

Gastrointestinal motility disorders: from pathogenesis to therapeutic strategies

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Received: 20 October 2025; Revised: 27 November 2025; Accepted: 24 December 2025

Published online: 11 February 2026

DOI 10.15212/AMM-2025-0075

ABSTRACT

Gastrointestinal motility disorders (GIMDs) are characterized by impaired gastrointestinal motility. The prevention and treatment of GIMDs remain challenging, because of their prevalence and complexity. The pathogenesis of GIMDs involves multiple factors, such as dysregulation of the enteric nervous system, smooth muscle dysfunction, neurotransmitter imbalance, chronic inflammation, and gut microbiota dysbiosis, which synergistically contribute to GIMD development and progression. Currently, modern medicine remains the primary approach for treating GIMDs, with prokinetic agents such as mosapride and domperidone. However, traditional Chinese medicine (TCM) has attracted attention as a complementary and alternative therapy that can considerably alleviate GIMDs. Accordingly, this review is aimed at comprehensively summarizing the pathogenesis and current management of GIMDs, on the basis of articles in the PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) databases. Future GIMD research should focus on the discovery of new therapeutic targets and the deep synergies between TCM and modern medicine, to achieve a transition from evidence-based medicine to precision medicine, which may aid in the development of more effective interventions and optimization of GIMD management.

Keywords: Gastrointestinal motility disorders, Pathogenesis, Therapeutic Strategies

1. INTRODUCTION

Gastrointestinal motility disorders (GIMDs) are characterized by impaired gastrointestinal motility. Modern medicine classifies GIMDs into subtypes such as functional dyspepsia (FD), gastroparesis, irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), chronic intestinal pseudo-obstruction (CIPO), postoperative ileus (POI), and systemic sclerosis, on the basis of etiology, pathophysiology, and clinical phenotypes [1-3] (Figure 1). The global prevalence of GIMDs continues to rise, particularly among younger populations, and might be associated with risk factors such as Western dietary habits, elevated stress, and sedentary lifestyles [4]. For example, the incidence of FD and IBS has significantly increased in Asian countries in recent years, and is closely associated with growing consumption of fast food and an accelerated pace of life [5, 6]. Furthermore, GIMDs severely affect patients' quality of life and pose a substantial socioeconomic burden through rising healthcare costs and decreased productivity [7-9].

Currently, the clinical treatment of GIMDs relies on modern pharmacotherapies, including targeted

modulation with prokinetic agents, microbiota-gut-brain axis interventions, and neuromodulatory interventions. For example, prokinetic agents such as mosapride and domperidone can relieve symptoms in some patients, but their single-target mechanisms limit efficacy [10, 11]. Long-term use of these drugs can also lead to drug resistance and adverse effects, such as arrhythmias and extrapyramidal symptoms [10, 12-16]. Traditional Chinese medicine (TCM) has attracted attention in recent years as a complementary therapy, with its potential for multi-target and holistic regulation in controlling GIMD. Thus, TCM itself holds high promise and warrants further investigation.

This review provides a comprehensive overview of GIMDs, focusing on their pathogenesis and current therapeutic strategies, to provide a theoretical basis and clinical insights for future mechanistic studies and the development of new therapies against GIMDs.

2. PATHOGENESIS OF GIMDS

2.1 Imbalances in the neural modulation network

The regulation of gastrointestinal motility by the nervous system is achieved through three hierarchical levels:



Figure 1 | Occurrence of gastrointestinal motility disorders (GIMDs).

Modern medicine classifies GIMDs into subtypes of functional dyspepsia (FD), gastric weakness, irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), chronic pseudo-intestinal obstruction (CIPO), postoperative intestinal infarction (POI), and systemic sclerosis, according to etiology, pathophysiology, and clinical phenotypes. This figure was created in [BioRender.com](https://www.biorender.com).

the first level is the central nervous system (CNS), the second level is the autonomic nervous system (ANS), and the third level is the enteric nervous system (ENS). The gut-brain axis is a complex two-way communication network connecting the gastrointestinal tract to the CNS: it integrates neural, endocrine, immune, and microbial signaling pathways in maintaining homeostasis in the body, and influencing physical and mental health [17] (Figure 2).

2.1.1 Central nervous system. The CNS comprises the brain and spinal cord, and is responsible for integrating and processing the afferent signals from internal and external environments [18]. After integration, regulatory signals are transmitted via the ANS and ENS to the intrinsic neural plexuses of the gastrointestinal tract (e.g., myenteric or submucosal plexuses) or act directly on gastrointestinal smooth muscle cells (SMCs) [19]. Extensive studies have demonstrated a strong

link between psychosocial factors and mechanisms of intestinal dysmotility and visceral hypersensitivity [20]. A meta-analysis has demonstrated that depression and anxiety influence intestinal activity and consequently exacerbate symptoms of IBS through complex pathways [20]. Different encephalic regions may play important roles in GIMDs. Under stress stimuli, the paraventricular nucleus in the hypothalamus, a core part of the hypothalamic-pituitary-adrenal (HPA) axis, exhibits enhanced neuronal activity [21, 22] and secretes corticotropin-releasing hormone (CRH), which in turn activates the locus coeruleus in the brainstem, thus augmenting sympathetic outflow and suppressing gastric emptying [23]. In anxiety states, amygdala hyperactivation inhibits prefrontal cortex regulation of the dorsal motor nucleus of the vagus via glutamatergic projections and leads to gastric dysrhythmias [24]. Diminished serotonergic activity in the dorsal raphe nucleus decreases cholinergic activity in the ENS and results in delayed colonic transit [25].

