The Evidence to Support Health Claims for Probiotics

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Abstract

As the health benefits of ingesting live bacteria become more evident, foods are now being produced that contain probiotic bacteria. The data to support label health claims for probiotic products are often difficult to provide. The experimental evidence to identify probiotic microorganisms and to demonstrate their efficacy in clinical trials is more challenging than for other functional foods because effects are mediated by living microorganisms and may therefore be influenced by the status of these microorganisms. Clinical trials to show efficacy are expensive. Obtaining appropriate samples is difficult. A scientific consensus is building to support the claim that the ingestion of certain probiotic bacteria reduces lactose intolerance and can reduce the duration of rotavirus diarrhea. Some probiotic bacteria have “generally accepted as safe” status; proof of the safety of any probiotic is essential. Japanese health regulatory officials, using their Foods for Specific Health Use system, have approved human health claims for over 20 probiotic products. On the other hand, at this time, no probiotic product is sold in Canada that carries a label health claim. This illustrates the considerable discrepancies across countries in perception of health effects of probiotics. J. Nutr. 138: 1250S–1254S, 2008.

Introduction

Fermented foods and foods that contain live bacteria are known throughout the world (1,2). Traditionally, foods were fermented to extend shelf life by reducing pH or to improve taste by producing flavorful bacterial metabolites or texture by breaking down some carbohydrates. Fermentation may also improve the nutritive value of foods by producing vitamins and breaking down nonnutritive factors. With the increasing evidence that some bacteria can be beneficial to human health and metabolism (3,4), the interest in foods containing live bacteria has increased, and today food manufacturers are adding beneficial bacteria to a wide variety of foods and beverages. Both fermented products, e.g., milk, soy, meat, and nonfermented foods, e.g., breakfast cereals and fruit juices, may now contain bacteria that are considered to be beneficial. Thus, in the broad category of functional foods, foods that have added health benefits, there is a subgroup of foods termed probiotics—foods that may be beneficial to health because they contain probiotic bacteria (Table 1).

Most probiotic products on the market to date contain 1 or more bacteria, although some products such as kefir also contain yeasts (2). Lactic acid bacteria (LAB)3 including Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei Shirota, Lactobacillus gasseri, and Bifidobacterium bifidum are the most common probiotic bacteria added to food products because LAB are presumed to impart beneficial effects on the host such as improving intestinal tract health, enhancing the host’s immune system, reducing the symptoms of lactose intolerance, and reducing the risk of certain cancers (8). LAB are found in many fermented foods, are normal colonizers of the human body (9), and have had a low level of infection attributed to them. For these reasons, most LAB are generally recognized as safe (10).

The objective of this article is to outline the main challenges associated with accumulating evidence in support of health claims for probiotics and to give a perspective of the scientific gaps that need to be addressed to advance these functional foods. This article addresses probiotics in a food or beverage format. Unless otherwise stated, references to regulations apply to Canadian regulations or to those that apply worldwide.

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3 Abbreviations used: FOSHU, Foods for Specific Health Use; GI, gastrointestinal; HC, Health Canada; LAB, lactic acid bacteria; NHPD, Natural Health Products Directorate.
Challenges associated with establishing health claims for probiotics

**Identification of microorganisms.** Worldwide, food manufacturers are developing new functional foods. An important part of the marketing of these new products is the ability to label these foods with a health claim. Any petition to a regulatory agency for a health claim will have to name or describe the active ingredients in the product to be approved and provide evidence of efficacy. Companies seeking approved label health claims for probiotics may find this somewhat problematic. For example, definitive identification of the microorganisms contained in the probiotic product often requires rigorous molecular biology and informatics techniques (11). Polyphasic characterization combining phenotypic, biochemical, genotypic, and sequencing results is now being used to reliably identify bacteria to the strain level (12). This is particularly important because it is now evident that even closely related bacterial species can have different properties. Properties such as pH sensitivity and resistance to bile salts or other characteristics may affect their ability to survive in the gastrointestinal (GI) tract and exert their beneficial effects (13, 14). It is essential, therefore, that the bacteria included in a probiotic be identified to the species or subspecies level. In some cases, the bacterial strain used is proprietary, which can make verification of its identity by regulatory agencies more difficult.

