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## **Molecular signalling during cross talk between gut brain axis regulation and progression of irritable bowel syndrome: A comprehensive review**

Singh SV *et al.* Interaction of gut-brain-axis and IBS progression

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### **Abstract**

Irritable bowel syndrome (IBS) is a chronic functional disorder which alters gastrointestinal (GI) functions, thus leading to compromised health status. Pathophysiology of IBS is not fully understood, whereas abnormal gut brain axis (GBA) has been identified as a major etiological factor. Recent studies are suggestive for visceral hyper-sensitivity, altered gut motility and dysfunctional autonomous nervous system as the main clinical abnormalities in IBS patients. Bidirectional signalling interactions among these abnormalities are derived through various exogenous and endogenous factors, such as microbiota population and diversity, microbial metabolites, dietary uptake, and psychological abnormalities. Strategic efforts focused to study these interactions including probiotics, antibiotics and fecal transplantations in normal and germ-free animals are clearly suggestive for the pivotal role of gut microbiota in IBS etiology. Additionally, neurotransmitters act as communication tools between enteric microbiota and brain functions, where serotonin (5-hydroxytryptamine) plays a key role in pathophysiology of IBS. It regulates GI motility, pain sense and inflammatory responses particular to mucosal and brain activity. In the absence of a better understanding of various interconnected crosstalk in GBA, more scientific efforts are required in the search of novel and targeted therapies for the management of IBS. In this review, we have summarized the gut microbial composition, interconnected

signalling pathways and their regulators, available therapeutics, and the gaps needed to fill for a better management of IBS.

**Key Words:** Irritable bowel syndrome; Microbiota; Gut brain axis; Stress; Serotonin

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**Core Tip:** Irritable bowel syndrome (IBS) is a prevalent gastrointestinal disorder with a dysregulated gut brain communication. Gut microbiota functional characterization is still underappreciated but their roles have been found to be pivotal. Various microbial species and their metabolites with altered composition and diversity have been found to be specific to IBS. Clinical manipulation of these microbial species improved the symptom profile in IBS patients while the associated mechanisms have been identified for a bidirectional communication between gut microbiota and brain. This in turn seems promising for future treatments specific to microbiota manipulation and targeting various cross-talk for the management of IBS and associated symptoms.

## **INTRODUCTION**

Human body consist of trillions of microbial cells, majority of which inhabit the gastrointestinal (GI) tract thus forming a microbial colonization with a dynamic ecological environment, commonly known as “microbiota”<sup>[1,2]</sup>. This microbiota is comprised of approximately 500 transient and indigenous species of bacteria, viruses, fungi and protozoa<sup>[3,4]</sup>. Among all, bacteria are the most abundant microbial community dominated with the members of *Firmicutes* and *Bacteroidetes* phyla<sup>[5,6]</sup>. In recent years, research focusing intestinal microbiota functional characterization led the identification of a bidirectional crosstalk between brain and gut microbiota, thus forming a gut-brain axis (GBA)<sup>[7,8]</sup>. Moreover, GBA includes central nervous system (CNS), enteric nervous

system (ENS), hypothalamic-pituitary-adrenal (HPA) axis, gut and its microbiota (Figure 1). Interestingly, these components have been identified to be interconnected through various coordinated signalling pathways<sup>[8,9]</sup>. Abnormalities in these pathways and their regulators have been identified for the etiology of irritable bowel syndrome (IBS). IBS is a common GI bowel disorder featured with altered GI motility, visceral hypersensitivity, post-infection reactivity, small intestinal bacterial overload, carbohydrate mal-absorption and intestinal inflammation<sup>[10,11]</sup>. These abnormalities result in dysbiosis, recurrent abdominal pain and distressed bowel habits.

IBS is affecting 10%-25% of global world population, especially in developed countries with a poorly deciphered pathophysiology<sup>[12]</sup>. Considering the predominant symptoms and bowel habits, IBS is further classified into four subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed IBS (IBS-M), and unclassified IBS<sup>[13,14]</sup>. Interestingly, women are more susceptible (1.67 times) than men for IBS. In recent years, IBS symptoms have been predominantly found to be associated with environmental factors such as, diet, enteric microbial communities, host genetics and psychology<sup>[15]</sup>. However, the ways these factors contributing to the etiology of IBS are not fully deciphered. The treatments available for IBS are also not very specific. Generally, dietary fiber supplementation for IBS-C, opioids for IBS-D and abdominal pain with bloating, and low doses of antidepressants are recommended for the management of various symptoms associated with IBS<sup>[12,13,15]</sup>. However, modulating the gut-brain axis seems to be a promising target for the development of novel therapeutic for IBS<sup>[16]</sup>. In addition to this, various metabolic disorders have also been identified to be massively regulated by gut microbiota and their metabolites<sup>[6,17,18]</sup>. Involvement of gut microbiota metabolites in maintaining homeostasis including host immunity, physiological functions (digestion and nutrition) and biosynthesis of vitamins have also been recently validated by various research groups<sup>[18,19]</sup>. Experimental sets of data intoning functional cruciality of microbiota in IBS advocate their widespread interactions not localized only with intestinal cells and ENS, but also directly with CNS through neuroendocrine and metabolic pathways<sup>[19,20]</sup>. The ENS



composed of semiautonomous effector system, which is also connected to central autonomic network and modulated *via* afferent and efferent communications through parasympathetic and sympathetic nerves<sup>[21,22]</sup>.

Ongoing bidirectional brain-gut interactions are significantly influenced by serotonergic [5-hydroxytryptamine (5-HT)] pathway, where serotonin also known as 5-HT is an important neurotransmitter and paracrine signalling molecule<sup>[23,24]</sup>. Serotonin is synthesized by enterochromaffin cells (EC) of the gut and by serotonergic neurons in the CNS<sup>[25]</sup>. Aberrant 5-HT signalling has been found to accountable for various GI disorders, including IBS, diarrhea and chronic constipation, and functional dyspepsia<sup>[26,27]</sup>. Various components of serotonin signalling, including EC cells count, serotonin level, tryptophan hydroxylase activity, and expression of serotonin-selective reuptake transporters have also been found to be altered in IBS<sup>[28]</sup>. 5-HT signalling in between 5-HT receptors (on postsynaptic and presynaptic neurons at CNS and intestinal serotonergic neurons) and serotonin transporters (SERT) of various cell types of GI tract is crucial for proper functioning of gut-brain communication<sup>[29,30]</sup>. Additionally, 5-HT is produced by the chemical conversion of tryptophan to 5-hydroxytryptamine, a reaction catalyzed by enzyme tryptophan hydroxylase (TPH1 in EC cells and TPH2 in neurons)<sup>[31]</sup>. <sup>2</sup> Stored into vesicles formed through the vesicular monoamine transporter (VMAT; VMAT1 in EC cells and VMAT2 in neurons), 5-HT is further released into the extracellular space where its binds to different serotonin receptors (5-HTR)<sup>[32]</sup>. Further, it is known to regulate peristaltic, secretory, vasodilatory, vagal and nociceptive reflexes (Figure 2)<sup>[26,27,33]</sup>.

