needed to clarify the precise functional roles, orientations, and interactions of these transporters in CNS BA homeostasis [45–48]. Notably, BA transport also relies on the conjugating status. Non-conjugated BAs can passively diffuse across the BBB due to the hydrophobic nature of BAs. Conjugated BAs, including glycine and taurine-bound BAs, necessitate active transportation through the above-mentioned transporters [45]. The existence of these transport mechanisms and expression sites reveals the potential impact of BAs in the CNS.

The balance of BA transport, however, will be disrupted in pathologic cholestasis. Quinn et al. [49] utilized a bile duct ligation (BDL) model to determine the impact of cholestasis on BBB permeability. The study findings suggested that the accumulation of circulating BAs compromised BBB integrity. Specifically, high concentrations (100 μ M) of DCA and CDCA activate Rac1, leading to an increase in tyrosine phosphorylation of the occludin protein. This phosphorylation is directly associated with

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disruption of tight junctions and enhanced BBB permeability. Additionally, DCA and CDCA (100 μ M) treatment resulted in relocation of occludin, ZO-1 (zonula occludens-1), and ZO-2 from the cell membrane to the cytoplasm, thereby compromising rat brain microvascular endothelial cell (RBMEC) monolayer integrity. Quinn et al. [49] further demonstrated that administration of DCA or CDCA (3 μ g/rat/day) through tail vein injection for 5 consecutive days (resulting in a serum BAs concentration of approximately 47 μ M) directly increases BBB permeability in healthy rats.

Disruption of the BBB, as observed in cholestatic conditions, may significantly contribute to the development of depression through various mechanisms. This compromise in BBB integrity allows for enhanced infiltration of pro-inflammatory molecules and immune cells into the brain, potentially triggering or exacerbating neuroinflammation and leading to neuronal damage and dysfunction that can impact mood-regulating neural circuits. Altered BBB function can also disrupt the intricate balance of neurotransmitters in the brain. Given these observations, we propose that BAs may contribute to depression not only through direct accumulation in the brain but also by mediating BBB damage-related neuronal injury and neuroinflammation. However, we acknowledge that the role of BAs in BBB integrity and the contribution to depression might not always be directly reflected by significant changes in CSF BA levels, as suggested by Reinicke et al. [20]. The effects of BAs may involve more complex mechanisms, including indirect modulation of BBB function, neuroinflammation, and neuronal injury. Targeting the repair and protection of the BBB could represent a novel therapeutic strategy for depression, especially in patients with cholestatic conditions or BA dysregulation. Further research should focus on elucidating the precise mechanisms and targets underlying the effects of BAs on BBB integrity and the contribution to depression development and progression.

2.2 Major BA receptors in the CNS have bidirectional roles in the development of depression

The majority of BAs receptors, such as TGR5, the FXR, liver X receptor (LXR), pregnane X receptor (PXR), vitamin D receptor (VDR), and sphingosine-1-phosphate receptor 2 (S1PR2), are widely distributed across various brain regions, including the cerebral cortex, hippocampus, and hypothalamus [50-53]. Therefore, the direct regulation of biological processes in the CNS by BAs may be attributed to the presence of BAs receptors in the brain.

2.2.1 BA-mediated FXR activation contributes to depression. FXR is a nuclear BA receptor that has a pivotal role in regulating BA, lipid, and glucose homeostasis, thereby exerting a significant influence on the progression of diverse diseases [54, 55]. FXR expression is primarily localized in tissues closely associated with

metabolic functions [56]. Further research has confirmed FXR expression in brain tissues, including the hippocampus, cerebellum, and prefrontal cortex [50, 57]. The predominant localization of FXR in cultured neurons has been demonstrated within the nucleus, whereas in neurons *in vivo* FXR is predominantly within the cytoplasm. Within nuclear compartments neuronal FXR exhibits a punctate distribution pattern. Activation of FXR results in increased mRNA and protein expression of small heterodimer partners (SHPs) in cultured neurons and brain tissues [58]. Chen et al. [57] utilized human neuroblastoma SH-SY5Y cells and mouse hippocampal nerve cells as a model system. Co-immunoprecipitation (Co-IP) analysis demonstrated that pharmacologic activation with 2 μ M of 6ECDCA facilitated the interaction between FXR and cAMP response element-binding protein (CREB), leading to suppression of CREB and down-regulation of brain-derived neurotrophic factor (BDNF) expression. A more in-depth investigation revealed that FXR disrupts CREB-BDNF signaling in the hippocampal CA1 region, which contributes to the development of depression-like behaviors. In this case, FXR directly interacts with CREB to form an inhibitory complex, drives the cytoplasmic translocation of CRTC2, a critical co-activator of CREB, and reduces the transcriptional activities of CREB and subsequent BDNF production [59]. These results indicate that the accumulation of BAs in the brain may serve as a potential risk factor, potentially inducing or exacerbating depressive-like manifestations by inhibiting the neuroprotective effects of BDNF. Furthermore, Chen et al. [50] showed that FXR overexpression in the normal rat hippocampus induces significant depression-like behavior by suppressing the expression of BDNF through an undefined CREB-independent mechanism. Knocking down FXR in the hippocampus had an antidepressant-like effect and restored CUMS-induced deficiency in BDNF expression. Previous studies have also demonstrated a close association between depression and inflammatory response neurotransmitter imbalances and alterations in synaptic plasticity within the brain [60-64]. Upregulation of inflammatory factors, reduction of synaptic connections, and disruption of neurotransmitter systems resulting from FXR activation may have a significant role in the pathogenesis of depression. Consequently, pharmacologic targeting FXR potentially emerges as a future antidepressant therapy in cholestatic patients.

