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Probiotics in the United States FREE

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Abstract

Probiotics are live microbial products that have a defined health benefit. Scientific research has established that there are validated indications for the use of some probiotics available in the United States; however, in many cases, they are often used for conditions for which no benefit has been established. This article will review the uses of probiotics in the United States, as well as the current state of regulatory issues surrounding probiotics. Although the use and scientific understanding of probiotics are rapidly increasing, it is evident that there is a need to clarify the regulatory issues, which, at present, are unclear and subject to misinterpretation. In addition to efficacy, safety issues must be considered in determining when and how probiotics are to be used.

Topic: [probiotics](#), [safety](#), [regulation](#)

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The history of medicine dates back to 2000 b.c., when humans used roots as a treatment measure. From that time, humans have progressed to using prayer and then potions, and, ultimately, in the 1940s, to the discovery and use of pharmaceuticals, particularly antibiotics. Currently, it is becoming increasingly apparent that medications, although curative for many conditions, are not without risk and may have many adverse effects. This is particularly evident with the use of antibiotics, which are leading to the creation of resistant strains of bacteria that are often more deadly, as well as to numerous adverse events, such as *Clostridium difficile* colitis. To counteract these effects of antibiotics, scientists have returned to natural substances, such as probiotics.

Probiotics are live microorganisms that, when ingested, produce some therapeutic or preventive health benefit [1]. The health-promoting concept has been around for a long time, dating back ~100 years, to the work of Metchnikoff [2]. Originally, live bacteria and other microorganisms were commonly ingested in food, and organisms were extensively used for food preservation. Additionally, bacteriologists have long noted that certain organisms, primarily species of *Lactobacillus* or *Bifidobacterium*, appear to have health-promoting benefits. However, with the advent of refrigeration and with a tendency toward manufacturing and consumption of processed foods in a sterile food supply, the ingestion of microorganisms has become much more limited.

The consumption of good bacteria in our diets results in the transient changes in the bacteria in our intestines or intestinal tract. This is because humans receive their first exposure to bacteria during the birthing process, and it is during early infancy that the intestinal immune system learns to recognize these bacteria as desired, or healthy, bacteria necessary for the development of the systemic immune system. For the rest of one's natural life, any attempt to change the bacterial flora or to alter it with additional organisms will trigger an immune response targeted to kill the new organisms and eradicate them from the gastrointestinal tract. The organisms ingested at birth, however, are well tolerated throughout life [3, 4].

US Market

The US market is becoming much more open-minded in terms of alternative therapies, including probiotics. There is a desire to take control of health matters, including gaining a greater understanding of disease processes, treatment aspects, and preventive or health-promoting measures. Much of this has derived from a general dissatisfaction with conventional medical therapy, including the limited access to care and the increasing costs of traditional medical therapies.

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There are certain unique features of the US market that make the promotion of food-based probiotics somewhat challenging. There is a general lack of fermented food choices and a low

consumption of the limited available fermented foods in the United States. This partially relates to food taste preferences, which tend toward the sweet and fatty flavors instead of the sour and strong flavors associated with fermented food products [5]. An even greater hindrance to probiotic acceptance is the strong fear of all bacteria. Since the discovery of penicillin and the understanding of bacteria as disease-causing agents, the healthy aspects of bacteria have been totally ignored; this was unchanged until recently. In addition to the food industry's enhancement of the shelf stability of foods by eradicating most organisms from the foods, the increasing fear of foodborne illness has created an atmosphere of consumers who demand germ-free products.

There is a growing and probably justifiable skepticism of the advertising claims for many natural and food products; therefore, the ability to educate consumers about good bacteria is somewhat limited [6]. In this light, there also appears to be so many promoted health claims about foods that adding another appears to be the tipping point in terms of believability. Finally, cost is always a consideration because most insurance plans do not cover most over-the-counter or alternative therapies, such as probiotics.

