Protection from gastrointestinal diseases with the use of probiotics[1–3]

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ABSTRACT Probiotics are nonpathogenic microorganisms that, when ingested, exert a positive influence on the health or physiology of the host. They can influence intestinal physiology either directly or indirectly through modulation of the endogenous ecosystem or immune system. The results that have been shown with a sufficient level of proof to enable probiotics to be used as treatments for gastrointestinal disturbances are *1*) the good tolerance of yogurt compared with milk in subjects with primary or secondary lactose maldigestion, *2*) the use of *Saccharomyces boulardii* and *Enterococcus faecium* SF 68 to prevent or shorten the duration of antibiotic-associated diarrhea, *3*) the use of *S. boulardii* to prevent further recurrence of *Clostridium difficile*–associated diarrhea, and *4*) the use of fermented milks containing *Lactobacillus rhamnosus* GG to shorten the duration of diarrhea in infants with rotavirus enteritis (and probably also in gastroenteritis of other causes). Effects that are otherwise suggested for diverse probiotics include alleviation of diarrhea of miscellaneous causes; prophylaxis of gastrointestinal infections, which includes traveler's diarrhea; and immunomodulation. Trials of gastrointestinal diseases that involve the ecosystem are currently being performed, eg, *Helicobacter pylori* infections, inflammatory bowel disease, and colon cancer. *Am J Clin Nutr* 2001;73(suppl):430S–6S.

KEY WORDS Probiotics, bifidobacteria, lactobacilli, intestinal infections, antibiotic-associated diarrhea, gastroenteritis, traveler's diarrhea, intestinal flora, inflammatory bowel disease, colon cancer

INTRODUCTION

Probiotics can be defined as nonpathogenic microorganisms that, when ingested, exert a positive influence on the health or physiology of the host (1). They consist of either yeast or bacteria, especially lactic acid bacteria. Their fate in the gastrointestinal tract and their effects differ among strains (2). The effects of probiotics can be direct or indirect through modulation of the endogenous flora or of the immune system (2). Many health claims have been made concerning probiotics, especially concerning their potential to prevent or help cure intestinal disturbances; however, only a few probiotic strains were shown to be efficacious in randomized placebo-controlled clinical trials. In this article, we summarize the present knowledge on the therapeutic effects of probiotics in human gastrointestinal diseases.

IMPROVED LACTOSE DIGESTION AND OTHER DIRECT ENZYMATIC EFFECTS

Lactose maldigestion occurs frequently, especially in adults (primary lactose maldigestion) and in persons with bowel resection or enteritis (secondary lactose maldigestion). It is well established that persons with lactose maldigestion experience better digestion and tolerance of the lactose contained in yogurt than of that contained in milk (3). The mechanisms involved have been extensively investigated. The importance of the viability of lactic acid bacteria was speculated as pasteurization reduced the observed digestibility. At least 2 mechanisms, which do not exclude each other, have been shown: digestion of lactose in the gut lumen by the lactase contained in the yogurt bacteria (the yogurt bacteria deliver lactase when lyzed by bile acids) and slower intestinal delivery or transit time of yogurt compared with milk (3–6). In clinical practice, the replacement of milk with yogurt or fermented dairy products allows for better digestion and decreases diarrhea and other symptoms of intolerance in subjects with lactose intolerance, in children with diarrhea, and in subjects with short-bowel syndrome (3, 4, 7, 8). An enhanced digestion of a sucrose load was shown in infants with sucrase deficiency when they consumed *Saccharomyces cerevisiae*, ie, a yeast that contains the enzyme sucrase (9). This is yet another example of a direct effect of a probiotic; however, its relevance in the treatment of sucrase deficient subjects is not established.

