Natural-Based Nutraceuticals Targeting the Gut-Brain Axis

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Doi: **https://doi.org/10.5281/zenodo.22303669**
Received: 10th July 2026
Accepted: 20th July 2026

Abstract

The gut-brain axis (GBA) represents a bidirectional communication network linking the gastrointestinal tract and central nervous system through neural, endocrine, immune, and metabolic pathways. Emerging evidence demonstrates that gut dysbiosis, visceral hypersensitivity, and intestinal barrier dysfunction play pivotal roles in IBS pathophysiology. This review comprehensively examines natural-based nutraceuticals from plant, marine, mineral, and animal sources that modulate the GBA and offer therapeutic potential for IBS management. Plant-derived nutraceuticals including probiotics, prebiotics, berberine, curcumin, and ginger demonstrate significant promise in modulating gut microbiota composition, enhancing short-chain fatty acid production, and reducing visceral hypersensitivity. Marine-derived omega-3 fatty acids and seaweed bioactive compounds exhibit potent anti-inflammatory and neuroprotective properties. Essential minerals including magnesium, zinc, and vitamin D address common micronutrient deficiencies while supporting intestinal barrier integrity and neural function. Animal-derived compounds such as bovine colostrum and L-glutamine contribute to mucosal healing and immune modulation. This review synthesizes current clinical evidence, elucidates mechanistic pathways, and examines commercially available formulations, providing a foundation for evidence-based nutraceutical interventions targeting the GBA in IBS management.

Keywords: gut-brain axis, irritable bowel syndrome, nutraceuticals, probiotics, omega-3 fatty acids, berberine, short-chain fatty acids, gut microbiota

1. Introduction

Irritable bowel syndrome (IBS) stands as one of the most prevalent functional gastrointestinal disorders worldwide, affecting an estimated 11% of the global population with substantial variation across geographic regions [1]. Characterized by recurrent abdominal pain associated with altered bowel habits including diarrhea, constipation, or mixed presentations, IBS significantly impairs quality of life and imposes considerable economic burden through healthcare utilization and lost productivity [2]. Despite its high prevalence, the pathophysiology of IBS remains incompletely understood, with current evidence supporting a multifactorial etiology encompassing gut dysbiosis, visceral hypersensitivity, intestinal barrier dysfunction, abnormal gut motility, and psychosocial factors [3].

The gut-brain axis (GBA) represents a sophisticated bidirectional communication network that integrates the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and the gut microbiota [4]. This complex interplay occurs through neural pathways primarily via the vagus nerve, endocrine signaling through gut hormones, immune-mediated cytokine transmission, and metabolic communication through microbial metabolites including short-chain fatty acids (SCFAs) and tryptophan derivatives [5]. In IBS, disruption of this axis manifests as altered gut motility, enhanced visceral pain perception, and concurrent psychological symptoms including anxiety and depression, which affect up to 50% of patients [6].

Conventional pharmacological treatments for IBS including antispasmodics, laxatives, antidiarrheals, and low-dose tricyclic antidepressants provide symptomatic relief for many patients but are often limited by adverse effects, incomplete efficacy, and failure to address underlying pathophysiological mechanisms [7]. This therapeutic gap has catalyzed growing interest in natural-based nutraceuticals, bioactive compounds derived from food sources that confer health benefits beyond basic nutrition. These compounds offer multimodal mechanisms of action targeting the GBA, including microbiota modulation, barrier restoration, anti-inflammatory effects, and neuromodulation [8]. This review comprehensively examines the therapeutic potential of plant, marine, mineral, and animal-derived nutraceuticals in targeting the GBA for IBS management.

2. The Gut-Brain Axis in IBS Pathophysiology

The GBA operates through multiple interconnected pathways that become dysregulated in IBS. Neural communication primarily occurs via the vagus nerve, which transmits afferent signals from intestinal mechanoreceptors, chemoreceptors, and immune cells to the brainstem and higher CNS centers [9]. Efferent vagal signals modulate gut motility, secretion, and immune function through the cholinergic anti-inflammatory pathway. Enterochromaffin cells within the intestinal epithelium synthesize over 90% of the body's serotonin, playing a critical role in regulating gut motility and visceral sensitivity [10]. Tryptophan metabolism represents another crucial pathway, with gut microbiota influencing the balance between serotonin synthesis and kynurenine degradation, thereby impacting both intestinal function and mood regulation [11].

