SUPPLEMENT ARTICLE

# From Yaks to Yogurt: The History, Development, and Current Use of Probiotics

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**The development of probiotics, which are living bacteria or yeasts used to confer a health benefit on the host, has paralleled our research in food preservation, microbiologic identification techniques, and our understanding of how the complex interactions in microbiota impact the host's health and recovery from disease. This review briefly describes the history of probiotics, where probiotic strains were originally isolated, and the types of probiotic products currently available on the global market. In addition, the uses or indications for these probiotics are described, along with the types of clinical investigations that have been done. Continuing challenges persist for the proper probiotic strain identification, regulatory pathways, and how healthcare providers can choose a specific strain to recommend to their patients.**

***Keywords.*** probiotics; marketing; antibiotic-associated diarrhea; *Saccharomyces boulardii*; lactobacilli; yogurt.

The use of probiotics stretches back into a time before microbes were discovered. Fermented milk products were pictured in Egyptian hieroglyphs, and fermented yak milk has traditionally been used by Tibetan nomads to preserve milk during their long treks [1]. The apparent health effect of ingesting quantities of fermented milk products was noticed by scientists in the 1800s, but the reason for these health effects remained undiscovered. Louis Pasteur identified the bacteria and yeasts responsible for the process of fermentation, but did not link these microbes to any apparent health effects [2]. In 1905, Elie Metchnikoff, who had worked with Pasteur in the 1860s, was credited with making the association of longevity among Bulgarians, not to the yogurt they consumed, but rather to the lactobacilli used to ferment the yogurt and the presence of these lactobacilli in the colon [3]. In 1906, Henry Tissier isolated *Bifidobacterium* from an infant and claimed it could displace pathogenic bacteria in the gut [4]. These discoveries helped catalyze research into health-promoting microbes and their role in disease prevention. One of the earliest human studies, in 1922, used *Lactobacillus acidophilus* in 30 patients with chronic constipation, diarrhea, or eczema and found improvements for all 3 conditions [5]. It was not until 10 years later, in 1932, that a study confirmed the effect of *L. acidophilus* in patients with constipation and mental disease [6].

In the 1930s, the idea that yogurts were the best delivery vehicle for probiotics was questioned when the bacteria used as yogurt starters (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) were found incapable of colonizing the human intestine. A different strain, *L. acidophilus,* was added to milk instead, as this species does not produce high levels of acid (causing curdling) and was also found to colonize the human colon [7]. Most of the microbiologic research during the 1940s centered on identifying pathogenic bacteria, not identifying health-promoting strains of bacteria or yeasts.

In the 1950s–1980s, probiotic research focused on screening potential probiotic strains from isolates in nature or from human hosts, and defining the mechanisms of actions for probiotic strains. Continued research furthered the understanding of the complex interactions of normal flora and its ability to resist pathogenic bacteria invasion, termed colonization resistance [8]. As shown in Figure 1, the explosion of studies on probiotics is reflected by the increase in the number of publications about probiotics (from 176/year in 2000 to 1476/year in

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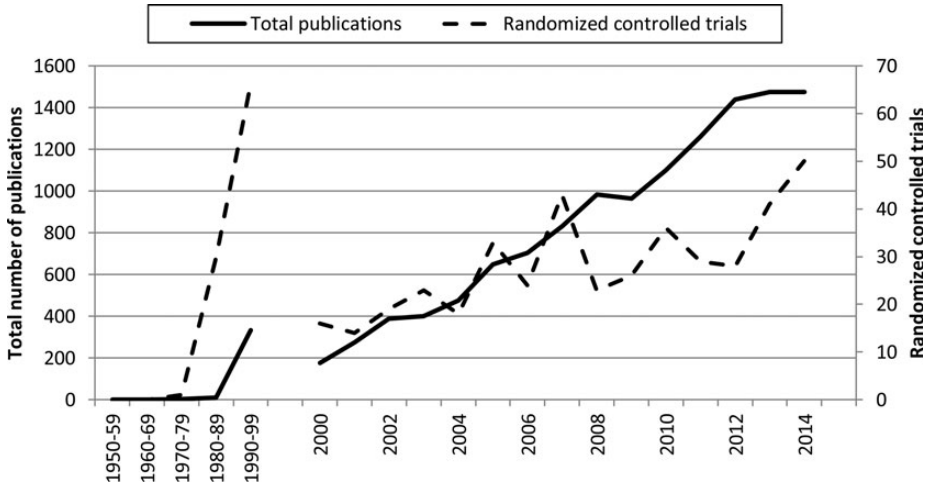


**Figure 1.** Number of publications (solid line) and randomized controlled trials (dashed line), by decade (1950–1990) or by year (after 2000), on probiotics from PubMed search, 1950–2014. Total of 12 947 publications and 477 randomized trials. The year 2014 is censored at August 2014.

