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Review Article

An Update on Probiotic Safety and Efficacy

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Abstract

Probiotics are live microorganisms that have recently gained popularity for being beneficial to human health and digestion. There are several forms of probiotics, perhaps the more widely used form is the lactic acid producer. Studies with the strongest clinical evidence have shown beneficial effects of probiotics for acute infectious diarrhea in children, antibiotic-associated diarrhea, among several others. Some studies have shown promising prophylactic effects for necrotizing enterocolitis, the common cold, irritable bowel syndrome, cancer, mucosal immunity, allergies, and urinary tract infections. While probiotics are generally known to be safe, there are occasional reports of adverse effects. Chief among the safety concerns is the ability of these organisms to invade the blood stream causing bacteremia or fungemia. Another concern relates to modifying the gut immune system, the largest immune organ, at a young age if probiotics are given to infants. With regards to lactic acid-producing probiotics, there is concern that accumulation of lactic acid in the body and the development of lactic acidosis can cause clinically significant problems. This article will provide an update on the safety and efficacy of probiotics and summarize the current literature about probiotics, including the issue of quality control.

HISTORY AND OVERVIEW

Fermented foods and cultured milk have been used by humans for many centuries. The first written scientific report was not until 1908 when the Nobel Prize Russian scientist Elie Metchnikoff made observations that human health and longevity were associated with the ingestion of lactic acid-producing bacteria. He noted that Bulgarian peasants who consumed large quantities of sour milk containing the bacteria now known as *Lactobacillus bulgaricus,* lived longer [1]. Hence was born the concept of probiotics, one that is ever-evolving as evidenced by the surge of publications exceeding several thousand articles.

"Pro-biotics" mean "for life" and are defined as live microorganisms, which when consumed in adequate amounts, confer a health effect on the host. In vitro studies suggest that probiotics provide benefit by acting through several different mechanisms [2]. They have an antimicrobial effect through secreting antibacterial substances, compete with pathogens to prevent their adhesion to the intestinal epithelium, compete for

nutrients necessary for pathogen survival, produce an antitoxin effect, and reverse some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration [3,4]. Probiotics are also capable of modulating the immune system [5], regulating the allergic immune cell response of the body [6] and reducing cell proliferation in cancer [7]. The effects of these agents may go beyond the gastrointestinal tract to distant areas, such as the skin and respiratory mucosa, and it may not be necessary to administer the intact probiotic organism to achieve benefits. At the basic research level, products of probiotics such as secreted proteins and DNA can block inflammation and stop the death of epithelial cells [8,9]. For example, DNA from some probiotic preparations can suppress experimental colitis in several animal models [10].

Probiotic products vary greatly from single agents, double agents, or as combination therapies. Examples of such strains include E-coli, lactobacilli, bifidobacteria, and saccharomyces. Considerable differences exist in the bioavailability, biological activities, doses and composition among probiotic preparations and probiotic studies are frequently characterized by significant heterogeneity. It is also important to recognize that *in vitro* effects of a probiotic may display opposite behavior *in vivo* [11]. Therefore, while probiotics are promising agents to unravel the mystery of gut microbial interactions, our understanding of their use for children in the appropriate clinical circumstances is still in its early stages. The purpose of this review is to provide an update on the safety and efficacy of probiotics with a focus on children.

PROBIOTIC EFFICACY

A. Digestive disorders

a. Infectious diarrhea:

The role of probiotics in infectious diarrhea has been a focus of several research studies related to either treatment or prevention of the infection.

i. Treatment: Several studies investigating the potential beneficial effect of probiotics in mild to moderate infectious diarrhea are summarized in several meta-analyses, all of which found an overall reduction in the duration of diarrhea by about one day (1.12 days, 95% confidence interval [CI]-1.16 to 0.38) [12-18]. Good evidence support efficacy for *Lactobacillus* especially *rhamnosus* GG [12,17,19] and *Saccharomycesboulardii [18]*.

However, in children with more severe diarrhea there was no demonstrable benefit [20,21]. This phenomenon is further supported by studies from Bangladesh and Indonesia showing lack of efficacy of probiotics in severe diarrhea, while being effective in ameliorating less severe, non-rotavirus diarrhea [22, 23].

ii. Prevention**:** The role of probiotics in preventing nosocomial infectious diarrhea has shown contradicting evidence. A double-blinded randomized control trial using *Lactobacillus* GG in 81 children ages 1-36 months showed a significant reduction in the risk of rotavirus gastroenteritis (2.2% versus 6.7%) [24]. Seven children would need to be treated to prevent one patient from developing nosocomial rotaviral gastroenteritis [24]. However, a larger double-blinded randomized study in 220 children did not show a statistically significant protective effect of the same probiotic for nosocomial rotaviral infection [25]. Another randomized trial studying 55 infants admitted to a chronic care pediatric hospital showed a lower risk of developing nosocomial diarrhea when infants were fed probiotic-containing formula (7% versus 31%) [26]. This protective effect becomes far less significant if the incidence of diarrhea (episodes per patient-month) rather than the percentage of patients with diarrhea is taken into account [27].