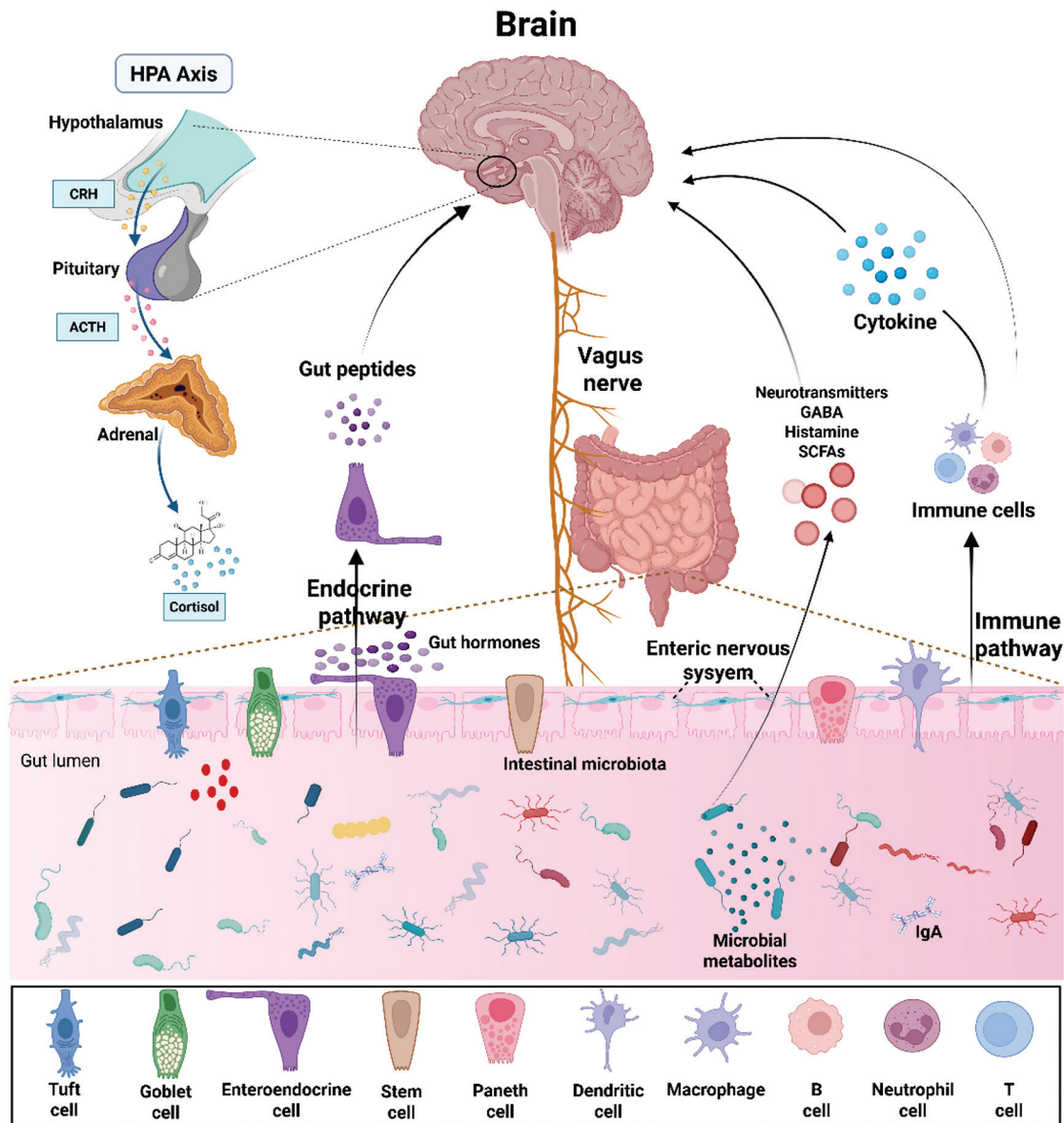


Figure 2 | The gut-brain axis. This schematic integrates the multidimensional interactions among the nervous, endocrine, immune, and microbial systems, and elucidates the central role of the gut-brain axis in gastrointestinal motility disorders (GIMDs).

Central stress signals inhibit intestinal function via the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system, whereas gut dysbiosis, immune activation, and neurotransmitter imbalances exacerbate central dysregulation through ascending signaling pathways, thus forming a vicious cycle. Targeting any component of this loop (e.g., through microbial modulation or neuro-anti-inflammatory interventions) may disrupt the pathological feedback, thereby offering novel therapeutic strategies. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; GABA, gamma-aminobutyric acid; SCFAs, short chain fatty acids; IgA, immunoglobulin A. This figure was created in BioRender.com.

Therefore, selective serotonin reuptake inhibitors improve postprandial gastric regulation in patients with FD by restoring functional connectivity between the prefrontal cortex and amygdala [26].

2.1.2 Autonomic nervous system. The ANS regulates gastrointestinal motility through a dynamic balance

between sympathetic and parasympathetic nerves [27]. Sympathetic nerves release norepinephrine when they are excessively activated, which in turn suppresses the activity of cholinergic neurons in the ENS via α 2-adrenergic receptors, and decreases acetylcholine (ACh) release and gastric antral contraction frequency [28, 29]. However, parasympathetic dysfunction is exemplified by

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vagus nerve damage, as observed in diabetic gastroparesis [30, 31]. Hyperglycemia induces demyelination and axonal degeneration of vagal fibers, whereas the accumulation of advanced glycation end-products (AGEs) activates the receptor for AGE/nuclear factor kappa-B (RAGE/NF- κ B) pathway, increases interleukin-6 (IL-6) release, triggers neuroinflammation, and ultimately leads to delayed gastric emptying [32-36].

2.1.3 Enteric nervous system. The ENS is the third division of the ANS and the largest collection of neurons outside the CNS [37]. Also known as the “brain in the gut” or the “body’s second brain,” the ENS regulates a wide range of gastrointestinal functions through its highly integrated neural circuits. The ENS regulates gastrointestinal functions primarily through smooth muscle activity [38, 39]. Simultaneously, interactions between specialized cell types also contribute to gut function. These cell types include enteric glial cells, which resemble astrocytes in their support and modulation of neuronal activity; interstitial cells of Cajal (ICCs), the gastrointestinal pacemakers that facilitate neuromuscular transmission; and enteroendocrine cells, which release a variety of bioactive substances that influence gut physiology [40, 41]. Additionally, dynamic interactions exist among the immune system, gut microbiota, and the brain-gut axis, which form a complex cross-system communication network that is critical for gastrointestinal homeostasis [42-45]. Therefore, dysregulation or damage to the intricate network of ENS can lead to neuromuscular dysfunction in GIMDs, and pathological lesions of the ENS are characterized by loss of ICC and neurotransmitter imbalance.

2.1.3.1 Interstitial cells of Cajal

ICCs, specialized cells in the gastrointestinal tract, play a critical role in regulating gastrointestinal motility [46]. They are distributed primarily between the submucosal and muscular layers, and, by interacting with ENS neurons and SMCs, they generate slow-wave electrical activity, which orchestrates rhythmic contractions of the gut [47, 48]. The slow waves produced by ICCs depolarize SMCs, thus initiating fundamental contractile activities in the gastrointestinal tract [49]. Studies in streptozotocin-induced diabetic models have shown that decreased gastric emptying is associated with a decline in ICC numbers within the muscular and submucosal layers of the gastric antrum, as well as ENS neuron loss [50, 51]. Therefore, diabetes-induced ICC depletion might be a critical factor contributing to gastroparesis.

Hirschsprung’s disease, a congenital disorder, is characterized by an absence of ganglion cells in the distal colon, because of failed migration of enteric neural crest cells. Abnormalities in both ICCs and enteric neurons within the proximal ganglionic colon segments have been observed in patients with Hirschsprung’s disease; their dysfunction might therefore have potential

roles in the development of postoperative colonic dysmotility [52].

C-cytokine receptor (c-kit) is a receptor tyrosine kinase with critical roles in multiple cell types, particularly within the gastrointestinal tract, where it is essential for the development, survival, and functional integrity of ICCs [53, 54]. This kinase regulates these functions by activating downstream signaling pathways (e.g., PI3K, RAS/mitogen-activated protein kinase (MAPK), and JAK/STAT) through binding its ligand, stem cell factor [55]. Abnormal c-kit signaling contributes to decreased populations or functional impairment of ICCs, which are associated with various GIMDs [56, 57]. In slow-transit constipation rat models, GIMDs have been associated with excessive autophagy and apoptosis in ICCs [58]. Overexpressed microRNA 222 targets and suppresses c-kit expression, thus resulting in functional ICC defects in slow-transit constipation models [58]. Current therapeutic strategies targeting the c-kit signaling pathway have shown progress in certain diseases. For example, tyrosine kinase inhibitors such as imatinib have been demonstrated to restore ICC populations [59, 60]. Future studies should focus on elucidating the dynamic regulatory mechanisms of c-kit signaling in ICC-ENS interactions and developing selective modulators to balance efficacy and safety, thereby advancing precision therapies for GIMDs and c-kit-associated diseases.

In conclusion, ICCs are central to gastrointestinal motility regulation, and their dysfunction is closely associated with various GIMDs. Therefore, advancing understanding of ICC biology and developing targeted therapies to restore ICC function might offer new hope for improving the treatment of gastrointestinal motility-related diseases.

2.1.3.2 Neurotransmitter imbalance

2.1.3.2.1 ACh and substance P

ACh, the primary excitatory neurotransmitter in neuromuscular transmission within the gut, stimulates smooth muscle contraction by activating muscarinic receptors. Substance P, another excitatory neuropeptide, participates in colonic propulsion through activation of neurokinin receptors (specifically the neurokinin A receptor) [61]. Under decreased release or depletion of ACh and substance P, the contractile force of intestinal smooth muscle weakens, and colonic transit is delayed [62, 63].

2.1.3.2.2 Nitric oxide and the cyclic guanosine monophosphate pathway

Nitric oxide (NO) is a crucial inhibitory neurotransmitter with a critical role in the regulation of intestinal motility [64, 65]. NO is synthesized by nitric oxide synthase (NOS), which exists in three isoforms: neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase, and inducible nitric oxide synthase (iNOS) [66]. Under inflammatory conditions, upregulated iNOS expression leads to excessive NO production [67, 68]. NO exerts its biological effects through the activation of soluble guanylate

cyclase, which in turn catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate [65, 66]. The cyclic guanosine monophosphate activates protein kinase G and subsequently phosphorylates multiple target proteins, including myosin light chain phosphatase. This phosphorylation cascade ultimately results in myosin dephosphorylation and smooth muscle relaxation [66]. Consequently, iNOS-mediated NO overproduction inhibits myosin phosphorylation via the cyclic guanosine monophosphate pathway, thus causing colonic smooth muscle relaxation and delayed colonic transit [66].

