Chapter 2

Probiotics: A Comprehensive Review of Their Classification, Mode of Action and Role in Human Nutrition

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Additional information is available at the end of the chapter

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Abstract

Probiotics are live microorganisms that live in gastrointestinal (GI) tract and are beneficial for their hosts and prevent certain diseases. In this chapter, after a complete introduction to probiotics, definition, mechanism of action, and their classification, currently used organisms will be discussed in detail. Moreover, different kinds of nutritional synthetic products of probiotics along with their safety and drug interaction will be noticed. This chapter mentions all clinical trial studies that have been done to evaluate probiotic efficacy with a focus on gastrointestinal diseases.

In the end, findings of our pilot study regarding the effect of probiotic on Small Intestinal Bacterial Overgrowth (SIBO) will be presented. The nutritional effects of Probiotics on a host's health will be collected and their usage criteria will be discussed. Some suggestions for the Probiotics daily consumption will be presented and the follow-up for their new adverse reaction will be emphasized, if any.

Keywords: probiotics, gastrointestinal (GI) tract, nutrition, related disorders, probiotic products

1. Introduction to probiotics

The term probiotic is derived from Greek and literally means "for life." It was first coined in 1965 by Lilley and Stillwell to describe substances secreted by one microorganism that stimulate the growth of another [1, 2]. In 1974, Parker modified this definition to "…organisms

and substances which contribute to intestinal microbial balance" [1, 3]. The current definition of probiotics by Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) is "live microorganisms which when administered in adequate amounts confer a health benefit to the host" [4–6]. Probiotic organisms require certain characteristics to enable them to exert maximum therapeutic effects. Of these characteristics, there are some that are considered almost essential for a probiotic to have therapeutic effects, including gastric acid and bile salt stability, ability to adhere to the intestinal mucosa, and ability to colonize the intestinal tract [1, 7].

2. Mechanism of action

The exact mechanisms by which probiotics accomplish their beneficial actions have not been well documented. However, there are several postulated mechanisms that explain many of their favorable effects [8] (**Figure 1**).

One of such mechanisms is a competition for adhesion sites, which means probiotics fight for cellular attachments. Many pathogenic organisms must associate with the GI tract epithelium to colonize effectively [9]. However, some strains of bifidobacteria and lactobacilli can adhere to the epithelium and act as "colonization barriers" by preventing pathogens from adhering to the mucosa [1, 10]. This effect was demonstrated with the *Lactobacillus rhamnosus* strain GG and *Lactobacillus plantarum* 299v. Both of these organisms showed the ability to inhibit attachment of *Escherichia coli* to human colon cells [1, 11].

Another possible mechanism of action is the modification of the microbial flora through the synthesis of antimicrobial compounds [12]. Many types of lactobacilli and bifidobacteria produce bacteriocinsor and other antimicrobial compounds. Bacteriocins are defined as "compounds produced by bacteria that have a biologically active protein moiety and a bactericidal action" [1, 13]. Other biologically active compounds produced by lactic acid bacteria include hydrogen peroxide, diacetyl, and short-chain fatty acids. The release of these compounds by probiotic organisms results in a beneficial modification of the microflora [1, 14]. However, not all strains of lactobacilli or bifidobacteria produce antimicrobial compounds, and some produce compounds that are fairly nonspecific in their activity, so that beneficial bacteria, as well as pathogenic organisms, may be negatively affected [1].

It has also been observed that probiotics can stimulate the immune response [15]. This immune response may take the form of increased secretion of immunoglobulin-A (IgA) [1, 16], elevated numbers of natural killer cells, or enhanced phagocytic activity of macrophages [1, 17]. Increased secretion of IgA may decrease numbers of pathogenic organisms in the gut, thus improving the composition of the microflora [1, 10]. Due to these immunomodulating effects, some researchers think probiotics might not only fight intestinal and urogenital pathogens, but might also be helpful for conditions, such as inflammatory bowel disease (IBD), pouchitis, food allergy, and for use as an adjuvant to vaccination [18–22]. Probiotics may also compete for nutrients that would otherwise be utilized by pathogens [1, 23]. This situation occurs with *Clostridium difficile*, a potentially pathogenic organism that is dependent upon monosacchar-

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ides for its growth. Probiotic organisms in sufficient numbers can utilize most of the available monosaccharides, which results in the inhibition of *C. difficile* [1, 24].

