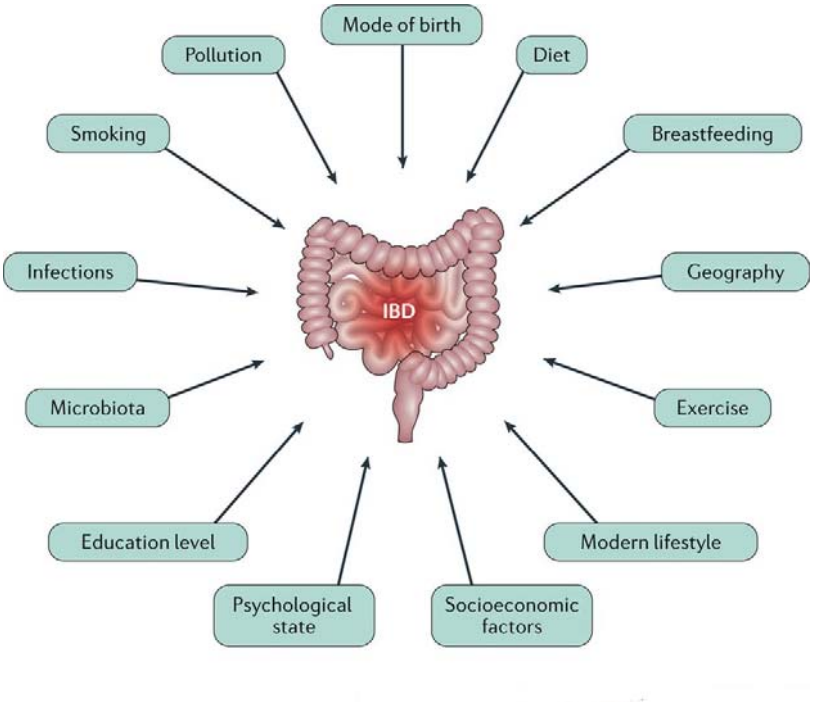

Figure 6. Environmental triggers in IBD.

A wide variety of environmental triggers have been associated with IBD pathogenesis, including the gut microbiota, diet, pollution and early-life factors.Smoking remains the most widely studied and replicated risk factor, contributing to increased risk and severity of CD while conferring protection against UC. Lower plasma vitamin D is associated with an increased risk of Crohn's disease, and vitamin D supplementation may prevent relapse of disease. Several medications including oral contraceptives, post-menopausal hormone replacement, aspirin, NSAIDs, and antibiotics may increase risk of CD or UC with the mechanisms of effect remaining inadequately defined. There is continuing evidence that depression and psychosocial stress may play a role in the pathogenesis of both CD and UC, while at the same time also increasing risk for disease flares. There is also a growing understanding of the role of diet on IBD, in particular through its effect on the microbiome. Animal protein intake and n-6 fatty acids may increase risk of UC while n-3 fatty acids and dietary fiber may confer protection. The effect of diet on established disease remains poorly studied. There is need for routine measurement of a spectrum of environmental exposures in prospective studies to further our understanding (Source: Ananthakrishnan AN. Environmental triggers for inflammatory bowel disease. Curr Gastroenterol Rep. 2013;15(1):302).

7.1. Prevalence and Economic Burden of IBD

IBD, including UC and CD, are chronic, disabling, and progressive disorders characterized by lifelong treatment and whose incidences are increasing in Asia [141].EIMs of IBD occur in up to 55% of patients with CD and 35% of those with UC.Although arthritis/arthralgia is the most common EIM in both disorders, multiple organs may be affected including skin, eye and liver[145]. Approximately 2.5 million–3 million people in Europe are affected by IBD. The highest rates of IBD are reported in Scandinavia and the UK. The incidence and prevalence of UC in the UK is estimated to be 14 cases per 100,000 person-years and 244 cases per 100,000 people, respectively. The incidence and prevalence of CD in the UK is estimated to be 7-11 per 100,000 and 85–145 cases per 100,000 people, respectively [144].An increasing number of these children are being treated with immunosuppressive and biological medications. Although these medications can improve the short-term outcome and quality of life of children with IBD, they have been associated with opportunistic infections, malignancy, and lymphoproliferative disorders among IBD populations.It is estimated that 15% to 20% of all cases of IBD are diagnosed in the childhood and adolescent period [146].Patients with IBD have a 2- to 3-fold increased risk of colorectal cancer death; therefore, colorectal cancer surveillance via colonoscopy is recommended for IBD patients [147]. Environmental factors probably have a major role in IBD; antibiotic use, childbirth mode, breastfeeding, air pollution, NSAID use, hypoxia or high altitude, diet and urban environments have been studied [148].