2.1.3.2.3 Vasoactive intestinal peptide and potassium channel activation

Vasoactive intestinal peptide (VIP), another critical inhibitory neuropeptide, plays a major role in regulating intestinal motility. VIP, after binding its receptors, elevates intracellular cyclic adenosine monophosphate levels and activates protein kinase A [69]. Protein kinase A phosphorylates potassium channels, thus inducing channel opening and enhanced potassium efflux, and triggering smooth muscle hyperpolarization. VIP activates multiple potassium channel subtypes including large-conductance calcium-activated potassium (BKCa) channels and voltage-dependent potassium channels [70]. This hyperpolarization elevates the threshold for membrane depolarization, thereby suppressing smooth muscle contraction and delaying colonic transit [71].

In conclusion, neurotransmitter dysfunction, characterized by decreased ACh and SP release, excessive NO production, and VIP-mediated potassium channel activation, collectively induces colonic smooth muscle relaxation and delayed colonic transit. These neurochemical imbalances are pathophysiologically associated with gastrointestinal disorders such as constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation [72, 73].

2.2 Abnormalities in smooth muscle structure and function

Smooth muscle dysfunction is a central pathological mechanism underlying GIMDs. This condition involves complex interactions among ion channel defects, metabolic injury, and fibrotic remodeling.

2.2.1 Ion channels. Gastrointestinal motility is intricately regulated by ion channel networks. Dysfunction in these channels disrupts electromechanical coupling in smooth muscle tissue and leads to motility disorders. Recent studies have highlighted the critical role of Piezo-type mechanosensitive ion channel component 1 (Piezo1), a mechanosensitive channel expressed in the CNS, which directly senses luminal mechanical forces (e.g., pressure from food propulsion) [74]. By mediating calcium influx, Piezo1 activates neurons and consequently coordinates rhythmic contraction and relaxation of smooth muscle, thereby maintaining normal peristalsis [74]. Piezo1 knockout in cholinergic neurons impairs intestinal transit

and pressure-stimulated peristaltic acceleration, thus linking Piezo1 dysfunction to conditions such as chronic constipation and pseudo-obstruction [75]. Concurrently, sodium voltage-gated channel alpha subunit 5 mutations indirectly impair L-type calcium channels (Cav1.2) via altered $\text{Na}^+/\text{Ca}^{2+}$ exchange, thereby decreasing calcium currents and slow-wave depolarization amplitudes. These electrophysiological impairments are what underlie the weakened colonic propulsion in CIPO [76]. Anoctamin 1, a Ca^{2+} -activated Cl^- channel in ICCs, is essential for generating slow-wave activity. Anoctamin 1 mutations disrupt coordinated Ca^{2+} transients in ICC, and consequently lower slow-wave frequency and contribute to GIMDs [77-80].

The precise regulation of gastrointestinal motility also relies on the coordinated action of multiple ion channels, such as transient receptor potential cation channel subfamily V member 4 (TRPV4), BKCa, two-pore-domain potassium channel (K2P), and cystic fibrosis transmembrane conductance regulator (CFTR) channels, which contribute to mechanosensation, electrical rhythm generation, and secretory balance through distinct mechanisms [81] (Figure 3). TRPV4, a mechano-osmosensitive channel, collaborates with Piezo1 in sensing luminal distension or changes in content viscosity, enhancing slow-wave amplitude and promoting peristaltic reflexes via calcium influx in enteric neurons or ICCs [82, 83]. In contrast, BKCa mediates rapid repolarization after smooth muscle contraction, thereby providing negative feedback regulation of Cav1.2 activity, preventing hypercontraction, and maintaining rhythmic stability [84]. K2P channels stabilize the resting membrane potential of ICCs and smooth muscle by sustaining background potassium currents. Dysfunction in these channels can lead to slow-wave arrhythmias, such as gastrointestinal spasms or hypotonia [85, 86]. CFTR primarily regulates chloride ion secretion in epithelial cells [87, 88]. In cystic fibrosis, mutations in CFTR lead to a fluid imbalance that increases mucus viscosity. This altered mechanical environment of the intestinal lumen impairs Piezo1/TRPV4-mediated mechanosensory signaling and disrupts slow-wave propagation. Consequently, this cascade ultimately contributes to cystic fibrosis-associated intestinal dysmotility [89-91].

Importantly, these channels form a dynamic network. Whereas the TRPV4-BKCa axis balances mechanical stimuli and contraction intensity, the K2P-CFTR axis regulates basal electrical activity and secretory homeostasis [81, 92, 93]. Dysfunction in any component, such as TRPV4 hyperactivity in IBS or BKCa deficiency in slow-transit constipation, can disrupt calcium oscillations, membrane potential, or mechanochemical coupling, thus triggering a pathological cascade that progresses from localized rhythm disturbances to systemic GIMDs [76, 85, 94, 95].

2.2.2 Metabolic injury. Metabolic damage impairs contractile function through oxidative stress, particularly in conditions such as diabetic gastroparesis [96].

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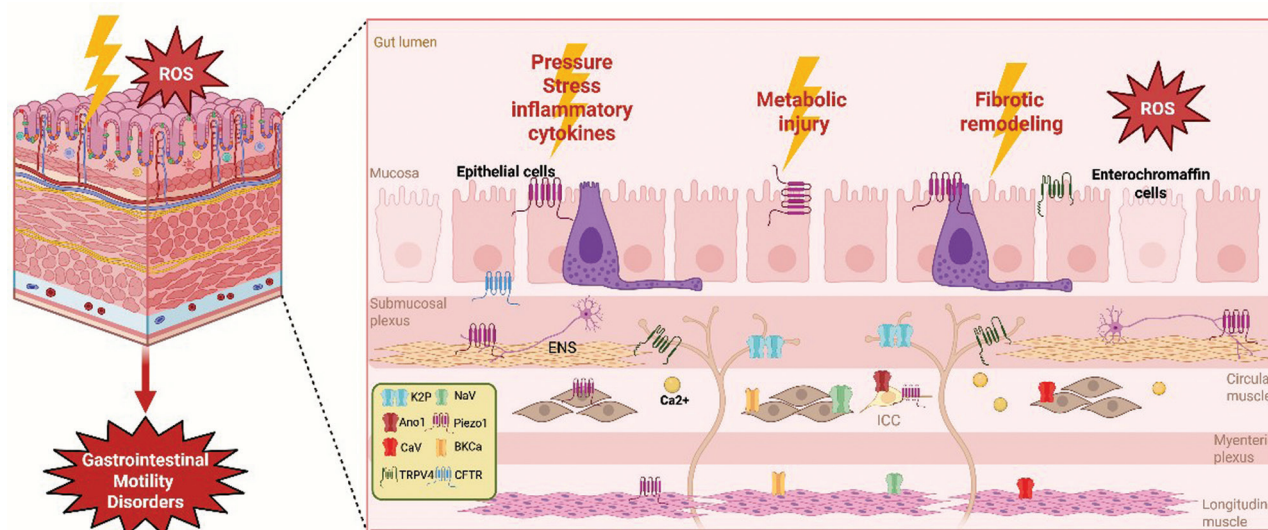


Figure 3 | The pathological mechanism of GIMDs involves smooth muscle dysfunction, driven by the interplay among ion channel abnormalities (e.g., Piezo1 and TRPV4), metabolic damage (hyperglycemia and oxidative stress), and fibrotic remodeling (excessive extracellular matrix deposition).

Metabolic injury activates fibrosis through inflammation, and the fibrotic microenvironment further disrupts ion channels and metabolic functions, thus creating a vicious cycle. Gut dysbiosis exacerbates the disease by modulating motor function. GIMDs, Gastrointestinal motility disorders; Piezo1, Piezo-type mechanosensitive ion channel component 1; NaV, voltage-gated sodium channel; Ano1, Anoctamin 1; TRPV4, transient receptor potential cation channel subfamily V member 4; BKCa, large-conductance calcium-activated potassium; K2P, two-pore-domain potassium; CaV, L-type calcium; CFTR, cystic fibrosis transmembrane conductance regulator. This figure was created in [BioRender.com](https://www.biorender.com).