The present review summarizes recent updates consisting key components of microbiota derived GBA, molecular signalling during cross talk between GBA regulation and in the progression of IBS. Herein, we have also discussed the diagnostic and therapeutic implications of microbiota in the management of IBS and related symptoms.

## **IBS**

IBS is a GI disorder characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause which significantly affects the quality of life<sup>[34]</sup>. It is the most diagnosed functional GI disorder accounting for approximately 30 percent of all referrals to gastroenterologists<sup>[35]</sup>. The pathophysiology of IBS is the result of aberrated and interconnected signalling networks, especially between gut microbiome and brain<sup>[34,35]</sup>. However, the associated mechanisms and pathways are still unclear.

### ***Pathophysiology of IBS***

Traditionally, IBS was known to be associated with altered GI motility, visceral hypersensitivity and distorted pain perception<sup>[34,35]</sup>. Studies on IBS indicated the pivotal role of inflammation, alterations in fecal flora, and bacterial overgrowth<sup>[36]</sup>. IBS is also known as a psychosomatic illness since it is associated with mood disorders with abnormal psychiatric conditions<sup>[36,37]</sup>. Furthermore, mucosal immune activation, inflammatory cells and elevated inflammatory markers have been recorded in IBS patients<sup>[34,35]</sup>. Various studies associated with the effect of antibiotics in changing the gut microbiota diversity and complexities are co-related with gut microbiota profiles and IBS symptoms<sup>[34,38]</sup>. Perturbations in GBA have been also proposed as the main mechanisms in the pathophysiology of IBS. In a recent study, corticotrophin-releasing hormone (CRH) was also found to have an important role in IBS and in augmentation of intestinal mucosal inflammation<sup>[39-41]</sup>.

### ***Role of stress in IBS***

Studies are suggestive for co-morbidity of stress-related psychiatric illness and IBS, since 50%-60% of IBS patients have been diagnosed with various psychosocial health issues<sup>[42,43]</sup>. Psychological stress plays an important role in the pathophysiology of IBS, since it critically influences gut-brain axis and its associated metabolism<sup>[44]</sup>. It is also known to regulate intestinal motility and permeability, visceral hypersensitivity, immune responses, and gut microbiota composition<sup>[45,46]</sup>. Among the possible mechanisms for this regulation, immune response dependent secretion of various

proinflammatory cytokines seems to be the pivotal one<sup>[47]</sup>. These cytokines activate the HPA and hypothalamic-autonomic nervous system (ANS) axes along with the release of corticotropin releasing factor, adrenocorticotrophic hormone and cortisol, and all these subsequently control the gut homeostasis (Figure 3)<sup>[48]</sup>. It is established that these also alter neurotransmitter release within the enteric nervous system which thereafter affect gut motility, secretion and epithelial permeability *via* tight junction dysregulation<sup>[49]</sup>. An abnormal progression of monoamine neurotransmitter systems, including 5-HT and noradrenaline have been noticed in many stress related disorders. Furthermore, serotonin is known for its pivotal role in emotional response and in pain management by modulating brain-gut-microbiota axis, which is also significantly affected by early life stress<sup>[50]</sup>.

### **MICROBIOTA AND GBA**

Human GI tract hosts various genera of bacteria that are present on its mucosal surface. The term “microbiota” refers to the ecological system composed of various commensal bacteria in the GI tract, particularly localized on the lining of mucosal surface<sup>[51]</sup>. The term “microbiome” refers to metagenome of the microbiota and their genetic architecture<sup>[52]</sup>. Mucosal surface is the only layer separating host tissues from various germ lines by which host immune system remains protective against various pathogens in GI tract<sup>[52,53]</sup>.

#### ***Microbial colonization***

Although, majority of microbiota is still uncharacterized, it consists of a very delicate community of commensal organisms that have evolved over millions of years. Among all, four bacterial phyla including gram-positive *Firmicutes* (*Lactobacillus* spp.) and *Actinobacteria* (*Bifidobacteria* spp.) along with gram-negative *Bacteroides* and *Proteobacteria* are the most prevalent<sup>[6,54,55]</sup>. In addition to bacterial strains, various viruses, protozoa, archae, and fungus also constitute GI microbiota. Multidisciplinary studies were also performed to characterize the gut microbiota, thus revealing the

system as a state of symbiosis<sup>[56-59]</sup>. Homeostasis of host immune system and mucosal barrier are generally altered by dysbiosis, which in turn promotes the invasion and growth of pathogenic species. Microbiota also regulates gut inflammation with the presence of immune cells in gut wall<sup>[60]</sup>. Although, the complete sketch of a balanced microbiome is still unknown and each person is assumed to have a distinct microbiota (called as microbiome fingerprint), healthy individuals are generally known to have similar profile and distribution of bacterial phylotypes<sup>[61]</sup>.

Microbial colonization is a vital early life phenomenon as a part of development of a healthy microbiota which seems to be crucial for the development of GBA<sup>[62,63]</sup>. Altered microbial colonization in human GI tract has been clearly identified to exhibit adverse health effects in the later years of the host<sup>[63]</sup>. The colonization process is also regulated with various factors such as birth mode and feeding of babies, since the breastfed and vaginally born babies were reported to be initially colonised by the member of *Bifidobacteriae*, *Lactobacilli*, and *Bacteroides* species<sup>[64]</sup>. As compared to pre-term babies, full-term babies are reported for rapid maturation of gut microbiome in their first year of life. There is several evidence supporting the existence of a microbiota and foetal meconium, where the colonisation is reported to start even before the delivery, which suggest that these organisms could also colonise the foetal gut<sup>[65]</sup>. Various bacteria like *Staphylococcus*, *Streptococcus*, *Bifidobacterium*, and *Lactobacillus* are also reported in human milk<sup>[66]</sup>. Thus, colonization is significantly affected in neonatal period by human breast milk and the technique of delivery<sup>[67]</sup>. Moreover, mononuclear cells carrying bacterial population from the mother's gut to the mammary gland through an entero-mammary pathway are also playing pivotal role in gut immunological maturation of the infant<sup>[68]</sup>. This mammary microbiome also possesses anti-infective, anti-inflammatory, immunomodulatory and metabolic activities which also constitute for microbiota colonization in neonatal gut<sup>[69,70]</sup>.

