gastrointestinal disorders

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Review

Gut–Brain Axis, Microbiota and Probiotics—Current Knowledge on Their Role in Irritable Bowel Syndrome: A Review

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Abstract: Irritable bowel syndrome (IBS) is a common digestive disorder with a significant impact on both individuals and society in terms of quality of life and healthcare costs. A growing body of research has identified various communication pathways between the microbiota and the brain in relation to motility disorders, with the gut–brain axis being key to the pathogenesis of IBS. Multiple factors contribute to the pathogenetic pathways in IBS, including immune mechanisms, psychosocial factors, increased oxidative stress and pro-inflammatory cytokine release, as well as genetic and hormonal factors. Increased permeability of the normal intestinal barrier allows bacterial products to access the lamina propria, providing a mechanism for perpetuating chronic inflammation and characteristic symptoms. The microbiota influences inflammatory processes in IBS by altering the balance between pro-inflammatory factors and host defence. Probiotics modulate the pathophysiological mechanisms involved in IBS by influencing the composition of the microbiota and improving intestinal motility disorders, visceral hypersensitivity, immune function of the intestinal epithelium, metabolic processes in the intestinal lumen, dysfunction of the microbiota-GBA, and are recognised as effective and safe in IBS therapy. Our study aimed to provide a comprehensive overview of the relationship between the gut–brain axis, microbiota, and IBS, based on current information.

Keywords: irritable bowel syndrome; gut–brain axis; gut microbiota; inflammation; visceral hypersensitivity; probiotics

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1. Introduction

Irritable bowel syndrome (IBS) is a relatively common digestive disorder. It is estimated that IBS has a prevalence of 10–15% in the general population in industrialized countries and is a factor with a significant impact on both the individual and society in terms of quality of life and health care costs [1].

Depending on symptomatology, comorbidities, quality of life and healthcare needs, IBS can have a mild, moderate, or severe clinical course. Some studies have shown that the severe form occurs in 15–40% of patients with IBS [2].

IBS is defined as an intestinal disorder associated with abdominal pain and dyspepsia in the absence of proven pathology by paraclinical investigations. The ROMA IV criteria, presented at the Digestive Disease Week in May 2016, included significant changes in the diagnostic criteria in terms of symptomatology and incidence [3], which appeared to be necessary due to the progress made in recent years in both basic research and clinical trials. Functional digestive disorders have been redefined as abnormalities of the gut–brain interaction, a group of diseases characterised by gastrointestinal symptoms related to a series of abnormalities: motility disorders; visceral hypersensitivity; disturbances of the digestive mucosa and local immunity mechanisms; alteration of the microbiota; alteration of CNS information [3].

In this study, we aimed to review current literature and summarize information about the gut–brain axis and IBS that is both scientifically accurate and relevant for physicians.

2. Pathogenetic Hypotheses in IBS

Multiple mechanisms were proposed to explain in the pathogenesis of IBS (Figure 1).

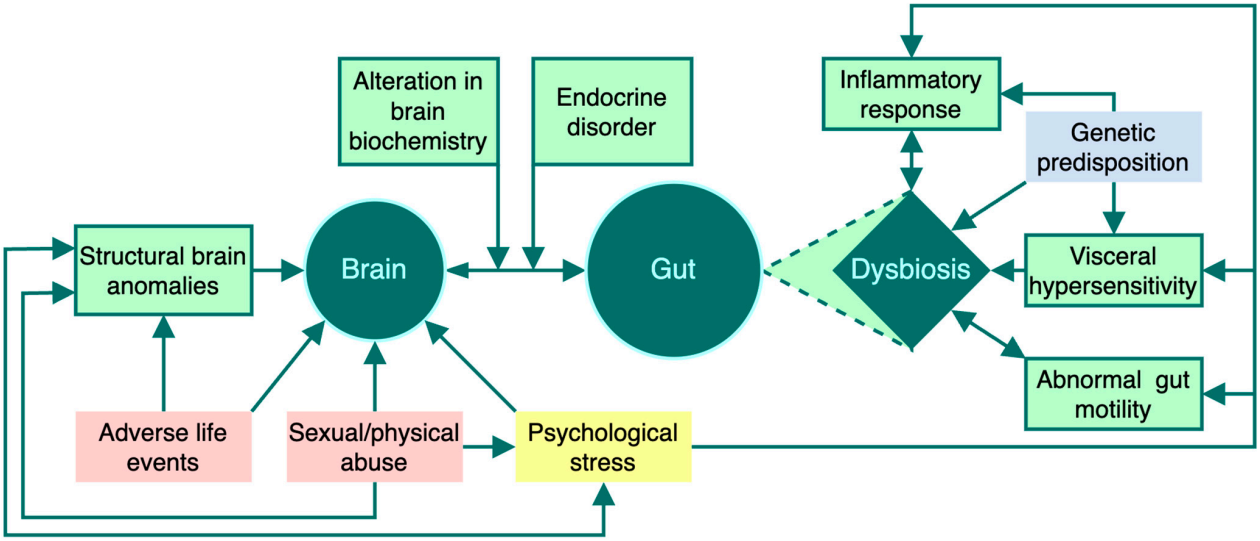

Figure 1. Pathogenetic mechanisms involved in irritable bowel syndrome.

2.1. The Gut-Brain Axis

A growing body of research suggests that various communication pathways between the microbiota and the brain are involved in functional disorders. Gut microbiota can modulate the gut–brain axis (GBA) through several pathways, including endocrine (cortisol), immune (cytokines) and neural—vagus, enteric nervous system (ENS) and spinal nerves [4]. Certain gut microbes have the ability to produce neurotransmitters (γ-aminobutyric acid (GABA), norepinephrine and dopamine) that affect target cells in the gut. Neuroactive microbial metabolites can modulate the brain and determine epithelial cell changes leading to gut barrier dysfunction; enteroendocrine cells (EEC) release gastrointestinal hormones; dendritic cells (DC) modulate immune function. Specialised structures of the EEC (neuropod cells) transmit sensory signals from the gut environment to the brain, forming synapse-like connections with afferent nerves, including the vagus nerve. The ENS integrates these signals and communicates with the brain via vagal and spinal pathways [5].

Large individual differences exist in the composition of the gut microbiome, its composition being influenced by diet, antibiotic use, and lifestyle (pet ownership, exercise, sleep) [6]. The microbiota is a critical factor in the normal development of the gut. In healthy individuals, the microbiota is responsible for important morphological changes in the gut, including the depth of the crypts, the architecture of the villi, the proliferation of stem cells, and the density of the blood vessels [6]. Studies show that in sterile mice, the distal small intestine has thinner and longer villi with underdeveloped vascular

networks [7]. Microbiota and microbial metabolites have been implicated in a variety of neurological and psychiatric disorders, including Parkinson's disease, autism spectrum disorders, Alzheimer's disease, and depression [8]. One pathogenetical pathway involves digestive epithelium, immune cells, and local nerve endings. For example, the presence of *lactobacilli* generates the expression of opioid and cannabinoid receptors on the surface of epithelial cells [9]. Microbiota also influences the physiology of the gut by local production of gases: CO_2, H_2, methane, and hydrogen sulphide, recently classified as a gasotransmitter, due to its effect in modulating inflammation in the gut [10].

Non-specific immunity is essential for digestive tract function, being responsible for the balance between immune tolerance to commensal microflora and defence response to the pathogenic microbes [11]. In addition, immunity also plays an essential role in mediating communication between gut microbiota, ENS and the brain. Toll-like receptors (TLRs) and peptidoglycans (PGNs) interfere with the immune response to microbes behaving as sensors of microbial constituents [12]. Pathogenic agents are detected by a non-specific membrane and cytosolic receptors of enterocytes, mainly from the TLRs, Nod-like receptors (NLR) and retinoic acid inducible gene-I-like receptors (RIG). These receptors belong to pattern recognition receptors (PRRs), which recognise common microbial structures for many pathogenic microorganisms—pathogen-associated molecular patterns (PAMPs) [13]. Stimulation of PRRs triggers local cytokine synthesis [14,15], inducing the epithelial proliferation, and the activation of non-specific (inflammation, synthesis of antimicrobial peptides) and specific (IgA synthesis) immunity. The microbiota stimulates PRRs, modulating the expression of genes involved in inflammation, the release of antimicrobial peptides, and pain intensity. Dysbiosis has been shown to alter the expression of TLR4 and TLR7, leading to sensitisation and motility disorders, while the expression of PRRs can alter the microbiota [16]. It has been shown in animal models that reduced expression of the NOD2 gene and TLR5 leads to dysbiosis [17,18]. Therefore, normal gut barrier function also prevents inappropriate activation of immune cells and the development of systemic immune activation (Figure 2).

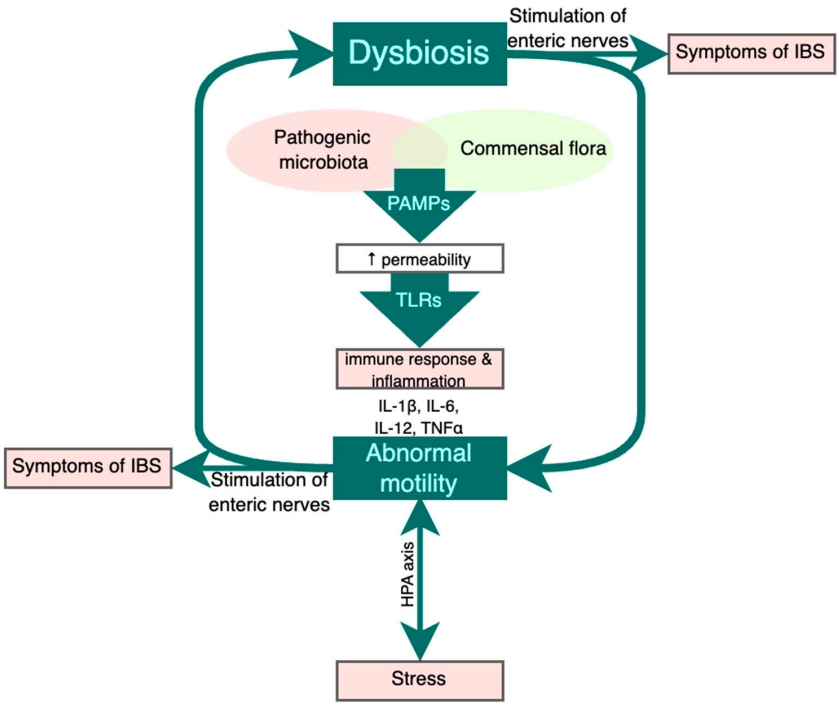

Figure 2. The immune response in dysbiosis and irritable bowel syndrome. IBS, irritable bowel syndrome. PAMPs, pathogen-associated molecular patterns. TLR, toll-like receptors. The one-direction arrow means leads to and the double-direction arrow means the two things can be interconnected.

