



Probiotic Foods for Gastrointestinal Health

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Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The use of probiotics is based in part on the hypothesis that the types and activities of microbes that colonize our bodies may not be optimal, and that the addition of beneficial types of microbes in the form of probiotics can improve health.

The term *probiotic* should be used only for products that contain a live microbe at an efficacious level that has been tested in well-designed clinical trials and shown to confer some health benefit.¹ Unfortunately, most countries have not codified this scientific definition, so the term *probiotic* is sometimes used for commercial products that do not meet these minimum criteria.

Although probiotics have been available as dietary supplements for years, there recently has been rapid growth in the variety of food products that contain probiotics. However, it is important to recognize that not all food products that are labeled as such actually contain clinically tested probiotic strains at efficacious concentrations, as the scientific definition is generally not enforced. When considering which probiotic formulation—supplements or foods—to recommend to patients, the most important criterion is that the probiotic has been clinically tested and shown to be useful for the particular indication. This article will review the existing clinical evidence that supports the use of probiotics to promote gastrointestinal (GI) health and will provide examples of probiotic foods that are commercially available in the United States.

The Probiotic Hypothesis

The use of probiotics is based in part on the idea that the addition of beneficial bacteria to host microbiota in the form of probiotics can improve health. In support of

Table 1. Physiologic Effects of Probiotics

Alteration of pain sensation²

Improved gut integrity

- Decreased bacterial and macromolecular translocation³
- Restoration of gut barrier integrity when perturbed by stress or pathogen exposure⁴

Inhibition of pathogens

- Inhibition of pathogenic activity by production of antibacterial peptides⁵
- Production of short-chain fatty acids, reduction of pH in the lumen⁶
- Stimulation of mucin production, resulting in decreased pathogen adherence to intestinal epithelial cells⁷

Modulation of microbiota populations or activities⁸

Regulation of immune system

- Downregulation of inflammatory response⁹
- Upregulation of adaptive immune response¹⁰

this hypothesis, some probiotics have been shown in controlled trials to have a positive impact on several host physiologic end points, including regulation of the immune system, alteration of pain sensation, inhibition of pathogens, and maintenance of gut integrity (Table 1).²⁻¹⁰

Probiotics may use similar mechanisms employed by our own colonizing microbiota to impact host physiology, although it should be recognized that host immune reaction to native colonizers (oral tolerance) may be different than for “foreign” microbes, such as probiotics.¹¹ A limitation to the probiotic hypothesis worth noting is that the exact microbiota associated with optimal health has yet to be defined, although progress is being made.¹²⁻¹⁵

Strain Specificity

Probiotics are comprised of a variety of different types of microbes at the genus, species, and strain levels. The most common types of probiotics used in food are species of the *Lactobacillus* and *Bifidobacterium* genera. Strains of *Streptococcus thermophilus*, *Bacillus coagulans*, *Saccharomyces cerevisiae*, *S. boulardii*, *Pediococcus freudenreichii*, *Lactococcus lactis*, and *Escherichia coli* also have been studied, and used, as probiotics.

It is important to note that the benefits of probiotics are strain-specific. This has been observed in several head-to-head comparisons in humans. For example, Weizman et al¹⁶ found that *L. reuteri* ATCC 55730 was more effective than *B. lactis* BB-12 in decreasing the number of days with fever, clinic visits, absences, and antibiotic prescriptions in infants aged 4 to 10 months

in child-care centers. Additionally, Canani et al¹⁷ found that only 2 of 5 commercial probiotic preparations were effective at reducing the duration of acute diarrhea in children. And Wickens et al¹⁸ found that *L. rhamnosus* HN001, but not *B. lactis* HN019, reduced symptoms of eczema when given to infants up to 2 years of age. It should be noted that although none of these studies compared different strains of the same species (eg, 2 different strains of *L. casei* were not compared head to head), these results emphasize that different probiotic preparations are not clinically equivalent, and recommendations must be based on the clinical efficacy of a specific product. Furthermore, although different strains of probiotics have been shown to have similar effects (eg, different probiotic strains have been shown to be effective in reducing the duration of infectious diarrhea in children¹⁹), this should not be interpreted to mean that all strains will have this effect.

