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Review

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New perspectives on microbiome-dependent gut-brain pathways for the treatment of depression with gastrointestinal symptoms: from bench to bedside

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Abstract: Patients with depression are more likely to have chronic gastrointestinal (GI) symptoms than the general population, but such symptoms are considered only somatic symptoms of depression and lack special attention. There is a chronic lack of appropriate diagnosis and effective treatment for patients with depression accompanied by GI symptoms, and studying the association between depression and GI disorders (GIDs) is extremely important for clinical management. There is growing evidence that depression is closely related to the microbiota present in the GI tract, and the microbiota-gut-brain axis (MGBA) is creating a new perspective on the association between depression and GIDs. Identifying and treating GIDs would provide a key opportunity to prevent episodes of depression and may also improve the outcome of refractory depression. Current studies on depression and the microbially related gut-brain axis (GBA) lack a focus on GI function. In this review, we combine preclinical and clinical evidence to summarize the roles of the microbially regulated GBA in emotions and GI function, and summarize potential therapeutic strategies to provide a reference for the study of the pathomechanism and treatment of depression in combination with GI symptoms.

Key words: Depression; Gastrointestinal disorders; Gut-brain axis; Pathomechanism; Treatment

1 Introduction

Depression is a common mood disorder, with the World Health Organization (WHO) ranking it as the third largest contributor to the global burden of disease and predicting that the disorder will rank first by 2030 (Malhi and Mann, 2018). The lifetime prevalence of depression is 15%–18% (Bromet et al., 2011; Kessler and Bromet, 2013). The most likely period for the first onset of depression is from adolescence to the late 40s, with the prevalence in women almost twice as high as in men. The surge in depression cases during the global coronavirus disease 2019 (COVID-19) pandemic has further increased the burden of disease. In addition to major psychological symptoms, depression often presents with medically unexplained somatic symptoms involving multiple systems, such as digestive, respiratory, and circulatory systems, causing many complaints and distress (Yan et al., 2022). Gastrointestinal (GI) symptoms are among the most prominent somatic symptoms in patients with psychiatric disorders (Maguen et al., 2014; Zvolensky et al., 2018; Bjørklund et al., 2020). The appropriate diagnosis and effective treatment of depression with GI symptoms are chronically lacking in outpatient services. The primary complaint of somatic symptoms increases the difficulty of identifying depression, and it is more difficult to obtain effective treatment for patients with somatic symptoms than for patients without somatic symptoms (Smith, 2014). Most patients are diagnosed

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with unilateral depression or GI disorders (GIDs), resulting in delayed or even ineffective treatment. This not only brings a huge socio-economic burden but also seriously affects patients' quality of life.

Similarly, GI symptoms are very common in outpatient clinics and include abdominal pain, diarrhea, constipation, bloating, fullness, nausea, and vomiting. GID is a spectrum of diseases that combine both kinetic alterations and organic lesions, including functional GIDs (FGIDs), gastroesophageal reflux disease (GERD), gastritis, peptic ulcer disease (PUD), and inflammatory bowel disease (IBD) (Zhang et al., 2018). Epidemiological surveys have shown that in 50% of cases, FGIDs begin with psychological distress followed by GI symptoms, while in the other 50% of cases, intestinal dysfunction occurs first, followed by psychological distress (Koloski et al., 2012, 2016; Jones et al., 2017). At present, it is unclear whether depressed mood or GI symptoms occur first in depressed patients with GI symptoms. Recently, a European-based Mendelian randomization study evaluated the potential causality of major depressive disorder (MDD) with GERD, irritable bowel syndrome (IBS), PUD, and non-alcoholic fatty liver disease (NAFLD). The analysis found that gene-predicted MDD may increase the risk of GERD, IBS, PUD, and NAFLD. Genetic prediction of GERD or IBS may increase the risk of MDD (Chen et al., 2023). Another Mendelian randomization study systematically explored the association between depression and 24 GIDs. The results suggested that depression may play a causal role in many GIDs (Ruan et al., 2023).

From the above epidemiologic findings, it is clear that GI symptoms are not simply a somatic symptom accompanying depression. Current treatments focus on psychological and GI symptoms rather than identifying and addressing specific underlying pathological mechanisms. In this review, we summarize the role of the microbially regulated GBA in mood and GI function. This could help elucidate the mechanisms of MDD and GI comorbidities and may provide better potential treatment options in the clinic.

2 Bidirectional relationship between depression and GIDs

2.1 Clinical symptoms

There is a strong clinical association between depressed mood and GI symptoms. Among depressed patients over 60 years of age, 75% had GI comorbidities, with the strongest correlations with diseases such as IBD, PUD, and diverticulosis, and the strongest correlations for symptoms including anorexia, vomiting/nausea, constipation, flatulence, dysphagia, abdominal pain, indigestion, and heartburn (Aguado and del Álamo, 2020). In subjects with depressive episodes, more than 70% had GI symptoms, and multiple linear regression analysis showed that suicidal ideation, anxiety, insomnia, anger, feelings of failure, and physical pain were independently associated with GI symptoms in depressed patients (Huang J et al., 2021). Notably, studies have found that depressive symptoms in mothers are associated with GI symptoms in infants (de Kruijff et al., 2019), which seems to suggest a role for gut microbiota. GI issues can also have an impact on a patient's physical and mental well-being. A cross-sectional study showed that 29%, 31%, 16%, and 15% of patients presenting with GI symptoms had mild, moderate, severe, and very severe depressive symptoms, respectively (Saha et al., 2021). GI symptoms may be a risk factor for depression (Avramidou et al., 2018; Wen et al., 2019). The probability of developing depression increased with age, stress, daily restrictions, and GIDs, and having GI problems increased the chance of suffering from depression by 7% (Cantarero-Prieto and Moreno-Mencia, 2022). The study found that the severity of depressive symptoms was independently associated with total GI symptom burden (Söderquist et al., 2020).

2.2 Microbiota's role in GIDs and depression

A meta-analysis in 2020 showed that Prevotellaceae, *Corprococcus*, and *Faecalibacterium* were all decreased in MDD patients compared to controls (Sanada et al., 2020). Alpha-diversity and beta-diversity in the microbiota of depressed patients were found to differ from those of healthy controls (Barandouzi et al., 2020). Bacteroides species in the gut microbiome of MDD patients can influence susceptibility to depression (Zhang YY et al., 2022). The systematic review identified 17 studies (10 human and 7 animal studies) that evaluated gut microbiota and anxiety/depressive symptoms among the IBS cohort, with lower alpha-diversity in patients with IBS combined with anxiety/depressive symptoms than in controls and the IBS-only group (Simpson et al., 2020). A model of chronic mild social defeat stress leads to alterations in the composition

of the gut microbiota (McGaughey et al., 2019). Fecal microbial transplantation (FMT) improves depression-like symptoms through metabolic and inflammatory pathways (Kelly et al., 2016; Pearson-Leary et al., 2020). The fecal microbiota of patients with IBS with diarrhea (IBS-D) and depression are similarly altered, which may be related to the pathogenesis of the disease (Liu et al., 2016).

3 Microbiome impact on gut-brain pathway in depression and GIDs

The relationship between the GI tract and the brain has been the subject of important research, and the specific link between the GI tract and the central nervous system (CNS) has been termed the gut-brain axis (GBA) (Stilling et al., 2014; Dinan and Cryan, 2017). The communication network between the gut and the CNS is complex and includes the enteric nervous system (ENS), sympathetic and parasympathetic nerves, and immunomodulatory and neuroendocrine signaling pathways (Dinan and Cryan, 2012; Foster et al., 2017; Li et al., 2018; Liang et al., 2018; Cryan et al., 2019). In recent years, the regulation of the GBA by the microbiota has attracted much attention. The microbiota regulates the host brain and behavior by affecting signaling pathways from the GI tract to the brain (Cryan et al., 2019). There is growing evidence that metabolic, endocrine, immune, and neural pathways contribute to the communication between gut microbes and the brain (Du et al., 2020).