With regards to prevention of community-acquired diarrhea, randomized controlled studies suggest a modest protective effect. A Peruvian study of 204 malnourished children showed a reduction of the number of episodes of diarrhea per child per year from 6.02 to 5.21 favoring *Lactobacillus* GG. On the contrary, a study from Finland involving 571 children attending daycare centers did not show a significant difference in the number of days with diarrhea when *Lactobacillus* GG was used. However, there was a 16% reduction in the number of days of absence due to gastrointestinal and respiratory illnesses[28]. Another study involving 210 healthy children in child health care centers showed a lower frequency and shorter duration of diarrhea when *Lactobacillus reuteri* or Bifidobacterium *Lactis* were given to the children[29].

Prevention of diarrhea in daycare settings has been the focus of several studies in Europe and in the United States [30,31]. The outcome of these studies has been summarized in 2010 by the American Academy of Pediatrics reporting that the evidence to support efficacy of probiotics in preventing acute diarrhea is very modest [32].

b. Antibiotic-associated diarrhea (AAD) and Clostridium difficile infection:

Many of the studies evaluating the efficacy of probiotics in AAD are small and have methodological flaws. However, two meta-analyses suggest a reduction in AAD by approximately 60%. The probiotic agents showing efficacy in this condition were Saccharomyces *boulardii* [33] and Lactobacillus *GG* in children [34-36]. A recent meta-analysis of data from pediatric studies showed both probiotic agents to be moderately effective in preventing AAD in children [34]. For every ten patients treated, one will not develop AAD [37]. Not all probiotics are equally effective in this condition as evidenced by lack of efficacy of a combination of Lactobacillus *acidophilus* and Lactobacillus *bulgaricus* in preventing diarrhea in children receiving amoxicillin therapy during a double-blind placebo-controlled trial [38].

i. Clostridium difficile treatment: Significant reduction of pediatric *Clostridium Difficile* Infection (pooled RR=0.34, 95%CI=0.16-0.74) was suggested when pooling four different types of probiotics including *Saccharomyces boulardii* and *Lactobacillus* GG [34].

c. Inflammatory bowel disease (IBD):

The use of probiotics in IBD has been recently rekindled as reports of the role, relevance and importance of gut microbes in the pathogenesis of IBD have been confirmed [39]. Furthermore,

bench research appears to show promising beneficial effects of probiotics in models of IBD. Subsequently, there have been a large number of clinical studies that investigate the efficacy of probiotics in human disease. Much of these studies have revealed disappointing results especially in treatment of Crohn's disease.

Many studies have examined the effect of probiotics in Crohn's disease including a pediatric study by Bousvaros and colleagues which showed no significant benefit of *Lactobacillus GG* in maintaining remission compared to placebo [40]. Similarly, many other studies, mostly in adults, failed to show efficacy. In 2006, Rolfe [41] and then Rahimi in 2008 [42] independently reported meta-analyses failing to demonstrate the efficacy of probiotics in maintaining remission or preventing clinical and endoscopic recurrence of Crohn's disease.

Likewise, there have been a number of studies in ulcerative colitis. Most studies show a modest effect comparable to the benefit seen with 5-aminosalicylate use. Probiotics have been studied as agents to induce remission as well as to maintain remission. Mallon and colleagues published a Cochrane analysis in 2007 [43] and concluded that the addition of probiotics to conventional therapy does not improve overall remission rates in mild to moderate disease activity but that probiotics may have a modest role in reducing disease activity. Another meta-analysis was published in 2010 by Sang and colleagues [44] and a 2011 Cochrane analysis by Naidoo and colleagues[45] showed similar results. While the authors concluded that there was significant heterogeneity seen in the published studies, that probiotics provided no additional benefit in inducing remission of ulcerative colitis, they also note that probiotic auxiliary therapy is better than non-probiotics for maintenance therapy in mild to moderate disease. A small double-blind, placebo-controlled pediatric trial of VSL#3®in 29 children with newly diagnosed ulcerative colitis showed that subjects receiving the probiotic along with 5-ASA maintenance therapy were less likely to relapse compared to placebo and 5-ASA [46]. While the results of this study are quite interesting and are in keeping with the recognition of the important role of the gut microbiota, it should be pursued in larger studies before recommendation of wide use in maintenance therapy in children with ulcerative colitis.

Perhaps the most promising role for probiotics in IBD is in pouchitis. The early studies were done by Gionchetti and colleagues and suggested good efficacy of the polymicrobial probiotic supplement VSL#3®. Those studies were followed by several others, mostly confirming those findings. A meta-analysis by Elahi and colleagues further affirmed that there is a role for probiotics in the management of pouchitis [47]. In 2010, a Cochrane analysis by Holubar and colleagues concluded that for chronic pouchitis as well as for the prevention of pouchitis, VSL#3® was more effective than placebo [48]. Given the relative safety of probiotics in general, their use is recommended as adjuvant therapy in pouchitis.

d. Irritable bowel syndrome (IBS):

A number of studies have evaluated the response of IBS to probiotic preparations. While results between studies are difficult to compare because of differences in study design, probiotic dose, strain, and duration of therapy, some studies suggest symptom improvement. Most systematic reviews demonstrate a beneficial impact on global IBS symptoms, abdominal pain and flatulence. However, not surprisingly with the degree of heterogeneity of both disease and therapy, different probiotic products can vary in their effect from beneficial to worsening symptoms, confirming that response is strain and symptom-specific [49,50].

