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Research Progress on the Gut Microbiota-Bile Acid Interplay and Diarrhea-Predominant Irritable Bowel Syndrome

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Abstract This article systematically reviews the characteristics of gut microbiota dysbiosis in IBS-D and associated therapeutic modulation strategies. It elaborates on the biosynthetic and metabolic pathways of bile acids, the phenotypes of bile acid dysregulation in IBS-D patients, and the related pathogenic molecular mechanisms. A primary focus is placed on dissecting the interaction mechanisms between the gut microbiota and bile acids, specifically the regulatory role of the gut microbiota in bile acid transformation and the influence of bile acids on the structure of the gut microbiota. Based on current research evidence, this article proposes the gut microbiota-bile acid axis as a potential therapeutic target for IBS-D. It aims to provide theoretical insights and novel perspectives for exploring innovative treatment strategies for IBS-D and elucidating its pathogenesis.

Key words Diarrhea-predominant irritable bowel syndrome, Gut microbiota, Bile acids, Interaction mechanisms, Research progress

1 Introduction

Irritable bowel syndrome (IBS) is a chronic, functional gastrointestinal disorder that affects the normal functioning of the intestines. Its primary clinical manifestations include abdominal pain, bloating, or discomfort, symptoms which often alleviate to some degree following defecation. Furthermore, IBS patients commonly experience alterations in bowel habits, specifically manifested as changes in stool frequency (increased or decreased) and abnormal stool form. In China, the prevalence of IBS ranges widely from 1.0% to 16.0%, with an overall prevalence rate of approximately 6.5%. The primary age of onset is between 30 and 59 years[1]. Based on stool form, IBS can be categorized into four subtypes: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), and unsubtyped (IBS-U). Relevant surveys indicate that diarrhea-predominant IBS (IBS-D) accounts for the highest proportion, approximately 75%[2]. To date, the precise pathogenesis of IBS has not been fully elucidated and remains a major research focus in the medical field. Research suggests that the pathogenesis of IBS-D likely involves multiple interacting factors, primarily including abnormalities in the gut-brain axis, low-grade intestinal inflammation, dysregulated bile acid metabolism, gastrointestinal motility disorders, visceral hypersensitivity, and gut microbiota dysbiosis. In recent years, a growing body of evidence indicates a close association between gut microbiota-bile acid interactions and the pathogenesis of IBS-D. This article will summarize the relevant research progress concerning gut microbiota-bile acid interactions in the pathogenesis of IBS-D, aiming to provide a reference basis for the in-depth investigation of IBS-D pathogenesis.

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2 Association between gut microbiota and IBS-D and related modulation strategies

2.1 Physiological functions of gut microbiota and characteristics of dysbiosis in IBS-D The gut microbiota constitutes an extremely complex microecosystem composed of diverse microorganisms, including bacteria, viruses, and fungi. Often referred to as the human "second genome", it plays crucial roles in numerous physiological processes of the host. It participates in nutrient metabolism, immune regulation, and the degradation of harmful substances. Additionally, it enhances intestinal barrier function and maintains intestinal homeostasis[3-4]. Dysbiosis within this ecosystem is prone to trigger a range of health problems, including IBS. Studies demonstrate that gut microbiota imbalance can act upon the "microbiota-gut-brain axis" via pathways such as the vagus nerve, indirectly modulating central nervous system function and ultimately contributing to the development of IBS[5].

Among the various clinical subtypes of IBS, the characteristics of gut microbiota dysbiosis are particularly pronounced in IBS-D. This is characterized by a significant reduction in beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, alongside a marked increase in potentially pathogenic bacteria like *Clostridium* and *Escherichia coli*. This significant alteration in microbial community structure can be quantified by a decrease in the *Bifidobacterium*-to-*Enterobacteriaceae* ratio (B/E ratio) falling below 1[6], revealing a state of severe imbalance in the intestinal microecology. Microbiota dysbiosis contributes to the pathogenesis of IBS-D through multiple pathways: it can damage the intestinal mucosal barrier, activate mucosal immune-inflammatory responses, alter gastrointestinal motility, impair the normal function of the gut-brain axis[7], and even heighten visceral sensitivity[8]. Furthermore, microbiota dysbiosis is closely linked to abnormalities in bile acid metabolism[9]. These mechanisms collectively exacerbate IBS-D symptoms, significantly impacting patients' quality of life.

The correlation between gut microbiota dysbiosis and IBS-D manifests in several aspects: Firstly, the reduction of dominant beneficial bacteria and the increase in pathogenic bacteria directly

worsen intestinal microecological deterioration. Secondly, the impairment of microbial population diversity and balance compromises the intestine's defensive capabilities. Finally, IBS-D shares similarities with other diarrheal diseases in terms of the quantity and structural composition of the gut microbiota, suggesting that microbiota imbalance may represent a common pathological basis for such conditions.