Labeling and Indications

Depending on how probiotics are used and labeled, they may be categorized as foods, dietary supplements, or drugs.¹ From a US regulatory perspective, the use and labeling of substances that are intended to cure, treat, prevent, or mitigate diseases constitutes a drug use. Currently, only probiotic foods and dietary supplements are available in the United States; therefore, the only allowable claims refer to their ability to impact the normal functioning of the human body (known as structure/function claims), or to reduce the risk for disease. The former claim requires no FDA approval, but the latter does. To date, no claims of the latter type have been approved for probiotics in the United States. This situation results in some claims that, to a medical professional, may seem nonspecific.

Evidence Supporting Use of Probiotics In Patients With Gastrointestinal Disorders

The use of probiotics in GI disorders represents the intersection of 2 very contrasting worlds: complementary medicine and molecular microbiology. The former is best illustrated by the quite longstanding use of a wide variety of purported probiotic products by those who suffer from irritable bowel syndrome (IBS) and other functional GI disorders.²⁰ In this instance, widespread use has long preceded clinical science. In contrast, the application of modern molecular techniques to the study of the enteric microbiota, as well as the immunologic response of the host only now is beginning to reveal the true diversity of the microbiota,²¹ its immunologic and metabolic potential, and the complexity and importance of its immune engagement with the host, both locally in the gut and in immune tissues throughout the body.^{22,23} Because of the absence, until recently, of a solid scientific basis for the use of probiotics in gastroenterology and the consequent bias among many in the medical community against probiotics, which have been viewed as “fringe” and “alternative,” there has been a reluctance to take this approach

to therapy seriously. Continuing issues with the interpretation of in vitro and animal studies, quality control of products used in man, and a proliferation of extravagant health claims not supported by clinical data do not help to reassure the skeptical clinician.²⁴

So where are we with the use of probiotics in gastroenterology on 2009?

Although experimental observations suggest potential benefits for probiotics in a variety of GI, pancreatic, and liver disorders, solid clinical data is confined to three main areas: infection, inflammatory bowel disease (IBD), and IBS (Table 2).^{25,26}

With regard to infectious diarrhea, there appear to be 2 main areas of efficacy for probiotics: rotavirus-associated diarrhea and *Clostridium difficile*-associated diarrhea. Several studies have reported that probiotics may be beneficial for patients with rotavirus-induced diarrhea, resulting in a shortening of the duration of this infection, which is a scourge of day-care centers and similar environments.²⁷ A meta-analysis of 9 double-blind, placebo-controlled trials, suggested that probiotics (*S. boulardii*, *L. acidophilus* ATCC 4962, *L. acidophilus* NCFB 1748, *L. bulgaricus* ATCC 33409, *Enterococcus faecium* SF68, *B. longum* BB 536, and *L. rhamnosus* GG [LGG]) appear to be effective in preventing antibiotic-associated diarrhea.²⁸ The proteolytic digestion of toxin A and B molecules by protease may explain, at least in part, the protective effects of *S. boulardii* against *C. difficile*-induced diarrhea. Others have shown that *L. plantarum* prevents recurrent episodes of *C. difficile*-associated diarrhea and have even suggested that the administration of nontoxigenic strains of *C. difficile* may prevent toxigenic *C. difficile*-associated diarrhea in 87% to 97% of patients.²⁹

The rationale for the therapeutic use of probiotics in patients with IBD and complications of the disease, such as pouchitis and postoperative recurrence of Crohn's disease, is derived from the hypothesis that the endogenous intestinal microflora plays a crucial role in the pathogenesis of these disorders.³⁰ Evidence from several controlled trials featuring a number of probiotic organisms, including nonpathogenic *E. coli* Nissle 1917, *S. boulardii*, *B. breve* strain Yakult, and *B. bifidum* strain Yakult, have suggested benefits of probiotics for maintenance of remission and management of flares in patients with mild to moderate ulcerative colitis; however, other studies have been less favorable.³¹ VSL#3, a probiotic cocktail containing 8 different strains, has proven effective in the primary prevention and maintenance of remission of pouchitis.^{32,33} In one study, remission was maintained in 85% of patients on VSL#3 compared with 6% of those on placebo.³² In contrast to these somewhat encouraging findings in patients with ulcerative colitis, a review of the available literature on the use of probiotics in the management of acute illness or maintenance of remission in patients with Crohn's disease provides little encouragement.