7.2. Rationale of DS and Probiotics in IBD

A recent survey by de Vries et.al., 2019, DS were used by 68% of the IBD patients. Although over 71% had received dietary advice mainly by dieticians, 81% stated that the main source of their nutritional knowledge related to IBD was their own experience [137]. Despite recent advancements, Crohn's disease and ulcerative

colitis remain chronic and progressive diseases. One of the primary reasons for persistent inflammation and bowel damage is failure of medical therapy. With growing therapeutic options, there is an increased temptation to quickly move to the next therapy and label the prior therapy as a failure; however, this can lead to inadequate optimization of medications and poor control of disease. On the other hand, failure to recognize ongoing mucosal inflammation despite optimized treatment and moving to the next agent can lead to progression of disease and long-term complications [138].Anti-tumor necrosis factor antibodies have led to a revolution in the treatment of IBD; however, a sizable proportion of patients does not respond to therapy.There is increasing evidence suggesting that treatment failure may be classified as mechanistic (pharmacodynamic), pharmacokinetic, or immune-mediated. Data regarding the contribution of these factors in children with IBD treated with infliximab (IFX) are still incomplete [139]. Endoscopic therapy has been explored and used in the management of strictures, fistulas/abscesses, colitis-associated neoplasia, postsurgical acute or chronic leaks, and obstructions [140].For several decades, medical treatments for IBD were limited to non-biological therapies (i.e., aminosalicylates, thiopurines, and steroids), which provide symptomatic improvement but do not change the disease course [141]. Anti-TNF agents (infliximab, adalimumab, and certolizumab) have reduced the need for surgery and hospitalization and have improved the quality of life of patients by changing the course of the disease. Thus, guidelines recommend the use of anti-TNF agents initially in moderate-to-severe IBD or if non-biological therapy fails. However, these treatments have not been effective in all patients, and patients who initially responded to treatment have also lost their responsiveness over time. Furthermore, although anti-TNF agents are generally well tolerated, their use is associated with adverse effects, including risks of infection and malignancies[142,143].

7.3. Use of Herbs and Probiotics

The use of herbal therapy in IBD is increasing worldwide.It can be assumed that the efficacy of herbal therapies in IBD is promising. The most important clinical trials conducted so far refer to the use of mastic gum, tormentil extracts, wormwood herb, triticum aestivum, germinated barley foodstuff, and boswellia serrata. In ulcerative colitis, *Triticum aestivum, Andrographis paniculata* extract and topical Xilei-san were superior to placebo in inducing remission or clinical response, and curcumin was superior to placebo in maintaining remission; boswellia serrata gum resin and plantago ovata seeds were as effective as mesalazine, whereas oenothera biennis had similar relapse rates as ω-3 fatty acids in the treatment of ulcerative colitis. In Crohn's disease, mastic gum, Artemisia absinthium, and Tripterygium wilfordii were superior to placebo in inducing remission and preventing clinical postoperative recurrence, respectively [149].

Exhibit 7. Herbs used for treatment of IBD

Herbal medicine	Type of study	Ref No.	Results
Triticum aestivum (Poaceae)	randomized, double-blind, placebo-controlled study	150	Treatment was associated with significant reduction in the overall disease activity index and in the severity of rectal bleeding. Apart from nausea, no other serious side effects were noticed
Andrographis paniculata	Randomized, double-blind multicentre study	151	Compared with Mesalazine (4.5 mg/day), there were no significant differences between the two treated groups when considering the clinical efficacy rates or the safety profile
Boswellia serrata (Burseraceae)	Single Centered study	152	Compared with Sulfasalazine, all parameters tested improved after treatment with Boswellia serrata gum in 82% patients
Artemisia absinthium	Randomized, double-blind multicentre study	153	Compared with placebo, after 8 weeks of treatment with wormwood, there was almost complete remission of symptoms in 65% of the patients,
Tripterygium wilfordii Hook F (TWHF)	Randomized controlled trials	154	Patients receiving mesalazine experienced less adverse events, but no significant difference was found about ADEs resulted withdrawal in the 3 groups. In addition, compared with low-dose TwHF and mesalazine, the authors also detected significant superiority of high-dose TwHF arm in the decrease of CDAI and SESCD
Evening primrose oil*Oenothera biennis*	Randomized controlled trials	155	*Oenothera biennis*had similar relapse rates as omega-3 fatty acids in the treatment of UC