2014). An exponential increase (starting in 2000) is seen in the number of evidence-based clinical trials testing both efficacy and safety of these products. The sheer number of publications of clinical trials with hundreds of different types of probiotics makes it difficult for healthcare providers and the public to know which probiotic is most appropriate for specific disease indications. Meta-analyses combine the outcomes from multiple clinical trials, resulting in a pooled estimate of efficacy, but early meta-analyses were often flawed due to pooling of different probiotic strains or pooling different indications together [9, 10]. As the efficacy of probiotics was discovered to be strain-specific, it is recommended that future meta-analyses pool results only within

**Table 1. Sources of Common Probiotic Strains**

| Strains | First Isolated | First Apparent Action | Main Reference, First Author |
|---|---|---|---|
| *Bifidobacteria bifidum* | Henry Tissier isolated from an infant stool sample | Displaced pathogenic bacteria | Tissier, 1906 [4] |
| *Clostridium butyricum 588* | Isolated from the soil in 1963 | Change in normal intestinal microflora | Meng, 1999 [20] |
| *Escherichia coli* Nissle DSM6601 | In 1917, Alfred Nissle isolated from healthy soldier during WWI | Prevent salmonellosis and shigellosis | Jacobi, 2011 [21] |
| *Lactobacillus acidophilus* Lb | Isolated from human intestinal tract | Diarrhea | Ljungh, 2006 [22] |
| *Lactobacillus bulgaricus* | In 1905, isolated from fermented milk by Stamen Grigorov | Yogurt fermentation | Grigoroff, 1905 [23] |
| *Lactobacillus casei* subsp *Shirota* | Isolated from human feces. Minoru Shirota discovered it in 1935 | Resists pathogen colonization | Shirota, 1966 [24] |
| *Lactobacillus plantarum* 299v (DSM9843) | Isolated from human colon | Reduces inflammation | Molin, 2001 [25] |
| *Lactobacillus reuteri* DSM 55730 | In 1990, isolated from human breast milk in Peru | Establish normal infant intestinal microflora | Spinler, 2008 [26] |
| *L. reuteri* DSM 17938 | Daughter strain of *L. reuteri* 55730 | Safer, deleted plasmid with 2 antibiotic resistant genes | Spinler, 2008 [26] |
| *Lactobacillus rhamnosus* GG (ATCC 53013) | In 1983, isolated from healthy human feces by Goldin and Gorbach | Improve normal colonic flora | Goldin, 1992 [27] |
| *L. rhamnosus* CNCM I-1720 | In 1976, isolated from dairy starter cultures | Peptic ulcer healing | Foster, 2011 [28] |
| *L. helveticus* CNCM I-1722 | In 1990, isolated from acidophilus milk starter | Peptic ulcer healing | Foster, 2011 [28] |
| *Saccharomyces boulardii* CNCM I-745 | In 1920, Henri Boulard isolated yeast on surface of lychee fruit | Prevented cholera | McFarland, 2010 [29] |