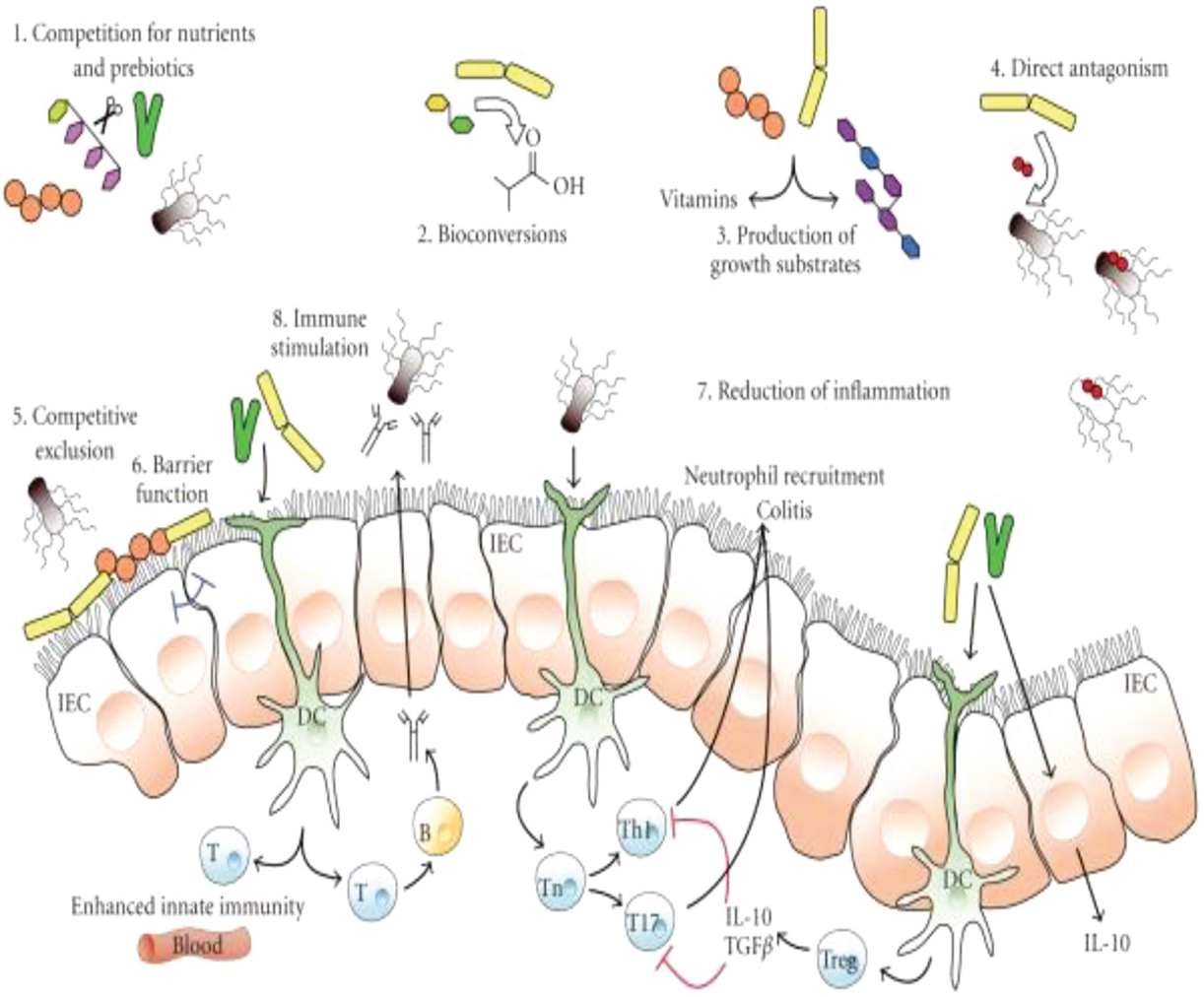

Figure 1. Schematic diagram illustrating potential or known mechanisms whereby probiotic bacteria might impact on the microbiota. These mechanisms include (1) competition for dietary ingredients as growth substrates, (2) bioconversion of, for example, sugars into fermentation products with inhibitory properties, (3) production of growth substrates, for example, EPS or vitamins, for other bacteria, (4)direct antagonism by bacteriocins, (5) competitive exclusion for binding sites, (6) improved barrier function, (7) reduction of inflammation, thus altering intestinal properties for colonization and persistence within, and (8) stimulation of innate immune response (by unknown mechanisms). IEC : intra epithelial cells, DC: dendritic cells, T:T-cells.

3. Classification

There are many different microorganisms currently used as probiotics [1, 20, 25] (**Table 1**). To better understand how bacteria are named and classified, the following discussion may be helpful. Genus is the first name of a bacterium (e.g., *Lactobacillus*). It is somewhat general and

refers to a grouping of organisms based on similarity of qualities, such as physical characteristics, metabolic needs, and metabolic end products.

Species is a bacterium's second name (e.g., *acidophilus*). It is a much more narrow classification based on shared common characteristics that distinguish them from other species. Strain is an even more specific classification that divides members of the same species into subgroups based on several properties that these bacteria have in common that are distinct from other members of the species (e.g., strain LA5) [1, 26].

Lactobacillus spp.	acidophilus
	plantarum
	rhamnosus
	paracasei
	fermentum
	reuteri
	johnsonii
	brevis
	casei
	lactis
	delbrueckii gasseri
Bifidobacterium spp.	Breve
	infantis
	longum
	bifidum
	thermophilum
	adolescentis
	animalis
	lactis
Bacillus spp.	coagulans
Streptococcus spp.	thermophilus
Enterococcus spp.	faecium
Saccharomyces spp.	cerevisiae

Table 1. Common probiotic microorganisms.

3.1. Lactobacillus species

Lactobacillus refers to a group of lactic acid–producing Gram-positive rods that are obligate and facultative anaerobes in the human gastrointestinal and genitourinary tracts [27, 29–32]. The name lactobacillus refers to the bacterium's ability to produce lactic acid, not to the ability to digest lactose [28]. Lactobacilli are used therapeutically as probiotics, the opposite of antibiotics. They are considered "friendly" bacteria and are taken for the purpose of recolonizing areas of the body to provide nutritional benefits including inducing growth factors and

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increasing the bioavailability of minerals [32]. Lactobacilli also stabilize the mucosal barrier and decrease intestinal permeability [33].

Altering the normal flora allows for potential colonization by pathogenic organisms [34], which can result in side effects, such as diarrhea, cramping, and less commonly pseudomembranous colitis (PMC), caused by *C. difficile*. The theory is that taking lactobacillus probiotics during antibiotic treatment can prevent or minimize normal flora depletion and pathogenic bacteria colonization. There is some evidence to support this theory [35, 36]. Hydrogen peroxide–producing lactobacilli are bactericidal to the vaginal pathogen *Gardnerella vaginalis*, and their presence in the vagina has been associated with decreased frequencies of bacterial vaginosis and trichomoniasis [37]. In the vagina, lactic acid from lactobacilli lowers vaginal pH, which can prevent pathogen growth.