Altered gut bacteria and bacterial metabolic pathways are two important factors in initiation and progression of IBD. However, efficacy of probiotics in remission of patients with IBD has not been characterized [156].Among the effects claimed for probiotics are beneficial immunomodulation, reduction of serum cholesterol, improved lactose digestion and protection against colon cancer [157,158]. Probiotic administration improved the clinical symptoms, histological alterations, and mucus production in most of the evaluated animal studies, but some results suggest that caution should be taken when administering these agents in the relapse stages of IBD [158]. In CD, the entire gastrointestinal tract can be involved and the inflammation can extend through the intestinal wall from mucosa to serosa. Areas of inflammation may be interspersed with relatively normal mucosa. In CD, the predominant symptoms are diarrhea, abdominal pain and weight loss whereas in UC diarrhea is the main symptom, often accompanied by rectal bleeding. Both diseases are common in the industrialized world, with highest incidences in North America and Northern Europe [159].

Exhibit 8. Summary of probiotic anti-inflammatory effects in In Vitro studies. [160]

Cell Type	Probiotic Strain	Type of Study	Main Outcome
human DC	*L. casei* Shirota	In vitro	DC from UC patients samples have an increase of IL-4 production and loss of IL-22 and IFN-γ secretion. *L. casei* Shirota treatment restored the normal stimulatory capacity through a reduction in the TLR-2 and TLR4 expression
IPEC-J2 model	*L. plantarum* strain CGMCC1258	In vitro	*L. plantarum* decreased transcript abundances of IL-8, TNF-α, and negative regulators of TLRs. Moreover, *L. plantarum* treatment decreased the gene and protein expression of occludin
PIE cells	*L. delbrueckii* subsp. *delbrueckii* TUA4408L	In vitro	The activation of MAPK and NF-κB pathways induced by *E. coli* 987P were downregulated through upregulation of TLR negative regulators, principally by TLR2
IEC-6	*E. coli* Nissle 1917 and *L. rhamnosus* GG	In vitro	Pre-treatment with these probiotics could prevent or inhibit enterocyte apoptosis and loss of intestinal barrier function induced by 5-FU
DC	*L. paracasei* CNCM I-4034, *B. breve* CNCM I-4035, and *L. rhamnosus* CNCM I-4036	In vitro	Induction of TLR-9 expression and TGF-β2 secretion. CFS treatment decreased the pro-inflammatory cytokines and chemokines

8. Peptic Ulcer Disease (PUD)

The presenting symptoms of PUD vary depending on the age of the patient. Hematemesis or melena is reported in up to half of patients with PUD. Infants and younger children usually present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena [161].The major symptom of uncomplicated PUD is upper abdominal dyspepsia such as bloating, early satiety, and nausea. H. pylori infection plays a crucial role in the pathogenesis of PUD. H. pylori infection is involved in various gastroduodenal pathologies, and evokes the production of proinflammatory interleukin-1beta, leading to the reduction of blood flow to the gastroduodenal tract and increasing the risk of peptic ulcers. H. pylori can colonize not only in the stomach, but also in the oral cavity. The oral cavity may be a reservoir for H. pylori and a potential source for infection of the stomach [162]. EGD is most accurate diagnostic test with sensitivity and specificity up to 90% in diagnosing gastric and duodenal ulcers. Surgical treatment is indicated if the patient is unresponsive to medical treatment, noncompliant or at high risk of complications. Surgical options include vagotomy or partial gastrectomy [163].Factors that increase risk of developing peptic ulcer include smoking, older individuals, O blood type, and stress. Peptic ulcers that tend to heal longer than duodenal ulcer is at higher risk of developing gastritis and gastric malignancy [168]. Classically, patients with duodenal ulcers complain of worsening abdominal pain on an empty stomach and describe hunger or abdominal pain two to three hours after meals or at night. In contrast, patients with gastric ulcers report nausea, vomiting, weight loss and post-prandial abdominal pain. Elderly patients are often minimally symptomatic and some patients with untreated PUD may have intermittent symptoms due to spontaneous healing and then relapse due to persistence of risk factors, such as continued NSAIDs use or H. pylori infection [169].