Microbial metabolites serve as essential signaling molecules within the GBA. SCFAs, primarily acetate, propionate, and butyrate, are produced through bacterial fermentation of dietary fibers and exert profound effects on gut barrier integrity, immune modulation, and neural function [12]. Butyrate, in particular, serves as the primary energy source for colonocytes, upregulates tight junction proteins including occludin and claudin-1, and attenuates visceral hypersensitivity through multiple receptor-mediated pathways [13]. Meta-analytic evidence indicates that alterations in fecal SCFA profiles correlate with IBS symptom severity, with propionate emerging as a potential biomarker for diarrhea-predominant IBS [14].

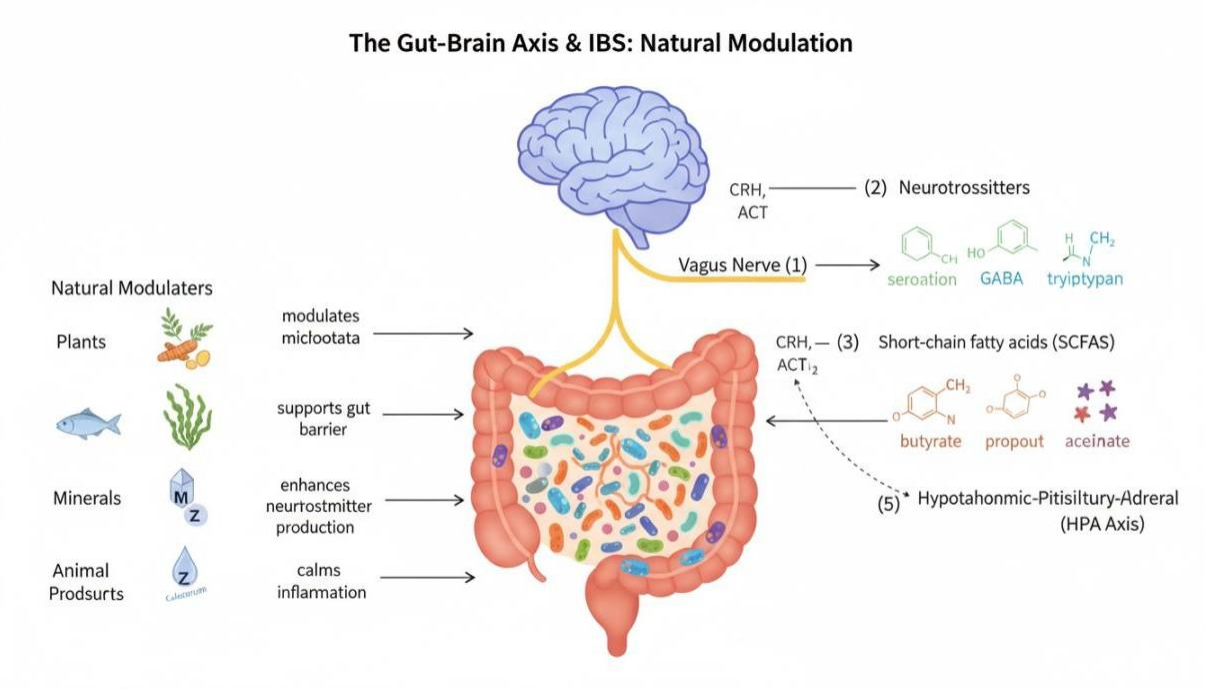

Figure 1: The Gut-Brain Axis in IBS and modulation by natural-based nutraceuticals from plant, marine, mineral, and animal sources.

3. Plant-Based Nutraceuticals

3.1 *Probiotics and Prebiotics*

Probiotics, defined as live microorganisms conferring health benefits when consumed in adequate amounts, represent the most extensively studied nutraceutical intervention for IBS. An umbrella review of 27 systematic reviews demonstrated that probiotics, particularly strains from Lactobacillus and Bifidobacterium genera, produce modest but statistically significant reductions in global IBS symptoms, abdominal pain, and bloating, with numbers needed to treat ranging from 4 to 7 [15]. Multi-strain formulations including VSL#3 and specific combinations such as Bifidobacterium longum with Lactobacillus rhamnosus demonstrate superior efficacy compared to single-strain products [16]. Mechanistically, probiotics modulate the GBA through enhancement of SCFA production, preservation of tight junction integrity, attenuation of pro-inflammatory cytokines including TNF-alpha and IL-6, and modulation of tryptophan metabolism [17].

