

Probiotics and prebiotics

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A Resource Sensitive Solution

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Contents

1	Probiotics—the concept	3
2	Products, health claims, and commerce	6
3	Probiotics—the science	12
4	Clinical applications	14
5	Probiotics, prebiotics and evidence—the global picture	17

List of tables

Table 1	Definitions used by the international scientific associations for probiotics and prebiotics	3
Table 2	Definitions	4
Table 3	Nomenclature for microorganisms	6
Table 4	Examples of probiotic strains in products	7
Table 5	Information on suppliers of probiotics and prebiotics	9
Table 6	Human intestinal microbiota. The gut microbiota form a diverse and dynamic ecosystem, including bacteria, Archaea, and Eukarya that have adapted to live on the intestinal mucosal surface or within the gut lumen	12
Table 7	Mechanisms of probiotic/host interaction. Symbiosis between microbiota and the host can be optimized by pharmacological or nutritional interventions in the gut microbial ecosystem using probiotics or prebiotics	13
Table 8	Evidence-based pediatric indications for probiotics and prebiotics in gastroenterology	18
Table 9	Evidence-based adult indications for probiotics and prebiotics in gastroenterology	21

List of figures

Fig. 1	Electron micrograph of <i>Lactobacillus salivarius</i> 118 adhering to Caco-2 cells	4
Fig. 2	Spectrum of interventions that can affect health and disease	6
Fig. 3	The normal microbiota and probiotics interact with the host in metabolic activities and immune function and prevent colonization of opportunistic and pathogenic microorganisms	14

1 Probiotics—the concept

History and definitions

A century ago, Elie Metchnikoff (a Russian scientist, Nobel laureate, and professor at the Pasteur Institute in Paris) postulated that lactic acid bacteria (LAB) offered health benefits capable of promoting longevity. He suggested that “intestinal auto-intoxication” and the resultant aging could be suppressed by modifying the gut microbiota and replacing proteolytic microbes such as *Clostridium*—which produce toxic substances including phenols, indoles, and ammonia from the digestion of proteins—with useful microbes. He developed a diet with milk fermented with the bacterium he called “Bulgarian bacillus.”

In 1917, before Sir Alexander Fleming’s discovery of penicillin, the German professor Alfred Nissle isolated a nonpathogenic strain of *Escherichia coli* from the feces of a First World War soldier who did not develop enterocolitis during a severe outbreak of shigellosis. Disorders of the intestinal tract were frequently treated with viable nonpathogenic bacteria to change or replace the intestinal microbiota. The *Escherichia coli* strain Nissle 1917 is one of the few examples of a non-LAB probiotic.

A *Bifidobacterium* was first isolated by Henry Tissier (of the Pasteur Institute) from a breast-fed infant, and he named the bacterium *Bacillus bifidus communis*. Tissier claimed that bifidobacteria would displace the proteolytic bacteria that cause diarrhea and recommended the administration of bifidobacteria to infants suffering from this symptom.

The term “probiotics” was first introduced in 1965 by Lilly and Stillwell; in contrast to antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other organisms (Table 1). In 1989, Roy Fuller emphasized the requirement of viability for probiotics and introduced the idea that they have a beneficial effect on the host.

Table 1 Definitions used by the international scientific associations for probiotics and prebiotics

Probiotics	Live microorganisms that confer a health benefit on the host when administered in adequate amounts
Prebiotic	Selectively fermented ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health
Synbiotics	Products that contain both probiotics and prebiotics

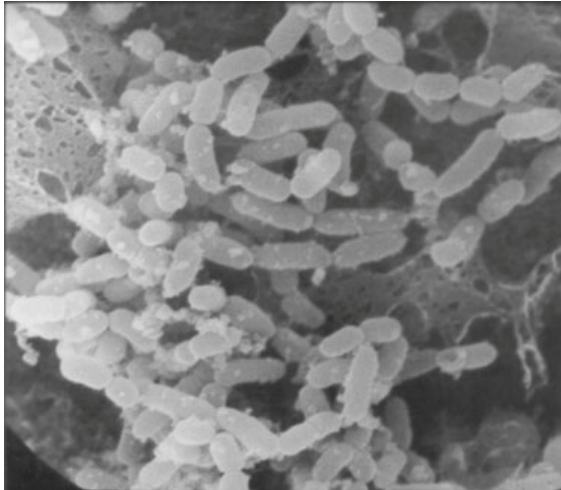


Fig. 1 Electron micrograph of *Lactobacillus salivarius* 118 adhering to Caco-2 cells.

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What are probiotics?

Probiotics are live microbes that can be formulated into many different types of product, including foods, drugs, and dietary supplements. Species of *Lactobacillus* (Fig. 1) and *Bifidobacterium* are most commonly used as probiotics, but the yeast *Saccharomyces cerevisiae* and some *E. coli* and *Bacillus* species are also used as probiotics. Lactic acid bacteria, including *Lactobacillus* species, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents for food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term “probiotic” should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit. Fermentation of food provides characteristic taste profiles and lowers the pH, which prevents contamination by potential pathogens. Fermentation is globally applied in the preservation of a range of raw agricultural materials (cereals, roots, tubers, fruit and vegetables, milk, meat, fish etc.).

