

# Promoting Gut Health with Probiotics

## *Living Medicines for Treating Digestive Disorders*

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**P**robiotics are foods or dietary supplements that contain live microorganisms that can restore needed balance to the intestinal microflora. Probiotic products, such as yogurt with live bacterial cultures, have a long history of use in traditional diets and medicine. Probiotics are increasingly being studied scientifically regarding their role in treating inflammatory bowel disease and other digestive disorders. This paper explores the research-based evidence for such applications of probiotics.

### Terminology

Probiotics are commonly called “good” bacteria and include live cultures found in some brands of yogurt and acidophilus milk. Most probiotics are bacterial strains but the yeast *Saccharomyces boulardii* is also used as a probiotic.<sup>1</sup> Probiotics have been defined as “living microorganisms which upon ingestion in certain numbers, produce health benefits beyond supporting inherent general nutrition.”<sup>2</sup>

Other terms that are associated with probiotics are prebiotics and synbiotics. Prebiotics, such as nondigestible sugars in foods, known as fructo-oligosaccharides (FOS), stimulate the growth of beneficial bacteria. Because sufficient FOS to treat health conditions is difficult to obtain from foods, supplements are generally recommended.<sup>3</sup> Other prebiotics include inulin, bran, psyllium, and germinated barley foodstuff.<sup>4</sup> The term “synbiotics” was coined to describe the synergistic actions of pre- and probiotics.<sup>5</sup>

To describe this innovative approach to calibrating the complex ecology of the gut microflora with probiotics, the terms “ecoimmunonutrition,”<sup>5</sup> “ecotherapeutics,”<sup>6</sup> and “biotherapeutics”<sup>7</sup> have been used.

### Background

In Europe, Japan, and Australia, probiotics and related products to improve intestinal health currently represent the largest segment of the functional foods market. The European Commission has sponsored research projects on these products’ safety and efficacy.<sup>8</sup> Probiotics are also now among the most popular selling supplements in the United States.<sup>9</sup>

Physiologist Elie Metchnikoff (a cowinner of the Nobel Prize in physiology and medicine in 1908 for identifying phagocytosis)

first brought the health benefits of beneficial bacteria to public attention. Believing that this process could enhance health and longevity, Dr. Metchnikoff named one of the primary bacteria in yogurt cultures, *Lactobacillus bulgaricus*, for the famously long-lived, yogurt-loving Bulgarians.<sup>10</sup>

*Lactobacillus acidophilus* and Bifidobacteria are other strains of bacteria that have long been utilized in traditional diets and medicine to balance the beneficial and pathogenic bacteria in the gastrointestinal (GI) tract for general immune-system enhancement. These lactic acid-producing bacteria are major constituents of the resident intestinal microflora in humans. *Streptococcus thermophilus* is another “friendly” bacterium used to culture true yogurt, (i.e., a fermented dairy product that has culturing bacteria that have not been destroyed in the pasteurization process). Natasha Trenev, a Southern California-based producer of, and recognized authority on, probiotics cautions that some yogurt is produced with minimally beneficial strains of bacteria.<sup>10</sup>

### Standards and Formulations

For the aforementioned reason, the National Nutritional Foods Association (NNFA) adopted the NNFA Probiotic Labeling Standard in 1989. This standard recommends that probiotic supplement suppliers specify on their product labels the type and quantity of the living bacteria present, a viable cell count, expiration date, certification of the absence of pathogens, storage requirements, and a list of any additional ingredients. (See box entitled Resources.)

Ms. Trenev wrote that “unfortunately. . .virtually none of the probiotic suppliers adheres to these standards.”<sup>10</sup> (See box entitled Recommended Reading.) Of the probiotic supplements tested more recently by ConsumerLabs.com, approximately one third contained far fewer than the labeled number of organisms.<sup>9</sup>

Probiotic supplements are available as capsules, freeze-dried powders, wafers, and liquids. Dairy-free acidophilus products are available for vegans and patients who are allergic to milk products. Ms. Trenev advises against using liquid probiotics, stating that they lose their potency rapidly and may contain buffering additives. For optimum benefit for general health purposes, she recommends taking powdered probiotics in conjunction with combined *L. acidophilus*, *Bifidobacterium bifidum*, and *L. bulgaricus* in a sunflower oil-matrix capsule with unchilled filtered water; the total dose is 1 capsule, 2 times per day, with one-half of a teaspoon of each of these powdered super strains.<sup>10</sup>