Prebiotics, non-digestible substrates selectively utilized by beneficial gut microorganisms, complement probiotic therapy by promoting endogenous SCFA production. Inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS) have demonstrated capacity to increase Bifidobacterium abundance and enhance butyrate production [18]. Partially hydrolyzed guar gum (PHGG) exhibits particularly favorable tolerability in IBS patients, with clinical trials showing significant relief from bloating symptoms at doses of 6 grams daily [19]. Synbiotic combinations, pairing probiotics with prebiotics, offer synergistic benefits by enhancing microbial colonization and metabolic activity [20].

3.2 *Herbal Bioactive Compounds*

Berberine, an isoquinoline alkaloid derived from Berberidaceae plants, has emerged as a potent modulator of the GBA with particular relevance to IBS. Clinical and preclinical studies demonstrate that berberine promotes beneficial bacteria including Bacteroides, Bifidobacterium, and Lactobacillus while suppressing pathogenic Escherichia coli [21]. In IBS models, berberine nanoparticles reduced visceral hypersensitivity and diarrhea through modulation of serotonin, vasoactive intestinal peptide, and NF-kappaB signaling pathways [22]. Berberine additionally enhances intestinal epithelial barrier function by upregulating tight junction proteins and reducing intestinal permeability [23].

Curcumin, the primary bioactive constituent of turmeric (Curcuma longa), exhibits multimodal GBA-modulating properties through antioxidant, anti-inflammatory, and neuromodulatory mechanisms. In IBS rat models, curcumin significantly reduced abdominal withdrawal reflex scores while increasing hippocampal serotonin, brain-derived neurotrophic factor (BDNF), and cAMP response element-binding protein (pCREB) [24]. Clinical studies demonstrate that curcumin supplementation at 500 mg daily significantly reduces anxiety scores and gastrointestinal symptom rating scale scores in patients with functional digestive complaints [25]. Formulations combining curcumin with essential fennel oil improved IBS severity indices and quality of life measures across diverse patient populations [26].

Ginger (Zingiber officinale) has been traditionally utilized for gastrointestinal complaints across multiple medical systems. Its active constituents, gingerol and shogaol, modulate gut motility through muscarinic receptor activation and serotonin pathways while exerting potent anti-inflammatory effects [27]. Clinical trials indicate that ginger accelerates gastric emptying and reduces symptoms of functional dyspepsia, with doses of 1000-2000 mg daily demonstrating efficacy in reducing nausea, bloating, and abdominal discomfort [28]. These mechanisms position ginger as a valuable adjunctive therapy for IBS symptom management.

3.3 Polyphenols and the Gut-Brain Axis

Dietary polyphenols have emerged as promising modulators of the GBA through reciprocal interactions with the intestinal microbiota [54]. Because many polyphenols are poorly absorbed in the small intestine, substantial amounts reach the colon, where resident microbes metabolize them into smaller phenolic derivatives with improved bioavailability and bioactivity [55]. In parallel, polyphenols selectively promote beneficial taxa such as Bifidobacterium, Lactobacillus, and Akkermansia along with other SCFA-producing bacteria, while suppressing inflammatory or pathogenic microbes, thereby reshaping intestinal ecology and metabolite production [56].

These microbial shifts are associated with enhanced SCFA production, improved tight junction integrity, reduced lipopolysaccharide-driven inflammation, and modulation of neurotransmitter-related pathways involving serotonin, GABA, and tryptophan metabolism [56]. Preclinical studies further suggest that polyphenols such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), kaempferol, and anthocyanins can reduce neuroinflammation, support blood-brain barrier integrity, and improve behavioral or cognitive outcomes by acting through the microbiota-gut-brain axis [56]. Although IBS-specific clinical data remain limited, these mechanisms closely overlap with core IBS pathophysiology, supporting polyphenols as plausible adjunctive nutraceuticals for future gut-brain-targeted interventions.