IgA class immunoglobulins predominate in mucosal fluids and play a significant role in the formation of the gut microbiota by controlling its proliferation, motility, and colonization. As a result, a lack of IgA synthesis leads to an increase in Firmicutes phylum (segmented filamentous bacteria) in the ileal segment and a "skewed intestinal microbiota composition" with a rise in anti-inflammatory cytokines and CD 4+ T cells [19]. Aside from their role in regulating the intestinal microbiome, IgA also participates in the process of pathogen neutralisation thus maintaining a balance between pathological and physiological microbiota [20].

The process of bacterial fermentation in the colon produces metabolites such as acetic acid, propionic acid, and butyric acid (short-chain fatty acids). These by-products have been shown to be involved in the normal functioning of the intestinal barrier by maintaining its integrity, stimulating mucus production, and protecting against inflammation [21].

There is experimental evidence highlighting the relationship between microbiota and gastrointestinal motility. An alteration of intestinal motility by certain bacterial products that stimulate epithelial cell receptors (TLR, NOD) involved in non-specific immunity has been described [22]. In vitro studies in the colon model have shown that some soluble factors produced by the probiotic strain *E. coli* Nissle 1917 directly stimulate colonic muscle cells, whereas lipopolysaccharides (LPS) from pathogenic strains of *E. coli* inhibit their contractility [23].

2.2. The Role of Genetic and Perinatal Factors in IBS Pathogenesis

Positive family history and genetic variations in a number of potential genes have been linked to IBS [24,25]. Genes related to IBS in various studies include single nucleotide polymorphisms (SNPs) in genes associated with signalling pathways involved in the regulation of intestinal motility in IBS, such as serotonin system, tryptophan hydroxylase (TPH), cholecystokinin (CCK), catechol-O-methyltransferase (COMT), voltage-gated sodium channels (Nav), serotonin transporter (SERT) reuptake, cannabinoids, and ion channels. SNPs related to immune pathogenesis have been studied in IBS based on growing research showing immune activation [26]. However, findings were variable among studies and the association of genes such as tumour necrosis factor (TNFα) and IL-10 was not clear [14,27]. A recent meta-analysis, which included 12 published case-control studies, found no significant association of polymorphisms in genes such as IL-4/IL-6/IL-8/IL-10 or TNFα with IBS [28].

Perinatal factors such as gestational age of birth, delivery mode and dietary factors/alimentation/nutrition have a major impact on intestinal microbiota in early life. A study performed in 2019 has shown that depending on differences in perinatal factors, children develop different microbial profiles in the first four years of life [29]. A large cohort study was conducted by Waehrens et al. [30] in order to find a correlation between several perinatal and familial factors and the risk of developing IBS later on in life. A highly significant association was observed in caesarean delivery, maternal marital status and education and familial history of IBS [30].

2.3. Psychosocial Factors

Numerous studies have proven that abuse history and stressful life events are factors involved in the development of functional gastrointestinal disturbances. Psychosocial factors can interact with communication between the CNS and ENS, being involved in the onset of IBS, in treatment response and outcome.

The connection between psychosocial factors and gastrointestinal tract function is done by the brain–gut axis. This involves a bidirectional system between the gastrointestinal tract and the brain, by both nervous, neuroimmune and neuroendocrine mechanisms [31]. The neuroimmune signalling systems ensure the complex interactions between the autonomic nervous system, the HPA, the ENS, and the digestive mucosa. Effector cells are mainly digestive epithelial cells, smooth muscle fibres and entero-chromaffin cells. Their activation influences the microbiota indirectly, by modulating local processes (motility,

secretion, intestinal permeability, local immune response), but also directly by signalling molecules [32,33]. Influences occur bidirectionally, with microbiota influencing the neuroendocrine centres by direct stimulation of the ENS and also by various metabolites [22].

Psychological evaluation of patients with IBS, compared with normal individuals or with other medical conditions, reveals abnormal personality traits, a high incidence of stressful events, and even psychiatric afflictions [34]. Effects of psychosocial factors are relevant to gut physiology, on modulation of symptoms, influence on disease behaviour and outcome, as well as on therapeutic options. Psychological factors, such as personality type, and history of previous physical or sexual abuse, may have a major contribution to determining health-seeking behaviour [34].

Assessment of the psychosocial history of patients with IBS suggested that some clinical features of IBS may be characteristics of the patient's adaptive behaviour. The psychiatrist can help by treating IBS as a biological vulnerability, providing appropriate diagnosis and treatment of coexisting psychiatric conditions, and developing a multimodal therapeutic approach, including psychotherapeutic and pharmacological management [34].

The link between stress and IBS is very complex. Acute stress represents a well-known symptom trigger, and chronic stress causes IBS due to an altered microbiota. The stress hormones are cortisol, corticotropin-releasing hormone (CRH), and adrenocorticotropic hormone (ACTH). Cortisol is increased in women with IBS, compared to healthy subjects. Cortisol activates the hypothalamic–pituitary–adrenal axis (HPA) and induces a Th2 response from the mucosa and an increasing number of mast cells, that will consequently release abundant histamine, serotonin, and proteases and cause an increased excitation of primary afferent neurons in patients with IBS compared to control groups [35].

Although it has been hypothesised that digestive tract motility issues are a significant factor in IBS, studies utilising intestinal manometry in patients with IBS have not yielded conclusive outcomes that could define a diagnostic or therapeutic profile [36,37]. It was found that intense psychological stress changes the duodenojejunal motility both in patients with IBS and in healthy subjects, and, on the other hand, over 50% of patients with IBS presented no changes in motility during manometry on 24 h [36].

Activation of the HPA axis alters gut microbiota composition and increase gut permeability, favouring the development of IBS. Alterations in gut microbiota and gut permeability have been correlated with the occurrence of anxiety and depression, due to altered communication across the HPA axis [38]. There is overwhelming evidence that dysbiosis can affect the activity of the microbiota–GBA, thus anxiety and depression are common comorbidities in patients with IBS; the increased ratio of *Firmicutes*:*Bacteroides* encountered in some patients with IBS, correlates with anxiety and depression [39]. A meta-analysis published in 2019 by Zamani et al. [40] estimates that 39.1% and 28.8% of adult patients with IBS reported anxiety and depressive symptoms respectively, while 23% were diagnosed with anxiety disorders and 23.3% were diagnosed with depressive disorders [40]. Overlap of disorders of gut–brain axis is a common occurrence, with the highest prevalence recorded in tertiary care settings (47.3%). These patients report more severe symptoms and associate psychological comorbidities more frequently [41].

Besides the relevance of hormones along the HPA axis to IBS, other modulators were extensively studied, including brain-derived neurotrophic factor (BDNF), leptin, and transforming growth factor beta 1 (TGF-β1) [38].

It was reported that patients with IBS secrete more CRH than healthy controls, with increased ACTH and cortisol production in response to CRH [42]. CRH causes an increased stress-related intestinal muscle activity, notable in patients with IBS.

A study conducted by Giuseppe Marano et al. [42] reported no difference in cortisol response in patients with and without IBS, but higher CRH and ACTH responses in patients with IBS compared to the control group.

Previous studies highlighted increased numbers of inflammatory cells and serotonin-containing enterochromaffin cells in the mucosa of the small intestine in IBS after acute gastroenteritis due to *Campylobacter jejuni*. Patients with post-infectious IBS have elevated

postprandial serotonin levels in contrast to healthy subjects and patients with constipation-predominant IBS (IBS-C) [43]. A low turnover of serotonin was observed in the rectal mucosa of patients with IBS-C, proven by a low ratio between 5-hydroxy indole acetic acid and 5-hydroxytryptamine. Paradoxically, in patients with post-infectious IBS, a low ratio was also found. An explanation for this contradiction is the serotonin recycling deficiency [44].

2.4. The Role of Visceral Hypersensitivity in IBS

Cortical and subcortical hubs gathering sensorial information from the gut can modulate bowel motility and sensitivity by nervous and humoral pathways. It is considered that visceral hypersensitivity (VH) represents a significant element in IBS etiopathogenesis. VH was highlighted by a lowering of the pain threshold during rectal distension [45].

The two major components of VH are hyperalgesia and allodynia. Hyperalgesia is defined as an increased pain sensation in response to stimuli that usually cause pain, while allodynia refers to an increased nociceptive sensation in response to normal stimuli. VH can be simply defined as a low pain threshold for gastrointestinal stimuli [46]. Previous studies have shown that VH is generated by peripheral sensitive pathways and/or CNS disorders. Epidemiological studies have shown the different prevalence of VH in patients with IBS, from 33% to 90%, VH being more common in diarrhoea-predominant IBS (IBS-D) patients, who have an increased intestinal permeability [47].

The hypothesis that abnormal cerebral processing of intestinal stimuli contributes to VH is supported by imaging studies, that showed changes in the irrigation of some areas (anterior cingulate cortical area, amygdala, frontal cortex areas), as a response to bowel distention in patients with IBS. The cerebral processing of visceral stimuli can be influenced by emotions or stress, with an increased perception of painful stimuli [48].

Inflammation has an essential role in VH, a condition associated with pain and discomfort in patients with IBS [49]. Previous studies have shown that patients with irritable bowel syndrome have higher levels of pro-inflammatory cytokines than healthy control groups [50]. Patients with IBS have significantly more immune cells in the lamina propria of the colonic mucosa than healthy subjects, indicating low-grade inflammation [51]. Interleukin (IL) 8 is an important modulator of the inflammatory process. Its biological activity is inhibited by IL-1. The balance between these two cytokines determine the bioavailability of IL-8 and its contribution to inflammation [52]. Gwee et al. [53] conducted a study that compared biopsies obtained from the mucous membranes of patients with acute gastroenteritis. Biopsies were obtained during and three months after infection and interleukin 8 mRNA was measured. IL-8 expression was greatly increased during acute infection. In patients who developed post-infectious irritable bowel, IL-8 expression continued to increase 3 months after the infection was cured, while IL-8 expression decreased in patients that did not develop this condition [53].

If low-grade inflammation plays a role in sensory-motor dysfunction in IBS, the distribution of increased inflammatory cells may explain regional differences in colonic motor dysfunction [53] or VH [47]. In addition, inflammation and oxidative stress are linked, since leukocytes activated by endothelial and smooth muscle cells produce reactive oxygen species (ROS) [54], including superoxide anion, hydroxyl radical, hydrogen peroxide, dioxygen, and nitric oxide. ROS can react with all macromolecules such as carbohydrates, lipids, proteins, nucleic acids, and especially polyunsaturated fatty acids of the cell membrane. Oxidative stress initiated by ROS can be regulated by the antioxidant defence mechanisms, which include enzymatic (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase) and non-enzymatic (vitamin C, vitamin E and flavonoids) antioxidants [55]. Previous research highlighted the alteration of the oxidant–antioxidant balance in patients with IBS compared to healthy subjects, showing increased serum levels of pro-oxidants and decreased serum levels of antioxidants [55].