To obtain a health claim for a probiotic product, food manufacturers will have to precisely define their microorganism. Identification methods are constantly being improved, and this will make definitive identification easier.

**Enumeration of microorganisms.** The definition of probiotic emphasizes that the organism must be taken in adequate amounts to be effective. To support a health claim, it is thus imperative that the product manufacturer provides data about the total number of live microorganisms in the product when consumed as well as methodology that can be used to verify these values. To the consumer, “more is better,” and so efforts are often made by food manufacturers to highlight the large numbers of bacteria in their product. Enumerating bacteria or other microorganisms in a food matrix is not easy (15), and if the product contains more than 1 microorganism, individual methods may have to be used to enumerate each microorganism. Although there are accepted methods for the counting and reporting of pathogenic and spoilage organisms in food, such universally accepted methods do not exist for probiotic bacteria.

At this time, in many other jurisdictions, there is no requirement for a company to state which bacteria are contained in its product, no requirement to use accepted nomenclature for the bacteria in the product, no requirement to state the number of bacteria in the product, and no requirement to ensure that the numbers of bacteria quoted on the label are alive.

Stating the type, viability, and number of bacteria contained in a probiotic product is important to both the consumer and health regulatory officials. At the present time, there is little incentive for manufacturers to include this information on their product; the costs for such quality assurance would be high. As regulations become clearer as they relate to probiotics, manufacturers can expect that they will be required to state this information. Consumers are also becoming more educated about probiotics, and so, they too will be pressuring food manufacturers for this information.

**Efficacy testing.** No single biomarker has been identified that applies to all clinical trials involving probiotics because of the wide variety of diseases and conditions that have been studied. The efficacy of probiotics has been studied for a variety of diseases and metabolic problems including Crohn’s disease (16–18), irritable bowel syndrome (19, 20), cholesterol metabolism (21, 22), anticancer properties (23, 24), and diverticulitis (25). It must be noted, however, that the degree of success that has been obtained for these conditions/diseases in probiotic feeding trials has not been uniform, and it would be wrong to assume that there exists good evidence to suggest that all of these conditions may be improved with probiotics. In many cases the GI tract has been the primary target (26, 27), but it is becoming evident that other conditions including allergies, obesity, and urogenital infections not initially associated with the gut microbiota might also be affected (28–30). A variety of mechanisms have been proposed to explain the responses to probiotics, including production of organic acids, production of bacteriocins (bacterial substances produced by a strain of certain bacteria and harmful to another strain within the same family), and reduction of toxin-producing organisms (31) as well as effects on the mucosal epithelium and the gut-associated lymphoid tissue (32). The suggestion that probiotics may be stimulating the immune system has generated a great deal of interest because of possible consequences to health and metabolism. However, studies are not often replicated, and therefore, efficacy is hard to establish. Some articles often lacked details such as the bacterial strain fed, the numbers of live bacteria consumed, or the timing of the consumption, e.g., with or without other foods, which limits their usefulness to prove efficacy. Hove et al. (33) concluded, after their review of the current literature, that a scientific consensus was being achieved concerning the beneficial effects of some probiotic bacteria for 2 applications in particular: lactose intolerance and diarrhea. Several studies have reported that the consumption of certain probiotic bacteria resulted in reduced lactose intolerance symptoms in human subjects (34, 35). Furthermore, a meta-analysis of the treatment of both childhood and rotavirus-associated childhood diarrhea with probiotic bacteria showed a significant reduction in the duration of the diarrhea episode (36). These 2 applications of probiotics appear to be the best documented and have enough reliable data to support a human health claim.