Reflecting, perhaps, the paucity of truly disease-modifying therapies that are available to relieve the

Table 2. Gastrointestinal Indications For Probiotics

Antibiotic-associated diarrhea

Clostridium difficile infection

Infectious diarrhea

Irritable bowel syndrome

Pouchitis

Rotavirus infections

Ulcerative colitis

symptoms of IBS, patients with this disorder commonly resorted to the use of complementary and alternative medical remedies and practices.²⁰ Foremost among such approaches have been various dietary manipulations, including exclusion diets, and a variety of dietary supplements. In Europe, in particular, where several such products are advertised widely for their general "immune-boosting" and "health-enhancing" properties, probiotic dietary supplements have been widely used by patients with IBS. Recently, based on in vitro data and some evidence from clinical trials, the use of probiotics in patients with IBS has begun to wend its way into the realm of conventional medicine. Although probiotics have been used on an empiric basis for some time, several recent developments provide a more logical basis for their use in patients with IBS. These include the clear recognition that IBS may be induced by bacterial gastroenteritis (post-infectious IBS) and that qualitative changes in the intestinal microbiota, as well as immune dysfunction, may be prevalent in patients with IBS in general.³⁴ Leading up to 2000, a small number of studies evaluated the effects of probiotic preparations in patients with IBS, and although results between studies were difficult to compare because of differences in study design and probiotic dose and strain, there was some evidence of symptom relief. Since then, further studies have produced discernible trends.³⁵ Thus, although a number of organisms, such as LGG, *L. plantarum* 299V, *L. acidophilus* SDC 2012, 2013, *L. casei* GG, the probiotic cocktail VSL#3, and *B. lactis* DN-173-010, have been shown to alleviate individual IBS symptoms (eg, bloating, flatulence, constipation), only a few products have been shown to have an effect on pain and global symptoms of IBS.³⁶⁻³⁹ Among these, *B. infantis* 35624 has attracted particular attention.⁴⁰ Further large, long-term, randomized controlled trials of this and other promising strains are warranted in IBS, and detailed explorations of its mechanism(s) of action are indicated.

Safety

Many different preparations of probiotics have been used for decades and by millions of healthy people and individuals with disease, yet definitive data on safety

Table 3. Examples of Probiotic Food Products Commercially Available in the United States^a