B. Miscellaneous digestive disorders

a. Non-alcoholic fatty liver disease (NAFLD):

Evidence suggests that the source of hepatic triglyceride accumulation can be derived from gut microbiota. They can also play a role in the development of insulin resistance, hepatic steatosis, necroinflammation and fibrosis. Furthermore, probiotics may improve the mucosal barrier, and decrease bacterial translocation and endotoxemia according to animal and human studies. Gut microbiota can also reduce oxidative and inflammatory liver damage. In a recent meta-analysis, probiotic therapies were found to reduce liver transaminitis, total-cholesterol, tumor necrosis alpha (TNF-α), and improve insulin resistance in NAFLD patients. Modulation of the gut microbiota represents a new avenue for treatment of NAFLD [51].

b. Necrotizing enterocolitis (NEC):

Necrotizing enterocolitis is a condition seen mostly in premature infants, and can result in small but significant morbidity and mortality with massive bowel resection in severe cases. In 2013, a meta-analysis and systematic review concluded that the use of probiotics is effective for prevention of NEC and its associated complications including length of hospitalization, sepsis and death[52].

c. Hepatic encephalopathy:

The role of probiotics in the treatment of hepatic encephalopathy was examined in a Cochrane review which identified systematic and random errors but still concluded that probiotics appear to reduce serum ammonia levels in those subjects[53].

d. Helicobacter pylori (H. pylori):

Fermented probiotic preparations improve H. pylori eradication rates by 5-15%, however, the probiotic role inamelioratingadverse effects of antimicrobial therapy is variable[54].

C. Non-Digestive disorders

a. Upper respiratory tract infections (URTIs):

The administration of Lactobacillus rhamnosus GG has the potential to reduce the incidence of acute otitis media, upper respiratory infections and antibiotic use in children [55]. A Cochrane review confirms that probiotics are better than placebo in reducing the number of subjects with acute URTIs, the rate of episodes of acute URTIs and reducing antibiotic use [56].

b. Allergic disorders:

Probiotics have been shown to reduce inflammatory cytokines and intestinal permeability in vitro. Such an effect would be beneficial in allergic disorders. Therefore, several

studies have investigated the efficacy of probiotics in allergic conditions. . A meta-analysis of eleven studies showed significant benefit of probiotics compared with placebo in reducing the Scoring of Atopic Dermatitis Severity Index score. Children with moderately severe Atopic Dermatitis (AD) were more likely to benefit but the duration of probiotic administration, age, and type of probiotic used did not affect the outcome [57]. Another meta-analysis showed that while probiotics could be an option for the treatment of AD, especially for moderate to severe AD in children and adults, however they are not as effective in infants [58].

c. Prenatal probiotic administration:

Studies show that there is a moderate effect of probiotics in the prevention of AD and IgE-associated AD in infants. The favorable effect was similar regardless of the time of probiotic use; whether during pregnancy or early infancy, or the type of subjects receiving probiotics; whether mother, infant or both [59].

SUMMARY OF THE QUALITY OF EVIDENCE FOR THE USE OF PROBIOTICS

Probiotics hold promise for a variety of digestive and non-digestive disorders. In specific clinical circumstances, there is clear evidence of benefit such as in acute viral gastrointestinal infections and antibiotic associated diarrhea. The beneficial effect of the probiotic can be modest and the anticipated advantage has to be viewed along with associated cost and available alternatives. The evidence to support the use of probiotics in a variety of disorders is summarized in table 1. When prescribing probiotics, one has to consider the probiotic formulation, including live or killed, single strain or compounded preparations, the effective dose to use, as well as the type of disease targeted. Since "not all probiotics are created equal", one cannot extrapolate specific actions or doses of a given probiotic, and generalize these properties to other doses or strains of probiotic bacteria.

Table 1: Highlights of the effect of probiotics in different diseases.

Type of disease	Comments
Pouchitis	Efficacy clearly shown in adult studies with VSL#3®
Pediatric Crohn's disease	No evidence of efficacy
Ulcerative colitis	Efficacy suggested (equivalence to 5-ASA preparations).
Irritable bowel syndrome	Efficacy possible but variable results.
Antibiotic associated diarrhea	Efficacy clearly shown but not all probiotics are effective (mainly Saccharomyces *boulardii* and Lactobacillus *GG*).
C. *difficile* diarrhea	Efficacy clearly shown especially with Saccharomyces *boulardii and Lactobacillus GG*.
Mild to moderate acute diarrhea	Efficacy clearly shown, Treatment: Shortens duration of illness by one day Prevention: Modest effect with some conflicting reports
Necrotizing enterocolitis	Efficacy proven in preventing NEC and its complications
Hepatic encephalopathy	Reduce serum ammonia
Helicobacter pylori eradication	Eradication rates of 5-15%
Allergy	Efficacy clearly shown in preventing atopic dermatitis
Respiratory infections	Efficacy clearly shown in preventing acute upper respiratory tract infecitons
Non-alcoholic fatty liver	reduce liver transaminases, total-cholesterol, TNF-α, and improve insulin resistance

SAFETY AND QUALITY CONTROL

Safety issues

In general probiotics are considered safe in children. Some studies on immune-compromised patients with HIV [60] and the transplant[61] population have been reassuring. However, there are multiple reports of bacteremia and fungemia [62-77] with lactobacilli and Saccharomyces organisms, especially in subjects with indwelling central venous catheters. Interestingly, some of such patients did not directly receive probiotics, but were in the same hospital unit as patients who received the probiotics. Contamination of the air, environmental surfaces, and hands is suggested in these cases [70].