Oxidative stress plays a critical role in the pathogenesis of diabetic gastroparesis [97]. Hyperglycemia-induced excessive reactive oxygen species (ROS) decrease mitochondrial membrane potential and trigger SMC apoptosis via an elevated BCL-2-associated X protein/B-cell lymphoma-2 ratio [98, 99]. ROS directly damages gastrointestinal SMCs and neurons and leads to GIMDs. Furthermore, oxidative stress activates inflammatory responses and consequently exacerbates gastrointestinal injury.

2.2.3 Fibrotic remodeling. Fibrotic remodeling, excessive deposition of extracellular matrix in gastrointestinal tissues, leads to alterations in tissue structure and function [100]. Because fibrosis impairs gastrointestinal compliance and contractility, it contributes to motility disorders [101]. Inflammation, a critical driver of fibrotic remodeling, triggers the release of pro-fibrotic cytokines such as transforming growth factor-beta, which in turn promote the synthesis of extracellular matrix [102]. S-doped red fluorescent carbonized polymer dots have been demonstrated to protect the intestine by scavenging ROS, decreasing DNA damage, and subsequently slowing fibrosis progression [103]. Abnormal extracellular matrix composition and structural remodeling are closely associated with elevated intestinal stiffness and intestinal dysfunction. Fibrotic remodeling, driven by hyperactivated transforming growth factor- β /Smad3 signaling pathways, prompts fibroblasts to produce excessive type I/

III collagen, which replaces the normal smooth muscle layer. Subsequently, an elevated elastic modulus of the intestine results in heightened stiffness [104]. Concurrently, elastin expression is markedly decreased, and abnormal accumulation of fibronectin and hyaluronic acid substantially decreases intestinal wall compliance.

On the basis of the above findings, the pathogenesis of GIMDs involves complex interactions among ion channel dysfunction, metabolic injury, and fibrotic remodeling. Moreover, metabolic damage (e.g., hyperglycemia and oxidative stress) directly impairs ion channel functionality [105] while simultaneously activating excessive extracellular matrix deposition through inflammatory responses, thus driving fibrotic progression [101]. In contrast, fibrotic remodeling alters the cellular microenvironment and further disrupts ion channel activity and metabolic processes [106] in a vicious cycle. Additionally, gut dysbiosis acts as an independent risk factor by modulating intestinal motor function during disease progression [107]. Potential therapeutic strategies targeting this pathological network include developing specific ion channel modulators that restore smooth muscle excitability, implementing metabolic interventions to regulate glucose and inflammation levels, using anti-fibrotic agents to block abnormal extracellular matrix deposition, and reconstructing gut microbial homeostasis through microbiota transplantation or probiotics. Multi-target combination therapies have promise in breaking this pathological cycle and

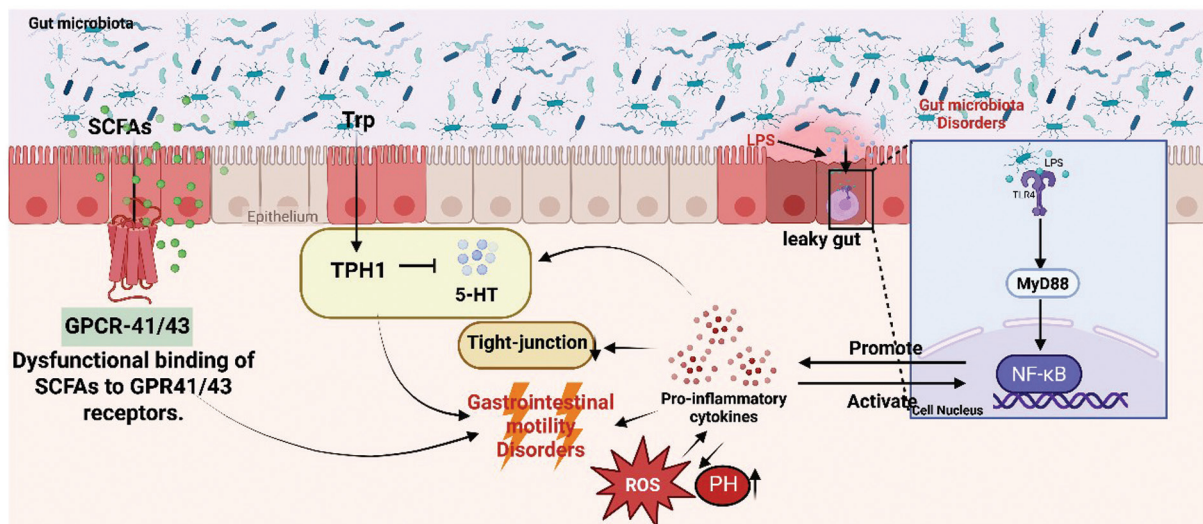


Figure 4 | Bidirectional dysbiosis-inflammation interaction and metabolic axis in GIMDs.

In GIMDs, gut dysbiosis and inflammatory responses exacerbate each other through a bidirectional vicious cycle. Microbial imbalance triggers the release of inflammatory cytokines, disrupts intestinal neuromuscular function, and deteriorates the microenvironment, whereas inflammation-induced leaky gut syndrome allows lipopolysaccharides to enter the bloodstream, thus activating the TLR4/NF- κ B pathway, and further driving systemic inflammation and microbial dysregulation. Concurrently, dysregulation of microbial metabolic axes (e.g., impaired SCFA binding GPR41/43; tryptophan metabolism skewed toward indole derivatives, thereby decreasing 5-HT synthesis; and pro-inflammatory metabolites activating chronic inflammation) directly compromises gastrointestinal motility and barrier function. These processes amplify pathological damage through a metabolism-inflammation cycle and sustained TLR4/NF- κ B signaling, and ultimately contribute to the development of GIMDs. GIMDs, gastrointestinal motility disorders; Trp, tryptophan; tryptophan hydroxylase 1, TPH1; TLR4/NF- κ B, Toll-like receptor 4/nuclear factor- κ B; MyD88, myeloid differentiation factor 88; SCFA, short chain fatty acid; GPCR41/43, G-protein-coupled receptor 41/43; 5-HT, 5-hydroxytryptamine. This figure was created in [BioRender.com](https://www.biorender.com).

consequently improving patients' clinical symptoms and quality of life.

2.3 Interplay between inflammation and gut microbiota dysbiosis

The complex bidirectional relationship between gut microbiota dysbiosis and inflammatory responses leads to a vicious cycle that exacerbates GIMDs (**Figure 4**). This interaction involves multiple mechanisms, as described below.

2.3.1 Bidirectional regulation between inflammation and microbial dysbiosis. Gut microbiota dysbiosis disrupts the intestinal microecological balance and leads to an imbalance between symbiotic and pathogenic bacteria [108]. Toxins from harmful bacteria directly damage intestinal epithelial cells and activate immune cells to release inflammatory factors such as IL-6 and tumor necrosis factor- α (TNF- α) [109]. These inflammatory factors interfere with the normal function of intestinal nerves and muscles, and lead to GIMDs [110]. Inflammation also alters the intestinal microenvironment, such as by decreasing oxygen levels and altering pH levels [111]. These changes are unfavorable for beneficial bacteria but promote the growth of harmful bacteria and further aggravate the imbalance [112]. In turn, dysbiosis triggers stronger inflammatory responses. In addition, microbial dysbiosis impairs

intestinal barrier function and increases gut permeability, and consequently leads to "leaky gut" syndrome [113]. When the intestinal barrier is compromised, bacteria and their metabolites (e.g., lipopolysaccharides) enter the systemic circulation, activate the immune system, and trigger systemic inflammatory responses [114]. Lipopolysaccharides bind Toll-like receptor 4 (TLR4), activate the NF- κ B signaling pathway, and promote the release of pro-inflammatory cytokines such as TNF- α and IL-6 [115, 116]. This vicious cycle continually worsens GIMDs and severely affects the normal functioning of the digestive system.