## Research on Probiotic Therapy At-a-Glance

Condition	Effect	Reference number
Malabsorption of nutrients	Assisted absorption of calcium, other minerals, and vitamins	18
Acute diarrheal infections	Shortened courses of pediatric bouts of acute diarrheal infections	32
Antibiotic-induced diarrhea	Decreased symptoms in 22 studies	11
<i>Clostridium difficile</i> colitis	Prevented recurrent bouts	12
Colon cancer	<i>Lactobacillus acidophilus</i> reduced levels of procarcinogenic enzymes	10
	Inhibited tumor growth in animals	13
Chronic constipation	Prebiotic lactulose alleviated constipation safely	31
<i>Helicobacter pylori</i> infections	Inhibited ulcer-causing bacteria	3
Inflammatory bowel disease	A multibacterial product prevented postsurgical pouchitis <sup>a</sup>	1
	Achieved remission in ulcerative colitis	29
Irritable bowel syndrome (IBS)	Reduced IBS symptoms markedly	3
Lactose intolerance	Yogurt enhanced lactose digestion	31

The product tested was VSL#3™ (VSL Pharmaceuticals, Inc., Ft. Lauderdale, Florida).

### Main Clinical Uses of Probiotics

#### Counteracting Antibiotic GI Side-Effects

A common modern medical application of probiotics, taken as fermented dairy products or as supplements, is to counteract the effects of antibiotic therapy, which destroys protective bacteria as well as targeted pathogens. Diarrhea and stomach upset are common side-effects of the elimination of beneficial GI bacteria when broad-spectrum antibiotics are used for an extended period of time. A meta-analysis of 22 studies supported probiotic efficacy in treating antibiotic-associated diarrhea.<sup>11</sup>

To counter such adverse effects, Ms. Trenev recommends taking, after each prescribed dose of antibiotic, 2 capsules each of *L. acidophilus* and *B. bifidum* along with 1 teaspoon of *L. bulgaricus* powder mixed in 6–8 ounces of unchilled filtered water. Another dose of the powders may be taken at bedtime. Ms. Trenev also advises doubling or tripling this regimen for up to 2 weeks to ensure recolonization of the beneficial enteric bacteria.<sup>10</sup>

Probiotics are being studied as a novel modality for treating *Clostridium difficile* colitis, the leading cause of nosocomially acquired intestinal infection in the United States. It has been estimated that 20 percent of patients will have recurrent bouts of this

bacterial bowel infection, even after treatment with the potent antibiotics metronidazole and/or vancomycin. *Lactobacillus* GG was found to be effective in reducing patients' symptoms of diarrhea and abdominal cramps and the infection recurrence rate at 3 weeks compared to placebo. The researcher who conducted this study concluded that probiotics hold promise for treatment of primary as well as recurring *Clostridium difficile*.<sup>12</sup>

#### Providing Natural Antibiotics and Antivirals

Researchers in the 1970s discovered that strains of friendly bacteria produced microbial-inhibiting substances in addition to acids. Acidolin and acidophilin were isolated from *L. acidophilus*, and bulgarican was extracted from super strain DDS-14 of *L. bulgaricus*. These natural alternatives to standard antibiotics are unique in that they appear to be active against both bacteria and viruses.<sup>10</sup> This is a particularly important development with pathogens becoming increasingly drug-resistant. Some strains of *L. lactobacilla* also secrete viridical compounds (e.g., hydrogen peroxide) that kill viruses.<sup>10</sup>

#### Boosting the Immune System

Being that approximately 70 percent of the body's immune system is GI tract-based, it is hardly surprising that the GI microflora have a major influence on overall health and disease. It has been noted that the collective metabolic activity of the estimated 400–500 species of anaerobic and other bacteria that populate the gut justify this microflora being considered "the neglected organ."<sup>13</sup>

S. Bengmark, M.D., of Lund University, Lund, Sweden, and colleagues opined that not only is the gut vulnerable to inflammation and cancer because of the organ's sheer size but also because of Western hygiene practices, antibiotics, and diets that frequently expose the gut to enzyme additives used to extend the shelf-life of processed foods.<sup>14</sup>