Table 2 Definitions

Lactic acid bacteria (LAB)	A functional classification of nonpathogenic, nontoxigenic, Gram-positive, fermentative bacteria that are associated with the production of lactic acid from carbohydrates, making them useful for food fermentation. Species of <i>Lactobacillus</i> , <i>Lactococcus</i> , and <i>Streptococcus thermophilus</i> are included in this group. Since the genus <i>Bifidobacterium</i> is not associated with food fermentation and is taxonomically distinct from the other LABs, it is not usually grouped as a member of the LABs. Many probiotics are also LABs, but some probiotics (such as certain strains of <i>E. coli</i> , spore-formers, and yeasts used as probiotics) are not
Fermentation	A process by which a microorganism transforms food into other products, usually through the production of lactic acid, ethanol, and other metabolic end-products

Prebiotics and synbiotics

Prebiotics are dietary substances (mostly consisting of nonstarch polysaccharides and oligosaccharides poorly digested by human enzymes) that nurture a selected group of microorganisms living in the gut. They favor the growth of beneficial bacteria over that of harmful ones.

Unlike probiotics, most prebiotics are used as food ingredients—in biscuits, cereals, chocolate, spreads, and dairy products, for example. Commonly known prebiotics are:

- Oligofructose
- Inulin
- Galacto-oligosaccharides
- Lactulose
- Breast milk oligosaccharides

Lactulose is a synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy. The prebiotic oligofructose is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, and leeks. Oligofructose can also be isolated from chicory root or synthesized enzymatically from sucrose.

Fermentation of oligofructose in the colon results in a large number of physiologic effects, including:

- Increasing the numbers of bifidobacteria in the colon
- Increasing calcium absorption
- Increasing fecal weight
- Shortening gastrointestinal transit time
- Possibly, lowering blood lipid levels

The increase in colonic bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

Synbiotics are appropriate combinations of prebiotics and probiotics. A synbiotic product exerts both a prebiotic and probiotic effect.

Genera, species, and strains

Probiotic research suggests a range of potential health benefits. However, the effects described can only be attributed to the strain or strains tested, and not to the species or the whole group of LABs or other probiotics.

The implications of the strain-specificity of effects are:

- Documentation of health effects must be conducted on the specific strain being sold in the product.
- Results and review articles from studies conducted on specific strains cannot be used as evidence to support health effects of untested strains.
- Studies that document the efficacy of specific strains at a specific dosage are not sufficient evidence to support health effects at a lower dosage.

The role of the vehicle/filler substances in delivering functional benefits also has to be taken into account. Some effects may not be reproduced using a different vehicle/filler—for instance, due to reduced viability of the strain.

A probiotic strain is identified by the genus, species, and an alphanumeric designation. In the scientific community, there is an agreed nomenclature for microorganisms—for example, *Lactobacillus casei* DN-114 001 or *Lactobacillus rhamnosus* GG (Table 3).

Table 3 Nomenclature for microorganisms

Genus	Species	Strain designation
<i>Lactobacillus</i>	<i>rhamnosus</i>	GG
<i>Lactobacillus</i>	<i>casei</i>	DN-114 001

Marketing and trade names are not regulated, and companies can call their products' probiotics whatever they want—for example, LGG.

2 Products, health claims, and commerce

Market potential

High-profile probiotic-containing products have been hugely successful in Europe, Asia, and, more recently, in other regions of the world. This marketing success will promote consumption, product development, and research.

Probiotics are often recommended by nutritionists and sometimes by doctors, and a range of product types are available on the market (Fig. 2).

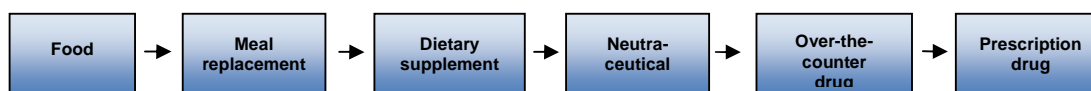


Fig. 2 Spectrum of interventions that can affect health and disease.

Health claims

Probiotics are intended to assist the body's naturally occurring gut microbiota. Some probiotic preparations have been used to prevent diarrhea caused by antibiotics, or as part of the treatment for antibiotic-related dysbiosis. Studies have documented probiotic effects on a variety of gastrointestinal and extraintestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), vaginal infections, and immune enhancement. Some probiotics have been shown to increase survival of preterm neonates. Probiotics have also been investigated in relation to atopic eczema and complications of liver cirrhosis. Although there is some clinical evidence for the role of probiotics in lowering cholesterol, the results are conflicting.

In general, the strongest clinical evidence for probiotics is related to their use in improving gut health and stimulating immune function.

Justification—research and proof

Claims of benefit for probiotics can take different forms, depending on the intended use of the product. The most common claims are those that relate probiotics to the normal structure and functioning of the human body, known as “structure–function claims.” Often considered “soft” claims, as no mention of disease or illness is allowed, these claims still have to be substantiated by consistent results from well-designed, double-blind, placebo-controlled human studies. In vitro and animal studies, though important in developing clinical strategies, are not considered sufficient to document such claims.

The Council for Agricultural Science and Technology (www.cast-science.org) has published a paper on probiotics that makes the following statements concerning product claims:

- It is unfortunate that products can currently be labeled as probiotics without being either well defined or substantiated with controlled human studies.
- The pace of research into probiotics has accelerated in recent years: in 2001–2005, more than four times as many human clinical trials on probiotics were published as in 1996–2000.
- There are significant gaps for some products between what research has shown to be effective and what is claimed in the marketplace.
- Failures of products to meet label claims with regard to the numbers and types of viable microbes present in the product, and about the quantity that needs to be consumed for a health benefit, have been documented.
- The guidelines for examining the scientific evidence on the functional and safety aspects of probiotics in food [FAO/WHO 2002], should be used as a starting-point for governments to devise their own policy with regard to new probiotic strains to be introduced for human use.
- It is suggested that manufacturers label the genus, species, and strain for each probiotic in a product, along with the number of viable cells of each probiotic strain that will remain up to the end of shelf-life.