According to Johnson et al. [56], there is currently no complete animal model for IBS exists, but there are several highly validity models with translational relevance that can be

used to further our understanding of the physiopathological mechanisms involved in IBS and to develop new and reliable therapeutic strategies. Several experimental data have shown that the microbiota can modulate some mechanisms of VH. Antibiotic-induced dysbiosis altered intestinal sensitivity and motility in mice, by increasing TLR4 and TLR7 expression and by decreasing antinociceptive cannabinoid-1 and μ-opioid receptors' expression [57]. Microbiota alteration by subjecting the mice to stress increased the local expression of cannabinoid-2 receptors and isoform 1 of the tryptophan-hydroxylase enzyme, with an increased VH [58].

In patients with IBS, bacterial overpopulation, chronic constipation, and associated dysbiosis induced VH [59]. Bacteria used as probiotics can modify intestinal sensitivity: administration of *L. reuteri* to mice inhibited the nociceptive response to colorectal distension [60].

2.5. The Role of Hormonal Factors in IBS Pathogenesis

Hormonal factors, such as oestrogen, contribute to the physiology and pathology of the gastrointestinal tract, being involved in the regulation of motor and sensory function. Sex hormones interfere with the gut–brain axis (GBA) pathways, promoting changes in motility, VH, permeability and immune activation of the gut mucosa. IBS affects more females than males with a 3:1 ratio, highlighting the potential role of female sex hormones in the development of IBS [61]. Therefore, females with IBS, compared to males with IBS, are more susceptible to reporting symptoms of constipation, bloating or pain. Studies also support this idea describing slow transit for females with IBS compared to males with IBS [62].

Alternation in ovarian hormones (oestrogen and progesterone) during the menstrual cycle can influence GI contractility (muscle function), transit time, VH (pain), and immune function along the gastrointestinal tract and brain [63].

Strogen hormones interfere with serotonin and corticotropin-releasing factor (CRF) signalling pathways, with a significant role in symptoms related to oestrogen levels. The different distribution of oestrogen receptors throughout GBA further explains these interactions [64].

Pregnancy is characterised by high levels of ovarian hormones as well as an accentuated opioid-mediated antinociception. Pregnancy can relieve some symptoms but is commonly associated with constipation and reflux due to increased progesterone levels [64].

IBS symptoms can be accentuated during the decline in ovarian hormone secretion. Postmenopausal IBS women have more severe symptoms than premenopausal IBS women [65].

The involvement of intestinal hormones such as cholecystokinin (CCK), motilin and vasoactive intestinal peptide (VIP) in IBS pathogenesis is less relevant rather than sex hormones' role [66]. CCK and motilin are involved in postprandial symptoms. VIP can be abnormally concentrated in IBS, causing abdominal pain and watery diarrhoea. A study published by Osadchuk and Burdina in 2015 highlighted an increased level of VIP and motilin expression in the colonic mucosa of patients with IBS compared to healthy subjects [67].

2.6. The Role of Mast Cells in IBS Pathogenesis

It has been observed that the number of mast cells in the mucosa of the terminal ileum is increased both in patients with post-infectious IBS and in those with non-infectious IBS. Wang et al. [68] demonstrated that in patients with both infectious and non-infectious IBS there is a greater density of nerves around mast cells, with an increased release of histamine and tryptase from the mucosa. Mast cells also play a role in increasing intestinal permeability, which has been reported in post-infectious IBS. The increase in permeability implies a disruption of the normal gut barrier, which allows the access of bacterial products to the lamina propria, representing a mechanism for the perpetuation of chronic inflammation [69].

While some dietary factors can alter the intestinal permeability other dietary components can increase the barrier integrity. A study by Khoshbin and Camilleri [70] performed in 2020 examines in both healthy and ill individuals the effect diet components have on the intestinal barrier. Patients with food intolerance and food allergies present similar symptoms such as bloating, diarrhoea, abdominal pain, and nausea. Therefore, the difference in pathogenesis can only be made by performing a radioallergosorbent test, total serum IgE test or skin prick test. However, the majority of patients with IBS report worsening of symptoms after food ingestion without any proof of food hypersensitivity [71].

3. Postinfectious IBS

Evidence suggests that an episode of acute gastroenteritis may lead to the development of IBS symptoms only if other factors favour activation of mast cells and other gastrointestinal inflammatory cells via psychological, neural, and endocrine mechanisms. [72].

Postinfectious IBS (PI-IBS) has been reported after acute infections with *Campylobacter*, *Salmonella* and *Shigella*. A recent study conducted by Liang et al. [73] in 2020 on 2669 individuals diagnosed with *Helicobacter pylori* infection revealed an increased risk of developing IBS in these patients and suggested that a strength eradication therapy can reduce the risk of IBS.

This hypothesis is sustained by the evidence of *Helicobacter pylori* involvement in other related complications, such as atrophic gastritis, intestinal metaplasia, and gastric cancer [74].

Recent studies focused on the impact of the COVID-19 pandemic on the development of gastrointestinal symptoms, including IBS, COVID-19 gastroenteritis being an established risk factor for the development of disorders of the gut–brain axis (DGBI), particularly PI-IBS, showing that over 39% of the studied patients met ROME IV criteria for IBS diagnosis [75]. Additionally, COVID-19 infection was associated with worsening severity of symptoms in patients previously diagnosed with IBS [76].

Dysbiosis in patients with COVID-19 persists after acute disease, with an alteration of microbiota and a decrease in, short-chain fatty acid–forming bacteria [77]. Several review articles showed the beneficial effects of probiotics as adjuvant treatment in patients with COVID-19 for alleviating the gastrointestinal effects determined by dysbiosis [78,79].

Patients who develop IBS present increased numbers of enterochromaffin (EC) cells and lymphocytes at 3 months after acute infection compared to patients without IBS. An increased intestinal permeability associated with higher interleukin-1β (IL-1β) levels is described in the mucosa of patients with PI-IBS. Recent studies suggest an increased cytokine production from mononuclear cells, that can be ameliorated by probiotic treatment. Complete recovery from PI IBS can be difficult, with approximately 50% of patients showing symptoms at 5 years [42].

The development of PI-IBS is correlated with changes in the gut microbiota, immunity, and neuronal function. An increased *Firmicutes*:*Bacteroides* ratio and a decreased diversity are described in PI-IBS. These changes can alter the luminal environment by changing the composition of bile acids, bile salts and proteases [80]. Increased density of enteroendocrine cells, and increased release of serotonin may alter intestinal motility. An accentuated gut permeability function may contribute to immune dysregulation and nerve hypersensitivity. Moreover, immunophenotypic changes such as proinflammatory cytokine expression, correlated with an increased mast cell density and increased Th1/Th2 cell ratio, may mediate chronic intestinal dysfunction and neuronal excitability. Finally, nerve damage and nerve remodelling can affect motility and secretion [81].

4. Role of Probiotics in IBS Pathogenesis and Management

Experimental and clinical studies carried out in the last decades have suggested several mechanisms by which probiotics favourably modulate the pathophysiological mechanisms involved in IBS. Table 1 presents the bacterial strains commonly used in probiotics.

Table 1. The most important organisms used as probiotics in clinical practice.

Genus	*Lactobacillus*	*Bifidobacterium*	*Other*
Species	*Lactobacillus acidophilus*	*Bifidobacterium animalis* spp. *Lactis*	*Bacillus coagulans*
	Lactobacillus casei	*Bifidobacterium breve*	*Enterococcus faecalis*
	Lactobacillus helveticus	*Bifidobacterium infantis* spp. *Lactis*	*Saccharomyces boulardii*
	Lactobacillus johnsonii	*Bifidobacterium longum*	*Streptococcus thermophilus*
	Lactobacillus paracasei		
	Lactobacillus plantarum		
	Lactobacillus reuteri		
	Lactobacillus rhamnosus		

Probiotics serve a key role in improving IBS symptoms, including flatulence, abdominal pain, and bloating [82]. Probiotics mainly influence the composition of the microbiota, improving intestinal motility, VH, immune function, and metabolic processes, with a beneficial effect on dysfunctions of the microbiota-GBA and psychiatric conditions. The main benefits discussed in the literature are presented in Table 2.

Table 2. Benefits observed with the use of probiotics in irritable bowel syndrome.

Benefit	Probiotics	References
Pathogenic microbiota development inhibition	*Bifidobacterium* spp., *Lactobacillus* spp.	[83,84]
Intestinal motility improvement	*Bifidobacterium lactis*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bacillus subtilis*, *Streptococcus faecium*, *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*	[85–89]
Antinociception	*Bifidobacterium lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, *Lactococcus lactis*	[90,91]
Decrease in inflammatory and immune response	*Bifidobacterium infantis*, *Lactobacillus lactis*, *Lactobacillus acidophilus*, *E. coli Nissle*	[92,93]
Stress response improvement	*Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Streptococcus casei*, *Lactobacillus rhamnosus*, *Lactobacillus helveticus*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus bulgaricus*	[94,95]

4.1. Role of Probiotics in the Restoration of Microbiota Composition

By increasing in *Lactobacilli* and *Bifidobacteria*, probiotics participate in restoring and stabilizing an unfavourable intestinal ecosystem for pathogenic bacteria, both by metabolites (lactic acid, short-chain fatty acids, hydrogen peroxide) and by bacteriocins (lactocin, acidophilin, bifidin, bifidocin) [83].

The competition for nutrients inhibits the development of pathogen microbes, particularly certain species of *Clostridium*, *Escherichia coli*, *Salmonella*, *Shigella*, and *Pseudomonas*. There are studies that have shown that probiotics stimulate the local production of mucins, thus decreasing adhesion of pathogenic bacteria [84].

A relationship between probiotic administration and the production of short chain fatty acids has been reported in animal models in a study published by Nagpal et al. [96] in 2018. The results show that probiotics administration led to an increase in short chain fatty acids production, improving the intestinal microbiota function.

4.2. Role of Probiotics in Improving Intestinal Motility

Numerous studies have demonstrated improved transit in patients with constipation. Administration of *Bifidobacterium lactis HN019* and *Bifidobacterium lactis DN-173 010* decreased transit time in adult subjects with chronic constipation [85]. Both in vitro and in

human studies, *B. lactis HN019*™ reduced intestinal transit time in functional constipation by modulating the gut–brain–microbiota axis, mainly by the serotonin signalling pathway, via short-chain fatty acids produced by bacterial fermentation. *B. lactis HN019*™ is thus a probiotic that can improve the intestinal dysmotility-related disorders [85,86].

Fermented dairy products containing *Bifidobacterium lactis DN-173 010* both decreased abdominal distension and transit time in a cohort of IBS-C patients [87].

Daily administration of *Bifidobacterium lactis* decreased the incidence of functional disorders in patients with abnormal transit and flatulence.

The combination of *Bacillus subtilis* and *Streptococcus faecium* probiotics improved the symptoms of patients with IBS without diarrhoea [88]. A combination of probiotics containing *Lactobacillus acidophilus*, *L. plantarum*, *L. rhamnosus*, *Bifidobacterium breve*, *B. lactis*, *B. longum,* and *Streptococcus thermophilus* improved symptoms in patients with IBS-D, with superior results and no notable adverse reactions [89].

A meta-analysis investigating randomized controlled trials concluded that administration of *Bifidobacterium lactis* decreased transit time in patients with chronic constipation [83,97–100].