There is some preliminary evidence that lactobacilli and other probiotics might help protect against cancer. In animal models, lactobacillus has been shown to bind dietary carcinogens [38] and decrease development of tumors in the colon after carcinogen challenge [39, 40]. Preliminary research also suggests that lactobacilli, especially *L. plantarum*, can reduce the severity of chemotherapy-induced enterocolitis [41]. According to other research studies, *Lactobacillus bulgaricus* and *Lactobacillus sporogenes* might have hypolipidemic and antiatherosclerotic effects. Limited clinical evidence suggests that it can reduce total and low-density lipoprotein (LDL) cholesterol with no effect on high-density lipoprotein (HDL) [42, 43]. Fermented dairy products, such as yogurt and acidophilus milk, also seem to have a beneficial effect on cholesterol. Lactobacilli and other probiotic bacteria seem to bind bile acids to cholesterol. They also seem to increase fatty acid production in the intestine, which decreases circulatory fatty acid concentrations either by inhibiting hepatic cholesterol synthesis or redistributing cholesterol from the plasma to the liver.

Most researchers agree that the effectiveness of lactobacilli and other probiotics for all indications depends on their ability to colonize an area of tissue. To do this, lactobacillus preparations must contain live and viable organisms. Products stored for long periods of time or stored improperly may contain few live and active organisms. For oral preparations, bacteria must also remain viable after passing through the gut, and then they must be able to latch on to the intestinal epithelium. Lactobacilli strains might vary in their effectiveness due to differences in their ability to adhere to the epithelial cells by host factors such as hormone levels [30, 44, 45]. This ability can change during a woman's menstrual cycle in response to changing hormone levels. In postmenopausal women, correcting low estrogen levels can help restore lactobacillus colonization without supplementation [29, 30].

3.2. Bifidobacterium species

Bifidobacterium is an anaerobic, Gram-positive, nonspore-forming, pleomorphic rod. Bacteria in the *Bifidobacterium* genus produce lactic and acetic acids as by-products of glucose utilization. BB536 is a type of probiotic bacteria, which, according to secondary sources, was first isolated from the intestinal tract of healthy infants. Bifidobacteria, in combination with *Lactobacillus* species and the probiotic yeast *Saccharomyces boulardii*, seem to reduce the adverse effects of *Helicobacter therapy*, but do not seem to improve compliance [46]. In addition,

Bifidobacterium infantis in combination with *Lactobacillus acidophilus* seems to reduce the incidence of NEC and NEC-associated mortality in critically ill neonates [47].

3.3. Bacillus species

Bacillus coagulans is a Gram-positive rod, which produces lactic acid, and therefore is often misclassified as lactic acid bacteria, such as lactobacillus. In fact, some commercial products containing *B. coagulans* are marketed as *Lactobacillus sporogenes* or "spore-forming lactic acid bacterium." It forms spores, which is an important factor in differentiating these species. *B. coagulans* is used therapeutically in a similar manner as other probiotics such as lactobacillus and bifidobacterium; however, *B. coagulans* is not a component of the normal human flora. In order to be effective for restoring normal flora and prevent pathogenic colonization, probiotics must have the ability to persist and colonize in the intestinal mucosa. When the Bacillus spore is ingested by humans, it is unknown what happens to the spore. It is unknown if the Bacillus spore is capable of germinating in the intestinal tract or if colonization occurs [48].

B. coagulans might reduce pathogenic bacteria colonization through several mechanisms. *B. coagulans* produces coagulin and lactic acid, which have antibacterial activity and might reduce pathogenic bacteria growth through this mechanism [29, 49, 50]. Animal model research also suggests that ingesting bacillus spores increases immune response [48]. Proponents of *B. coagulans* suggest that this species of probiotics offers advantages over others such as lactobacillus because Bacillus species can be stored indefinitely in desiccated forms [48]. Bacillus spores are also resistant to high temperatures and to acid.

3.4. *Saccharomyces* spp.

S. boulardii, also known as *Saccharomyces cerevisiae*, is a nonpathogenic yeast strain that has been used for the treatment and prevention of diarrhea resulting from multiple etiologies. *S. boulardii* has been isolated from the skins of tropical fruits found in Indochina. The indigenous population of Indochina has long used these fruit skins to prevent and treat diarrhea [51].

S. boulardii is prepared by lyophylization (freeze drying) of live yeast organisms and encapsulation using lactose in the preparation. *S. boulardii* cannot be distinguished from other *S. cerevisiae* strains by phenotypic criteria, so identification of these infections requires molecular typing. Comparative molecular studies show that *S. boulardii* is genetically very close or nearly identical to *S. cerevisiae* [52]. Results suggest that microsatellite polymorphism analysis of the YKL139w and YLR177w genes and the analysis by Ty917 hybridization are the most useful tools for the correct identification of *S. boulardii* strains [53]. However, metabolically and physiologically, *S. boulardii* shows a very different behavior than *S. cerevisiae*, particularly in relation to growth yield and resistance to temperature and acidic stresses, which are important characteristics for a microorganism to be used as a probiotic. The German Commission E monograph lists *S. boulardii* as *S. cerevisiae* Hansen CBS 5926.

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4. Commercial forms

There are two main forms in which probiotic organisms can be ingested—fermented foods and supplements. Fermented foods can be of both dairy and vegetable origin, with the most commonly known of each being yogurt and sauerkraut, respectively. Probiotic supplements consist of freeze-dried (lyophilized) bacteria in powder, capsule, or tablet form. Regardless of the form in which the microorganisms are consumed, for clinical efficacy, products containing probiotic organisms must provide live organisms in sufficient numbers to exert therapeutic effects. Both types of fermented foods and supplements are able to do this. Pros (advantage) and cons (disadvantage) of common probiotic delivery systems are compared [1] (**Table 2**).

