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REVIEW

Probiotics and gastrointestinal diseases

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There is increasing evidence indicating health benefits by consumption of foods containing microorganisms, i.e. probiotics. A number of clinical trials have been performed to evaluate the effects in the prevention and treatment of gastrointestinal diseases caused by pathogenic microorganisms or by disturbances in the normal microflora. Gastrointestinal infections caused by *Helicobacter pylori*, traveller's diarrhoea, rotavirus diarrhoea, antibiotic-associated diarrhoea (AAD) and *Clostridium difficile*-induced diarrhoea are conditions that have been studied. There are also studies performed on the preventive effect of probiotics on radiation-induced diarrhoea and diarrhoea in tube-fed patients. Inflammatory bowel disease and irritable bowel syndrome, two idiopathic conditions where alterations in the normal microflora have been implicated as responsible for initiation, are two further areas where the use of probiotics has been regarded as promising. The results from clinical studies have not been conclusive in that the effects of probiotics have been strain-dependent and different study designs have been used. Treatment of acute diarrhoea in children and prevention of AAD are the two most justified areas for the application of probiotics.

Keywords: diarrhoea, gastrointestinal diseases, probiotics.

The intestine harbours a complex and dynamic microbial ecosystem that has several major functions. The functions include metabolic activities, trophic effects on the intestinal epithelium and interactions with the immune system of the host [1]. The resident microflora also acts as a barrier that prevents colonization of opportunistic and pathogenic microorganisms [2] (Fig. 1).

There is an increasing amount of evidence indicating health benefits by consumption of food-containing probiotics [3, 4]. Probiotics were recently redefined by an expert group to 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' [5]. The expert panel further concluded that the health benefits for which probiotics can be applied include gastrointestinal infections and certain bowel disorders. Microorganisms most commonly used as probiotics are lactic acid-producing lactobacilli and bifidobacteria. Both bacterial groups belong to the normal microflora and several strains produce not only lactic acid but also other antimicrobial substances like hydrogen peroxide and bacteriocins [6]. Probiotic agents further compete with pathogens for microbial adhesion sites and are claimed to modulate the immune response of the host. The specific effects on the immune system are, however, still unclear [7]. Other less commonly used probiotic microorganisms are strains of *Streptococcus*, *Escherichia coli*, *Bacillus* and *Saccharomyces*. *Streptococcus thermophilus* has been used in probiotics to enhance digestion of lactose in intolerant subjects [8].

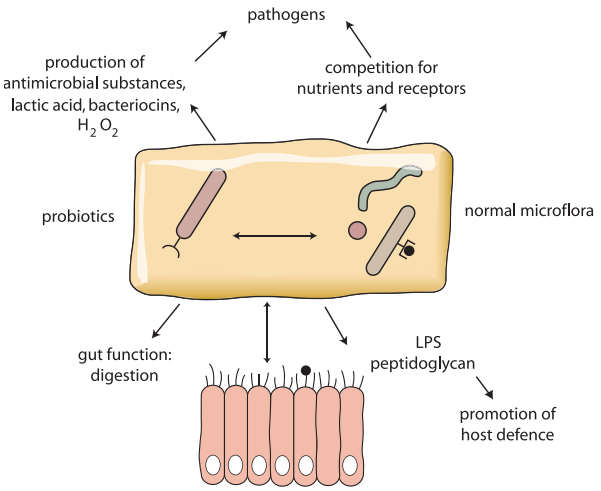

Fig. 1 The normal microflora and probiotics interact with the host in metabolic activities and immune function, and prevent colonization of opportunistic and pathogenic microorganisms.

Nonpathogenic strains of *E. coli* have been shown to inhibit adhesion and growth of invasive *E. coli* [9] and to prevent colonization of the intestines by microbial pathogens in infants [10]. The beneficial mechanisms of spores of *Bacillus* species have not been fully understood. The anti-*Helicobacter pylori* activity has however been shown to be due to the production of at least two antimicrobial agents [11]. The nonpathogenic yeast, *Sac. boulardii* produces a protease that interferes with toxins from *Clostridium difficile* [12] and possesses antisecretory properties of importance for prevention of castor oil induced diarrhoea in rats [13]. However, the complexity of the possible interaction between the gastrointestinal microflora at each ecological habitat, the probiotic strains, pathogens and the host, renders the prediction of the outcome hazardous in single subjects. The quality of the different probiotic strains is distinctive and not always fully evaluated and further work is needed for a better understanding of the clinical effects of probiotics.

The aim of this review article is to summarize the present knowledge of the impact of probiotics in the prevention and treatment of gastrointestinal diseases.

Helicobacter pylori *infections*

Helicobacter pylori is associated with chronic gastritis, peptic ulcers and gastric cancer. It has been strongly recommended in several categories of patients that *H. pylori* should be eradicated [14]. Recommended therapy is triple therapy using a proton-pump inhibitor combined with clarithromycin and amoxicillin or metronidazole [14]. This therapy is efficient, although frequently associated with adverse events, and there are fears that the treatment will soon give rise to a rapid development of antimicrobial-resistant strains that will limit the usefulness of the treatment [15].