#### Serving as Anticancer Agents

Probiotics have demonstrated anticancer properties. Early laboratory studies with mice identified glycopeptides from the cell walls of *L. bulgaricus* bacteria that exhibited antitumor activity.<sup>15</sup> *Lactobacillus* GG was later found to reduce the incidence of induced tumors in an animal model of colon cancer.<sup>16</sup> In humans, *L. acidophilus*, supplied via milk or supplements, reduced the levels of enzymes considered to be procarcinogenic.<sup>10</sup> Unlike standard chemotherapy agents, probiotic-derived agents target tumor cells without harming normal cells or causing immune suppression and other adverse side-effects.<sup>15</sup> These bacteria compete with or inhibit the pathogenic bacteria.

Proposed mechanisms by which lactobacilli play an anticancer role include: (1) neutralizing procarcinogenic substances (e.g., nitrates) produced by harmful bacteria before they are converted into active carcinogens (e.g., nitrosamines) in the intestinal tract; (2) suppressing the metabolic action of such bacteria as *Clostridium* and certain Bacteroides, which produce higher amounts of enzymes (e.g., beta glucuronidase and b-glucosidase) that act by cleaving glucuronic acid conjugates of environmental toxins or steroidal hormones and allowing the unconjugated forms to go

back into the enterohepatic circulation and by outcompeting healthy bacteria for nutrients; and (3) suppressing the induction and growth of some tumors directly.<sup>10</sup>

#### *Assisting Vitamin and Mineral Uptake*

Probiotics increase the bioavailability of vitamins and protein in the GI tract as a result of increased acidification of the gut pH by the lactic acid produced by bacterial strains. Compared to milk, yogurt results in better absorption of such vitamins and minerals as calcium, copper, iron, manganese, phosphorus, and zinc.<sup>10</sup> Prebiotics also improve calcium bioavailability.<sup>17,18</sup> Malabsorption of nutrients can be a serious problem in inflammatory bowel disease (IBD) and other digestive ailments.

#### *Reducing the Immune Overresponse in Inflammatory Bowel Disease*

Accruing experimental and clinical evidence suggests that an overgrowth of bacterial organisms that may also exist in healthy people (e.g., *Helicobacter pylori*, *Mycobacterium paratuberculosis*, *Bacterioides vulgatus*)—in conjunction with genetic and environmental factors that impair the intestinal lining and immune response—plays an etiologic role in IBD (the collective term for Crohn's disease and ulcerative colitis). Serving as more than just a barrier for pathogens, the enteric lining of the GI tract contains resident bacteria that engage in crucial intercellular communication with the epithelial cells and other components of the mucosa.<sup>19</sup>

It has been hypothesized that probiotics can help to turn off the inappropriate, overreactive immune response in IBD by controlling regulatory signaling between the bacteria and these cells, and influencing mucosal integrity favorably.<sup>19</sup> Animals who are raised in germ-free environments as experimental models of IBD have deficits in protective gut functions, such as decreased tolerance of ingested antigens.<sup>13</sup>

This focus on the complex ecology of the GI tract reflects a major shift from an emphasis on regulating immune mediators and the inflammatory response via systemic drugs to more biologic targeted therapies and recognition of defective regulation of the patient's macro- and microenvironments in initiating or perpetuating IBD. According to Joseph B. Kirsner, M.D., Ph.D., University of Chicago Medical Center, Illinois, these differing emphases are what distinguish twenty-first century from twentieth century treatment for IBD.<sup>20</sup>

Until recently, in biomedicine, the role of diet in IBD has been largely limited to alleviating symptoms and compensating for nutritional deficiencies. Thus, the use of probiotics for modifying the enteric flora represents a major shift in the dietary management of IBD.<sup>21</sup> Such alternative therapies are clearly needed because standard pharmaceuticals for IBD are often not effective for many patients.<sup>22</sup>

## Healing Reactions to Probiotics

Although probiotics are considered to be safe even in amounts exceeding those recommended by their manufacturers, a newly introduced regime of probiotics may elicit such temporary symptoms as bloating, gas, and/or headaches in patients with toxic

## Resources

### **Crohn's & Colitis Foundation of America, Inc. (CCFA)**

386 Park Avenue South, 17th Floor  
New York, NY 10016  
Phone: (800) 932-2423 or (212) 685-3440  
Web site: [www.ccfa.org](http://www.ccfa.org)

The CCFA sponsors support group chapters nationwide for patients with inflammatory bowel disease (IBD) and their families, educational materials, workshops, advocacy, and funding for research toward a cure for IBD. Probiotics is a recent area of the CCFA's research focus.