Despite the long list of conditions that have been tested with various probiotic products, very few health/metabolism conditions have been studied enough to obtain a label health claim. Efficacy experiments must be replicated and have appropriate numbers of subjects to achieve scientific consensus. The claim of efficacy will be greatly enhanced if a plausible mechanism can be suggested, or demonstrated, that explains the beneficial effect.

**Clinical trials and active ingredients.** A double-blind, placebo-controlled clinical trial is considered as the “gold standard” for most efficacy experiments, but researchers testing probiotics,
like most trials testing foods, have difficulty finding an appropriate control (37,38). Adding to this problem is the fact that it is often difficult to define what is the active ingredient in a probiotic food (Fig. 1). If the product has undergone fermentation, the number of possible candidates include the live bacteria themselves, components such as the cell wall, metabolites of the bacteria including exopolysaccharides, or ingredients produced during the fermentation process such as bioactive peptides. Most probiotic products today emphasize the number of live bacteria. However, in some cases, the ingredients responsible for the beneficial effects, such as a product of fermentation or a bacterial metabolite, may not require that the probiotic bacteria be viable when consumed.

Most studies provide data to show that the probiotic consumed can be found in the fecal material of the subjects during the dosing period (39,40). Fecal enzymes, pH, and short-chain fatty acid data are often provided to show changes to digesta composition and characteristics that accompany changes in the intestinal microbiota (41,42). Such changes, however, may not be related to beneficial clinical effects.

Health regulation officials worldwide require scientific evidence before they will approve a label health claim. Although biochemical, animal, and in vitro data can be used as supporting evidence, data from double-blind, placebo-controlled experiments are required. These experiments are expensive, but there is no substitute for these trials. Both from a scientific and a regulatory perspective, the identification of the active ingredient in a probiotic product is necessary. The probiotic producer also needs this information so that the active ingredient can be protected or extracted to be used in other products including nutraceuticals.

**Dosage of probiotic bacteria.** The number and the status of the bacteria to be consumed to obtain a beneficial effect are important characteristics of probiotic products that are often not well defined.

There is no consensus as to the minimum number of bacteria that need to be consumed to produce a beneficial effect on human metabolism and health. Each application for a health claim will be different. It can be anticipated that recommended doses will differ depending on the application (e.g., prevention vs. treatment of diarrhea). Differences between the properties (e.g., pH sensitivity) of bacterial strains will also have to be considered when recommendations on dosage levels are made.

The Fermented Milks and Lactic Acid Bacteria Beverages Association of Japan has set a minimum of $10^7$ bifidobacteria/g or mL (43), but others have suggested a lower level of $10^5$ (44). The harsh conditions in the GI tract and negative environment associated with low stomach pH, bile salts, and digestive enzymes require that large numbers of probiotic bacteria be consumed to ensure that an adequate number survive and reach their site of action in the lower GI tract. A wide range of numbers of bacteria fed can be found in the scientific literature. Many studies have shown that probiotics must be consumed every day because they do not colonize the gut and are quickly flushed out of the GI tract when consumption is stopped (45).

At this time, microbiological analyses of fecal material are the only way to show that the probiotic bacteria have remained viable during their passage through the GI tract. This is a major limitation because the site of action of probiotics is the large intestine or even higher up the GI tract. Therefore, even if companies are able to report how many viable bacteria are contained in their product when consumed, they are not able to report how many bacteria actually produce the beneficial effect at the site of action.

Probiotics are food products, but because their benefits impact on health, the concept of dose becomes important. At the present time, no probiotic bacterium has been shown to colonize the gut and persist after the cessation of consumption. Data from efficacy and clinical experiments will be needed to advise consumers how much of the product needs to be consumed each day to obtain a beneficial effect.