2.3.2 Microbial metabolite axis. The gut microbiota and their metabolites, short-chain fatty acids (SCFAs), exert multidimensional roles in gastrointestinal motility regulation and disease progression through the microbiota-metabolite axis. SCFAs, such as butyrate, propionate, and acetate, are core products of dietary fiber fermentation. These molecules directly enhance smooth muscle contraction by activating G protein-coupled receptors 41/43, whereas abnormal propionate levels can delay gastric emptying [117]. Furthermore, physiological studies have demonstrated that 5-HT, a potent prokinetic agent, influences intestinal ion transport by proteins such as CFTR, Na⁺-K⁺-2Cl⁻ cotransporter (NKCC), Na⁺-HCO₃⁻ cotransporter (NBC), Cl⁻/HCO₃⁻ exchanger, or K channels [118, 119]. Tryptophan

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is another important gut metabolite. Under inflammation, tryptophan metabolism can shift toward indole derivatives, thus inhibiting tryptophan hydroxylase 1 in the ENS and consequently decreasing 5-HT synthesis, disrupting neurotransmitter balance, and exacerbating GIMDs [120]. Metabolomic studies have revealed substantial enrichment of pro-inflammatory metabolites (e.g., phenylacetic acid and p-cresol sulfate) in fecal samples from patients with GIMDs; consequently, a pro-inflammatory metabolite-inflammation vicious cycle further disrupts the intestinal barrier, activates the TLR4/NF- κ B pathway, and drives chronic inflammation [121, 122]. This process not only affects gastrointestinal motility but also is closely associated with the pathogenesis and progression of multiple diseases, including inflammatory bowel disease, IBS, and neurodegenerative disorders [123, 124].

3. THERAPEUTIC STRATEGIES IN MODERN MEDICINE AND TRADITIONAL CHINESE MEDICINE

The precision treatment of GIMDs requires in-depth understanding of pathogenesis, integrating targeted interventions from modern medicine with the multidimensional regulatory advantages of TCM to develop individualized, stage-specific therapeutic approaches. The following sections discuss advancements in modern medicine, TCM innovations, and integrated TCM and modern medicine strategies.

3.1 Current status of modern medical therapeutics for GIMDs

3.1.1 Targeted regulation of prokinetic drugs.

3.1.1.1 5-hydroxytryptamine (serotonin) receptor 4 receptor agonists

The 5-hydroxytryptamine (serotonin) receptor 4 (5-HT₄) receptor agonists, such as mosapride and prucalopride, play major roles in regulating gastrointestinal function, particularly in enhancing lower esophageal sphincter pressure, accelerating gastric emptying, and ameliorating symptoms of FD and GERD [125-127]. These agonists promote the release of neurotransmitters such as acetylcholine, thereby strengthening gastrointestinal motility [72, 128]. Mosapride stimulates 5-HT₄ receptors to promote gastric motility and accelerate gastric emptying [129, 130]. Additionally, combination therapy with mosapride and proton pump inhibitors has been extensively studied for GERD. Combination therapy has been found to improve esophageal peristaltic function and decrease gastric acid reflux [130, 131].

In summary, 5-HT₄ receptor agonists, as prokinetic agents, have clinical value in improving lower esophageal sphincter pressure, accelerating gastric emptying, and alleviating symptoms of FD and GERD. However, their practical application requires comprehensive evaluation of individual patient factors, disease

characteristics, and potential drug risks to formulate optimal treatment strategies.

3.1.1.2 Dopamine receptor antagonists

Dopamine is a neurotransmitter with critical roles in modulating GIMDs [132]. Dopamine receptor antagonists, such as domperidone, enhance gastrointestinal motility by blocking the inhibitory effects of dopamine within the gastrointestinal tract [133].

Domperidone, a peripherally acting dopamine D2 receptor antagonist, compared with other dopamine receptor antagonists (e.g., metoclopramide), exhibits limited penetration of the blood-brain barrier and therefore elicits fewer extrapyramidal adverse effects [134]. This characteristic confers a favorable safety profile for long-term oral administration. Clinical studies have demonstrated domperidone's efficacy in treating gastroparesis [135]. However, its use has become controversial in recent years, because of safety concerns, particularly its potential arrhythmogenic risk [12]. Therefore, careful evaluation of patient-specific risk factors and vigilant monitoring for cardiac adverse effects are imperative in clinical practice. Furthermore, in the treatment of GIMDs, prokinetic agents such as domperidone are often combined with proton pump inhibitors to enhance therapeutic efficacy [136]. However, the use of prokinetic drugs in critically ill patients receiving enteral nutrition requires further research to clarify their effectiveness and safety.

In summary, domperidone, a dopamine D2 receptor antagonist, has clinical value in regulating gastrointestinal motility. Nevertheless, its potential cardiac risks warrant heightened vigilance. Future research should focus on developing safer, more effective novel dopamine receptor antagonists and on elucidating the precise mechanisms of dopamine receptors in various gastrointestinal diseases.

3.1.1.3 Novel ion channel modulators

Linaclotide, a novel ion channel modulator, activates the guanylate cyclase-C receptor and consequently stimulates intestinal fluid secretion and accelerates peristalsis; therefore, it is used as a first-line therapeutic agent for constipation-predominant IBS-C [137, 138]. Linaclotide, characterized by low oral bioavailability, exerts its effects locally within the gastrointestinal tract. By activating guanylate cyclase-C receptors, it increases intracellular cyclic guanosine monophosphate levels, thereby promoting intestinal fluid secretion, accelerating colonic transit, and potentially decreasing visceral pain sensitivity [139, 140]. Clinical trials have demonstrated its ability to markedly improve stool frequency, stool consistency, abdominal pain, bloating, and overall quality of life in patients with IBS-C [141]. As a novel intestinal secretagogue, linaclotide offers advantages including rapid onset of action, consistent efficacy, and a favorable tolerability profile. However, this treatment has limitations: some patients experience adverse

effects such as diarrhea, and the long-term safety and efficacy of linaclotide require further investigation [142, 143].

With advancing insights into the pathogenesis of IBS-C, innovative drugs may be developed to target diverse molecular pathways. Concurrently, deeper exploration of linaclotide's mechanisms of action might reveal novel clinical applications, such as potential utility in other functional gastrointestinal disorders or visceral pain syndromes. Furthermore, structural optimization and improvements in drug delivery systems might further enhance the therapeutic efficacy and safety of linaclotide.

3.1.2 Microbiota-gut-brain axis intervention. Interventions based on the microbiota-gut-brain axis theory, such as fecal microbiota transplantation and combined probiotics/prebiotics therapy, offer novel approaches to ameliorate GIMDs and related neuropsychiatric symptoms [144]. Fecal microbiota transplantation restores gut microbial balance by introducing healthy donor microbiota, enhancing SCFA metabolism, and consequently regulating intestinal motility and immune responses; moreover, microbial metabolites (e.g., gamma-aminobutyric acid and 5-HT precursors) modulate CNS function [145]. However, clinical application requires caution regarding infection risks and donor standardization. Probiotics (e.g., *Bifidobacterium* and *Lactobacillus*) combined with prebiotics suppress pathogens, decrease inflammatory cytokines, strengthen the gut barrier, and influence gut-brain signaling via tryptophan metabolism [146]. Nonetheless, because treatment efficacy depends on strain specificity and individual variations, personalized strategies guided by metagenomic profiling are necessary.

Future studies should further investigate the mechanism of action of SCFAs in multiple disease models and develop precise intervention strategies targeting the microbiota-metabolite axis to improve the therapeutic outcomes of GIMDs and related diseases. For example, modulating the composition of the gut microbiota and the production of SCFAs through dietary fiber supplementation or probiotic interventions might be an effective approach to treat GIMDs and chronic inflammation. In addition, the specific molecular mechanisms of the inflammation-microbiota axis in GIMDs can be explored in depth to clarify the roles of key inflammatory mediators, microbial species, and their metabolites. More precise diagnostic methods must be developed that combine gut microbiota analysis with inflammatory biomarker detection for early diagnosis and personalized treatment. In addition, existing intervention strategies must be optimized, such as by designing more effective probiotics and prebiotics, and exploring new therapeutic approaches, including microbial metabolite-based drug development. These advances would expand the range of therapeutic options for GIMDs and increase efficacy.