**Table 2. Examples of Different Types of Probiotic Products**

| Probiotic Strain | Formulation | Brand Name (Manufacturer) | Evidence-Based Efficacy |
|---|---|---|---|
| Single-strain probiotics | | | |
| *Bifidobacterium animalis* subsp *lactis* DN-173010 | Yogurt | Activia (Danone) | Constipation |
| *B. animalis* subsp *lactis* Bb-12 | Capsules, powder in sticks, fermented milk | BB-12 (Chr Hansen) | Eczema |
| *Bifidobacterium infantis* 35624 | Drink, capsules | Align (Procter & Gamble) | IBS |
| *Clostridium butyricum 588* | Tablets, drink | MIYA-BM (Miyarisan Pharm) | AAD<br>*Helicobacter pylori* infection |
| *Enterococcus faecium* SF 68 | Powder, sachets | Bioflorin (Cerbios-Pharma) | Acute adult diarrhea |
| *Escherichia coli* Nissle 1917 | Capsules | Mutaflor (Ardeypharm) | No trends |
| *Lactobacillus acidophilus* Lb | Sachets, capsules | Lacteol (PUMC Pharm) | Acute pediatric diarrhea |
| *Lactobacillus casei* subsp *Shirota* | Fermented milk | Yakult (Yakult) | Constipation, *H. pylori* infection |
| *L. casei* DN-114001 | Fermented drink, yogurt | Actimel, DanActive (Danone) | AAD, prevention of pediatric diarrhea, respiratory infections |
| *L. rhamnosus* Lcr35 | Vaginal capsules | Gynophilus | BV |
| *Lactobacillus johnsonii* La1 | Milk | NC1 (Nestle) | *H. pylori* infections |
| *Lactobacillus plantarum* 299v (DSM9843) | Fermented oat gruel in fruit drink, capsules | ProViva (Probi)<br>Darolac-IBS (Araisto) | IBS, CDI |
| *Lactobacillus reuteri* DSM 17938 | Capsules, yogurt | Protectis (BioGaia) | Acute pediatric diarrhea, cholesterol |
| *L. rhamnosus* GG (ATCC 53013) | Yogurt, capsules | Culturelle (Amerifit Brands)<br>Vifit (Valio) | Acute pediatric diarrhea, AAD |
| *Saccharomyces boulardii* CNCM I-745 (lyo) | Capsules | Florastor, Codex, UltraLevure (Biocodex) | AAD, CDI, acute adult and pediatric diarrhea, TD, *H. pylori* infections |
| Mixtures of probiotic strains | | | |
| *L. acidophilus* CL1285 + *L. casei* Lbc80r + *L. rhamnosus* CLR2 | Fermented drink, capsules | Bio K+ (BioK+ Intl) | AAD, CDI |
| *Lactobacillus helveticus* R0052 (CNCM I-1722) + *L. rhamnosus* R0011 (CNCM I-1720) | Capsules, sachets | Lacidofil (Lallemand)<br>A'Biotica (Institut Rosell) | *H. pylori* infection, AAD |
| *L. helveticus (bulgaricus)* 4962 + *L. acidophilus* | Capsules | Lactinex (BD Diagnostics) | Acute adult diarrhea |
| *L. reuteri* DSM17938 + *L. reuteri* PTA5289 | Lozenges, powder, capsules | Prodentis (BioGaia) | Dental infections |
| *L. acidophilus* + *B. animalis* subsp *lactis* | Yogurt | AB Yogurt | Improves normal flora |
| *L. acidophilus* + *Bifidobacterium bifidum* | Capsules | Infloran Berna (Intituo Sieroterapico) | Respiratory tract infections |
| *L. acidophilus* subsp *gasseri* + *Bifidobacterium infantis* | Capsules | Linex (Sandoz) | AAD |
| *Bacillus clausii* (4 strains: O/C, N/R84, T84, Sin8) | Capsules, spores in vial | Enterogermina (Sanofi-Aventis) | Antidiarrheal |
| *Bifidobacterium breve, Bifidobacterium longum, B. infantis, L. acidophilus, L. plantarum, L. casei, L. bulgaricus, Streptococcus thermophilus* | Sachets | VSL#3 (Sigma-Tau Pharm Inc) | IBS<br>UC |

Abbreviations: AAD, antibiotic-associated diarrhea; BV, bacterial vaginosis; CDI, *Clostridium difficile* infection; IBS, irritable bowel syndrome; TD, traveler's diarrhea; UC, ulcerative colitis.

a specific strain [11]. The evolution of meta-analytic techniques has allowed a better estimate of efficacy for specific probiotic strains for specific diseases [12, 13].

With the advent of newer tools to detect noncultivatable microbes (75%–95% of colonic microbes cannot be grown in standard culture media), a better understanding of the dynamics of the microbiome is developing. The Human Microbiome Project, using metagenomic analysis (DNA sequencing of bacteria), has identified >40 000 species in the colon and is creating profiles of the normal microbiologic constituents found in healthy humans [14, 15]. These newer tools enable researchers to focus on how the microbiota is altered by disruptive factors, such as antibiotic exposure or chronic disease, and the ways various probiotic strains can correct or restore this balance [16].