Table 1. Representative dietary polyphenols implicated in gut-brain axis modulation.

Polyphenol (Class)	Dietary Source	Gut Microbiota Effect	Proposed GBA-Related Mechanism
Curcumin (curcuminoid)	Turmeric (Curcuma longa)	Increases Lactobacillus and Bifidobacterium; raises butyrate-producing taxa	Anti-inflammatory; raises hippocampal BDNF and serotonin; supports barrier integrity
Resveratrol (stilbene)	Grapes, red wine, berries	Shifts Firmicutes-to-Bacteroidetes ratio; supports SCFA-producing taxa	Reduces neuroinflammation; supports blood-brain barrier integrity
Quercetin (flavonol)	Onions, apples, tea	Promotes Akkermansia muciniphila abundance	Suppresses microglial NF-kB and NLRP3 inflammasome activation
EGCG (flavan-3-ol/catechin)	Green tea	Enhances Bifidobacterium; colonic conversion to bioactive valerolactone metabolites	Antioxidant and anti-inflammatory metabolite generation
Kaempferol (flavonol)	Kale, broccoli, berries	Modulates barrier-associated microbial populations	Neuroprotective; supports tight-junction protein expression
Anthocyanins (flavonoid)	Berries, dark grapes, red cabbage	Increases SCFA-producing taxa; lowers pathogenic bacterial load	Reduces oxidative stress; supports cognitive and behavioral outcomes

4. Marine-Based Nutraceuticals

4.1 *Omega-3 Fatty Acids*

Omega-3 polyunsaturated fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived from fatty fish, krill, and algal sources, constitute essential components of neuronal membrane phospholipids and exert profound anti-inflammatory effects within the GBA [29]. EPA and DHA modulate eicosanoid production, reducing pro-inflammatory mediators while promoting specialized pro-resolving lipid mediators including resolvins and protectins [30]. These fatty acids preserve intestinal barrier integrity by maintaining tight junction protein expression and reducing lipopolysaccharide translocation, while simultaneously supporting CNS function through enhancement of neurogenesis, synaptic plasticity, and neurotransmission [31]. Additionally, omega-3 fatty acids influence gut microbiota composition, promoting beneficial bacterial

populations including Bifidobacterium and Akkermansia muciniphila [32].

4.2 Seaweed-Derived Bioactive Compounds

Marine algae and seaweeds represent rich sources of bioactive compounds with GBA-modulating potential. Fucoidan, a sulfated polysaccharide abundant in brown algae including Fucus vesiculosus and Undaria pinnatifida, demonstrates antioxidant, anti-inflammatory, and anti-apoptotic activities that may protect intestinal epithelial cells and modulate neuroinflammation [33]. Fucoxanthin, a carotenoid pigment found in brown seaweeds, exhibits neuroprotective properties and supports autophagy and mitochondrial function [34]. Marine bioactive peptides derived from enzymatic hydrolysis of seaweed proteins show promise in modulating neuroinflammation and oxidative stress, though human clinical evidence remains limited [35]. Ulvan, derived from green algae, possesses immunomodulatory and antioxidant properties relevant to intestinal health [36].

5. Mineral-Based Nutraceuticals

Micronutrient deficiencies are prevalent among IBS patients, with systematic reviews documenting inadequate intake of vitamins A, B2, B9, B12, calcium, and zinc compared to healthy controls and dietary reference values [37]. Vitamin D deficiency occurs in 70-80% of IBS patients and correlates significantly with symptom severity and quality of life impairment [38]. Supplementation trials demonstrate that vitamin D reduces inflammatory markers including IL-17 and TNF-alpha while improving IBS symptom severity scores and quality of life measures [39]. The mechanisms involve vitamin D receptor-mediated modulation of intestinal barrier function, immune regulation, and antimicrobial peptide production.

Magnesium plays essential roles in smooth muscle relaxation and nervous system regulation, making it particularly relevant for IBS management. Magnesium deficiency exacerbates gut dysmotility and stress responses, while supplementation regulates bowel function by relaxing digestive tract smooth muscles and modulating the stress response through the HPA axis [40]. Zinc supports intestinal epithelial integrity, wound healing, and immune function, with dietary intake significantly lower in IBS patients compared to healthy controls [41]. Zinc and magnesium demonstrate complementary actions in addressing both gut-driven inflammation and stress-driven symptom flares [42].