The unique features of the US market were the prime reason behind the medical marketing strategy used by the US distributor (Amerifit Brands) of the probiotic *Lactobacillus rhamnosus* strain GG (*Lactobacillus* GG). It was decided that the benefits of the probiotics were best established with sound clinical studies based on scientific rigor and performed at reputable academic institutions. It was through the publication and presentation of these studies at academic meetings that physician awareness was raised about the benefits of *Lactobacillus* GG. The press releases related to the meeting events and publications then disseminated the information into the general public awareness.

Uses of Probiotics

To be a successful probiotic, bacteria must be ingested in an active form, must be able to colonize in the gut (i.e., reproduce to the extent that they can be identified in the stool), and must have the ability to both attach (via a direct connection mechanism) and adhere (being present on the surface but not directly attached) to the lining of the gastrointestinal tract to provide significant immunomodulating benefits [7]. Probiotic effects tend to be strain specific. For example, only a few strains of *Lactobacillus acidophilus* appear to be capable of functioning as a true probiotic—that is, to induce beneficial health benefits. Likewise, the same is true for certain strains of *Lactobacillus casei*, *L. rhamnosus*, and *Bifidobacterium* species. Perhaps the most well-studied strain is *Lactobacillus* GG, although data on other strains are appearing almost daily.

In general, clinical studies have validated the used of probiotics for the following conditions:

1. Viral diarrhea [8–13]
2. Antibiotic-associated diarrhea [14–17]
3. *C. difficile*–associated diarrhea [17–19]
4. Traveler's diarrhea [20–23]
5. Atopic dermatitis [24–27]
6. Pouchitis [28, 29]
7. Irritable bowel syndrome [30–32]

Case reports and preliminary data exist for the use of probiotics for the following conditions:

1. Rheumatoid arthritis [33]
2. Crohn disease and/or ulcerative colitis [34–38]
3. Small-bowel bacterial overgrowth [39–41]
4. Dental caries [42, 43]
5. Infantile allergies and/or asthma (prevention) [44, 45]
6. Lactose intolerance [46, 47]
7. Colon cancer (reduction) [48–50]
8. High cholesterol [51, 52]

Studies of *L. acidophilus*, *Lactobacillus* GG, and *Lactobacillus reuteri* have all demonstrated ameliorating effects with regard to both the severity and the duration of acute viral diarrhea in children [8–10]. *Lactobacillus* GG has been shown to reduce the incidence of traveler's diarrhea. *Lactobacillus* GG, the yeast *Saccharomyces boulardii*, and certain other probiotics have been shown to reduce the risk of relapse of *C. difficile*–associated diarrhea [18, 53]. A mixture of different species of lactobacilli has been shown to be efficacious in the prevention of pouchitis in patients who underwent colectomy for ulcerative colitis [28]. The incidence of antibiotic-associated diarrhea in children can be reduced with *Lactobacillus* GG, as can the occurrence of diarrheal disease in day care centers [44]. There is even some preliminary evidence that respiratory disease can, to some extent, be prevented by the use of probiotics such as *Lactobacillus* GG through the effects of the probiotic on the systemic immune system [54].

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There are some data indicating that probiotics may be helpful in the treatment of irritable bowel syndrome in some subsets of people [30]. Many studies are in the process of looking at probiotic

treatment of inflammatory bowel disease, specifically Crohn disease and ulcerative colitis [34–36, 55]. Perhaps the most interesting observation is that the severity of allergic disease in children may be reduced through the administration of probiotics—namely, *Lactobacillus* GG—in the neonatal and early infancy period [24, 25]. In this sense, probiotics appear to redirect the immune system toward the production of chemical mediators that are more useful in controlling infections, rather than mediators that induce the allergic response.