A number of clinical studies on the effects of probiotics on the eradication rates of *H. pylori* have been carried out, for a summary see Table 1. Subjects attending a screening programme for the assessment of prevalence and risk factors for *H. pylori* have been enrolled in a study on the effects of *Lactobacillus* GG in combination with standard triple eradication therapy [16]. No significant differences were observed between the supplemented and the placebo group in eradication rates measured with the ^{13}C-urea breath test 6 weeks after completion of therapy. Canducci *et al.* [17] evaluated an inactivated preparation of *L. acidophilus* (LB) in conjunction with standard triple therapy on *H. pylori*-positive patients. A significantly increased eradication rate was observed in the group receiving the supplement, 88% compared with 72% in the placebo group (or 87% compared with 70% using intention-to-treat analyses). A milk drink containing *L. casei* strain Shirota was administered to *H. pylori*-positive subjects to determine the inhibitory effect of the probiotic on the growth of *H. pylori* [18]. The urease activity decreased in 64% of the subjects receiving the probiotic drink compared with 33% in the control group ($P = 0.22$). In another study, 85 asymptomatic patients were examined and randomized into four groups [19]. All patients received a 1-week triple therapy in combination with *Lactobacillus* GG or *Sac. boulardii*, a combination of *L. acidophilus* and *Bifidobacterium lactis* (Ferzym, Specchiasol, Milan, Italy) or a placebo product. The *H. pylori* eradication rate did not differ between the groups. *Helicobacter pylori*-infected volunteers were given either a fermented milk product-containing *L. johnsonii* (La1) or placebo for 3 weeks [20]. During the last 2 weeks, all subjects also received clarithromycin. The probiotic product induced a decrease in *H. pylori* density in the antrum and the corpus. There was also a reduction in inflammation and gastritis activity in the antrum and in the corpus. The eradication rate was not

Table 1 Clinical studies on the effect of probiotics on *Helicobacter pylori* infections

Probiotic strain	Study design	Number of patients	Treatment period (week)	Follow-up period (week)	Additional treatments and results	Reference
Lactobacillus GG	DBPC	60	2	6	1-week standard therapy, no significant differences in success of *H. pylori* eradication	[16]
L. acidophilus strain LB (lyophilized)	OPC	120	1	6	1-week standard therapy, increased eradication rate of standard therapy in active group	[17]
L. casei strain Shirota	OPC	20	3	–	No additional treatment, trend towards suppressive effect in active group	[18]
Lactobacillus GG, *Saccharomyces boulardii*, *L. acidophilus* + *Bifidobacterium lactis*	TBPC	85	2	5–7	1-week standard therapy, *H. pylori* eradication rates similar in all groups	[19]
L. johnsonii La1	DBPC	52	3	4–8	2-week clarithromycin treatment, reduced density of *H. pylori*, reduced inflammation and gastritis activity	[20]
L. johnsonii La1 supernatant	O	20	2	4	2-week treatment with omeprazole/placebo, decreased breath test values, persistence of *H. pylori* in all subjects regardless of treatment	[21]
L. acidophilus NAS	O	14	8	8	No additional treatment, eradication of *H. pylori* in six of 14 patients	[22]
L. johnsonii Lj1	DBPC	50	16	–	No additional treatment, severity and activity of gastritis was reduced	[23]
L. gasseri LG21	O	29	8	–	No additional treatment, decreased number of *H. pylori* and reduced gastric mucosal inflammation	[24]
Lactobacillus species, *Bifidobacterium* species	DBPC	160	5	8	1-week standard therapy, improved intention-to-treat eradication rates of *H. pylori*	[25]
Lactobacillus spp. (three strains)	O	27	4	4	No additional treatment, 26 of 27 subjects remained positive in urea breath test after administration of probiotic	[26]

DB, double-blind; O, open study; TB, triple-blind; PC, placebo-controlled.

improved by the probiotic administration. The effect of a drink made of whey-based *L. johnsonii* (La1) supernatant on *H. pylori* has been evaluated in infected subjects [21]. The subjects were randomized to receive a concomitant treatment with omeprazole or placebo tablets. Four weeks after the end of treatment, the urea breath test values were still significantly below the pretreatment values regardless of treatment group. Analysis of biopsies showed that *H. pylori* infection and gastritis scores were not affected by the treatment. This finding is in contrast to a study where *H. pylori*-positive subjects took a milk product with added *L. acidophilus* (NAS) as the only therapy during 8 weeks [22]. *Helicobacter pylori* was eradicated in six of the 14 patients. The effect of *L. johnsonii* (Lj1) has been evaluated in *H. pylori* asymptomatic volunteers [23]. Individuals took a fermented milk preparation twice daily for 3 weeks and once daily for the next 13 weeks. No subject with *H. pylori* infection was cured but the severity and activity of the gastric inflammation were diminished. In a crossover study, the suppressive effect of *L. gasseri* OLL 2716 (LG21) has been evaluated [24]. The regimen induced two- to 100-fold decreases in number of *H. pylori*, but the microorganism was never completely eradicated. Patients receiving triple therapy for eradication of *H. pylori* were randomly assigned a supplement of *Lactobacillus* and *Bifidobacterium*-containing yoghurt (AB-yoghurt, President Corp., Tainan, Taiwan) [25]. By intention-to-treat analysis, the probiotic group had a higher eradication rate than the group

receiving only the triple therapy (91% vs. 78%). Per protocol analyses yielded no differences between the groups. Asymptomatic women positive for *H. pylori* were recruited and administered a yoghurt-containing *L. casei* 03, *L. acidophilus* 2412 and *L. acidophilus* ACD1 and a commercial starter culture (containing *L. bulgaricus*, *S. thermophilus* and *L. acidophilus*) [26]. One month after ingestion of the yoghurt, the urea breath test values remained positive in the majority of women although the probiotic strains were shown to be effective in the inhibition of *H. pylori* growth *in vitro*.