Delivery system	Pros	Cons
Fermented dairy	-Affordability and easy Availability -Ease of incorporation into daily patterns -Additional nutritional benefits -Enhanced bacterial survival through upper GI tract (100× less bacteria can be given per dose) -Effective in the upper GI tract	-Contains dairy proteins and lactose -Taste can be issue -Not suitable when travelling -Not suitable for vegans
Capsules	-Ease of administration -Contain no binders	-Not therapeutic in upper GI tract (unless opened or chewed) -May contain allergenic excipients -Higher cost
Tablets	-Ease of administration -Effective in the upper GI tract	-May contain allergenic or otherwise problematic binders and excipients (e.g., gluten) -Higher cost
Powders	-Effective in the upper GI tract -Dosages can be easily adjusted -Can be incorporated into foods or drinks -Contain no binders	

Table 2. The pros and cons of different probiotic delivery systems.

4.1. Using the right strain

To achieve successful and reproducible clinical outcomes, it is imperative to use the exact probiotic strain that has been proven to have the specific therapeutic action that is desired. For example, *L. rhamnosus* GG was found to prevent viral gastroenteritis [1, 54] and maintain ulcerative colitis in remission [1, 55]. Other strains of *L. rhamnosus* cannot be assumed to act in a similar manner. The clinician who chooses to use the exact strain that had the effects in clinical

trials can be confident of similar results. Using another closely related strain may or may not have any effect. Whenever possible, use the exact strain used in research, as other strains, even closely related ones, may not have the same effects [1].

4.2. Dosage

The dosage of probiotic foods and supplements is based solely upon the number of live organisms present in the product. Successful results have been attained in clinical trials using between $10^7$and 10^{11} viable bacteria per day [1, 56, 57]. Interestingly, it appears that 100 times fewer viable bacteria need to be given in a dairy medium than in a freeze-dried supplement to achieve similar numbers of live bacteria in the lower bowel [1, 58]. Dairy appears to work as an ideal transport medium for the bacteria, enhancing their survival through the upper GI tract [1, 59].

4.2. Safety and adverse reactions

While probiotics are used widely and adverse effects are uncommon, there is no systematic reporting system for probiotics. Most studies did not report a statistically significant increase in adverse events compared with controls, but it has been questioned if probiotics are safe in immunosuppressed individuals [60]. There are isolated case reports of bacteremia with Lactobacillus and fungemia with *S. boulardii*. A case-review study found sepsis, liver abscess, and endocarditis from *Lactobacillus GG* to occur mostly in patients with severe illness [61]. The same paper reviewed *S. boulardii* fungemia and found numerous cases, some related to ingestion of *S. boulardii*, but others resulting from suspected contamination of central lines when the product capsules were opened, and the lyophilized yeast was allowed to become airborne. Again, most, but not all, cases were in immunosuppressed individuals [60, 62]. Two systematic reviews and an Agency for Healthcare Research and Quality study have evaluated the safety of probiotics and concluded that adverse effects are uncommon, but serious infections with *Lactobacilli or S. boulardii* can occur [63, 64]. Given this conclusion, it is prudent to avoid probiotics in individuals who are immunosuppressed or severely ill.

4.3. Drug interaction

Lactobacilli and bifidobacteria are negatively affected by alcohol and antibiotics [1, 65]. Although there is no evidence that the organism interferes with the activity of most antibiotics, the metabolism of sulfasalazine, chloramphenicol palmitate, and phthalylsulfathiazole may be affected by some strains of *L. acidophilus* [1, 66].

4.4. Clinical studies of probiotics

Table 3 lists conditions for which probiotics have been studied in more than 800 randomized, controlled clinical trials (RCT) [4]. It is notable that there has been at least one clinical trial in a variety of clinical conditions. GI tract conditions, such as inflammatory illnesses (e.g., inflammatory bowel diseases or necrotizing enterocolitis in neonates) or enteric infections, have been studied most often [4, 67].

Abdominal conditions

Acute amebiasis

Acute pancreatitis

Alcoholic liver injury

Collagenous colitis

Constipation

Colorectal neoplasia prevention

Diverticular colonic disease

Gas and bloating

Gastrointestinal transit time
and gastric emptying

Gastrointestinal symptoms
after loop ileostomy reversal

Helicobacter pylori infection

Hematochezia in breastfed infants
and in presumed infant allergic colitis

Hepatic encephalopathy

Infant colic

Inflammatory bowel diseases
(Crohn's disease, ulcerative colitis, pouchitis)

Irritable bowel syndrome (IBS)

Lactose intolerance

Nonalcoholic steatohepatitis

NSAID-induced small bowel injury

Prevention and treatment of pediatric cow's milk allergy

Prevention and treatment of
diarrheal diseases (infectious and noninfectious)

Prevention of antibiotic-associated diarrhea (AAD)

Prevention of necrotizing enterocolitis (NEC)

Primary sclerosing cholangitis (PSC) in patients with IBD

Small intestinal bacterial overgrowth (SIBO)

Tolerance of enteral feeds in ICU patients

Viral shedding

Oral and respiratory tract conditions

Gingivitis

Dental caries

Halitosis

Prevention of upper respiratory tract infections (URTI)

Pulmonary exacerbations in cystic fibrosis (CF)

Urinary and reproductive tract conditions

Prevention and treatment of bacterial vaginosis and fungal vulvovaginosis

Prevention of preterm deliveries associated with bacterial vaginosis

Recurrent urinary tract infections (UTI)

Recurrent bladder cancer

Allergic or skin conditions

Atopic dermatitis

Allergic rhinitis and rhinosinusitis

Allergic asthma

Cutaneous viral warts

Prevention and treatment of pediatric eczema

Skin burns

Other

Acute otitis media

Chronic kidney disease

Effect on infant mortality in preterm infants

Effect on CD4 count in patients with HIV

Estrogen metabolism

Fasting glucose, insulin sensitivity, and glucose control in diabetic patients

Hyperlipidemia

Hypertension

Infant blood pressure and metabolic profile from mothers treated with probiotics

Inhibition of nasal, oral, or fecal colonization with pathogenic bacteria

Markers of metabolic syndrome and cardiovascular disease

Mastitis

Pediatric otitis media

Pregnancy after *in vitro* fertilization (IVF)
Prevention and treatment of gestational diabetes
Prevention of type-1 diabetes mellitus
Prevention of infections in preterm infants, infants, and young children
Prevention of nosocomial infections in ICUs
Prevention of infections in the postoperative setting
Prevention of skeletal muscle damage under oxidative stress
Psychological distress, mood, and cognition
Reduction of biologically active aflatoxin
Rheumatoid arthritis (RA)
Spondyloarthropathy
Urinary oxalate excretion (risk factor for nephrolithiasis)
Vaccine-specific antibody development
Waist circumference and obesity

Table 3. Clinical conditions or settings studied in randomized, controlled clinical trials to evaluate probiotic efficacy.