2.2 Research on gut microbiota modulation-based therapeutic strategies for IBS-D Research on various gut microbiota modulation strategies for treating IBS-D is currently underway. These include probiotic supplementation, prebiotic application, the use of non-absorbable antibiotics[10], and fecal microbiota transplantation (FMT). However, due to significant variations in the types of agents used, dosages, and treatment durations among these therapeutic approaches, a unified academic consensus on their specific impacts on the gut microbiota has yet to be established.

2.2.1 Application value of prebiotics and probiotics. Prebiotics, defined as substances selectively utilized by host gut microbiota to confer beneficial effects, have garnered considerable attention in IBS-D treatment in recent years. Studies demonstrate that prebiotics effectively promote an increase in *Bifidobacterium* populations within the colon, accelerating their colonization in the gut and thereby improving the intestinal microecology[11]. Probiotics, on the other hand, exert a therapeutic effect on IBS-D by directly supplementing beneficial microorganisms, thereby modulating the balance of the gut microbiota.

2.2.2 Clinical exploration of non-absorbable antibiotics. Rifaximin is a non-systemically distributed antibiotic that targets the gastrointestinal tract, exhibiting broad-spectrum antibacterial activity against Gram-negative bacteria, Gram-positive aerobic bacteria, and anaerobic bacteria. It modulates the structure of the gut microbiota by increasing the abundance of beneficial bacteria such as *Lactobacillus*[12], while also exerting significant anti-inflammatory effects on the intestinal epithelial mucosal barrier[13]. This drug has received approval from the U. S. Food and Drug Administration (FDA) for the treatment of IBS in adults, with multiple studies confirming its efficacy and safety in treating IBS-D[14].

2.2.3 Potential value of fecal microbiota transplantation. FMT is an emerging therapeutic approach whose core principle involves transferring functional microbial communities from the feces of healthy donors into the patient's intestine to restore the imbalanced gut microecology. Research indicates that FMT can significantly improve the gut microecology in IBS-D patients and effectively alleviate clinical symptoms in the short term.

2.2.4 Importance of dietary modulation in microbiota regulation. Diet constitutes a critical factor in regulating the gut microbiota and maintaining intestinal microecological homeostasis. Adjusting dietary patterns, such as restricting the intake of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), can significantly alleviate symptoms in IBS-D patients, with particularly notable effects on reducing abdominal pain and bloating.

3 Role of bile acid metabolic dysregulation in the pathogenesis of IBS-D

3.1 Biosynthetic pathways and physiological functions of bile acids Bile acids implicated in IBS-D are the primary components of bile, synthesized through a series of enzymatic reactions from cholesterol within hepatocytes[15]. Bile acids play indispensable roles in regulating glucose and lipid metabolism, maintaining energy homeostasis, and modulating immune responses[16]. In adults, the liver synthesizes approximately 0.5 g of bile acids per day[17], primarily via the classical and alternative pathways[18]. The classical pathway is the dominant route, generating chenodeoxycholic acid (CDCA) and cholic acid (CA). Under normal physiological conditions, this pathway accounts for over 75% of total bile acid production[19-20], with its rate-limiting step catalyzed by CYP7A1. The alternative pathway primarily produces CDCA, with CYP27A1 and CYP7B1 serving as its key enzymes. It is noteworthy that the gut microbiota can significantly influence the expression levels and catalytic activities of enzymes involved in both these biosynthetic pathways[21].

3.2 Characteristics of bile acid metabolic dysregulation in IBS-D patients Bile acids in the intestine have been shown not only to mediate lipid absorption but also to participate in regulating intestinal motility, mucosal secretion, and barrier function, among other aspects[22]. Studies have revealed significant differences in fecal bile acid composition between IBS-D patients and healthy controls[23-24], suggesting a potential role for bile acids in the pathogenesis of IBS-D. Bile acid metabolic dysregulation is prevalent among IBS-D patients, with approximately one-third exhibiting abnormally increased bile acid synthesis or excretion. Meta-analysis[25] results indicate that approximately 68% of IBS-D patients exhibit elevated fecal total bile acid (TBA) concentrations or bile acid malabsorption. A clear causal relationship exists between bile acid malabsorption and diarrhea. Even in those IBS-D patients without overt malabsorption, fecal bile acids can still significantly influence colonic transit. Analysis of 4-hour and 48-hour fecal samples in one study found a positive correlation between primary bile acid (PBA) and secondary bile acid (SBA) levels, indicating that bile acid dysmetabolism may exist in IBS-D patients regardless of concomitant malabsorption[26]. Furthermore, bile acid sequestrants such as colestipol and colesevelam have been proven effective in alleviating symptoms in IBS-D patients, further corroborating the significant role of bile acids in IBS-D pathogenesis. Therefore, bile acid metabolic dysregulation is likely a key pathogenic mechanism in IBS-D. Future research should delve deeper into its specific roles to provide a theoretical foundation for developing more effective therapeutic strategies.