Conclusions

The results of the above-mentioned studies indicate a suppressed growth of *H. pylori* by probiotic strains although there are differences in the effectiveness between the strains. Probiotics are not recommended in the treatment or as an adjunct for *H. pylori* eradication, and further studies are needed to evaluate the long-term effects of ingestion on *H. pylori*-associated diseases [15]. Additional double-blind and placebo-controlled studies are justified to verify the effect of probiotics on *H. pylori* infections. The probiotic and placebo products should be administered in conjunction with the triple therapy that is recommended for the eradication of *H. pylori*.

Acute gastroenteritis

Traveller's diarrhoea

Enterotoxinogenic *E. coli*, shigellae and salmonellae account for about 80% of cases with an identified pathogen in acute diarrhoea in travellers [27]. Studies have been performed to analyse the preventive effect of probiotic strains. *Lactobacillus* GG has been used as prophylaxis in two placebo-controlled studies [28, 29]. In the first study, a reduction in the incidence of diarrhoea was reported in tourists going to one destination in Turkey (the incidence in the lactobacilli group was 23.9% vs. 39.5% in the placebo group, $P = 0.04$) whilst no effect was observed at another destination (38.9% vs. 42.3%, $P = 0.51$). In the second study, a modest reduction in frequency of diarrhoea was observed after exclusion of subjects that did not comply with the treatment (risk of diarrhoea in the treatment group was 3.9% vs. 7.4% in the placebo group, $P = 0.05$). A mixture of *L. acidophilus* and *L. bulgaricus* was tested in tourists travelling to Mexico [30]. Prophylactic ingestion of the preparation did not reduce the incidence or the duration of diarrhoea (35% vs. 29%, $P > 0.05$). British soldiers deployed to Belize were randomly administered *L. fermentum* strain KLD, *L. acidophilus* (LA) or placebo [31]. There were no significant differences in the incidence of diarrhoea between any groups after 3 weeks (23.8%, 25.7% and 23.8% respectively). Prophylaxis with a mixture of *L. acidophilus*, *B. bifidum*, *L. bulgaricus* and *S. thermophilus* has been shown to significantly reduce the frequency of diarrhoea in travellers in Egypt (43% vs. 71%, $P = 0.019$) [32]. In a randomized, placebo-controlled study the preventive effect of *Sac. boulardii* on traveller's diarrhoea was investigated [33]. Only one-third of the subjects were compliant and when evaluated there was a reduction in the incidence of diarrhoea that was dependent on region and dose (incidence in subjects receiving high dose of *Sac. boulardii* was 28.7% vs. 39.1% in the placebo group, $P = 0.005$).

Conclusions

Several of the studies have been connected with methodological problems and at the present time it is not possible to medically recommend any probiotic to prevent traveller's diarrhoea [34]. More thorough studies are needed.

Prevention of diarrhoea in children

Probiotic strains have been evaluated for the ability to prevent nosocomial diarrhoea in children. Prophylactic use of *Lactobacillus* GG compared with a placebo product has been shown to significantly reduce the risk of in particular rotavirus gastroenteritis (2.2% compared with 17%, $P = 0.02$) in hospitalized children [35]. However, the effect of the same strain similarly prepared and the impact of breast-feeding were assessed in another study where *Lactobacillus* GG was found to be ineffective whilst breast feeding was effective in preventing nosocomial rotavirus infections [36]. Two strains, *B. bifidum* and *S. thermophilus*, were fed to children admitted to hospital as supplement to a standard infant formula [37]. Eight of 26 children receiving the placebo formula and two of 29 children receiving the

supplemented probiotic formula developed diarrhoea ($P = 0.035$).

Prophylactic use of *Lactobacillus* GG to prevent diarrhoea in undernourished children from a developing country has also been evaluated [38]. Children received either the probiotic or a placebo 6 days a week for 15 months. Children receiving *Lactobacillus* GG had fewer episodes of diarrhoea than children in the placebo group (5.2 episodes compared with 6.0, $P = 0.028$). However, the preventive effect varied between children in different age groups and between breastfed and nonbreastfed children. In the youngest infants no benefits were observed whilst there was a significant preventive effect observed in breastfed 18–19-month-old infants. In the oldest age group, 30–41-month-old children, breastfed children were found to experience significantly more diarrhoea when receiving *Lactobacillus* GG. Another strain of *Lactobacillus* (*L. casei* DN-114001) has been studied in order to determine if the strain could decrease the incidence of acute diarrhoea in children attending a day care centre [39]. The incidence of diarrhoea was shown to be similar in children receiving the probiotic and the placebo product, but the severity of diarrhoea was less in children in the active group.