Indication	**Efficacy and quality of evidence**
Infectious diarrhea	
Prevention	Moderate
Treatment	High
Traveler's diarrhea prevention	Moderate
Antibiotic-associated diarrhea prevention	High
Clostridium difficile infection (CDI)	
Prevention	Moderate
Treatment	None
Recurrent CDI treatment	Low to moderate
IBD	
UC treatment	Moderate
Pouchitis treatment and prevention	High
Crohn's disease treatment	Low
IBS treatment	Moderate

Table 4. Indications, efficacy, and quality of evidence for probiotics in GI diseases.

4.5. Efficacy in GI diseases

An ambitious meta-analysis of 11 species of probiotics evaluated their efficacy in the prevention and/or treatment of eight major GI tract diseases and concluded that there was efficacy in treatment of infectious diarrhea, antibiotic-associated diarrhea (AAD), *C. difficile* infection (CDI), *Helicobacter pylori* eradication, IBS, and pouchitis; there was a lack of efficacy for traveler's diarrhea (TD) and necrotizing enterocolitis (NEC) [60, 68]. Some of these results conflict with meta-analyses of individual diseases, and results of all studies should be interpreted with caution. Rigorous blinded RCTs of specific probiotics are needed to provide robust data on efficacy, adverse events, and cost benefit before widespread use can be recommended for many products on an evidence-based approach (**Table 4**);despite the lack of data, these products are widely used [60].

5. A pilot study to evaluate the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO)

Generally, small intestinal bacterial overgrowth (SIBO) can be the result of a change in the clinical condition which has altered the pH and the bowel movements. In addition, immune deficiency and malnutrition are the other risk factors accompanying it [69, 70]. SIBO can leads to steatorrhea, vitamin B12-absorptive impairment, injury to the small intestinal microvilli, which itself causes malabsorption, coma, neurological deficit, and acidosis-induced shock [70]. SIBO has also been proposed to be a common causative factor in the pathogenesis of irritable bowel syndrome (IBS) [71]. The diagnosis of this syndrome is made by hydrogen breath test (HBT) [71, 72].

This study was performed on the patients with chronic stomach pain and discomfort or changes in their defecation, who were referred to the Infectious and Internal Diseases Clinics of Quaem Hospital, Mashhad, Iran, from May 2010 to October 2011 [73]. The study protocol was approved by the Research Council Ethics Committee of Mashhad University of Medical Sciences. Accordingly, the diagnosis was confirmed by hydrogen breath test (HBT) after obtaining informed written consent. Thirty consecutive cases with a positive test result were included in the study and were randomized in a double-blind manner into two groups: probiotic drug user and control group. After an initial 3-week aggressive therapy with broad-spectrum antibiotics, a 15-day maintenance antibiotic therapy with minocycline, 100 mg twice a day, and 15 days with a probiotic (named Lactol), including *Bacillus coagulan* spores and fructo-oligosaccharides (Bioplus Life Sciences Pvt. Ltd., India), twice a day after meals, were administered for the study group, and the same regimen without probiotic for the control group. After 6 months, the HBT result and the GI symptoms were analyzed and compared between the two groups.

As presented in the following tables, the number of patients with complaints of bloating, belching and diarrhea was remarkably less in the patients receiving a probiotic in comparison to controls (**Tables 5** and **6**). In spite of the aggressive and maintenance treatments adminis-

tered for all the cases, 93.3% patients showed negative result of the HBT at the end of treatment in the study group compared to 66.7% in the control group, showing the effectiveness of the probiotic treatment. As an additional finding, 33.3% patients of the study group and 53.3% of the controls had a Bachelor degree or higher education, with no significant difference [75–79].

Parameter	Study group	Control group	Total
Gender(M/F)			
Male	8 (53.3)	7 (46.7)	15(50.0)
Female	7 (46.7)	8 (53.3)	15(50.0)
Age (years)	34.60 ± 10.68	42.86 ± 16.61	38.73 ± 14.35
Location of pain			
Epigastric	8 (53.3)	5 (33.3)	13 (43.3)
Umbilical	6 (40.0)	6 (40.0)	12 (40.0)
Other sites	1 (6.7)	4 (26.7)	5 (16.7)
Flatulence			
Yes	6 (40.0)	11 (73.3)	17 (56.7)
No	9 (60.0)	4 (26.7)	13 (43.3)
Belching			
Yes	9 (60.0)	10 (66.7)	19 (63.3)
No	6 (40.0)	5 (33.3)	11 (36.7)
Nausea			
Yes	3 (20.0)	3(20.0)	6 (20.0)
No	12 (80.0)	12(80.0)	24 (80.0)
Vomiting			
Yes	4 (26.7)	3 (20.0)	7 (23.3)
No	11 (73.3)	12(80.0)	23 (77.7)
Constipation			
Yes	9 (60.0)	3 (20.0)	12 (40.0)
No	6 (40.0)	12 (80.0)	18 (60.0)
Diarrhea			
Yes	2 (13.3)	8 (53.3)	10 (33.3)
No	13 (86.7)	7 (46.7)	20 (66.7)
Loss of appetite			
Yes	6(40.0)	5 (33.3)	11 (36.7)
No	9(60.0)	10 (66.7)	19 (63.3)

Table 5. Clinical characteristics of subjects at baseline (values in parentheses are percentages).