A meta-analysis published in 2022 by Zhang et al. [101] suggests that *B. coagulans* is highly effective as a therapeutical agent for IBS-D patients, improving symptoms and quality of life. In this study, *B. coagulans* ranked as the most effective probiotic in improving abdominal pain and straining scores. Moreover, it retained its substantial efficacy even compared to multiple types of probiotics combinations. The authors emphasize the need of future research regarding this species, suggesting that obtaining specimens with higher biological function by means of genetic engineering and development of probiotic combinations containing *B. coagulans* may represent future research targets [101].

4.3. Role of Probiotics in Visceral Hypersensitivity

Several studies on animal models have shown that probiotics exert a direct antinociceptive effect on gut sensitive nerve endings, through bacterial metabolites acting as neurotransmitters [102,103].

Other experiments support the hypothesis that probiotics also act by modulating the balance between nociceptive and antinociceptive stimuli at CNS level.

Administration of dairy products containing *Bifidobacterium animalis subsp. Lactis*, *Lactobacillus bulgaricus*, *Lactococcus lactis,* and *Streptococcus thermophiles* in healthy individuals, was correlated with significant changes in affective, viscerosensitive and somatosensitive cortical processes, on MRI studies. Therefore, a link between probiotics and the activity of the emotional processing centre was suggested [90,91].

4.4. Probiotics and the Modulation of Inflammatory and Immune Processes

The connection between IBS and the inflammatory and immune response of the intestinal mucosa is indirectly suggested by the appearance of IBS symptoms after a bacterial or viral intestinal infection.

A series of studies have shown that IBS is accompanied by an alteration of the non-specific and specific immune response both local and systemic [104,105]. Increased permeability of the intestinal mucosa is considered a marker of local inflammation [33].

Non-specific immune local reaction is highlighted by the subepithelial accumulation of mast cells, macrophages, and dendritic cells (acting as antigen-presenting cells).

Non-specific systemic immune response translates into increased levels of certain cytokines: IL-1b, IL-6, IL-8, IL-12, and TNFα [106,107].

A decrease of anti-inflammatory cytokine IL-10, a regulatory cytokine that inhibits both the release of pro-inflammatory cytokines and antigen presentation, was also observed; thus IL-10 is proposed as a strong anti-inflammatory biological therapy for IBS [108].

Numerous laboratory findings and clinical study findings demonstrate that probiotics reduce the inflammatory and immunological response in IBS through a number of different pathways. The normal permeability of the epithelial barrier is maintained by probiotics, which also correct the imbalance between pro-inflammatory and anti-inflammatory cy-

tokines (measured by the IL-10/IL-12 ratio) and reduce the local and systemic levels of several pro-inflammatory cytokines (TNF-a, IFN-g) [92,93].

4.5. Role of Probiotics in Stress Response

Numerous experimental and clinical data show that there are bidirectional influences between the microbiota and the CNS. Dysbiosis can induce alteration of the microbiota-GBA, while probiotics can contribute to the normalisation of this interaction [109].

Several studies have highlighted the protective effect of probiotics against anxiety-depression status induced by mental stress. Some probiotics (*Lactobacillus rhamnosus* and *Lactobacillus helveticus* strains) normalised the exaggerated response of the HPA in IBS [110].

Lactobacillus rhamnosus decreased the stress-induced corticosterone release by modulating GABA receptors involved in anxiety, decreasing the incidence and severity of abdominal pain episodes in patients with IBS [111–114].

A strain of *Bifidobacterium longum* had positive effects in a recent study conducted by Sabate et al. [93], who concluded that thirty days of *B. longum 35624* treatments reduced the severity of the disease and improved the quality of life of patients with IBS, especially those with severe forms. Stress-reduction induced by *Bifidobacterium* is most-likely related to tryptophan metabolism, as increased levels of tryptophan were observed after probiotic administration [115].

A mixture of strains from eight probiotic species (*Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus casei*, *L. acidophilus*, *L. plantarum*, *L. delbrueckii subsp. Bulgaricus* and *Streptococcus salivarius*) led to an increase in brain-derived neurotrophic factor (BDNF) level [94]. Dysfunctions in the epigenetic control, transport or signalling cascades of BDNF have been discussed regarding various neurological and psychiatric diseases [116]. There is also growing evidence of an important role played by BDNF in visceral pain and VH [117–119].

5. Role of Prebiotics in IBS Pathogenesis and Management

Prebiotics are "substrates that are selectively used by host microorganisms that confer a health benefit on the host". Prebiotics are usually dietary carbohydrates. Inulin fructans (ITFs) (fructose polymers) and galactooligosaccharides (GOS) (galactose polymers) are the most widely studied [120]. Extensive studies have demonstrated that prebiotics have the ability to specifically increase *Bifidobacteria* in healthy subjects [121]. In addition, prebiotics increase faecal short-chain fatty acids and decrease inflammatory markers [122], thus providing their role in symptom management in IBS.

One of the most exhaustive meta-analyses on the role of prebiotics in IBS therapy, published in 2019 by Bridgette Wilson et al. [123], concluded that prebiotics did not improve gastrointestinal symptoms, outcome, or quality of life in patients with IBS, but increased faecal *Bifidobacteria*. However, the administration of a galactooligosaccharide prebiotic for four weeks in patients with IBS and anxiety led to a decrease in symptoms and an improvement in quality of life [124]. Also, the dose and duration of administration did not improve the general symptoms, with individual differences between type and dose being observed. Non-ITF prebiotics improved flatulence while ITF prebiotics worsened flatulence; doses $\leq$ 6 g/day reduced flatulence, whereas higher doses had no effect [123].

Short-chain fructooligosaccharides (scFOS) were also studied by Azpiroz et al. [125], who described the influence of prebiotics on anxiety in IBS individuals.

Niv et al. [126] proved the efficacy of partially hydrolysed guar gum (PHGG) for patients with IBS accusing mainly bloating, without any side effects. However, it showed no effect on the rest of the possible IBS symptoms.

However, prebiotic therapy must be further investigated, as the results of the studies carried out so far are unconcluded [127].

6. Clinical Microbiota-Altering Treatment

In IBS, a major role in induction of symptoms is played by diet. Current evidence suggests that FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) exclusion is the most effective dietary intervention, as their osmotic effect leads to increased water volume in the small intestine and introduce undigested dietary components to the gut microbiota [71]. At this point the food is fermented, producing gas, and causing the distension of colon, triggering abdominal pain in the context of VH [71]. In 2017, McIntosh et al. [128] published evidence that low-FODMAP diet reduces the levels of urinary histamines, thus speculating that patients with a specific microbiota profile producing high levels of histamine may benefit from a low-FODMAP diet. Other studies support the claim that low-FODMAP diet represents an effective therapeutic tool, improving symptoms and inducing changes in inflammatory cytokines and microbiota profile after 3 weeks of dieting [129].

Usage of faecal microbiota transplantation (FMT) in patients with IBS showed contradictory results in the past. It seems that for a successful FMT, a donor with favourable specific microbial signature and a normal dysbiosis index is required [71]. In 2021, Cui et al. [130] published a retrospective analysis of the long-term effects of FMT for IBS, suggesting that repetitive transplantations may be necessary to maintain a long-lasting effect.

7. Discussion

The human microbiota is a complex ecosystem, composed mainly of bacteria, but also viruses (e.g., bacteriophages), archaea (e.g., Methanobrevibacter), and eukaryotes (fungi). Gut microbiota is considered a virtual organ, which actively influences and modulates a multitude of physiological processes, mainly related to gut development, nutrient processing, specific local and systemic immune response, resistance to pathogenic bacteria, and CNS activity. There are about 100 trillion bacteria in an adult's body, 80% of which exist in the gut, about ten times more than the cells in the human body [131].

The microbiota contains over 1000 bacterial species, including 17 families, which mainly belong to four phyla (*Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria*). *Actinobacteria* and *Proteobacteria* decrease with age, thus *Firmicutes* and *Bacteroidetes* become predominant in adults [132].

The exact composition of the microbiota is specific to each individual and changes throughout life, being influenced by environmental factors: diet, lifestyle, stress, medication (especially oral antibiotics), and some invasive procedures (e.g., colonoscopy) [10].

Numerous studies have highlighted links between dysbiosis and a series of pathologies: diabetes, metabolic syndrome, cancer, inflammatory diseases, and psychiatric disorders. This can be explained by several mechanisms.

The multitude of bacterial metabolites absorbed into the blood may influence GBA [80], stimulating the neuromodulators (noradrenaline, dopamine, acetylcholine, serotonin, gamma-aminobutyric acid—GABA) synthesis [133]. By influencing bidirectional communication between the CNS and the ENS, microbiota modulates a series of local processes: bowel motility, intestinal secretion, nonspecific and specific immune defence, and sensitivity [80].

Previous studies have described an increase in the number of bacteria attached to the intestinal lining, a rise in the number of aerobes compared to anaerobes, a decrease in microbial diversity, a reduction in the variability of microbiota composition, and an accentuated temporal instability in the microbiota of patients with IBS. [134]. There is evidence for an immune response in the gut, characterized by an increased intraepithelial lymphocyte, mast cells and serotonin-secreting enterochromaffin cells [135,136]. Microbiota influences the inflammation processes in IBS, by altering the balance between pro-inflammatory factors and host defence. Therefore, microbial antigens may act similarly, causing subclinical inflammation in patients with IBS [15].

We acknowledge that our study had some limitations. Therefore, there is insufficient prior research regarding a few topics we discussed in our study: relationship between food

allergies and IBS, role of microbiota on the development of the human gut, and PI-IBS among other. Further research is needed to help achieve a better understanding of these subjects. Other limitations are represented by the broadness of addressed topic and lack of systematic reviewing. However, we consider these necessary trade-offs for providing a comprehensive, yet accessible resource for physicians.

8. Conclusions

The global incidence of IBS is increasing in industrialized countries. The pathogenesis of IBS is multifactorial, and microbiota plays a central role in the development of this condition.

Genetic and environmental factors influence the composition of the microbiota, with an essential role in modulating the immune response.

The interrelation between microbiota, immunity and IBS is complex, because the same commensal bacteria can induce either a protecting or a pathogenic/inflammatory response, depending on individual susceptibility.

The characterisation of the human microbiota profile will allow the development of a new type of "biological fingerprint", which will be useful in assessing the drug therapy response or a specific diet, ultimately leading to the development of personalised therapies.

The use of probiotics and prebiotics obtains acceptable results, being recognised as effective and safe in IBS therapy.

A comprehensive approach by a multidisciplinary team of healthcare professionals, including gastroenterologist physicians, clinical microbiologists, and molecular genomics experts, is necessary for an accurate diagnosis and appropriate management of IBS.