3.1.3 Neuromodulation technologies. Neuromodulation technologies offer innovative therapeutic approaches for refractory gastrointestinal disorders. In gastroparesis, vagus nerve stimulation activates the vagal-enteral pathway via electrical impulses, enhances antral contractions and small intestinal propulsive motility, and ultimately alleviates delayed gastric emptying; however, its long-term efficacy and device tolerance require further validation [147-149]. For functional GIMDs (e.g., IBS and FD) with comorbid psychological factors (e.g., anxiety or depression), selective serotonin reuptake inhibitors (such as fluoxetine) modulate central and enteric 5-HT levels, and consequently decrease visceral hypersensitivity and GIMDs [150]. When combined with cognitive behavioral therapy, which targets maladaptive symptom-related cognitions and avoidance behaviors, this dual approach achieves bidirectional improvement in psychological state and gastrointestinal function [151]. Selective serotonin reuptake inhibitors and cognitive behavioral therapy have been found to synergistically decrease symptom severity and relapse rates, but individualized evaluation of drug adverse effects (e.g., gastrointestinal discomfort or sexual dysfunction) and adherence to psychological interventions is required [151]. Future research may focus on closed-loop neuromodulation (e.g., responsive vagus nerve stimulation) and precision applications of multimodal mind-body therapies.

3.2 TCM therapeutics for GIMDs

TCM conceptualizes GIMDs through syndrome patterns reflecting systemic functional imbalances. TCM theory attributes the core pathogenesis to "disorder in the ascending-descending movement of Qi in the spleen and stomach," which is closely associated with pathological factors such as liver stagnation, damp-heat accumulation, and toxin stasis [152]. Additionally, non-pharmacological therapies such as acupuncture play major roles in GIMD management. Therefore, TCM interventions, emphasizing multidimensional regulation, are a highly promising therapeutic approach worthy of further investigation [153].

3.2.1 Classical TCM formulae.

3.2.1.1 Ban-Xia-Xie-Xin decoction

Ban-Xia-Xie-Xin decoction (BXXXD), combining cold (e.g., *Coptis chinensis* Franch. (Huanglian)) and hot herbs (e.g., *Zingiber officinale* Rosc. (Ganjiang)), balances acid secretion, whereas *Pinellia ternata* (Thunb.) Breit. (Banxia) promotes gastric emptying, and alleviates acid reflux and epigastric fullness. Numerous clinical studies have demonstrated that BXXXD effectively alleviates core symptoms of FD, including bloating, early satiety, belching, and loss of appetite [154]. Its therapeutic mechanism is associated with enhanced motilin secretion and promotion of gastric emptying [155].

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Furthermore, BXD's favorable safety profile highlights its potential in the treatment of FD [156].

Animal studies have shown that BXXXD enhances gastric motility in rats by upregulating miRNA-451-5p in ICC, activating the stem cell factor/c-kit signaling pathway, and consequently promoting ICC proliferation and inhibiting apoptosis [157]. BXXXD also partially reverses abnormalities in the ENS and small intestinal ICC, enhances c-kit expression, and stimulates motilin and substance P secretion, thereby maintaining normal gastrointestinal biological functions and ameliorating GIMDs in diabetic rats [158, 159]. Furthermore, BXXXD enhances gastric motility in diabetic gastroparesis mice by suppressing AGE levels and RAGE expression, promoting nNOS expression, and ultimately regulating the proliferation of ICCs and ICC stem cells [160].

3.2.1.2 Bu-Zhong-Yi-Qi decoction

Bu-Zhong-Yi-Qi decoction (BZYQD), a well-known compound TCM prescription for "tonifying Qi" and "rising Yang," is used to treat GIMDs such as constipation. BZYQD uses *Astragalus membranaceus* (Fisch.) Bge. (Huangqi) and *Codonopsis pilosula* (Franch.) Nannf. (Dangshen) to enhance vagal tone and promote antral contractions, whereas *Cimicifuga foetida* L. (Shengma) and *Bupleurum chinense* DC. (Chaihu) lift middle Qi and ameliorate motility deficits in gastric ptosis. This treatment is commonly prescribed for diabetic gastroparesis [161]. Metabolomics studies have revealed that the amelioration of GIMDs in spleen-deficient rats by BZYQD might be associated with its influences on metabolite profiles and regulation of glutamine metabolism, primary bile acid biosynthesis, unsaturated fatty acid biosynthesis, and amino acid metabolism [162]. In a loperamide-induced rat constipation model, BZYQD has been found to regulate the arachidonic acid pathway by inhibiting the NF- κ B signaling pathway, and to decrease levels of inflammatory factors, such as interleukin-1 β (IL-1 β) and TNF- α , in the serum and colon. Moreover, BZYQD treatment increases serum levels of inositol, motilin, and gastrin, and promotes gastrointestinal motility [163]. The above pharmacological studies have indicated that BZYQD can improve GIMDs by decreasing levels of inflammatory factors, enhancing immune function, and regulating levels of gastrointestinal hormones.

3.2.1.3 Chai-Hu-Shu-Gan San

Chai-Hu-Shu-Gan San (CHSGS) is a classic formula for destressing the liver and relieving depression, promoting Qi, relieving pain, strengthening the spleen, and harmonizing the stomach. It consists of seven types of Chinese herbal medicines: *Bupleurum chinense* DC. (Chaihu), *Citrus reticulata* Blanco (Chenpi), *Ligusticum Szechuanense* Hort. (Chuanxiong), *Citrus aurantium* L. (Zhiqiao), *Cyperus rotundus* L. (Xiangfu), *Cynanchum otophyllum* Schneid. (Baishao), and *Glycyrrhiza uralensis* Fisch. (Gancao).

In clinical studies on patients with FD with liver Qi stagnation syndrome, CHSGS treatment significantly increases motilin levels, decreases CRH levels, and improves gastrointestinal motility [164, 165]. Additionally, CHSGS alleviates symptoms such as bloating and loss of appetite in patients with FD by downregulating the abundance of *Blautia* in the gut microbiota, thus indirectly indicating its ability to modulate gastric emptying time and influence intestinal peristalsis [166]. Animal studies have further demonstrated that CHSGS enhances gastric emptying and small intestinal motility by upregulating postprandial motilin and leptin levels, while decreasing CRH production, thereby alleviating visceral hypersensitivity [167]. Ferulic acid, an active compound in the formula, has also been confirmed to ameliorate GIMDs [168].

3.2.1.4 Da-Cheng-Qi decoction

Da-Cheng-Qi decoction (DCQD), a powerful formula for excess heat and stagnation, consists of four components: *Rheum palmatum* L. (Dahuang), *Magnolia officinalis* Rehd. Et Wilis. (Houpo), *Citrus aurantium* L. (Zhiqiao), and sodium sulfate crystals. DCQD contains anthraquinones, which directly stimulate the enteric plexus and enhance colonic propulsive motility. The volatile oils synergistically relieve intestinal spasms. This treatment is clinically used for acute intestinal obstruction or post-operative ileus to restore motility [169-171]. Studies have also demonstrated that DCQD can effectively regulate gastrointestinal hormones, mitigate smooth muscle injury in the gastrointestinal tract, protect or repair ICC, enhance intestinal peristalsis, and promote recovery from GIMDs [172].

3.2.1.5 Si-Mo decoction

Si-Mo decoction (SMD), a classic empirical formula for regulating Qi and alleviating bloating, consists of four herbs: *Panax ginseng* C. A. Mey. (Renshen), *Aquilaria sinensis* (Lour.) Gilg (Chenxiang), *Lindera aggregata* (Sims) Kosterm (Wuyao), and *Areca catechu* L. (Binlang). Numerous clinical studies have demonstrated that SMD exhibits significant therapeutic efficacy in treating FD and has a favorable safety profile. Its mechanism in alleviating FD in patients with liver-spleen Qi stagnation syndrome may be associated with the modulation of serum levels of somatostatin and substance P [173].

SMD has been suggested to promote gastric emptying by facilitating the release of substances, such as motilin and substance P [174]. Furthermore, SMD ameliorates GIMDs in diabetic rats, potentially through a mechanism of action involving upregulation of substance P and downregulation of VIP and nNOS [175].