In conclusion, the results of this pilot study showed that addition of a probiotic to the maintenance regimen may improve the GI tract symptoms and prevent the probable complications in patients with SIBO. Therefore, based on low side effects of the probiotics, it seems that their long-term prescription in SIBO, considering the recurrence favor of this syndrome, is desirable (e.g., probiotic containing dairy products or supplement daily drugs).

Parameter	Study group	Control group	Total	P value
Location of pain				
Epigastric	0 (0.0)	3 (20.0)	3 (10.0)	0.002
Umbilical	0 (0.0)	3 (20.0)	3 (10.0)	
Other sites	0 (0.0)	2 (13.3)	2 (6.7)	
Without pain	15 (100.0)	7 (46.7)	22 (73.3)	
Flatulence				
Yes	2 (13.3)	8 (53.3)	10 (33.3)	0.049
No	13 (86.7)	7 (46.7)	20 (66.7)	
Belching				
Yes	3 (20.0)	9 (60.0)	12 (40.0)	0.025
No	12 (80.0)	6 (40.0)	18 (60.0)	
Nausea				
Yes	0 (0.0)	1 (6.7)	1 (3.3)	0.999
No	15 (100.0)	14 (93.3)	29 (96.7)	
Vomiting				
Yes	1 (6.7)	1 (6.7)	2(6.7)	0.999
No	14 (93.3)	14 (93.3)	28 (93.3)	
Constipation				
Yes	1 (6.7)	2 (13.3)	3 (10.0)	0.999
No	14 (93.3)	13 (86.7)	27 (90.0)	
Diarrhea				
Yes	1 (6.7)	8 (53.3)	9 (30.0)	0.014
No	14 (93.3)	7 (46.7)	21 (70.0)	
Loss of appetite				
Yes	1 (6.7)	4 (26.7)	5 (16.7)	0.330
No	14 (93.3)	11 (73.3)	25 (83.3)	
Hydrogen breath test				
Positive	1 (6.7)	5 (33.3)	6 (20.0)	0.169
Negative	14 (93.3)	10 (66.7)	24 (80.0)	

Table 6. Clinical characteristics data of subjects after 6 months of treatment (values in parentheses are percentages).

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References

[1] Hawrelak J, BNat(Hons). Probiotics. In: Pizzorno JE, Murray MT, editors. Textbook of Natural Medicine. 4th ed. St. Louis, Missouri: Churchill Livingstone Elsevier; 2013. p. 979–94.

[2] Lilly DM, Stillwell RH. Probotics: growth-promoting factors produced by microorganisms. Science (New York, NY). 1965;147(3659):747–8.

[3] Parker R. Probiotics, the other half of the antibiotic story. Animal Nutrition and Health. 1974;29:4–8.

[4] Chen LA, Sears CL. Prebiotics, Probiotics, and Synbiotics. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, PA: Saunders Elsevier; 2015. p. 19–25.e1.

[5] Sanders ME. Probiotics: definition, sources, selection, and uses. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2008;46 Suppl 2:S58–61; discussion S144–51.

[6] Guarner F, Schaafsma GJ. Probiotics. International Journal of Food Microbiology. 1998;39(3):237–8.

[7] Dunne C, O'Mahony L, Murphy L, Thornton G, Morrissey D, O'Halloran S, et al. In vitro selection criteria for probiotic bacteria of human origin: correlation with in vivo findings. The American Journal of Clinical Nutrition. 2001;73(2 Suppl):386s–92s.

[8] O'Toole PW, Cooney JC. Probiotic bacteria influence the composition and function of the intestinal microbiota. Interdisciplinary Perspectives on Infectious Diseases. 2008; 2008:175285.

[9] Fuller R. Probiotics in human medicine. Gut. 1991;32(4):439–42.

[10] Fuller R, Gibson GR. Modification of the intestinal microflora using probiotics and prebiotics. Scandinavian Journal of Gastroenterology Supplement. 1997;222:28–31.

[11] Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA. Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. The American Journal of Physiology. 1999;276(4 Pt 1):G941–50.

[12] Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. The Journal of Nutrition. 2000;130(2S Suppl):396s–402s.

[13] Juven BJ, Meinersmann RJ, Stern NJ. Antagonistic effects of lactobacilli and pediococci to control intestinal colonization by human enteropathogens in live poultry. The Journal of Applied Bacteriology. 1991;70(2):95–103.

[14] Mishra C, Lambert J. Production of anti-microbial substances by probiotics. Asia Pacific Journal of Clinical Nutrition. 1996;5(1):20–4.

[15] Perdigon G, Alvarez S, Rachid M, Aguero G, Gobbato N. Immune system stimulation by probiotics. Journal of Dairy Science. 1995;78(7):1597–606.

[16] Link-Amster H, Rochat F, Saudan KY, Mignot O, Aeschlimann JM. Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS Immunology and Medical Microbiology. 1994;10(1):55–63.

[17] Schiffrin EJ, Rochat F, Link-Amster H, Aeschlimann JM, Donnet-Hughes A. Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. Journal of Dairy Science. 1995;78(3):491–7.

[18] Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. The American Journal of Gastroenterology. 2000;95(1 Suppl):S19–21.

[19] Sutas Y, Hurme M, Isolauri E. Down-regulation of anti-CD3 antibody-induced IL-4 production by bovine caseins hydrolysed with Lactobacillus GG-derived enzymes. Scandinavian Journal of Immunology. 1996;43(6):687–9.

[20] Goldin BR. Health benefits of probiotics. The British Journal of Nutrition. 1998;80(4):S203–7.

[21] Pelto L, Isolauri E, Lilius EM, Nuutila J, Salminen S. Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology. 1998;28(12):1474–9.

