International Journal of General Medicine

Dovepress
Taylor & Francis Group

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REVIEW

The Gut-Brain Axis in Comorbidity of Inflammatory Bowel Disease and Anxiety/Depression: Mechanisms, Controversies, and Future Directions

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Abstract: Inflammatory bowel disease (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBD-U), frequently cooccurs with anxiety and depression, a comorbid pattern that severely impairs patients' quality of life and has thus attracted increasing attention in clinical practice. The gut-brain axis (GBA)—an intricate bidirectional communication network encompassing neural, immune, endocrine, and microbial pathways—serves as a key framework for unraveling the biological underpinnings of this comorbidity. This review systematically synthesizes existing literature to dissect the GBA mechanisms driving IBD-anxiety/depression comorbidity, focusing on four core inflammatory pathways: immune inflammation, gut microbiota-metabolite interactions, neural signaling, and the hypothalamic-pituitary-adrenal (HPA) axis. We also critically examine ongoing research controversies in inflammopharmacology and propose future breakthrough directions grounded in current evidence. Our synthesis reveals that these four pathways form a self-reinforcing inflammatory vicious cycle: intestinal inflammation may disrupt central nervous system (CNS) function through proinflammatory factors, microbiota-derived metabolites, and neural signals, thereby contributing to emotional disorders. Conversely, psychological stress and negative emotions may exacerbate intestinal inflammation via neural and endocrine pathways. Key controversies include unresolved causal relationships between IBD and emotional disorders, debates over dominant regulatory mechanisms, poor reproducibility of gut microbiota studies, and variable efficacy of single-target anti-inflammatory interventions. Moving forward, future research should leverage longitudinal cohort designs, advanced omics technologies, and artificial intelligence tools to deepen mechanistic insights. Developing multi-target anti-inflammatory interventions and robust biomarker systems will facilitate integrated gastroenterological and psychiatric care, enabling precise diagnosis and treatment to enhance patients' physical and mental rehabilitation.

Keywords: gut-brain axis, inflammatory bowel disease, anxiety, depression, gut-brain crosstalk, inflammatory pathways, gut microbiota, HPA axis, inflammopharmacology

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBD-U), is a chronic, recurrent intestinal inflammatory disorder that often presents alongside anxiety and depression, creating substantial challenges for clinical management.[1] Meta-analyses indicate that approximately one-third of IBD patients experience anxiety, while a quarter suffer from depression, with this population facing a significantly higher lifetime risk of depression compared to the general public.[2] This bidirectional interplay between physical and psychological health forms a vicious cycle: intestinal symptoms such as abdominal pain and diarrhea amplify emotional distress, which in turn aggravates intestinal inflammatory responses.[3] Intestinal pain also activates spinal and vagal pathways, amplifies stress signaling, promotes neural sensitization, and directly contributes to anxiety and depression.

The gut-brain axis (GBA) has emerged as a pivotal concept for explaining this comorbidity. Far more than a simple anatomical pathway, it functions as a complex bidirectional network integrating neural, immune, endocrine, and microbial signals.[4] The intestine, often termed the "second brain", modulates CNS function through local inflammation, microbiota

https://doi.org/10.2147/IJGM.S612029
Received: 29 March 2026
Accepted: 1 June 2026
Published: 6 June 2026

composition, and metabolic byproducts. Simultaneously, the brain regulates intestinal motility, secretion, immunity, and barrier permeability via the autonomic nervous system and the HPA axis.[5] Probable disruption of this GBA crosstalk is widely regarded as a central pathophysiological basis for IBD-anxiety/depression comorbidity, and its inflammatory regulatory mechanisms have become a research hotspot in the field of inflammopharmacology.