8.1. Prevalence and Economic Burden of PUD

The prevalence of PUD ranges from 0.12 to 1.5% and increases with age [162]. H. pylorus is a gram-negative bacillus that is found within the gastric epithelial cells. This bacterium is responsible for 90% of duodenal ulcers and 70% to 90% of gastric ulcers, up to 85% of individuals infected with H. pylori are asymptomatic and have no complications [163], [165]. PUD is a global problem with a lifetime risk of development ranging from 5% to 10% [164]. In many studies worldwide (United States, Brazil and China), the prevalence of H. pylori among subjects with dyspepsia was 28.9%, 57%, and 84% respectively [165]. The prevalence differs in the world population between the duodenal and gastric ulcers, and the mean age of people with the disease is between 30 and 60 years, but it can happen in any age [166]. Environmental elements such as alcohol and nicotine can inhibit or reduce secretion of mucus and bicarbonate, increasing acid secretion. Genetic factors can influence, and children of parents with duodenal ulcer are three times more likely to have ulcer than the population [167]. 30% PUD patients are smoker [168]. NSAIDs account for over 90% of all ulcers and approximately 25% of NSAID users will develop peptic ulcer disease [169]. Approximately 500,000 persons develop PU in the United States each year [170].Peptic ulcers accounted for 301,000 deaths in 2013, which is down from 327,000 deaths in 1990 [174]. Low socioeconomic status and concrete life difficulties are associated with peptic ulcer in the general population cross-sectionally and prospectively after adjustment for major physical risk factors, lending credence to a relationship between psychological stress and peptic ulcer [175].

8.2. Lifestyle Modification for PUD

The physicochemical properties of fiber fractions produce different physiological effects in the organism. Soluble fibers, found in apple, oatmeal, and pear are responsible, for instance, for an increased viscosity in the intestinal content. Insoluble fibers (whole grains, granola, flaxseed) increase stool bulk, reduce transit time in the large intestine, and make fecal elimination easier and quicker [171]. Physical activity has numerous health benefits and may also represent a cost-effective approach to the prevention of peptic ulcers. At the levels observed in this study among the moderately active group (walking or jogging <10 miles a week), possible adverse effects—for example, injuries—are minimized. In the general population, only about a third of adults undertake this much physical activity

Strategies to promote safe walking, jogging, and cycling may benefit many aspects of health in addition to the cardiovascular and musculoskeletal systems [173].Moderate physical activity could have a favorable impact on a number of risk factors for peptic ulceration. It could reduce gastric secretions and enhance immune function, with the latter reducing the risk of Helicobacter pylori infection. Moderate activity might also reduce anxiety and encourage the adoption of a healthy lifestyle, with avoidance of smoking and an excessive consumption of alcohol. However, prolonged endurance exercise seems likely to have a negative impact, suppressing immune function, reducing mucosal blood flow, and calling for frequent administration of NSAIDs [176].

Exhibit 9. Allowed foods, foods that should be consumed with caution, and foods that must be avoided [172]			
Food groups	**Allowed**	**Use with caution**	**Prohibited**
Dairy	Milk, low-fat cheeses, yogurt, fermented milk	Fatty cheeses (mascarpone, cream cheese, gorgonzola)	-
Oilseeds	Flaxseed, Brazilian nut, walnuts	-	-
Oils and olive oils	Vegetable oils, olive oil	-	Fried foods
Fruits	Apple, papaya, melon, banana	Orange, pineapple, acerola, passion fruit	Lemon
Vegetables	Leafy dark green vegetables, carrot, beet, green bean, spinach, kale, radish, zucchini, leek	Broccoli, cauliflower, cabbage, cucumber, onion, red pepper	Spicy peppers (black pepper, chilies)
Legumes	Bean soup, lentils, chickpeas, soybean	Beans	-
Meats	Lean meat (beef, pork, chicken, fish)	Fatty meats, organ meats and sausages	-
Sweets	-	Concentrated sweets	Chocolate
Beverages	Natural juices	Citrus/acidic fruit juices	Coffee, black tea, fizzy/cola drinks
Other foods	-	Industrialized seasonings, spices and condiments (Ketchup, mayonnaise, mustard)	Mustard grain

8.3. Herbs and Probiotics for PUD Management

The potential of plants as source of new drugs still offers a large field for scientific research. Even if is observed a large number of known plants, a small percentage has already been phytochemically investigated and only a fraction of them has already been assessed to determine its pharmacological potential.