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References

1. Sebastián Domingo, J.J. Síndrome del intestino irritable. *Med. Clínica* **2022**, *158*, 76–81. [CrossRef]
2. Mearin, F.; Rey, E.; Santander, C. Síndrome del intestino irritable: Cómo mejorar la toma de decisiones en la práctica clínica. *Med. Clínica* **2018**, *151*, 489–497. [CrossRef]
3. Schmulson, M.J.; Drossman, D.A. What Is New in Rome IV. *J. Neurogastroenterol. Motil.* **2017**, *23*, 151–163. [CrossRef] [PubMed]
4. Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* **2018**, *12*, 49. [CrossRef] [PubMed]
5. Kennedy, P.J.; Cryan, J.F.; Dinan, T.G.; Clarke, G. Irritable Bowel Syndrome: A Microbiome-Gut-Brain Axis Disorder? *World J. Gastroenterol.* **2014**, *20*, 14105–14125. [CrossRef] [PubMed]
6. Gilbert, J.A.; Blaser, M.J.; Caporaso, J.G.; Jansson, J.K.; Lynch, S.V.; Knight, R. Current Understanding of the Human Microbiome. *Nat. Med.* **2018**, *24*, 392–400. [CrossRef]

7. Sommer, F.; Bäckhed, F. The Gut Microbiota—Masters of Host Development and Physiology. *Nat. Rev. Microbiol.* **2013**, *11*, 227–238. [CrossRef]
8. Bastiaanssen, T.F.S.; Cowan, C.S.M.; Claesson, M.J.; Dinan, T.G.; Cryan, J.F. Making Sense of . . . the Microbiome in Psychiatry. *Int. J. Neuropsychopharmacol.* **2019**, *22*, 37–52. [CrossRef]
9. Rousseaux, C.; Thuru, X.; Gelot, A.; Barnich, N.; Neut, C.; Dubuquoy, L.; Dubuquoy, C.; Merour, E.; Geboes, K.; Chamaillard, M.; et al. Lactobacillus Acidophilus Modulates Intestinal Pain and Induces Opioid and Cannabinoid Receptors. *Nat. Med.* **2007**, *13*, 35–37. [CrossRef] [PubMed]
10. Popa, G.; Gheorghe, A.; Preda, M.; Popa, M.I. The Intestinal Microbiota Reconfigures the Boundaries of Knowledge. *Infectio* **2017**, *49*, 5–9. [CrossRef]
11. Burns, G.; Carroll, G.; Mathe, A.; Horvat, J.; Foster, P.; Walker, M.M.; Talley, N.J.; Keely, S. Evidence for Local and Systemic Immune Activation in Functional Dyspepsia and the Irritable Bowel Syndrome: A Systematic Review. *Am. J. Gastroenterol.* **2019**, *114*, 429. [CrossRef] [PubMed]
12. Chu, H.; Mazmanian, S.K. Innate Immune Recognition of the Microbiota Promotes Host-Microbial Symbiosis. *Nat. Immunol.* **2013**, *14*, 668–675. [CrossRef] [PubMed]
13. Shukla, R.; Ghoshal, U.; Ranjan, P.; Ghoshal, U.C. Expression of Toll-like Receptors, Pro-, and Anti-Inflammatory Cytokines in Relation to Gut Microbiota in Irritable Bowel Syndrome: The Evidence for Its Micro-Organic Basis. *Neurogastroenterol. Motil.* **2018**, *24*, 628–642. [CrossRef] [PubMed]
14. Bashashati, M.; Rezaei, N.; Shafieyoun, A.; McKernan, D.P.; Chang, L.; Öhman, L.; Quigley, E.M.; Schmulson, M.; Sharkey, K.A.; Simrén, M. Cytokine Imbalance in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Neurogastroenterol. Motil.* **2014**, *26*, 1036–1048. [CrossRef]
15. Bennet, S.M.P.; Polster, A.; Törnblom, H.; Isaksson, S.; Capronnier, S.; Tessier, A.; Le Nevé, B.; Simrén, M.; Öhman, L. Global Cytokine Profiles and Association With Clinical Characteristics in Patients With Irritable Bowel Syndrome. *Am. J. Gastroenterol.* **2016**, *111*, 1165. [CrossRef]
16. Mu, C.; Yang, Y.; Zhu, W. Crosstalk Between The Immune Receptors and Gut Microbiota. *Curr. Protein Pept. Sci.* **2015**, *16*, 622–631. [CrossRef]
17. Ray, A.; Dittel, B.N. Interrelatedness between Dysbiosis in the Gut Microbiota Due to Immunodeficiency and Disease Penetrance of Colitis. *Immunology* **2015**, *146*, 359–368. [CrossRef]
18. Liu, Z.; Zhang, Y.; Jin, T.; Yi, C.; Ocansey, D.K.W.; Mao, F. The Role of NOD2 in Intestinal Immune Response and Microbiota Modulation: A Therapeutic Target in Inflammatory Bowel Disease. *Int. Immunopharmacol.* **2022**, *113*, 109466. [CrossRef]
19. Nagaishi, T.; Watabe, T.; Kotake, K.; Kumazawa, T.; Aida, T.; Tanaka, K.; Ono, R.; Ishino, F.; Usami, T.; Miura, T.; et al. Immunoglobulin A–Specific Deficiency Induces Spontaneous Inflammation Specifically in the Ileum. *Gut* **2022**, *71*, 487–496. [CrossRef]
20. Pietrzak, B.; Tomela, K.; Olejnik-Schmidt, A.; Mackiewicz, A.; Schmidt, M. Secretory IgA in Intestinal Mucosal Secretions as an Adaptive Barrier against Microbial Cells. *Int. J. Mol. Sci.* **2020**, *21*, 9254. [CrossRef]
21. Silva, Y.P.; Bernardi, A.; Frozza, R.L. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front. Endocrinol.* **2020**, *11*, 25. [CrossRef] [PubMed]
22. El-Salhy, M.; Hausken, T.; Gilja, O.H.; Hatlebakk, J.G. The Possible Role of Gastrointestinal Endocrine Cells in the Pathophysiology of Irritable Bowel Syndrome. *Expert. Rev. Gastroenterol. Hepatol.* **2017**, *11*, 139–148. [CrossRef] [PubMed]
23. Bär, F.; Von Koschitzky, H.; Roblick, U.; Bruch, H.P.; Schulze, L.; Sonnenborn, U.; Böttner, M.; Wedel, T. Cell-Free Supernatants of Escherichia Coli Nissle 1917 Modulate Human Colonic Motility: Evidence from an in Vitro Organ Bath Study. *Neurogastroenterol. Motil.* **2009**, *21*, 559-e17. [CrossRef] [PubMed]
24. Levy, R.L.; Whitehead, W.E.; Von Korff, M.R.; Feld, A.D. Intergenerational Transmission of Gastrointestinal Illness Behavior. *Am. J. Gastroenterol.* **2000**, *95*, 451–456. [CrossRef] [PubMed]
25. Locke, G.R., 3rd; Zinsmeister, A.R.; Talley, N.J.; Fett, S.L.; Joseph Melton, L. Familial Association in Adults with Functional Gastrointestinal Disorders. *Mayo Clin. Proc.* **2000**, *75*, 907–912. [CrossRef]
26. Czogalla, B.; Schmitteckert, S.; Houghton, L.A.; Sayuk, G.S.; Camilleri, M.; Olivo-Diaz, A.; Spiller, R.; Wouters, M.M.; Boeckxstaens, G.; Lorenzo Bermejo, J.; et al. A Meta-Analysis of Immunogenetic Case–Control Association Studies in Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2015**, *27*, 717–727. [CrossRef]
27. Cheung, C.K.; Wu, J.C. Genetic Polymorphism in Pathogenesis of Irritable Bowel Syndrome. *World J. Gastroenterol.* **2014**, *20*, 17693–17698. [CrossRef]
28. Gazouli, M.; Wouters, M.M.; Kapur-Pojskić, L.; Bengtson, M.-B.; Friedman, E.; Nikčević, G.; Demetriou, C.A.; Mulak, A.; Santos, J.; Niesler, B. Lessons Learned—Resolving the Enigma of Genetic Factors in IBS. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 77–87. [CrossRef]
29. Fouhy, F.; Watkins, C.; Hill, C.J.; O'Shea, C.-A.; Nagle, B.; Dempsey, E.M.; O'Toole, P.W.; Ross, R.P.; Ryan, C.A.; Stanton, C. Perinatal Factors Affect the Gut Microbiota up to Four Years after Birth. *Nat. Commun.* **2019**, *10*, 1517. [CrossRef]
30. Waehrens, R.; Li, X.; Sundquist, J.; Sundquist, K.; Zöller, B. Perinatal and Familial Risk Factors for Irritable Bowel Syndrome in a Swedish National Cohort. *Scand. J. Gastroenterol.* **2018**, *53*, 559–566. [CrossRef]
31. Jones, M.P.; Dilley, J.B.; Drossman, D.; Crowell, M.D. Brain-Gut Connections in Functional GI Disorders: Anatomic and Physiologic Relationships. *Neurogastroenterol. Motil.* **2006**, *18*, 91–103. [CrossRef] [PubMed]