Treatment of diarrhoea in children

Acute infectious diarrhoea in children is common, and rotavirus accounts for approximately 45% of all cases worldwide [40]. There are a number of studies performed on probiotic therapy of acute and dehydrating diarrhoea. The results of some of the performed double-blind, placebo-controlled studies are seen in Table 2. The efficacy of killed *L. acidophilus* (LB) has been evaluated in the treatment of acute diarrhoea in infants and toddlers [41]. The recovery rates were similar in both the probiotic and the placebo groups but the time to passage of the first normal stool was decreased in children receiving lactobacilli ($P = 0.05$). *Lactobacillus* GG has been used as a probiotic in a study performed in Brazil [42]. There was no significant reduction in diarrhoea duration, neither for the whole group of children nor for children positive for rotavirus. The children in this study were severely affected by diarrhoea and dehydration. The same strain has been administered in two preparations (fermented milk or freeze-dried powder) after oral rehydration to well-nourished children [43]. Both preparations were found to be beneficial for recovery from diarrhoea. A fermented milk product-containing *Lactobacillus* GG has also been compared with a placebo (the same fermented product after pasteurization) in well-nourished children [44]. All children studied were rotavirus-positive and the recovery rate was promoted by the probiotic. Administration of oral rehydration solution containing *Lactobacillus* GG has been evaluated in a multicentre study [45]. The treatment was found to result in shorter duration of diarrhoea and reduced number of watery stools, in particular in children affected by rotavirus. The effect of *Lactobacillus* GG has also been studied in children with acute diarrhoea in Thailand [46]. There was no significant difference in overall clinical response between the treated and the placebo group apart from a shorter duration of diarrhoea in the *Lactobacillus* group when only children with nonbloody diarrhoea were included in the analyses. The treatment in this study was only continued for 48 h. Three probiotic microorganisms in lyophylized form (*S. thermophilus* sp. *lactis*, *L. acidophilus* and *L. bulgaricus*) (Fermalac-Rougier Laboratories, Montreal, Canada) did not shorten the course of diarrhoea in infants [47]. Children with intestinal microflora already disturbed by antimicrobial treatment (34% of children in the treatment group and 20% in the placebo group) did not benefit either. A combination of two lactobacilli strains, *L. rhamnosus* (19070-2) and *L. reuteri* (DSM 12246), has been evaluated in hospitalized children and in children attending day care centres [48, 49]. For the total group of hospitalized children, no statistically significant difference was found in duration of diarrhoea between the treatment and the control group. However, 5 days after enrolment only three of 30 patients in the treatment group compared with 13 of 39 in the control group still had loose stools. For children attending the day care centres, two of 24 patients in the treatment group vs. seven of 19 in the control group still had loose stools 5 days after enrolment. Another strain of *L. reuteri* (SD 2112) also shortened the duration of diarrhoea to a certain extent, although the result was not statistically significant [50]. Two oral rehydration solutions and *Lactobacillus* GG or placebo were used for treatment of acute diarrhoea in children [51]. There were no differences between children receiving the two solutions of rehydration, and children with

Table 2 Double-blind placebo-controlled studies on the effect of probiotics in the treatment of acute diarrhoea in children

Probiotic strain/placebo probiotic and/or ORS	Pathogen (%)			Number of children	Duration of diarrhoea (days)	*P*-value	Comments	Reference
	RV	Bacteria	n.i.					
Lactobacillus acidophilus LB	49	–	–	38	1.1	>0.05	Hospitalized children	[41]
Placebo				23	1.1		ORS when required	
LGG + ORS	52	–	48	61	1.6	0.59	Hospitalized children	[42]
ORS	48	–	52	63	1.6			
LGG fermented milk + ORS	92	–	–	24	1.4	<0.001	Hospitalized children	[43]
LGG freeze-dried + ORS	74	–	–	23	1.4			
Placebo + ORS	79	–	–	24	2.4			
LGG	100	–	–	22	1.1	0.001	Hospitalized children	[44]
Placebo				17	2.5			
LGG + ORS	38	17	31	147	2.4	0.03	86% hospitalized children	[45]
ORS	32	19	39	140	3.0		14% outpatients	
LGG + ORS	10	–	–	20	1.9[a]	<0.05	Hospitalized children	[46]
ORS	26	–	–	19	3.3[a]		41% ab prior admission	
Streptococcus thermophilus + *L. acidophilus* + *L. bulgaricus*	–	2	98	53	2.7	>0.05	Hospitalized children 28% ab prior admission	[47]
Placebo	–	2	98	41	2.1			
L. rhamnosus 19070-2 + *L. reuteri* DSM 12246 + ORS	58	6	29	30	3.4	0.07	Hospitalized children	[48]
ORS				39	4.2			
L. rhamnosus 19070-2 + *L. reuteri* DSM 12246	58	5	23	24	3.2	0.05	Children attending day care centres	[49]
Placebo				19	4.8			
L. reuteri SD 2112 + ORS	63	–	27	19	1.7	0.07	Hospitalized children	[50]
ORS	86	–	14	21	2.9			
LGG + ORS	22	19	59	59	2.7	0.02	Hospitalized children	[51]
ORS	33	23	44	64	3.8		21% treated with ab	
L. acidophilus LB + ORS	51	2	47	37	1.8	0.03	Hospitalized children	[52]
ORS	44	–	56	36	2.4		55% ab prior admission	
L. reuteri high dose + ORS	100	–	–	21	1.5	0.01	Hospitalized children	[53]
L. reuteri low dose + ORS	100	–	–	20	1.9			
Placebo + ORS	100	–	–	25	2.5			

RV, rotavirus; n.i., no identity confirmed; LGG, *Lactobacillus* GG; ORS, oral rehydration solution; ab, antibiotics.
[a]Figures regard subgroup of children with nonbloody diarrhoea.

confirmed bacterial aetiology (*Salmonella* or *Shigella*) did not benefit from treatment with *Lactobacillus* GG. All patients received further antimicrobial treatment. In the subgroup of rotavirus-positive patients, there was however a significant shorter duration of diarrhoea in the lactobacilli group. Heat-killed *L. acidophilus* (LB) was assessed as an adjunct to oral rehydration therapy [52]. The mean duration of diarrhoea decreased with *L. acidophilus*, which was particularly marked in children with no antibiotic therapy before inclusion. *Lactobacillus reuteri* (BioGaia Biologics AB, Göteborg, Sweden) has been used as bacteriotherapy in children with rotavirus gastroenteritis [53]. The administration significantly reduced the duration of watery diarrhoea. The effect was found to be dose-dependent.

