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Review Article

The Functional Gastrointestinal Disorders in Infancy and the Fundamental Role of Probiotics: A Review on the Pathophysiology, Current Research and Future Therapy

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Abstract: Probiotics are the live microorganisms that they provide health benefits when consumed, generally by improving or restoring the gut flora. Now a day, the general public, researchers, International organization like WHO/FAO, pharmaceutical companies and food industries are becoming more interested in probiotics. According to the growth of, products, publications and public knowledge, research into the effectiveness of probiotics is gaining traction. "Let healthy microorganisms work for you in various domains acquire their advantages and take a break," says probiotics. Food digestion, the synthesis of helpful compounds to fight undesirable microorganisms, the complementing of the activities of missing digestive enzymes, the maintenance of the digestive system's pH, and so on are examples of such activity. Probiotics will boost the effectiveness of our digestive system's biological fermenters. Many writers have written on the history and development of probiotics as well as their many uses. In this study, we will primarily concentrate on three points: health improvement, infection control, and illness management, all of which might be avoided by using various forms of direct Probiotics or foods containing Probiotics. The most prevalent functional gastrointestinal diseases are infantile colic, constipation, functional abdominal pain, and irritable bowel syndrome. The present data on the use of probiotics in the treatment of this FGID will be reviewed in this chapter. Although the etiology of FGID is complex, the role of the gut microbiota in its development has been frequently stressed. As a result, the function of probiotics in their therapy is being investigated more closely. The use of Lactobacillus reuteri DSM 17938 at a dosage of 108 CFU/day for the treatment of infantile colic in breastfed babies currently has the greatest evidence of effectiveness. Lactobacillus rhamnosus at a dosage of 3 109 CFU and a multi-strain formulation for the treatment of IBS have limited but promising data. There is some evidence for the use of L. reuteri DSM 17938 at a dosage of at least 108 CFU/day in the treatment of FAP. Irritable bowel syndrome, functional dyspepsia, abdominal migraine, and functional abdominal pain not otherwise specified are among the pediatrics functional abdominal pain disorders, also known as diseases of gut-brain interaction, as described by the Rome IV diagnostic criteria. Functional abdominal pain problems affect 3-16 percent of the population, depending on the nation, age, and gender. The diagnosis is difficult, although it is based mostly on clinical symptoms and the elimination of alternative organic causes, with a focus on avoiding intrusive diagnostic techniques. Improved knowledge and treatment of these puzzling illnesses are expected in the next decades.

Keywords: Functional Abdominal Pain, Infantile Colic, Irritable Bowel Syndrome, Lactobacillus, Probiotics, Treatment's

1. Introduction

Since there is a lack of knowledge of the underlying anatomical or chemical abnormalities, functional gastrointestinal disorders are a common category of illnesses diagnosed exclusively by symptomatology [1]. Patients with FGIDs often report stomach discomfort, dyspepsia, regurgitation, bloating, constipation, diarrhea, incontinence, food or stool passage issues, or a combination of these symptoms. Disruption in motility, changed mucosal and immunological function, visceral hypersensitivity, disturbance in gut microbiota, and altered visceral signal processing in the central nervous system are all thought to have a role in pathogenesis. GERD, functional dysphagia, functional dyspepsia, gastroparesis, irritable bowel syndrome, functional constipation, diarrhea, and fecal Incontinence are all common FGIDs [2]. It is commonly known that individuals with FGIDs have co-existing psychosocial symptoms such as stress, worry, and depression in addition to gastrointestinal symptoms [3]. The gut-brain axis refers to the bidirectional communication routes between the gut and the brain that are implicated in the etiology of FGIDs. The hypothalamus-pituitary axis, limbic system, autonomic nervous system, and endocrine system all play a role in this communication, as do environmental and anatomical variables like the hypothalamus-pituitary axis, limbic system, autonomic nervous system, and endocrine system. The gut microbiota has lately emerged as a potential axis influencer, attracting much-needed study attention. FGIDs in infants and toddlers are a group of symptoms that are commonly age-related, chronic, or recurring and are not explained by structural or biochemical abnormalities [4]. Functional symptoms in children might occur as a consequence of maladaptive behavioral reactions to internal or external stimuli. The clinical manifestation of a FGIDs changes with age and is dependent on a person's developmental stage, notably in terms of physiologic, autonomic, emotional, and cognitive development. It is feasible to identify pain-predominant FGIDs after the kid has developed the appropriate linguistic abilities to communicate discomfort. Children cannot reliably describe sensations such as nausea or discomfort during their early years. Infants and preschoolers are unable to distinguish between emotional and physical suffering. As a result, physicians rely on the reports and interpretations of parents, who are the most familiar with their children, as well as the observations of the clinician, who is educated to distinguish between health and disease. FGIDs is divided into three types in children and adolescents: stomach discomfort and defecation-related FGIDs, vomiting, and aerophagia. Abdominal pain-related FGIDs affects 0.3-19% of schoolchildren in the United States and Europe, and is one of the most common reasons for a visit to the pediatrician [5]. In the Western world, functional constipation affects 3% of people [6]. Although the prognosis for FGIDs is favorable, the disease's overall effect may significantly reduce people's well-being and quality of life [1]. This review attempted to concentrate on functional gastrointestinal diseases in children and the critical role of probiotics and recommendations for the future therapy.