### ***Role of microbiome in GBA***

The human microbiota play fundamental role in host physiology and pathology, and alteration in microbial population (dysbiosis) has been found to be significantly associated with various GI disorders<sup>[71]</sup>. A balanced interaction between microbiota and its host seems to be beneficial and essential for intestinal health and host metabolism. Under normal conditions, mucosal microbiota have been found to have significant role in digestion of food, vitamins synthesis, angiogenesis, epithelial cell and in development and maturation of the host defense system<sup>[72]</sup>. Recently, it has been evident that the intestinal bacterial population significantly affects the CNS physiology and gut inflammation, mainly by a bidirectional communication consisting of various signalling pathways. This communication is commonly known as GBA<sup>[73]</sup>, consists of multiple inter-connections including vagus nerve, immune components, and microbial metabolites<sup>[74,75]</sup>.

An enhanced size of microbiota and neuronal development takes place generally in starting five years of an infant, where the neuronal development is mainly configured by maternal microbiota<sup>[76]</sup>. The effect of gut microbiota on neurodevelopment of an infant was also examined and proved using various experiments on germ-free (GF) or specific pathogen-free mice. These mice were treated with various antibiotics to alter the microbial diversity and thereby to study their importance in gut microbiome<sup>[77,78]</sup>. These experiments clearly suggested that various neurological problems appeared in the treated animals due to improper maturation of gut microbiome. Results of these studies are suggestive of exaggerated HPA axis in germ free animals with impaired social behaviors, reduced anxiety and increased motor activity<sup>[79,80]</sup>. In the same experiment, altered neuronal developments and behaviors were found to be improved when the newborn infants were supplemented with various microbial flora<sup>[81]</sup>. These altered behavioral phenotypes were also found to deregulate various genes and metabolites involved in HPA axis regulation. Among these, some common regulators are adrenaline, 5-hydroxytryptophan, postsynaptic density protein 95, dopamine and synaptophysin<sup>[82]</sup>.



Scientific reports are suggesting that production of various neuroactive molecules by gut microbes directly or indirectly play critical role in GBA<sup>[83]</sup>. Among these neurotransmitters, acetylcholine,  $\gamma$ -aminobutyric acid and serotonin are released by various bacterial populations belonging to *Bifidobacteria*, *Lactobacillus*, *Enterococcus*, and *Streptococcus* species<sup>[84]</sup>. Interestingly, 90% of total serotonin is produced by gut microbiota, and used for mood disorders and functional regulation of CNS and GI tract<sup>[84,85]</sup>. Serotonin is known to bind to 5-HT receptors on microglial surface, thus inducing the release of inflammatory cytokines, which in turn play important role in the maintenance of gut inflammation<sup>[86]</sup>. In addition to 5-HT, tryptophan is also a serotonin precursor and known for influencing microglia activity in gut lumen. Moreover, tryptophan and its derivatives have been found to regulate CNS inflammation, particularly following an aryl hydrocarbon receptor (Ahr) mediated mechanism, which in turn is responsible for microglial activation and transcriptional regulation of astrocytes<sup>[87]</sup>. The vitality of tryptophan and its metabolism in maintaining CNS homeostasis has been reported recently, where GF animals were found to have augmented 5-HT levels and 5-hydroxyindoleacetic acid in the hippocampus and serum samples, compared to conventionally colonized control mice<sup>[87,88]</sup>. These findings are suggestive towards the ability of microbiota in maintaining CNS serotonergic neurotransmission, mainly through systemic circulation. These initial findings were also validated by colonizing these animals post-weaning, where they were found to have sufficient levels of tryptophan in peripheral samples and reduced anxiety. Interestingly, this colonization was found ineffective in reversing the CNS neurochemical consequences exhibited by GF animals<sup>[89]</sup>. In a recent study, one major finding was listed where an intact and diversified microbiota (post birth) was found to produce quinolinic acid and N-methyl-D-aspartate agonist, as a part of tryptophan metabolism regulated by microglial cells<sup>[90]</sup>. Both have a critical role in the pathogenesis of several neurological conditions such as Huntington's disease and behavioral disorders<sup>[91]</sup>. In experimental setup where GF mice were recolonized with bacterial

population belonging to *Clostridium tyrobutyricum*, they exhibited colonized mucus layer, and regulated immune and gut barrier homeostasis<sup>[92]</sup>.

Furthermore, *Lactobacillus rhamnosus* (JB-1) containing probiotics supplementations in previously colonized mice were found to be able to reduce anxiety and depressive like behavior<sup>[93]</sup>. Recently, researchers also found that microbiota dependent alterations in neural synapses along with fear extinction behavior are not mainly due to altered HPA axis, they are also due to a reduction in various neuroactive metabolites levels such as phenyl sulfate, pyrocatechol sulfate, and indoxyl sulfate<sup>[94,95]</sup>. This was further confirmed with the abraded levels of these metabolites in various samples collected from experimental animals, such as fecal, serum, and CSF. Collectively, gut microbiome and its associated bacterial populations were found to be pivotal in maintaining the level of various neuroactive metabolites through which they regulate the behavioral patterns in healthy subjects.

#### ***Regulatory crosstalk between intestinal microbiome and brain***

In humans, ENS is generally referred as the second brain which is located inside the digestive tract wall and shielded by a mucous membrane from gut lumen, having five times higher neurons and ganglia than spinal cord. An autonomous system regulating microbiome and GBA is known to be bidirectional whereas somatic sensory system received signals in pathological conditions causes abnormal feelings like discomfort, nausea, and pain which in turn exhibit bowel associated problems<sup>[96]</sup>. Herein, ANS transports afferent signals received from gut lumen to CNS through various routes such as enteric, spinal and vagal<sup>[96]</sup>. In these communications, vagus nerve plays a critical role as it has millions of nerve terminals (80% are afferent). Moreover, the same pathway is also used to send efferent signals from CNS to the gut wall<sup>[97]</sup>. In case of stress and anxiety, neuroendocrine system in response to stress regulates various vital body functions, including digestion and immunity which are mainly dependent on the HPA axis<sup>[98]</sup>. For example, generation of corticosteroids in response to environmental stress is also found to be dependent on HPA axis<sup>[97]</sup>. Collectively, neural and hormonal

signals regulate brain and microbiome for further regulation of gut cell activity in controlled conditions.