### **National Nutritional Foods Association (NNFA)**

3931 MacArthur Boulevard, Suite 101  
Newport Beach, CA 92660-3013  
Phone (800) 966-6632 or (949) 622-6272  
Fax: (949) 622-6266  
Web site: [www.nnfa.org](http://www.nnfa.org)

As the nation's largest and oldest nonprofit organization devoted to the natural foods industry, the NNFA created and adopted the NNFA Probiotic Labeling Standard in 1989.

levels of harmful bacteria. This Herxheimer reaction, named after one of the German physicians who identified this "healing crisis" phenomenon, is the consequence of a sudden, massive die-off of harmful bacteria. While this reaction is considered to be a positive sign of the healing process, it and the discomfort it causes patients, can be averted by gradually increasing the amount and frequency of probiotic intake.<sup>10</sup>

## Research on Major Additional Uses of Probiotics

### *Preventing Colitis*

"Knockout" experimental models of IBD, in which genetic engineering methods breed selectively for the lack of a protective element in the immune system, have shown that animals bred in this way experience an increase in aerobic luminal bacteria that invade their intestinal linings aggressively. Mice born without IL-10 have decreased GI levels of beneficial *Lactobacillus* bacteria. When normal *Lactobacillus* levels were restored in one study, the levels of problematic bacteria were reduced and the development of colitis was prevented.<sup>23</sup>

In related work, testing the hypothesis that prebiotics (such as certain nondigestible carbohydrates) can promote bacterial growth, a research group found that lactulose could prevent inflammation of the gut.<sup>24</sup>

### *Developing Specific-Purpose Bacteria*

Whereas *L. acidophilus* and some strains of *Lactobacillus* reside primarily in, and are protective of, the small intestine and colon, Bifidobacteria inhabit the colon. *L. bulgaricus* is a transient strain that works with the other two strains as it passes through the digestive tract.<sup>10</sup> According to Fergus Shanahan, M.D., of Cork University Hospital, Wilton, Ireland, the diverse clinical courses of these diseases "implies that strain-specific properties may be required for subset-specific categories of patients."<sup>25</sup> Thus,

## Recommended Reading

### For health professionals

*Handbook of Probiotics*

By Yuan-Kun Lee, Koji Nomoto, Seppo Salminen,  
and Sherwood L. Gorbach  
New York: John Wiley & Sons, 1999

### For professionals and their patients

*Probiotics: Nature's Internal Healers*

By Nancy Trenev  
Garden City Park, NY: Avery Publishing Group, 1998

specifically formulated supplements, rather than foods, would generally be preferred for delivering therapeutic strains and doses to patients.

#### *Performing Reflorastration*

The concept of “reflorastration” in normalizing enteric bacteria in IBD was described by McCann and colleagues in a 1994 paper. In a 3-year study of patients with IBD, McCann sought to normalize their compromised bowel flora using *L. acidophilus* (DDS-1 strain), *B. bifidum* (Mayloth strain), and benign *E. coli* bacteria (Nissel 1917 strain). McCann’s protocol involved using antibiotics and antifungals to depopulate the patients’ bodies of all bacteria. Normal bacteria were reintroduced via oral supplementation and retention enemas. All of the patients (N was unspecified in the review paper) went into remission and those who continued the bacterial supplementation remained in remission. McCann concluded: “Reflorastration is not only a method that has the potential to identify putative etiologic antigens, it is also a clinical method to induce long-term remissions without the use of toxic drugs.”<sup>10</sup>

#### *Treating IBD Pouchitis with Multibacterial Probiotics*

To date, the efficacy of probiotic therapy in IBD has shown the most promise in preventing flareups of chronic IBD pouchitis in clinical trials that have examined the effects of the probiotic preparation VSL#3<sup>TM</sup> (VSL Pharmaceuticals, Inc., Ft. Lauderdale, Florida) on patients with recurring pouchitis. Pouchitis is an inflammatory condition that can occur in patients with ulcerative colitis who have had total proctocolectomies with ileal pouch–anal anastomoses, in which the ends of the small intestines are formed into ileoanal pouches so that bowel habits can be normalized after the diseased colon is removed. This is the most frequent complication following ileostomy closure and is most likely to occur during the first postsurgical year.