3.1 Microbial derivatives

Gut microbes transform and metabolize molecules of dietary and host origin to produce a wide range of metabolites with local and systemic effects. They not only play an important role in the control of GI motility (Barbara et al., 2016), but also modify the homeostasis of the body in response to stressful conditions (Westfall and Pasinetti, 2019). The GI tract can express a range of receptors that can sense bioactive substances of different gut microbial origin, such as Toll-like receptors (TLRs), G-protein-coupled receptors (GPCRs), aryl hydrocarbon receptors (AhRs), and ligand-gated ion channels. These receptors can perceive cellular components and metabolites of microorganisms generally including lipopeptides, peptidoglycan (PGN), lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), bile acids (BAs) and tryptophan (Trp) (Fleshner et al., 2017; Ma et al., 2019). The regulation of GI motility (Zheng et al., 2022) and mood by the gut microbiota is mediated through interactions with the endocrine system, CNS, ENS, intestinal mucosal barrier, blood–brain barrier (BBB) (Braniste et al., 2014), intestinal smooth muscle, and immune system. Taken together, these findings highlight the roles of microbial derivatives in establishing microbiota-gut-brain axis (MGBA) communication and maintaining homeostasis within the host.

3.1.1 Microbe-derived cellular components

The cellular components produced by the degradation of microbiota are mainly polysaccharide A (PSA), LPS, or PGN on the surface of bacteria (Medzhitov, 2007; Boller and Felix, 2009). They affect GI motility by binding to certain isoforms of host TLRs. TLRs are expressed in enteric neurons, intestinal epithelial cells (IECs), enteric glial cells (EGCs), smooth muscle cells (SMCs), and innate immune cells. TLRs are innate immune receptors that are activated by exogenous or endogenous ligands to cause inflammation. One study found that repeated social defeat stress (R-SDS) activates microglia via TLR2 and TLR4 expressed in microglia in the medial prefrontal cortex (mPFC), thereby attenuating the stress response in mPFC neurons and inducing social avoidance via interleukin-1α (IL-1α) and tumor necrosis factor-α (TNF-α) (Nie et al., 2018). TLR2 and TLR4 are the most important bacterial sensing regulators of gut motility and ENS receptors, with TLR2 recognizing lipopeptides and PGN, and TLR4 recognizing LPS (Kawai and Akira, 2011).

TLR4 is the best receptor to recognize LPS. Injection of LPS can induce the establishment of animal models of depression (Fang et al., 2020; Tang et al., 2020; Li WF et al., 2021) and also induce an inflammatory response in the GI tract leading to smooth muscle dysfunction and GI paralysis. The binding of LPS to TLR4 expressed on muscle macrophages (MMs) can stimulate the release of bone morphogenetic protein 2 (BMP2), which regulates GI motility through activating BMP receptor (BMPR), and this is also influenced by colony-stimulating factor-1 (CSF-1) generated by enteric neurons to promote homeostasis in MMs. TLR2 can be expressed in enteric neurons, SMCs,

EGCs, and dendritic cells (DCs) (Wang et al., 2006). The binding of lipopeptides, PGN, and lipoteichoic acid to TLR2 stimulates the release of glial cell-derived neurotrophic factor (GDNF), maintains neurons and neurogenesis, acts as an anti-inflammatory agent, and improves GI motility (Brun et al., 2013). Mice treated with antibiotics showed decreased TLR2 expression in the intestine, delayed GI transit, and significantly reduced fecal excretion frequency (Grasa et al., 2015). TLR2 deficiency impairs recovery from depression-like states in male mice, and TLR2 and TLR4 act in opposite ways to balance mood-related stress responses (Medina-Rodriguez et al., 2020). Specific cell wall components of other commensal bacteria may also induce the viability of interstitial cells of Cajal (ICCs) by activating c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) signaling pathways in a TLR2-dependent way, thereby promoting GI motility (Sui et al., 2018) (Fig. 1).

3.1.2 Microbe-derived metabolites

Specific gut microbiota metabolites can alter the ratio of pro-inflammatory T helper 17 (Th17) cells to anti-inflammatory regulatory T (Treg) cells, thereby modulating the inflammatory response (Arpaia et al., 2013; Britton et al., 2019). The imbalance between Th17 and Treg cells is linked to the development of chronic stress-induced depression in mice (Hong et al., 2013). In addition to the modulation of the immune response, different metabolites can also bind to corresponding receptors to regulate GI function. The two most studied metabolites involved in host–microbiota interactions are SCFAs and metabolites of Trp (Blacher et al., 2017) (Fig. 2).

3.1.3 SCFAs

SCFAs are produced by the fermentation of dietary fibers such as complex carbohydrates in the intestine by microorganisms, including acetate, propionate, and butyrate (Koh et al., 2016; Dalile et al., 2019). Compared with healthy controls, depressed women had reduced levels of acetate and propionate and significantly higher level of isocaproic acid (Skonieczna-Żydecka et al., 2018). Butyrate was found to promote anti-inflammatory immune responses in depressed patients (Valles-Colomer et al., 2019). Sodium butyrate ameliorates LPS-induced depression-like behavior by inhibiting neuroinflammation and oxidative nitrosative

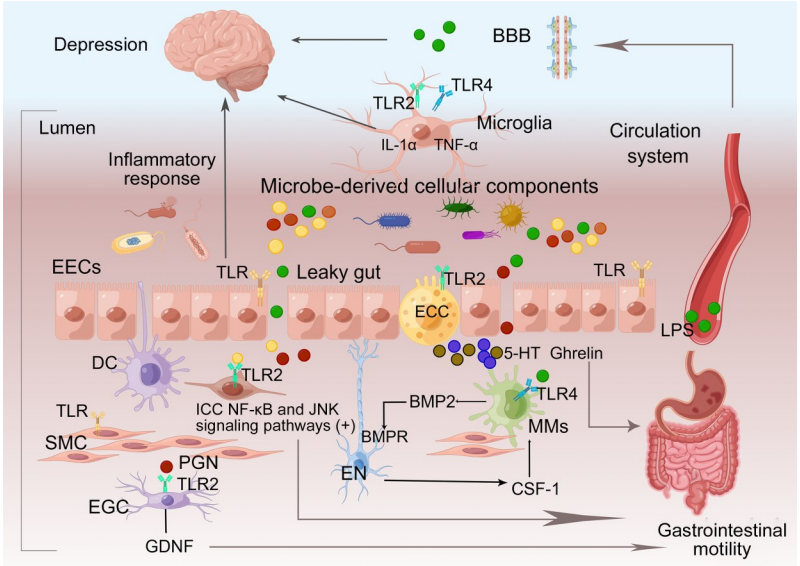

Fig. 1 Schematic overview of the effects of microbial-derived cellular components on the gastrointestinal (GI) tract and brain function. The lipopolysaccharide (LPS) and peptidoglycan (PGN) regulate the enteric nervous system (ENS), intestinal smooth muscle, intestinal endocrine, and immune systems through the Toll-like receptor (TLR) leading to alterations in GI motility and mood. BBB: blood–brain barrier; IL-1α: interleukin-1α; TNF-α: tumor necrosis factor-α; EECs: enteroendocrine cells; ECC: epidermal club cell; DC: dendritic cell; 5-HT: serotonin; SMC: smooth muscle cell; ICC: interstitial cell of Cajal; NF-κB: nuclear factor-κB; JNK: c-Jun N-terminal kinase; BMP2: bone morphogenetic protein 2; BMPR: bone morphogenetic protein receptor; EN: enteric neuron; MMs: muscle macrophages; CSF-1: colony-stimulating factor 1; EGC: enteric glial cell; GDNF: glial cell-derived neurotrophic factor.