In four recent review articles, the effect of probiotics in acute diarrhoea in children has been systematically analysed [54–57]. The authors are concluding that probiotics shorten the duration of acute diarrhoea in children by approximately 1 day.

Conclusions

The apparent decrease in duration of diarrhoea observed in several studies is still quite modest and all strains used have not been effective. The benefits for children in developing countries have been contradictory. The cost-effectiveness of the treatment ought to be included in further analyses.

Antibiotic- and *Clostridium difficile*-associated diarrhoea

A common complication of treatment with antimicrobial agents is the development of antibiotic-associated diarrhoea (AAD) in 5–25% of patients [58]. The incidences vary with the class of antibiotics used and with risk factors in patients treated. *Clostridium difficile* is responsible for 15–25% of cases of AAD and for almost all cases of pseudomembraneous colitis [59]. A number of studies have been performed on prevention of AAD. See Table 3 for a summary of clinical trials.

Antibiotic-associated diarrhoea

The effect of *Lactobacillus* GG for prevention of AAD has recently been evaluated in two clinical trials in adults. Asymptomatic *H. pylori*-infected patients were treated with triple therapy with or without the probiotic strain. The supplementation significantly reduced diarrhoea, nausea and taste disturbances associated with the treatment [16]. In the second study, patients received antibiotics initially in the hospital setting, supplemented with *Lactobacillus* GG or a placebo product [60]. The occurrence of diarrhoea did not differ between the groups, and subgroup analyses of those treated with β-lactams versus non-β-lactams yielded no further differences. The same probiotic strain has also been evaluated in children with respiratory tract infections [61] and with acute infectious disorders [62]. *Lactobacillus* GG was found to be effective in both studies in reducing the incidence of AAD in children. Three probiotic preparations (*Lactobacillus* GG, *L. acidophilus* and *B. lactis*; Ferzym, Specchiasol, Milan, Italy) or *Sac. boulardii* were evaluated and compared with placebo for the prevention of side-effects in the treatment of *H. pylori* [19]. In all probiotic-supplemented groups, there was a significantly lower incidence of diarrhoea compared with the placebo group. *Saccharomyces boulardii* has also been investigated for the prevention of AAD in elderly patients [63] and in hospitalized adult patients receiving new prescriptions for β-lactam antimicrobial agents [64]. There was no evidence of a preventive effect of the probiotic in elderly patients. Significantly fewer patients receiving *Sac. boulardii* in the second study developed diarrhoea during β-lactam administration. There were differences in the amount of *Sac. boulardii* used in these two studies with the lowest dose administered to the elderly patients. Furthermore, in the first

Table 3 Double-blind, placebo-controlled studies on the effect of probiotics in the prevention of antibiotic-associated diarrhoea

Probiotic strain	Number of patients	Treatment	Percentage of patients with diarrhoea		*P*-value	Reference
			Active groups	Placebo		
Lactobacillus GG	60	Clarithromycin and tinidazole	3	27	0.04	[16]
Lactobacillus GG	267	Antimicrobial treatment of hospitalized patients	29	30	0.93	[60]
Lactobacillus GG	119	Antimicrobial treatment of acute respiratory infections in children	5	16	0.05	[61]
Lactobacillus GG	188	Children with acute infectious disorders	8	26	0.05	[62]
Lactobacillus GG	85	Clarithromycin and tinidazole	5	30	0.018	[19]
L. acidophilus + *Bifidobacterium lactis*			5			
Saccharomyces boulardii			5			
S. boulardii	69	Antimicrobial treatment of patients >65 years acutely admitted to hospital	21	14	–	[63]
S. boulardii	193	Hospitalized patients receiving β-lactam antibiotics	7	15	0.02	[64]
S. boulardii	180	Antimicrobial treatment of hospitalized patients	9	22	0.038	[65]

study the probiotic was administered throughout the time the patients received the antibiotic whilst the administration continued for 3 days after the discontinuation of antibiotics in the second study. In an earlier study using the higher dose of *Sac. boulardii* that continued for 2 weeks after the last antibiotic dose, the incidence of AAD in hospitalized patients was also shown to be reduced [65].

In several of the studies examinations for growth of *C. difficile* or detection of toxin produced by *C. difficile* have also been performed [60, 61, 63–65]. The groups of patients were in general too small for statistical analyses but the incidence of *C. difficile* was not influenced to any major degree by the treatment with probiotics.

There are three recent reviews available on the prevention of AAD [66–68]. The authors conclude that the results from controlled trials indicate benefits of probiotic administration on diarrhoea but further data are needed.

Conclusions

There seems to be a potential role for the use of probiotics in prevention of AAD. High-risk individuals should be identified and further studies should include safety and cost–benefit analyses [68].