The VSL#3 product is a combination of eight different lactic acid bacteria: four strains of *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. plantarum*, and *L. delbrueckii bulgaricus*); three strains of *Bifidobacterium* (*B. longum*, *L. breve*, and *B. infantis*); and a strain of *Streptococcus salivarius thermophilus*.

Forty patients were randomized to receive either a packet of VSL#3, containing 900 billion viable bacteria, per day (with a maize starch filler) or an identical placebo for 12 months. Patients

were evaluated clinically, histologically, and endoscopically after 1, 3, 6, 9, and 12 months. The subjects also rated their health-related quality of life on a standard IBD questionnaire at baseline and at these other intervals.

This highly concentrated dose of VSL#3 was found to be effective in lowering the incidence of relapse in patients with chronic pouchitis who had been previously treated with antibiotics. Only 2 of the 20 patients (10 percent) treated with the probiotic experienced an acute episode of pouchitis—after 9 and 11 months compared to 8 of the 20 placebo-treated patients (40 percent). Treatment-group patients who did not develop pouchitis also reported a significantly higher quality of life and lower stool frequency. No side-effects or significant deviation from any of the baseline laboratory parameters were noted in either patient group.<sup>1</sup> This study confirmed an earlier review of the research suggesting that probiotics can be an effective therapy for maintaining remission in patients with chronic pouchitis.<sup>26</sup>

#### *Maintenance Treatment of IBD*

Jeffrey A. Katz, M.D., associate professor of medicine, division of gastroenterology, Case Western Reserve University School of Medicine in Cleveland, Ohio, speculated that: “Given the similarity between pouchitis and ulcerative colitis, probiotic therapy could also prove useful in the maintenance treatment of this condition.”

Dr. Katz also noted that probiotics are a promising alternative to the continuous regimen of antibiotics, corticosteroids, immune modulators, and other drugs that are typically used to treat chronic pouchitis. Because there is some correlation between chronic pouchitis and developing dysplasia and carcinoma, probiotics may help prevent to cancers of the GI tract. However, prophylactic treatment with probiotics for chronic conditions would also probably need to be long-term.<sup>27</sup>

Richard Fedorak, M.D., a professor of medicine and director of the division of gastroenterology, at the University of Alberta, Edmonton, Canada, reported that 86 percent of patients with mild-to-moderate ulcerative colitis who were not responding to conventional drug therapy had a favorable response to VSL#3.<sup>28</sup>

In a randomized study of 32 patients with Crohn’s disease in clinical remission, those who took the nonpathogenic yeast *Saccharomyces boulardii* in addition to mesalamine had a significantly lower relapse rate than those who took mesalamine alone (6 percent versus 37.5 percent).<sup>29</sup>

## Additional Potential Applications for Probiotics

#### *Reducing Lactose Intolerance*

It is well-known that dairy products and supplement products with added lactobacilli bacteria enable many people with some degree of lactose intolerance to digest the milk sugar, lactase. However, probiotics will not work for patients who are unable to digest casein, a milk protein.<sup>10</sup>

Lactose intolerance can also trigger irritable bowel syndrome (IBS).<sup>10</sup>

### Addressing Irritable Bowel Syndrome

Lactobacilli are also useful for treating patients with IBS, a condition that is characterized by abnormal muscle contractions of the bowels, because they release several amino acids, including tryptophan, which produces the calming neurotransmitter serotonin. Besides anxiety, lactose intolerance can trigger IBS.<sup>10</sup>

In a double-blinded clinical trial of 18 patients with IBS, subjects were treated for 6 weeks with *L. acidophilus* in capsule form. After a 2-week washout period, the subjects continued to take the supplement for another 6 weeks. The patients who received the probiotic experienced a 50-percent improvement compared to placebo.<sup>3</sup>