[22] Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. The American Journal of Gastroenterology. 2009;104(2):437–43.

[23] Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. Journal of Pediatric Gastroenterology and Nutrition. 1998;27(3):323–32.

[24] Wilson KH, Perini F. Role of competition for nutrients in suppression of Clostridium difficile by the colonic microflora. Infection and Immunity. 1988;56(10):2610–4.

[25] Macfarlane GT, Cummings JH. Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health? BMJ (Clinical Research ed). 1999;318(7189):999–1003.

[26] McKane L, Kandel J, eds. Microbiology: Essentials and Applications. New York: McGraw-Hill; 1986.

[27] Fujisawa T, Benno Y, Yaeshima T, Mitsuoka T. Taxonomic study of the *Lactobacillus acidophilus* group, with recognition of *Lactobacillus gallinarum* sp. nov. and *Lactobacillus johnsonii* sp. nov. and synonymy of *Lactobacillus acidophilus* group A3 (Johnson et al. 1980) with the type strain of *Lactobacillus amylovorus* (Nakamura 1981). International Journal of Systematic Bacteriology. 1992;42(3):487–91.

[28] Vanderhoof JA, Young RJ. Current and potential uses of probiotics. Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology. 2004;93(5 Suppl 3):S33–7.

[29] McGroarty JA. Probiotic use of lactobacilli in the human female urogenital tract. FEMS Immunology and Medical Microbiology. 1993;6(4):251–64.

[30] Bruce AW, Reid G. Intravaginal instillation of lactobacilli for prevention of recurrent urinary tract infections. Canadian Journal of Microbiology. 1988;34(3):339–43.

[31] Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, Stamm WE. Inverse association of H2O2-producing lactobacilli and vaginal *Escherichia coli* colonization in women with recurrent urinary tract infections. The Journal of Infectious Diseases. 1998;178(2):446–50.

[32] Madsen KL, Doyle JS, Jewell LD, Tavernini MM, Fedorak RN. Lactobacillus species prevents colitis in interleukin 10 gene-deficient mice. Gastroenterology. 1999;116(5):1107–14.

[33] Shornikova AV, Casas IA, Isolauri E, Mykkanen H, Vesikari T. Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. Journal of Pediatric Gastroenterology and Nutrition. 1997;24(4):399–404.

[34] Reid G, Bruce AW, Cook RL, Llano M. Effect on urogenital flora of antibiotic therapy for urinary tract infection. Scandinavian Journal of Infectious Diseases. 1990;22(1):43–7.

[35] Alander M, Satokari R, Korpela R, Saxelin M, Vilpponen-Salmela T, Mattila-Sandholm T, et al. Persistence of colonization of human colonic mucosa by a probiotic strain,

Lactobacillus rhamnosus GG, after oral consumption. Applied and Environmental Microbiology. 1999;65(1):351–4.

[36] Sullivan A, Barkholt L, Nord CE. *Lactobacillus acidophilus, Bifidobacterium lactis* and Lactobacillus F19 prevent antibiotic-associated ecological disturbances of *Bacteroides fragilis* in the intestine. The Journal of Antimicrobial Chemotherapy. 2003;52(2):308–11.

[37] Maggi L, Mastromarino P, Macchia S, Brigidi P, Pirovano F, Matteuzzi D, et al. Technological and biological evaluation of tablets containing different strains of lactobacilli for vaginal administration. European Journal of Pharmaceutics and Biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2000;50(3):389–95.

[38] El-Nezami H, Kankaanpaa P, Salminen S, Ahokas J. Ability of dairy strains of lactic acid bacteria to bind a common food carcinogen, aflatoxin B1. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association. 1998;36(4):321–6.

[39] Goldin BR, Gualtieri LJ, Moore RP. The effect of Lactobacillus GG on the initiation and promotion of DMH-induced intestinal tumors in the rat. Nutrition and Cancer. 1996;25(2):197–204.

[40] McIntosh GH, Royle PJ, Playne MJ. A probiotic strain of *L. acidophilus* reduces DMH-induced large intestinal tumors in male Sprague-Dawley rats. Nutrition and Cancer. 1999;35(2):153–9.

[41] Mao Y, Nobaek S, Kasravi B, Adawi D, Stenram U, Molin G, et al. The effects of Lactobacillus strains and oat fiber on methotrexate-induced enterocolitis in rats. Gastroenterology. 1996;111(2):334–44.

[42] Doncheva NI, Antov GP, Softova EB, Nyagolov YP. Experimental and clinical study on the hypolipidemic and antisclerotic effect of *Lactobacillus Bulgaricus* strain GB N 1 (48). Nutrition Research. 2002;22(4):393–403.

[43] Losada MA, Olleros T. Towards a healthier diet for the colon: the influence of fructo-oligosaccharides and lactobacilli on intestinal health. Nutrition Research. 2002;22(1):71–84.

[44] Oberhelman RA, Gilman RH, Sheen P, Taylor DN, Black RE, Cabrera L, et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. The Journal of Pediatrics. 1999;134(1):15–20.

[45] Reid G, Cook RL, Bruce AW. Examination of strains of lactobacilli for properties that may influence bacterial interference in the urinary tract. The Journal of Urology. 1987;138(2):330–5.

[46] Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, et al. Effect of different probiotic preparations on anti-Helicobacter pylori therapy-related side

effects: a parallel group, triple blind, placebo-controlled study. The American Journal of Gastroenterology. 2002;97(11):2744–9.

[47] Hoyos AB. Reduced incidence of necrotizing enterocolitis associated with enteral administration of *Lactobacillus acidophilus* and *Bifidobacterium infantis* to neonates in an intensive care unit. International Journal of Infectious Diseases: IJID: official publication of the International Society for Infectious Diseases. 1999;3(4):197–202.