Despite significant advancements in mechanistic research, critical knowledge gaps persist. Key controversies include unclear causal sequencing between IBD and emotional disorders, debates over which of the four inflammatory pathways dominates regulation, poor reproducibility of gut microbiota findings, and inconsistent efficacy of single-target anti-inflammatory interventions.[6–8] While previous reviews have explored subsets of these topics—such as individual pathways or specific intervention strategies—this review uniquely integrates four interactive inflammatory pathways, systematically analyzes inflammopharmacology controversies, and proposes translational multi-target strategies, distinguishing it from existing pathway-focused reviews.[9–11] It emphasizes the interconnected nature of the GBA and underscores the need for integrated anti-inflammatory therapeutic approaches, aiming to inform clinical practice and precision medicine in this field.

Methods

Study Design

This is a systematic review that synthesizes the latest evidence on the gut-brain axis (GBA) mechanisms underlying the comorbidity of inflammatory bowel disease (IBD) and anxiety/depression, as well as current research controversies and future translational directions in inflammopharmacology. The review strictly adheres to the principles of systematic literature evaluation to ensure the comprehensiveness and objectivity of included studies.

Search Terms and Strategy

The search combined keywords related to the three core components of the review: IBD, anxiety/depression, and the gut-brain axis. Key search terms included: (“inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis”) AND (“anxiety” OR “depression” OR “mood disorders”) AND (“gut-brain axis” OR “brain-gut axis” OR “intestinal microbiota” OR “gut microbiome” OR “inflammatory pathways” OR “neural pathways” OR “HPA axis”).

Search filters were applied to limit results to peer-reviewed articles published in English between January 2018 and December 2024. This time frame was chosen to focus on recent advancements while ensuring sufficient depth of evidence. Additional manual searches were performed on reference lists of key review articles and seminal studies to identify relevant literature missed by database searches.

Inflammatory Mechanisms of the Gut-Brain Axis in Comorbidity

The comorbidity of IBD and anxiety/depression is mediated by four interconnected inflammatory pathways within the GBA: immune inflammation, gut microbiota-metabolite interactions, neural pathways, and the HPA axis. These pathways operate synergistically to form a self-reinforcing inflammatory vicious cycle, which drives disease progression (Figure 1).

Immune-Inflammatory Pathways

In patients with IBD, chronic intestinal inflammation activates mucosal immune cells (including macrophages and T cells), triggering excessive release of proinflammatory cytokines (PICs) such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[6] These PICs compromise the integrity of the intestinal mucosal barrier, leading to local tissue damage, edema, and digestive dysfunction.[7] Notably, elevated serum levels of TNF-α and IL-6 in active IBD correlate with the severity of intestinal inflammation, indicating systemic dissemination of inflammatory signals.[8]

Inflammatory factors influence CNS function through two primary routes: either directly crossing the blood-brain barrier or signaling via vagal afferent fibers.[9] Within the CNS, these factors may activate microglia, which in turn release secondary inflammatory mediators (such as nitric oxide and prostaglandins) that disrupt neurotransmitter balance (eg., dopamine, serotonin) and impair neural transmission.[10] Animal studies further support this link, as exogenous TNF-α injection has been shown to induce anxiety- and depression-like behaviors.[11] Targeted inhibition of these PICs (eg., anti-TNF-α monoclonal antibodies, IL-6 receptor antagonists) has been proven to alleviate both intestinal inflammation and