2. Literature Review

2.1. Functional Gastrointestinal Disorders

FGDs are digestive system illnesses in which the existence of a structural or tissue defect does not explain the symptoms [6]. Because there are no biomarkers for FGDs, they are diagnosed based on their symptom profile, as with other functional diseases. Gastrointestinal symptoms are common, but many individuals who encounter them don't have a biological explanation for them [5]. A functional gastrointestinal condition, such as irritable bowel syndrome, functional dyspepsia, or functional constipation, will be diagnosed in the majority of these persons. At any one moment, up to 40% of individuals are affected by these illnesses, with two-thirds of those affected experiencing chronic, fluctuating symptoms. The pathophysiology of functional gastrointestinal disorders is complex, but it includes microbial dysbiosis within the gut, altered mucosal immune function, visceral hypersensitivity, and abnormal gastrointestinal motility, as well as bidirectional dysregulation of gut-brain interaction. As a result, the illnesses are referred to as disorders of gut-brain connection in nomenclature. Psychological comorbidity is widespread; however, it's unclear whether it comes before or after symptoms [7]. Patients with functional gastrointestinal disorders may feel stigmatized, and clinicians often fail to explain this diagnosis properly, and little education is offered. It is critical to identify and treat these conditions as soon as possible because they have a significant impact on health-care systems and society as a whole due to repeated consultations, unnecessary investigations and surgeries, prescriptions and over-the-counter medicine use, and decreased health-related quality of life and ability to work. To reach a diagnosis, symptom-based criteria are utilized, with restricted investigations performed sparingly in certain cases. Treatment is based on a biopsychosocial concept and involves managing physical symptoms as well as, if applicable, psychological comorbidities [8]. Treatment for functional gastrointestinal diseases will likely become more individualized in the future, based not just on symptoms but also on underlying pathophysiology and psychology.

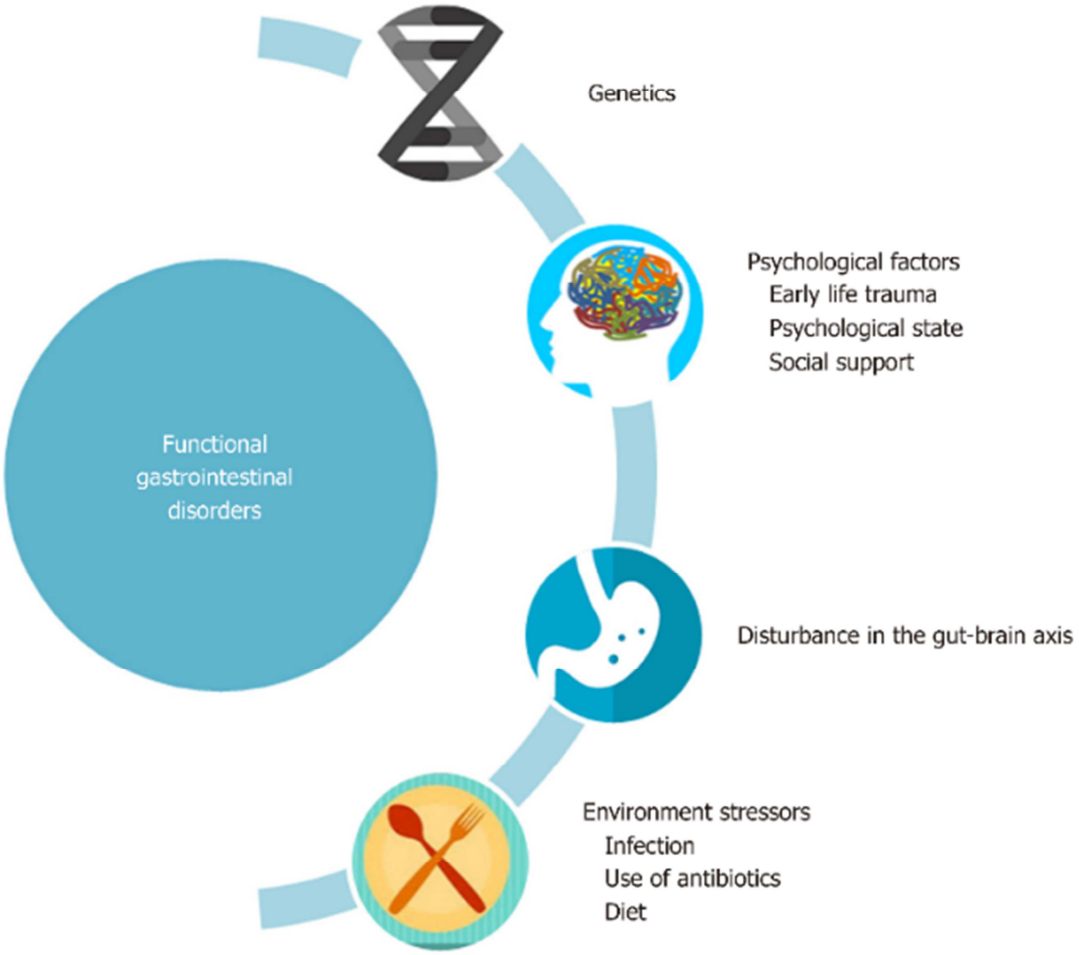

Figure 1. *Fundamental Gastrointestinal Disorders.*

2.2. Infantile Colic

Infantile colic is a frequent issue in otherwise healthy developing newborns, marked by inconsolable sobbing, impatience, and fussing [9]. The symptoms normally go away by 3-4 months of age, or 3-4 months beyond term in the case of preterm newborns; the weeping peak is usually around 4-6 weeks, and then it gradually fades away by 12 weeks [9]. Despite the fact that it affects a large number of newborn babies throughout the globe, it is still little understood and a difficult condition for parents and caregivers, owing to the lack of effective treatment alternatives [10]. The reported incidence ranges from 4% to 28% [11]. with the vast variation attributable to caregiver's perceptions of the severity and length of crying episodes, data collection methods, and culturally influenced baby care practices [12]. Inconsolable weeping may lead caregivers to experience psychosocial distress and sadness, as well as hinder the bonding process between mother and child [10]. As a result, parents regularly visit health-care institutions and frequently use alternate, untested, and sometimes dangerous ways to calm screaming newborns [13].