3.2.1.6 Shen-Ling-Bai-Zhu San

Shen-Ling-Bai-Zhu San (SLBZS) is a classic formula for treating spleen deficiency with a dampness exuberance pattern. Its core functions are to fortify Qi, strengthen

the spleen, drain dampness, and stop diarrhea. The formula consists of the following herbs: *Panax ginseng* C.A.Mey. (Renshen), *Poria cocos* (Schw.) Wolf (Fuling), *Atractylodes macrocephala* Koidz. (Baizhu), *Dioscorea opposita* Thunb. (Shanyao), *Dolichos Lablab* L. (Baibiandou), *Nelumbo nucifera* Gaertn. (Lianzi), *Coix lacryma-jobi* L. var. *ma-yuen* (Rom.Caill.) Stapf (Yiyiren), *Amomum villosum* Lour. (Sharen), *Platycodon grandiflorum* (Jacq.) A.DC. (Jiegeng), and *Glycyrrhiza uralensis* Fisch. (Gancao). Clinical studies have revealed that SLBZS exhibits therapeutic effects on FD with spleen deficiency and Qi stagnation syndrome, and its mechanism is associated with increased neuropeptide Y and motilin levels, decreased serotonin levels, as well as modulation of gastric myoelectric activity [176].

SLBZS modulates the gut microbiota by enhancing SCFA synthesis via *Poria cocos* (Schw.) Wolf (Fuling) and *Atractylodes macrocephala* Koidz. (Baizhu), thereby improving colonic motility and ameliorating antibiotic-associated diarrhea in rats. SLBZS has been found to restore intestinal homeostasis in diarrheal models by reconstructing the gut microbial architecture and enriching beneficial bacterial populations [177]. Further investigation in an FD rat model has revealed that SLBZS administration normalizes microbiota dysbiosis, upregulates energy metabolism pathways, and mitigates oxidative stress and bacterial pathogenicity. Therefore, SLBZS might ameliorate dyspepsia and correct the composition and dysfunction of the gut microbiota, by treating dyspepsia via a gut microbiota route [178].

3.2.1.7 Tong-Xie-Yao Fang

Tong Xie Yao Fang (TXYF) is an effective formula for treating pain and diarrhea caused by deficiency in the liver and spleen. TXYF is composed primarily of *Atractylodes macrocephala* Koidz. (Baizhu), *Cynanchum otophyllum* Schneid. (Baishao), *Citrus reticulata* Blanco (Chenpi), and *Saposhnikovia divaricate* (Turcz) Schischk (Fangfeng). In recent years, TXYF has been clinically demonstrated to be effective in relieving the symptoms of IBS [179].

TXYF decreases the expression of 5-HT and substance P, regulates ENS activity, and improves IBS [180]. TXYF regulates the Cl^- - and HCO_3^- secreted by colon mucosa through Cl^- channels, $\text{Cl}^-/\text{HCO}_3^-$ exchangers, NBC, and NKCC of CFTR, thereby ameliorating IBS [181]. In addition, TXYF ameliorates IBS-D in rats by inhibiting apoptosis through regulating the general control non-derepressible 2/Perk-eIF2 α -activating transcription factor 4 signaling pathway, which is activated by amino acid deficiency and endoplasmic reticulum stress [182]. In addition, 16S rRNA sequencing analyses and fecal transplantation experiments have suggested that TXYF decreases 5-HT levels in the colon and alleviates IBS-D symptoms by modulating microbiota levels in the gut microbiota [183].

3.2.1.8 Wei Chang An

Wei Chang An (WCA), a commercial drug approved by the China Food and Drug Administration, has been widely used for GIMD treatment for decades. WCA has been reported to reduce the defecation frequency in mice with castor oil-induced diarrhea, accelerate intestinal transit, and inhibit gastric emptying in mice with neostigmine or 5-fluorouracil-induced diarrhea [184–186]. In addition, WCA ameliorates diarrhea and constipation by modulating the levels of NO, VIP, substance P, and 5-HT [187].

In conclusion, TCM formulae (e.g., DCQD or Chai-Hu-Shu-Gan San) have been clinically and experimentally demonstrated to be effective for GIMDs through their multi-component and multi-target synergistic effects. The advantages of these treatments lie in the overall regulation (e.g., shunning the liver and regulating qi, strengthening the spleen, and dissolving dampness) rather than single-target intervention, in line with the multifactorial pathology of GIMDs. However, owing to the complexity of the composition of TCM formulas, further study is necessary to clarify the core functional components and synergistic mechanisms; focus on the component-mechanism-disease research paradigm; and promote the transition from empirical formulas to precision medicine by combining traditional experience with modern technology, thereby promoting a transformation from empirical prescription to precision medicine, and providing safer and personalized solutions for GIMDs.

3.2.2 Acupuncture and acupoint stimulation. Modern medical research has systematically elucidated the regulatory effects of acupuncture and acupoint stimulation on gastrointestinal function. The core mechanisms involve synergistic modulation across multi-level neural networks. Among classic acupoint combinations, the triad of Zusanli (ST36), Neiguan (PC6), and Zhongwan (CV12) has exceptional synergistic efficacy.

3.2.2.1 ST36: a vagus nerve regulatory hub

ST36, a critical regulator of the vagus nerve, activates the cholinergic pathway of the deep peroneal nerve and specifically stimulates the nucleus tractus solitarius and dorsal motor nucleus of the vagus [188]. Functional magnetic resonance imaging studies have revealed that stimulation at this acupoint achieves a 78% activation rate, thus effectively decreasing postoperative bowel sound recovery time from 18 hours to 12 hours. Electroacupuncture at ST36 may activate the $\alpha 7$ nicotinic acetylcholine receptor on intestinal macrophages via the cholinergic anti-inflammatory pathway, thereby suppressing inflammatory responses. Additionally, it may alleviate intestinal ischemia-reperfusion injury by inducing microRNA-124, which in turn inhibits the signal transducer and activator of transcription 3 (STAT3)/IL-6 signaling pathway [189]. Furthermore, electroacupuncture at ST36 has been shown to modulate gastric

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motility through protein kinase C and MAPK signaling transduction pathways [190].

3.2.2.2 PC6: suppression of gastric acid secretion

PC6 inhibits gastric acid secretion through the spinal-hypothalamic-pituitary axis. Clinical data have demonstrated a 43% decrease in gastrin levels and significant alleviation of functional dyspepsia symptoms. Moreover, acupuncture stimulation at PC6 and ST36 modulates the activity of gastric-related neurons in the paraventricular nucleus of the hypothalamus in rats with gastric distension [191].

3.2.2.3 CV12: enhancement of gastric motility

CV12 enhances gastric motility by activating TRPV1 channels to induce motilin release [192]. When combined with ST36, this acupoint elevates gastric emptying in rats, as supported by ultrasound evidence demonstrating an increase in gastric antral contraction amplitude. Electroacupuncture at CV12 and ST36 improves gastrointestinal function in permanent middle cerebral artery occlusion rats by modulating cholinergic efferent signals in the dorsal vagal complex, thereby driving vagus nerve activity [193].

3.2.2.4 Synergistic effects and clinical applications

This synergistic approach via electroacupuncture at ST36, PC6, and CV12 achieves comprehensive intervention spanning ANS balance and gastrointestinal motility enhancement [194, 195]. Multiple studies have demonstrated that electroacupuncture at single or multi-acupoint combinations significantly accelerates gastrointestinal functional recovery in patients undergoing laparoscopic cholecystectomy [196]. For individuals with FD, acupuncture at ST36 improves gastric emptying and modulates hormone levels, including motilin and somatostatin [197]. A randomized controlled trial has further highlighted the efficacy of neostigmine injection at ST36 in treating paralytic postoperative ileus after radical gastrectomy for gastric cancer [198].