32. Vanuytsel, T.; Bercik, P.; Boeckxstaens, G. Understanding Neuroimmune Interactions in Disorders of Gut–Brain Interaction: From Functional to Immune-Mediated Disorders. *Gut* **2023**, *72*, 787–798. [CrossRef] [PubMed]
33. Hanning, N.; Edwinson, A.L.; Ceuleers, H.; Peters, S.A.; De Man, J.G.; Hassett, L.C.; De Winter, B.Y.; Grover, M. Intestinal Barrier Dysfunction in Irritable Bowel Syndrome: A Systematic Review. *Therap Adv. Gastroenterol.* **2021**, *14*, 1756284821993586. [CrossRef] [PubMed]
34. Radovanovic-Dinic, B.; Tesic-Rajkovic, S.; Grgov, S.; Petrovic, G.; Zivkovic, V. Irritable Bowel Syndrome—From Etiopathogenesis to Therapy. *Biomed. Pap. Med. Fac. Univ. Palacky. Olomouc Czech Repub.* **2018**, *162*, 1–9. [CrossRef]
35. Vanuytsel, T.; van Wanrooy, S.; Vanheel, H.; Vanormelingen, C.; Verschueren, S.; Houben, E.; Rasoel, S.S.; Tóth, J.; Holvoet, L.; Farré, R.; et al. Psychological Stress and Corticotropin-Releasing Hormone Increase Intestinal Permeability in Humans by a Mast Cell-Dependent Mechanism. *Gut* **2014**, *63*, 1293–1299. [CrossRef] [PubMed]
36. Bassotti, G.; Bologna, S.; Ottaviani, L.; Russo, M.; Dore, M.P. Intestinal Manometry: Who Needs It? *Gastroenterol. Hepatol. Bed Bench* **2015**, *8*, 246–252.
37. Bhattarai, Y.; Muniz Pedrogo, D.A.; Kashyap, P.C. Irritable Bowel Syndrome: A Gut Microbiota-Related Disorder? *Am. J. Physiol. Gastrointest. Liver Physiol.* **2017**, *312*, G52–G62. [CrossRef]
38. Weaver, K.R.; Boulineaux, C.M.; Robinson, J.M.; Butler, K.; Heitkemper, M.M.; Henderson, W.A. Sex Hormones, BDNF, Leptin, and TGF-B1 in Females With IBS: A Pilot Investigation. *Biol. Res. Nurs.* **2021**, *23*, 231–237. [CrossRef]
39. Jeffery, I.B.; O'Toole, P.W.; Öhman, L.; Claesson, M.J.; Deane, J.; Quigley, E.M.M.; Simrén, M. An Irritable Bowel Syndrome Subtype Defined by Species-Specific Alterations in Faecal Microbiota. *Gut* **2012**, *61*, 997–1006. [CrossRef]
40. Zamani, M.; Alizadeh-Tabari, S.; Zamani, V. Systematic Review with Meta-Analysis: The Prevalence of Anxiety and Depression in Patients with Irritable Bowel Syndrome. *Aliment. Pharmacol. Ther.* **2019**, *50*, 132–143. [CrossRef]
41. Fairlie, T.; Shah, A.; Talley, N.J.; Chey, W.D.; Koloski, N.; Yeh Lee, Y.; Gwee, K.-A.; Jones, M.P.; Holtmann, G. Overlap of Disorders of Gut-Brain Interaction: A Systematic Review and Meta-Analysis. *Lancet Gastroenterol. Hepatol.* **2023**, *8*, 646–659. [CrossRef] [PubMed]
42. Marano, G.; Mazza, M.; Lisci, F.M.; Ciliberto, M.; Traversi, G.; Kotzalidis, G.D.; De Berardis, D.; Laterza, L.; Sani, G.; Gasbarrini, A.; et al. The Microbiota–Gut–Brain Axis: Psychoneuroimmunological Insights. *Nutrients* **2023**, *15*, 1496. [CrossRef] [PubMed]
43. Wheatcroft, J.; Wakelin, D.; Smith, A.; Mahoney, C.R.; Mawe, G.; Spiller, R. Enterochromaffin Cell Hyperplasia and Decreased Serotonin Transporter in a Mouse Model of Postinfectious Bowel Dysfunction. *Neurogastroenterol. Motil.* **2005**, *17*, 863–870. [CrossRef] [PubMed]
44. Wood, J.D. Enteric Neuroimmunophysiology and Pathophysiology. *Gastroenterology* **2004**, *127*, 635–657. [CrossRef]
45. Ludidi, S.; Conchillo, J.M.; Keszthelyi, D.; Van Avesaat, M.; Kruimel, J.W.; Jonkers, D.M.; Masclee, A.A.M. Rectal Hypersensitivity as Hallmark for Irritable Bowel Syndrome: Defining the Optimal Cutoff. *Neurogastroenterol. Motil.* **2012**, *24*, 729-e346. [CrossRef]
46. Ludidi, S.; Mujagic, Z.; Jonkers, D.; Keszthelyi, D.; Hesselink, M.; Kruimel, J.; Conchillo, J.; Masclee, A. Markers for Visceral Hypersensitivity in Patients with Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2014**, *26*, 1104–1111. [CrossRef]
47. Farzaei, M.H.; Bahramsoltani, R.; Abdollahi, M.; Rahimi, R. The Role of Visceral Hypersensitivity in Irritable Bowel Syndrome: Pharmacological Targets and Novel Treatments. *J. Neurogastroenterol. Motil.* **2016**, *22*, 558–574. [CrossRef]
48. Thijssen, A.Y.; Jonkers, D.M.; Leue, C.; van der Veek, P.P.J.; Vidakovic-Vukic, M.; van Rood, Y.R.; Clemens, C.H.M.; Masclee, A.A.M. Dysfunctional Cognitions, Anxiety and Depression in Irritable Bowel Syndrome. *J. Clin. Gastroenterol.* **2010**, *44*, e236. [CrossRef]
49. Spiller, R.; Aziz, Q.; Creed, F.; Emmanuel, A.; Houghton, L.; Hungin, P.; Jones, R.; Kumar, D.; Rubin, G.; Trudgill, N.; et al. Guidelines on the Irritable Bowel Syndrome: Mechanisms and Practical Management. *Gut* **2007**, *56*, 1770–1798. [CrossRef]
50. Choghakhori, R.; Abbasnezhad, A.; Hasanvand, A.; Amani, R. Inflammatory Cytokines and Oxidative Stress Biomarkers in Irritable Bowel Syndrome: Association with Digestive Symptoms and Quality of Life. *Cytokine* **2017**, *93*, 34–43. [CrossRef]
51. O'Sullivan, M.; Clayton, N.; Breslin, N.P.; Harman, I.; Bountra, C.; McLaren, A.; O'Morain, C.A. Increased Mast Cells in the Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2000**, *12*, 449–457. [CrossRef]
52. Zhou, Y.; Zhang, F.; Mao, L.; Feng, T.; Wang, K.; Xu, M.; Lv, B.; Wang, X. Bifico Relieves Irritable Bowel Syndrome by Regulating Gut Microbiota Dysbiosis and Inflammatory Cytokines. *Eur. J. Nutr.* **2023**, *62*, 139–155. [CrossRef]
53. Gwee, K.A.; Collins, S.M.; Read, N.W.; Rajnakova, A.; Deng, Y.; Graham, J.C.; McKendrick, M.W.; Moochhala, S.M. Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. *Gut* **2003**, *52*, 523–526. [CrossRef]
54. Balmus, I.-M.; Ilie, O.-D.; Ciobica, A.; Cojocariu, R.-O.; Stanciu, C.; Trifan, A.; Cimpeanu, M.; Cimpeanu, C.; Gorgan, L. Irritable Bowel Syndrome between Molecular Approach and Clinical Expertise—Searching for Gap Fillers in the Oxidative Stress Way of Thinking. *Medicina* **2020**, *56*, 38. [CrossRef] [PubMed]
55. Mete, R.; Tulubas, F.; Oran, M.; Yılmaz, A.; Avci, B.A.; Yildiz, K.; Turan, C.B.; Gurel, A. The Role of Oxidants and Reactive Nitrogen Species in Irritable Bowel Syndrome: A Potential Etiological Explanation. *Med. Sci. Monit.* **2013**, *19*, 762–766. [CrossRef] [PubMed]
56. Johnson, A.C.; Farmer, A.D.; Ness, T.J.; Meerveld, B.G.-V. Critical Evaluation of Animal Models of Visceral Pain for Therapeutics Development: A Focus on Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2020**, *32*, e13776. [CrossRef] [PubMed]
57. Aguilera, M.; Cerdà-Cuéllar, M.; Martínez, V. Antibiotic-Induced Dysbiosis Alters Host-Bacterial Interactions and Leads to Colonic Sensory and Motor Changes in Mice. *Gut Microbes* **2015**, *6*, 10–23. [CrossRef] [PubMed]

58. Aguilera, M.; Vergara, P.; Martínez, V. Stress and Antibiotics Alter Luminal and Wall-Adhered Microbiota and Enhance the Local Expression of Visceral Sensory-Related Systems in Mice. *Neurogastroenterol. Motil.* **2013**, *25*, e515–e529. [CrossRef]
59. Wei, L.; Singh, R.; Ro, S.; Ghoshal, U.C. Gut Microbiota Dysbiosis in Functional Gastrointestinal Disorders: Underpinning the Symptoms and Pathophysiology. *JGH Open* **2021**, *5*, 976–987. [CrossRef]
60. Hegde, S.; Lin, Y.-M.; Fu, Y.; Savidge, T.; Shi, X.-Z. Precision Lactobacillus Reuteri Therapy Attenuates Luminal Distension-Associated Visceral Hypersensitivity by Inducing Peripheral Opioid Receptors in the Colon. *Pain* **2020**, *161*, 2737. [CrossRef]
61. Anton, C.; Ciobica, A.; Doroftei, B.; Maftei, R.; Ilea, C.; Darii Plopa, N.; Bolota, M.; Anton, E. A Review of the Complex Relationship between Irritable Bowel Syndrome and Infertility. *Medicina* **2020**, *56*, 592. [CrossRef]
62. Kim, Y.S.; Kim, N. Sex-Gender Differences in Irritable Bowel Syndrome. *J. Neurogastroenterol. Motil.* **2018**, *24*, 544–558. [CrossRef] [PubMed]
63. Camilleri, M. Sex as a Biological Variable in Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2020**, *32*, e13802. [CrossRef] [PubMed]
64. Camilleri, M. Physiological Underpinnings of Irritable Bowel Syndrome: Neurohormonal Mechanisms. *J. Physiol.* **2014**, *592*, 2967–2980. [CrossRef] [PubMed]
65. Lenhart, A.; Naliboff, B.; Shih, W.; Gupta, A.; Tillisch, K.; Liu, C.; Mayer, E.A.; Chang, L. Postmenopausal Women with Irritable Bowel Syndrome (IBS) Have More Severe Symptoms than Premenopausal Women with IBS. *Neurogastroenterol. Motil.* **2020**, *32*, e13913. [CrossRef]
66. Han, B. Correlation between Gastrointestinal Hormones and Anxiety-depressive States in Irritable Bowel Syndrome. *Exp. Ther. Med.* **2013**, *6*, 715–720. [CrossRef]
67. Osadchuk, M.A.; Burdina, V.O. Irritable bowel syndrome with extraintestinal manifestations from a position of neuroendocrine pathology. *Eksp. Klin. Gastroenterol.* **2015**, *2*, 29–34.
68. Wang, L.; Fang, X.; Pan, G. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. *Gut* **2004**, *53*, 1096–1101. [CrossRef]
69. Barbara, G.; Stanghellini, V.; De Giorgio, R.; Corinaldesi, R. Functional Gastrointestinal Disorders and Mast Cells: Implications for Therapy. *Neurogastroenterol. Motil.* **2006**, *18*, 6–17. [CrossRef]
70. Khoshbin, K.; Camilleri, M. Effects of Dietary Components on Intestinal Permeability in Health and Disease. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2020**, *319*, G589–G608. [CrossRef]
71. Hillestad, E.M.R.; van der Meeren, A.; Nagaraja, B.H.; Bjørsvik, B.R.; Haleem, N.; Benitez-Paez, A.; Sanz, Y.; Hausken, T.; Lied, G.A.; Lundervold, A.; et al. Gut Bless You: The Microbiota-Gut-Brain Axis in Irritable Bowel Syndrome. *World J. Gastroenterol.* **2022**, *28*, 412–431. [CrossRef] [PubMed]
72. Gasbarrini, A.; Lauritano, E.C.; Garcovich, M.; Sparano, L.; Gasbarrini, G. New Insights into the Pathophysiology of IBS: Intestinal Microflora, Gas Production and Gut Motility. *Eur. Rev. Med. Pharmacol. Sci.* **2008**, *12* (Suppl. S1), 111–117. [PubMed]
73. Liang, C.-M.; Hsu, C.-H.; Chung, C.-H.; Chen, C.-Y.; Wang, L.-Y.; Hsu, S.-D.; Chang, P.-K.; Hong, Z.-J.; Chien, W.-C.; Hu, J.-M. Risk for Irritable Bowel Syndrome in Patients with Helicobacter Pylori Infection: A Nationwide Population-Based Study Cohort Study in Taiwan. *Int. J. Environ. Res. Public. Health* **2020**, *17*, 3737. [CrossRef] [PubMed]
74. Marginean, C.M.; Cioboata, R.; Olteanu, M.; Vasile, C.M.; Popescu, M.; Popescu, A.I.S.; Bondari, S.; Pirscoveanu, D.; Marginean, I.C.; Iacob, G.A.; et al. The Importance of Accurate Early Diagnosis and Eradication in Helicobacter Pylori Infection: Pictorial Summary Review in Children and Adults. *Antibiotics* **2023**, *12*, 60. [CrossRef]
75. Chan, W.W.; Grover, M. The COVID-19 Pandemic and Post-Infection Irritable Bowel Syndrome: What Lies Ahead for Gastroenterologists. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 2195–2197. [CrossRef]
76. Kamp, K.J.; Levy, R.L.; Munson, S.A.; Heitkemper, M.M. Impact of COVID-19 on Individuals With Irritable Bowel Syndrome and Comorbid Anxiety and/or Depression. *J. Clin. Gastroenterol.* **2022**, *56*, e149–e152. [CrossRef]
77. Mizutani, T.; Ishizaka, A.; Koga, M.; Ikeuchi, K.; Saito, M.; Adachi, E.; Yamayoshi, S.; Iwatsuki-Horimoto, K.; Yasuhara, A.; Kiyono, H.; et al. Correlation Analysis between Gut Microbiota Alterations and the Cytokine Response in Patients with Coronavirus Disease during Hospitalization. *Microbiol. Spectr.* **2022**, *10*, e0168921. [CrossRef]
78. Sharifi-Rad, J.; Rodrigues, C.F.; Stojanović-Radić, Z.; Dimitrijević, M.; Aleksić, A.; Neffe-Skocińska, K.; Zielińska, D.; Kołożyn-Krajewska, D.; Salehi, B.; Milton Prabu, S.; et al. Probiotics: Versatile Bioactive Components in Promoting Human Health. *Medicina* **2020**, *56*, 433. [CrossRef]
79. Islam, M.T.; Quispe, C.; Martorell, M.; Docea, A.O.; Salehi, B.; Calina, D.; Reiner, Ž.; Sharifi-Rad, J. Dietary Supplements, Vitamins and Minerals as Potential Interventions against Viruses: Perspectives for COVID-19. *Int. J. Vitam. Nutr. Res.* **2022**, *92*, 49–66. [CrossRef]
80. Distrutti, E.; Monaldi, L.; Ricci, P.; Fiorucci, S. Gut Microbiota Role in Irritable Bowel Syndrome: New Therapeutic Strategies. *World J. Gastroenterol.* **2016**, *22*, 2219–2241. [CrossRef]
81. Berg, L.K.; Goll, R.; Fagerli, E.; Ludviksen, J.K.; Fure, H.; Moen, O.S.; Sørbye, S.W.; Mollnes, T.E.; Florholmen, J. Intestinal Inflammatory Profile Shows Increase in a Diversity of Biomarkers in Irritable Bowel Syndrome. *Scand. J. Gastroenterol.* **2020**, *55*, 537–542. [CrossRef] [PubMed]
82. Satish Kumar, L.; Pugalenthi, L.S.; Ahmad, M.; Reddy, S.; Barkhane, Z.; Elmadi, J. Probiotics in Irritable Bowel Syndrome: A Review of Their Therapeutic Role. *Cureus* **2022**, *14*, e24240. [CrossRef]