In addition, signal transducing cells such as enterochromaffine cells (EC) and dendritic cells (DC) produce various neurotransmitters (Figure 2) *viz.*, 5-HT, somatostatin, cholecystokinin and CRH<sup>[99-101]</sup>. All these are important for signal-based regulation of microbiota and CNS as these directly affect the microbial behavior. EC serve as luminal sensors for observing a great range of bacteria and microbial compounds in the gut<sup>[102]</sup>. These microbial populations have neurotransmitter receptors, and their activation is a key factor to understand the mode of microbiota functions and composition. A specialized process called as “*inter-kingdom signalling*” is a well-known regulatory pathway through which bacteria communicate with gut epithelial cells, mainly by using oligopeptides and monoamines which are also known for their neurotransmitter behavior<sup>[103,104]</sup>. Numerous neurotransmitters are produced by ENS exhibiting critical roles in GBA regulation, where each has a specific signalling pathway. Some neurotransmitters such as 5-HT, somatostatin, dopamine, neuropeptide Y, peptide YY, cholecystokinin, and corticotropin-releasing factor are also necessary for GBA regulation<sup>[96,101,104]</sup>.

EC in GI tract produces majority of body's 5-HT and dopamine. An increased synthesis of 5-HT has been found as a key regulator through which microbiota regulates HPA<sup>[97]</sup>. Additionally, gut microbiota senses the EC cells mainly *via* short-chain fatty acids (SCFA) (butyrate and acetate) to promote 5-HT synthesis that regulates GI motility, secretion and immunological responses<sup>[96]</sup>. Hence, a change in microbiota composition significantly affects the levels of 5-HT and its altered level contributes towards the pathophysiology of IBS. Interestingly, microbiota is also connected with CNS through TLR signalling pathway<sup>[105,106]</sup>. TLR is principally expressed on immune cells of gut wall and neurons of the ENS. Among microbial populations, gram-negative bacterial membrane component lipopolysaccharide (LPS) is selectively detected by TLR which in turn is responsible for the production of proinflammatory cytokines *via* NF- $\kappa$ B pathway<sup>[106]</sup>. In colonic biopsies of IBS-D patients, higher TLR expression has been



recorded suggesting microbiota and host immune system interaction<sup>[102,104]</sup>. Furthermore, smooth muscle dysfunction and paralysis in septic ileus is also known to be significantly influenced by the number of cytokines produced by immune cells, in response to LPS through TLR mediated signalling<sup>[106]</sup>.

## **INTESTINAL MICROBIOME AND SEROTONERGIC SIGNALLING**

### ***Serotonergic system***

5-HT is an important neurotransmitter and paracrine signalling molecule in the gut where its major role has been identified in the modulation of gut-brain communication and in functional GI disorders<sup>[21]</sup>. In previous studies, altered levels of 5-HT have been reported in various CNS related disorders including anxiety, depression, obsessive compulsive disorder, phobias and in other psychiatric disorders<sup>[67,69]</sup>. 5-HT modulators including SSRIs and specific 5-HT receptor agonists and antagonists have also been used to treat various metabolic disorders such as, migraine, nausea, obesity, chronic pain, hypertension, vascular disorders, and sexual dysfunction<sup>[107]</sup>.

### ***5-HT signalling in GI tract motility***

Among all the neurotransmitter-based regulations of GBA, 5-HT mediated signalling is primary where 5-HT mainly targets receptor subtypes of seven 5-HT family receptors, having 15 subtypes of recognition sites<sup>[85]</sup>. Additionally, seven types of 5-HT receptors have a wide range of biological tasks including enhancing mucosal permeability and visceral hypersensitivity, inflammation and immune cell activation, and gut motility<sup>[107]</sup>. Currently, 7 families of 5-HT receptors have been identified, where 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors are in intestine, presynaptic positions and, in sensory and mesenteric neurons<sup>[107]</sup>. In clinical practices, medications that are known to target these receptors have been frequently used for the management of IBS complications. Enteric microbiota has also been found to control the expression of 5-HT receptors<sup>[107]</sup>. 5-HT mainly activates peristaltic reflexes in GI tract (Figure 4) thus causing ascending contractile and descending relaxant limbs. 5-HT has been also found to control segmental motor

patterns in small intestine. A study performed in tryptophan hydroxylase deficient (Tph2<sup>-/-</sup> mice) mice demonstrated the functional aspects of 5-HT in GI motility mainly by attributing with significant reductions in contractile complexes and synaptic transmission due to lower level of 5-HT<sup>[108,109]</sup>. This is further indicative for the significance of serotonergic neurons, comparing to EC cells for constitutive GI motility. Additionally, ENS dopaminergic neurons were found to be immature in Tph2<sup>-/-</sup> mice, which are responsible for homeostatic GI movement<sup>[110]</sup>. Moreover, *in vivo* and *in vitro* studies have shown decreased intestinal motility in mice with SERT Ala56 mutation which was restored by 5-HT<sub>4</sub> receptor antagonists<sup>[111]</sup>. A SERT antagonist named 'fluoxetine' was found to improve GI motility in SERT<sup>-/-</sup> mice, along with a higher level of 5-HT, thus indicating the importance of 5-HT in GI motility, by targeting SERT<sup>[112]</sup>.

Various antibiotic treatments have been found to impede GI motility along with a reduced production of peripheral 5-HT level, which was also confirmed by GF animal studies where a slower GI transit was recorded in these animals compared to control mice having normal gut microbiota<sup>[66,112]</sup>. In GF mice, treatment with pharmacological blockers of 5-HT<sub>4</sub> receptors significantly improved GI transit along with a higher level of luminal 5-HT level<sup>[113]</sup>. Additionally, 5-hydroxyindole has been produced as a key metabolite of serotonin metabolic pathway (Figure 4), mainly by increasing the colonic motility, especially by activating L-type calcium channels<sup>[114]</sup>. Recently, in a BTBR (BTBR T+ Itpr3tf/J) mice model of autism spectrum disorder, an altered serotonergic pathway has been found along with downregulation of Tph1 gene, while SERT expression was upregulated along with a reduced level of 5-HT and its producing host (*Blautia* spp)<sup>[115]</sup>. A list of various enteric microbiota and their mode of regulating serotonergic pathway are listed in Table 1. Additionally, 5-HT level in combination with gut microbial stimulus can also lift the proportion of M20000 macrophages, which are known to be stimulatory for GI motility particularly in the colonic muscle layer located nearby ENS<sup>[117]</sup>. Various microbial byproducts such as SCFAs were also found to enhance colonic transit with the release of 5-HT intra-luminally, mainly by targeting

GPR43 receptor located on mucosal mast cells<sup>[117]</sup>. Therefore, these findings clearly suggest that through various mechanisms enteric microbial population controls 5-HT level and associated signalling for the control of GI motility, and dysregulation in this system resulted in abnormal GI movement, which is linked with IBS symptoms<sup>[116,117]</sup>. It has been widely accepted that IBS patients have altered motor and stool patterns, where enhanced GI motility produce abnormal gut contractions resulting in abdominal pain and discomfort.