Table 4 Examples of probiotic strains in products

Strain (alternative designations)	Brand name	Producer
<i>Bifidobacterium animalis</i> DN 173 010	Activia	Danone/Dannon
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bb-12	Chr. Hansen	
<i>Bifidobacterium breve</i> Yakult	Bifiene	Yakult
<i>Bifidobacterium infantis</i> 35624	Align	Procter & Gamble
<i>Bifidobacterium lactis</i> HN019 (DR10)	Howaru Bifido	Danisco
<i>Bifidobacterium longum</i> BB536		Morinaga Milk Industry
<i>Enterococcus</i> LAB SF 68	Bioflorin	Cerbios-Pharma
<i>Escherichia coli</i> Nissle 1917	Mutaflor	Ardeypharm

Strain (alternative designations)	Brand name	Producer
<i>Lactobacillus acidophilus</i> LA-5		Chr. Hansen
<i>Lactobacillus acidophilus</i> NCFM		Danisco
<i>Lactobacillus casei</i> DN-114 001	Actimel, DanActive	Danone/Dannon
<i>Lactobacillus casei</i> CRL431		Chr. Hansen
<i>Lactobacillus casei</i> F19	Cultura	Arla Foods
<i>Lactobacillus casei</i> Shirota	Yakult	Yakult
<i>Lactobacillus johnsonii</i> La1 (Lj1)	LC1	Nestlé
<i>Lactococcus lactis</i> L1A	Norrmejerier	
<i>Lactobacillus plantarum</i> 299V	GoodBelly, ProViva	NextFoods Probi
<i>Lactobacillus reuteri</i> DSM 17938	<i>L. reuteri</i> Protectis	BioGaia
<i>Lactobacillus rhamnosus</i> ATCC 53013 (LGG)	Vifit and others	Valio
<i>Lactobacillus rhamnosus</i> LB21	Verum	Norrmejerier
<i>Lactobacillus salivarius</i> UCC118		
<i>Saccharomyces cerevisiae</i> (<i>boulardii</i>) lyo	DiarSafe, Ultralevure, etc.	Wren Laboratories, Biocodex, etc.
Tested as mixture: <i>Lactobacillus acidophilus</i> CL1285 & <i>L. casei</i> Lbc80r	Bio K+	Bio K+ International
Tested as mixture: <i>Lactobacillus rhamnosus</i> GR-1 & <i>L. reuteri</i> RC-14	FemDophilus	Chr. Hansen
Tested as mixture: VSL#3 (mixture of one strain of <i>Streptococcus thermophilus</i> , four <i>Lactobacillus</i> spp., & three <i>Bifidobacterium</i> spp. strains)	VSL#3	Sigma-Tau Pharmaceuticals, Inc.
Tested as mixture: <i>Lactobacillus acidophilus</i> CUL60 & <i>Bifidobacterium bifidum</i> CUL 20		
Tested as mixture: <i>Lactobacillus helveticus</i> R0052 & <i>L. rhamnosus</i> R0011	A'Biotica and others	Institut Rosell
Tested as mixture: <i>Bacillus clausii</i> strains O/C, NR, SIN, and T	Enterogermina	Sanofi-Aventis

Products: dosages and quality

The most common forms for probiotics are dairy products and probiotic-fortified foods (Table 4). However, tablets, capsules, and sachets containing the bacteria in freeze-dried form are also available.

The dose needed for probiotics varies greatly depending on the strain and product. Although many over-the-counter products deliver in the range of 1–10 billion cfu/dose, some products have been shown to be efficacious at lower levels, while some require substantially more. For example, *Bifidobacterium infantis* 35624 was

effective in alleviating the symptoms of IBS at 100 million cfu/day, whereas studies with VSL#3 have used sachets with 300–450 billion cfu t.i.d. It is not possible to state a general dose that is needed for probiotics; the dosage has to be based on human studies showing a health benefit.

Despite the existing scientific consensus, there is no legal definition of the term “probiotic.” The minimum criteria that have to be met for probiotic products are that the probiotic must be:

- Specified by genus and strain—research on specific probiotic strains cannot be applied to any product marketed as a probiotic.
- Alive.
- Delivered in adequate dose through the end of shelf-life (with minimal variability from one batch to another).
- Shown to be efficacious in controlled human studies.
- Safe for the intended use.

As there are no universally established and/or enforced standards for content and label claims on products, the industry (Table 5) should maintain integrity in formulating and labeling the products so that consumers can have confidence in this product category.

Table 5 Information on suppliers of probiotics and prebiotics

Company	Description	URL
BioGaia	<i>Lactobacillus reuteri</i> culture comes in three different, producer-friendly forms: freeze-dried powder, freeze-dried DVS (Direct Vat Set) granules, and frozen pellets	www.biogaia.com
Bio K +	Producer and seller of probiotic mix including <i>L. acidophilus</i> and <i>L. casei</i>	www.biokplus.com
Chr. Hansen	The “nu-trish” brand probiotic culture range consists of Probio-Tec, Yo-Fast, and other nu-trish culture blends with a well-defined viscosity profile that ferment quickly	www.chr-hansen.com
Cerbios-Pharma	Producer of <i>Enterococcus</i> LAB SF 68	www.cerbios.ch
Danisco	The company’s cultures division produces, develops, and markets starter cultures, media, coagulants, and enzymes for cheese, fresh dairy, and other food products, and also supplies probiotic cultures for foods and supplements, as well as natural food protectants	www.danisco.com
Danone	Producer of several brands of fermented dairy products containing probiotics	www.danone.com
DSM	The Lafti line of probiotics is formulated for stability, survivability, and concentration, and includes <i>L. acidophilus</i> (Lafti L10), <i>L. casei</i> (Lafti L26), and <i>Bifidobacterium</i> (Lafti B94)	www.dsm.com
GTC Nutrition	NutraFlora short-chain fructo-oligosaccharides (scFOS) are a cane sugar	www.gtcnutrition.com