As previously stated, the genesis of the condition is unknown, despite the fact that many possible causes have been proposed. Some ideas concentrate on alterations in the digestive system, such as nervous/digestive system immaturity, changed gut flora, and moderate gastrointestinal inflammation [5]. Other explanations, mostly psychological in nature, have been presented, such as maternal worry, insufficient mother-infant bonding, or difficult newborn temperament [10]. The importance of gut bacteria has recently received increased attention. This is due to the fact that the onset of baby colic corresponds to the most significant changes in the microbiome of the intestine during the first weeks and months of life. [14]. Microbes engaged in intestinal colonization connect with host cells and have a significant influence on the immune system and future inflammatory response [15].

Newborns with colic have a different intestinal microbiome than healthy infants, with lower fecal bacterial diversity and higher fecal counts of gram-negative bacteria, particularly coliform bacteria [9]. Dubois and Gregory [9] found that babies with colic have more Proteobacteria and fewer Bifidobacteria and Lactobacillus than healthy controls [16]. Furthermore, the development of colic symptoms seems to be negatively related with Bacteroidetes phylum microorganisms [1]. Furthermore, microorganisms from the phyla Actinobacteria and Firmicutes tend to prevent infants against developing colic [17]. The presence of Bifidobacterium longum in human breast milk [6]. and the fact that Actinobacteria and Bifidobacterium quickly dominate the

intestine of newborns who do not have the colic phenotype [17]. suggest that these bacteria may play a key role in reducing inflammation and infant fussiness and crying. A research that found a negative association between pro-inflammatory indicators and Clostridium leptum and Clostridium coccoides, the key members of the normal intestinal microflora, added to the relevance of the interaction between microbiota and inflammation [18]. In addition, children with colic had higher levels of the cytokines MCP-1, MIP-1b, and IL-8, indicating that low-grade systemic inflammation plays a role in the pathophysiology of infantile colic [19]. Although there has been improvement in our understanding in recent years, no final conclusions can be taken, and additional species-specific study is clearly needed, since not all microorganisms interact with their hosts in the same manner [4]. Furthermore, like with other dysbioses, it is unclear if the detected alterations are the cause or result of the clinical disease. As a result of this new findings, as well as a lack of effective treatment alternatives, researchers are looking into novel therapy options aimed at changing the microbiome of the intestine via the use of probiotics.

2.3. Treatment of Infantile Colic with Probiotics

For the treatment of infantile colic, several therapy options have been recommended, however the majority of them have not been tested in well-designed randomized control studies. A recent network meta-analysis, [20] evaluated the existing data in the treatment of infantile colic, suggesting that Lactobacillus L. reuteri DSM 17938 at a dosage of 10 8 CFU/day decreased the length of crying episodes considerably. The superiority of L. reuteri DSM 17938 was established not only when compared to placebo, but also when compared to dietary or manipulative therapies, reassurance, massage, herbal therapy, acupuncture, and medications [21]. Five RCTs utilized the same dosage of L. reuteri DSM 17938, and four of them found that it had a beneficial impact. The variation in findings may be explained in part by the babies' feeding; whereas studies that reported a favorable benefit mostly included breastfed infants, the research that found no difference [15] included both breastfed and formula-fed infants. These trials were compared in a meta-analysis of individual participant data, which revealed that the probiotic group spent less time crying and/or fussing than the placebo group at all time periods. At all time periods, the probiotic group was almost twice as likely as the placebo group to have treatment success. Intervention effects were more dramatic in breastfed babies and were not significant in formula-fed infants, as previously stated [4].

Probiotics have been suggested to help with infantile colic via a number of processes. Enteric infections can be inhibited by probiotics, the gut microbiota can be modulated [14] and innate and adaptive immune responses may be elicited [12] L. reuteri administration causes a large rise in FOXP3 m RNA levels, which is a Treg marker. Increased IL-10 output, which is lowered not just in colitis models but also in children with colic [14]. might be responsible for the impacts on Treg lymphocytes. The impact might potentially be due to a lower response of capsaicin- and distension-evoked firing of spinal nerve action potentials, implying that L. reuteri DSM 17938 has reduced pain sensibility [6]. Finally, L. reuteri treatment was linked to a considerable reduction in fecal calprotectin levels, a clinical indication of intestinal inflammation in both adults and children [10].