#### *Role of gut microbe-mediated 5-HT signalling in visceral pain sensation*

Chronic abdominal pain is a crucial aspect of IBS which is also influenced by intestinal gut microbiota<sup>[118]</sup>. Animal studies are further suggestive for the ability of fecal microbiota to transmit hypersensitivity to colonic distension in rats<sup>[119]</sup>. These results suggest that abnormal pain perception associated with IBS is also critically derived from gut microbial components<sup>[118,119]</sup>. Additionally, neurotransmitters derived from gut microbiota have been also found to be decisive for the perception of visceral discomfort. Among the other neurotransmitters, a preferential role of 5-HT has been found to modulate the intestinal pain by activating mesenteric sensory nerve fibers along with the activation of vagal and spinal afferent fibers<sup>[120]</sup>. Microbial colonization and their commensal activities have been reported to be essential for promoting excitability of the gut sensory neurons, which are responsible for the development of homeostatic pain sensitivity<sup>[121]</sup>. In GF mice, where a little mucosal inflammation has been found to be associated with visceral hypersensitivity caused by abnormal pain processing in the brain, it can be corrected by fecal microbiota transplantation (FMT) therapies derived from conventional mice<sup>[122]</sup>. FMTs are also known to stimulate primary nociceptive neurons in the dorsal root ganglia (DRG) and various gut microbial components such as TLR ligands, formyl peptide receptor 1 agonists and SCFAs<sup>[122]</sup>. These can modulate direct or indirect enhancement of visceral pain sensitivity. Additionally, microbiota derived kynurenic acid, serine proteases and bile acids can

reduce pain sensitivity by inactivating DRG neurons or indirectly by releasing opioid-like factors, mainly from the mucosal immune cells<sup>[123,124]</sup>.

Interestingly, the mode of action of 5-HT mediated signalling depends on the type of 5-HT receptor activation and the release of enteric 5-HT, which has been significantly linked to the intensity of abdominal discomfort in IBS patients<sup>[125]</sup>. The etiology of IBS also includes visceral hypersensitivity along with the nociceptive process and these are mainly regulated with 5-HT<sub>3</sub> receptor activation, where it is mainly expressed on peripheral terminals of spinal afferent nerves and vagal afferent nerve endings in stomach<sup>[125]</sup>. 5-HT<sub>3</sub> receptor has been also identified to influence other neurotransmitters in the brain, where a 5-HT<sub>3</sub> receptor antagonist (Ramosetron) has been found to lower the visceral hypersensitivity and modifies GI transit in IBS-D patients<sup>[126]</sup>. Additionally, 5-HT<sub>3</sub> receptor antagonists have demonstrated anti-inflammatory effects particularly to the enhanced permeability of gut and mucosal inflammation reported to be caused by various microbial populations<sup>[125]</sup>. Moreover, an impaired intestinal barrier linked to dysfunctional 5-HT metabolism in IBS patients has been observed recently<sup>[126]</sup>. Collectively, these findings are indicative of the vitality of gut microbiota in 5-HT-mediated pain perception, where visceral hypersensitivity resulted from the dysfunction of serotonergic pathway has been linked to enteric dysbiosis as reported in IBS cases<sup>[127,128]</sup>.

#### *Role of gut-microbe-mediated 5-HT signalling in mucosal inflammation and immune response*

Among the various pathways underpinning the IBS pathogenesis, a persistent and low-grade mucosal inflammation has been reported in majority of clinical cases, with aberrant immune cell activation<sup>[90-129]</sup>. In IBS patients, abdominal pain has been characterized with a significant infiltration of mast cells in the colonic mucosa, which is also accompanied with an augmented level of mucosal 5-HT<sup>[28,29]</sup>. Although, exact underlying mechanisms and causes of mucosal inflammation are not completely known, dysbiosis of the gut microbiota along with altered serotonergic signalling have

been identified as the important contributors for the onset of IBS. Indeed, augmented numbers of mucosal and EC cells have been recorded in various inflammatory diseases, such as inflammatory bowel disease (IBD), where a range of 5-HT receptors are expressed to stimulate intestinal inflammation through serotonergic signalling<sup>[118]</sup>. In colitis, 5-HT directs proinflammatory cytokines generations by stimulating T cells, peritoneal macrophages and splenic DCs in NFκB-dependent manner<sup>[130]</sup>.

Moreover, enhanced 5-HT availability has been recorded in SERT-deficient animals sensitive to gut mucosal inflammation whereas Tph1-/- mice with a lower level of 5-HT have been found to be resistant to experimental colitis<sup>[131]</sup>. These results suggest that intestinal inflammation is significantly regulated by enteric 5-HT, mainly by acting as pro-inflammatory immune regulator. Various results derived from a post-inflammatory IBS rat model also reveal the onset of visceral hypersensitivity along with fecal microbial dysbiosis, along with an elevated serum level of 5-HT<sup>[132]</sup>. Additionally, in recent studies lamina propria mast cells (MC) were found to be significantly co-related with an enhanced and spontaneous release of 5-HT in IBS patients<sup>[133]</sup>. Interestingly, histamine has also been identified as an important biogenic amine found to have pathophysiological role in IBS, where the exact mechanism is still not fully deciphered.