[48] Duc le H, Hong HA, Barbosa TM, Henriques AO, Cutting SM. Characterization of Bacillus probiotics available for human use. Applied and Environmental Microbiology. 2004;70(4):2161–71.

[49] Velraeds MM, van der Mei HC, Reid G, Busscher HJ. Inhibition of initial adhesion of uropathogenic *Enterococcus faecalis* by biosurfactants from Lactobacillus isolates. Applied and Environmental Microbiology. 1996;62(6):1958–63.

[50] Hyronimus B, Le Marrec C, Urdaci MC. Coagulin, a bacteriocin-like inhibitory substance produced by *Bacillus coagulans* I4. Journal of Applied Microbiology. 1998;85(1):42–50.

[51] Buts JP. [Lyophilized *Saccharomyces boulardii*: example of a probiotic medicine]. Revista de gastroenterologia del Peru: organo oficial de la Sociedad de Gastroenterologia del Peru. 2005;25(2):176–88.

[52] Fietto JL, Araujo RS, Valadao FN, Fietto LG, Brandao RL, Neves MJ, et al. Molecular and physiological comparisons between *Saccharomyces cerevisiae* and *Saccharomyces boulardii*. Canadian Journal of Microbiology. 2004;50(8):615–21.

[53] Posteraro B, Sanguinetti M, Romano L, Torelli R, Novarese L, Fadda G. Molecular tools for differentiating probiotic and clinical strains of *Saccharomyces cerevisiae*. International Journal of Food Microbiology. 2005;103(3):295–304.

[54] Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. The Journal of Pediatrics. 2001;138(3):361–5.

[55] Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2006;23(11):1567–74.

[56] Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ (Clinical research ed). 2001;322(7298):1327.

[57] Shornikova AV, Casas IA, Mykkanen H, Salo E, Vesikari T. Bacteriotherapy with *Lactobacillus reuteri* in rotavirus gastroenteritis. The Pediatric Infectious Disease Journal. 1997;16(12):1103–7.

[58] Saxelin M. Colonization of the human gastrointestinal tract by probiotic bacteria. Nutrition Today. 1996;31(6):9S.

[59] Kailasapathy K, Chin J. Survival and therapeutic potential of probiotic organisms with reference to *Lactobacillus acidophilus* and Bifidobacterium spp. Immunology and Cell Biology. 2000;78(1):80–8.

[60] Surawicz CM, Brandt LJ. Probiotics and Fecal Microbiota Transplantation. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th ed. Philadelphia, PA: Saunders Elsevier; 2016. p. 2339–43.e3.

[61] Segarra-Newnham M. Probiotics for Clostridium difficile-associated diarrhea: focus on Lactobacillus rhamnosus GG and Saccharomyces boulardii. The Annals of Pharmacotherapy. 2007;41(7):1212–21.

[62] Elahi B, Nikfar S, Derakhshani S, Vafaie M, Abdollahi M. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. Digestive Diseases and Sciences. 2008;53(5): 1278–84.

[63] Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JN, Suttorp MJ, et al. Safety of probiotics used to reduce risk and prevent or treat disease. Evidence Report/Technology Assessment. 2011(200):1–645.

[64] Whelan K, Myers CE. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. The American Journal of Clinical Nutrition. 2010;91(3):687–703.

[65] Finegold S, Mathisen G, George W. Changes in the Human Intestinal Flora Related to the Administration of Antimicrobial Agents. In: Hentges DJ, editor. Human Intestinal Microflora in Health and Disease. London: Academic Press; 1983. p. 355–448.

[66] Pradhan A, Majumdar MK. Metabolism of some drugs by intestinal lactobacilli and their toxicological considerations. Acta Pharmacologica et Toxicologica . 1986;58(1):11–5.

[67] Goldin BR, Gorbach SL. Clinical indications for probiotics: an overview. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2008;46 Suppl 2:S96–100; discussion S44–51.

[68] Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One. 2012;7(4):e34938.

[69] Binder H. Disorders of Absorption. In: Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J, editors. Harrison's Principles of Internal Medicine. 18th ed. New york: McGraw Hill; 2012. p. 2460–76.

[70] Kleigman R, Behrman R, Jenson H, Stanton B. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA: Saunders; 2011.

[71] Quigley EM. Bacteria: a new player in gastrointestinal motility disorders – infections, bacterial overgrowth, and probiotics. Gastroenterology Clinics of North America. 2007;36(3):735–48, xi.

[72] O'Mahony S, Shanhan F. Enteric microbiota and small intestinal bacterial overgrowth. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's Gastrointestinal & Liver Disease: Pathophysiology, Diagnosis, Management. 9th ed. Philadelphia: Saunders Elsevier; 2010. p. 1772–7.

[73] Khalighi AR, Khalighi MR, Behdani R, Jamali J, Khosravi A, Kouhestani S, et al. Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO) – a pilot study. The Indian Journal of Medical Research. 2014;140(5):604–8.

[74] Soifer LO, Peralta D, Dima G, Besasso H. [Comparative clinical efficacy of a probiotic vs. an antibiotic in the treatment of patients with intestinal bacterial overgrowth and chronic abdominal functional distension: a pilot study]. Acta gastroenterologica Latinoamericana. 2010;40(4):323–7.

[75] Barrett JS, Canale KE, Gearry RB, Irving PM, Gibson PR. Probiotic effects on intestinal fermentation patterns in patients with irritable bowel syndrome. World Journal of Gastroenterology. 2008;14(32):5020–4.

[76] Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. Drugs. 2012;72(6):803–23.

[77] Rohde CL, Bartolini V, Jones N. The use of probiotics in the prevention and treatment of antibiotic-associated diarrhea with special interest in *Clostridium difficile*-associated diarrhea. Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition. 2009;24(1):33–40.

[78] Bixquert Jimenez M. Treatment of irritable bowel syndrome with probiotics. An etiopathogenic approach at last? Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva. 2009;101(8):553–64.

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