Table 1. *Randomized controlled trials using probiotics in the treatment of infantile colic.*

Author	Predominant Diet	Number of included children	Intervention	Crying duration
Savino 2010 (Savino et al. 2010)	Breastfeeding	50	L. reuteri DSM 17938, 108 CFU	Decreased
Szajewska 2013 (Szajewska et al. 2013)	Breastfeeding	80	L. reuteri DSM 17938, 108 CFU	Decreased
Chau 2014 (Chau et al. 2015)	Breastfeeding	52	L. reuteri DSM 17938, 108 CFU	Decreased
Mi 2015 (Mi et al. 2015)	Breastfeeding	42	L. reuteri DSM 17938, 108 CFU	Decreased
Sung 2014 (Sung et al. 2014)	Breastfeeding and formulae feeding	167	LGG 4.5 109 CFU	Not significant
Partty 2015 (Partty et al. 2015)	Breastfeeding and formulae feeding	30	Supplemented together with behavioral and nutritional intervention	Not significant

2.4. Functional Abdominal Pain

FAPDs are among the most prevalent childhood illnesses, affecting up to 25% of all children and babies globally [3]. FAPDs are now known as "disorders of gut-brain interaction"[5] because of their biopsychosocial etiology, which involves intricate interactions within the gut-brain axis. Furthermore, the gut-brain axis is now correctly referred to as the' microbiota-gut-brain axis,' reflecting an increase in our knowledge of the quantity, complexity, importance, and interconnections of the microbial communities that reside inside the gastrointestinal tract lumen [6, 1]. Visceral hyperalgesia and heightened central awareness of visceral stimuli are common features of FAPDs, which seem to be the result of sensitizing psychosocial and medical variables placed on a background of genetic susceptibility and early-life traumas. Although the gut-brain-microbiota axis seems to be most vulnerable during the prenatal period and the first years of life, early life is likely to cover all childhood and teenage periods when growth, as well as the structural and functional development of organs, occurs. FAPDs are classified based on their symptom profile, which varies depending on which part of the gastrointestinal tract is affected or if they are related to other disorders like headaches or migraines.

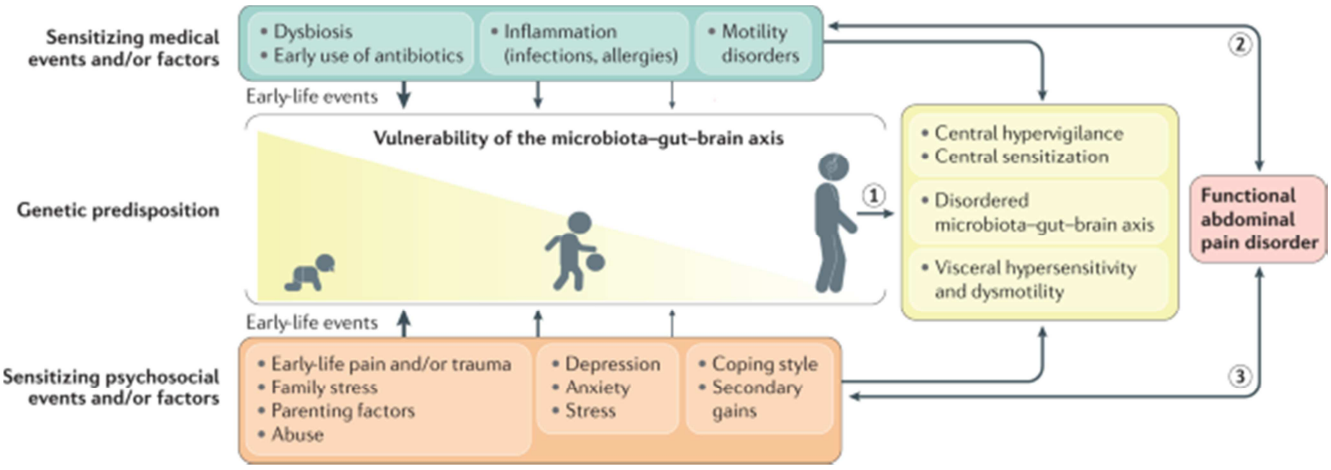

Figure 2. *Vulnerability of the Microbiota-gut-brain Axis.*

2.5. Risk Factors for FAPD

2.5.1. Sex

FAPDs are more common in females, both in adolescents and in younger children, according to studies from throughout the world [22]. The presence of non-organic abdominal pain in children with at least three episodes of abdominal pain and/or weekly episodes of abdominal pain and/or a symptom duration of at least three months was defined by a metanalysis [23]. on epidemiological studies reporting the prevalence or incidence of FAPD according to the different ROME criteria as well as other previously used criteria or defined by the presence of non-organic abdominal pain in children with at least three episodes of abdominal pain and/or weekly episodes of abdominal pain and/or a symptom duration of Only two of the 24 investigations found that females were more likely than boys to have FAPD. Girls had a substantially greater percentage of FAPDs than boys (15.9% vs 11.5%, pooled OR 1.5, 95% CI 1.3-1.7; P 0.01), according to the pooled prevalence statistics. This difference was also noticeable at a pre-pubertal age of ten years (9.9% female's vs 7.7% boys, OR 1.4, 95 percent CI 1.16-1.79; P 0.001) [22].

2.5.2. Age

The evidence for the involvement of age in the aetiology of FAPD is ambiguous, due to the disparate outcomes of research that looked at the impact of age. Nine research found no variations in prevalence with age, six studies found an increase in prevalence with age, and four studies found a reduction in prevalence with age when it came to IBS. These results are consistent with those of a meta-analysis published in 2015, which pooled data from studies throughout the globe encompassing children aged 12 and above, and found no significant difference in the prevalence of FAPDs between the two age groups [23]. In addition, one research found that the prevalence of IBS peaked around 11 years of age (12%) and thereafter declined in children younger and older than 11 years of age [24]. The varied age groups included in these research may explain the variety of outcomes from age studies.