Usually, histamine played critical roles in regulating GI motility, gastric acid and mucosal ion secretion<sup>[49,133]</sup>. Histamine H1 receptors (H1R) are known to be involved in mediating sensorineural signalling and vascular dilatation, where their activation is known to regulate food and water intake and diurnal feeding rhythm. In addition to this, stimulation of histamine H2 receptors (H2R) have been known for the degranulation of MCs and production of various antibodies, T helper (Th) 1 cytokines, and for T-cell proliferation<sup>[133,134]</sup>. However, evidences are indicative for the overproduction of histamine by MCs that has been known to cause diarrhea, with an increased neuronal secretomotor function. In constipation, histamine also induces altered enteric neuron function resulting in an excessive segmental contractile colonic motor activity<sup>[50,135]</sup>. Although, evidences suggested that use of various agents targeting



the histamine receptors (HRs) have been found to be potential therapeutic option for IBS patients<sup>[134]</sup>.

In addition to this, upregulated expression of various colonic receptors of 5-HT (5-HT<sub>3A</sub>/5-HT<sub>2B</sub>) along with impaired junction proteins has been found in test animals<sup>[136]</sup>. Additionally, 5-HT<sub>3A</sub> receptor antagonist administration or FMT derived from the faeces of normal healthy rats, were found to be able to alleviate IBS-like symptoms<sup>[136]</sup>. Moreover, SCFAs from the gut microbiota have been appeared to have a dual nature directing GI mucosal immunity and inflammation, which are known to be crucial for maintaining gut homeostasis<sup>[58]</sup>. These cause the over expression of G-protein coupled receptors and induction of regulatory T cells in the gut which in turn increases the integrity of epithelial cell barrier, and thus exhibiting anti-inflammatory effects<sup>[136]</sup>. In parallel to this, SCFAs are known to cause mucosal inflammation by promoting mucosal 5-HT synthesis (serotonergic pathway) and upregulation of TPH1 transcription<sup>[137]</sup>.

#### ***Microbiota mediated serotonergic signalling outside GI tract***

Various preclinical and clinical data have demonstrated the critical role of 5-HT derived from gut in glucose and lipid metabolism, and in various metabolic disorders<sup>[138,139]</sup>. Various antagonist specific to 5-HT receptors have been beneficial in reversing the clinical manifestations received by altered 5-HT metabolism. For example, fluoxetine was used to prevent *T. sanguinis* population by lowering serum triglyceride levels and changing the expression of lipid metabolism genes<sup>[139]</sup>. Additionally, the gut was found to be significantly regulated by its microbiota member "*Clostridium ramosum*" which is found to be associated with lipid transport and storage functions in animals. Furthermore, glucose homeostasis is also controlled by various members of enteric microbiota, mainly with the modulation of EC cell's 5-HT production where this was mainly targeted with the inhibition or genetic depletion of TPH1<sup>[140]</sup>. Purine metabolism was also found to be regulated with host-microbial metabolic route in IBS patients<sup>[141]</sup>.

These results are clearly indicative for the 5-HT-dependent regulation of various metabolic pathways in the pathogenesis of IBS.

### **ROLE OF GUT MICROBIOME DERIVED METABOLITES IN IBS**

The population of gut microbiota has been reported to be massive along with a modular genome which in turn reported to be benefitting the host and adapted to gut environment. These microbes carry out a variety of tasks, such as xenobiotic metabolism, vitamin production, pathogen defense, and dietary fiber fermentation<sup>[115,136,142]</sup>. Microbiota derived <sup>13</sup>metabolites are small substances synthesized as intermediate or end products of microbial metabolisms, which are also the principal regulators through which gut microbiota plays an important role in host specific metabolism<sup>[136]</sup>. These metabolites may be produced directly by bacteria, by alteration of host molecules like bile acids, or through bacterial metabolism of food components. Immunological maturation, immune homeostasis, host energy metabolism, and mucosal integrity maintenance are all identified to be influenced by microbial metabolites mediated endocrine signalling<sup>[11,12,14]</sup>. IBD's pathophysiology has been principally linked to certain groups of metabolites, such as bile acids, SCFAs, and tryptophan which have been found in a variety of biological tissues, including faeces, urine, serum, liver, and cerebrospinal fluid, thus having significant impact on the physiology of the host<sup>[17,136]</sup>. Additionally, some metabolites have been also found to be specific to Crohn's disease patients and non-IBD controls, where individuals with IBD were found to have higher amounts of bile acids, amino acids, and sphingolipids<sup>[143]</sup>. Interestingly, these individuals have lower levels of cholesterol, phenylbenzodioxanes, indoles, tetrapyrroles and long-chain fatty acids<sup>[144]</sup>. SCFAs are derived from carbohydrates and are localized to microbiome, regulating the function of intestinal macrophages, appetite, fat accumulation, intestinal motility and energy metabolism<sup>[145]</sup>. Other SCFAs produced by microbial fermentation include acetate, propionate, and butyrate, as well as the gases methane, hydrogen sulphide and some other intermediates<sup>[145,146]</sup>. Butyrate, along with other SCFAs, inhibits epithelial stem cells and

promotes epithelial homeostasis by producing IL-18 through inflammasome activation, which is known to be the main source of energy in colonic epithelial cells<sup>[147]</sup>.

Like SCFAs, medium-chain fatty acid levels have been found to be depleted in IBD. Thus, it is hypothesized that certain fatty acids, such as conjugated linoleic acid might exert some anti-inflammatory effects by activating the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ )<sup>[148]</sup>. Additionally, bile acids also influence host metabolism and immune system *via* interacting with receptors, such as the transmembrane G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR)<sup>[149]</sup>. By activating type 2 iodothyronine deiodinase, TGR5 enhances insulin sensitivity (*via* GLP1), thus regulating energy expenditure (in muscle and brown adipose tissue), and gall bladder relaxation<sup>[149]</sup>. Activation of bile acid receptor (FXR) also affects host metabolism through various ways, including decreased lipogenesis, hepatic gluconeogenesis, and liver regeneration, as well as by generating antimicrobial peptides for liver regeneration<sup>[150,151]</sup>. Constitutional makeup of gut microbiota is also significantly influenced by bile acid composition. Furthermore, activation of small intestine FXR also reduces bacterial translocation and growth<sup>[152]</sup>.