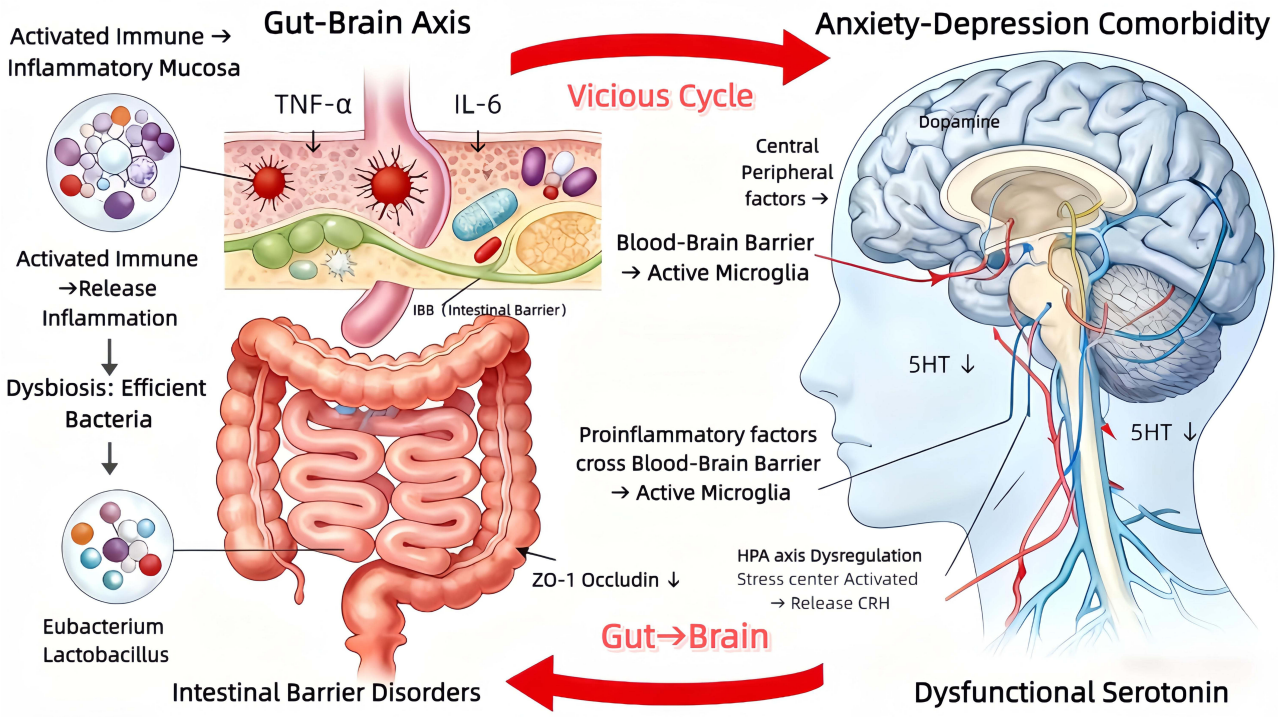

Figure 1 Schematic of the bidirectional inflammatory regulatory network of the gut-brain axis (GBA) in IBD-anxiety/depression comorbidity. This figure was generated by artificial intelligence tools: Doubao (version 13.3.0) and edited with Meitu Xiuxiu (version 12.9.0). Highlighted are four core inflammatory pathways of the GBA—immune inflammation, gut microbiota-metabolite interactions, neural signaling, and HPA axis activation—that form a self-reinforcing inflammatory vicious cycle driving the progression of IBD-anxiety/depression comorbidity. This figure provides a theoretical framework for identifying key anti-inflammatory pharmacologic targets in the GBA.

neuroinflammation in IBD patients, suggesting that these cytokines are potential core pharmacologic targets for breaking the GBA inflammatory cycle.

Probable CNS inflammation then exacerbates intestinal inflammation through a neuro-immune feedback loop. The brain modulates intestinal immunity via the sympathetic and parasympathetic nervous systems, and CNS inflammation disrupts this balance—leading to overactivation of intestinal immune cells and increased release of PICs.[12] Clinically, IBD patients with comorbid anxiety/depression exhibit more severe intestinal mucosal damage and inflammation,[10] suggesting that this neuro-immune feedback loop amplifies intestinal inflammatory pathology and functional and possibly inflammatory changes in the brain.

Gut Microbiota-Metabolite Inflammatory Pathways

The gut microbiota (a complex community of microorganisms) sustains intestinal health and modulates CNS function through metabolic products.[13,14] IBD patients typically display gut dysbiosis, characterized by reduced levels of anti-inflammatory beneficial bacteria (eg., Bifidobacterium, Lactobacillus) and overgrowth of proinflammatory harmful strains (eg., Escherichia coli, Enterococcus).[15] This dysbiosis alters the production of key metabolites that mediate GBA communication, most notably short-chain fatty acids (SCFAs) and tryptophan.[16]