Company	Description	URL
	or beet sugar–derived natural prebiotic fiber	
Lallemand	This Canadian supplier delivers probiotics and biosupplements to the nutraceuticals, functional-foods, and pharmaceuticals industries	www.lallemand.com
National Starch	The Hi-Maize brand corn-based resistant starch has multiple benefits, including acting as a prebiotic for digestive health	www.hi-maize.com
Orafti	BeneoSynergy1 is the unique, patented oligofructose-enriched inulin prebiotic used in the landmark SynCan project on synbiotics and colon cancer	www.orafiti.com
Probi	This biotech company develops and patents probiotic strains, including <i>L. plantarum</i> 299v and <i>L. rhamnosus</i> 271. <i>L. plantarum</i> 299 has not yet been commercialized, but it is in the out-licensing phase	www.probi.com
Proctor & Gamble	“Align” is a probiotic supplement produced by P&G. Align capsules contain <i>Bifidobacterium infantis</i> 35624	www.aligngi.com
Sanofi-Aventis	Producer of <i>Bacillus clausii</i> strains O/C, NR, SIN, and T, marketed in Europe, Asia, and South America as Enterogermina	www.sanofi-aventis.com
Sensus	Frutafit inulin and Frutalose fructo-oligosaccharides (FOS) are soluble dietary fibers with bifidogenic/prebiotic properties, suitable for a variety of food systems to enrich fiber, reduce calories, and replace sugars and fats	www.sensus.us
Solvay	Producer of lactulose (Duphalac) for treatment of constipation and hepatic encephalopathy	www.solvay.com
Valio	The <i>Lactobacillus rhamnosus</i> GG probiotic is the most researched in the world and was recently licensed to Dannon for the U.S. yogurt market. The GEFILUS family containing LGG is marketed worldwide	www.valio.fi
VSL Pharma-ceuticals	VSL#3 is a mixture of eight strains with 450 billion live bacteria per packet	http://www.vsl3.com
Winclove	The company sells mixtures of probiotic strains for different indications	www.winclove.com
Yakult	Produces probiotic drinks with <i>L. casei</i> Shirota	www.yakult.co.jp

Product safety

- Some species of lactobacilli and bifidobacteria are normal residents of, or common transients through, the human digestive system and as such do not display infectivity or toxicity.
- Traditional lactic acid bacteria, long associated with food fermentation, are generally considered safe for oral consumption as part of foods and supplements for the generally healthy population and at levels traditionally used.
- Regulations for dietary supplements are nonexistent in many countries, or much less strict than those that apply for prescription drugs.
- Currently, the Food and Drug Administration (FDA) in the United States has not been petitioned for (and therefore has not ruled on) any claims for probiotics that relate probiotics to a reduction in the risk of disease. Structure–function claims are commonly used for probiotics, but these do not require approval by the FDA for use.
- Dietary supplement production varies among manufacturers, and perhaps over time with the same manufacturer. Efficacy and side effects are likely to differ among strains, products, brands, or even within different lots of the same brand. Products purchased may not be identical with the form used in research.
- Long-term effects of most dietary supplements, other than vitamins and minerals, are not known. Many dietary supplements are not used long-term.
- The question of safety has been raised with the more recent use of intestinal isolates of bacteria delivered in high numbers to severely ill patients. Use of probiotics in ill persons is restricted to the strains and indications with proven efficacy, as described in section 5. Testing or use of probiotics in other disease indications is only acceptable after approval by an independent ethics committee.
- On the basis of the prevalence of lactobacilli in fermented food, as normal colonizers of the human body, and the low level of infection attributed to them, the safety of these microbes has been reviewed and their pathogenic potential is deemed to be quite low.
- On the basis of the FAO/WHO report [2002], a multidisciplinary approach is necessary to examine the pathological, genetic, toxicological, immunological, gastroenterological, and microbiological safety aspects of new probiotic strains. Conventional toxicology and safety evaluation is not sufficient, since a probiotic is meant to survive and/or grow in order to benefit humans.

From a scientific perspective, the suitable description of a probiotic product as reflected on the label should include:

- Genus and species identification, with nomenclature consistent with current scientifically recognized names
- Strain designation
- Viable count of each strain at the end of shelf-life
- Recommended storage conditions
- Safety under the conditions of recommended use
- Recommended dose, which should be based on induction of the claimed physiological effect
- An accurate description of the physiological effect, as far as is allowable by law
- Contact information for post-market surveillance

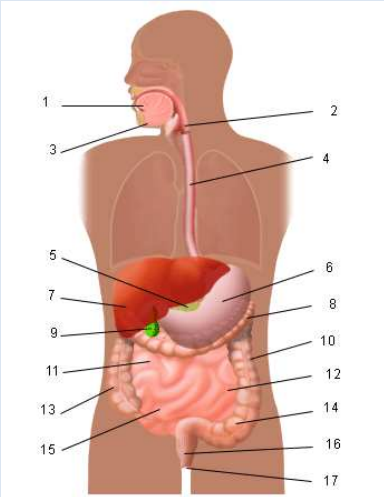
3 Probiotics—the science

Microbial ecosystem and mucosal immunity

The information available about the microbial composition of the intestinal ecosystem in health and disease is still limited (Table 6).