2.5.3. Psychiatric and Social Aspects

Although family history, other somatic symptoms, mental health status, and socioeconomic characteristics are often accepted as risk factors for all forms of FAPD, their impacts on prevalence are mostly documented. Several studies have shown that children and adolescents with FAPDs had poor mental health, with greater levels of anxiety, sadness, and emotional issues, as well as higher stress levels or stressful events, and a worse quality of life than healthy children [5]. Clinically significant anxiety or despair has been documented in up to 50% of children with FAPD [25]. Furthermore, FAPDs females are more likely to have had gastrointestinal illnesses or procedures earlier in childhood. Furthermore, children with FAPDs had higher extraintestinal somatic symptoms, such as headache, weariness, and sleep issues, then children without FAPDs [17]. Increased pain episodes in children have been related to social environment variables such as parental chronic pain. Children of moms with IBS had greater gastrointestinal problems, miss more school days, and seek medical help more often than children from control families [26]. Intriguingly, having chronic pain in both parents was linked to considerably worse health in children than having chronic pain in one or neither parent [27]. According to a large body of research, parents may impact their children's perceptions of pain by modeling their pain behavior and rewarding their children's pain complaints with solicitous responses [28] children express their pain in the same manner that their parents do.

2.5.4. Aspects of Genetics

IBS and other FAPDs have been linked to a familial history [7, 13, 18]. In the case of IBS, there has been a significant overlap in the prevalence of stomach symptoms between mothers and their children [26]. This overlap might be attributable to particular genes, but it's more likely owing to a variety of social circumstances, including parents' attentiveness to their children's pain behaviors [9]. Although twin studies demonstrate that monozygotic twins had a greater concordance rate of IBS (17.2%) than dizygotic twins (8.4%), suggesting genetic influence, the low total concordance

clearly suggests that social and environmental variables are at play [10]. Several adult studies have identified a variety of susceptibility genes for the development of FAPDs, however the findings are mixed. There have been no equivalent investigations in children, however a small pilot research found that 16% of children with IBS had pedigrees that imply maternal inheritance, probably linked to mitochondrial DNA-related dysfunction [15].

2.5.5. Pathophysiology

FAPDs are multifaceted diseases that seem to be caused by a breakdown in the functional and/or structural integrity of one or more parts of the microbiota-gut-brain axis. The complex and numerous relationships that underpin these disorders are encapsulated in a biopsychosocial model that may be applied to all FAPDs. The notions of visceral hypersensitivity and central hypervigilance are critical components of this approach, while the relative relevance of each of these components is uncertain and likely to differ across people. The impact of genetics vs environmental influences is unclear, and although both seem to be important, neither component appears to be sufficient in and of itself to contribute to the development of FAPDs. The idea of hypersensitivity happening anywhere from the periphery to the central nervous system, also known as visceral hypersensitivity and central hypervigilance, is important to the biopsychosocial model of FAPDs.