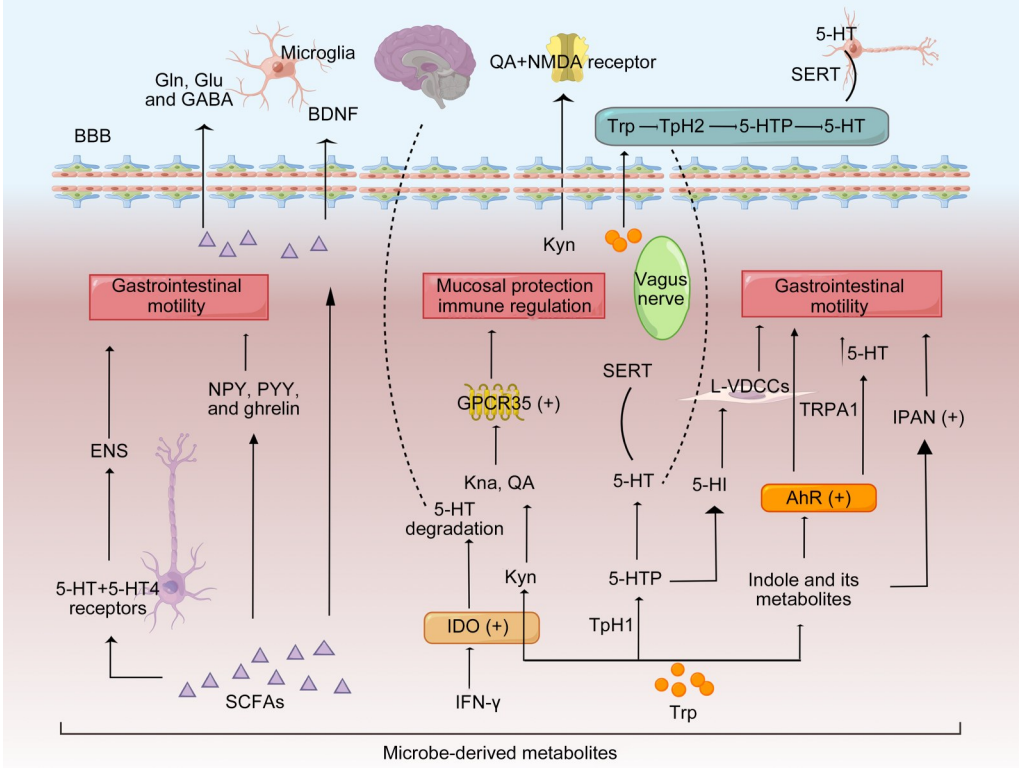

Fig. 2 Diagrammatic illustration of the modulatory process for the short-chain fatty acids (SCFAs) and metabolites of tryptophan (Trp) in gastrointestinal (GI) function and depression. BBB: blood–brain barrier; Gln: glutamine; Glu: glutamate; GABA: γ-aminobutyric acid; BDNF: brain-derived neurotrophic factor; QA: quinolinic acid; NMDA: *N*-methyl-D-aspartate; 5-HT: serotonin; SERT: serotonin transporter; TpH: serotonin-synthesizing enzyme tryptophan hydroxylase; 5-HTP: 5-hydroxytryptophan; Kyn: kynurenine; ENS: enteric nervous system; NPY: neuropeptide Y; PYY: peptide-YY; GPCR35: G-protein-coupled receptor 35; L-VDCCs: L-type voltage-dependent calcium channels; TRPA1: transient receptor potential anchor protein A1; IPAN: intrinsic primary afferent neuron; AhR: aryl hydrocarbon receptor; Kna: kynurenic acid; 5-HI: 5-hydroxyindole; 5-HT4: 5-hydroxytryptamine type 4; IDO: indoleamine 2,3-dioxygenase; IFN-γ: interferon-γ.

stress (Qiu et al., 2020) and abrogating hippocampal microglia activation (Yamawaki et al., 2018). A study showed that fecal concentrations of butyrate and propionate were reduced in patients with IBS with constipation (IBS-C) and increased in patients with IBS with diarrhea (IBS-D), demonstrating that SCFAs are associated with the regulation of GI motility (Luo et al., 2021).

SCFAs not only maintain the integrity of the intestinal epithelial barrier by regulating mucus production and expression of tight junction proteins, but also cross the BBB via monocarboxylate transporter (MCT) protein and mediate the overexpression of tight junction proteins to maintain the integrity of the BBB. SCFAs regulate the levels of neurotransmitters such as glutamine (Gln), glutamate (Glu), and γ-aminobutyric acid (GABA) in the hypothalamus, and also upregulate the expression of tryptophan hydroxylase 1 (TpH1) and tyrosine hydroxylase (TH), which is the rate-limiting enzyme in the synthesis of dopamine (DA), epinephrine, and norepinephrine (NE) (Dalile et al., 2019; Tian et al., 2020). SCFA ameliorates depression by modulating brain-derived neurotrophic factor (BDNF) levels, promoting neurogenesis, and influencing glial cell morphology and function, which in turn modulates neuroinflammation in the CNS. In addition, SCFAs stimulate the release of neuropeptide Y (NPY), peptide-YY (PYY), and ghrelin from IECs and attenuate anxiety and depression-like behaviors. Decreased SCFAs in germ-free and antibiotic-treated mice stimulate L cells, which produce glucagon-like peptide-1 (GLP-1) and PYY, both inhibiting GI motility (Marathe et al., 2011; Wichmann et al., 2013). Enterochromaffin cells (ECs) sense SCFAs and produce serotonin (5-HT), which promotes GI motility by activating 5-hydroxytryptamine type 4 (5-HT4) receptors expressed on enteric neurons

(Grider and Piland, 2007). In addition, butyric acid can also enter cells through MCT2 of enteric neurons to directly regulate ENS and control GI motility (Halestrap, 2013).

3.1.4 Trp metabolites

Trp metabolism is a key metabolic pathway for host-microbe crosstalk. Trp metabolism in the intestine mainly follows the kynurenine pathway (KP), 5-HT pathway, and indole pathway (Agus et al., 2018). Disturbances in Trp metabolism are involved in different GIDs, such as IBD and celiac disease (Lamas et al., 2016, 2020). The regulation of Trp metabolism to kynurenine (Kyn) or 5-HT by the gut microbiota is a particularly important pathway for depressive episodes (Dehhaghi et al., 2019). Therefore, it is necessary to elaborate on the role of Trp metabolism controlled by the gut microbiota in GI motility and brain function.

About 90% of Trp is metabolized by KP, a pathway that generates Kyn and its downstream products, such as quinolinic acid (QA), nicotinic acid, and kynurenic acid (Kna), from immune and epithelial cells via indoleamine 2, 3-dioxygenase (IDO) (Kennedy et al., 2017). The gut microbiota stimulates IDO activity, which can also be induced by pro-inflammatory factor stimulation during intestinal inflammation (Yeung et al., 2015). Interferon-γ (IFN-γ) is the most potent inducer (Jürgens et al., 2009). Activated IDO accelerates 5-HT degradation (Jeon and Kim, 2017) and exacerbates 5-HT deficiency, leading to disruption of neurotransmission and consequently depression. Reduced availability of peripheral Trp for 5-HT synthesis and increased activation of the Kyn pathway are associated with depression and suicide (Messaoud et al., 2019). In addition, Kyn can enter the circulation and cross the BBB to participate in the synthesis of these neuroactive metabolites in the CNS (Raison et al., 2010). Inflammation-induced changes in intestinal Kyn level lead to altered levels of Kyn, Kna, and QA in the brain. However, depression is also thought to be associated with an overproduction of neurotoxic QA and a decrease in Kna (Savitz et al., 2015). In the brain, QA is an agonist of the *N*-methyl-D-aspartate (NMDA) receptor, which plays a key role in the regulation of synaptic function (Husi, 2004). NMDA is activated upon binding to QA, which is thought to be able to induce depression (Dantzer, 2017). Kna may be activated through epithelial and immune cells expressing GPCR35 to exert mucosal protective and immunomodulatory effects (Gao et al., 2018). KP end products are involved in the regulation of a variety of host biological processes, including neurotransmission, inflammation, and immune responses.

About 3% of Trp is metabolized to 5-HT, a key neurotransmitter in the CNS that regulates mood and is associated with GI visceral hypersensitivity. In the brain Trp produces 5-HT via TpH2, but in the EC of the gut Trp produces 5-hydroxytryptophan (5-HTP) via TpH1, which is further metabolized to 5-HT, leading to more than 90% of 5-HT found in the body. A small amount is also present in the enteric nerves (Gershon, 2013). At specific flora and pH levels, 5-HTP may be transformed to 5-hydroxyindole (5-HI) via bacterial trypsin. 5-HI directly improves GI motility by activating L-type voltage-dependent calcium channels (L-VDCCs) situated on colonic SMCs and possibly by inducing the release of 5-HT receptors from enteroendocrine cells (EECs) to activate ENS afferent nerve endings (Waclawiková et al., 2021). Serotonin transporter protein (SERT; encoded by the *SLC6A4* gene), expressed in the apical and basolateral membranes of the IEC, eliminates EC-produced 5-HT. 5-HT reuptake in the brain is a key process in preventing neural hyperstimulation, and SERT regulates extracellular levels of 5-HT in the brain by transporting 5-HT into neurons and glial cells.