2.2.2 BA-activated TGR5 and glucocorticoid receptor protect neuroinflammation. TGR5 is a membrane-bound receptor that exhibits widespread distribution in various human tissues, including the CNS and several innate immune cells. Multiple studies have demonstrated that TGR5 is expressed in neural cells (primarily astrocytes and neurons) and can be activated by neurosteroids [65-67]. By activating TGR5, neurosteroids may regulate the excitability of neurons, the release of neurotransmitters, and neural plasticity. Similarly, some BAs, as natural

ligands of TGR5, may also regulate neuron function, thereby affecting mood and cognitive processes. This mechanism may have a role in the pathophysiology of depression because changes in neural plasticity and neurotransmitter balance are closely related to depression.

From the perspective of immune cells, the activation of TGR5 has an important role in regulating inflammatory responses and immune function. Specifically, Li et al. [68] found that chronic stress reduces TGR5 and increases GABAergic neuron excitability in the lateral hypothalamic area (LHA), which influence depressive-like behaviors. Modulating TGR5 levels or GABAergic excitability altered these behaviors. Pols et al. [69] showed that TGR5 activation inhibits the activity of NF- κ B through the cAMP signaling pathway, thereby reducing the production of pro-inflammatory cytokines in macrophages. Shi et al. [70] reported that TGR5 regulates NLRP3 inflammasome activity, which controls the inflammatory response and M1 polarization of macrophages. Furthermore, Yoneno et al. [71] showed that TGR5 activation not only reduces the production of pro-inflammatory cytokines but also stabilizes the macrophage M2 (non-inflammatory) phenotype. TGR5 expression in immune-related cells in the brain is also significantly involved in regulating neurologic disorders [67, 72, 73]. Yanguas-Casás et al. [74] reported that TUDCA binds to TGR5, leading to increased intracellular cAMP levels in microglia and inducing anti-inflammatory markers while reducing pro-inflammatory markers. UDCA, as well as the semi-synthetic TGR5 agonist, INT777, have been shown to have similar protective effects [75]. As expected, TUDCA has preventive effects against depressive- and anhedonia-like behaviors, along with anti-inflammatory effects on microglial activation and mitigation of oxidative stress, nitrative stress, and endoplasmic reticulum stress in the hippocampus and prefrontal cortex [76]. In addition to microglia activation, formation of neurotoxic reactive astrocytes (A1 phenotype) is another fundamental pathologic response of the CNS to various conditions, including LPS-induced neuroinflammation, acute CNS injury, and many neurodegenerative diseases [77]. Bhargava et al. [78] showed that TUDCA acts on astrocytes through TGR5 and blocks polarization to the A1 phenotype, indicating that TGR5 has an influence on inflammation-related CNS disorders. These findings suggest that activation of the TGR5 signaling pathway holds great promise as a novel therapeutic strategy for addressing neurologic disorders, including depression. However, the exact role of TGR5 in depression requires further elucidation, especially with respect to coordinating the interactions between the nervous and immune systems to influence the development and progression of depression.

In addition to TGR5, BA acts through the glucocorticoid receptor (GR). GR inhibits neuroinflammation and reduces the production and secretion of pro-inflammatory cytokines (interleukin-1 β [IL-1 β] and tumor necrosis factor- α [TNF- α]) and decreases the

pathology associated with multiple sclerosis, PD, and other neuroinflammatory diseases [79, 80]. Mcmillin et al. used a GR competitive activity assay in a mouse hypothalamic cell line and showed that both TCA and GCDCA led to increased GR activity, indicating that BAs directly induce GR signal transduction [81], and therefore potentially exert protective effects.

To summarize, the biological effects mediated by different BA receptors vary. Activation of FXR may promote neuroinflammation, whereas activation of TGR5 and GR exerts anti-inflammatory effects. Different types of BAs also exhibit varying abilities to activate or inhibit these receptors, as comprehensively summarized in a previous review [82]. TUDCA and UDCA act as agonists for TGR5, while acting as antagonists for FXR. Similarly, CDCA is the most potent FXR agonist, yet a weak activator of TGR5. These findings imply that the favorable effects of these BAs on the brain may be attributed to the simultaneous impact on TGR5 and FXR, thereby emphasizing the significance of comprehending the intricate interactions among diverse BA receptors and necessitating targeted therapies that selectively activate or inhibit specific receptors for treating neurologic disorders. Further research should concentrate on deciphering the BA exposure profile in the brain across various cholestatic disorders and specifically examining the composition and concentrations of BAs that directly interact with the brain environment. This approach will allow us to determine how these altered BAs engage with different BA receptors to modulate brain phenotypes. Such investigations will establish a theoretical foundation for understanding the development of cholestatic-related depression and identifying potential therapeutic targets (Figure 1).

3. BAS INDIRECTLY REGULATE DEPRESSION THROUGH THE GUT-BRAIN AXIS

In addition to directly entering the brain to exert effects, BAs indirectly affect the CNS by regulating the intestinal barrier, flora, and endocrine function, which are thought to be involved in the pathogenesis of depression. The intricate bidirectional interaction between the gut and the brain, commonly referred to as the “gut-brain axis,” is manifested in a captivating manner. The gut-brain axis includes the CNS, the enteric nervous system, the intestinal epithelial barrier, and the gut microbiota. Dysfunction of the gut-brain axis is closely related to psychiatric disorders, such as depression.