Exhibit 10. Herbs for PUD Management	
Plant name/family	**Description**
Acacia arabica (Mimosaceae)	Locally known as babul tree. Aqueous extract of A. arabica gum showed protection against meloxicam‐induced intestinal damage and attenuated intestinal enzyme activity. Chemical constituents reported in this plant are gum containing arabic acid combined with calcium, magnesium, and potassium and also small quantity of malic acid, sugar, moisture 14%, and ash 3-4%. As gargle it is useful as wash in haemorrhagic ulcer and wounds [178].
Psidium guajava L., popularly known as guava (Myrtaceae)	The leaves have shown the ability to protect the stomach against ulceration by inhibiting gastric lesions, reducing gastric secretory volume, and acid secretion, and raising the gastric pH. This anti-ulcer activity, resulting from the protection of the mucosa, was related to the flavonoids in the leaves [179]
Aegle marmelos (Rutaceae), Bael Fruit	Ulcers are induced by aspirin plus pylorus ligated gastric ulceration in rats and aqueous extract of leaves is to be administered orally for 21 days, daily dose of 1 gm/kg. The result indicated a significant reduction in the ulcer lesion count compared to control [180]
Allium sativum (Liliaceae) garlic	Chemical constituents in this plant arean acrid volatile oil which is the active principle, starch, mucilage, albumen, and sugar. Seeds yield aromatic oil. The juice, more particularly its oil constituents, is rich in organically bound sulphur, iodine, and salicylic acid combinations, apart from important nutrient and complementary substances containing vitamins [178]. Garlic extract has been also studied to show suppressive effect of Helicobacter pylori-induced gastric inflammation in vivo and reduction of gastric cancer incidence in a clinical trial [181]. AGE corrected the histopathological abnormalities in gastric tissue and proved (investigated in an experimental model of indomethacin-induced gastric ulcer) a promising gastroprotective role in gastric ulcer [182].

Azadirachta indica(Meliaceae) Neem	Administration of lyophilized powder of the extract for 10 days at the dose of 30 mg twice daily showed significant decrease (77%) of gastric acid secretion. The bark extract at the dose of 30–60 mg twice daily for 10 weeks almost completely healed the duodenal ulcers and one case of esophageal ulcer and one case of gastric ulcer healed completely when administrated at the dose of 30 mg twice daily for 6 weeks [184]
Bauhinia purpurea L. (Fabaceae)	Chemical constituents reported in this plant are quercetin, rutin, apigenin, and apigenin 7-0-glucoside. Bark contains tannin (tannic acid), glucose, and a brownish gum. The Bauhinia purpurea aqueous extract (BPAE) was prepared in the doses of 100, 500 and 1,000 mg/kg. Antiulcer activity of BPAE was evaluated by absolute ethanol- and indomethacin-induced gastric ulcer, and pyloric ligation models. Acute toxicity was also carried out.The BPAE exhibits antiulcer activity, which could be due to the presence of saponins or sugar-free polyphenols, and, thus, confirmed the traditional uses of Bauhinia purpurea in the treatment of ulcers [185]
T. indica (Caesalpinioideae) Tamarind	The methanolic extract of the seed coat of this plant (100 mg/kg and 200 mg/kg) has been evaluated for determining their antiulcer potential on ibuprofen, alcohol and pyloric ligation-induced gastric lesions using albino Wistar rats [63]. The results of this study showed that the methanolic extract reduced total gastric juice volume and free and total gastric secretion acidity in pylorus ligation-induced ulcer model, while reduced ulcer index (comparable with ranitidine, 50 mg/kg, as control) [186]
Flavonoids	Also known as bioflavonoids, some research suggested that these molecules may be beneficial in stomach ulcers, naturally present in many fruits and vegetables such as apple, soybeans, berries, and broccoli. As a disorder of the GI tract, pathological conditions in peptic ulcer could be alleviated by nutritional factors. Dietary consumption of a significant amount of "natural" protective supplements in early life leads to prevention or delayed peptic ulcer [187]
Deglycyrrhizinated licorice	It is beneficial in H. pylori‐associated ulcer. In modern medicine, licorice extract has been used for pepticulcer and as an alternative to bismuth that has a protective role against acid and pepsin secretions by covering the site of lesion and promoting the mucous secretion [188].
Honey	Natural honey is composed of around 82% carbohydrates, water, phytochemicals, proteins, minerals, and antioxidants. It is also beneficial in H. pylori‐associated ulcer because honey is a powerful antibacterial agent. In gastric curative effects of manuka honey in rat model with acetic acid-induced chronic gastric ulcer, manuka honey provided significant gastroprotective effects in acute gastric ulcer animal model [189]

It has been shown that lactobacilli are particularly useful in promoting gastric ulcer healing in rats, when administered as an individual probiotic strain, such as *Lactobacillus rhamnosus* GG, Lactobacillus gasseri OLL2716, or Lactobacillus acidophilus or as a probiotic mixture, VSL#3. *Lactobacillus rhamnosus* GG increases the cellular proliferation to apoptosis ratio and therefore promotes regeneration of epithelial cells, particularly at the ulcer margins. In clinical studies, a probiotic mixture was demonstrated to be better than a single strain for improving the characteristics of indigenous microflora[191].