**Safety aspects.** The final aspect of probiotics of concern to both consumers and regulators is that of safety. *Lactococcus* and *Lactobacillus* are most commonly given “generally recognized as safe” status, but some of the genera *Streptococcus* and *Enterococcus* and some other genera of LAB that could be potential probiotics contain opportunistic pathogens (46). The absence of pathogenicity of any potential probiotic strain must be shown to prove its safety. There are very few reports in the literature of adverse reactions resulting from consumption of probiotic bacteria, particularly *Lactobacilli* and *Bifidobacteria*; however, the possibility of transmitting plasmid-associated antibiotic resistance has been noted as a possible concern in the development of probiotic products (47).

At this time, there are laws and regulations related to the pathogens and microbial food contaminants. No jurisdiction will allow the sale of unsafe food. Probiotics already enjoy an implied good health claim that cannot be jeopardized by possible questions of food safety. Most LAB are considered safe for human consumption, and so their inclusion in probiotic products presents no problems. However, before any new probiotic microorganisms will be approved, data will have to be submitted that clearly show they are safe for human consumption.

**Health claims worldwide**

Around the world, although the number of functional foods is growing, the number of probiotics carrying approved health claims is not large (48). The jurisdictions of the European Community, Japan, the United States, and Canada all have legislation to cover the approval of health claims for functional foods, but it has been observed that only a limited number of claims have been approved (49). The Japanese Foods for Specific Health Use (FOSHU) system allows several health claims for probiotics (Table 2). As a result, by 1999, 21 probiotic products had received FOSHU approval in Japan (48).

Several articles have been published recently that give more details about the laws and regulations related to functional foods and probiotics, and these highlight the different standards and requirements of different jurisdictions for food label health claims (48–51).

**Health Canada regulations related to probiotics**

Health Canada (HC) is the regulator responsible for food label claims in Canada. Schedule 1 of the legislation creating the Natural Health Products Directorate (NHPD) of HC lists...
“probiotic” as 1 of the substances under their jurisdiction (7). NHPD has its own working definition of a probiotic (Table 1). For HC, a probiotic is limited to nonpathogenic microorganisms. Foods such as yogurt that contain “microbes” are controlled by the Food Products Directorate of HC.

As with other food products regulated by HC, probiotics can carry a structure/function claim, a risk reduction claim, or a treatment claim (Table 3). This compares with the United States, where a probiotic is regulated at the federal level as a dietary supplement, a food, or as a drug, depending on the intended use. Efficacy data to support any label health claim in Canada are judged based on a hierarchy of criteria used to measure the scientific rigor of the research that generated the data (50). The amount and quality of the data to be supplied depend on the claim that is sought (51).

The HC/NHPD regulations concerning probiotics have requirements related to toxicity and safety (52,53). It is suggested that a multidisciplinary approach be used to examine the pathological, genetic, toxicological, immunological, gastroenterological, and microbiological aspects of the safety of probiotic strains. In a discussion paper prepared for HC, it is stated that “lactobacilli and bifidobacteria have been reviewed and their pathogenic potential deemed to be quite low” (54), implying that less evidence would be needed to show the safety of such microorganisms. In contrast, HC lists 8 bacterial strains it will not accept in a potential health claim submission because of reported safety concerns.

Probiotic products in either capsule or liquid form as nutraceuticals or as functional foods can be found in the marketplace in Canada today. It is not known how many petitions HC has received from companies related to probiotics. However, since its inception in 2004, HC/NHPD has not issued an approved health claim for any probiotic product (55).

**TABLE 3** Examples of possible probiotic food label claims

<table>
<thead>
<tr>
<th>Structure/function claim</th>
</tr>
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<tbody>
<tr>
<td>[Name of probiotic bacteria] helps maintain a healthy intestinal microbiota.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk reduction claim</th>
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<tbody>
<tr>
<td>[Name of probiotic bacteria] reduces the risk of [name of disease].</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment claim¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from clinical trials show that [name of probiotic bacteria] can be used in the treatment and prevention of [name of disease].</td>
</tr>
</tbody>
</table>

¹ Treatment claims can be made only for drugs in Canada; other jurisdictions have similar claims structures.

Literature Cited