6. Animal-Based Nutraceuticals

Bovine colostrum, the nutrient-rich first milk produced post-parturition, contains a complex mixture of bioactive components including immunoglobulins (particularly IgG), lactoferrin, growth factors (IGF-1, TGF-beta, EGF), oligosaccharides, and bioactive peptides [43]. These components synergistically strengthen intestinal mucosal barriers, modulate gut-associated immunity, and neutralize endotoxins. Clinical studies demonstrate that bovine colostrum reduces intestinal permeability markers including stool zonulin and circulating bacterial DNA, indicating reduced microbial translocation [44]. For IBS specifically, colostrum's barrier-restoring and anti-endotoxin effects address the low-grade inflammation and epithelial leak characteristic of the condition, though targeted IBS trials remain limited [45].

L-glutamine, the most abundant free amino acid in the body, serves as the preferred fuel source for enterocytes and colonocytes and plays a critical role in maintaining intestinal barrier integrity [46]. Clinical evidence demonstrates

that glutamine supplementation reduces intestinal permeability, preserves tight junction protein expression, and attenuatesinflammatory responses across diverse patient populations [47]. In IBS, glutamine represents a conditionally essential nutrient during periods of physiological stress, with supplementation potentially addressing the increased intestinal permeability and immune activation observed in post-infectious IBS subtypes [48].

7. Market Availability and Commercial Formulations

The global IBS support supplements market has experienced substantial growth, driven by increasing consumer preference for natural therapeutic approaches and expanding scientific validation of nutraceutical efficacy. Major market players including Align (Procter & Gamble), Culturelle (i-Health), and VSL#3 (Sigma-Tau Pharmaceuticals) have developed proprietary probiotic formulations with strain-specific clinical evidence [49]. Align contains Bifidobacterium longum 35624, one of the most extensively studied probiotic strains for IBS, demonstrating significant improvement in abdominal pain and bloating [50]. Culturelle features Lactobacillus rhamnosus GG with documented benefits for gastrointestinal comfort and immune function.

Herbal formulations including Iberogast (STW 5), a multi-herbal preparation containing bitter candytuft, chamomile, peppermint, and other botanical extracts, demonstrate efficacy in functional dyspepsia and IBS through multimodal mechanisms involving spasmolytic, anti-inflammatory, and prokinetic effects [51]. Commercial berberine supplements typically provide 500 mg per capsule, often combined with bioavailability enhancers such as piperine. Marine-derived omega-3 supplements range from 1000-3000 mg combined EPA/DHA daily, with enteric-coated formulations improving gastrointestinal tolerability [52].

Table 2:

Category	Source	Key Compounds	Commercial Examples
Plant-Based	Fruits, vegetables, herbs	Probiotics, prebiotics, berberine, curcumin, ginger	Align, Culturelle, Iberogast, turmeric capsules
Marine-Based	Fish, seaweed, algae	Omega-3 (EPA/DHA), fucoidan, fucoxanthin	Nordic Naturals, krill oil supplements
Mineral-Based	Rocks, soil, water	Magnesium, zinc, vitamin D	Mg glycinate, Zn picolinate, D3 supplements
Animal-Based	Dairy, meat	Bovine colostrum, L-glutamine, lactoferrin	Colostrum powder, glutamine capsules

8. Conclusion and Future Directions

Natural-based nutraceuticals targeting the GBA represent a promising therapeutic frontier for IBS management, offering multimodal mechanisms that address the complex pathophysiology of this disorder. Plant-derived probiotics, prebiotics, and herbal compounds demonstrate the strongest clinical evidence, with marine, mineral, and animal-derived supplements providing complementary benefits. The convergence of microbiota modulation, barrier restoration, anti-inflammatory activity, and neuromodulation positions these compounds as valuable components of integrated IBS management strategies. Future research should prioritize large-scale randomized controlled trials with standardized outcome measures, stratification by IBS phenotype, and integration of biomarkers to identify responder populations and optimize therapeutic protocols [53]. Personalized nutraceutical approaches based on individual microbiome profiles and nutritional status may ultimately enhance treatment precision and improve patient outcomes in IBS management.

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