Efforts have also increased to guide healthcare providers, the public, and probiotic manufacturers regarding what constitutes

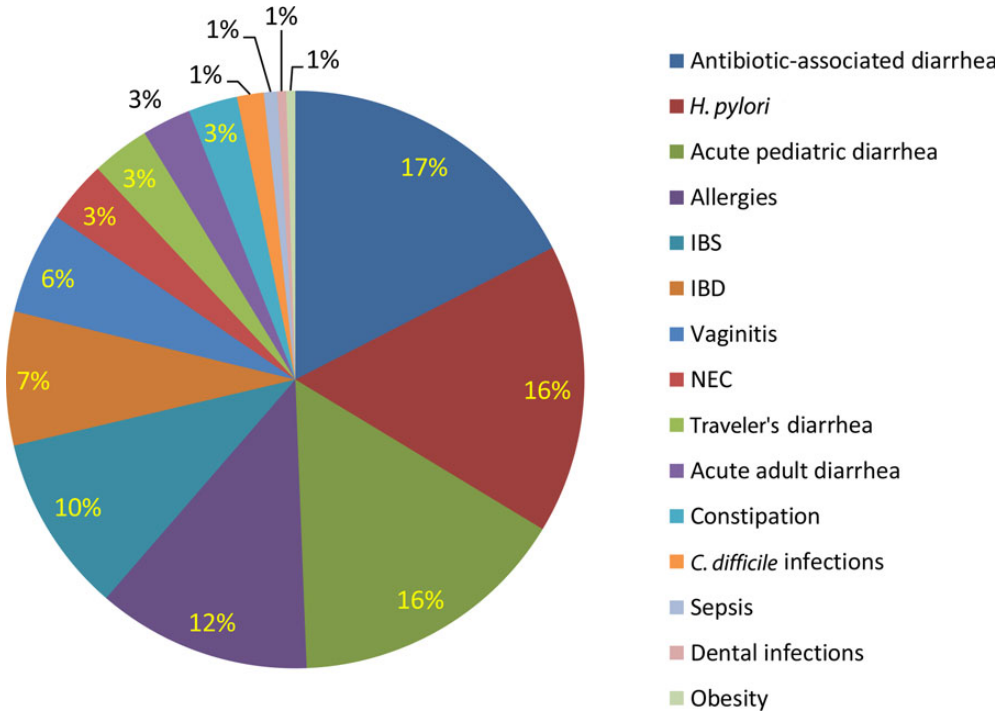


**Figure 2.** The 15 most commonly studied indications for probiotics from 420 randomized controlled trials, 1977–2014. Abbreviations: IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NEC, necrotizing enterocolitis.

a probiotic and which types of health claims or disease indication claims are appropriate. The term "probiotic" was first used by Lilley and Stillwell in 1965 to describe substances secreted by one microbe that stimulated the growth of another [17]. In 2001, the Food and Agriculture Organization of the United Nations redefined probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [18]. In 2013, the World Gastroenterology Organization published its global guidelines on probiotics and prebiotics, and confirmed that the efficacy of probiotics are strain-specific and dose-specific, dispelling the myth held by many that any yogurt can be considered a probiotic [11]. In 2014, a consensus statement reviewed the data on probiotics and defined 3 broad categories of probiotics: (1) those with no health claims (generally considered safe, no proof of efficacy needed), (2) as a food supplement with specific health claim (defined strain used, evidence-based efficacy from clinical trials or meta-analyses, use for reinforcing natural defenses or reducing symptoms) or (3) as a probiotic drug (clinical trials for specific indication or disease, defined strain used, risk-benefit justification, meeting regulatory standards for drugs) [19].

## IDEAL PROPERTIES FOR PROBIOTIC STRAINS

Screening for viable probiotic candidates can be labor intensive, but certain properties have proven useful. These properties fall into 5 broad categories: (1) survival to the target organ, (2) interaction with host systems, (3) antipathogenic actions, (4) safety, and (5) manufacturing concerns. The target organ can include the intestinal tract, skin surface, dental cavity, vagina, or urinary tract. Most probiotics are taken orally to reach the target organ (intestinal tract), and thus must survive transit from the mouth to the colon. This involves screening potential probiotic strains for resistance to gastric and bile acidity. The next step involves animal models or human volunteers to assess kinetics, percentage recovery of oral dose, ability to adhere to mucosal surfaces and ability to persist within the complex microecology of the gut. As shown in Table 1, potential probiotics have been isolated from a variety of sources: human stool samples, soil, dairy products, or the surfaces of fruit [4, 20–29]. Typically, many strains are screened before a viable candidate is found. Domig et al screened 127 lactobacilli from vaginal isolates and found only 4 (3%) had probiotic potential [30]. Gu et al screened 567 lactobacilli strains and found that only 36 (6%) were resistant to gastric and bile acids [31]. Once a potential candidate is identified, in vitro and in vivo testing for acid and bile resistance is done. For example, *Lactobacillus plantarum* 299v is currently used as a probiotic and was found to be resistant to both gastric acid and bile and produced a mannose-specific adhesin, allowing it to adhere to colonic mucosal cells [32, 33]. Abdulla et al tested 6 lactobacilli strains isolated