83. Eskesen, D.; Jespersen, L.; Michelsen, B.; Whorwell, P.J.; Müller-Lissner, S.; Morberg, C.M. Effect of the Probiotic Strain Bifidobacterium Animalis Subsp. Lactis, BB-12®, on Defecation Frequency in Healthy Subjects with Low Defecation Frequency and Abdominal Discomfort: A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Trial. *Br. J. Nutr.* **2015**, *114*, 1638–1646. [CrossRef] [PubMed]
84. Soltani, N.; Abbasi, S.; Baghaeifar, S.; Taheri, E.; Farhoudi Sefidan Jadid, M.; Emami, P.; Abolhasani, K.; Aslanshirzadeh, F. Antibacterial and Antibiofilm Activity of Lactobacillus Strains Secretome and Extraction against Escherichia Coli Isolated from Urinary Tract Infection. *Biotechnol. Rep.* **2022**, *36*, e00760. [CrossRef] [PubMed]
85. Cheng, J.; Laitila, A.; Ouwehand, A.C. Bifidobacterium Animalis Subsp. Lactis HN019 Effects on Gut Health: A Review. *Front. Nutr.* **2021**, *8*, 790561. [CrossRef] [PubMed]
86. Morovic, W.; Roos, P.; Zabel, B.; Hidalgo-Cantabrana, C.; Kiefer, A.; Barrangou, R. Transcriptional and Functional Analysis of Bifidobacterium Animalis Subsp. Lactis Exposure to Tetracycline. *Appl. Environ. Microbiol.* **2018**, *84*, e01999-18. [CrossRef] [PubMed]
87. Agrawal, A.; Houghton, L.A.; Morris, J.; Reilly, B.; Guyonnet, D.; Goupil Feuillerat, N.; Schlumberger, A.; Jakob, S.; Whorwell, P.J. Clinical Trial: The Effects of a Fermented Milk Product Containing Bifidobacterium Lactis DN-173 010 on Abdominal Distension and Gastrointestinal Transit in Irritable Bowel Syndrome with Constipation. *Aliment. Pharmacol. Ther.* **2009**, *29*, 104–114. [CrossRef]
88. Chen, Y.-M.; Li, Y.; Wang, X.; Wang, Z.-L.; Hou, J.-J.; Su, S.; Zhong, W.-L.; Xu, X.; Zhang, J.; Wang, B.-M.; et al. Effect of Bacillus Subtilis, Enterococcus Faecium, and Enterococcus Faecalis Supernatants on Serotonin Transporter Expression in Cells and Tissues. *World J. Gastroenterol.* **2022**, *28*, 532–546. [CrossRef]
89. Szajewska, H.; Hojsak, I. Health Benefits of Lactobacillus Rhamnosus GG and Bifidobacterium Animalis Subspecies Lactis BB-12 in Children. *Postgrad. Med.* **2020**, *132*, 441–451. [CrossRef]
90. Tillisch, K.; Labus, J.; Kilpatrick, L.; Jiang, Z.; Stains, J.; Ebrat, B.; Guyonnet, D.; Legrain-Raspaud, S.; Trotin, B.; Naliboff, B.; et al. Consumption of Fermented Milk Product with Probiotic Modulates Brain Activity. *Gastroenterology* **2013**, *144*, 1394–1401.e4. [CrossRef]
91. Zhou, L.; Foster, J.A. Psychobiotics and the Gut-Brain Axis: In the Pursuit of Happiness. *Neuropsychiatr. Dis. Treat.* **2015**, *11*, 715–723. [CrossRef]
92. Martín, R.; Chain, F.; Miquel, S.; Natividad, J.M.; Sokol, H.; Verdu, E.F.; Langella, P.; Bermúdez-Humarán, L.G. Effects in the Use of a Genetically Engineered Strain of Lactococcus Lactis Delivering in Situ IL-10 as a Therapy to Treat Low-Grade Colon Inflammation. *Hum. Vaccines Immunother.* **2014**, *10*, 1611–1621. [CrossRef] [PubMed]
93. Gad, M.; Ravn, P.; Søborg, D.A.; Lund-Jensen, K.; Ouwehand, A.C.; Jensen, S.S. Regulation of the IL-10/IL-12 Axis in Human Dendritic Cells with Probiotic Bacteria. *FEMS Immunol. Med. Microbiol.* **2011**, *63*, 93–107. [CrossRef] [PubMed]
94. Sabaté, J.-M.; Iglicki, F. Effect of Bifidobacterium Longum 35624 on Disease Severity and Quality of Life in Patients with Irritable Bowel Syndrome. *World J. Gastroenterol.* **2022**, *28*, 732–744. [CrossRef] [PubMed]
95. Konturek, T.J.; Martinez, C.; Niesler, B.; van der Voort, I.; Mönnikes, H.; Stengel, A.; Goebel-Stengel, M. The Role of Brain-Derived Neurotrophic Factor in Irritable Bowel Syndrome. *Front. Psychiatry* **2021**, *11*, 531385. [CrossRef]
96. Nagpal, R.; Wang, S.; Ahmadi, S.; Hayes, J.; Gagliano, J.; Subashchandrabose, S.; Kitzman, D.W.; Becton, T.; Read, R.; Yadav, H. Human-Origin Probiotic Cocktail Increases Short-Chain Fatty Acid Production via Modulation of Mice and Human Gut Microbiome. *Sci. Rep.* **2018**, *8*, 12649. [CrossRef]
97. Miller, L.E.; Ouwehand, A.C. Probiotic Supplementation Decreases Intestinal Transit Time: Meta-Analysis of Randomized Controlled Trials. *World J. Gastroenterol.* **2013**, *19*, 4718–4725. [CrossRef]
98. Choi, C.H.; Kwon, J.G.; Kim, S.K.; Myung, S.-J.; Park, K.S.; Sohn, C.-I.; Rhee, P.-L.; Lee, K.J.; Lee, O.Y.; Jung, H.-K.; et al. Efficacy of Combination Therapy with Probiotics and Mosapride in Patients with IBS without Diarrhea: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase II Trial. *Neurogastroenterol. Motil.* **2015**, *27*, 705–716. [CrossRef]
99. Ki Cha, B.; Mun Jung, S.; Hwan Choi, C.; Song, I.-D.; Woong Lee, H.; Joon Kim, H.; Hyuk, J.; Kyung Chang, S.; Kim, K.; Chung, W.-S.; et al. The Effect of a Multispecies Probiotic Mixture on the Symptoms and Fecal Microbiota in Diarrhea-Dominant Irritable Bowel Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Clin. Gastroenterol.* **2012**, *46*, 220–227. [CrossRef]
100. Dimidi, E.; Christodoulides, S.; Fragkos, K.C.; Scott, S.M.; Whelan, K. The Effect of Probiotics on Functional Constipation in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am. J. Clin. Nutr.* **2014**, *100*, 1075–1084. [CrossRef]
101. Zhang, T.; Zhang, C.; Zhang, J.; Sun, F.; Duan, L. Efficacy of Probiotics for Irritable Bowel Syndrome: A Systematic Review and Network Meta-Analysis. *Front. Cell Infect. Microbiol.* **2022**, *12*, 859967. [CrossRef]
102. Mayer, E.A.; Savidge, T.; Shulman, R.J. Brain-Gut Microbiome Interactions and Functional Bowel Disorders. *Gastroenterology* **2014**, *146*, 1500–1512. [CrossRef]
103. Johnson, A.C.; Greenwood-Van Meerveld, B.; McRorie, J. Effects of Bifidobacterium Infantis 35624 on Post-Inflammatory Visceral Hypersensitivity in the Rat. *Dig. Dis. Sci.* **2011**, *56*, 3179–3186. [CrossRef] [PubMed]
104. Bischoff, S.C.; Barbara, G.; Buurman, W.; Ockhuizen, T.; Schulzke, J.-D.; Serino, M.; Tilg, H.; Watson, A.; Wells, J.M. Intestinal Permeability--a New Target for Disease Prevention and Therapy. *BMC Gastroenterol.* **2014**, *14*, 189. [CrossRef] [PubMed]