It is also worthy to note that the effect of probiotics on the developing immune system in neonates, especially preterm infants, is not known and long term studies are vital in understanding the influence of early probiotic exposure.

The concern for the development of lactic acidosis relative to the consumption of lactic acid probiotics has been previously raised especially in high risk populations such as infants who undergo significant developmental changes in many organ systems during the first several months of life [78]. These changes place infants at a disadvantage in handling acid accumulation in the body in a population that is difficult to illicit clinical symptoms to recognize the development of lactic acidosis. Chidlren with short bowel syndrome are at risk for developing lactic acidosis and there have been previous reports of children developing lactic acidosis with the use of probiotics [79, 80].

Quality control

Probiotics are the elusive gems of healthcare whose dynamic potential is worth the exploration, but whose exact qualities have been challenging to pin down. The irony is that probiotics have been utilized in other countries as a part of their culinary identity for ages. Within the familiar package of fermented food choices such us yogurt, sauerkraut, and kimchi, countries such as Finland, Germany, and Japan, among others, have been exploiting their health benefits for ages. In fact, the practice of fermentation is one of the oldest methods of preservation that dates back to ancient civilizations[81]. Despite their lengthy history in various parts of the world, probiotics have only recently gained notoriety for being beneficial to human health. While Louis Pasteur's mid-19th century contribution of elucidating the actual involvement of microbes in fermentation[1] can partially explain the lag in current scientific understanding of probiotics, the challenge is complicated by several other factors that are either inherent to

the microorganism, the human microflora, or simply the logistics of differing jurisdictional legislation regarding functional foods. Notably, the live microorganisms in probiotics make it more difficult to isolate their clinical effects and determine causality compared to other functional foods because the effects can be variable and influenced by the status of the microorganism (figure 2) [82].

For all of their strengths and potential promise, probiotics have one significant drawback- their development requires complex quality control standards that make them difficult to research, standardize and market. Quality control is the avenue by which probiotics are evaluated in order to legitimately make health claims about their worth. To be characterized as effective, probiotic strains must retain the functional health characteristics for which they were originally selected. Important quality control properties that must be constantly controlled and optimized are the following: adhesive properties; bile and acid stability; viability and survival throughout the manufacturing process; effects on carbohydrate, protein, and fat utilization; and especially, colonization properties and immunogenicity[83]. Most of aforementioned properties are related to the physiologic properties of the strain, but long-term industrial processing and storage conditions may inadvertently influence probiotic properties[83].

In order to survive the journey through the stomach and small intestine, probiotics need to withstand their respective acidic and protease-rich environments and be able to grow in the presence of bile introduced via the small intestine. In vitro assays can easily be constructed to assess both acid tolerance and bile growth; the challenge, and what still remains to be done, is determining if these qualities still hold true in vivo[83]. Another, and arguably one of the more important, selection criterion is the ability to adhere to the intestinal mucosa since that establishes initial colonization. Adhesion subsequently triggers the stimulation of the immune system via M cells or Peyer's patches[83]. In several studies, adhesion was associated with a shortening of diarrhea duration, immunogenic effects, competitive exclusion, and other health effects[83]. If adhesion is unknowingly modified during industrial processes, probiotic effects may consequently also be altered. The current model for in vitro testing is by testing adhesion to intestinal cells as well as to human intestinal mucus preparations[83]. However, researchers suggest that demonstrated adhesion to colonic or intestinal biopsies, if possible, would best simulate in vivo conditions[83].

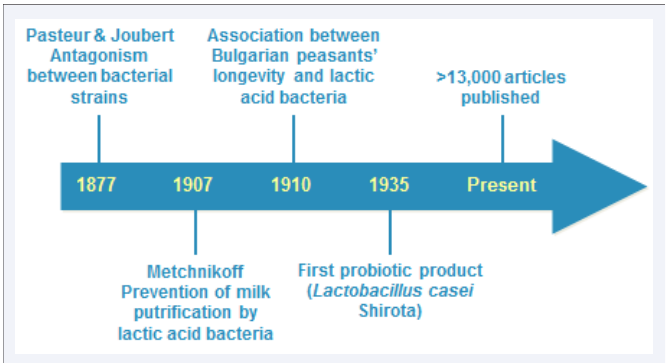

Figure 1 Probiotic history timeline.

Figure 2 Quality control, properties and challenges of probiotic products.

Challenges associated with establishing health claims

1. Identification of microorganisms: It seems as though the most basic of requirements, that is the naming and describing of the active ingredients in the product, is one of the primary challenges in the field of probiotics. Definitive identification of the microorganisms contained in a probiotic product often requires rigorous molecular biology and informatics techniques[82]. Polyphasic characterization combining phenotypic, biochemical, genotypic and sequencing results is now being used to reliably identify bacteria to the strain level[84]. This is especially important because even closely related bacterial species can have different properties, a fact that edifies the need for identification all the way down to the subspecies level.

2. Enumeration of microorganisms: Fecal studies tell us that probiotics temporarily re-populate the microflora, and need to be consistently replenished in order to be efficacious. So it is natural to expect that the product have an established threshold for the number of microorganisms required for the purported effect. 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[82]. Numerating bacteria or other microorganisms in a food matrix is not easy, and if the product contains more than 1 microorganism, individual methods may have to be used to enumerate each microorganism[82].