Clostridium difficile-associated diarrhoea

The majority of *C. difficile* infections are induced by antimicrobial agents. The greatest risk occurs during administration of agents that have a great impact on the normal gastrointestinal microflora [59]. The rate of recurrences or reinfections within 2 months after the first episode is estimated to be 15–35% [69]. The ability of *Lactobacillus* GG to prevent recurrences in *Clostridium difficile*-associated diarrhoea (CDAD) has been tested in a few uncontrolled studies and in one trial where the final results have not yet been published [68]. In a small, double-blind, placebo-controlled study, the impact of *L. plantarum* (299V) has been evaluated in the prevention of recurrent episodes of CDAC [70]. Recurrences were seen in four of 11 patients receiving metronidazole and the probiotic strain and in six of nine patients treated with the antimicrobial agent and a placebo product. *Saccharomyces boulardii* has been used in two smaller open trials in the treatment of recurrent *C. difficile* colitis. Eleven of 13 patients treated with vancomycin for 10 days and *Sac. boulardii* for 30 days had no further recurrences [71]. After an outbreak of *C. difficile*-induced colitis amongst patients with renal failures, seven patients suffered from persistent diarrhoea. These patients were treated with *Sac. boulardii* and in five cases the diarrhoea resolved [72]. In two randomized placebo-controlled studies, *Sac. boulardii* has been used in the treatment of patients with active *C. difficile*-associated disease. In the first study, it was shown that a combination of standard antimicrobial treatment and *Sac. boulardii* was effective in patients with recurrent disease (35% compared with 64% recurrence rate in the placebo group) but not in patients with an initial episode of CDAD [73]. The same research group performed the second study in patients with recurrent CDAD in order to control dose and duration of the antimicrobial treatment [74]. A significant decrease in recurrences (17% compared with 50%) was observed in patients treated with vancomycin (2 g day^{-1}) and *Sac. boulardii* but not with a lower dose of vancomycin or with metronidazole.

Conclusions

The few controlled clinical trials performed on the prevention of CDAD indicate that *Sac. boulardii* as an adjunct in the treatment of recurrent CDAD is effective. However, further studies are needed and the pathophysiology and risk factors for CDAD should be identified [68].

Radiation-induced diarrhoea

A common complication in cancer patients treated with radiotherapy is acute diarrhoea [75]. A probiotic preparation, VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD, USA), has been evaluated for the preventive effect in 190 patients who had postoperative radiotherapy after surgery for sigmoid, rectal or cervical cancer [76]. The probiotic product VSL#3 contained strains of *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbruekii* ssp. *bulgaricus*, *B. longum*, *B. breve*, *B. infantis* and *S. salivarius* ssp. *thermophilus*. In the placebo group, 52% of the patients developed diarrhoea compared with 38% of patients receiving VSL#3. Furthermore, patients treated with placebo developed more severe

diarrhoea. A double-blind and placebo-controlled study has been performed to determine the efficacy of *L. rhamnosus* (Antibiophilus®, Germania Pharmazeutika GmbH, Vienna, Austria) compared with a placebo product in the treatment of patients suffering from mild to moderate radiation-induced diarrhoea [77]. Two hundred and five patients with radiation-induced diarrhoea lasting for about 2 weeks before recruitment were included. The group receiving the active probiotic required less and later rescue medication (opioid treatment for pain management expected to induce constipation) compared with the placebo group. The difference between the groups was not statistically significant. The probiotic product showed superior efficacy with respect to the number of bowel movements and faeces consistency.

Conclusions

Results from a few studies indicate that probiotics can be of value in the prevention of radiation-induced diarrhoea and in enhancing the well being of the patients. Further studies are needed for confirmation of these studies.

Diarrhoea in tube-fed patients

Diarrhoea is the most common complication in enteral tube feeding, occurring in 2–63% of patients [78]. The diarrhoea has a range of aetiologies, hypoalbuminaemia and concomitant drug therapy have been implicated. The preventive effect of *Sac. boulardii* on diarrhoea in critically ill tube-fed patients has been assessed in a multicentre study [79]. The study was randomized, double-blind and placebo-controlled. Adult patients who were expected to require enteral nutrition for at least 6 days were included in the study. Diarrhoea occurred in 14% of feeding days in the active group and in 20% of feeding days in the placebo group (OR = 0.71, 95% CI: 0.54–0.95, $P = <0.01$). These findings are in contrast to the results of a study where *L. acidophilus* and *L. bulgaricus* (Lactinex) were used for the prevention of diarrhoea in patients that were tube-fed <5 days [80]. The administration of lactobacilli did not alter the risk of diarrhoea. However, in this study only the incidence of diarrhoea was measured and the influence by the length of the monitoring period was not adjusted for [78].

Conclusions

Current evidence for support of probiotics in the prevention of enteral tube-feeding diarrhoea has been regarded as insufficient and additional studies are warranted.

Inflammatory bowel diseases

The gastrointestinal microflora has been suggested to be involved in the pathogenesis of inflammatory bowel diseases in genetically predisposed subjects with immunological disregulation [81]. The number of microorganisms are increased and changes in the composition of the flora have also been observed [82]. Interactions between the commensal microflora and the intestinal mucosa stimulate the inflammatory activity [1]. Table 4 summarizes the results from clinical trials on the effect of probiotics on inflammatory bowel diseases.