Differences in the organism's gut microbiome can also interfere with the conversion of Trp to indole and its derivatives, such as indoleacetic acid (IAA), indolepropionic acid (IPA), tryptamine, indole-3-carboxaldehyde, and inosine. These further affect the function of the human GI tract and immune system, as well as the brain and behavior, as ligands for AhR (Alexeev et al., 2018). Tryptophanases converting Trp to indole were expressed in *Escherichia coli* and *Lactobacillus* (Hubbard et al., 2015), and *Peptostreptococcus russellii* 148 and *Lactobacillus* spp. 119 were able to produce ligands for AhR (Lamas et al., 2016; Wlodarska et al., 2017). The expression and activation of AhR regulates bowel movement (Obata et al., 2020) and can also be involved in the regulation of depressive behaviors (Vicentini et al., 2021). A multi-omics study on humans found elevated fecal tryptamine levels in IBS-D patients (Mars et al., 2020), suggesting that tryptamine may be related to intestinal dynamics. Metformin also modulates microbiota-derived inosine

and ameliorates methamphetamine-induced anxiety and depression-like symptoms in mice (Yang et al., 2022). Indole-3-carboxaldehyde modulates intestinal and vagus nerve (VN) pathways in response to microbial signals, activates IECs via transient receptor potential anchor protein A1 (TRPA1), increases 5-HT secreted by ECs, and stimulates intrinsic primary afferent neuron (IPAN), which activates cholinergic enteric neurons to promote GI peristalsis and is not dependent on AhR (Ye et al., 2021).

3.2 Endocrine pathway

3.2.1 Microbial endocrine

The intersection of microbiology and host neurophysiology, known as "microbial endocrinology," is based on the shared neuroendocrine signaling between bacteria and hosts that is thought to be central to host–microbiota interactions (Lyte, 2014). The neurochemicals produced by the microbiota are identical to those found in host tissues (Riley et al., 2013). They can enter the portal circulation from the gut, interact directly with receptors in the enteric nerve, or act through ENS–CNS communication (Lyte, 2014; Sun et al., 2020). Thus, probiotics-containing/producing neurochemicals may be considered as delivery vehicles for neuroactive compounds, and probiotics designed using microbial endocrinology may have potential as therapeutic strategies for the prevention and/or treatment of certain neurological and neurophysiological conditions (Lyte, 2011, 2014; Wall et al., 2014; Villageliú and Lyte, 2018).

Monoamine transmitters such as 5-HT, NE, and DA are known to be closely associated with depressive symptoms (Brigitta, 2002). In the GI tract, these neurotransmitters are produced in large quantities and play a key role in various GI functions as well as in the regulation of the GI immune system and commensal bacteria (Mittal et al., 2017; Winter et al., 2018). Currently, most reports on the production of neuroendocrine hormones by microorganisms are limited mainly to in vitro studies. For example, certain strains of *Lactobacillus* and *Bifidobacterium* isolated from the human GI tract produce large amounts of GABA in vitro (Barrett et al., 2012). GABA-rich soymilk significantly reduces the duration of inactivity before initiation of swimming in rats and has the same antidepressant effect as selective serotonin reuptake inhibitors (SSRIs) (Ko et al., 2013). Notably, GABA also inhibits the release of proinflammatory peptides by visceral sensory neuron and inflammatory immune cell activity, and the presence of GABA receptors on pro-inflammatory immune cells downregulates inflammatory responses (Bjurstöm et al., 2008). GABA production by intestinal probiotics may be responsible for the prevention of inflammatory conditions in the GI tract. Glutamic acid decarboxylase (GAD) in *Lactococcus lactis* NCDO2118 is active and delivers its GABA to the GI tract, reducing the stress-induced visceral hypersensitivity response. This generally recognized as safe (GRAS) bacterium opens new avenues in the management of visceral pain and anxiety depression in IBS patients (Laroute et al., 2022).

3.2.2 GI endocrine system

There is growing evidence that EECs are key sensors of the gut microbiota and its derivatives. Gut peptide concentrations vary according to the composition of the gut microbiota (Cani et al., 2013; Dockray, 2013), and bidirectional gut–brain communication may begin with sensory information in the GI tract that is subsequently translated into neural, hormonal, and immune signals to the CNS. With the widespread expression of peptides and their receptors in the brain and intestine, they can also diffuse into the bloodstream. The basal cytoplasm of EECs is connected to the ENS, VN, and spinal afferent fibers, which suggests a role for EECs in sensory nerve sensitization and supports their involvement in the activation of the GBA bidirectional pathway. Gut hormones not only play a role in the GI tract, but also are key regulators of anxiety and depression (Lach et al., 2018).

EECs can be classified into more than ten cell types according to their secreted hormones. The major secretagogues include 5-HT, growth inhibitory hormone, NPY, vasoactive intestinal peptide (VIP), substance P (SP), cholecystokinin (CKK), GLP-1/2, and ghrelin (Gunawardene et al., 2011; Fothergill and Furness, 2018). In addition, several hormones may be co-expressed in the same EEC (Egerod et al., 2012). 5-HT is thought to be key in depressed patients with comorbid GI symptoms. ECs synthesize and secrete more than 95% of the systemic content of 5-HT (Mawe and Hoffman, 2013). 5-HT is involved in the regulation of multiple physiological functions including GI motility, feeding, sleep, mood, and cognition. Extracellular 5-HT in the intestine is regulated by SERT that is expressed

in IECs and regulated by LPS (Bian et al., 2007). In addition, SCFAs can directly stimulate EECs to produce neuropeptides such as PYY, NPY, CCK, GLP-1/2, and SP (Psichas et al., 2015). Gastrin (GAS), SP, VIP, and CGRP, which are widely distributed in the brain and GI tract, also play a role in depression but their precise effects remain to be studied.

3.2.3 Hypothalamic-pituitary-adrenal axis

The stress-dependent hypothalamic-pituitary-adrenal (HPA) axis is an important part of the neuroendocrine system (Makris et al., 2021). Stress causes the hypothalamus to release corticotropin-releasing hormone or factor (CRH/CRF). This information is relayed to the anterior pituitary gland, where adrenocorticotropic hormone (ACTH) is produced. This stimulates the adrenal cortex to release cortisol (CORT) into the bloodstream, and elevated levels of CORT lead to a negative feedback loop that inhibits the secretion of CRH and ACTH (Joseph and Whirledge, 2017). Dysfunction of the HPA axis stimulates the release of a variety of neuroendocrine signaling molecules and cytokines, which in turn affects mood and GI function. It is now proposed that the gut microbiota is closely related to the development and function of the HPA axis (de Weerth, 2017). The gut microbiota can cross the BBB to activate the HPA axis via LPS, PGN (as microbe-associated molecular patterns (MAMPs)), and related products of proinflammatory mediators, or it can attenuate the HPA axis response via released metabolites such as SCFAs (Misiak et al., 2020). Early life stress and chronic stressors are risk factors for the development of depression and IBS, and HPA axis activation is also capable of influencing the composition of the gut microbiota and increasing GI permeability (Farzi et al., 2018).

A significant correlation between elevated levels of CORT and the development of depression has been demonstrated in the past in a number of studies. This may be due to dysregulation of the HPA axis resulting in excessive adrenal activity that has a destructive effect on the hippocampus. That stress can significantly affect neuronal plasticity, which in depression is defined as changes in hippocampal volume, inhibition of neurogenesis, and neuronal apoptosis (Ignácio et al., 2019; Bertollo et al., 2020). One study found that a probiotic intervention decreased psychological stress, anxiety, and CORT stress reactivity (Allen et al., 2016). In addition, CRF-mediated activation of the HPA axis is dependent on the intestinal flora. *Lactobacillus* suppressed plasma corticosterone and hypothalamic CRF-expressing cells in rats that underwent water-avoidance stress (Takada et al., 2016). A mixture of strains, including *Lactobacillus* and *Bifidobacterium*, reduced CRF receptor transcript levels in the rat hippocampus and alleviated depression-like behavior (Abildgaard et al., 2017). Conversely, CRF can alter intestinal flora in rats, such as a specific reduction in *Lactobacillus* (Murakami et al., 2017). In addition, the CRF system induces functional changes in the intestine, including slowed gastric emptying, colonic motility stimulation, and damage to the intestinal epithelial barrier (Rodiño-Janeiro et al., 2015) (Fig. 3).