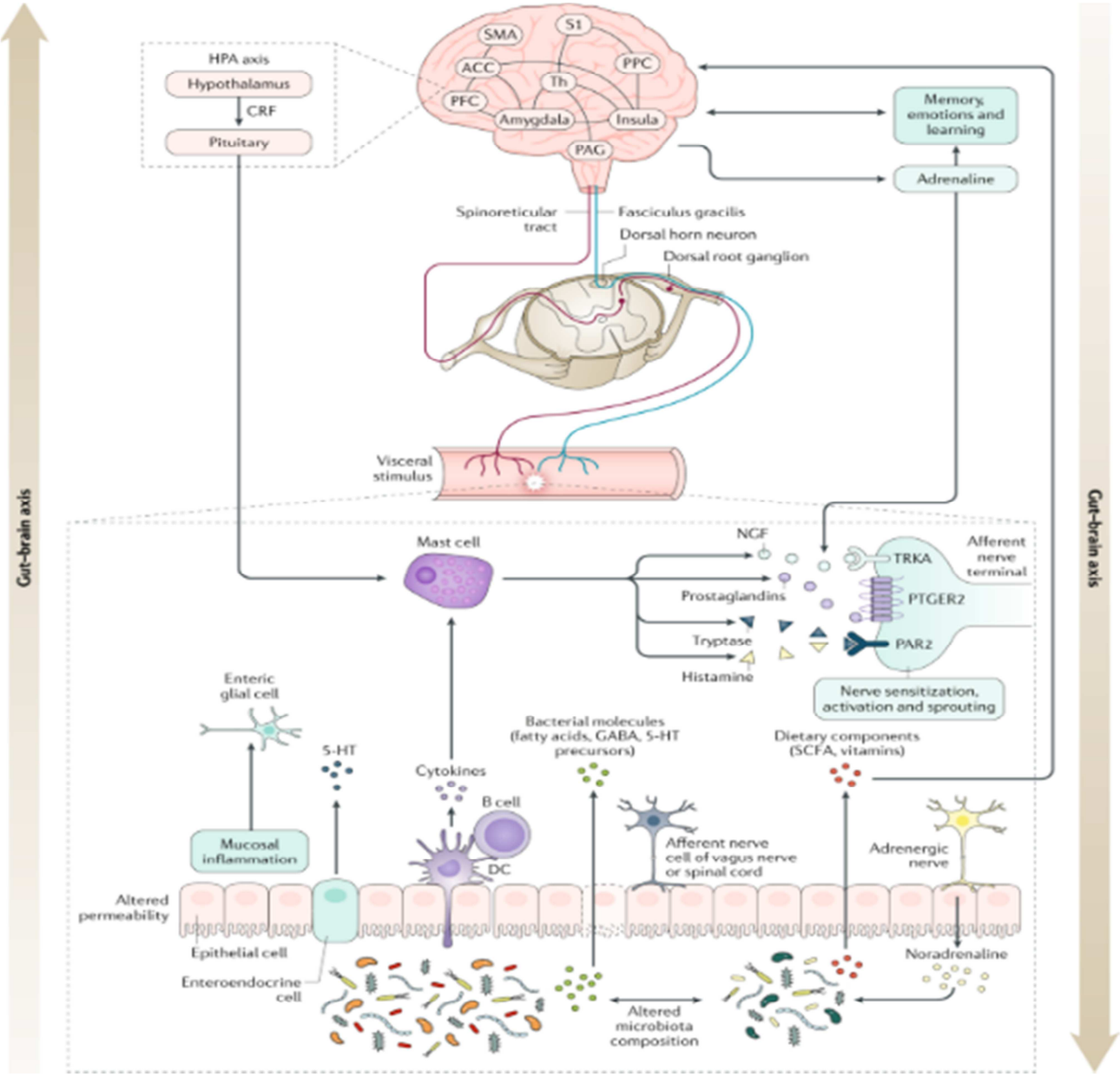

Figure 3. *Pathophysiology of Fundamental Gastrointestinal Disorders.*

The figure depicts the aetiopathogenesis that underpins the disturbance of one or more parts of the microbiota-gut-brain axis' functional and/or, more subtly, structural integrity. This axis is a bidirectional communication mechanism that allows

gut microbes to connect with the gut as well as the brain. The processes of connection between the stomach and the brain are complicated and not entirely understood, although they include neurological, endocrine, immunological, and metabolic pathways. Neurotransmitters produced by the gut microbiota may pass the mucosal layer of the intestines and impact the enteric nervous system and, indirectly, the brain. Short-chain fatty acids, for example, are microbial metabolic products that may have central effects. Immune-mediated production of cytokines like IL-1 and IL-6, which may pass via the circulation to the brain, also plays a role in signaling from the stomach to the brain. These cytokines may activate the hypothalamic-pituitary-adrenal axis in the hypothalamus, causing cortisol, a powerful stress activator, to be released. The brain-gut-microbiota axis is also influenced by the HPA axis. The amygdala integrates memory, emotions, and learning, as well as pain and stress and anterior cingulate cortex signals, and feeds them into a matrix of other brain centers, including the insula and the thalamus, which then integrate with signals from the periphery in the somatosensory cortex.

2.6. Irritable Bowel Syndrome

Irritable bowel syndrome is a collection of symptoms that affect the digestive system. It's a common, yet unpleasant, gastrointestinal condition. Gas, stomach discomfort, and cramps are common symptoms of IBS. IBS is classified by researchers according to the sort of bowel movement issues you encounter. The kind of IBS you have may have an impact on how you're treated. Particular medications are only effective in certain forms of IBS. People with IBS often have regular bowel motions on some days and abnormal bowel movements on others. The kind of IBS you have is determined by your irregular bowel movements:

1) IBS-C (Irritable Bowel Syndrome with Constipation): The majority of your stool is hard and lumpy.
2) IBS-D (Irritable Bowel Syndrome with Diarrhea): The majority of your stool is loose and watery.
3) IBS with mixed bowel habits (IBS-M): On the same day, you experience both hard and lumpy stool movements as well as loose and watery motions.

Children and adults with IBS [4] have been reported as having abnormal intestinal function and rectal perception. Colonic transit measures, such as radiopaque markers, wireless motility capsules, and scintigraphy, are often used to evaluate colonic function. When compared to the general population, [28] adults with IBS-constipation have slower colonic transit and those with IBS-diarrhoea had faster colonic transit. Unfortunately, the majority of research on colonic function in children have been undertaken in a subgroup of children with severe constipation, making inferences about colonic transit in IBS-D impossible. Motor changes in certain people with constipation [18] may be accompanied with abdominal discomfort. In children with constipation [13] three forms of colonic motility have been identified: normal motility, segmental dysmotility, and overall colonic dysmotility. Sadly, distinguishing symptoms like pain, constipation, and diarrhoea amongst people with varied colonic motilities has not always been easy. Pain is a common symptom of IBS that occurs regardless of whether or not there is any stool retention. In addition, children with IBS have a lower rectal compliance and contractile response to meals [17]. So yet, no definite link between motility problems and symptoms in children with all FAPDs [10] has been shown. It is yet unknown if the reported gastrointestinal motor abnormalities are significant, or whether they are a cause or result of FAPD. Indeed, treating merely the abnormalities of stomach motility does not give full symptom alleviation, highlighting the relevance of the sensory abnormalities that may accompany motor dysfunction. Despite this, motor dysfunction is understudied in both children and adults due to the intrusive nature of testing techniques. Children with IBS have a higher percentage of Proteobacteria, including genera like Dorea, Haemophilus, Ruminococcus, and Clostridium spp, as well as a higher Firmicutes to Bacteroidetes ratio [13]. In individuals with IBS, downregulation of bacterial colonization with Lactobacillus, Bifidobacterium, and Faecalibacteriumprausnitzii was discovered in a recent meta-analysis, notably in diarrhea-predominant IBS [8]. Veillonella, Prevotella, Lactobacillus, and Parasporbacterium levels seem to be higher in pediatric patients with diarrhea-predominant IBS, but Bifidobacterium and Verrucomicrobium levels appear to be lower [17]. These bacteria are thought to modify or impact visceral perception, gut motility, gut permeability, and intestinal gas production, all of which may contribute to pain-related FGIDs.