3.1 BAs and intestinal barrier function in gut-brain axis regulation

The intestinal mucosal barrier serves as the primary defense mechanism separating the intestine from the external environment and has a pivotal role in minimizing pathogen invasion and toxin absorption, which are significant triggers of BBB impairment. The intestinal mucosal barrier is a complex structure comprised of a

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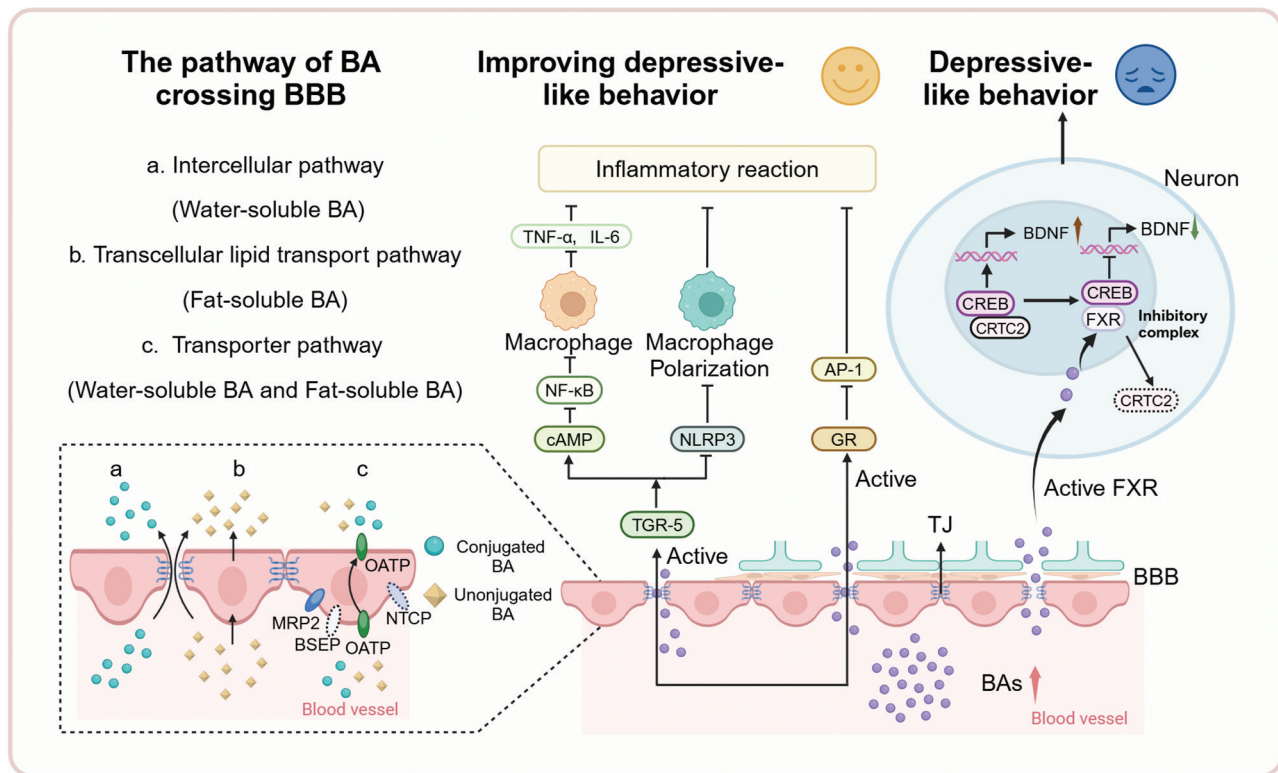


Figure 1 | Mechanism of BA transport across the BBB and role in modulating depressive-like behavior.

In the pathologic state of cholestasis, the level of peripheral circulating bile acids (BAs) is abnormally increased, leading to damage of the blood-brain barrier (BBB) structure, such as tight junctions (TJs), which increases permeability. This allows BAs to cross the BBB and activate receptors, such as FXR. In neurons, activated FXR competitively interacts with CREB to form the FXR-CREB complex. This inhibitory complex disrupts the CREB-BDNF signaling pathway, thereby reducing BDNF expression and contributing to depression-like behavior. Additionally, BAs activate inflammatory pathways involving macrophage polarization, NF- κ B, and cAMP signaling, further modulating depressive-like behavior.

surface mucus layer, epithelial cell layer, and mucosal basement membrane, which collectively function as mechanical, biochemical, and immune barriers [83].

The mechanical barrier is comprised of intact epithelial cells, a tightly packed lipid bilayer at the brush-like edge of the epithelial cells, and cell junctions primarily composed of tight junctions located at the lateral edge of cells. These tight junctions mainly consist of the ribbon closure protein (ZO-1), occludin, cadherin, claudin, and β -catenin. Under normal circumstances, these tight junctions effectively seal off any gaps between adjacent intestinal epithelial cells to prevent luminal bacteria, antigens, or other substances from entering the intestinal mucosal proper layer, which could activate immune cells in that layer and trigger abnormal mucosal immune responses [84].