3.3 Immunization pathway

Microbiota can influence the GI mucosa and systemic immunity (Natividad et al., 2015). Increasingly, studies have found that the immune system plays an important role in depression. A state of stress-mediated ecological dysregulation leads to increased intestinal permeability (leaky gut) and imbalance in tolerance to non-self-antigens (Koopman and El Aidy, 2017; Lerner et al., 2017), which is also thought to underlie chronic inflammation in the gut (Fig. 4).

3.3.1 Enteric immune response

Inflammation and subsequent responses due to disruption of GI barrier integrity are thought to be one of the mechanisms of depression, with MGBA playing a key role in this process (Liu et al., 2020). Gut microbes are potent regulators of the host immune response. When immune homeostasis is disrupted and contact with intestinal bacteria occurs, epithelial cells are activated, leading to bacterial influx, Treg reduces IL-10 secretion, and DCs are also activated, releasing IL-6, IL-12, and IL-23. T cells elevate the immune response by secreting TNF-α, IFN-γ, and IL-17 response grade. Upon arrival of infected T cells, neutrophils are recruited, which are essential for bacterial clearance. In addition, the intestinal flora promotes the secretion of antimicrobial peptides (AMPs) by IECs, which can directly kill bacteria and enhance tight junctions (Belkaid and Hand, 2014).

Innate lymphocytes (ILCs), recently identified, have a role in coordinating immune responses and maintaining tissue homeostasis. Unlike T and B

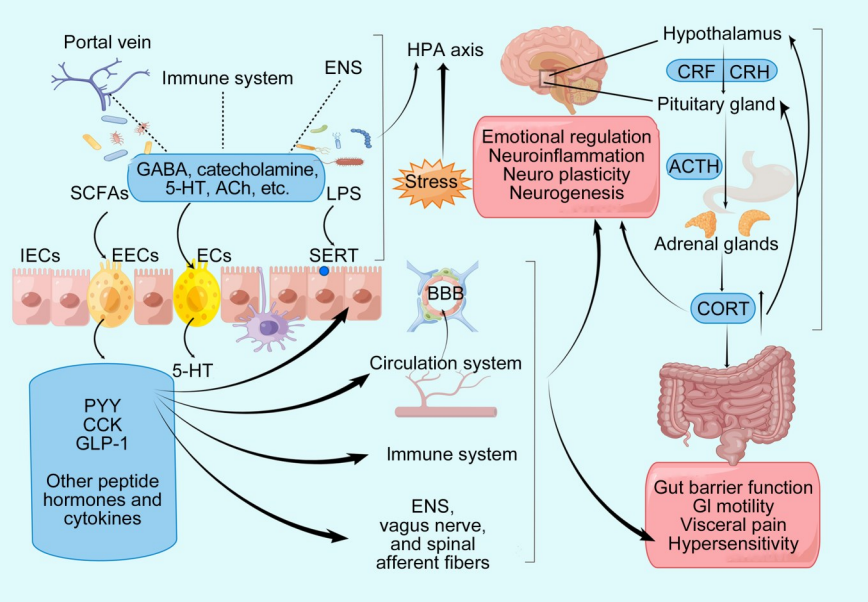

Fig. 3 Schematic diagram of the microbial endocrine, gastrointestinal (GI) endocrine system, and hypothalamic-pituitary-adrenal (HPA) axis pathways for the regulation of GI function and depressed mood. ENS: enteric nervous system; GABA: γ-aminobutyric acid; 5-HT: serotonin; ACh: acetylcholine; SCFAs: short-chain fatty acids; IECs: intestinal epithelial cells; EECs: enteroendocrine cells; ECs: endothelial cells; LPS: lipopolysaccharide; SERT: serotonin transporter; CRF: corticotropin-releasing factor; CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; BBB: blood–brain barrier; PYY: peptide-YY; CCK: cholecystokinin; GLP-1: glucagon-like peptide-1; CORT: cortisol.

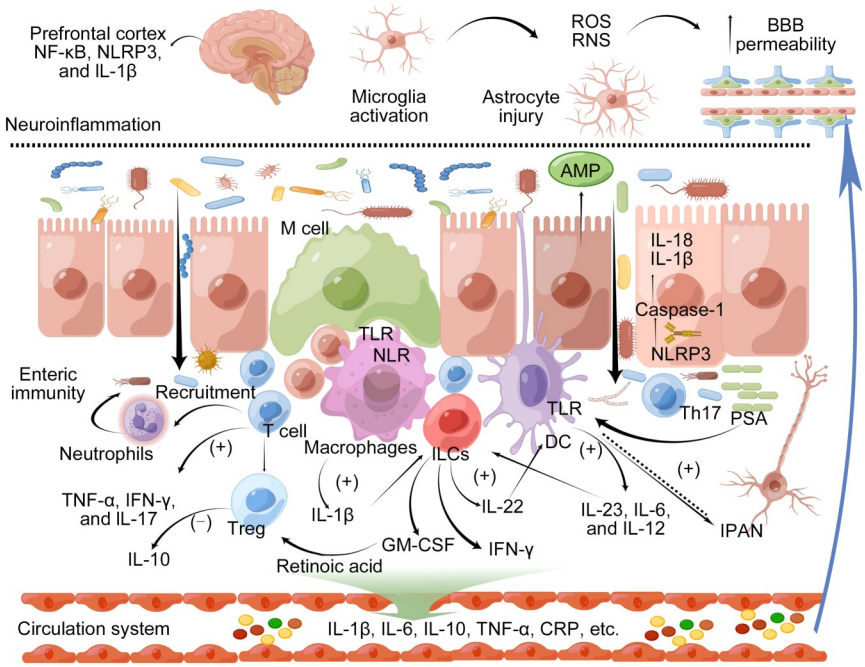

Fig. 4 Microbial activation of immune responses within the lamina propria of the intestine, circulatory inflammatory responses, and neuroimmunity. NF-κB: nuclear factor-κB; NLRP3: NLR family pyrin domain containing 3; IL: interleukin; ROS: reactive oxygen species; RNS: reactive nitrogen species; BBB: blood–brain barrier; M cell: mesophyll cell; AMP: antimicrobial peptide; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ; Treg: regulatory T; TLR: Toll-like receptor; NLR: NOD-like receptor; ILCs: innate lymphoid cells; DC: dendritic cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; Th17: T helper 17; PSA: polysaccharide A; IPAN: intrinsic primary afferent neuron; CRP: C-reactive protein.

lymphocytes, ILCs do not express adaptive antigen recognition receptors, and their development and function are impaired in germ-free (GF) mice (Britanova and Diefenbach, 2017). The group 3 ILCs (ILC3s) interact with DCs to maintain the epithelial barrier. DCs act as antigen-presenting cells, acquiring antigens from the intestinal microbiota and secreting IL-23, which stimulates ILC3s to produce IL-22. IL-22 then activates IECs to secrete ILC3s that also interact with macrophages to establish tolerance to commensal flora. Macrophages sense MAMPs in the GI tract directly through TLRs and NOD-like receptors (NLRs) to produce the proinflammatory cytokine IL-1β (Maynard et al., 2012; Thaiss et al., 2016). The release of IL-1β triggers the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) from ILC3s, which signals macrophages to induce retinoic acid and promote Treg differentiation (Mortha et al., 2014; Zhou et al., 2019). In addition, ILC3s acquire the ability to produce IFN-γ during chronic inflammation. A balance between anti-inflammatory Treg and pro-inflammatory Th17 cells regulated by gut microbes is maintained, thereby establishing immune homeostasis to prevent pathological intestinal and systemic inflammation. The specific cellular and molecular pathways by which gut microbes regulate innate and adaptive immune homeostasis have been extensively reviewed (Thaiss et al., 2016; Belkaid and Harrison, 2017). Th17 cells, along with IL-17 and IL-22 produced by ILC3s in response to the intestinal microbiota, ensure the maintenance of the intestinal barrier function (Martínez-López et al., 2019). Chronic social defeat stress causes a microbial-dependent increase in mesenteric lymph node Th17 and Treg cells (McGaughey et al., 2019; Werbner et al., 2019).