SCFAs—primarily acetate, propionate, and butyrate—are produced by microbial fermentation of dietary fiber. They play critical roles in maintaining intestinal barrier integrity, regulating immune-inflammatory function, and participating in energy metabolism.[16] In animal and mechanistic studies, reduced SCFA levels compromise blood-brain barrier function and decrease neurotransmitter synthesis (eg., serotonin), disrupting emotional regulation and exacerbating neuroinflammation in animal models.[17–19] Tryptophan, a precursor of serotonin, undergoes abnormal metabolism in the setting of gut dysbiosis—shifting toward the kynurenine pathway and producing neurotoxic and proinflammatory metabolites such as kynurenine and quinolinic acid.[20,21] This metabolic shift reduces brain serotonin availability in preclinical models and is biologically plausible to contribute to anxiety and depression in humans. Clinical studies have

https://doi.org/10.2147/IJGM.S612029

further linked abnormal tryptophan metabolism and gut microbiota composition to the severity of depressive symptoms in IBD patients.[5] Supplementation with SCFAs or probiotics (Bifidobacterium/Lactobacillus) exerts anti-inflammatory effects by restoring intestinal barrier integrity and regulating tryptophan metabolism, which provides a mechanistic strategy warranting further clinical validation in humans.

Neural Inflammatory Pathways

Neural pathways—primarily the vagus and sympathetic nerves—mediate bidirectional inflammatory communication between the gut and brain.[22] The vagus nerve transmits sensory signals (eg., pain, inflammation) from the intestine to stress response centers in the brain, such as the amygdala and hypothalamus, triggering the release of stress hormones and altering neural plasticity.[23] Anxiety is associated with reduced vagal tone and altered autonomic balance, which may impair intestinal motility, secretion, and mucosal barrier function—worsening intestinal inflammatory pathology.[24,25] Mechanistically, mood swings (a key feature of emotional disorders) can induce psychological stress, which activates the body's defensive responses, leading to reduced intestinal blood flow, increased local inflammation, and mucosal damage. The link between vagal function and intestinal barrier is supported by animal and experimental data, with associations observed in human studies. Animal studies support this mechanism: vagal stimulation has been shown to inhibit both intestinal and central neuroinflammation while improving emotional behaviors, while vagotomy exacerbates these inflammatory and behavioral phenotypes,[26] highlighting the potential of vagal modulation as an anti-inflammatory pharmacologic approach for GBA-related comorbidity. Notably, Mendelian randomization evidence confirms that this emotional stress-induced intestinal damage is not a reverse causal effect, further validating the direction of neural pathway regulation.[27]

The sympathetic nervous system is activated in response to stress, releasing norepinephrine.[28] This neurotransmitter causes intestinal vasoconstriction, reduced mucosal perfusion, and impaired immune defense,[29] while also directly worsening anxiety by modulating cerebral emotional centers and promoting neuroinflammation.[30] Clinical observations align with these findings, as major life stress or prolonged psychological tension often precipitates simultaneous exacerbation of IBD inflammatory activity and emotional symptoms—an association linked to sympathetic activation and subsequent proinflammatory mediator release.[31] Collectively, these neural pathways underscore how bidirectional GBA communication mediates the cross-talk between intestinal and central inflammatory responses, contributing to the progression of this comorbidity.

Endocrine (HPA Axis) Inflammatory Pathways

The HPA axis regulates stress responses through a tightly controlled negative feedback loop.[32] In patients with IBD-anxiety/depression comorbidity, this loop is disrupted, leading to sustained activation of the HPA axis and elevated cortisol levels.[33] Chronic hypercortisolism impairs intestinal mucosal repair, weakens barrier function, and disrupts immune-inflammatory balance—all of which exacerbate intestinal inflammation.[34,35] Clinically, serum cortisol levels correlate with IBD disease activity,[36] further supporting the role of HPA axis dysfunction in driving intestinal inflammatory progression.