A review of consumer purchasing of probiotics in the United States also suggests other uses, including the following:

1. Treatment of celiac disease
2. Treatment of autism
3. Treatment of chronic fatigue syndrome
4. Enhancement of digestive processes
5. Prevention and treatment of systemic candidiasis
6. Prevention and treatment of diaper rash
7. Prevention and treatment of tinea pedis
8. Small animal or pet uses, such as for birds, dogs, and cats
9. Facilitation of nutrient utilization before a race for swimmers or marathon runners

The use of probiotics for these conditions is not based on scientific study but typically is disseminated via organized groups of individuals seeking a solution to a specific problem (Amerifit Brands, personal communication).

Current Market for Probiotics in the United States

In the United States, there are many small probiotic distributors, but, unlike in European and Asian countries, there exist only a limited number of fermentation facilities. In most cases, probiotics are imported from outside the United States and then are formulated and packaged in the United States. Unfortunately, many of the distributors make outrageous claims based on little or no objective data. Added to that, it has been found that many of the products do not contain the stated bacteria, contain nonviable organisms, contain organisms in less-than-stated amounts, or provide organisms with no proven benefit. Some products even contain undefined organisms or other types of contaminants. This has created a skeptical attitude among both medical professionals and consumers who have had less-than-optimal

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experiences with probiotics. There are a few reputable companies who use products with scientific support but, unfortunately, provide them to consumers in less-than-innovative forms.

In the United States, probiotics are provided primarily in the form of capsules or sachet preparations. There are a limited number of true probiotic preparations available in food formats, such as yogurts with live active cultures in spoonable or drinkable forms. US sales of probiotics were estimated to be \$764 million in 2005 and are projected to be \$1.1 billion in 2010. Sales of probiotics used in the manufacture of food supplements are projected to reach \$291.4 million in 2010, and food applications are expected to dominate the market, with sales estimated at \$700 in 2010 [56]. Yogurts, kefir, and cultured drinks represent the major categories.

It is anticipated that companies in the United States will eventually provide probiotic foods, such as cheeses, juices, milk beverages, and infant formulas, similar to those that are currently available in Europe and Asia. Probiotics in the United States are distributed primarily in retail and hospital pharmacies and health food stores but are also available via direct mail and supermarkets.

The primary probiotics available in the United States include preparations containing *L. acidophilus*, *Lactobacillus GG*, *L. reuteri*, *Bifidobacterium* species, and *S. boulardii*. A great majority of preparations include numerous combinations of commonly recognized healthy bacteria and the products that contain poorly defined or unidentifiable organisms. A major lack of knowledge exists, even among physicians, about the individual differences among bacteria. For example, the only similarity that exists among *Lactobacillus* species is the fact that they only produce lactic acid as a by-product of their metabolism. Other characteristics, such as adherence capabilities, the environment in which they survive, and so forth, are vastly different and vary according to the species as well as the strain of individual species. These differences have been noted by the medical community and are noted in clinical studies, including studies of pouchitis, inflammatory bowel disease, traveler's diarrhea, *C. difficile* colitis, antibiotic-associated diarrhea, and irritable bowel syndrome.

Regulatory Issues

Regulatory issues in the United States are an area of great concern. There are numerous issues to be addressed, including what the industry officials need to know and how to provide protection for consumers. The US Food and Drug Administration (FDA) regulates the safety, labeling, and health claims of food and dietary supplement products. The Federal Trade Commission regulates advertising. Statements that relate the product to the prevention, diagnosis, treatment, cure, or mitigation of disease are forbidden (unless the statements are

specifically reviewed and approved by the FDA). Any other health statements, such as “structure/function statements,” must be truthful and not misleading but do not require preapproval. Structure/function statements are statements that relate the product to the normal functioning of the human body and are allowable with regard to conventional foods, as well as dietary supplements. Currently, most probiotics claim to have the status “generally regarded as safe” (GRAS) and therefore to be not subject to any specific standards. Unlike Canada and some European countries, the United States has no governmental standards for probiotics [57]. In Japan, there exists a term used to describe functional foods that have received approval by the Japanese Ministry of Health and Welfare: “foods for specific health use,” and many probiotics used there are in this category [58]. No disease-prevention or therapeutic claim is known to have been approved by any other government in the industrialized world. Without specific oversights or set standards, this has led to significant variability in products and a lack of coverage by third-party payers.