The biochemical barrier in the gastrointestinal tract consists of digestive juices, enzymes, lysozymes, mucopolysaccharides, glycoproteins, and glycolipids. The intestinal mucus layer is primarily composed of mucin (MUC) secreted by goblet cells. MUC2 and MUC3 are the main types found in the intestine. MUC has a unique hydrocarbon structure that acts as an ecologic checkpoint for bacterial adhesion and binding. MUC competitively

binds to bacteria attempting to bind to the intestinal epithelial cell checkpoint, causing the bacteria to remain in the mucus layer and cleared during intestinal peristalsis. Studies suggest that O-glycan glycosylation of intestinal mucin is necessary for synthesizing mature MUC2 with barrier function [85, 86]. There is also a complex microecosystem in the intestines, consisting of mutually dependent and interacting resident microbiota. The composition of the microecosystem is primarily comprised of anaerobic, facultative anaerobic, and aerobic bacteria. Among these bacteria, strictly anaerobic bacteria dominate with approximately 99% representation. These strictly anaerobic bacteria form a biofilm on the intestinal mucosa that exhibits antibacterial properties and modulates immune responses within the intestines. Additionally, the strictly anaerobic bacteria inhibit colonization by pathogenic bacteria while secreting short-chain fatty acids (SCFAs) and lactic acid to lower the pH of the intestines. This acidification process helps create an environment where invasive microbial populations struggle to grow due to competition for nutrients [87].

The intestinal immune barrier is mainly composed of gut-associated lymphoid tissue (GALT) and secreted immunoglobulin (SIgA). GALT helps defend against

pathogens while maintaining immune tolerance to food antigens and symbiotic bacteria, thus maintaining the integrity of the intestinal barrier [88]. SIgA is the main immunoglobulin on the surface of the intestinal mucosa. SIgA has a role in protecting the mucosa of the digestive tract and preventing pathogenic bacteria from attaching and multiplying on the intestinal mucosa [89].

3.1.1 Intestinal barrier dysfunction contributes to BBB impairment. In the healthy state, the intestinal barrier facilitates the selective osmosis mechanism to allow passage of nutrients and water while preventing invasion by pathogens, toxins, and other harmful substances [90]. However, when the integrity of the intestinal barrier is compromised, there may be translocation of intestinal flora and its metabolites across the epithelium into the bloodstream, a phenomenon known as “microbiota translocation.” Microbiota translocation can result in an influx of diverse pathogens, endotoxins, and inflammatory factors, such as lipopolysaccharides (LPSs) within the body, then trigger a robust immune response that manifests as systemic inflammatory response syndrome (SIRS) [91-93].

It is noteworthy that disruption of the gut barrier not only impacts local gut health but also exhibits a close association with disturbances in the gut-brain axis by compromising the integrity of the BBB through various mechanisms. First, microbiota translocation and its byproducts, such as LPS, enter the brain *via* bloodstream circulation, thereby inducing an increase in BBB permeability [94]. Additionally, systemic inflammation may indirectly affect BBB function through diffusion of inflammatory cytokines, which not only directly impair tight junction structures within the BBB but also further amplify neuroinflammatory responses by activating microglia within the brain. Furthermore, research has demonstrated that in the presence of a compromised gut barrier, inflammatory factors and other chemical signals can be transmitted to the CNS *via* the vagus nerve, thereby directly impacting neuronal function and altering the response of the nervous system. This dysregulation of the gut-brain axis could ultimately contribute to the development of depressive symptoms [95].

3.1.2 BA receptors regulate the integrity of the intestinal barrier. BAs have a crucial role in maintaining intestinal barrier function and the overall intestinal environment. The mechanism of action is complex and diverse, involving regulation of multiple BA receptors and signaling pathways. TGR5 occupies a central role within the complex mechanisms. Specifically, BAs specifically bind to and activate the TGR5 receptor, thereby promoting the expression of tight junction proteins, such as occludin and claudin, in colonic epithelial cells. This process is crucial for reinforcing the physical barrier of the intestinal epithelium and ensuring the integrity and stability of the epithelium structure [96]. Moreover, TGR5 activation also triggers a significant increase in mucins, particularly MUC2, which effectively repels external

pathogens and harmful substances [96]. Notably, TGR5 activation in intestinal stem cells promotes an epithelial regeneration and repair mechanism, which is of inestimable value in rapidly restoring the integrity of the barrier under intestinal damage or inflammatory conditions [97]. In pathologic conditions, such as obstructive jaundice, overexpression of TGR5 is tightly associated with reduced intestinal mucosal injury and accelerated epithelial cell proliferation, further confirming its critical role in maintaining intestinal barrier function [98]. In addition, TGR5 activation affects intestinal electrolyte and fluid transport through multiple signaling pathways, such as the cAMP/PKA pathway, further affecting intestinal barrier integrity [99].

In another extensive study involving the BA receptor, FXR, it was shown that FXR safeguards the integrity of the intestinal barrier through a multitude of mechanisms. Specifically, these mechanisms include preserving cohesion of epithelial cell junctions, suppressing inflammatory responses, and regulating the composition and functionality of the intestinal microbiota. Numerous studies have demonstrated that FXR enhances the integrity of the intestinal barrier by modulating the expression of tight junction proteins [100, 101]. Studies have also indicated that FXR safeguards the integrity of the intestinal barrier by suppressing the production of proinflammatory cytokines, thereby ameliorating inflammation-induced damage to the intestinal barrier [102-104]. Additionally, a well-functioning microbiota is crucial for maintaining intestinal barrier integrity, and FXR activation aids in suppressing harmful bacterial growth while promoting the proliferation of beneficial bacteria, thereby preserving a healthy state of the intestinal barrier [100, 105, 106]. Another interesting study by Zheng et al. revealed that a transient high-fat diet (HFD) is associated with impaired BA tolerance during the onset of colitis. The findings of this study suggested that BAs are potential opportunistic pathogenic factors in the gut, highlighting the possibility that modulating BA metabolism could restore intestinal barrier function [107].