In the brain, hypercortisolism inhibits the synthesis of serotonin and dopamine, causes structural damage to the hippocampus——a key region for emotional regulation——and promotes microglial activation and neuroinflammation in animal models.[37,38] IBD patients with depression often exhibit abnormal cortisol secretion rhythms, and pharmacologic modulation of the HPA axis (eg., cortisol receptor antagonists) has been shown to improve both emotional symptoms and intestinal inflammatory activity.[39] This pathway completes the GBA inflammatory vicious cycle, with all four pathways interacting synergistically to link intestinal inflammation and central emotional disorders (Figure 2).

Research Controversies in Inflammopharmacology

Research Controversies and Supporting Evidence for the Causal Relationship Between IBD and Anxiety/Depression

A consensus on the causal relationship between inflammatory bowel disease (IBD) and anxiety/depression has not yet been reached in academic circles. There are three core hypotheses in the field: the IBD-first hypothesis, the emotion-first

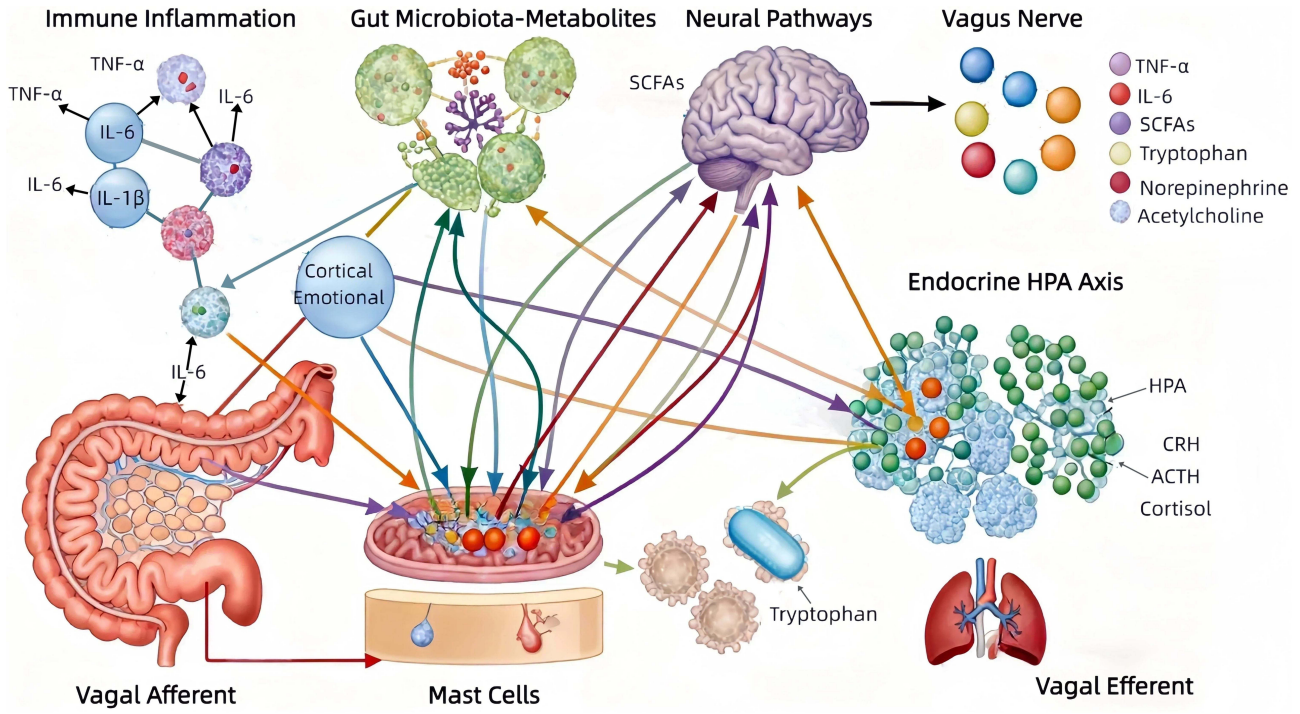

Figure 2 Schematic diagram of the four interconnected GBA inflammatory pathways mediating IBD-anxiety/depression comorbidity. This figure was generated by artificial intelligence tools: Doubao (version 13.3.0) and edited with Meitu Xiuxiu (version 12.9.0). The four pathways—immune inflammation, gut microbiota metabolites, neural pathways, and the HPA axis—do not function independently; rather, they interact through bidirectional signals to create a tightly connected regulatory network. This network collectively drives the progression of comorbidities between inflammatory bowel disease (IBD) and anxiety/depression. To illustrate the interactions within this complex network, the figure integrates core molecules, cells, and signaling flows from the four pathways. It clearly delineates the bidirectional regulatory pathways between the gut and the brain and emphasizes the "vicious cycle" of mutual reinforcement among these pathways.