3.3 Molecular mechanisms underlying bile acid regulation of intestinal dysfunction in IBS-D

3.3.1 Impact on gastrointestinal motility and gut-brain axis function. Clinical research has elucidated the regulatory effects of bile acids on intestinal function concerning gastrointestinal motility disturbances. In healthy individuals, rectal perfusion of CDCA or deoxycholic acid (DCA) increases intestinal water and chloride ion secretion.

Conversely, intravenous infusion of taurocholic acid or oral administration of CDCA effectively stimulates sigmoid colon motility, accelerates colonic transit, and increases bowel movement frequency. The bile acid membrane receptor TGR5 plays a pivotal role in inducing colonic motility: TGR5 overexpression accelerates colonic transit, while inhibition of its signaling pathway can alleviate diarrhea symptoms in post-cholecystectomy patients. Furthermore, abnormal bile acid metabolism may induce psychological symptoms such as anxiety and depression by interfering with gut-brain axis function. Key messengers of the gut-brain axis, calcitonin gene-related peptide (CGRP) and 5-hydroxytryptamine (5-HT, serotonin), can directly or indirectly activate the TGR5 receptor on intestinal cells, participating in the regulation of visceral hypersensitivity[27] and intestinal epithelial regeneration. Although bile acids generally do not readily cross the blood-brain barrier (BBB), under pathological conditions such as cholestasis or abnormally elevated serum bile acid concentrations, increased BBB permeability may allow bile acids to enter the central nervous system. This can disrupt central regulatory mechanisms for intestinal function, subsequently triggering abnormal colonic motility and contributing to IBS-D pathogenesis[28].

3.3.2 Regulatory role in visceral hypersensitivity. Visceral hypersensitivity is a key pathophysiological mechanism underlying abdominal pain in IBS-D and is closely associated with bile acid levels. Research has found a significant negative correlation between the initial perception threshold in rectal distension tests and CDCA levels, suggesting that visceral sensitivity may increase with rising CDCA concentrations. Furthermore, patients with a high PBA/SBA ratio experience more severe abdominal pain, indicating that bile acids are likely involved in regulating visceral hypersensitivity in IBS-D[29]. Animal experiments have shown that rectal perfusion of CDCA or DCA in rats significantly enhances their response to rectal distension. The underlying mechanism may involve bile acids inducing mast cells to express nerve growth factor (NGF), which subsequently upregulates the expression of the transient receptor potential vanilloid 1 (TRPV1) receptor[30]. NGF may further exacerbate visceral hypersensitivity and intestinal barrier dysfunction through NGF-mast cell-nerve axon interactions[31].

3.3.3 Central role of the TGR5 receptor in bile acid regulation. TGR5, a bile acid receptor, is widely distributed throughout the entire gastrointestinal tract. In the regulation of colonic motility, mice deficient in TGR5 exhibit prolonged transit times throughout the entire gastrointestinal tract and specifically in the colon, along with reduced defecation frequency and decreased fecal water content. Bile acids can act on TGR5 receptors located on intrinsic primary afferent neurons and enterochromaffin cells, triggering the release of calcitonin gene-related peptide (CGRP) and 5-hydroxytryptamine (5-HT, serotonin). This action directly promotes propulsive colonic contractions and also enhances colonic motor function through indirect pathways. Furthermore, TGR5 is also expressed on macrophages and is closely implicated in intestinal inflammatory processes. TGR5 agonists can ameliorate symptoms in murine models of colitis and significantly reduce the expression levels of inflammatory cytokines. This anti-inflammatory effect is mediated through a complex mechanism involving IL-10[32].

4 Bidirectional interaction mechanisms between gut microbiota and bile acids

A close and reciprocal interaction exists between the gut microbiota and bile acids[33-34]. Bile acids possess antimicrobial activity, and abnormal concentrations within the intestine can influence the composition of the gut microbiota in IBS-D patients. Research indicates that elevated levels of cholic acid (CA) in the gut may lead to an increase in *Gammaproteobacteria*. This finding offers new insights into the reason for the increased abundance of *Gammaproteobacteria* observed in IBS-D patients. Animal experiments have further delineated the specific regulatory effects of bile acid alterations on the gut microbiota: Following CA intake, the abundance of *Firmicutes* (particularly bacteria possessing 7α-dehydroxylation capability) significantly increased in the animal intestine, while the abundance of Bacteroidetes markedly decreased. This suggests that changes in bile acids can induce secondary alterations in the gut microbiota composition.