Exhibit 11. Summary of studies on the therapeutic effects of probiotics in Gastric Ulcer [191]			
Probiotic strain(s)	**Modeling method**	**Lesions**	**Effects of probiotics**
Lactobacillus spp.	Acetic acid	Gastric ulcer	Enhance healing of a pre-existing gastric ulcer
Lactobacillus rhamnosus GG	Acetic acid	Gastric ulcer	Inhibit cell apoptosis to proliferation ratio, and induce angiogenesis
Lactobacillus gasseri OLL 2716	Acetic acid	Gastric ulcer	Accelerate healing by enhancing generation of gastric mucosal prostaglandin E2
Lactobacillus acilidophilus encapsulated in ginger extract	Stress	Gastric ulcer	Improve healing by restoring all biochemical, physiological and histological changes
Lactobacillus acidophilus and alginate floating beads	Stress	Gastric ulcer	Improve healing by restoring all biochemical, physiological and histological changes
Probiotic mixture (VSL#3) (8 probiotic strains)	Acetic acid	Gastric ulcer	Enhance healing by promoting angiogenesis via upregulation of vascular endothelial growth factor
Saccharomyces boulardii	Ibuprofen	Gastric ulcer	Potential treatment or prevention
Polysaccharides fractions (PSFs) of *Bifidobacterium breve* and *bifidum*	Acetic acid and ethanol	Gastric erosion and ulcer	Repair and protect gastric mucosa by increasing expression of epidermal and fibroblast growth factors and 6-ketoprostaglandin F1
Probiotic mixture (2 bacterial strains) and composite probiotic (3 bacterial strains)	Stress	Gastric erosion and ulcer	Reduce lesions and intensity of bleeding through the restoration of pro- and antioxidant balance
Probiotic mixture (14 bacterial strains)	Stress	Gastric mucosal lesions	Enhance recovery of stress hormones, downregulate pro-inflammatory cytokines and upregulate anti-inflammatory cytokines

Promising results for studies exploring both prophylactic and therapeutic effects (Exhibit 11) of probiotics have been obtained. The studies concerning the roles of probiotics in gastric ulcer healing reported in the literature were mainly conducted in rats. These studies were based on the use of either individual probiotic strains, such as *Lactobacillus rhamnosus* GG, *Lactobacillus gasseri* OLL2716, Lactobacillus acidophilus, Escherichia coli Nissle 1917, Bifidobacterium animalis VKL/VKB, *Bifidobacterium bifidum*/brevis and *Saccharomyces boulardii*, or a mixture of probiotic strains, such as VSL#3. A number of studies have reported that probiotics not only inhibit the development of acute gastric mucosal lesions, but also accelerate the process of healing of induced gastric ulcers [191].