hypothesis, and the bidirectional cycle hypothesis. Each hypothesis is supported by relevant research evidence, yet all face common research limitations that compromise the accuracy of causal inference (Table 1).

Essentially, the controversies surrounding these three hypotheses reflect that the association between IBD and anxiety/depression is not a simple linear relationship, but a complex process regulated by multiple pathways of the gut-brain axis

Table 1 Inflammopharmacology Evidence and Limitations of Causal Hypotheses Linking IBD to Anxiety/Depression

Hypothesis Type	Core Supporting Evidence	Research Limitations
IBD-first	1. Elevated proinflammatory cytokines (TNF-α, IL-6) in IBD patients disrupt central nervous system (CNS) function and induce neuroinflammation; 2. Mendelian randomization studies demonstrate that genetic susceptibility to IBD increases the risk of depression (OR=1.09, 95% CI:1.04–1.14).[40]	1. The mediating role of intermediate variables such as the gut microbiota in the causal relationship has not been thoroughly explored; 2. The lack of dynamic data across different IBD disease stages fails to clarify the temporal association between inflammatory activity and emotional disorders.
Emotion-first	1. Prospective studies have found that pre-existing anxiety/depression increases the risk of developing IBD; 2. Mechanistic evidence confirms that emotional stress elevates intestinal permeability and triggers intestinal inflammatory responses.[41]	1. Insufficient study sample sizes make it difficult to rule out biases caused by individual differences; 2. Confounding factors such as diet, geography, and medication use have not been effectively controlled, leading to poor reproducibility of results.
Bidirectional cycle	1. Intestinal inflammation can induce emotional disorders through immune and neural inflammatory pathways, while emotional distress exacerbates intestinal inflammation via the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system; 2. Clinical observations show that IBD patients with comorbid anxiety/depression exhibit more severe intestinal mucosal damage and central neuroinflammation, presenting pathological characteristics of mutual reinforcement.	1. The initial inflammatory trigger of this vicious cycle has not been identified; 2. There is a lack of precise analysis on the intensity and primary/secondary pathways of the bidirectional interaction in different patient populations.

Notes: Core evidence and limitations of three causal hypotheses linking IBD to anxiety/depression, reflecting key controversies in inflammopharmacology research.

(GBA). The limitations of existing research also point out the direction for future studies: it is necessary to clarify the temporal and causal associations between the two conditions across different disease stages through large-scale longitudinal cohort studies, causal inference models and standardized research methods, so as to provide an accurate basis for the timing selection and formulation of inflammopharmacology intervention strategies.

Most researchers now lean toward a "bidirectional cycle" model: intestinal inflammation may trigger emotional disorders via immune and neural inflammatory pathways, while emotional distress may exacerbate intestinal inflammation through the HPA axis and autonomic nervous system.[42] That said, current evidence has notable limitations—including unexplored intermediate variables (eg., gut microbiota) and a lack of dynamic data in different IBD disease stages.[43] These gaps highlight the need for more nuanced studies to clarify how these conditions interact over time, which is critical for optimizing the timing of inflammopharmacologic interventions.