3. Efficacy testing: Unfortunately, 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,[82] as listed in Table 1. Various 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[82]as well as effects on the mucosal epithelium and the gut-associated lymphoid tissue[85].Efficacy experiments must be replicated and have appropriate numbers of subjects to achieve scientific consensus[82].If an acceptable mechanism can be elucidated, claims of efficacy are made even stronger.

CLINICAL TRIALS

A double-blinded, placebo-controlled clinical trial is regarded as the "gold standard" for most efficacy experiments, but researchers testing probiotics, like most trials testing foods, have difficulty finding an appropriate control.[3]Most studies provide data to show that the probiotic consumed can be found in the fecal material of the subjects during the dosing period[82], therefore, in directly demonstrating viability. Fecal enzymes, pH and short-chain fatty acid data are often provided to show changes to digestive composition and characteristics that accompany changes in the intestinal microbiota[82]. Such changes, however, may not necessarily be related to beneficial clinical effects[82]. Furthermore, because the site of action of probiotics is in the large intestine, fecal data do not necessarily decipher how many bacteria actually produce the beneficial effect at the very site of action[82]. The importance of clinical trials cannot be understated, as they are the only means by which to confirm all of the supportive studies (i.e. biochemical, animal, in vitro, etc.).

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 Lactobacillus that could be potential probiotics contain opportunistic pathogens[86].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 described as a possible concern in the development of probiotic products[86].As the whole science of probiotics is aimed at increasing health and wellness, it is expected that any data claims must resoundingly show evidence of safety for human consumption.

REGULATORY AGENCIES

Although the number of functional foods is growing on a worldwide scale, the number of probiotics carrying approved health claims is not correspondingly large. As concerns product labeling of probiotics or functional foods in general, since they are regulated as foods and dietary supplements, they are limited to making only one of two possible claims: either "structure/function" or "health" claims[87].Structure/function claims home in on maintenance of normal structures or functions of the body (e.g. it helps maintain healthy intestinal microbiota, helps maintain regularity, relieves occasional constipation, or helps support immune function) [87].These types of claims for foods do not need Center for Food Safety and Applied Nutrition (CFSAN) approval, but they must be truthful, not misleading and substantiated by competent and reliable scientific evidence [87]. Health claims, on the other hand, can be distinguished from structure/function claims by their focus on risk reduction of disease or health-related conditions (e.g. the product reduces the risk of traveler's diarrhea) [87].

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 only a limited number of health claims have been approved [82]. The Japanese Foods for Specific Health Use (FOSHU) system allows several health claims for probiotics, thus by 1999, 21 probiotic products had received FOSHU approval in Japan [82]. Health Canada (HC) is the regulator responsible for food label claims in Canada [82]. Probiotics in particular are under the purview of the Natural Health Products Directorate (NHPD) of HC.Through HC, probiotics can carry a structure/function claim, a risk reduction claim, or a treatment claim [82]. As of 2008, the HC/NHPD had not issued an approved health claim for any probiotic product [82]. Similarly, in the United States, a probiotic is regulated at the federal level as a dietary supplement, a food or as a drug, depending on the intended use [82]. The Center for Food Safety and Applied Nutrition (CFSAN) at the FDA regulates probiotic products under the broad category of food, including dietary supplements [87]. CFSAN is primarily responsible for overseeing post-marketing surveillance. The manufacturer, however, still carries the responsibility of ensuring that the food or supplement is safe before it is marketed in the first place and for substantiating labeling claims [87].

In 1994, the United States Congress passed the Dietary Supplement Health and Education Act (DSHEA). It created a variety of provisions for the regulation of dietary supplements, including: the definition of a dietary supplement, dietary supplement product safety, nutritional statements and claims, ingredient and nutritional labeling, the ability to establish good manufacturing practices (GMPs) and the classification of new dietary ingredients[88]. To claim prevention, treatment or cure for a particular pathology or disease is strictly forbidden under DSHEA 1994[88]. While DSHEA ensured the ability of the FDA to establish GMPs for the supplement industry, it was not until 2007 that such requirements became compulsory. The new GMP guidelines address several areas in the manufacture, packaging, labeling and storage of dietary supplements[88]. These include personnel, physical plant, equipment, record keeping and remediation practices[88]. Manufacturers are required to evaluate the identity, purity, quantity and composition of the dietary supplements using state of the art scientific practices[88]. While the United States is indeed far behind other countries in establishing good manufacturing practices for probiotics, the essential problem of probiotic standardization lies in the fact that regulations vary from one country to another.

FOOD AND AGRICULTURE ORGANIZATION/ WORLD HEALTH ORGANIZATION

Recommendations

1. In October of 2001, a joint Food and Agriculture Organization (FAO) of the United NationsWorld Health Organization (WHO) expert Consultation was held in Cordoba, Argentina. This Consultation was comprised of a group of experts coming together to focus on evaluation of the scientific evidence available on the properties, functionality, benefits, safety and nutritional features of probiotic foods. The following is the list of recommendations they created for advancement in the future of probioticsProbiotic strains must be identified by internationally accepted molecular techniques and named

according to the International Code of Nomenclature. Strains should preferably be deposited in a recognized culture collection.