- The intestine contains extensive microbiota—100 trillion bacteria cells that provide an average of 600,000 genes to each human being—located mainly in the colon and comprising hundreds of species of bacteria. Most bacterial cells in fecal specimens cannot be grown in culture.
- At the level of species and strains, the microbial diversity between individuals is quite remarkable: each individual harbors his or her own distinctive pattern of bacterial composition, determined partly by the host genotype and by initial colonization at birth via vertical transmission.
- In healthy adults, the fecal composition is stable over time. In the human gut ecosystem, three bacterial divisions dominate: Bacteroidetes, Firmicutes, and to a lesser extent Actinobacteria.

Table 6 Human intestinal microbiota. The gut microbiota form a diverse and dynamic ecosystem, including bacteria, Archaea, and Eukarya that have adapted to live on the intestinal mucosal surface or within the gut lumen

Stomach and duodenum	<ul style="list-style-type: none"> • Harbor very low numbers of microorganisms: $< 10^3$ bacterial cells per gram of contents • Mainly lactobacilli and streptococci • Acid, bile, and pancreatic secretions suppress most ingested microbes • Phasic propulsive motor activity impedes stable colonization of the lumen 	
Jejunum and ileum	<ul style="list-style-type: none"> • Numbers of bacteria progressively increase from approximately 10^4 cells in the jejunum to 10^7 cells per gram of contents in the distal ileum 	
Large intestine	<ul style="list-style-type: none"> • Heavily populated by anaerobes: 10^{12} cells per gram of luminal contents 	

1, mouth; 2, pharynx; 3, tongue; 4, esophagus; 5, pancreas; 6, stomach; 7, liver; 8, transverse colon; 9, gallbladder; 10, descending colon; 11, duodenum; 12, jejunum; 13, ascending colon; 14, sigmoid colon; 15, ileum; 16, rectum; 17, anus.

The normal interaction between gut bacteria and their host is a symbiotic relationship. An important influence of upper intestinal bacteria on immune function is suggested by the presence of a large number of organized lymphoid structures in

the small- intestinal mucosa (Peyer's patches). Their epithelium is specialized for the uptake and sampling of antigens, and they contain lymphoid germinal centers for induction of adaptive immune responses. In the colon, microorganisms can proliferate by fermenting available substrates from diet or endogenous secretions.

The intestine is the body's most important immune function-related organ; approximately 60% of the body's immune cells are present in the intestinal mucosa. The immune system controls immune responses against:

- Dietary proteins
- —Prevention of food allergies
- Pathogenic microorganisms
- —Viruses (rotavirus, poliovirus)
- —Bacteria (*Salmonella*, *Listeria*, *Clostridium*, etc.)
- —Parasites (*Toxoplasma*)

Mechanisms of action

Prebiotics affect intestinal bacteria by increasing the numbers of beneficial anaerobic bacteria and decreasing the population of potentially pathogenic microorganisms (Fig. 3). Probiotics affect the intestinal ecosystem by stimulating mucosal immune mechanisms and by stimulating nonimmune mechanisms through antagonism and competition with potential pathogens (Table 7). These phenomena are thought to mediate most beneficial effects, including reduction of the incidence and severity of diarrhea, which is one of the most widely recognized uses for probiotics. Probiotics reduce the risk of colon cancer in animal models, probably due to their role in suppressing the activity of certain bacterial enzymes that may increase the levels of procarcinogens, but this has not been proven in humans.

Table 7 Mechanisms of probiotic/host interaction. Symbiosis between microbiota and the host can be optimized by pharmacological or nutritional interventions in the gut microbial ecosystem using probiotics or prebiotics

Probiotics	
Immunologic benefits	<ul style="list-style-type: none"> • Activate local macrophages to increase antigen presentation to B lymphocytes and increase secretory immunoglobulin A (IgA) production both locally and systemically • Modulate cytokine profiles • Induce hyporesponsiveness to food antigens
Nonimmunologic benefits	<ul style="list-style-type: none"> • Digest food and compete for nutrients with pathogens • Alter local pH to create an unfavorable local environment for pathogens • Produce bacteriocins to inhibit pathogens • Scavenge superoxide radicals • Stimulate epithelial mucin production • Enhance intestinal barrier function • Compete for adhesion with pathogens • Modify pathogen-derived toxins

Prebiotics

- Metabolic effects: production of short-chain fatty acids, fat metabolism, absorption of ions (Ca, Fe, Mg)
- Enhancing host immunity (IgA production, cytokine modulation, etc.)

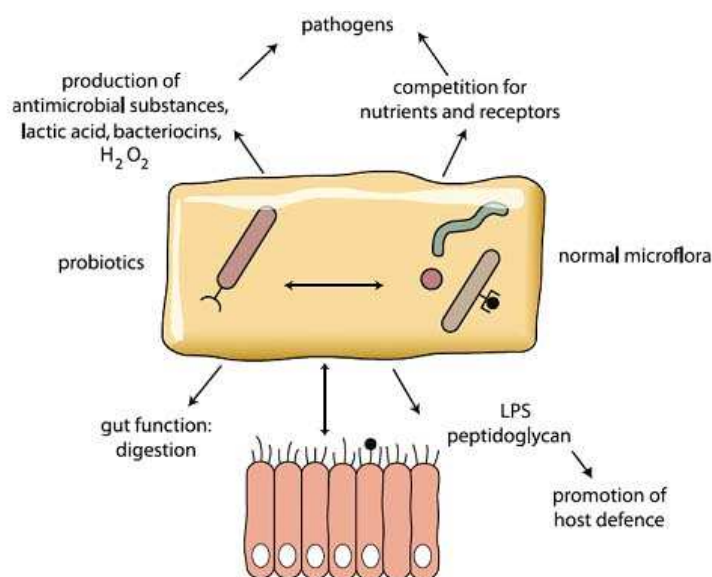


Fig. 3 The normal microbiota and probiotics interact with the host in metabolic activities and immune function and prevent colonization of opportunistic and pathogenic microorganisms.