Core Inflammatory Mechanism Debate

Early research focused on identifying a single dominant inflammatory pathway, but accumulating evidence now supports a "network regulation" paradigm. For instance,[44] anti-TNF-α therapy alleviates both intestinal and central inflammatory symptoms, probiotics balance the gut microbiota and reduce systemic inflammation,[45] vagal stimulation modulates both intestinal inflammation and anxiety-related neuroinflammation,[31] and HPA axis modulators improve both inflammatory and emotional symptom clusters.[46] Vitamin B12 further exemplifies this network regulation: it integrates gut microbial ecology, SCFA metabolism, intestinal mucosal barrier function, and neuroinflammation suppression to maintain GBA homeostasis,[47] interacting with immune, neural, and endocrine pathways to influence disease progression. This multi-dimensional regulation confirms that no single pathway dominates GBA-mediated comorbidity, underscoring the necessity of integrated therapeutic strategies. These findings suggest that the pathways are deeply interconnected: the gut microbiota influences microglial activation via SCFAs, vagal activity affects intestinal barrier function and microbiota composition, and HPA axis activation impacts intestinal immunity and neural inflammatory plasticity.[48] This network-based view challenges the notion of a single "core inflammatory mechanism" and underscores the need for integrated anti-inflammatory therapeutic strategies targeting multiple GBA pathways.

Reproducibility of Gut Microbiota Inflammatory Studies

Poor reproducibility is a major challenge in gut microbiota research, stemming from multiple factors: sample heterogeneity (eg., disease duration, inflammatory activity, medication use), geographic and dietary differences, and a lack of technical standardization. For example, 5-aminosalicylic acid (5-ASA) treatment has been shown to increase gut microbiota α-diversity and reduce intestinal proinflammatory responses, while European and Asian populations exhibit distinct microbiota changes and inflammatory profiles in IBD.[49] Even variations in DNA extraction kits can significantly affect study results and the identification of pro/anti-inflammatory microbiota taxa.[50] Addressing this issue will require standardized research methods, multi-center large-sample designs, and rigorous adjustment for confounding factors—steps that are critical for translating microbiota research into clinical inflammopharmacology practice.

Efficacy of Single-Target Anti-Inflammatory Interventions

The efficacy of single-target anti-inflammatory interventions varies widely, due in part to individual biological differences (eg., genetics, baseline microbiota, immune-inflammatory status), disease progression dynamics (single-target therapies are less effective in chronic inflammatory stages), pathway compensation (blocking one inflammatory pathway can activate alternative regulatory mechanisms),[50] and poor tissue selectivity of drugs. Most anti-TNF-α agents act systemically, which may cause off-target effects on the CNS and gut microbiota, further affecting the therapeutic effect on the GBA.[43] For instance, probiotic response rates vary fourfold based on microbiota ecotype, and the efficacy of single-target anti-inflammatory therapies declines in IBD patients with a disease duration of >5 years. These challenges highlight the need for stratified medicine—tailoring anti-inflammatory treatments to individual patient characteristics—and multi-target therapeutic approaches that address the network nature of the GBA inflammatory pathways.

Future Breakthrough Directions in Inflammopharmacology

Future research on IBD-anxiety/depression comorbidity should advance along three core paths: in-depth inflammatory mechanistic exploration, technological innovation, and clinical inflammopharmacology translation.

Inflammatory Mechanistic Research Advances

Large-scale longitudinal cohort studies, combined with causal inference models such as Mendelian randomization, will help clarify the temporal and causal relationships between IBD inflammatory activity and emotional disorders.[27] Single-cell and spatial transcriptomics will enable mapping of cell atlases in key intestinal and brain regions, identifying novel cell subsets and inflammatory signaling molecules involved in GBA communication.[50] Additionally, artificial intelligence and machine learning will integrate multi-omics data—including genomics, metagenomics, and metabolomics—to uncover inflammatory biomarker combinations, predict disease inflammatory trajectories, and simulate the pharmacologic regulation of the GBA.[51] These approaches promise to deepen our understanding of the network inflammatory mechanisms underlying this comorbidity.

Technological Innovation for Inflammopharmacology

The development of specialized "IBD-emotion comorbidity" animal models—such as dextran sulfate sodium (DSS)-induced colitis combined with chronic mild stress—will enable more rigorous preclinical inflammopharmacology research and the screening of novel anti-inflammatory drugs targeting the GBA.[52] Real-time monitoring technologies, including in vivo imaging, microfluidic sensors, and neural microelectrodes, will capture dynamic GBA inflammatory communication as it occurs.[37] Machine learning algorithms will also play a key role in validating inflammatory biomarker combinations for the early diagnosis and classification of comorbid patients, facilitating timely and targeted anti-inflammatory intervention.