3.1.3 Therapeutic potential of BAs-FXR-FGF19 and BAs-TGR5-GLP-1 pathways in depression. After release into the intestine, BAs activate intestinal FXR-FGF19 and TGR5-GLP-1 pathways, transmitting signals to the CNS to affect depression. Several clinical studies have shown that fasting serum CDCA activates FXR and independently regulates fibroblast growth factor-19 (FGF19) production [108, 109]. FGF19 (also known as FGF15 in rodents) is a member of the FGF endocrine subfamily and is mainly expressed in intestinal epithelial cells located in the terminal ileum [110, 111]. FGFs have a key role in the function, development, and metabolism of neurons. During neurodevelopment, FGFs control the growth and morphology of several brain structures, and in later stages FGFs continue to regulate neurogenesis, axon growth, neuroprotection, and the maintenance and repair of neural tissue. Studies by Galvez-Contreras

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et al. [112] have shown that FGFs have a significant impact on the occurrence and development of psychiatric disorders, such as anxiety, depression, schizophrenia, and bipolar disorder, and are expected to serve as new biomarkers for the diagnosis and prognosis of psychiatric disorders.

Several studies have shown that BAs also stimulate the release of glucagon-like peptide-1 (GLP-1) from intestinal TGR5 [113-115]. GLP-1 is an incretin hormone that acts as a neuropeptide for GLP-1 receptor (GLP-1R) in areas of the brain associated with mood and stress regulation, including the hippocampus [116]. Chen et al. [117] searched randomized controlled trials and prospective cohort studies from multiple electronic sources and concluded that GLP-1 functional agonists (GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) have significantly better antidepressant effects than control substances. Jin et al. [118] used a metabolomics approach and found that dulaglutide (a new long-acting GLP-1 receptor agonist) has a significant antidepressant effect in the chronic mild stress depression model. Furthermore, liraglutide has been shown to alleviate depression and anxiety-like behaviors in mice by improving hippocampal neuroplasticity [119-122]. Therefore, it can be inferred that GLP-1 and its receptor agonists can be used as a potential treatment strategy for depression.

3.2 Targeting the interaction between BAs and gut microbiota is a potential therapeutic strategy for cholestasis-associated depression

3.2.1 Gut microbiota dysbiosis in depression and cholestasis. Cholestasis is often accompanied by intestinal flora disturbance. A large number of studies in recent years have shown that altered composition of gut microbiota is closely related to the occurrence of depression [123]. These findings suggest that cholestasis may contribute to the development of depression through the induction of gut microbiota dysbiosis. Novel therapies targeting gut microbiota, including fecal microbiota transplantation (FMT) or supplementation of potential probiotics have been extensively evaluated in these two diseases and have achieved clear success [124-126]. This emerging trend also presents an opportunity to simultaneously address cholestasis and depression by targeting repair of these intestinal flora disorders.

Although findings vary across studies, consistent evidence suggests an abundance of pro-inflammatory bacteria and a reduction in anti-inflammatory bacteria in individuals with depression, mirroring patterns observed in other conditions associated with systemic and intestinal inflammation. Liu et al. [127] reported that individuals with depression exhibit significant alterations in bacterial phyla (Firmicutes, Actinobacteria, and Bacteroidetes) compared to healthy counterparts with an elevated Bacteroidetes-to-Firmicutes ratio and decreased levels of *Blautia*, *Faecalibacterium*, and *Coprococcus*. There is also consistent evidence indicating an increase in *Eggerthella*

with a decrease in *Sutterella* in patients diagnosed with major depression [127]. In addition, a decrease in the proportion of beneficial bacteria, such as *Lactobacillus*, and an increase in potentially harmful bacteria, such as *Clostridium*, have also been linked to the severity of depressive symptoms [128].

Similarly, there is an increased the Bacteroidetes-to-Firmicutes ratio in cholestasis patients. Additionally, cholestasis results in a reduction in the number of probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium* and some butyric acid-producing bacteria (*Clostridium*), which are thought to be protective in maintaining homeostasis of mucosal immunity and intestinal barrier function. Furthermore, some pathogenic bacterial populations may experience an upsurge. For example, members belonging to the Enterobacteriaceae family, such as *Escherichia coli* and *Klebsiella*, might exhibit significant increases in cholestasis. Excessive proliferation of these microorganisms can elevate the risk of intestinal infection and inflammation [129, 130].

Cholestasis and depression have similar characteristics from the perspective of intestinal flora disorders. For example, both disease states exhibit an elevated ratio of Bacteroidetes-to-Firmicutes. Additionally, a reduction in *Lactobacillus* and butyrate-producing bacteria, like *Faecalibacterium*, has been noted in both disease states. This alteration might impact the production of SCFAs and consequently influence intestinal health and immune function. Targeted supplementation of these bacteria may have a simultaneous therapeutic effect. There may be some common mechanisms underlying these similarities of gut microbiota changes, including gut BA homeostasis and chronic intestinal inflammation. However, patients with cholestasis, as well as cholestatic mice, display symptoms commonly associated with depression, such as reduced mood and activity levels, the alterations of which in gut microbiota have not been comprehensively characterized. It remains unclear whether the dysbiotic features of the gut microbiota are primarily associated with the characteristics of cholestasis or if the dysbiotic features also include the features observed in individuals with depression. Furthermore, additional corollary studies are warranted to determine whether prolonged cholestasis leads to gut dysbiosis similar to that observed in patients with depression. Addressing these issues will provide a more direct theoretical basis for targeting the changes in gut microbiota in cholestasis to alleviate the associated depressive state (Figure 2).