Recent studies have shown that inflammasomes have emerged as a key pathway involved in the regulation of immune interactions in the microbiota (Man, 2018). The assembly of inflammasome complexes is dependent on the perception of MAMPs (Rathinam and Fitzgerald, 2016). Activation of the inflammasome pathway leads to caspase-1-mediated release of the pro-inflammatory cytokines IL-1β and IL-18, with NLR family pyrin domain containing 3 (NLRP3) inflammatory vesicle involvement being associated with a variety of diseases (Yang et al., 2019). The protective effect of caspase-1 inhibition in animal models of chronic restraint stress involves modulating the relationship between stress and gut microbiota composition, suggesting that the gut microbiota-inflammasome-brain axis may provide a novel therapeutic target (Wong et al., 2016).

3.3.2 Systemic inflammatory response

Pro-inflammatory factors, toxins, and other harmful molecules are transported to the brain via the circulation, and migrating immune cells can also reach the brain directly (Lerner et al., 2017; Peirce and Alviña, 2019). Notably, elevated pro-inflammatory markers have a predictive value for the development of depression (Peirce and Alviña, 2019). The functional link between chronic intestinal inflammation and neurodegeneration may be due to an imbalance between pro- and anti-inflammatory gut microbes, resulting in loss of gut barrier function and systemic inflammation due to microbial translocation (Wu et al., 2017; Ho et al., 2018). Disruption of the GI barrier increases intestinal barrier permeability and the potential for transfer of bacteria and toxins through the intestinal lumen into the circulation, leading to impaired intestinal immune homeostasis and systemic immune activation (de Punder and Pruimboom, 2015). Elevated levels of circulating proinflammatory cytokines IL-1β, IL-6, IL-10, and TNF-α are associated with neuropsychiatric disorders in humans (Köhler et al., 2017; Khandaker et al., 2018; Chu et al., 2019). In a mouse model of depression, peripheral IL-6 was found to have a key role in the pathogenesis of depression (Zhang et al., 2017). Systemic inflammation of intestinal origin was found to be a driver of depression in combination with chronic liver disease (Kronsten et al., 2022). Elevated levels of pro-inflammatory factors such as TNF-α, IL-1β, IL-6, and CRP directly activate the VN nucleus, including the nucleus tractus solitarius (NTS) and dorsal motor nucleus (DMN), further stimulating the HPA axis and exacerbating stress and depressive symptoms (Slyepchenko et al., 2017). The stress-activated HPA axis aggravates ecological dysregulation and leaky gut. Inflammation and/or activation of the HPA axis also stimulates the Trp-Kyn pathway, one of the biological factors involved in the pathophysiology of major depression and suicide. In addition, centrally acting cytokines can affect the metabolism of neurotransmitters, including DA, 5-HT, and NE (Miller et al., 2009).

3.3.3 Neuroinflammation

Recent studies have indicated that systemic inflammation resulting from changes in the gut microbiota can reach CNS-regulated inflammatory pathways in different ways, particularly via microglia, which may affect the response to antidepressant treatment (Carlessi et al., 2021). NF-κB, NLRP3, and IL-1β levels are elevated in chronically stressed rat PFC, and microglia activation and astrocyte damage are observed, while antidepressant treatment with the drug fluoxetine reverses these changes (Pan et al., 2014). IL-1β and IFN-α reduce hippocampal neurogenesis and promote depression-like behavior in mice. Circulating inflammatory mediators originating from the gut penetrate the brain after BBB dysfunction and modulate local CNS glial cells. Neuroinflammation may be a key therapeutic target for future treatment strategies for major depression (Troubat et al., 2021). The in vivo colitis models provide evidence for enhanced BBB permeability and increased CNS immune responses triggered by enterotoxins and blood-borne inflammatory mediators, suggesting that neuroinflammation may also be responsible for depression and IBD co-morbidity (Craig et al., 2022).

Neuroinflammation can activate microglia to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which have deleterious effects on the BBB (Makris et al., 2021). Microglia are intrinsically immune effector cells within the CNS due to their polysynaptic and plastic characteristics. Microglia exert their neuronal functions through cytokine release, complement activation, and phagocytosis (Salter and Stevens, 2017). Fan et al. (2022) found that microglia secrete microRNA (miR)-146a-5p-containing exosomes to regulate neurogenesis in depression. However, the exact mechanisms by which microbes in the gut affect brain-resident microglia are not fully understood. The microbial metabolites of dietary fiber, SCFAs, can restore microglia function in GF and antibiotic-treated animals (Erny et al., 2015), and microbial signals from the gut have a long-range role in regulating microglia function. Astrocytes are involved in BBB formation and play an immunomodulatory role in CNS development and inflammation through antigen presentation and cytokine and chemokine production. Microbial metabolites of type I IFN and Trp regulate astrocyte activity and neuroinflammation via AhR (Rothhammer et al., 2016). Astrocytes release IL-33 to activate microglia synaptic phagocytosis (Vainchtein et al., 2018). Microbial metabolites from socially frustrated FMT in stressed mice increased the abundance of *Clostridium perfringens*, leading to elevated levels of IL-1β, IL-10, and microglia activation in the hippocampus (Pearson-Leary et al., 2020). Collectively, these findings suggest that gut microbes can influence the function of CNS resident innate and adaptive immune cells with neuropathological consequences.

3.4 Neural pathway

The CNS is closely associated with the GI tract and plays an important role in regulating intestinal function and homeostasis in vivo. In turn, gut flora can affect the nervous system and influence the pathogenesis and progression of neurological-related diseases. VN dissection eliminates the antidepressant effects of SSRIs, suggesting an important role for peripheral 5-HT and VN stimulation in modulating depressive behavior (McVey Neufeld et al., 2019). *Lactobacillus* strains modulate emotional behavior and central GABA through the VN in mice receptor expression, suggesting that VN-mediated communication between the gut and brain is one of the pathways, through which the gut flora acts in the host (Bravo et al., 2011). Furthermore, the cholinergic anti-inflammatory pathway via VN fibers can suppress peripheral inflammation and reduce intestinal permeability, therefore likely regulating the microbiota composition. It is also involved in the pathophysiology of GIDs, with patients with IBD and IBS exhibiting low vagal tension, favoring peripheral inflammation (Bonaz et al., 2018). The sympathetic nervous system and the VN act synergistically to inhibit TNF-α release from peripheral tissues and splenic macrophages via the splenic nerve. Because of its anti-inflammatory effects, the VN is considered a target for the treatment of chronic inflammatory diseases, with TNF-α as a key component (Bonaz et al., 2017). However, when considering the neural pathways of the microbiota that may affect the CNS, it is important to include the ENS as well. The ENS is a key player in disease pathogenesis, and its role in human health and disease has been largely overlooked (Niesler et al., 2021).

The GI tract is the only internal organ that has evolved its own independent nervous system, called the ENS (Spencer and Hu, 2020). The ENS is a highly conserved but complex network of neurons and glial

cells positioned along the GI canal wall to coordinate digestive processes and GI homeostasis. Communication between the ENS and CNS is bidirectional, and their crosstalk with the microbiota in the GI tract supports the so-called MGBA (Zhu et al., 2017). Sensory information reaches the CNS via IPANs and external primary afferent neurons, which follow the afferent routes of the spinal cord and VN. The CNS reaches the ENS and GI effector tissues via the VN, sympathetic, and pelvic nerve pathways (Furness, 2012). The ENS is integrated between the mucosal barrier and the muscle layer and interconnects with the enteroendocrine and GI immune systems, the peripheral nervous system (PNS), the CNS, and the intestinal flora to regulate not only GI motility but also a range of GI functions such as secretion, nutrient absorption, immune regulation, and defense (Niesler et al., 2021). There is evidence that the VN reflex controls the release of PYY from the distal small intestine (Onaga et al., 2002), and that the Peyer's patch (PP) of the ileum is dominated by the enteric nerve (Chiocchetti et al., 2008). In addition, sensory information about intestinal contents can be detected by IECs which release hormones acting on vagal afferent nerve endings (Raybould, 2010). Ghrelin signals to hypothalamic feeding centers via the VN (Yanagi et al., 2018). Experimental studies have shown that inflammation leads to long-term changes in the properties of spinal afferent nerves, causing neurons to become sensitive (Beyak, 2010; Feng et al., 2012). The gut flora has emerged as an environmental factor regulating CNS and ENS development (Heiss and Olofsson, 2019). However, factors such as diet, antibiotic use, environment, and hygiene can all have an impact on microorganisms (Schmidt et al., 2011; Willing et al., 2011; David et al., 2014; Rothschild et al., 2018). During depression episodes, the ANS couples with the neuroendocrine system to change the function of the ENS and HPA axis, which leads to the development of GIDs (Agrawal et al., 2020).