4.1 Regulatory role of gut microbiota in bile acid metabolism The gut microbiota plays a crucial regulatory role in key aspects of bile acid physiology, including synthesis, metabolic transformation, and the enterohepatic circulation. Primary bile acids (PBAs), synthesized via the classical and alternative pathways, undergo complex biochemical transformations upon entering the intestine under the influence of the gut microbiota. These transformations include deconjugation, 7α-dehydroxylation, oxidation, and esterification, ultimately generating secondary bile acids (SBAs)[35]. Specific bacterial groups, such as *Clostridium* and *Eubacterium* genera, play a pivotal role in the 7α-dehydroxylation process, although the precise mechanisms involved are not yet fully elucidated. Furthermore, the gut microbiota hydrolyzes conjugated bile acids (bound to glycine or taurine) to generate free bile acids. However, excessive bacterial activity can lead to an increased relative proportion of SBAs within the bile acid pool, thereby precipitating bile acid metabolic dysregulation.

Conversely, bile acids regulate the structure and diversity of the gut microbiota and directly influence the growth of specific bacterial populations. This regulation is crucial for maintaining gut microbiota equilibrium, preventing bacterial translocation, and inhibiting small intestinal bacterial overgrowth (SIBO)[36]. Studies have shown that mice deficient in the farnesoid X receptor (FXR) gene exhibit a significant increase in *Firmicutes* and a marked decrease in *Bacteroidetes* within their gut microbiome. This confirms that bile acids can significantly regulate gut microbiota diversity through the FXR signaling pathway. Further research revealed that FXR-knockout mice have a significantly higher bacterial load in the ileum and a substantially weakened intestinal barrier function. Administration of an FXR activator can mitigate these effects, underscoring the central role of FXR in the bidirectional interaction between gut microbiota and bile acid metabolism. In summary, the interaction between gut microbiota and bile acid metabolism is

complex and critical. They collectively regulate intestinal microecological balance and influence the pathogenesis of intestinal disorders such as IBS-D.

4.2 Impact of bile acids on gut microbiota structure Bile acids exert a dual role within the intestinal environment: they provide essential nutritional support for gut microorganisms, while simultaneously exhibiting direct antimicrobial activity and potentially contributing to disease pathogenesis through modulation of microbial community structure. Research demonstrates that bile acids at high concentrations possess significant cytotoxicity, capable of inducing cellular apoptosis and necrosis, triggering inflammatory responses, and causing DNA damage. These biological effects are closely associated with functional gastrointestinal disorders (FGIDs)[37-38]. Furthermore, bile acids can destabilize macromolecules through various mechanisms, such as disrupting RNA secondary structure, inducing DNA damage, and promoting protein misfolding, thereby exerting broad disruptive effects on the intestinal microbial community[39].

Among the various bile acid components, DCA exhibits particularly potent antimicrobial activity, with a capacity to inhibit microbial growth tenfold greater than that of CA[40]. Animal experiments have confirmed that feeding rats a diet containing CA leads to marked alterations in their gut microbiota composition: the relative abundance ratio of Firmicutes to Bacteroidetes increases, overall microbial diversity declines, while the growth of specific bacterial groups within the classes Erysipelotrichia and Clostridia is promoted.

5 Conclusions

In summary, the interaction between the gut microbiota and bile acids is complex and critically important, jointly regulating the intestinal microenvironment. Dysbiosis of the gut microbiota and dysregulation of bile acid metabolism are commonly observed in IBS-D patients. Bile acids modulate the structure of the gut microbiota through multiple mechanisms, while the gut microbiota actively participates in the transformation processes of bile acids. In recent years, increasing research utilizing animal models and involving IBS-D patients has further substantiated the importance of this bidirectional interaction, yet numerous unexplored questions and unknown aspects remain within this field. This review has focused on exploring the potential roles and interrelationships of bile acids and the gut microbiota in the pathogenesis and development of IBS-D. Building upon the substantial body of scientific evidence regarding the gut microbiota-bile acid interaction and the latest clinical research advances, targeting bile acid signaling pathways and modulating the gut microbiota present promising avenues as potential therapeutic strategies for IBS-D, offering innovative concepts and approaches for managing this disorder. In the future, as research deepens, it is anticipated that further insights into the gut microbiota-bile acid axis in IBS-D will be unveiled, paving the way for more precise and effective therapeutic regimens for patients.

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(From page 77)

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