3.2.2 Targeting the interaction between BAs and the gut microbiota may have therapeutic potential in cholestasis-associated depression. There is a complex and dynamic interaction between BAs and intestinal flora, which has a key role in maintaining intestinal homeostasis. BAs can directly affect the composition and metabolic capacities of intestinal flora. Alternatively, the

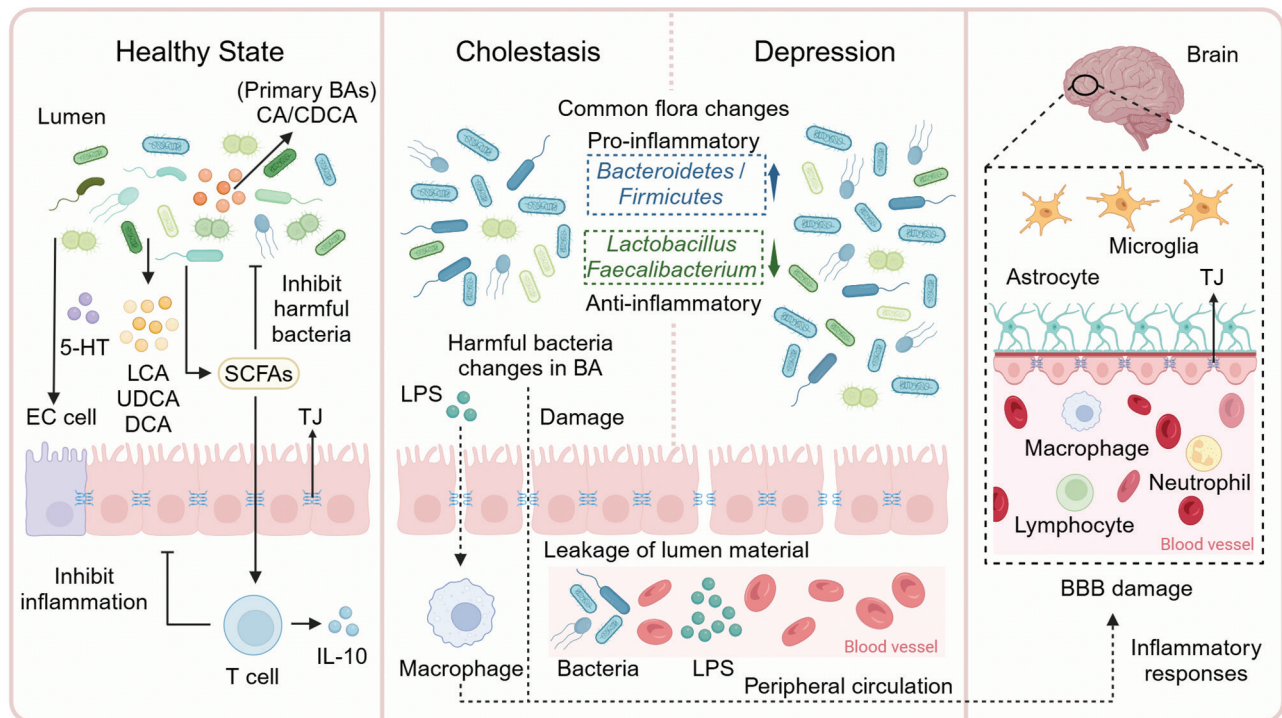


Figure 2 | Gut microbiota dysbiosis in cholestasis and depression: Mechanisms of inflammatory activation and BBB damage.

In a healthy state, the intestinal microbiota and its metabolites protect the intestinal barrier by regulating intestinal immunity and inhibiting inflammatory responses. However, in a state of cholestasis or depression, significant changes have been found in the intestinal flora, which are manifested as an increase in harmful flora and a decrease in beneficial flora, an imbalance in the microbiota, and damage to the intestinal barrier caused by harmful flora and toxins, such as LPS. This causes intestinal contents to enter the peripheral circulation, activates immune cells, such as macrophages, triggers a systemic inflammatory response, and ultimately leads to the destruction of the BBB, promoting inflammation in the central nervous system.

intestinal flora is involved in the metabolic transformation process of BAs.

3.2.2.1 Targeting host BA metabolism to improve gut microbiota dysbiosis. The antimicrobial properties of BAs enable BAs to directly affect the composition of the intestinal flora. Conjugated BAs have relatively weak antimicrobial ability due to strong hydrophilicity, while unconjugated BAs are highly hydrophobic and can destroy bacterial cell membranes, thereby inhibiting the growth of some bacterial flora. Additionally, Gram-positive bacteria are more sensitive to BAs than Gram-negative bacteria [131]. BAs could also disrupt bacterial amino acid, nucleotide, and carbohydrate metabolism and activate innate immune responses in the intestine to modify the composition of the gut microbiota [132, 133]. Therefore, the size and composition of the BA pool in the intestine can significantly affect the relative abundance of different bacterial flora.

Kurdi et al. [134] revealed a significant impact of CA and deoxycholic acid DCA concentrations on bacterial growth and cell membrane integrity. The experimental range for CA concentration varied from 0.1–20 mM. When the CA concentration exceeded 4

mM, substantial damage to the cell membrane and loss of bacterial viability occurred with potassium ion leakage reaching a maximum. Moreover, as the CA concentration further increased to 15–20 mM, there was an increase in leakage of cellular materials, such as proteins. DCA showed similar toxicity at concentrations ranging from 0.4–0.8 mM. Another study utilized 5 mM GCA and TCA, as well as 2.5 mM GDCA and TDCA. The findings revealed that lactic acid-producing bacteria exhibit high tolerance towards GCA and TCA, whereas the presence of GDCA and TDCA significantly inhibits its growth with GDCA exhibiting a more pronounced effect. Furthermore, bile salt hydrolase (BSH) produced by lactic acid bacteria has a crucial role in enabling lactic acid bacteria to withstand the toxicity posed by these BAs. Strains lacking BSH activity, referred to as Δ bshAB strains, experience significant growth limitations. Conversely, strains with BSH activity demonstrate enhanced viability in competitive conditions. These results underscore the differential sensitivities of bacteria that partially relies on the abilities to metabolize BAs [135].