2. The probiotic agent must offer defined health benefits on the host in the actual product vehicle that will be made available to humans.
3. There is a need for refinement of tests to predict the ability of probiotic microorganisms to function in humans.
4. There is a need for more statistically significant efficacy data in humans.
5. Good manufacturing practices must be applied for quality assurance, shelf-life conditions. Labeling should include minimum dosage and verifiable health claims.
6. The regulatory status of probiotics in food has to be established on an international level.
7. Establish a regulatory framework to address issues related to probiotics including efficacy, safety, labeling, fraud and claims.
8. Probiotic products showing health benefits should be permitted to describe these specific health benefits.
9. Surveillance systems, including trace-back and post marketing surveillance, should be put in place to record and analyze any adverse events associated with probiotics in food and monitor the long-term health benefits of probiotic strains.
10. Efforts should be made to make probiotic products more widely available, especially for relief work and populations at high risk of morbidity and mortality.
11. Further work is needed to address criteria and methodologies for probiotic development.

CONCLUSION

Probiotics are just beginning to come into their own medically and clinically relevant identity. They offer a perfect melding of the naturopathic and allopathic. In other words, they can be created from a naturally occurring substance, but require strict adherence to federal regulations in order to give them credence as a dependable treatment within the armamentarium of Western medicine. Various studies have been carried out to date that support their beneficial effects on the human body, but the trajectory of probiotic growth and utility has been attenuated by fragmented regulatory standards. The specific challenges associated with making health claims about probiotics include identification of and enumeration of microorganisms, efficacy testing, performing rigorous clinical trials and proving safety. Evidently, part of the probiotic dilemma is that some of their most basic features are the most formidable to pin down.

Why then spend so much effort trying to standardize probiotics? Their list of advantages include being inexpensive, easy to administer, relatively safe with few drug interactions, aiding the body in its own natural defenses, having multiple mechanisms of action and diversity of potential organisms. The FAO/WHO Consultation has composed a list of the changes that need to be established for the advancement of probiotics. As such, it is a topic replete with directions for future research. Standardized protocols, clinical studies using same strains, replicating studies, documenting risks and benefits, performing cost/benefit analyses, establishing adequate dose quantities are important future research considerations.

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REFERENCES

1. Metchnikoff E. Études sur la flore intestinale Deuxième mémoire. Ann Inst. Pasteur Paris. 1910; 24: 755-770.
2. Michail S. Mechanism of action of probiotics. Practical Gastroenterology. 2005; 24: 29-47.
3. Michail SF. Abernathy. Lactobacillus plantarum inhibits the intestinal epithelial migration of neutrophils induced by enteropathogenic Escherichia coli. J Pediatr Gastroenterol Nutr. 2003; 36: 385-391.
4. Michail SF. Abernathy. Lactobacillus plantarum reduces the in vitro secretory response of intestinal epithelial cells to enteropathogenic Escherichia coli infection. J Pediatr Gastroenterol Nutr. 2002; 35: 350-355.
5. Dahan S, Dalmasso G, Imbert V, Peyron JF, Rampal P, Czerucka D. Saccharomyces boulardii interferes with enterohemorrhagic Escherichia coli-induced signaling pathways in T84 cells. Infect Immun. 2003; 71: 766-773.
6. Kalliomäki MA, Isolauri E. Probiotics and down-regulation of the allergic response. Immunol Allergy Clin North Am. 2004; 24: 739-752.
7. Jijon H, Backer J, Diaz H, Yeung H, Thiel D, McKaigney C, et al. DNA from probiotic bacteria modulates murine and human epithelial and immune function. Gastroenterology. 2004; 126: 1358-1373.
8. Yan F, Polk DB. Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells. J Biol Chem. 2002; 277: 50959-50965.
9. Rachmilewitz D, Katakura K, Karmeli F, Hayashi T, Reinus C, Rudensky B, et al. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. Gastroenterology. 2004; 126: 520-528.
10. Ibnou-Zekri N, Blum S, Schiffrin EJ, von der Weid T. Divergent patterns of colonization and immune response elicited from two intestinal Lactobacillus strains that display similar properties in vitro. Infect Immun. 2003; 71: 428-36.
11. Freedman SB, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013; 8: 1123-1137.
12. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics. 2002; 109: 678-684.
13. Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. Dig Dis Sci. 2002; 47: 2625-2634.
14. Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. J Pediatr Gastroenterol Nutr. 2001; 33: 17-25.

15. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev. 2004: CD003048.

16. Szajewska H, SkÃ³rka A, RuszczyÅ„ski M, Gieruszczak-BiaÅ‚ek D. Meta-analysis: Lactobacillus GG for treating acute gastroenteritis in children--updated analysis of randomised controlled trials. Aliment Pharmacol Ther. 2013; 38: 467-476.

17. Dinleyici EC, Eren M, Ozen M, Yargic ZA, Vandenplas Y. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. Expert Opin Biol Ther. 2012; 12: 395-410.

18. Dinleyici EC, PROBAGE Study Group, Vandenplas Y. Lactobacillus reuteri DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. Acta Paediatr. 2014; 103: 300-305.

19. Costa-Ribeiro H, Ribeiro TC, Mattos AP, Valois SS, Neri DA, Almeida P, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. J Pediatr Gastroenterol Nutr. 2003; 36: 112-115.

20. Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M, Chea-Woo E, Sack RB. Lactobacillus casei strain GG in the treatment of infants with acute watery diarrhea: a randomized, double-blind, placebo controlled clinical trial [ISRCTN67363048]. BMC Pediatr. 2004; 4: 18.

21. Sarker SA, Sultana S, Fuchs GJ, Alam NH, Azim T, Brüssow H, et al. Lactobacillus paracasei strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. Pediatrics. 2005; 116: 221-228.