Crohn's disease

Crohn's disease is characterized by transmural inflammation that can affect any part of the gastrointestinal tract [83]. Conventional treatment is directed at modification of the host response but manipulation of the intestinal microflora is regarded as another option. A placebo-controlled study has been performed in order to evaluate the preventive effect of *Lactobacillus* GG on appearance of recurrent lesions of Crohn's disease after surgery [84]. The impact on the severity of lesions was also evaluated. At the end of 1 year, there were no statistically significant differences between the patients regarding endoscopic recurrence or severity of recurrent lesions. A combination of three *Bifidobacterium* species, four *Lactobacillus* species and *S. salivarius* ssp. *thermophilus* (VSL#3, VSL Pharmaceuticals) has been evaluated in a single-blind study for the prevention of recurrent inflammation after surgery [85]. The patients either received a nonabsorbable antibiotic (rifaximin) for 3 months followed by 9 months intake of the probiotic or mesalazine for 12 months. After 1 year there was a significantly lower rate of severe endoscopic recurrence in patients treated with the antibiotic and probiotic combination. Patients with active colonic Crohn's disease were treated with prednisolone on a standard schedule and were also

Table 4 Clinical studies on the effect of probiotics on inflammatory bowel diseases

Probiotic strain/treatment in the placebo group	Study design	Number of patients	Treatment period (week)	Inclusion criteria	Comments and results	Reference
Lactobacillus GG	DBPC	45	52	Resected patients with Crohn's disease	No preventive effect ($P = 0.297$)	[84]
VSL#3/mesalazine	SBPC	40	52	Resected patients with Crohn's disease	Initial rifaximin treatment-active group, 20 vs. 40% endoscopic recurrence ($P < 0.01$)	[85]
Escherichia coli Nissle 1917/prednisolone	DBPC	28	52	Colonic active Crohn's disease	Initial prednisolone treatment, reduced risk for relapse 33 vs. 64%	[86]
Saccharomyces boulardii/mesalamine three times daily	PC	32	28	Patients in clinical remission of Crohn's disease	Mesalamine twice daily-active group, reduced risk for relapse 6 vs. 38% ($P = 0.04$)	[87]
Bifidobacterium breve *B. bifidum* *L. acidophilus* YIT 0168/treatment according to routines	PC	21	52	Ulcerative colitis	Treatment according to routines, reduced frequency of relapses 27 vs. 90% ($P = 0.018$) not confirmed endoscopically	[89]
E. coli Nissle 1917/ mesalazine	DBPC	103	12	Inactive ulcerative colitis	Relapse rate 16 vs. 11%	[90]
E. coli Nissle 1917/ mesalazine	DBPC	116	52	Active ulcerative colitis	All patients treated initially with 1-week course of gentamicin, relapse rate 67 vs. 73%	[91]
Lactobacillus GG	DBPC	20	12	History of pouchitis and endoscopic inflammation	No effect on clinical or endoscopic response	[92]
VSL#3	DBPC	40	36	Clinical and endoscopic remission of chronic pouchitis	Relapse rate 15 vs. 100% ($P < 0.001$)	[93]
VSL#3	DBPC	36	52	Antibiotic-induced remission of pouchitis	Remission maintained in 85 vs. 6% ($P < 0.0001$)	[94]
VSL#3	DBPC	40	52	Patients with ileal pouch-anal anastomosis	Normal pouch in 90 vs. 60% after 1 year ($P < 0.05$)	[95]

DB, double-blind; SB, single-blind; PC, placebo-controlled; VSL#3, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L. delbrueckii* ssp. *bulgaricus*, *L. casei*, *L. plantarum*, *S. salivarius* ssp. *thermophilus*.

randomized to receive *E. coli* (Nissle 1917) or placebo for 1 year [86]. Patients in the two groups had similar rates of remission but patients treated with prednisolone and *E. coli* had fewer relapses than patients in the placebo group. The difference was not statistically significant. Patients with Crohn's disease in clinical remission have been randomly treated with mesalamine (3 g daily) or with mesalamine (2 g daily) plus a preparation of *Sac. boulardii* [87]. Clinical relapses at 6 months were observed in one of 16 patients in the supplemented group and in six of 16 patients in the mesalamine group ($P = 0.04$).

Conclusions

Further studies are needed on the effect of probiotics in maintenance of remission in Crohn's disease and it has been recommended that future studies should attempt to distinguish between colonic Crohn's disease and disease with ileal involvement [88].

Ulcerative colitis

A product (BFM, Yakult Co. Ltd, Tokyo, Japan) containing *B. breve*, *B. bifidum* and *L. acidophilus* YIT 0168 has been evaluated as a dietary adjunct in the

treatment of ulcerative colitis [89]. During the 1-year duration of the study, exacerbation of symptoms occurred in three of 11 patients in the supplemented group and in nine of 10 patients in the placebo group but no difference was seen in the colonoscopic findings. In two studies, a nonpathogenic strain of *E. coli* (Nissle 1917) has been compared with mesalazine in the efficacy of maintaining remission of ulcerative colitis [90, 91]. The study by Kruis *et al.* [90] was performed in a double-blind fashion on 103 patients during 12 weeks. Relapse rates were 11% for mesalazine and 16% for *E. coli*. A similar methodology was used in the second study but all patients were also given a 1-week initial course of gentamicin. Here, the relapse rates were 73% in the mesalazine group and 67% in the *E. coli* group during 1 year.

Conclusions

The evidence for the benefits of probiotics for maintenance therapy for ulcerative colitis is still regarded as weak since the effect is comparable with the effect of placebo observed in earlier studies [88].