ANTIBIOTIC-ASSOCIATED DIARRHEA

Diarrhea occurs in ≤20% of patients who receive antibiotics. Antibiotic-associated diarrhea (AAD) results from a microbial imbalance that leads to a decrease in the endogenous flora that is usually responsible for colonization resistance and to a decrease in the fermentation capacity of the colon. *Clostridium difficile* and *Klebsiella oxytoca* contribute to the occurrence of AAD in some cases and play a role in the pathogenesis of colonic lesions. Several attempts have been made to determine whether the administration of probiotics would prevent antibiotic-associated

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TABLE 1
Randomized controlled trials showing a significant therapeutic effect of probiotics in the prevention of antibiotic-associated intestinal symptoms (mainly diarrhea)

Antibiotic	Probiotic	Blind study	Therapeutic effect[1]	Reference
Ampicillin	*Lactobacillus acidophilus* + *Lactobacillus bulgaricus*	Yes	8.3% compared with 21%	10 (n = 98)
Neomycin	*L. acidophilus* + *L. bulgaricus*	No	20% compared with 42%	11 (n = 39)
Amoxicillin-clavulanate	*L. acidophilus* + *L. bulgaricus*	No	Positive[2]	12 (n = 27)
Antituberculous	*Enterococcus faecium* SF68	No	5% compared with 18%	13 (n = 200)
Miscellaneous	*E. faecium* SF68	Yes	8.7% compared with 27.2%	14 (n = 45)
Erythromycin	*Bifidobacterium longum*	Yes	Positive[2]	15 (n = 10)
Erythromycin	*Lactobacillus rhamnosus* GG	No	Positive[2]	16 (n = 16)
Miscellaneous	*L. rhamnosus* GG	No	17% compared with 48%	17 (n = 188)
Clindamycin	*B. longum* + *Lactobacillus*	Yes	Positive[2]	18 (n = 10)
β-lactamins or tetracyclins	*Saccharomyces boulardii*	Yes	4.5% compared with 17.5%	19 (n = 388)
Miscellaneous	*S. boulardii*	Yes	9.5% compared with 21.8%	20 (n = 180)
β-lactamins	*S. boulardii*	Yes	7.2% compared with 14.6%	21 (n = 193)

[1] Percentage of subjects with antibiotic-associated intestinal symptoms in the probiotic and control groups, respectively.
[2] The authors reported a positive effect of the probiotic but did not provide the percentage of subjects with antibiotic-associated adverse effects in the 2 groups.

intestinal symptoms (mainly AAD). Randomized controlled trials that showed a significant therapeutic effect of probiotics are shown in **Table 1**; the effects of probiotics on *C. difficile* and *K. oxytoca* are shown in the next section. Three randomized, double-blind, placebo-controlled studies showed that oral administration of *Saccharomyces boulardii* (Ultralevure, Biocodex, France) can decrease the risk of AAD (Table 1). Another study showed that *S. boulardii* significantly shortened the duration of AAD (22). The mechanism involved is unclear because multiple biological effects of the yeast in the gastrointestinal tract have been shown, which may contribute to the clinical efficacy of *S. boulardii* (ie, effects against the population levels of *C. difficile*, toxins, and intestinal secretion) (23, 24). The therapeutic efficacy of other probiotics is not as well established. It is possible that differences in probiotic preparation may explain why a mixture of freeze-dried lactobacilli significantly prevented diarrhea in 1 study but not in 2 other studies (10, 11, 25; Table 1). Whether yogurt may help to prevent or cure AAD was suggested in open trials but has not been studied in controlled experiments (2).

GASTROENTERITIS

Gastroenteritis is the main cause of acute diarrhea and is a frequent disorder that usually heals spontaneously within a few days. Gastroenteritis can be due to several viral or bacterial pathogens or to parasites, but the most frequent cause in children is rotavirus infection. The use of oral rehydration solutions is the main treatment, but it does not shorten the duration of diarrhea.