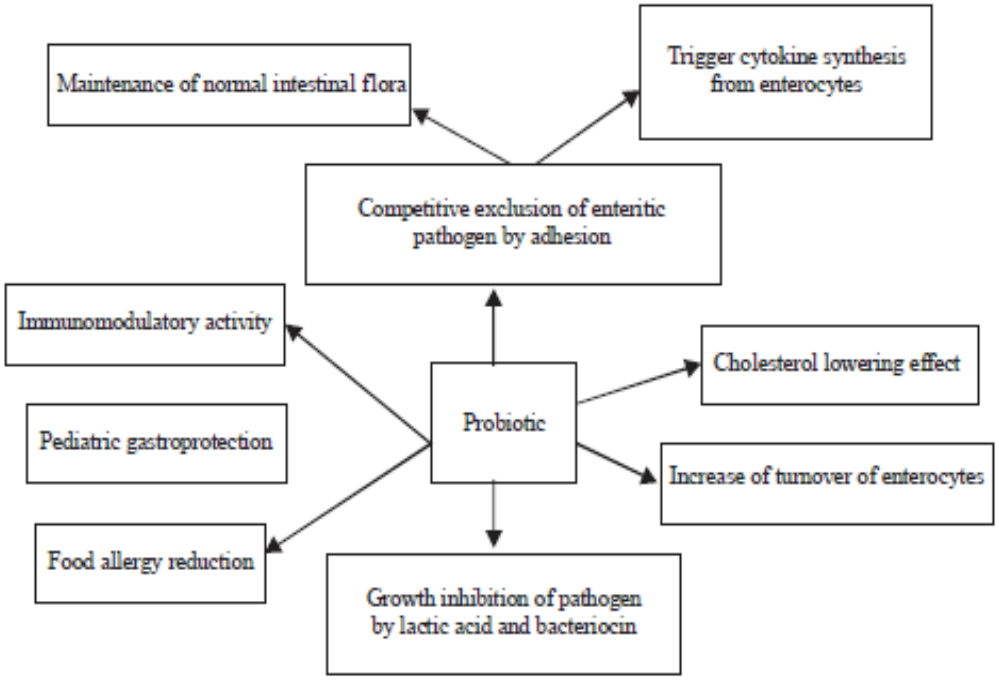

Figure 7. Mechanisms of action of probiotics.

Probiotics are engaged to adherence to host epithelial tissue, acid resistance and bile tolerance, elimination of pathogens or reduction in pathogenic adherence production of acids, hydrogen peroxide and bacteriocins antagonistic to pathogen growth, safety, non-pathogenic and non-carcinogenic, and Improvement of intestinal microflora. Prebiotics of proven efficacy are able to modulate the gut microbiota by stimulating indigenous beneficial flora while inhibiting the growth of pathogenic bacteria therein. Preferred target organisms for prebiotics are specific. belonging to the Lactobacillus and Bifidobacterium genera. The most efficient prebiotics may also reduce or suppress numbers and activities of organisms seen as pathogenic (Bandyopadhyay B, Mandal NC. Probiotics, Prebiotics and Symbiotic - In Health Improvement by Modulating Gut Microbiota: The Concept Revisited. Int. J.Curr. Microbiol. App. Sci (2014) 3(3): 410-420)

Probiotics can also protect the integrity of the gastric mucosal barrier by upregulating prostaglandin, mucous secretion, tight junction protein expression and cell proliferation, and by inhibiting apoptosis (43,48,130–132). In rats, the administration of *Bifidobacterium bifidum* BF-1 or *Bifidobacterium animalis* VKL and VKB has been found to protect the gastric mucosa through either preventing the mucous barrier from degradation or increasing gastric mucous production. The probiotic mixture VSL#3 protects the epithelial barrier and upregulates the expression of tight junction proteins (occludin and zonula occludens-1) in vivo and in vitro via the activation of p38 or mitogen-activated protein (MAP) kinase and extracellular signal-regulated kinase (ERK) signaling pathways. Mennigen et al demonstrated that probiotics can strengthen the gastric mucosal barrier by inhibiting the redistribution and expression of tight junction proteins and blocking apoptosis (135). The probiotic strains Lactobacillus gasseri OLL2716, Lactobacillus rhamnosus GG and Escherichia coli Nissle 1917 are able to protect the altered gastric mucosal barrier (43,48,114). In humans, Gotteland et al found that pretreatment with Lactobacillus GG protected against indomethacin-induced disruption of the gastric mucosal barrier [191].

Exhibit 11. Selection criteria of probiotic strains [190]

Criterion	Required Properties
Safety	• Human or animal origin. • Isolated from the gastrointestinal tract of healthy individuals. • History of safe use. • Precise diagnostic identification (phenotype and genotype traits). • Absence of data regarding an association with infective disease. • Absence of the ability to cleave bile acid salts. • No adverse effects. • Absence of genes responsible for antibiotic resistance localized in non-stable elements.
Functionality	• Competitiveness with respect to the microbiota inhabiting the intestinal ecosystem. • Ability to survive and maintain the metabolic activity, and to grow in the target site. • Resistance to bile salts and enzymes. • Resistance to low pH in the stomach. • Competitiveness with respect to microbial species inhabiting the intestinal ecosystem (including closely related species). • Antagonistic activity towards pathogens (e.g., *H. pylori*, *Salmonella* sp., *Listeria monocytogenes*, *Clostridium difficile*). • Resistance to bacteriocins and acids produced by the endogenic intestinal microbiota. • Adherence and ability to colonise some particular sites within the host organism, and an appropriate survival rate in the gastrointestinal system.
Technological usability	• Easy production of high biomass amounts and high productivity of cultures. • Viability and stability of the desired properties of probiotic bacteria during the fixing process (freezing, freeze-drying), preparation, and distribution of probiotic products. • High storage survival rate in finished products (in aerobic and micro-aerophilic conditions). • Guarantee of desired sensory properties of finished products (in the case of the food industry). • Genetic stability. • Resistance to bacteriophages.