4 Clinical implications

We provide a comprehensive overview of the role of the gut microbiota in regulating mood and GI function via gut-brain pathways, hypothesizing that simultaneous treatment of GI symptoms and depressed mood may enhance recovery and reduce the risk of relapse, and that effective therapeutic pathways may have a profound impact on mood, GI tract, and health. Potential therapies for the treatment of depression with GI symptoms that depend on the gut microbiota are summarized in Table 1.

4.1 Dietary strategies to regulate microbiota

One dietary strategy to modulate the microbiota is the consumption of dietary fiber and prebiotics, which can be metabolized by microorganisms in the GI tract (Holscher, 2017). The choice of diet determines the selection of metabolic substrates for certain microorganisms (Heiman and Greenway, 2016). A study dedicated to uncovering the interactions among diet, gut microbiota, and its ability to induce intestinal inflammation found that processed and animal-derived foods were associated with a higher abundance of Firmicutes, *Ruminococcus* species of the *Blautia* genus and the endotoxin synthesis pathways. In contrast, plant foods and fish were positively associated with symbiotic bacteria and nutrient metabolism pathways that produce SCFAs (Bolte et al., 2021). The production of SCFAs by the gut microbiota may reflect health status. Gut symptoms are common in depressed patients, and detection of acetate, butyrate, and propionate levels in stool samples by nuclear magnetic resonance (NMR) spectroscopy revealed that depressive symptoms were positively correlated with acetate level and negatively correlated with butyrate and propionate levels. Diarrheal symptoms were positively correlated with acetate, and negatively correlated with propionate and total SCFA levels (Müller et al., 2021). In addition, dietary Gln supplementation may improve GI barrier function (Ma et al., 2021).

In addition to diet, probiotics and prebiotics, among others, are commonly used to maintain a healthy microbiome or restore homeostasis. Studies have demonstrated that various prebiotic molecules and probiotic strains can exert beneficial effects on host immune responses, metabolic processes, and neuroendocrine pathways (Quigley, 2019). Many probiotic strains exhibit anti-inflammatory properties (Orel and Kamhi Trop, 2014). Studies have found that metabolites produced by synbiotics may promote recovery from stress-induced depression-like behaviors by regulating Th17/Treg cell imbalance (Westfall et al., 2021). There is general support for the antidepressant effect of probiotics (Vlainić et al., 2016; Liu et al., 2019; Mörkl et al.,

Table 1 Potential therapies for depression with GI symptoms

Potential therapy	Mechanism	Result	Reference
Dietary supplementation	Increasing symbiotic bacteria that produce SCFAs	Improved depression	Bolte et al., 2021
Probiotics, prebiotics, and synbiotics	Regulation of Th17/Treg cell imbalance	Improved depressive-like behavior	Westfall et al., 2021
	Mediation of butyric acid production in MGBA	Effect on depression susceptibility	Suda and Matsuda, 2022
	Microbial immunity pathway	Alleviated depression and colitis	Yoo et al., 2022
	Increasing production of SCFAs and hormone secretion	Improved constipation	Zhuang et al., 2019
	Regulation of the serotonergic system	Improved MDD and GI syndromes	Tian et al., 2023
Xiaoyao Pills	Inhibition of fatty acid amide hydrolase level in the brain by microbial metabolites	Improved depression	Zhang et al., 2023
Cuscutae semen	Regulation of the gut microbiota-neuroinflammation axis	Improved depressive-like behavior and synaptic structure	Hou et al., 2023
Chaihu-Shugan-San	Regulation of levels of gut microbiota, bile acids, etc.	Improved depressive-like behavior	Ma et al., 2022
Morinda officinalis oligosaccharides	Promotion of the 5-HTP production by gut microbiota	Improved depressive-like behavior	Zhang ZW et al., 2022
Coniferyl ferulate	Lowering the levels of IL-6, IL-1β, and TNF-α; reorganization of the gut microbiome and microbial metabolism	Improved symptoms of colitis and depression	Hao et al., 2021
Crocetin	Regulation of the MEK/ERK pathway and the gut microbiota	Improved depressive-like behavior	Lin et al., 2021
Kai-Xin-San	Regulation of the gut microbiota-inflammation-stress system	Improved depressive-like behavior	Cao et al., 2020
Tiansi Liquid	Regulation of gut microbiota composition and Trp-Kyn pathway	Improved depressive-like behavior	Cheng et al., 2018
Rifaximin	Modulation of the inflammatory function of microglia by gut flora and SCFAs	Prevented stress-induced depression-like behavior	Li HN et al., 2021
Electroacupuncture treatment	Upregulation of Gln and GABA in the hippocampus by increasing the density of SCFA-producing bacteria	Alleviated IBD and depression-like behavior	Zhou et al., 2022

SCFAs: short-chain fatty acids; Th17: T helper 17; Treg: regulatory T; MGBA: microbiota-gut-brain axis; 5-HTP: 5-hydroxytryptophan; IL: interleukin; TNF-α: tumor necrosis factor-α; MEK: mitogen-activated protein kinase (MAPK) kinase; ERK: extracellular signal-regulated kinase; Trp: tryptophan; Kyn: kynurenine; Gln: glutamine; GABA: γ-aminobutyric acid; MDD: major depressive disorder; GI: gastrointestinal; IBD: inflammatory bowel disease.

2020). Probiotics affect psychological variables associated with depression susceptibility (Chahwan et al., 2019). In particular, butyric acid-producing probiotics that mediate MGBA have good therapeutic potential (Suda and Matsuda, 2022). In addition to improving depressed mood, probiotics, prebiotics, and synbiotics have beneficial effects on IBS (Simon et al., 2021). Anti-inflammatory probiotics NK151, NK173, and NK175 alleviate gut microbiota-induced depression and colitis in mice (Yoo et al., 2022). The probiotic-rich and butyrate-producing microorganisms manage constipation through SCFA production and hormone secretion (Zhuang et al., 2019). After two months of using probiotic products, symptoms of anxiety and depression were significantly improved in patients with chronic GI symptoms (Dao et al., 2021). Probiotics have also been found to improve major depression and concomitant GI syndrome through modulation of the serotonergic system (Tian et al., 2023).

4.2 Traditional drugs and ingredients for regulating microbiota

Rapid advances in microbial technology have revealed a broad and close association between gut microbial communities and host health or disease states. The gut microbial-mediated mechanisms of interaction

between bioactive natural products (NPs) and the host have been gradually elucidated, and understanding the crosstalk among conventional drugs, NPs, and gut microbiota is essential for the development of clinical interventions and personalized drugs (Dai et al., 2023).