Product (Manufacturer)	Food Type	Claims ^b	Probiotic Strain(s) (Marketing Name)	Dose (CFU) per Serving of Live Probiotic ^c	Comments
Activia (The Dannon Company, Inc)	Yogurt	Helps regulate the digestive system; helps with slow intestinal transit	<i>Bifidobacterium animalis</i> DN-173 010 (Bifidus regularis)	10 billion ^c	ST and LB also present
Attune (Attune Foods)	Nutrition bar	Clinically proven to support digestive health and promote a strong immune system	<i>Lactobacillus acidophilus</i> NCFM <i>L. casei</i> Lc-11 <i>B. lactis</i> HN019	6.1 billion ^c	
BioK+ (Bio-K+ International Inc)	Cultured milk	Regulates intestinal functions; acts on the whole digestive system, reaching the intestine to quickly provide anticipated well-being	<i>L. acidophilus</i> CL1285 <i>L. casei</i> LBC80R	50 billion ^c	1/2-bottle per day; count reflects total of both strains
DanActive (The Dannon Company, Inc)	Cultured milk	Helps strengthen the body's natural defenses	<i>L. casei</i> DN-114 001 (<i>L. casei</i> Immunitas)	10 billion ^c	ST and LB also present
Danimals (The Dannon Company, Inc)	Cultured milk	Helps kids stay healthy	<i>L. rhamnosus</i> GG (LGG)	Billions of live and active cultures per bottle, including LGG ^d	Stated count does not differentiate between ST and LB and LGG
Good Belly (NextFoods)	Fruit drink	Clinically tested to support digestive and immune health	<i>L. plantarum</i> 299v	20 billion	
Naked Juice (Naked Juice Company)	Fruit juice	Can help promote a healthy digestive and immune system	<i>B. lactis</i> HN019	"Billions" ^d	
Nestlé Good Start Protect Plus (Nestlé Infant Nutrition)	Powdered infant formula	Beneficial cultures like those found in breast milk to help support a baby's healthy immune system	<i>B. lactis</i> BB-12	10 million per 4 ounces (~daily intake of 100 million/d) ^c	
Stonyfield Farm yogurts (Stonyfield Farms)	Yogurt	Enhances digestive and immune health	<i>L. rhamnosus</i> HN001 (<i>B. lactis</i> , <i>L. acidophilus</i> , <i>L. casei</i>)	1 billion (<i>L. rhamnosus</i>) ^c	ST and LB also present; strain designations and levels only provided for HN001 strain
Yakult (Yakult Honsha Co, Ltd)	Cultured milk	Helps balance the digestive system and support immune function	<i>L. casei</i> Shirota	8 billion ^c	1-2 bottles per day
Yo-Plus (Yoplait USA, Inc)	Yogurt	Helps naturally regulate digestive health	<i>B. lactis</i> Bb-12	>5 billion ^c	ST and LB also present; 3 g inulin per serving; 1 yogurt per day

CFU, colony-forming units; LB, *Lactobacillus bulgaricus*; ST, *Streptococcus thermophilus*

^a Products listed in this table and their probiotic strain components have been subjected to human, clinical studies ranging in number and quality. It is beyond the purview of this review to provide a critical overview of the strength of evidence. For details on supporting peer-reviewed literature for any given product, contact the respective manufacturer.

^b All claims are "structure/function" claims and are as indicated by the manufacturer. Validity of the claims was not assessed for this review.

^c Probiotic levels guaranteed through end of shelf life of product.

^d No precise count of probiotic provided.

Table 4. Examples of Probiotic Supplements With Demonstrated GI Benefits Sold in the United States^a

Product (Manufacturer)	Formulation	Claims ^b	Probiotic Strain(s)	Dose (CFU) per Serving of Live Probiotic ^c
Align (Procter & Gamble)	Capsule	Clinically proven to protect against episodic constipation, diarrhea, urgency, gas, and bloating; naturally builds a stronger, healthier digestive system	<i>Bifidobacterium infantis</i> 35624	1 capsule per day (1 billion ^c live bacteria per capsule)
Culturelle (Amerifit Nutrition, Inc.)	Capsule	Promotes good digestion; maintains regularity; enhances the immune system; helps to return to optimal health	<i>Lactobacillus rhamnosus</i> GG	1-2 capsules per day (10 billion ^c live active cells per capsule)
Florastor (Biocodex, Inc.)	Capsule	Maintains balance of intestinal flora; maintains healthy intestinal function; promotes “good” microorganisms in the gut	<i>Saccharomyces boulardii</i>	1 capsule, bid (5 billion ^c live cells per 250-mg capsule)
VSL#3 (Sigma-Tau Pharmaceuticals, Inc.)	Packet	Provides probiotic bacteria to help protect the GI tract; aids in the dietary management of ulcerative colitis, IBS, and an ileal pouch	<i>B. breve</i> ; <i>B. infantis</i> ; <i>B. longum</i> ; <i>L. acidophilus</i> ; <i>L. bulgaricus</i> ; <i>L. casei</i> ; <i>L. plantarum</i> ; <i>Streptococcus thermophilus</i>	0.5-8 packets per day (450 billion ^c live lactic acid bacteria per packet)

CFU, colony-forming units; GI, gastrointestinal; IBS, irritable bowel syndrome

^a Products listed in this table and their probiotic strain components have been subjected to human, clinical studies ranging in number and quality. It is beyond the purview of this review to provide a critical review of the strength of evidence. For details on supporting peer-reviewed literature for any given product, contact the respective manufacturer.