Additionally, Islam et al. [136] investigated the impact of CA on cecal flora by supplementing rat diets with

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varying concentrations, as follows: 1.25 mmol/kg (M-CA group); and 5 mmol/kg (H-CA group). The findings revealed that CA intake significantly altered the composition of cecal flora, particularly leading to a significant increase in the *Firmicutes* population, while causing a notable decrease in *Bacteroides* relative abundance. Furthermore, CA supplementation resulted in a substantial elevation of DCA levels within the cecum. This secondary BA has potent antimicrobial activity and exerts strong selective pressure on intestinal flora, thereby reducing microbial diversity and significantly diminishing the production of SCFAs in the intestine, especially acetic acid and butyric acid. These findings suggest that in patients with cholestasis, excessive exposure to BAs may directly regulate the composition of the gut microbiota and present a potential risk to the intestinal barrier by altering the metabolic capabilities. Furthermore, excessive exposure to BAs could subsequently contribute to the development of BBB disruption and depressive behavior. Improving BA synthesis and secretion is a possible way to reverse gut microbiota dysbiosis and address cholestasis-associated depression.

3.2.2.2 Targeting intestinal bacteria-mediated BA metabolism to improve intestinal barrier function. BAs are primarily synthesized by the liver, but the diversity of BA types is driven by the intestinal flora [133, 137]. Briefly, >90% of BAs secreted in the gut are conjugated BAs, mainly tauro- or glycol-conjugated, and BSH expressed by gut microbiota is responsible for deconjugation of BAs. Another bacterial enzyme, 7 α -dehydroxylase, transforms primary BAs into secondary BAs. Recently, differential isomerization of BAs, reverse conjugation with various amino acids, sulfation, and succination was shown to increase the diversity of the intestinal BA pool. These enzymatic transformations predominantly take place in the distal segment of the gastrointestinal tract [138, 139]. Unconjugated secondary BAs were previously considered to directly induce stress of intestinal epithelial cells and inhibit the self-renewal and repair capabilities of the epithelium. However, some newly identified secondary BAs have a protective effect. Hang et al. and Lee et al. screened bile acid metabolites and reported that two different metabolites of LCA (3-oxoLCA and isoalloLCA) regulate the balance between the pro-inflammatory T_H17 cells and the anti-inflammatory T_{reg} cells, thereby regulating host immunity [82, 140]. Another more in-depth study found that 3 β -hydroxydeoxycholic acid (isoDCA) and ω -polyphenolic acid (ω -MCA) facilitate the differentiation of Foxp3⁺ T_{reg} cells without affecting T_H17 cells and further showed that intestinal FXR was involved [82, 141]. Future research is warranted to identify the gut microbiota responsible for producing these beneficial BA metabolites and to examine the changes in these bacterial species in patients or animal models with cholestasis-related depression. Developing strategies to

supplement these bacterial strains or metabolites may provide new opportunities for improving cholestasis and depression (Figure 3).

3.3 Other bacterial metabolites that improve the homeostasis of gut-brain axis

In addition to BAs the intestinal flora also mediates protective effects on the intestine through a variety of metabolites. Among the metabolites, SCFAs, including acetate, propionate, and butyrate, are the main products of dietary fiber fermentation, which have significant anti-inflammatory effects and promote energy metabolism in intestinal epithelial cells. SCFAs regulate intestinal barrier function as well as mucosal and systemic immunity through evolutionarily conserved processes involving G protein-coupled receptor signaling or histone deacetylase activities, which have been thoroughly reviewed elsewhere [142, 143]. Additionally, it is noteworthy that tryptophan metabolites, such as indole and its derivatives, have the ability to activate host aromatic receptors (e.g., AHR receptors) and inhibit excessive inflammation to protect intestinal barrier function. Furthermore, these tryptophan metabolites also have critical roles in regulating inflammatory responses in the CNS, potentially influencing the pathologic processes associated with depression [144]. It is apparent that tryptophan is also the precursor of 5-hydroxytryptamine (5-HT [also known as serotonin]), an important neurotransmitter that regulates mood in the brain. Approximately 95% of serotonin in the intestine is produced by enterochromaffin (EC) cells and the production of CA, DCA, butyrate, propionate, and tyramine by indigenous spore-forming bacteria significantly stimulate the biosynthesis of 5-HT in these cells [145]. By increasing colonization of these bacteria or directly supplementing these metabolites, it is possible to enhance intestinal 5-HT synthesis. This, in turn, can promote intestinal motility to accelerate BA excretion, alleviating cholestasis. Additionally, the enhanced 5-HT can directly improve depressive-like behavior by transmitting signals to the CNS.