In the United States, the question arises as to how probiotics should be regulated; the options include as dietary supplements, functional foods, medical foods, over-the-counter drugs, or possibly an independent category. Most probiotics are regulated as dietary supplements, which were defined in 1994 by the FDA via the Dietary Supplement and Health Education Act [59]. The act basically defines dietary supplements as products other than tobacco that are intended to supplement the diet and contain β 1 of the following ingredients:

1. Vitamins or minerals
2. Herbs or other botanicals
3. Amino acids
4. Substances used to increase total dietary intake
5. Concentrate, metabolite, constituent, extract, or a combination of above

In the United States, probiotic products fall into the category of a dietary supplement; however, most dietary supplements customarily are foods or drinks for human consumption. According to the FDA, the determining factor as to whether a probiotic is a dietary supplement is whether it is or has been used as or in a food. Many do not understand that because a probiotic has GRAS status for use in a food does not necessarily mean that it has GRAS status for use in a capsule or sachet format. It has been left to the manufacturer, not the FDA, to determine whether the supplement presents a potential risk of adverse events based on the recommended suggested uses displayed on the label [60].

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Some have suggested that probiotic food products would more appropriately qualify as functional foods, although currently there are none in the United States. In part, this is because there is no universally accepted definition of a functional food. The International Food

Information Council has suggested that this category be classified as foods that provide health benefits beyond basic nutrition. The Institute of Medicine of the National Academy of Sciences has suggested that functional foods are those in which the concentrations of β 1 ingredient have been manipulated or modified to enhance their contribution to a healthy diet [61]. Oat bran was the first food with an FDA-approved health claim regarding the benefits in reducing the risk of heart disease.

Another category in which probiotics may fit is medical foods. According to the FDA, medical foods are defined as foods that are formulated to be consumed or administered enterally under the supervision of a physician and that are intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. An example of a medical food is a food for use by persons with phenylketonuria—that is, foods formulated to be free of the amino acid phenylalanine. Medical foods are not meant to be used by the general public and may not be available in stores or supermarkets. Medical foods do not include those foods normally present in a healthy diet that tend to decrease the risk of disease, such as reduced-fat foods or low-sodium foods, and they are not weight-loss products.

Some probiotics with significant research may actually qualify as an over-the-counter product. These products typically have characteristics in which the benefits outweigh the risks, have a low potential for misuse and abuse, and can be adequately labeled. Additionally, they are also products that the consumer can use for self-diagnosed conditions and for which health practitioners are not needed for safe and effective use [62]. To meet these requirements, significant investment in research and development are required by the FDA, which provides tighter oversight of this category compared with the category of dietary supplements or medical foods.

Safety

Safety concerns for any product suggested for health promotion or disease prevention should be considered [63, 64]. For example, a woman with diabetes developed a *Lactobacillus* GG-related liver abscess after consuming a *Lactobacillus* GG-containing drink, and several cases of sepsis with *Lactobacillus* GG have been reported in children with short bowel syndrome; most have had indwelling central venous catheters. It must be understood by individuals who use these products that they contain bacteria, and caution should be taken when dealing with the sterile situations required for manipulation of central venous catheters. Sepsis has also been reported with the probiotic *S. boulardii*.

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These issues raise questions about the overall safety of probiotics and may create a barrier for regulatory approval in the future. This issue is unlikely to be specific to a certain group of

probiotics but more likely will be raised for specific strains, again underscoring the importance of identifying the characteristics of specific strains.

In summary, it is evident that there are some validated indications for probiotic use, but, in many cases, probiotics are used for conditions for which no benefit has been established. The use and scientific understanding of probiotics are rapidly increasing, and there is a need to clarify the regulatory issues, which, at present, are unclear and subject to misinterpretation. In addition to efficacy, safety issues must be considered in determining when and how probiotics are to be used.

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