In conclusion, the classic combination of ST36, PC6, and CV12 exhibits remarkable synergistic effects in improving gastrointestinal function through multi-level neural regulatory mechanisms, thereby offering critical insights for clinical practice [199]. This triad exemplifies how targeted acupoint interventions can integrate autonomic, central, and ENS modulation to address complex GIMDs, thus bridging traditional acupuncture theory to evidence-based therapeutic strategies. Future research should investigate synergistic interactions between acupuncture and other therapeutic modalities, such as herbal medicine and dietary interventions, to develop holistic and comprehensive treatment protocols [200]. This exploration would enhance understanding of integrative medicine approaches and might enable optimization of therapeutic outcomes for complex gastrointestinal disorders through multi-modal synergy.

4. CONCLUSION AND FUTURE PERSPECTIVES

GIMDs, as multifactorial and multi-mechanistic clinical syndromes, involve complex pathophysiological interactions, including dysregulated neural modulation, smooth muscle dysfunction, neurotransmitter imbalance, chronic inflammation, and gut microbiota dysbiosis [201-203]. In recent years, the role of the mechanosensitive ion channel Piezo1 in gastrointestinal motility regulation has garnered increasing attention [204, 205]. As a mechanically gated calcium channel, Piezo1 not only participates in transmitting mechanical sensing signals in the gut but also directly modulates smooth muscle contraction and ENS activity through calcium influx [206]. Piezo1 dysfunction has been suggested to contribute to GIMDs [207]. This discovery offers novel insights into GIMD mechanisms and highlights Piezo1 as a potential therapeutic target. Moreover, recent breakthrough research has demonstrated a novel strategy for cell therapy in GIMDs. In that work, human pluripotent stem cells were used to construct a functional model of the ENS, and this model was used to identify key signaling pathways and regulatory drugs promoting the differentiation of nitrergic neurons (which release NO) [208]. Ultimately, transplantation of these stem-cell-derived nitrergic neurons into mice significantly improved gastrointestinal motility [208]. Transplant experiments confirmed that the human-derived neurons integrated into the host's intestinal neural circuitry and markedly alleviated motility dysfunction. This pioneering work provides a new therapeutic strategy for enteric neuropathies and new hope for patients with GIMDs.

The prevention and treatment of GIMDs involve multiple approaches, most prominently modern medicine and TCM. Modern medicine, the current mainstream approach, is favored for its stable efficacy and rapid onset. Currently, modern medical approaches to alleviate GIMDs include 1) targeted modulation of prokinetic agents (e.g., 5-HT₄ receptor agonists, dopamine receptor agonists, and ion channel modulators); 2) microbiota-gut-brain axis interventions (e.g., fecal microbiota transplantation and probiotic/probiotic combination therapies); and 3) neuromodulatory techniques (e.g., selective serotonin reuptake inhibitors). Because of the multifactorial and multistep pathogenesis of GIMDs, single-target therapies are often insufficient. Consequently, clinical management relies primarily on multi-drug regimens tailored to disease type and severity. However, this approach has substantial limitations, including high costs and severe adverse effects that limit its clinical utility. For example, the use of prokinetic agents is often hampered by serious adverse reactions that compromise patient adherence. A key example is domperidone, which is associated with elevated risk of sudden cardiac death and ventricular arrhythmia [12].

TCM, as a complementary and alternative therapy, has gained attention for its ability to ameliorate GIMDs while systematically controlling toxicity. Yet the clinical

research on TCM for GIMDs is relatively scarce and of lower quality than modern medicine research. The complex chemical composition of TCM, derived from multiple sources, poses challenges in ensuring batch-to-batch consistency in formula composition, purity, and potency, as well as in identifying key components for meaningful clinical trials. To address these challenges, researchers use comprehensive strategies, such as selecting single or multiple components as evaluation indicators, and establishing chromatographic fingerprinting methods such as thin-layer chromatography, gas chromatography, high-performance liquid chromatography, and capillary electrophoresis [209]. Professor Liu Changxiao's introduction of the concept of quality markers (Q-Markers) for TCM in 2016 further strengthened the links among clinical efficacy, safety, and quality consistency of TCM [210]. Additionally, network pharmacology, systems biology, and correlation analysis can be integrated to establish a TCM quality control system based on Q-Markers [211]. Building on this foundation of quality control, integrating network pharmacology, systems biology, and correlation analysis enables the construction of a component-target-pathway-disease network. This systematic approach is critical for scientifically elucidating the mechanisms of action of TCM formulae in GIMD treatment. Greater emphasis must be placed on such integrated basic and clinical research, to clarify these mechanisms and advance applications of TCM in GIMDs.

Integrating TCM into clinical practice and advancing its internationalization are crucial for overcoming current bottlenecks in GIMD treatment. To achieve this goal, a multi-faceted and stage-specific strategy is essential. Drawing on the application of integrated TCM and Western medicine in oncology [212], we propose a structured framework for GIMD management. During the acute phase, Western medicine is the primary treatment mode, and TCM plays a synergistic role in decreasing adverse effects and enhancing efficacy; in the remission or prevention phase, TCM assumes the dominant role through holistic regulation to prevent recurrence. Furthermore, inspired by Academician Chen Xiangmei's integrative method, an individualized treatment path can be established by combining Western diagnosis, TCM syndrome patterns, and biomarker profiling [213]. To validate such strategies, a combined efficacy evaluation system incorporating both Rome IV criteria and TCM syndrome scoring should be established [214, 215]. Large-scale, multi-center randomized controlled trials are warranted to assess the long-term benefits of TCM interventions for specific GIMD subtypes. In summary, GIMD research has entered an era of multi-disciplinary integration, wherein the holistic and multi-target advantages of TCM offer innovative solutions to current therapeutic limitations [216]. Future efforts may leverage modern technologies to transition from evidence-based medicine to precision medicine, a paradigm shift propelled by breakthroughs ranging from novel target

discovery (e.g., Piezo1) and regenerative approaches such as stem-cell-derived neuronal transplantation, complemented by the fruitful dialogue between TCM's holistic, syndrome-based treatment principles and the targeted, mechanistic approach of modern medicine.

ABBREVIATIONS

Ach, acetylcholine; AGEs, advanced glycation end-products; ANS, autonomic nervous system; BXXXD, Ban-Xia-Xie-Xin decoction; BZYQD, Bu-Zhong-Yi-Qi-decoction; BKCa, large-conductance calcium-activated potassium; CNS, central nervous system; c-kit, C-cytokine receptor; CRH, corticotropin-releasing hormone; CIPO, chronic intestinal pseudo-obstruction; Cav1.2, L-type calcium channels; CHSGS, Chai-Hu-Shu-Gan San; CV12, Zhongwan; CFTR, cystic fibrosis transmembrane conductance regulator; DCQD, Da-Cheng-Qi decoction; ENS, enteric nervous system; FD, functional dyspepsia; GIMDs, gastrointestinal motility disorder; GERD, gastroesophageal reflux disease; HPA axis, hypothalamic-pituitary-adrenal axis; iNOS, inducible NO synthase; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IL-6, interleukin-6; ICC, interstitial cells of Cajal; K2P, two-pore-domain potassium channel; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; NBC, $\text{Na}^+\text{-HCO}_3^-$ cotransporter; NKCC, $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter; NO, nitric oxide; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NF- κ B, nuclear factor kappa-B; POI, post-operative ileus; Piezo1, Piezo-type mechanosensitive ion channel component 1; PC6, Neiguan; RAGE, receptor for AGE; ROS, reactive oxygen species; SLBZS, Shen-Ling-Bai-Zhu San; SMD, Si-Mo decoction; SMC, smooth muscle cells; SCFA, short chain fatty acid; ST36, Zusanli; STAT3, signal transducer and activator of transcription 3; TXYP, Tong-Xie-Yao Fang; TCM, traditional Chinese medicine; TNF- α , tumor necrosis factor- α ; TRPV4, transient receptor potential cation channel subfamily V member 4; TLR4, toll-like receptor 4; VIP, vasoactive intestinal peptide; WCA, Wei Chang An; 5-HT, 5-hydroxytryptamine; 5-HT4, 5-hydroxytryptamine (serotonin) receptor 4.

FUNDING

This article was funded by the National Natural Science Foundation of China (No. 82174143) and Innovative Team Project of Ordinary Universities in Guangdong Province (No. 2022KCXTD016).

ACKNOWLEDGMENTS

All figures and the graphical abstract were created in BioRender.com.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported herein.

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