According to nutrition specialist James Scala, Ph.D., anything that chronically upsets the normal balance of intestinal flora can result in IBS. Therefore, replenishing the beneficial bacteria can normalize the gut environment and relieve IBS symptoms. Dr. Scala recommends taking active cultures of *L. acidophilus* and *B. bifidum* containing a level of at least 15 billion organisms.<sup>30</sup>

### Relieving Acute Gastroenteritis, Food Poisoning, and Diarrhea

A meta-analysis of 18 studies of acute-onset diarrhea in children concluded that probiotic therapy shortened the duration of acute gastroenteritis by approximately one day.<sup>31,32</sup>

In 1998, the Food and Drug Administration approved the use of Preempt™ (MS BioScience, Madison, Wisconsin), a probiotic culture of 29 bacteria intended to prevent *Salmonella contamination* in chickens. Tests indicated that the product may be useful against other bacteria that cause food poisoning, (e.g., *Campylobacter* and *Listeria*).<sup>10</sup>

There is also some evidence suggesting probiotics' efficacy in treating traveler's diarrhea and diarrhea related to pelvic radiotherapy for uterine or cervical cancer.<sup>30</sup>

### Addressing Chronic Constipation

Lactulose syrup has been successfully used to alleviate elderly patients' symptoms of chronic constipation. Unlike many other laxatives, this prebiotic product is not habit-forming, can be used by patients with diabetes as it does not effect blood sugar levels, and produces minimal side-effects.<sup>33</sup>

### Treating *Helicobacter pylori* Infections

*L. Acidophilus* has been demonstrated to inhibit the ulcer-causing *H. pylori* bacteria.<sup>3,30</sup>

### Inhibiting Colon Cancer

Preliminary evidence from animal models of colitis suggests that lactobacillus may inhibit the progression of colonic dysplasia to carcinoma.<sup>13</sup>

## Possible Mechanisms of Action

Mechanisms of action of probiotics that have been suggested include receptor competition, effects on mucin secretion (i.e., microproteins secreted by mucous membranes), and/or immunomodulation of gut-associated lymphoid tissue. Oral administration has been considered to be safe and well-tolerated.<sup>24</sup>

After noting that preliminary results regarding probiotics for management of IBD are promising, Gary R. Lichtenstein, M.D., in the department of gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, similarly summarized the probable mechanisms of action of probiotics as basically involving increased immunosuppressive and decreased proinflammatory mediators.<sup>33</sup>

## Conclusions and Future Directions

Foods, such as yogurt, have a venerable history of being used for health-enhancement purposes. Recent controlled studies of the health benefits of this traditional food and the use of supplementary probiotics for relieving the symptoms of IBD have generated considerable interest in the potential of beneficial bacterial to remedy the imbalance of intestinal flora that is characteristic of these serious chronic bowel disorders. Correcting this imbalance may help modulate gut mucosal barrier functions and immune responses.

Probiotics are an innovative, natural, and apparently safe adjunct to management options for IBD and other conditions that rely heavily on immunosuppressants and immunomodulating drugs, all of which have high toxicity profiles.

Probiotics also offer a significant treatment alternative to antibiotics, to which many pathogens are becoming increasingly resistant. While "[evidence] for the role of probiotics in the maintenance of health or prevention of disease is mounting," consumers should still be wary of unsubstantiated health claims made for specific products.<sup>34</sup>

Basic research will undoubtedly continue to elucidate the complex microbial ecology of the human gut and its role in the pathogenesis of such bowel diseases as IBD. Controlled clinical studies need to be conducted comparing probiotic strains to ascertain which strains might be optimal for treating specific disorders and to tailor probiotic therapy and dosages to individual patient needs. Additional comparison of probiotics with more standard therapies should also be pursued.

Probiotics represent a new role for diet in IBD in biomedicine, akin to nutrition's central place in alternative and complementary medicine. One physician-researcher stated: "Dietary modification of the enteric flora by functional foods, including probiotics, may empower patients. . . and provide a simple method to achieve a greater sense of control in the management of their illness."<sup>13</sup> That role also raises the issue of whether probiotics are to be regulated as functional foods, dietary supplements, or pharmaceutical drugs.<sup>2</sup> □

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