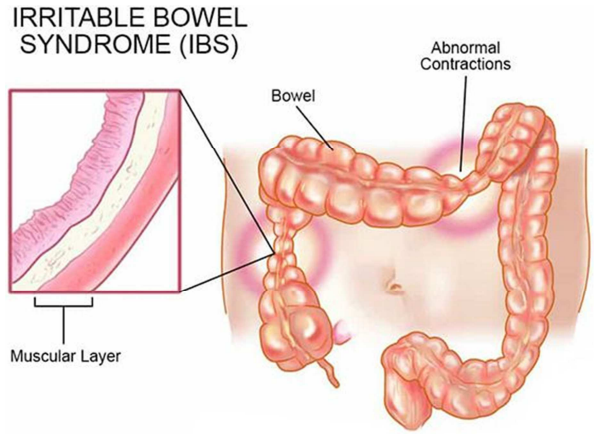

Figure 4. *Irritable bowel syndrome of Fundamental Gastrointestinal Disorders.*

2.7. Probiotics as a Treatment for FAP/IBS

Unfortunately, children with IBS and FAP have few therapy choices. Pharmaceutical therapies have very little evidence, and no solid recommendations for their usage can yet be provided [29]. There is very little information on the impact of dietary modifications on FAP and IBS symptoms. Despite the fact that a diet low in fermentable oligo-, di-, monosaccharide, and polyol (FODMAP) has been proven to be helpful in multiple adult trials, it has only been tested in one small RCT in children with IBS [11]. Cognitive behavioral therapy (CBT) and

mindfulness-based cognitive therapy (MBCT) are two more treatments that are available. Indeed, these methods have been shown to alleviate pain in the short and medium term [29]. but they are unfortunately not generally accessible. It is important to note that a good diagnosis of FGIDs from the outset boosts the likelihood of symptom alleviation [29]. To achieve better symptom management, it is critical to recognize the presence of discomfort and to communicate the benign nature of the condition to the patient and parents from the start. The most investigated probiotic strains are Lactobacillus rhamnosus GG (LGG) [29] and Lactobacillus reuteri DSM 17938 [15]. LGG reduces post-intervention pain intensity (MD-0.44, 95 percent CI-0.82 to 0.05) in a meta-analysis of published RCTs. Importantly, when only children with IBS were included (MD-0.60, 95 percent CI-0.97 to 0.23), the impact was much stronger (MD -0.60, 95 percent CI -0.97 to 0.23) [13]. There are two randomized, placebo-controlled clinical trials investigating multi-strain preparations: one with a proprietary specific mixture of Lactobacillus, Bifidobacterium, and a Streptococcus, [18]. and the other with a combination of different Bifidobacterium strains [8].

Table 2. *Randomized controlled trials using probiotics in the treatment of functional abdominal pain (FAP) and irritable bowel syndrome (IBS).*

Author	No	Intervention	Main results
Bauserman 2005 (Bauserman and Michail 2005)	50	LGG, 10 10 CFU	Not significant for IBS
Francavilla 2010 (Francavilla et al. 2010)	60	LGG, 10 10 CFU	Increases treatment success in IBS
Gawronska 2007 (Gawronska et al. 2007	48	LGG, 10 10 CFU	Moderately increases treatment success in IBS
Giannetti 2017 (Giannetti et al. 2017)	59	LGG, 10 10 CFU	Increases treatment success in IBS
Guandalini 2010 (Guandalini et al. 2010)	40	Bifidobacteriumlongum BB536, 3 10 9 CFU, Bifidobacterium infantis M-63, 109 CFU; Bifidobacteriumbreve M-16 V, 109 CFU	Increases treatment success in IBS
Eftekhari 2015 (Eftekhari et al. 2015)	55	De Simone Formulation	Not significant for FAP
Jadresin 2017 (Jadresin et al. 2017)	54	L reuteri DSM 17938, 10 8 CFU	Decreased pain intensity mainly in FAP
Maragkoudaki 2017 Maragkoudaki et al. 2017	104	L reuteri DSM 17938, 10 8 CFU	Not significant for FAP

2.8. Role of Probiotics in Health Improvement

One of the aspects of probiotics discussed in this review is their involvement in health improvement. In reality, we predict that healthy people will be the first to require Probiotics, which will enhance their overall health and, as a consequence, protect them against various illnesses.

2.9. Infection Prevention

The processes by which probiotics work are largely unclear, and many research questions remain unanswered. Probiotics, on the other hand, help to regulate gut pH, fight infections by creating antimicrobial compounds, compete for pathogen binding and receptor sites as well as available nutrients and growth factors, stimulate immunomodulatory cells, and produce lactase The most essential aspect of probiotics is that they have been shown to be safe, cost-effective, and have the potential to interfere with microbial illness. When widely given medicines become ineffective due to antibiotic resistance, the World Health Organization designated probiotics as thenext-most essential immune defense mechanism in 1994 [30]. Microbial interference therapy refers to the use of probiotics in the treatment of antibiotic resistance [9].