The mode of action of probiotics is not completely understood but they may act as surrogate normal microflora following antibiotic therapy until recovery is achieved. However, probiotic combinations appeared to induce only minor changes in the microbiota. For instance, the mechanisms of action of S. boulardii include luminal action (anti-toxic effect, antimicrobial activity), trophic action (enzymatic activity, increased IgA) and mucosal-anti-inflammatory signaling effects (decreased synthesis of inflammatory cytokines). Short-chain fatty acids (SCFAs) and bacteriocin proteins have been implicated in the inhibition of H. pylori by lactic acid bacteria. SCFAs such as formic, acetic, propionic, butyric and lactic acids are produced as a result of the metabolism of carbohydrates by probiotics and play an important role in decreasing the pH in vitro. Their antimicrobial activity could be due to the inhibition of urease activity by high lactic acid producers, such as *Lactobacillus salivarius* and *Lactobacillus casei* Shirota. *Lactobacillus salivarius* significantly decreased IL-8 production [IL-8 is induced after injection of virulence factor CagA into epithelial cells] upon exposure to H. pylori and led to CagA accumulation in H. pylori cells, presumably as a result of loss of functionality of the Cag secretion system. Alterations in gastrointestinal permeability are an initial step in the development of lesions such as ulcers. Probiotics may stabilize the intestinal barrier by stimulating the expression of gastric mucins, decreasing bacterial overgrowth and stimulating local immune responses and the release of antioxidant substances [192].

Conclusion

This review is conducted and correlate the published literature on the effectiveness of herbs and probiotics, for the treatment of FAPDs. Despite its common use, research on the efficacy, safety, and optimal dosage remains limited. Many responsible members of the dietary supplements industry have taken significant steps to regain consumer trust by improving transparency along the supply chain, enhancing traceability of raw botanical materials, and bringing attention to ingredients with potential adulteration concerns, among other efforts. Lifestyle and food habit also found important factor to improve GI related disorders to much extent. Several randomized controlled trials have now shown that microbial modification by probiotics may improve gastrointestinal symptoms and multiorgan inflammation in rheumatoid arthritis, ulcerative colitis, and multiple sclerosis. In the USA, microorganisms used for consumption purposes should have the GRAS status, regulated by the FDA. In Europe, EFSA introduced the term of QPS. The QPS concept involves some additional criteria of the safety assessment of bacterial supplements, including the history of safe usage and absence of the risk of acquired resistance to antibiotics. Future work will need to carefully assess safety issues, selection of optimal strains and combinations, and attempts to prolong the duration of colonization of beneficial microbes.This doesn't mean conventional therapies don't work, it just means that experts haven't studied them enough to know if they do. The most important thing is safe healing and better life. To ensure this, researchers needs to work more on both conventional and complimentary drugs.

Abbreviations: The American College of Gastroenterology (ACG); Gastroesophageal Reflux Disease (GERD); Proton Pump Inhibitors (PPIs); Recurrent Abdominal Pain (RAP); Functional gastrointestinal disorders (FGIDs); Postprandial Distress Syndrome (PDS); Complementary and Alternative Medicine (CAM); Functional Dyspepsia (FD); Chronic Constipation (CC); Quality Of Life (QoL); European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN); North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN);Congenital Sucrase-Isomaltase Deficiency (CSID); FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols); SIBO (Small Intestinal Bacterial Overgrowth); NCGS (Nonceliac Gluten Sensitivity); ATIs (α-Amylase/Trypsin Inhibitors); Ni ACM (Nickel Allergic Contact Mucositis); Health-Related quality of life (HRQoL); Healthcare Resource Utilization (HRU); 5-Hydroxytryptamine-3 Receptor (5-HT3); Food and Agriculture Organization of the United Nations (FAO); Department of Health (DOH); Artichoke Leaf Extract (ALE); Inflammatory Bowel Disease (IBD); Parkinson's Disease (PD); Crohn's Disease (CD); Ulcerative Colitis (UC); Dietary Supplement (DS); Extraintestinal Manifestations (EIMs); Crohn's Disease Activity Index (CDAI); Simple Endoscopic Score for Crohn's Disease (SES-CD); Peptic Ulcer Disease (PUD); Esophagogastroduodenoscopy (EGD); Bauhinia Purpurea Aqueous Extract (BPAE); Herbal Dietary Supplements (HDS); Generally Regarded As Safe (GRAS); Qualified Presumption of Safety (QPS); European Food Safety Authority (EFSA); Mitogen-Activated Protein (MAP); Extracellular Signal-Regulated Kinase (ERK); Short-Chain Fatty Acids (SCFAs); Cytotoxin-associated gene A (CagA)

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