105. Camilleri, M.; Lasch, K.; Zhou, W. Irritable Bowel Syndrome: Methods, Mechanisms, and Pathophysiology. The Confluence of Increased Permeability, Inflammation, and Pain in Irritable Bowel Syndrome. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2012**, *303*, G775–G785. [CrossRef] [PubMed]
106. Mitselou, A.; Grammeniatis, V.; Varouktsi, A.; Papadatos, S.S.; Katsanos, K.; Galani, V. Proinflammatory Cytokines in Irritable Bowel Syndrome: A Comparison with Inflammatory Bowel Disease. *Intest. Res.* **2020**, *18*, 115–120. [CrossRef] [PubMed]
107. Bashashati, M.; Rezaei, N.; Bashashati, H.; Shafieyoun, A.; Daryani, N.E.; Sharkey, K.A.; Storr, M. Cytokine Gene Polymorphisms Are Associated with Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Neurogastroenterol. Motil.* **2012**, *24*, 1102-e566. [CrossRef] [PubMed]
108. Kumar, S.; Shukla, R.; Ranjan, P.; Kumar, A. Interleukin-10: A Compelling Therapeutic Target in Patients With Irritable Bowel Syndrome. *Clin. Ther.* **2017**, *39*, 632–643. [CrossRef] [PubMed]
109. Le Morvan de Sequeira, C.; Kaeber, M.; Cekin, S.E.; Enck, P.; Mack, I. The Effect of Probiotics on Quality of Life, Depression and Anxiety in Patients with Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2021**, *10*, 3497. [CrossRef]
110. Pusceddu, M.M.; Murray, K.; Gareau, M.G. Targeting the Microbiota, From Irritable Bowel Syndrome to Mood Disorders: Focus on Probiotics and Prebiotics. *Curr. Pathobiol. Rep.* **2018**, *6*, 1–13. [CrossRef]
111. Messaoudi, M.; Violle, N.; Bisson, J.-F.; Desor, D.; Javelot, H.; Rougeot, C. Beneficial Psychological Effects of a Probiotic Formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in Healthy Human Volunteers. *Gut Microbes* **2011**, *2*, 256–261. [CrossRef] [PubMed]
112. Messaoudi, M.; Lalonde, R.; Violle, N.; Javelot, H.; Desor, D.; Nejdi, A.; Bisson, J.-F.; Rougeot, C.; Pichelin, M.; Cazaubiel, M.; et al. Assessment of Psychotropic-like Properties of a Probiotic Formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in Rats and Human Subjects. *Br. J. Nutr.* **2011**, *105*, 755–764. [CrossRef] [PubMed]
113. Moloney, R.D.; Johnson, A.C.; O'Mahony, S.M.; Dinan, T.G.; Greenwood-Van Meerveld, B.; Cryan, J.F. Stress and the Microbiota–Gut–Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. *CNS Neurosci. Ther.* **2016**, *22*, 102–117. [CrossRef] [PubMed]
114. Francavilla, R.; Miniello, V.; Magistà, A.M.; De Canio, A.; Bucci, N.; Gagliardi, F.; Lionetti, E.; Castellaneta, S.; Polimeno, L.; Peccarisi, L.; et al. A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain. *Pediatrics* **2010**, *126*, e1445–e1452. [CrossRef] [PubMed]
115. Raskov, H.; Burcharth, J.; Pommergaard, H.C.; Rosenberg, J. Irritable Bowel Syndrome, the Microbiota and the Gut-brain Axis. *Gut Microbes* **2016**, *7*, 365–383. [CrossRef] [PubMed]
116. Benarroch, E.E. Brain-Derived Neurotrophic Factor: Regulation, Effects, and Potential Clinical Relevance. *Neurology* **2015**, *84*, 1693–1704. [CrossRef]
117. Qi, Q.; Chen, F.; Zhang, W.; Wang, P.; Li, Y.; Zuo, X. Colonic N-Methyl-d-Aspartate Receptor Contributes to Visceral Hypersensitivity in Irritable Bowel Syndrome. *J. Gastroenterol. Hepatol.* **2017**, *32*, 828–836. [CrossRef]
118. Distrutti, E.; O'Reilly, J.-A.; McDonald, C.; Cipriani, S.; Renga, B.; Lynch, M.A.; Fiorucci, S. Modulation of Intestinal Microbiota by the Probiotic VSL#3 Resets Brain Gene Expression and Ameliorates the Age-Related Deficit in LTP. *PLoS ONE* **2014**, *9*, e106503. [CrossRef]
119. Savignac, H.M.; Tramullas, M.; Kiely, B.; Dinan, T.G.; Cryan, J.F. Bifidobacteria Modulate Cognitive Processes in an Anxious Mouse Strain. *Behav. Brain Res.* **2015**, *287*, 59–72. [CrossRef]
120. Gibson, G.R.; Hutkins, R.; Sanders, M.E.; Prescott, S.L.; Reimer, R.A.; Salminen, S.J.; Scott, K.; Stanton, C.; Swanson, K.S.; Cani, P.D.; et al. Expert Consensus Document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) Consensus Statement on the Definition and Scope of Prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 491–502. [CrossRef]
121. Wilson, B.; Whelan, K. Prebiotic Inulin-Type Fructans and Galacto-Oligosaccharides: Definition, Specificity, Function, and Application in Gastrointestinal Disorders. *J. Gastroenterol. Hepatol.* **2017**, *32* (Suppl. S1), 64–68. [CrossRef] [PubMed]
122. O'Keefe, S.J.D.; Li, J.V.; Lahti, L.; Ou, J.; Carbonero, F.; Mohammed, K.; Posma, J.M.; Kinross, J.; Wahl, E.; Ruder, E.; et al. Fat, Fibre and Cancer Risk in African Americans and Rural Africans. *Nat. Commun.* **2015**, *6*, 6342. [CrossRef] [PubMed]
123. Wilson, B.; Rossi, M.; Dimidi, E.; Whelan, K. Prebiotics in Irritable Bowel Syndrome and Other Functional Bowel Disorders in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am. J. Clin. Nutr.* **2019**, *109*, 1098–1111. [CrossRef] [PubMed]
124. Silk, D.B.A.; Davis, A.; Vulevic, J.; Tzortzis, G.; Gibson, G.R. Clinical Trial: The Effects of a Trans-Galactooligosaccharide Prebiotic on Faecal Microbiota and Symptoms in Irritable Bowel Syndrome. *Aliment. Pharmacol. Ther.* **2009**, *29*, 508–518. [CrossRef] [PubMed]
125. Azpiroz, F.; Dubray, C.; Bernalier-Donadille, A.; Cardot, J.-M.; Accarino, A.; Serra, J.; Wagner, A.; Respondek, F.; Dapoigny, M. Effects of ScFOS on the Composition of Fecal Microbiota and Anxiety in Patients with Irritable Bowel Syndrome: A Randomized, Double Blind, Placebo Controlled Study. *Neurogastroenterol. Motil.* **2017**, *29*, e12911. [CrossRef] [PubMed]
126. Niv, E.; Halak, A.; Tiommny, E.; Yanai, H.; Strul, H.; Naftali, T.; Vaisman, N. Randomized Clinical Study: Partially Hydrolyzed Guar Gum (PHGG) versus Placebo in the Treatment of Patients with Irritable Bowel Syndrome. *Nutr. Metab.* **2016**, *13*, 10. [CrossRef] [PubMed]

127. Chen, Q.; Ren, Y.; Lu, J.; Bartlett, M.; Chen, L.; Zhang, Y.; Guo, X.; Liu, C. A Novel Prebiotic Blend Product Prevents Irritable Bowel Syndrome in Mice by Improving Gut Microbiota and Modulating Immune Response. *Nutrients* **2017**, *9*, 1341. [CrossRef] [PubMed]
128. McIntosh, K.; Reed, D.E.; Schneider, T.; Dang, F.; Keshteli, A.H.; Palma, G.D.; Madsen, K.; Bercik, P.; Vanner, S. FODMAPs Alter Symptoms and the Metabolome of Patients with IBS: A Randomised Controlled Trial. *Gut* **2017**, *66*, 1241–1251. [CrossRef]
129. Hustoft, T.N.; Hausken, T.; Ystad, S.O.; Valeur, J.; Brokstad, K.; Hatlebakk, J.G.; Lied, G.A. Effects of Varying Dietary Content of Fermentable Short-Chain Carbohydrates on Symptoms, Fecal Microenvironment, and Cytokine Profiles in Patients with Irritable Bowel Syndrome. *Neurogastroenterol. Motil.* **2017**, *29*, e12969. [CrossRef]
130. Cui, J.; Lin, Z.; Tian, H.; Yang, B.; Zhao, D.; Ye, C.; Li, N.; Qin, H.; Chen, Q. Long-Term Follow-Up Results of Fecal Microbiota Transplantation for Irritable Bowel Syndrome: A Single-Center, Retrospective Study. *Front. Med.* **2021**, *8*, 710452. [CrossRef]
131. Sender, R.; Fuchs, S.; Milo, R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol.* **2016**, *14*, e1002533. [CrossRef] [PubMed]
132. de Vos, W.M.; de Vos, E.A. Role of the Intestinal Microbiome in Health and Disease: From Correlation to Causation. *Nutr. Rev.* **2012**, *70*, S45–S56. [CrossRef] [PubMed]
133. Cryan, J.F.; Dinan, T.G. Mind-Altering Microorganisms: The Impact of the Gut Microbiota on Brain and Behaviour. *Nat. Rev. Neurosci.* **2012**, *13*, 701–712. [CrossRef] [PubMed]
134. Tap, J.; Derrien, M.; Törnblom, H.; Brazeilles, R.; Cools-Portier, S.; Doré, J.; Störsrud, S.; Le Nevé, B.; Öhman, L.; Simrén, M. Identification of an Intestinal Microbiota Signature Associated with Severity of Irritable Bowel Syndrome. *Gastroenterology* **2017**, *152*, 111–123.e8. [CrossRef] [PubMed]
135. Vahora, I.S.; Tsouklidis, N.; Kumar, R.; Soni, R.; Khan, S.; Vahora, I.S.; Tsouklidis, N.; Kumar, R.; Soni, R.; Khan, S. How Serotonin Level Fluctuation Affects the Effectiveness of Treatment in Irritable Bowel Syndrome. *Cureus* **2020**, *12*, e9871. [CrossRef]
136. Krammer, L.; Sowa, A.S.; Lorentz, A. Mast Cells in Irritable Bowel Syndrome: A Systematic Review. *J. Gastrointestin Liver Dis.* **2019**, *28*, 463–472. [CrossRef]