Gut microbiota-based metabolites of Xiaoyao Pills (a typical traditional Chinese medicine (TCM)) ameliorate depression by reducing fatty acid amide hydrolase levels in the brain (Zhang et al., 2023). Fermented red ginseng (fRG) attenuates Alzheimer's disease (AD) and colitis in mice by modulating the MGBA (Shin et al., 2023). *Cuscutae semen* ameliorates chronic unpredictable stress (CUS)-induced depressive-like behavior and synaptic structural defects in mice via the gut microbiota-neuroinflammatory axis (Hou et al., 2023). Chaihu-Shugan-San alleviates depression-like behavior in mice exposed to CUS by altering the gut microbiota and levels of the BAs, hyocholic acid, and 7-ketodeoxycholic acid (7-ketoDCA) (Ma et al., 2022). *Morinda officinalis* oligosaccharides increase 5-HT in the brain and ameliorate depression via promoting 5-HTP production in the gut microbiota (Zhang ZW et al., 2022). Shugan pellets help improve depression-like behavior in CUS-stimulated rats by altering the gut microbiota (Li et al., 2022). Antidepressant Shugan Jieyu capsules alter the gut microbiota in rats with chronic unpredictable mild stress (CUMS)-induced depression (Tan et al., 2022). Oral coniferyl ferulate significantly improved colitis and depressive symptoms, reduced IL-1β, IL-6, and TNF-α levels, and reorganized the gut microbiota and microbial metabolism (Hao et al., 2021). Puerarin ameliorates depression-like behaviors in CUMS mice by remodeling their gut microbiota (Song et al., 2021). *Gastrodia elata* Blume water extract modulates neurotransmitters and alters the gut microbiota in a mild social defeat stress-induced depression mouse model (Huang YJ et al., 2021). Total glycosides from stems of *Cistanche tubulosa* alleviate depression-like behaviors. This effect might be achieved through the bidirectional interaction of the phytochemicals and gut microbiota (Fan et al., 2021). Crocetin improves depression-like behavior in mice by modulating the mitogen-activated protein kinase (MAPK) kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway and gut microbiota (Lin et al., 2021). The Chinese medicine formula Kai-Xin-San ameliorates depression-like behaviors in CUMS mice by regulating the gut microbiota-inflammation-stress system (Cao et al., 2020). Tiansi Liquid (a traditional Chinese herbal medicine) modulates gut microbiota composition and Trp-Kyn metabolism in rats with hydrocortisone-induced depression (Cheng et al., 2018).

4.3 Other therapeutic methods for microbiota regulation

Repeated exposure to antibiotics is associated with an increased risk of depression and anxiety (Lurie et al., 2015). People who took antibiotics within the past three months showed stronger emotional bias toward grief (Johnson and Steenbergen, 2022), which may be related to antibiotics disrupting microbial homeostasis. However, rifaximin can modulate microglia inflammation by regulating intestinal flora and SCFA function, preventing stress-induced depression-like behavior (Li HN et al., 2021). Immune responses are involved in the pathophysiology of MDD. In recent years, cyclooxygenase-2 (COX-2) inhibitors have been increasingly studied for the treatment of depression. Adjuvant therapy with celecoxib has better efficacy compared to placebo, but only four studies were included in the meta-analysis. Further studies of longer duration based on larger sample sizes are necessary to fully assess the efficacy and tolerability of non-steroidal anti-inflammatory drugs (NSAIDs) added to antidepressants in patients with MDD (Musil et al., 2011; Na et al., 2014). The antidepressant activity of celecoxib may be related to its ability to reduce IL-6 concentration (Abbasi et al., 2012). In addition, Zhou et al. (2022) found that electroacupuncture treatment modulates the composition of the gut microbiota by significantly increasing the density of SCFA-producing bacteria, upregulates Gln and GABA in the hippocampus, and attenuates anxiety and depression-like behavior in IBD rats. In conclusion, for patients with depression combined with GI symptoms, the choice of medication and the balancing of symptoms is a great challenge for clinicians and requires more patience, otherwise patient compliance will be reduced.

5 Discussion

The treatment of depression with GI symptoms by TCM warrants further discussion. The theory of

Chinese medicine is that the human body is a whole, and if the pathogenesis of different diseases is the same, they can be recognized as the same syndrome, and the same medication can be used in their treatment. This theory is also known as "homotherapy for heteropathy." The addition of TCM to mesalazine treatment can improve the clinical symptoms of patients with ulcerative colitis combined with depression, reduce disease activity, inhibit inflammatory response, and at the same time show greater advantages in improving depressive symptoms and elevating serum DA and 5-HT levels (Wang et al., 2019). A meta-analysis showed that the efficacy of Shugan Jieyu capsules in the treatment of functional dyspepsia with anxiety and depression was better than that of conventional Western medicines, with a lower relapse rate and a higher safety profile (Cheng et al., 2021). Patients with depression often have accompanying symptoms of "spleen deficiency" such as fatigue, drowsiness, loss of appetite, bloating, diarrhea, or constipation. We believe that "spleen deficiency" is the main pathogenesis of depression with GI symptoms. Dysbiosis of the gut microbiota is closely associated with "spleen and stomach dysfunction" in Chinese medicine, which may be the biological basis for "spleen deficiency" (Gao et al., 2020). The "spleen and stomach" are similar to the modern anatomy of the digestive system, playing digestive, immune, endocrine, and other functions. The function of the gut microbiota and the function of the "spleen and stomach" of Chinese medicine have the same characteristics (Gao et al., 2019). Many clinical and animal experimental studies have shown that TCM helps to regulate and restore the disordered gut microbiota (Gao et al., 2020). TCM has great potential for the treatment of depression with GI symptoms, but the specific pathways mediated by the gut microbiota need to be further explored.

GI side effects (SEs) are frequently observed in patients with depression who are taking antidepressants. Research studies have shown that GI symptoms are strongly associated with discontinuation in depressed patients (Huang et al., 2022). In a meta-analysis of 304 studies, all antidepressants considered showed a higher incidence of GI SEs than placebo. Escitalopram and sertraline were the least GI-tolerated antidepressants and were associated with all considered SEs except constipation and increased appetite. Mirtazapine was shown to have less SEs on the gut and was associated only with increased appetite. Commonly used antidepressants show different GI SE profiles, possibly related to their mechanism of action (Oliva et al., 2021). However, venlafaxine is considered an effective treatment for improving the severity of GI symptoms, depression, and stress in patients with IBS (Sharbafchi et al., 2020). Some studies have found that it may improve depression by modulating gut bacteria (Shen et al., 2023). Further studies with larger sample sizes and longer treatment durations are recommended. Therefore, clinicians should consider GI tolerability when prescribing antidepressants to improve patient compliance and treatment outcomes. It is also imperative to actively seek new approaches that can effectively treat depression in combination with GIDs.

In clinical treatment, depressed patients with and without GI symptoms should be treated separately. Patients with only altered mood can be given commonly used antidepressants such as fluoxetine hydrochloride, mirtazapine, and venlafaxine according to the specific situation, and should be monitored for the development of SEs after taking the medication. Depressed patients with combined GI symptoms can be treated with reference to the use of dietary modification strategies, probiotics and traditional medications as adjuncts, with emphasis on the patients' GI symptoms. However, differences across studies regarding probiotic doses, bacterial strains, and strain combinations limit the comparability of current clinical trials (Ng et al., 2018). The efficacy of specific combinations of probiotics or a particular strain on depression needs to be validated in future studies with larger sample sizes (Goh et al., 2019). Most studies of traditional drugs and ingredients also focus on the regulation of gut flora in depression, lacking in-depth studies of microbial-mediated immune, endocrine, and neurological alterations.

6 Summary and prospects

In this review we have discussed the pathological mechanisms by which the GBA regulated by intestinal flora leads to depression comorbid with GI symptoms, detailing the crosstalk between microbiota and metabolic, immune, endocrine, and neural networks. These studies support the view that the MGBA is a cause or contributor to the comorbid GI symptoms of depression. The therapeutic aspect, regarding the

improvement of depression and GI symptoms by dietary modifications and probiotic use, also illustrates this point, where modulation directly targeting microorganisms and their metabolism seems to work more fundamentally. Due to space limitations, not all studies of modulating gut flora to improve depression and GIDs are mentioned, but it is sufficient to illustrate the potential of microbiome-dependent gut-brain pathways for the treatment of depression with GI symptoms. In the future, dynamic changes in the microbiome should be applied to the diagnosis and treatment of depression, rather than being limited to studies of mere correlation. On the one hand, studies to identify strains and isolate bacteria should be increased, and on the other hand, key pathways of immune, endocrine, and neural responses mediated by specific microbiota should be the focus of future research. In conclusion, further research on the MGBA is needed to develop better treatment options for the comorbidity of depression and GIDs, or even for comorbidity of any brain disorders with GIDs.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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Author contributions

Huayi LIU contributed to the conception and design of the review. Menglin LIU and Genhao FAN wrote the first draft of the manuscript and created all the figures. Lingkai MENG and Kuo YANG critically revised the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Menglin LIU, Genhao FAN, Lingkai MENG, Kuo YANG, and Huayi LIU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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