from milk, yogurt, or cheese, and found not only different adherent abilities (ranging from 8% to 50%), but also varying abilities to inhibit pathogenic bacteria [34]. The ability to inhibit or interfere with pathogenic organisms is paramount for a successful probiotic candidate, although not all probiotics act directly against a pathogen. Some probiotics act on the host's immune system, either downregulating or upregulating the immune response, typically for chronic intestinal conditions, such as inflammatory bowel disease or irritable bowel disease [35, 36]. Several mechanisms of action directly focus on the pathogens: the production of bacteriocins, interference with the pathogen attachment site, and destruction of toxins produced by pathogens. Sometimes the probiotic may act as a "decoy binding site," when the pathogen attaches to the probiotic surface rather than to the host's mucosal surface [11, 29]. Ideally, the probiotic strain is also unaffected by concomitant medications or antibiotics taken at the same time as the probiotic. For example, *Saccharomyces boulardii* is a yeast that can be taken at the same time as oral antibiotics, because it is affected only by antifungal medications and not antibiotics. The probiotic also should be safe to take, with a good safety profile from animal and human volunteer studies (showing a lack of translocation out of the target organ, lack of pathogenesis, and few serious adverse reactions). Manufacturing concerns may include ease of production, production of a stable line of probiotic strain batches, stability over time (shelf life), resistance to humidity and other common storage conditions, cost-effectiveness, and a competitive marketing edge (perhaps a unique property or proven efficacy). As a result of extensive screening and testing, many probiotics have made the journey from the laboratory to the therapeutic arena. There are >90 different probiotic products available in the United States, 65 in Japan, 31 in New Zealand, and >100 globally. Probiotics are currently available as tablets, capsules, sachets, wafers, in fermented milks or drinks, in yogurts and cheese, and even in chocolates. Probiotic products can be obtained from pharmacies, drugstores, grocery stores, health food stores, or from websites on the Internet. Some examples of common probiotic products are shown in Table 2.

## CONTEMPORARY DATA ON CONSUMER USE (MARKETING)

Probiotics have been used for decades in Europe and Asia, and are becoming more popular in the United States and other parts of the world. Their use is expanding dramatically as our understanding of how probiotics work grows and as we identify which strains are effective for specific conditions. Probiotics have an annual market growth of 7% globally, and are forecast to reach sales of $48 billion by 2017 [37]. Although the use of probiotics differs from country to country, generally probiotics are used by women aged <50 years and most rely on their doctor for information on probiotics, although many patients retrieve information on probiotics from the Internet [38].

## DISEASE INDICATIONS

A literature review reveals that probiotics have been tested over a wide variety of indications, as seen in Figure 2. A literature review from 420 randomized controlled trials (from 1977 to 2014) found that the most common indications are prevention of antibiotic-associated diarrhea (17%), treatment of *Helicobacter pylori* infection (16%), treatment of pediatric acute diarrhea (16%), prevention of allergies (12%), treatment of chronic irritable bowel disease (10%) or inflammatory bowel disease (7%), and treatment of vaginitis and bacterial vaginosis (6%); less commonly, prevention of necrotizing enterocolitis in newborns (3%), prevention of traveler's diarrhea (3%), treatment of adult acute diarrhea (3%), treatment of constipation (3%), and treatment of *Clostridium difficile* infection (3%); and, rarely, for sepsis, dental infections, and obesity (1% each). Findings of clinical efficacy vary by probiotic strain and by type of indication (Table 2) and have been well addressed by reviews and guidelines in the literature [11, 39]. The role of probiotics for *C. difficile* infection has been previously addressed [40] and will be covered by other articles in this supplement.

In summary, the field of probiotics continues to grow, not only by the increasing number of people who use probiotics, but also by the variety of probiotic products. A suggestion for future studies is to report detailed descriptions of the probiotic tested (genus, species and strain, daily dose and duration used) so the appropriate data may be pooled and analyzed [41, 42]. The challenges for healthcare providers, the public, and manufacturers continue to be focused on consistent regulatory standards and providing guidance for strain-specific, evidence-based therapy.

### Notes

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