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4 Clinical applications

Current insights into the clinical applications for various probiotics or prebiotics are summarized below (in alphabetical order).

Cardiovascular disease

- The use of probiotics/prebiotics for preventative medicine and decreasing risk of cardiovascular disease is still unproven.

Colon cancer

- The SYNCAN study tested the effect of oligofructose plus two probiotic strains in patients at risk of developing colonic cancer. The results of the study suggest that a synbiotic preparation can decrease the expression of biomarkers for colorectal cancer.

Diarrhea

Treatment of acute diarrhea:

- It has been confirmed that different probiotic strains (see Tables 8 and 9), including *L. reuteri* ATCC 55730, *L. rhamnosus* GG, *L. casei* DN-114 001, and *Saccharomyces cerevisiae* (boulardii) are useful in reducing the severity and duration of acute infectious diarrhea in children. The oral administration of probiotics shortens the duration of acute diarrheal illness in children by approximately 1 day.
- Several meta-analyses of controlled clinical trials have been published that show consistent results in systematic reviews, suggesting that probiotics are safe and effective. The evidence from studies on viral gastroenteritis is more convincing than the evidence on bacterial or parasitic infections. Mechanisms of action are strain-specific: there is evidence for efficacy of some strains of lactobacilli (e.g., *Lactobacillus casei* GG and *Lactobacillus reuteri* ATCC 55730) and for *Saccharomyces boulardii*. The timing of administration is also of importance.

Prevention of acute diarrhea:

- In the prevention of adult and childhood diarrhea, there is only suggestive evidence that *Lactobacillus* GG, *L. casei* DN-114 001, and *S. boulardii* are effective in some specific settings (see Tables 8 and 9).

Antibiotic-associated diarrhea:

- In antibiotic-associated diarrhea, there is strong evidence of efficacy for *S. boulardii* or *L. rhamnosus* GG in adults or children who are receiving antibiotic therapy. One study indicated that *L. casei* DN-114 001 is effective in hospitalized adult patients for preventing antibiotic-associated diarrhea and *C. difficile* diarrhea.

Radiation-induced diarrhea:

- There is inadequate research evidence to be certain that VSL#3 (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, and *Streptococcus thermophilus*) is effective in the treatment of radiation-induced diarrhea.

Eradication of *Helicobacter pylori*

- Several lactobacilli and bifidobacterial strains, as well as *Bacillus clausii*, appear to reduce the side effects of antibiotic therapies and improve patient compliance. Several strains were effective in decreasing side effects, but did not have effects on the eradication rate. A recent meta-analysis of 14 randomized trials suggests that supplementation of anti-*H. pylori* antibiotic regimens with certain probiotics may also be effective in increasing eradication rates and may be considered helpful for patients with eradication failure. There is currently insufficient evidence to support the concept that a probiotic alone, without concomitant antibiotic therapy, would be effective. In summary, there is literature suggesting that certain probiotics may be helpful as adjuvant therapy with antibiotics in the eradication of *H. pylori* infection.

Allergy

- The strongest evidence is for the prevention of atopic dermatitis when certain probiotics are administered to pregnant mothers and newborns up to 6 months of age. However, a recent clinical trial did not confirm these results. With regard to the treatment of allergic disease, a few well-designed studies have provided evidence that specific probiotic strains can be effective in the treatment of a subset of patients with atopic eczema. Little is known about the efficacy of probiotics in preventing food allergy.

Hepatic encephalopathy

- Prebiotics such as lactulose are commonly used for the prevention and treatment of this complication of cirrhosis. Minimal hepatic encephalopathy was reversed in 50% of patients treated with a synbiotic preparation (four probiotic strains and four fermentable fibers, including inulin and resistant starch) for 30 days.

Immune response

- There is suggestive evidence that several probiotic strains and the prebiotic oligofructose are useful in boosting the immune response. Indirect evidence has been obtained in studies aimed at preventing acute infectious disease (nosocomial diarrhea in children, influenza episodes in winter) and studies that tested antibody responses to vaccines.

Inflammatory bowel disease (IBD)

Pouchitis:

- There is good evidence for the usefulness of probiotics in preventing an initial attack of pouchitis (VSL#3), and in preventing further relapse of pouchitis after the induction of remission with antibiotics. Probiotics can be recommended to patients with pouchitis of mild activity, or as maintenance therapy for those in remission.

Ulcerative colitis:

- The probiotic *E. coli* Nissle strain may be equivalent to mesalazine in maintaining remission of ulcerative colitis. The probiotic mixture VSL#3 has shown efficacy to induce and maintain remission in children and adults with mild-to-moderate ulcerative colitis.

Crohn's disease:

- Studies of probiotics in Crohn's disease have been disappointing, and the Cochrane systematic review concluded that there is no evidence to suggest that probiotics are beneficial for maintenance of remission in Crohn's disease.

Irritable bowel syndrome (IBS)

- Several studies have demonstrated significant therapeutic gains with probiotics in comparison with placebo. A reduction in abdominal bloating and flatulence as a result of probiotic treatments is a consistent finding in published studies; some strains may ameliorate pain and provide global relief (*B. infantis* 35624) in addition. *Lactobacillus reuteri* may improve colicky symptoms within one week of treatment, as shown in a recent trial with 90 breastfed babies with infantile colic. In summary, there is literature suggesting that certain probiotics may alleviate symptoms in persons with functional abdominal pain.

Lactose malabsorption

- *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* improve lactose digestion and reduce symptoms related to lactose intolerance. This was confirmed in a number of controlled studies with individuals consuming yogurt with live cultures.