22. Hegar B, Waspada IM, Gunardi H, Vandenplas Y. A Double Blind Randomized Trial Showing Probiotics to be Ineffective in Acute Diarrhea in Indonesian Children. Indian J Pediatr. 2014;.

23. Szajewska H, Kotowska M, Mrukowicz JZ, ArmaÅ‚ska M, MikoÅ‚ajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr. 2001; 138: 361-365.

24. Mastretta E, Longo P, Laccisaglia A, Balbo L, Russo R, Mazzaccara A, et al. Effect of Lactobacillus GG and breast-feeding in the prevention of rotavirus nosocomial infection. J Pediatr Gastroenterol Nutr. 2002; 35: 527-531.

25. Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet. 1994; 344: 1046-1049.

26. Szajewska H, Mrukowicz JZ. Use of probiotics in children with acute diarrhea. Paediatr Drugs. 2005; 7: 111-122.

27. Hatakka K, Savilahti E, Pönkä A, Meurman JH, Poussa T, Näse L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ. 2001; 322: 1327.

28. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics. 2005; 115: 5-9.

29. Hojsak I, Snovak N, AbdoviÄ‡ S, Szajewska H, Misak Z, Kolacek S,. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. Clin Nutr. 2010; 29: 312-316.

30. Merenstein D, Murphy M, Fokar A, Hernandez RK, Park H, Nsouli H, et al. Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: the DRINK study. A patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. Eur J Clin Nutr, 2010. 64: 669-77.

31. Thomas DW, Greer FR. American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. Pediatrics. 2010; 126: 1217-1231.

32. Micklefield G. [Saccharomyces boulardii in the treatment and prevention of antibiotic-associated diarrhea]. MMW Fortschr Med. 2014; 156: 18-22.

33. McFarland LV. Deciphering meta-analytic results: a mini-review of probiotics for the prevention of paediatric antibiotic-associated diarrhoea and Clostridium difficile infections. Benef Microbes. 2014;.

34. Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, et al. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. Aliment Pharmacol Ther. 2002; 16: 1461-1467.

35. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ. 2002; 324: 1361.

36. Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. Aliment Pharmacol Ther. 2005; 22: 365-372.

37. Tankanow RM, Ross MB, Ertel IJ, Dickinson DG, McCormick LS, Garfinkel JF. A double-blind, placebo-controlled study of the efficacy of Lactinex in the prophylaxis of amoxicillin-induced diarrhea. DICP. 1990; 24: 382-384.

38. Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014; 15: 382-392.

39. Bousvaros A, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. Inflamm Bowel Dis. 2005; 11: 833-839.

40. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2006; CD004826.

41. Rahimi R, Nikfar S, Rahimi F, Elahi B, Derakhshani S, Vafaie M, et al. A meta-analysis on the efficacy of probiotics for maintenance of remission and prevention of clinical and endoscopic relapse in Crohn's disease. Dig Dis Sci. 2008; 53: 2524-2531.

42. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007; CD005573.

43. Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. World J Gastroenterol. 2010; 16: 1908-1915.

44. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2011; CD007443.

45. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. Am J Gastroenterol. 2009; 104: 437-443.

46. Elahi B, Nikfar S, Derakhshani S, Vafaie M, Abdollahi M. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. Dig Dis Sci. 2008; 53: 1278-1284.

47. Holubar SD, Cima RR, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database Syst Rev. 2010; : CD001176.

48. Whelan K1. Probiotics and prebiotics in the management of irritable bowel syndrome: a review of recent clinical trials and systematic reviews. Curr Opin Clin Nutr Metab Care. 2011; 14: 581-587.

49. Bauserman M, Michail S. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. J Pediatr. 2005; 147: 197-201.

50. Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on

nonalcoholic fatty liver disease: a meta-analysis. World J Gastroenterol. 2013; 19: 6911-6918.

51. Bernardo WM, Aires FT, Carneiro RM, Sá FP, Rullo VE, Burns DA. Effectiveness of probiotics in the prophylaxis of necrotizing enterocolitis in preterm neonates: a systematic review and meta-analysis. J Pediatr (Rio J). 2013; 89: 18-24.

52. McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. Cochrane Database Syst Rev. 2011; : CD008716.

53. Sachdeva A, J. Nagpal. Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: a systematic review and meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol, 2009; 21: 45-53.

54. Liu S, Hu P, Du X, Zhou T, Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. Indian Pediatr. 2013; 50: 377-381.

55. Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2011; CD006895.

56. Michail SK, Stolfi A, Johnson T, Onady GM. Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol. 2008; 101: 508-516.

57. Kim SO, Ah YM, Yu YM, Choi KH, Shin WG, Lee JY. Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol. 2014; 113: 217-226.

58. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology. 2012; 23: 402-414.

59. Apostolou E, Kirjavainen PV, Saxelin M, Rautelin H, Valtonen V, Salminen SJ, et al. Good adhesion properties of probiotics: a potential risk for bacteremia? FEMS Immunol Med Microbiol. 2001; 31: 35-39.

60. Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation--a randomized, double-blind trial. Am J Transplant. 2005; 5: 125-30.

61. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. Lactobacillus sepsis associated with probiotic therapy. Pediatrics. 2005; 115: 178-181.

62. Arpi M, Vancanneyt M, Swings J, Leisner JJ. Six cases of Lactobacillus bacteraemia: identification of organisms and antibiotic susceptibility and therapy. Scand J Infect Dis. 2003; 35: 404-408.