Clinical Inflammopharmacology Translation

Multi-target anti-inflammatory combination therapies—such as biologics paired with probiotics/prebiotics, cognitive behavioral therapy (CBT), and vagal nerve stimulation—should be evaluated in randomized controlled trials.[30] CBT reduces psychological stress, normalizes HPA axis function, restores autonomic balance, and directly breaks the gut-brain inflammatory vicious cycle. The development of novel anti-inflammatory drugs targeting the GBA (eg., gut-restricted anti-TNF-α agents, CNS-penetrating SCFA analogs) and the exploration of natural products (eg., curcumin, berberine) with dual anti-inflammatory and neuroprotective effects will further enrich the pharmacologic intervention system for this comorbidity. Curcumin modulates immune inflammation, gut microbiota composition, and HPA axis activity to exert integrated gut-brain protective effects.[53] Multi-omics technologies will screen for GBA inflammatory biomarkers (eg., PICs, SCFAs, specific pro/anti-inflammatory microbiota taxa) to enable early warning and monitoring of anti-inflammatory treatment efficacy.[15] Patient engagement strategies—including digital self-management tools and systematic health education—will promote active stress management and lifestyle adjustments, improving long-term clinical inflammatory and emotional outcomes.[5] Collectively, these translational efforts will bridge the gap between basic inflammatory mechanistic research and clinical inflammopharmacology practice.

Conclusions

The comorbidity of IBD and anxiety/depression is mediated by an interconnected gut-brain axis (GBA) inflammatory network involving immune inflammation, gut microbiota-metabolite interactions, neural pathways, and the HPA axis. These pathways form a self-reinforcing inflammatory vicious cycle, a feature that explains the limited efficacy of single-target anti-inflammatory therapies. Current research controversies in inflammopharmacology—including unresolved causality between IBD inflammation and emotional disorders, debates over core inflammatory mechanisms, poor microbiota study reproducibility, and variable efficacy of single-target anti-inflammatory interventions—highlight the need to move beyond linear research paradigms toward a holistic "GBA inflammatory ecosystem" perspective.

Future research should integrate multi-dimensional data to unravel the network inflammatory mechanisms of the GBA, innovate dynamic inflammatory monitoring tools, and develop multi-target anti-inflammatory combination therapies. This approach will facilitate integrated gastroenterological and psychiatric care, enabling precise diagnosis and treatment to improve patients' physical and mental rehabilitation. Unresolved gaps include clarifying the initial inflammatory triggers of the vicious cycle, standardizing gut microbiota inflammatory research methods, and validating biomarker-guided personalized anti-inflammatory therapies. Addressing these gaps will usher in a new era of precision inflammopharmacology for IBD-anxiety/depression comorbidity and provide new insights for the treatment of other GBA-related inflammatory and neuropsychiatric disorders.

Declaration of AI Use

We used artificial intelligence (AI) tools to assist with language polishing, English translation, and the creation of conceptual schematic diagrams during the preparation of this manuscript. We confirm the originality and accuracy of all content. The AI tools employed are Doubao (version 13.3.0) for language polishing, translation, and figure generation, and Meitu Xiuxiu (version 12.9.0) for image editing and optimization. We have reviewed the terms of service for all AI tools used and confirm that the generated content complies with publication requirements. We affirm that we hold the legitimate right to publish all AI-generated content and figures and have obtained all necessary permissions for their publication. The authors take full responsibility for the integrity of the overall content, including the accuracy of all references. All versions of the figures and the corresponding prompt records have been retained by the authors for future verification.

Acknowledgments

We thank the entire research team for the support and assistance with this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by the Horizontal Project of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (Grant No. 2025HX009).

Disclosure

The authors declare no competing interests in this work.

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