Curative treatment

Several controlled randomized trials showed a beneficial effect of probiotics and fermented dairy products in infantile or, less often, adult gastroenteritis; however, this is not a general property of all probiotics (26–28). *Lactobacillus rhamnosus* GG (*L.* GG, Valio, Finland) has been shown to be effective in the treatment of infant rotavirus diarrhea (**Table 2**). *L. rhamnosus* GG repeatedly reduced the duration of diarrhea by about half in randomized controlled trials (Table 2). It also proved effective in the treatment of acute diarrhea in children in Asia (34, 35). Guandalini et al (38) recently reported the results of a double-blind multicenter European trial in children with acute diarrhea. Two-hundred eighty-seven children aged 1–36 mo with acute diarrhea were enrolled; they received oral rehydration solution formulated according to usual recommendations in addition to *L. rhamnosus* GG [$\geq 10^9$ colony-forming units (CFU)/250 mL] or placebo. The duration of diarrhea was 58 ± 28 h in the *L. rhamnosus* GG group and 72 ± 36 h in the placebo group (NS); diarrhea was significantly reduced by *L. rhamnosus* GG in children with rotavirus infection (56 ± 17 h compared with 77 ± 42 h; $P < 0.05$) but not in the 186 children who were rotavirus negative (59 ± 33 h compared with 69 ± 22 h). Administration of *L. rhamnosus* GG also shortened the duration of the hospital stay and the course of weight gain (38). The results of one study suggested that heat-inactivated *L. rhamnosus* GG was as effective as living *L. rhamnosus* GG in reducing the duration of diarrhea; however, the effect of the living probiotic was more pronounced on rotavirus specific immunoglobulin A response (45). *Enterococcus faecium* SF 68 (Bioflorin, Giuliani, Switzerland) was shown to significantly shorten the duration of diarrhea in 4 randomized controlled trials, 2 in infants and 2 in adults (Table 2). Other probiotics are probably also effective (Table 2). Boudraa et al performed a randomized study of yogurt compared with a milk formula in 112 young Algerian children with acute diarrhea (data not published). Both formulas were comparable in terms of lactose content, pH, flavor, and texture. The mean duration of diarrhea was significantly reduced from 65 ± 5 h in the milk group to 44 ± 5 h in the yogurt group. At 48 h, 35% of children in the milk group were cured of their diarrhea, compared with 64% in the yogurt group. The difference was even more pronounced when only the 72 infants with rotavirus were considered: 27% were cured with milk, compared with 68% with yogurt (G Boudraa, unpublished observations, 1996). Note that a significant shortening of gastroenteritis was reported in adults treated with heat-killed lactobacilli (Lacteol fort, Lactéol du Dr Boucard, France) (46).

Prevention

Several nonrandomized trials suggest a preventive effect of some fermented products on the risk of diarrhea in children (2, 47). Saavedra et al (44) showed that feeding *Bifidobacterium bifidum* and *Streptococcus thermophilus* to infants admitted to the hospital significantly reduced the risk of diarrhea and the shedding of rotavirus (Table 2). In a double-blind placebo-controlled trial, 55 children admitted to a chronic medical care unit were randomly assigned to receive a standard formula or a standard formula with

TABLE 2
Randomized controlled trials showing a significant therapeutic effect of probiotics to shorten the duration of acute gastroenteritis

	Probiotic	Study population	Reference
Curative treatment			
Rotavirus-associated diarrhea	*Lactobacillus rhamnosus* strain GG	Infants	29 (n = 71)
	L. rhamnosus strain GG	Infants	30 (n = 39)
	L. rhamnosus strain GG	Infants	31 (n = 49)
	L. rhamnosus strain GG	Infants	32 (n = 42)
	Lactobacillus casei strain Shirota	Infants	33 (n = 32)
Gastroenteritis	*L. rhamnosus* strain GG	Infants	34 (n = 32)
	L. rhamnosus strain GG	Infants	35 (n = 26)
	L. rhamnosus strain GG	Infants	36 (n = 100)
	L. rhamnosus strain GG	Infants	37 (n = 123)
	L. rhamnosus strain GG	Infants	38 (n = 287)
	Enterococcus faecium SF68	Infants	39 (n = 104)
	E. faecium SF68	Adults	40 (n = 56)
	E. faecium SF68	Adults	14 (n = 78)
	E. faecium SF68	Adults	41 (n = 211)
	Yogurt	Infants	—[1] (n = 112)
	Saccharomyces boulardii	Infants	42 (n = 38)
	Lactobacillus reuteri	Infants	43 (n = 66)
Prevention			
Acute diarrhea or rotavirus	*Bifidobacterium bifidum* and *Streptococcus thermophilus*	Infants	44 (n = 55)

[1] G Boudraa, unpublished observations, 1996.