In addition to other metabolic intermediates, <sup>1</sup>tryptophan is a well-known precursor for the synthesis of several metabolites such as serotonin, melatonin, nicotinamide and vitamin B3<sup>[153]</sup>. Gut is the main site of tryptophan synthesis and metabolism, where it is converted by commensal microbiota into indoles agonists of pregnane X receptor and AhR, which have pivotal roles in mucosal immunity and homeostasis<sup>[154,155]</sup>. Moreover, dysbiosis in IBD also causes a significant decrease in microbial tryptophan activation, which in turn increases metabolism (Figure 4)<sup>[148,149]</sup>. Indole also <sup>1</sup>stimulates GLP1 release while other indole derivatives [such as indoleacetic acid, indole-3-acetaldehyde, indole-3-aldehyde, indoleacrylic acid (IA) and IPA] are also known to act as agonists for AhR<sup>[156]</sup>. Additionally, AhR also act as a transcription factor which having developmental and tissue-dependent effects on T cell immunity<sup>[157]</sup>. Reduced AhR expression has been noted in inflamed mucosal samples from Crohn's disease patients whereas serum samples from these patients were also found to have altered xenobiotic



metabolism<sup>[158]</sup>. Moreover, enhanced catabolism of fatty acids, reduced level of <sup>1</sup>amino acid metabolites including serotonergic and indole derivatives of tryptophan, as well as decreased levels of phenylalanine and histidine metabolite ergothioneine has been also found in these patients<sup>[153,155,158]</sup>.

### **MICROBIOME TARGETED THERAPEUTICS FOR IBS**

Restoring the gut microbiome seems to be promising and therapeutic strategy for the management of IBS with diversified clinical scenarios. Moreover, maintaining the GI microbiome to a level of optimal health with the ideal fecal product is known to be challenging and beneficial to human being. In recent years, FMT has been introduced to yield promising results in various gut disorders such as in *Clostridioides difficile* infection, where FMT has shown high cure rates, compared to other standard therapies<sup>[55,159,160]</sup>. This initial lead has been also implanted with microbiome manipulation for the treatment of IBD, ulcerative colitis and Crohn's disease, with a higher rate of cure and effectively<sup>[161,162]</sup>. However, designing FMT formulations as the treatment for IBS is very challenging, since the optimal microbiome composition in healthy people is poorly defined with a higher degree of variability<sup>[163]</sup>. In addition to this, disrupted microbiota which would be ideally restored *via* FMT is known to be highly variable.

Interestingly, dysbiosis of several inflammatory markers is known to induce the expansion of facultative anaerobes, where the mechanisms by which microbiota are disrupted remain unclear. At the same time, GI tract is known to be contributory for key determinants of FMT success whereas, some patients that received FMT also developed systemic infections owing to the adverse effects of FMT<sup>[61,63,148]</sup>. To avoid the side effects received from FMT application, one more way is to administer autologous FMT (auto-FMT also known as microbiome restoration), where <sup>11</sup>patient sample is screened for various pathogens, banked and then re-administered to the same patient after disrupting microbiome. In this case, restoring the microbiome samples for a long period of time has storage and safety issues, leading to future health problems.

Meanwhile, several IBS therapeutics (Table 2) have been developed which are known to target the gut microbiota and target secondary consequences of alterations in the gut microbiota<sup>[164]</sup>.

## **CONCLUSION**

IBS is a prevalent GI disorder where mechanisms regulating the interconnected cross talk between brain and gut microbiota have been found to be altered. Various metabolic pathways and diseases have also been found to be associated with gut microbiota architecture. The pathophysiology of IBS is still not fully deciphered, whereas a complex network of interaction between various genes, metabolic pathways, behavioral events, host immune response and psychosocial factors has been found to be contributory for IBS and its associated symptoms. Interestingly, serotonin (5-HT) as a neurotransmitter secreted by EC cells regulates GI motility, secretion and sensation, whereas altered 5-HT signalling has been found contributory in the pathophysiology of IBS. Furthermore, environmental stress has a significant impact on IBS etiology where it significantly regulates the neuroendocrine system and gut functions, mainly through immune system mediated mechanisms. The dietary composition and its intake have a pivotal role in the regulation of IBS, hence usage of quality foods which are gluten free, low fat and FODMAP content, tryptophan and fiber rich may be prominent approach for the management of IBS.

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## Figure Legends

**Figure 1 Regulatory cross talk between gut and brain.** The central nervous system and enteric nervous system mainly communicate through vagal and autonomic pathways to control various gastrointestinal functions in a bidirectional approach. These signalling cascades are also regulated through mood and cognitive processes and significantly affected by environmental factors and early adverse events. These signalling crosstalks are significantly altered in irritative bowel syndrome (IBS) thus resulting in abnormal gastrointestinal motility, visceral hypersensitivity and bowel movements. Perturbations in the gut microbiome composition and diversity through various sources alter this cross talk, thus resulted in interceptive feedback to brain and causing functional and neuroplastic changes. Microbial metabolites released from various microbial populations have critical role in these crosstalks, thus having therapeutic values for the management of IBS. ANS: Autonomic nervous system; HPA: Hypothalamic-pituitary-adrenal axis; ECC: Enterochromaffin cells; ICC: Interstitial cells of Cajal; SMC: Smooth muscle cells; SCFAs: Short chain fatty acids; ENS: Enteric nervous system.

**Figure 2 Serotonin mediated bidirectional cross talk between gut microbiota and brain.** Serotonin (5-HT) plays a key role in microbiota-gut-brain communications to modulate gastrointestinal (GI) and central nervous system (CNS) functions. Serotonin action is mediated through various signalling mechanisms between 5-HT receptors located in postsynaptic and presynaptic neurons at CNS and intestinal serotonergic neurons, and in different cell types of GI tract. Serotonin is synthesized by enterochromaffin cells (EC) in the gut and serotonergic neurons in the CNS. Microbial associated molecular patterns from microbiota directly affect the serotonergic system,



mainly through modulating the activity and expression of serotonin transporter (SERT) and serotonin receptors (5-HT<sub>Rs</sub>), as well as the synthesis of 5-HT in GI tract. Stored into vesicles forms through the vesicular monoamine transporter (VMAT; VMAT1 in EC cells and VMAT2 in neurons), 5-HT is further released into the extracellular space where it binds to different serotonin receptors (5-HT<sub>R</sub>). At the same place taken up by the neurons, enterocytes or platelets through the SERT limit the 5-HT mediated signalling crosstalk. 5-HT: 5-Hydroxytryptamine; TLR: ; NLR: SFCA: MAMP: Molecular patterns from microbiota; SERT: Serotonin transporter; VMAT: Vesicular monoamine transporter.