63. De Groote MA, Frank DN, Dowell E, Glode MP, Pace NR. Lactobacillus rhamnosus GG bacteremia associated with probiotic use in a child with short gut syndrome. Pediatr Infect Dis J. 2005; 24: 278-280.

64. Young RJ, Vanderhoof JA. Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. J Pediatr Gastroenterol Nutr. 2004; 39: 436-437.

65. Salminen MK, Rautelin H, Tynkkynen S, Poussa T, Saxelin M, Valtonen V, et al. Lactobacillus bacteremia, clinical significance, and patient outcome, with special focus on probiotic L. rhamnosus GG. Clin Infect Dis. 2004; 38: 62-69.

66. Saxelin M, Chuang NH, Chassy B, Rautelin H, Mäkelä PH, Salminen S, et al. Lactobacilli and bacteremia in southern Finland, 1989-1992. Clin Infect Dis. 1996; 22: 564-566.

67. Rijnders BJ, Van Wijngaerden E, Verwaest C, Peetermans WE. Saccharomyces fungemia complicating Saccharomyces boulardii treatment in a non-immunocompromised host. Intensive Care Med. 2000; 26: 825.

68. Niault M, Thomas F, Prost J, Ansari FH, Kalfon P. Fungemia due to Saccharomyces species in a patient treated with enteral Saccharomyces boulardii. Clin Infect Dis. 1999; 28: 930.

69. Hennequin C, Kauffmann-Lacroix C, Jobert A, Viard JP, Ricour C, Jacquemin JL, et al. Possible role of catheters in Saccharomyces boulardii fungemia. Eur J Clin Microbiol Infect Dis. 2000; 19: 16-20.

70. Marco Cassone,,* Pietro Serra, Francesca Mondello, Antonietta Girolamo, Sandro Scafetti, Eleonora Pistella, et al., Outbreak of Saccharomyces cerevisiae subtype boulardii fungemia in patients neighboring those treated with a probiotic preparation of the organism. J Clin Microbiol. 2003. 41: 5340-3.

71. Herbrecht R, Nivoix Y. Saccharomyces cerevisiae fungemia: an adverse effect of Saccharomyces boulardii probiotic administration. Clin Infect Dis. 2005; 40: 1635-1637.

72. Enache-Angoulvant A, Hennequin C. Invasive Saccharomyces infection: a comprehensive review. Clin Infect Dis. 2005; 41: 1559-1568.

73. Cesaro S, Chinello P, Rossi L, Zanesco L. Saccharomyces cerevisiae fungemia in a neutropenic patient treated with Saccharomyces boulardii. Support Care Cancer. 2000; 8: 504-505.

74. Perapoch J, Planes AM, Querol A, López V, Martínez-Bendayán I, Tormo R, et al. Fungemia with Saccharomyces cerevisiae in two newborns, only one of whom had been treated with ultra-levura. Eur J Clin Microbiol Infect Dis. 2000; 19: 468-470.

75. Bassetti S, Frei R, Zimmerli W. Fungemia with Saccharomyces cerevisiae after treatment with Saccharomyces boulardii. Am J Med. 1998; 105: 71-72.

76. Pletincx M, Legein J, Vandenplas Y. Fungemia with Saccharomyces boulardii in a 1-year-old girl with protracted diarrhea. J Pediatr Gastroenterol Nutr. 1995; 21: 113-115.

77. Mack DR. D(-)-lactic acid-producing probiotics, D(-)-lactic acidosis and infants. Can J Gastroenterol. 2004; 18: 671-675.

78. Munakata S, Arakawa C, Kohira R, Fujita Y, Fuchigami T, Mugishima H. A case of D-lactic acid encephalopathy associated with use of probiotics. Brain Dev. 2010; 32: 691-694.

79. Ku WH, LDC, Huen KF. Probiotics provoked D-lactic acidosis in short bowel syndrome: Case report and literature review. Hong Kong J. Paediatr. 2006; 11: 246-254.

80. Farnworth E.R., Handbook of fermented functional foods 2nd Edition ed. 2008, Boca Raton: CRC Press.

81. Farnworth ER. The evidence to support health claims for probiotics. J Nutr. 2008; 138: 1250-1254.

82. Tuomola E, Crittenden R, Playne M, Isolauri E, Salminen S. Quality assurance criteria for probiotic bacteria. Am J Clin Nutr. 2001; 73: 393-398.

83. Saavedra JM, Tschernia A. Human studies with probiotics and prebiotics: clinical implications. Br J Nutr. 2002; 87: 241-246.

84. Salminen S, von Wright A, Morelli L, Marteau P, Brassart D, de Vos WM, et al. Demonstration of safety of probiotics a review. Int J Food Microbiol. 1998; 44: 93-106.

85. Michail, Sonia, Sherman, Philip M. Probiotics in Pediatric Medicine, ed. S.a.S. Michail, P. 2009: Humana Press.

86. Gupta P, Andrew H, Kirschner BS, Guandalini S. Is lactobacillus GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. J Pediatr Gastroenterol Nutr. 2000; 31: 453-457.

87. Klein M, Sanders ME, Duong T, Young HA. Probiotics: from bench to market. Ann N Y Acad Sci. 2010; 1212: 1-14.

88. Klein M, et al. Probiotics: from bench to market. Ann N Y Acad Sci. 2010; 1212: E1-14.

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