B. bifidum and *S. thermophilus*. During follow-up, diarrhea occurred in 7% of the children receiving the probiotic and in 31% of the control subjects ($P = 0.035$), and shedding rotavirus occurred in 10% of children compared with 39% ($P = 0.025$), respectively.

INTESTINAL INFECTIONS AND COLONIZATION BY PATHOGENIC BACTERIA

The protective effects of probiotics against intestinal infections were shown in animal models (23, 24, 47). Mechanisms that may be implicated include the production of acids, hydrogen peroxide, or antimicrobial substances; competition for nutrients or adhesion receptors; antitoxin actions; and stimulation of the immune system.

Open trials suggested that some probiotics may help to eradicate pathogens in chronic carriers of salmonella and campylobacter (48, 49). Several reports related to patients experiencing a recurrence of *C. difficile* infections. This serious clinical problem occured in ≈20% of the subjects treated for a first episode of infection with this microorganism and in >40% of subjects who experienced several episodes. Several open studies performed in a limited number of subjects suggest a beneficial role of *L. rhamnosus* GG, *S. boulardii*, and *Lactobacillus plantarum* LP299v during *C. difficile*–related infections (50–56). Although these studies suggested a therapeutic effect, especially because they pertained to subjects with recurrent infection, they did not have the proof level of randomized controlled trials.

McFarland et al (57) performed a study that included 124 patients who were randomly asigned to receive a standard antibiotic treatment combined with either *S. boulardii* (1 g/d for 28 d) or a placebo. The risk of clinical recurrence for the subjects who had experienced several episodes of *C. difficile* infection was significantly reduced in the *S. boulardii* group: 34.6% compared with 64.7% in the placebo group ($P = 0.04$). The administration of *L. rhamnosus* GG to preterm infants hospitalized in a neonatal intensive care unit was attempted to decrease the risk of *K. oxytoca* colonization but was ineffective (58).

Helicobacter pylori would be a good target for an efficient probiotic therapy. Colonization of the gastric mucosa is strongly associated with gastritis, duodenal and gastric ulcers, and some malignancies. Antagonistic actions of some *Lactobacillus* strains against *H. pylori* in vitro were reported (59). Attempts to eradicate *H. pylori* in vivo with a probiotic have failed until now (60). However, a significant reduction of urease activity was reported in patients treated with a supernatant of *Lactobacillus johnsonii* LA1 (Nestlé, Switzerland Lausanne) associated with omeprazole (61).

TRAVELER'S DIARRHEA

Acute diarrhea occurs in about half of travelers who visit high-risk areas. Although most cases are mild and self-limiting, there is a considerable morbidity. Antibiotics are effective prophylaxis but are not recommended for widespread use (62, 63) and there is thus a need for cost-effective alternative treatments. Several studies were performed with the use of probiotics (**Table 3**). Some studies that used lactobacilli had negative results, whereas 4 studies that used diverse probiotics reported positive results (Table 3). Black et al (67) treated 94 Danish tourists participating in a 2-wk trip to Egypt with a mixture of *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, bifidobacteria, and *S. thermophilus* or a placebo in a randomized study. The frequency of traveler's diarrhea was reduced from 71% (very high) to 43% ($P < 0.001$). In a double-blind randomized study, Oksanen et al (69) reported a reduction of diarrhea by *L. rhamnosus* GG administration to subjects traveling to Turkey; however, the effect was significant for only one destination in Turkey. Another study used the same strain in 400 American travelers who were randomly assigned to receive *L. rhamnosus* GG or a placebo (70). One hundred fifty-five travelers were excluded, mainly because they did not take the medication. When only the subjects who took the capsules were considered, the risk of having diarrhea on any given day was 3.9% for patients treated with the probiotic compared with 7.4% in those not treated ($P = 0.05$).