Necrotizing enterocolitis

- Clinical trials have shown that probiotic supplementation reduces the risk of necrotizing enterocolitis in preterm neonates. Systematic reviews of randomized controlled trials have also shown a reduced risk of death in probiotic treated groups. The numbers-needed-to-treat to prevent 1 death from all causes by treatment with probiotics is 20.

Nonalcoholic fatty liver disease

- The usefulness of probiotics as a treatment option has not been sufficiently confirmed through randomized clinical trials.

Prevention of systemic infections

- There is insufficient evidence to support the use of probiotics and synbiotics in critically ill adult patients in intensive-care units.

5 Probiotics, prebiotics and evidence—the global picture

Tables 8 and 9 summarize a number of clinical conditions for which there is evidence, from at least one well-designed and properly powered clinical trial, that oral administration of a specific probiotic strain or a prebiotic is effective and beneficial for a healthy or therapeutic outcome. The list may not be complete, as the flow of new published studies has been continuous during the past few years. The level of evidence may vary between the different indications. Recommended doses are those shown to be useful in the trials. The order of the products listed is random. Currently,

there is insufficient evidence from comparative studies to rank the products with proven efficacy.

Table 8 Evidence-based pediatric indications for probiotics and prebiotics in gastroenterology

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
Treatment of acute infectious diarrhea	<i>Lactobacillus rhamnosus</i> GG	10^{10} – 10^{11} cfu, twice daily	1a	1	Meta-analysis of RCTs; ESPGHAN/ESPID recommendation
	<i>Saccharomyces boulardii</i> , strain of <i>S. cerevisiae</i>	200 mg, three times daily	1a	2	Meta-analysis of RCTs; ESPGHAN/ESPID recommendation
	Indian Dahi containing <i>Lactococcus lactis</i> , <i>L. lactis cremoris</i> and <i>Leuconostoc mesenteroides cremoris</i>	10^{10} cfu of each strain, 2 or 3 times per day	2b	3	
Prevention of antibiotic associated diarrhea	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	250 mg, twice daily	1a	4,5	Meta-analysis of RCTs
	<i>L. rhamnosus</i> GG	10^{10} cfu, once or twice daily	1b	6,7	
	<i>Bifidobacterium lactis</i> Bb12 + <i>Streptococcus thermophilus</i>	$10^7 + 10^6$ cfu/g of formula	1b	8	
	<i>L. rhamnosus</i> (strains E/N, Oxy and Pen)	2×10^{10} , twice daily	1b	9	
Prevention of nosocomial diarrhea	<i>L. rhamnosus</i> GG	10^{10} – 10^{11} cfu, twice daily	1b	10,11	
	<i>B. lactis</i> Bb12 + <i>S. thermophilus</i>	$10^8 + 10^7$ cfu/g of formula	1b	12	
Prevention of common gastrointestinal infections acquired in the community	<i>L. casei</i> DN-114 001 in fermented milk	10^{10} cfu, once daily	1b	13,14, 15	
	<i>B. lactis</i> Bb-12 or <i>L. reuteri</i> ATCC 55730	10^7 cfu/g of formula powder	1b	16	
	<i>L. casei</i> Shirota in fermented milk	10^{10} cfu, once daily	1b	17	

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
Adjuvant therapy for <i>H. pylori</i> eradication	<i>L. casei</i> DN-114 001 in fermented milk	10^{10} – 10^{12} cfu daily, for 14 days	1b	18	The probiotic was given together with a 7-day course of eradication triple therapy with omeprazole, amoxicillin, and clarithromycin
Alleviates some symptoms of functional bowel disorders	<i>L. rhamnosus</i> GG	10^{10} – 10^{11} cfu, twice daily	1a	19	Meta-analysis of RCTs
	<i>L. reuteri</i> DSM 17938	10^8 cfu, twice daily	1b	20,21	
Infantile colic	<i>L. reuteri</i> DSM 17938	10^8 cfu/day	1b	22	Meta-analysis of pooled data from RCTs testing different probiotic preparations confirms significant benefits of probiotic supplements in reducing death and disease in preterm neonates [26]
Prevention of necrotizing enterocolitis in preterm infants	<i>B. bifidum</i> NCDO 1453, <i>L. acidophilus</i> NCDO 1748	10^9 cfu each strain, twice daily	1b	23	
	Infloran®: <i>L. acidophilus</i> + <i>B. infantis</i>	10^8 cfu each, twice daily	1b	24	
	<i>B. infantis</i> , <i>B. bifidum</i> , <i>S. thermophilus</i>	10^9 cfu each, once daily	1b	25	
Treatment of mildly active ulcerative colitis	VSL#3 mixture	4 to 9×10^{11} cfu, twice daily	1b	27	

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Table 9 Evidence-based adult indications for probiotics and prebiotics in gastroenterology

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
Treatment of acute diarrhea in adults	<i>Enterococcus faecium</i> LAB SF68	10 ⁸ cfu, three times daily	1b	1	
	<i>Lactobacillus paracasei</i> B 21060 or <i>L. rhamnosus</i> GG	10 ⁹ cfu twice daily	2b	2	
	<i>Saccharomyces boulardii</i> , strain of <i>S. cerevisiae</i>	10 ⁹ cfu per capsule of 250mg, 2–6 capsules per day	1b	1,3,4	
Prevention of antibiotic associated diarrhea in adults	<i>E. faecium</i> LAB SF68	10 ⁸ cfu, twice daily	1b	5	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	1 g or 4 × 10 ⁹ cfu per day	1b	5	
	<i>L. rhamnosus</i> GG	10 ¹⁰ –10 ¹¹ cfu, twice daily	1b	5	
	<i>L. casei</i> DN-114 001 in fermented milk	10 ¹⁰ cfu, twice daily	1b	6	
	<i>Bacillus clausii</i> (Enterogermina strains)	2 × 10 ⁹ spores, three times daily	1b	7	
	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R	5 × 10 ¹⁰ cfu, once or twice daily	1b	8,9	The strains were administered in capsules or in fermented milk vehicle
Prevention of <i>C. difficile</i> diarrhea in adults	<i>L. casei</i> DN-114 001 in fermented milk	10 ¹⁰ cfu, twice daily	1b	6	
	<i>L. acidophilus</i> + <i>B. bifidum</i> (Cultech strains)	2 × 10 ¹⁰ cfu each strain, once daily	1b	10	Strain designations not provided in paper
	Oligofructose	4 g, three times per day	1b	11	