**Figure 3 Impact of stress on irritable bowel syndrome.** A bidirectional signalling has been identified between brain and gut, under stress condition in irritable bowel syndrome (IBS). Stress induces the activation of HPA axis which results the release of various stress factors such as corticotropin-releasing factor from hypothalamus, thus causing the release of glucocorticoids from adrenal glands. This collectively alters bowel function and stimulates the upregulation of immune system, which directly or indirectly regulates gut function. In addition to this, stress also modulates the tryptophan metabolism by up-regulating kynurenine pathway which generates neurotoxic and neuroprotective metabolites. Enzymes responsible for the degradation of tryptophan are significantly affected by immune pathways (indoleamine-2,3-dioxygenase, IDO) and stress levels (tryptophan-2,3-dioxygenase, TDO). Under stressed conditions and due to excess availability of kynurenine and its metabolites, the activation of these pathways leading to potential serotonergic deficiency along with altered enteric nervous system (ENS) and central nervous system (CNS) functionalities, thus leading to microbial dysbiosis, as a classical symptom of IBS. CRF: Corticotropin-releasing factor; ANS: Autonomic nervous system; CNS: Central nervous system; ACTH:

**Figure 4 Tryptophan derived serotonergic metabolism in gut brain axis cross talk.**

Upon absorption in the gut, L-tryptophan is metabolized through three pathways, particular to bacterial cells (indole pathway) of gut microbiota and mammalian cells (kynurenine and serotonin pathways). Tryptophan is converted to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase and there after converted to -5-HT by the enzyme aromatic L-amino acid decarboxylase. In addition to this, tryptophan is also metabolized to indole derivatives and kynurenine, which also perform various biological functions. Tryptophan derived 5-HT regulates various functions in central nervous system (including emotion, cognition, stress, and visceral perception) and also in enteric nervous system (gastrointestinal motility and secretion). CRF: Corticotropin-releasing factor; ANS: Autonomic nervous system; CNS: Central nervous system; GI: Gastrointestinal; 5-HT: 5-Hydroxytryptamine.

**Table 1 Types of regulation of serotonergic (5-Hydroxytryptamine) pathway by specific enteric microbiota in gastrointestinal tract**

<i>Microbiota spp</i>	5-HT pathway	Mechanisms of action and observations	Ref.
<i>Akkermansia muciniphila</i> (Amuc_1100)	Upregulation	Promote intestinal 5-HT biosynthesis and extracellular availability through TLR2 signalling	[129]
<i>Akkermansia muciniphila</i> (extracellular vesicles)	Upregulation	Increase expression of the Htr4 gene, and decreases expression of the Htr2B, Htr3B, and Htr7 genes	[129]
<i>Bacteriodes thetaiotaomicron</i>	Upregulation	Restore 5-HT+ EC cells and shape EC networks in the GI tract of GF mice by producing SCFAs	[130]
<i>Bifidobacterium dentium</i>	Upregulation	Increase intestinal 5-HT level; expressions of 5-HTra receptors 2a and 4, and SERT by producing acetate	[131]
<i>Bifidobacterium longum</i> and <i>Lactobacillus acidophilus</i>	Downregulation	Upregulate SERT expression	[132]
<i>Bifidobacterium pseudolongum</i>	Downregulation	Diminish EC cells	[133]
<i>Clostridium ramosum</i>	Upregulation	Promote 5-HT synthesis in colonic EC cells and program differentiation of intestinal stem progenitors toward a secretory 5-HT-producing lineage	[134]
<i>Corynebacterium</i> spp., <i>Enterococcus</i> spp., <i>Streptococcus</i> spp.	Upregulation	Enable the direct production of 5-HT	[135]
<i>Escherichia coli</i> Nissle 1917	Upregulation	Enhance 5-HT bioavailability in ileal tissue through interaction with compounds secreted	[136]

		from host tissue	
Indigenous spore-forming bacteria	Upregulation	Enhance colonic 5-HT pathway by upregulation of Htr4	[137]
<i>Lactobacillus acidophilus</i>	Down regulation	Upregulate SERT expression	[138]
<i>Lactobacillus plantarum</i> IS-10506	Upregulation	Increase gut 5-HT production along with brain 5-HTT, neurotrophin, and brain-derived neurotrophic factor	[139]
<i>Lactobacillus plantarum</i> PS128	Upregulation	Increase 5-HT+ cells in the gut and alter expression levels of Tph1, Chga, Slc6a4, and Htr4	[140]
<i>Lactobacillus rhamnosus</i>	Down regulation	Upregulate gene and protein level of SERT	[141]
<i>SadA</i> -expressing <i>Staphylococci</i> , <i>Trichinella spiralis</i> and <i>Campylobacter jejuni</i> (pathogens)	Upregulation	Promote converting 5-HTP into 5-HT; increase EC cell number and reduce SERT expression	[141]

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5-HT: 5-Hydroxytryptamine; 5-HTP: 5-Hydroxytryptophan; EC: Enterochromaffin cell; SERT: Serotonin transporters.

**Table 2 Various therapies prescribed for the treatment of irritable bowel syndrome along with their possible mode of action**

Therapy	Description	Proposed mechanism(s) of action
Prebiotics	Ingested compounds targeted to stimulate gut microbiota	Mechanism of action undefined, but may include: Anti-inflammatory effects; inhibition of pathogen adherence; and growth of intestinal mucosal layer
Probiotics	Ingested microorganisms (e.g., bacteria)	Mechanism of action undefined, but may include: Inhibition of pathogenic microorganism colonization; support intestinal barrier integrity and function; production of beneficial micronutrients; and activation and augmentation of the enteric nervous system
Rifaximin	Nonabsorbable, bile-soluble antibiotic indicated for the treatment of adults with IBS-D	Antibacterial against Gram-positive and Gram-negative bacteria: Modulation of gut-immune signalling; inhibition of bacterial translocation; SIBO eradication (in some patients); causing decreases in GI methane concentrations in combination; and with the antibiotic neomycin (in patients with IBS-C)
SBI	Prescription medical food for patients with IBS-D	Modulation of gut microbiota: Causing decreases in GI permeability
SYN-010	Derivative of the HMG-CoA reductase inhibitor lovastatin lactone; currently in development for the treatment of patients with IBS-C	Inhibition of methane production by <i>Methanobrevibacter smithii</i>
Dietary modification	Variable; one example is the low FODMAP diet	Causing decreases in GI gas production Causing decreases in intra-luminal fluid production

FODMAP: Fermentable oligo-, di-, monosaccharides and polyols; GI: Gastrointestinal; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; IBS-C: Constipation-predominant irritable bowel syndrome; IBS-D: Diarrhea-predominant irritable bowel syndrome; SBI: Serum-derived bovine immunoglobulin; SIBO: Small intestinal bacterial overgrowth.

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