TABLE 3
Randomized controlled trials of probiotics to prevent traveler's diarrhea

Probiotic	Therapeutic effect[1]	Reference
Lactobacillus acidophilus + *Lactobacillus bulgaricus*	35% compared with 29% (NS)	64 (n = 50)
Lactobacilli	55% compared with 51% (NS)	65 (n = 212)
Lactobacillus fermentum strain KLD	23.8% compared with 23.8% (NS)	66 (n = 282)
L. acidophilus (unspecified strain)	25.7% compared with 23.8% (NS)	66 (n = 282)
Lactobacilli + bifidobacteria + streptococci	43% compared with 71% (P = 0.02)	67 (n = 81)
Saccharomyces boulardii	28.7% compared with 39.1% (P < 0.05)	68 (n = 1016)
Lactobacillus rhamnosus strain GG	41.0% compared with 46.5% (P = 0.065)	69 (n = 756)
L. rhamnosus strain GG	3.9%/d compared with 7.4%/d (P = 0.05)	70 (n = 245)

[1] Percentage of subjects with traveler's diarrhea in the probiotic and control groups, respectively.

Kollaritsch et al (68) used *S. boulardii* in a double-blind placebo-controlled trial in which only 1016 of 3000 Austrian travelers were compliant. The protection against the occurrence of diarrhea was mild but significant and was dose-dependent (68; Table 3).

IRRITABLE BOWEL SYNDROME AND VARIOUS CONDITIONS WITH DIARRHEA

Some probiotics, including acidophilus or bifidus milk, were reported to relieve constipation in a short series of patients (2); however, these studies were not controlled. In a randomized placebo-controlled study including only 34 patients, Maupas et al (71) observed that *S. boulardii* decreased functional diarrhea but did not influence other symptoms of irritable bowel syndrome. Halpern et al (72) suggested in a randomized, double-blind, crossover trial that administration of heat-killed lactobacilli for 6 wk was more efficient than was placebo in relieving symptoms of irritable bowel syndrome. However, only 18 of 29 randomly assigned subjects were studied and this poor compliance was a weakness of that study. Hentschel et al (73) assessed the efficacy of 2 probiotic preparations containing lactobacilli and *Escherichia coli* (Hylac and Hylac N forte, Merckle, Blaubeuren, Germany) in 126 subjects suffering from nonulcer dyspepsia and did not observe any amelioration.

S. boulardii decreased the duration of diarrhea induced by tube feeding in 3 trials (74–76). The most recent study was double-blind and compared the administration of 2 g *S. boulardii*/d with placebo in 128 critically ill tube-fed patients (76). Treatment with the probiotic reduced the percentage of days patients experienced diarrhea from 18.9% to 14.2% (P = 0.007). Two open studies proposed that lactobacilli might have some efficacy against small intestinal bacterial overgrowth (77, 78), but *S. boulardii* was ineffective in the only randomized placebo-controlled study (79).

Diarrhea is a nearly constant adverse effect of irradiation of the pelvis. A randomized controlled study by Salminen et al (80) showed a significant decrease in diarrhea in patients receiving *L. acidophilus* NDCO 1748 during pelvic irradiation. Previous open trials suggested the efficacy of freeze-dried lactic acid bacteria cultures for the same indications (80). Such potentially interesting therapeutic effects should be studied more thoroughly. Elmer et al (81) reported that high doses of *S. boulardii* might be effective in some subjects with HIV-related chronic diarrhea; however, further evaluation is warranted before firm conclusions can be drawn.

WELL-BEING

Compared with the numerous studies in patients, there have been only a few investigations of otherwise healthy people with or without mild gastrointestinal symptoms, and the often-claimed improvement of well-being by probiotics has not been proven until now.