^b All claims are “structure/function” claims and are as indicated by the manufacturer. Validity of the claims was not assessed for this review.

^c Probiotic levels guaranteed through end of shelf life of product.

are scant. In a careful and critical 2006 review, Boyle, Robins-Browne, and Tang concluded that although probiotics have an excellent overall safety record, they should be used with caution in certain patient groups, particularly neonates born prematurely or with immune deficiency.⁴¹ They reviewed case reports of instances of abscesses and endocarditis in relation to probiotic use; in many instances the probiotic cultured from the infected tissue was most likely an innocent contaminant rather than the real pathogen. Fears that live probiotic organisms might translocate across the gut and lead to systemic sepsis also have been allayed by the absence of such reports from studies among patients with IBD and other situations where the intestinal barrier may be compromised. Two notes of caution must be mentioned. The first relates to reports of septicemia occurring among infants with short bowel syndrome^{42,43} and the second to instances of increased mortality among patients with severe acute pancreatitis who had been administered a probiotic cocktail through a nasogastric

tube. These deaths were associated, not with sepsis, but with intestinal ischemia, the etiology of which remains unclear.⁴⁴

Formulations and Use in Clinical Practice

When determining the preferred probiotic formulation—supplements or foods—to recommend to a patient, the most important criterion is that the probiotic has been tested and shown to be useful for the particular indication. Probiotics that have not been tested for specific end points may be effective, but they cannot be strongly recommended. Additional considerations include patient preference, convenience, likelihood of compliance, storage requirements (eg, room temperature-stable products for patients who are traveling), intolerance or allergy to accompanying food ingredients, and calorie management.

Tables 3 and 4 list a variety of probiotic foods and supplements that are available in the US market. These tables should not be considered complete, nor should

Table 5. Additional Resources on Probiotics

“Probiotics. What they are and what they can do for you,” American Gastroenterology Association. Available at: www.gastro.org/user-assets/Documents/09_Patient_Center/brochure_Probiotics.pdf

“Probiotics and prebiotics: World Gastroenterology Organization Practice Guideline,” World Gastroenterology Organization. May 2008. Available at: www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/19_probiotics_prebiotics.pdf

Usprobiotics.org, www.usprobiotics.org

the products listed be considered equivalent. Each of the products and their probiotic content is different and each has been tested with different patient cohorts, study end points, and degrees of rigor. Recommendation of any product should be based on the patient's needs and the evidence in support of that benefit. Some evidence-based recommendations have been provided by Floch et al.²⁵ Additionally, the International Scientific Association for Probiotics and Prebiotics provides some guidelines on the use of probiotics; the guidelines were developed by the scientists within that organization, which specializes in the study of probiotics.⁴⁵

Conclusion

Patients with GI disorders have been using putative probiotics since long before clinical evidence supported such use. However, recent advances in the study of probiotics in patients with a variety of GI disorders have provided some solid clinical data in support of their use, specifically in the areas of infection, IBD, and IBS. Advances in the study of probiotics continue to open new avenues of potential therapeutic applications in gastroenterology and throughout medicine. Many of these intriguing ideas remain to be clinically tested or translated into widespread use by patients.⁴⁶

Table 5 provides some examples of online resources for readers interested in learning more about the use of probiotics in gastroenterology.⁴⁷⁻⁴⁹

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AUTHOR DISCLOSURE—Dr. Quigley has served as a consultant for Boehringer Ingelheim, Ironwood, Movetis, Ortho-McNeil, Procter & Gamble, Salix, Schering-Plough, and Sucampo/Takeda. He has received honoraria and served as a speaker for Danone, Norgine, Procter & Gamble, and Yakult, and has received research support from Procter & Gamble. Dr. Quigley is also a non-executive director of Alimentary Health, which holds intellectual property rights in the area of gut flora.

Dr. Sanders is a paid consultant to numerous companies commercially involved in probiotics.

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