2.10. Diseases of the Intestines (Diarrhoea)

Probiotics are showing to be useful in preventing and controlling diarrhea following antibiotic therapy. Bifidobacteria spp., Lactobacillus GG, Lactobacillus reuteri, and S. boulardii, are used to treat diarrhea [23]. Probiotics may also help to prevent traveler's diarrhea [7] and rotavirus-related diarrhea in young infants [20]. Lactobacillus spp., L. reuteri, Lactobacillus casei, S. boulardii, Bifidobacteriumbifidum, and S. thermophilus are among the probiotic species used with children [26]. Probiotics may protect against diarrhea-causing germs by competing with harmful viruses or bacteria for epithelial cell binding [9] or by generating bacteriocins like nisin [26].

2.11. Infections with Helicobacter Pylori

Lactobacillus salivarius may produce large levels of lactic acid, which inhibits the development of H. pylori in vitro, according to [31]. Probiotic bacteria may suppress the stomach colonization and activity of H. pylori, which is linked to gastritis, peptic ulcers, and gastric cancer, according to early research. In vitro and in mouse tests, L. salivarius was reported to suppress H. pylori colonization [7]. The use of probiotics in the treatment of H. pylori infection has been recommended as a way to improve eradication rates, tolerability, and compliance with various antibiotic regimens [30].

2.12. Probiotic's Role in Disease Treatment

Probiotics have the potential to not only enhance our health and control pathogenic infections, but also to aid in the treatment and management of actual diseases. Part of the foundation for doing such activities is built on the same Probiotic functions notions outlined in the preceding sections. However, how may probiotics aid in the treatment and management of actual diseases? Understanding disease behavior and its causal agents are the most crucial elements. Diseases associated with genetic abnormalities, for example, might result in deficits such as lactose intolerance. In such cases, the role of probiotics will be to remove deficiencies through various mechanisms, such as I supplying our bodies with the products of missing gene products, (ii) suitable

alternative products supplying our bodies, (iii) supplying our bodies with the final products of a complete pathway. As in the case of people suffering from retinoblastoma. In this situation, the crucial foundation for Knudson hypnosis will be entirely disrupted, and no one gene will be subjected to extreme stress that may result in a mutation [10]. (v) Probiotics will be the greatest support for us as we age. It will lessen the strain on our biological systems and allow us to engage in more activities, especially those that improve our capacity to consume food. Here are some of the functions that probiotics play in sustaining our health, as well as in the treatment and management of diseases:

1) Suppression of putrefactive-type fermentation, which was one of IlyaIlyich Metchinkoff's hypotheses concerning probiotic's use [15].
2) Antibiotics are used to decrease the damaging effects of antibiotics and to restore any beneficial microflora that has been lost. While certain Bacillus species are resistant to antibiotics, they are nonetheless approved for use with them [28, 32].
3) Diarrheal disorders are treated. Various diarrheal illnesses were treated using Saccharomyces cerevisiaevarboulardii. [7, 23].
4) Improving the health of the intestines [20].
5) Boosting the immune system, increasing nutrient synthesis, and increasing nutrient bioavailability [7].
6) Reducing lactose intolerance symptoms and the incidence of allergy in lactose-intolerant people [23].
7) Lowering the chance of developing certain malignancies [27, 32].
8) Controlling serum cholesterol levels is number eight on the list [27].
9) Lactose digestion is improved by eating lactose-containing meals.
10) Probiotics may alter the defensive activities of the intestinal mucosa, such as antibacterial peptide production and secretion [32].
11) Hypertension (regulation of blood pressure) [27].
12) The genitourinary tract's state [32].

3. Conclusion

Due to the absence of a causative therapy for all pain-related FGIDs, the importance of probiotics is becoming more widely acknowledged, not only for treatment but also for prevention, [15] however evidence for this is still limited. Furthermore, as with other probiotic indications, it's important to remember that recommendations should only be made for strains that have been demonstrated to be effective. The use of L. reuteri DSM 17938 at a dosage of 10 8 CFU/day for the treatment of infantile colic in breastfed babies has strong evidence. For the treatment of pain associated with IBS, minimal evidence exists for LGG at a dosage of 3x10 [19]. CFU or De Simone Formulation, and even more limited evidence exists for the use of L. reuteri DSM 17938 at a dose of at least 10 [4] CFU/day for FAP. The mother's health and the environment in which the kid is born decide the first species that colonizes his body and has an impact on his health throughout his life. Good microbial strain colonies of microflora will lead to better health and provide us with a variety of advantages. Many things in our lives disrupt our beneficial microflora; in these cases, exo-sources should be utilized. Exo-sources containing beneficial bacteria, often known as Probiotics, may be found in a variety of meals, fermented foods, milk, and milk products. In addition, research, scientists, and contemporary businesses supply us with various sorts of probiotics for various illnesses. The early human observations, researchers, and many uses for Probiotics in their various forms demonstrate how much such great bacteria can do to enhance our health, protect us, and assure illness treatment or management. Perhaps the most important aspect of probiotics is that they are available in natural forms and fulfill natural, risk-free functions. This overview provides a concise compilation of probiotic strains, kinds, applications, and some of the firms working in such domains, as well as the names of similar types of probiotic-rich foods. Probiotics, the promising bacteria, will be more popular in the future.

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