In a recent controlled, randomized, double-blind study (de Vrese and Schrezenmeir, unpublished observations, 1998), 66 healthy, lactose-tolerant adults in 3 groups—after a 3-wk preperiod without fermented food—consumed 125 g/d of a chemically acidified milk product without bacteria (control) or with 2 strains of probiotic *Lactobacillus* (10^{10} CFU/d). Gastrointestinal symptoms and well-being were recorded by validated questionnaires and expressed as a sum score of 5 characteristics concerning intestinal function and pain. Within 1 wk, both probiotics, but not the artificially acidified milk product without bacteria, improved well-being and decreased gastrointestinal symptoms, from 6 to 4 points (on a scale of 0–30 points). These differences were significant (P < 0.05) with respect to both the control subjects and the preperiod without probiotics. This was the first time that such an effect was observed in healthy persons.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease refers to disorders of unknown cause that are characterized by chronic or recurrent intestinal inflammation. Such disorders include ulcerative colitis, Crohn disease, and pouchitis. The mechanisms responsible for initiation and perpetuation of the inflammatory process remains unknown, but the main theory is that inflammatory bowel disease may result from abnormal host responses to some members of the intestinal flora or from a defective mucosal barrier (82, 83). Treatment may be difficult and there is a need for new treatments to decrease the occurrence of symptoms and to prevent recurrence.

Several studies showed interesting effects of probiotics on inflammatory bowel disease in animals. Intracolonic administration of *L. reuteri* R2LC to rats with acetic acid-induced colitis significantly decreased the disease, whereas *Lactobacillus* HLC was ineffective (84). Administration of *Lactobacillus reuteri* R2LC and *Lactobacillus plantarum* DSM 9843 to rats with methotrexate-induced enterocolitis was associated with low intestinal permeability, bacterial translocation, and plasma endotoxin concentrations compared with rats with enterocolitis and no treatment (85). A few studies were also performed in patients. In an open study, a 10-d administration of *L. rhamnosus* GG to 14 children with active or inactive Crohn disease resulted in an increase in immunoglobulin A–secreting cells to β-lactoglobulin and casein, which indicates an interaction between the probiotic and the local immune system (86). The lactobacilli did not influence the disease activity, however, because the study group was too small and the study was too

short to assess accurately a clinical effect (86). Plein and Hotz (87) performed a pilot, double-blind, controlled study of the efficacy of *S. boulardii* on symptoms of Crohn disease. Twenty patients with active, moderate Crohn disease were randomly assigned to receive either *S. boulardii* or a placebo for 7 wk in addition to the standard treatment. A significant reduction in the frequency of bowel movements and in disease activity was observed in the group receiving *S. boulardii* but not in the placebo group.

Two studies (88, 89) compared the efficacy of an oral *E. coli* preparation [*E. coli* strain Nissle (Mutaflor, Ardeypharm GmbH, Herdecke, Germany)] and mesalazine (ie, the standard treatment) in maintaining remission of ulcerative colitis. The first study included a total of 120 patients with inactive ulcerative colitis. After 12 wk, 11.3% of the subjects treated with mesalazine had relapsed, compared with 16% of those treated with the probiotic. The second study included 116 patients and also showed that the probiotic preparation was as effective as mesalazine in inducing remission and preventing relapse (89). Several studies are currently testing the effects of probiotics on inflammatory bowel disease in Europe (90).

COLON CANCER

The endogenous flora and the immune system play a role in the modulation of carcinogenesis. Both may be influenced by probiotics and this has led to trials investigating the role of probiotics in preventing or curing tumors in animals (91). Several authors showed that some probiotics may decrease the fecal concentrations of enzymes, mutagens, and secondary bile salts that may be involved in colon carcinogenesis (91). Some but not all epidemiologic studies also suggest that consumption of fermented dairy products may have some protective effect against large colon adenomas or cancer (92). It is thus impossible to draw any conclusion at this time. Clinical studies are currently ongoing in Europe to study the effects of probiotics and prebiotics in subjects with colonic adenomas.

CONCLUSIONS

The concept of probiotics may occasionally favor overestimation of effects; however, accumulating research evidence suggests that probiotics may have a role in human therapies. In our opinion, the proven medical indications of probiotics for gastrointestinal disturbances are the following: *1*) replace milk with yogurt in subjects with lactose intolerance, *2*) use freeze-dried *S. boulardii* or *E. faecium* SF 68 to prevent AAD, *3*) use freeze-dried *S. boulardii* to prevent further recurrence of relapsing diarrhea because of *C. difficile*, and *4*) use fermented milk containing *L. rhamnosus* GG to shorten the duration of the diarrhea during rotavirus enteritis in children. Many other potential applications exist, but more controlled studies are required.

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