Other trace metabolites, such as pyrroles and polyphenolic metabolites, possess antioxidant and anti-inflammatory properties, thereby safeguarding the intestinal mucosa. Research has demonstrated that specific polyphenolic metabolites (e.g., salicylic acid, dihydroxyphenylacetic acid, and hydroxycinnamic acid) mitigate oxidative DNA damage and suppress the expression of proinflammatory cytokines, like IL-1 β , IL-8, and TNF- α [146]. Polyphenols, such as apple peel polyphenols, inhibit the NF- κ B signaling pathway and reduce the expression of cyclooxygenase-2 (COX-2) [147]. Pyrroloquinoline quinone (PQQ), as a pyrrole compound, has been shown to effectively reduce intestinal inflammatory damage with similar mechanisms [148]. Polyphenol extracts in red wine can further reduce oxidative stress-induced damage to the intestine by

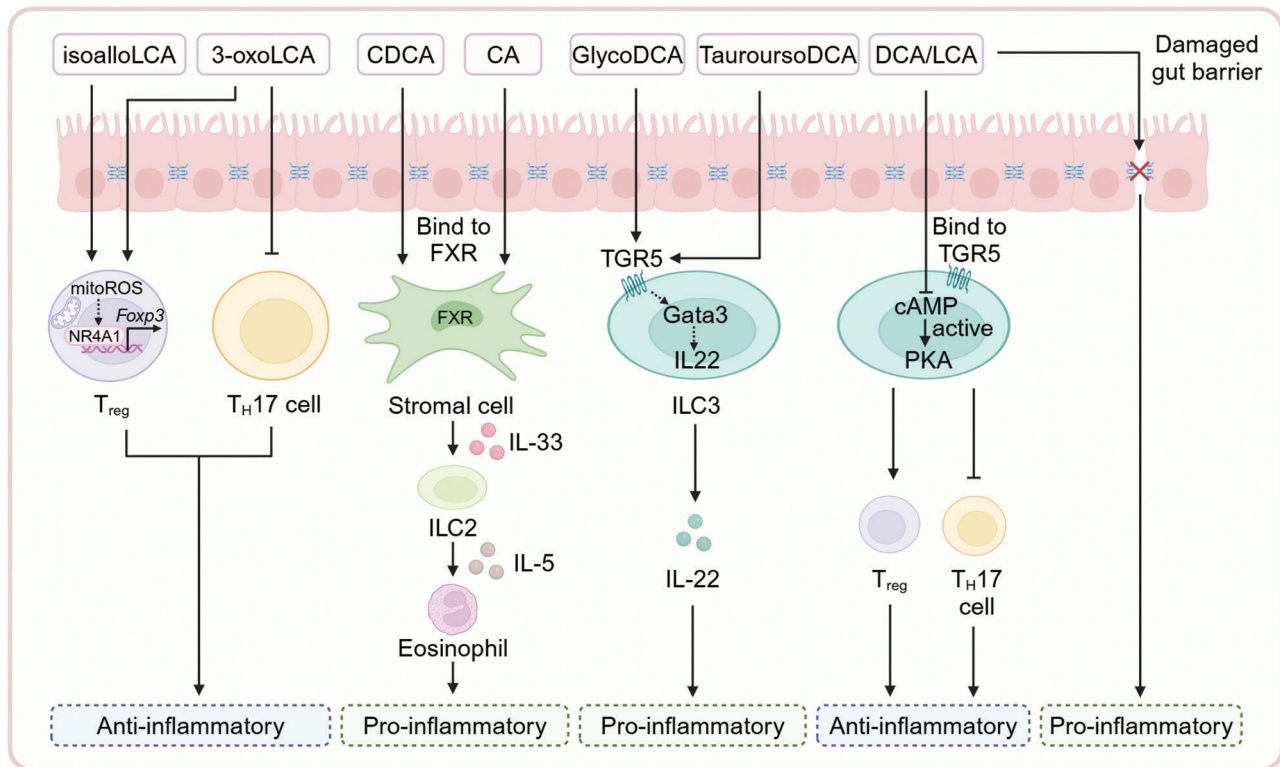


Figure 3 | Bile acids regulate immune cell function and gut barrier integrity.

Different bile acids and bile acid metabolites regulate the functions of immune cells, such as T_{reg} cells and T_H17 cells) and affect the integrity of the intestinal barrier by activating signaling pathways, such as FXR and TGR5.

upregulating the Nrf2 signaling pathway and increasing the expression of antioxidant enzymes, such as glutathione peroxidase [149].

4. CONCLUSION

The incidence of depression in patients with cholestatic liver disease is significantly higher than the general population, suggesting that cholestasis may contribute to the development of depression through multiple mechanisms. Our review has comprehensively revealed that the excessive accumulation of BAs during cholestasis may have critical roles in regulating the CNS by directly influencing the BBB or through interactions with the gut microbiota within the gut-brain axis. Modulating downstream signaling mediated by BAs and BA receptors appears to be essential for addressing this issue. Strategies, such as alleviating neuroinflammation, supplementation with potential probiotics, and utilizing beneficial gut microbiota metabolites (including protective bile acids), also represent feasible approaches for treating cholestasis-associated depressive states. However, several unresolved questions impede our ability to address this problem clinically. For example, can BAs directly enter the CNS

in cholestatic patients and is the concentration of BAs sufficient to produce significant biological effects? Is BBB damage a direct consequence of BAs in the bloodstream during cholestasis or a secondary effect following gut barrier disruption? Would targeting the gut microbiota, providing protective BA metabolites, or restoring gut barrier function through potential probiotics be adequate to reverse BBB damage? Is BBB damage a key driving factor in the development of depressive-like behavior in cholestatic patients? It is believed that only by resolving these questions can we identify truly effective therapeutic targets or strategies within this complex interplay. Future research should further enhance cross-validation between animal models and clinical samples to facilitate the discovery, evaluation, and translation of innovative therapies to promptly address the burden of depression in patients with cholestasis.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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