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
	<i>L. rhamnosus</i> HN001 + <i>L. acidophilus</i> NCFM	10 ⁹ cfu each, once daily	2b	12	Probiotic administration reduced fecal counts of <i>C. difficile</i> in elderly patients without diarrhea
	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R	5 × 10 ⁹ cfu, once or twice daily	1b	9	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	2–3 × 10 ⁹ for 28 days, followed for another 4 weeks	1b	13,14	
Coadjuvant therapy for <i>H. pylori</i> eradication in adults	<i>L. rhamnosus</i> GG	6 × 10 ⁹ cfu, twice daily	1b	15	
	<i>B. clausii</i> (Enterogermina strains)	2 × 10 ⁹ spores, three times daily	1b	15	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	500 mg–1 g or 2–4 × 10 ⁹ cfu per day	1b	15–19	
	Kefir	250 mL twice daily	2b	20	Improves eradication rates (78% vs 50%)
	<i>L. reuteri</i> ATCC 55730	10 ⁸ cfu/day	1b	21	
Reduces symptoms associated with lactose maldigestion	Yogurt with live cultures of <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> and <i>Streptococcus thermophilus</i>	At least 10 ⁸ cfu of each strain per gram of product	1a	22	Systematic review of RCTs
Alleviates some symptoms of irritable bowel syndrome	<i>Bifidobacterium infantis</i> 35624	10 ⁸ cfu, once daily	1b	23, 24, 25	
	<i>B. animalis</i> DN-173 010 in fermented milk	10 ¹⁰ cfu, twice daily	1b	26, 27, 25	
	<i>L. acidophilus</i> SDC 2012, 2013	10 ¹⁰ cfu per day	2b	28, 25	

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
	<i>L. rhamnosus</i> GG, <i>L. rhamnosus</i> LC705, <i>B. breve</i> Bb99 and <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i>	10 ¹⁰ cfu, once daily	1b	29, 30, 25	
	<i>B. longum</i> 101 (29%), <i>L. acidophilus</i> 102 (29%), <i>Lactococcus lactis</i> 103 (29%), and <i>S. thermophilus</i> 104 (13%)	10 ¹⁰ cfu, once daily	1b	31, 25	
	Short-chain fructo-oligosaccharides	5 g per day	2b	32	
	Galacto-oligosaccharides	3.5 g per day	2b	33	
	<i>Bacillus coagulans</i> GBI-30, 6086	2 × 10 ⁹ cfu, once daily	2b	34	
Maintenance of remission in ulcerative colitis	<i>Escherichia coli</i> Nissle 1917	5 × 10 ¹⁰ viable bac, twice daily	1b	35	
Treatment of mildly active ulcerative colitis or pouchitis	VSL# 3 mixture of eight strains (one <i>S. thermophilus</i> , four <i>Lactobacillus</i> , three <i>Bifidobacterium</i>)	2 × 9 × 10 ¹¹ cfu, twice daily	1b	36, 37, 43	
Prevention and maintenance of remission in pouchitis	VSL# 3 mixture of eight strains (one <i>S. thermophilus</i> , four <i>Lactobacillus</i> , three <i>Bifidobacterium</i>)	2 × 4.5 × 10 ¹¹ cfu, twice daily	1b	38	
Treatment of constipation	Lactulose	20–40 g/day	1a	39	Review of cohort studies
	Oligofructose	> 20 g/day	2a	40	Review of cohort studies
Treatment of hepatic encephalopathy	Lactulose	45–90 g/day	1a	41	Systematic review of RCTs

Disorder, action	Probiotic strain / prebiotic	Recommended dose	Evidence level	Ref.	Comments
Prevention of common infections in athletes	<i>L. casei</i> Shirota in fermented milk	10 ¹⁰ cfu, once daily	1b	42	

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6 Automatic searches and further reading

Automatic PubMed searches

Precise literature search for probiotics research published in the last 6 months in the top clinical journals

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7 Useful web sites

- <http://www.isapp.net>
ISAP: The International Scientific Association for Probiotics and Prebiotics
The organization aims to engender and disseminate information on high-quality, multidisciplinary, scientific investigations in the fields of probiotics and prebiotics, and to advance the development of scientifically substantiated, health- promoting probiotic and prebiotic products worldwide.
- <http://www.usprobiotics.org>
Webcast: Probiotics: Applications in Gastrointestinal Health & Disease
Presented in conjunction with the American College of Gastroenterology's 72nd Annual Scientific Meeting, Autumn 2007)
- http://www.fao.org/ag/agn/agns/micro_probiotics_en.asp
The FAO food safety and quality site for probiotics.
- <http://www.nestlefoundation.org/>
- <http://www.dannonprobioticscenter.com/index.asp>
A Danone company—one of the leading research organizations in the field of probiotics.

8 Queries and feedback

The Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some procedures are associated with extra risk? Tell us about your own experience. You are welcome to e-mail the address below and let us know your views.



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