Pouchitis

Pouchitis is a nonspecific inflammation of the ileal reservoir after ileal-anal anastomosis for ulcerative colitis [88]. Disturbances in the intestinal microflora have been implicated as a triggering factor in the pathogenesis. Patients with endoscopic and histological signs of inflammation of the pouch mucosa were included in a double-blind study on the effects of *Lactobacillus* GG [92]. *Lactobacillus* GG induced changes in the pouch microflora (increased ratio of total faecal lactobacilli: total anaerobes) but was inefficient as primary therapy for the clinical improvement of pouch inflammation. The probiotic preparation VSL#3 has been evaluated for the efficacy in maintaining remission of pouchitis [93, 94] and for prevention of onset of acute pouchitis during the first year after ileal pouch-anal anastomosis [95]. All subjects in the placebo group ($n = 20$) of the first study had relapses whilst 85% of patients (17 of 20) treated with VSL#3 were still in remission after 9 months [93]. Similar results were obtained in the second study where remission was maintained at 1 year in one patient in the placebo group (one of 16) and in 17 of 20 patients in the VSL#3-treated group [94]. Treatment with VSL#3 was considered effective also in the prevention of acute pouchitis after surgery [95]. Eight of 20 patients treated with placebo and two of 20 treated with the probiotic product had an episode of acute pouchitis within 1 year.

Conclusions

The literature on the role of probiotics in the treatment of pouchitis is still regarded as limited and it has been recommended that further studies should use stricter defined entry criteria [88].

Irritable bowel syndrome

The irritable bowel syndrome (IBS), is a functional bowel disorder characterized by symptoms of abdominal pain or discomfort that is associated with disturbed defecation [96]. The prevalence amongst adults in the United States is 12% [97] and is of similar order in other Western countries [96]. There is evidence suggesting that the intestinal microflora of patients with IBS differs from that of healthy subjects and that the patients have an abnormal fermentation of food residues, which may have a potential role in the aetiology of IBS [98]. There are several trials performed on the effect of probiotics in patients suffering from IBS. Halpern *et al.* [99] performed a crossover study using a heat-killed strain (strain LB) of *L. acidophilus*. Eighteen patients were evaluated using a questionnaire and received treatment with the probiotic or placebo for 6 weeks, followed by a 2-week washout period and a new 6-week treatment period. The authors concluded that the product demonstrated a statistically significant therapeutic benefit in 50% of the patients. A fruit-drink containing *L. plantarum* (299V) has been assessed in 40 patients during 4 weeks [100]. All patients treated with the active product experienced resolution of abdominal pain. Improvement concerning the overall IBS symptoms was observed in 95% of patients in the lactobacilli group vs. 15% of patients in the placebo group. The same strain was given in a rose-hip drink during 6 weeks to patients with IBS [101]. The 52 patients fulfilled the Rome criteria [102] and were recording their gastrointes-

tinal symptoms throughout the study and again 12 months after the end of the study. Flatulence was reduced in the test group whilst abdominal pain was reduced in both groups. In patients in the test group, improvement in gastrointestinal function remained 12 months later. *Lactobacillus plantarum* (299V) has also been evaluated for the effect on colonic fermentation in patients with IBS according to the Rome criteria [103]. Six weeks of treatment did not alter colonic fermentation or improve symptoms. Nineteen patients with clinical diagnosis of IBS compatible with the Rome criteria were recruited to a crossover study (8-week double-blind treatment, 2-week washout period and a final 8-week double-blind treatment) [104]. The *Lactobacillus* GG strain was used as treatment but did not significantly improve symptoms in the patient group studied.

Conclusions

It has been pointed out that the reported effect of placebos has been as high as 50% in some trials with a salutary effect appearing for at least 3 months in some patients with IBS [97]. Therefore, it is of great importance that studies performed on this group of patients are placebo-controlled. Furthermore, different inclusion criteria have been used in the performed studies and the patients have been rather heterogeneous. The results must be considered as inconclusive. There is a need for further studies on the effect of probiotics on IBS and it would be of great value if the study designs include a long-term follow-up of the patients [105].

General conclusions

A pharmacological approach for assessing the effect, the pharmacokinetic and pharmacodynamic properties of probiotics has been advocated [106]. Live microbial strains that are intended for use in foods should be well identified by genotypic and phenotypic methods. They should also be functionally characterized and assessed for safety. Adherence properties, production of toxins and antimicrobial resistance are some important qualities that should be evaluated. Furthermore, translocation and permanent colonization are characteristics that most urgently need to be studied [107]. With the above requirements fulfilled, further placebo-controlled clinical trials are warranted. Promising but inconclusive results have been achieved with probiotics for prevention and treatment of a number of gastrointestinal conditions. In several investigations on the treatment of *H. pylori*, probiotics have been shown to have suppressive effect but in other studies no effects have been observed. The results of studies on probiotics for prevention of acute gastroenteritis have not been decisive whilst some probiotic strains used in the treatment of gastroenteritis in children shorten the duration of diarrhoea, however, modestly. Probiotics seem to have a potential role also in the prevention and treatment of AAD and CDAD. However, conflicting results have been observed in that the same strain has yielded dissimilar effects in different studies. The evidence for a role of probiotics in the prevention of radiation-induced diarrhoea, diarrhoea in tube-fed patients, in inflammatory bowel diseases and in IBS is regarded as insufficient.

Conflict of interest statement

No conflict of interest was declared.

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