



SUMMARY

Probiotics – living microorganisms that when consumed in sufficient amounts provide health benefits beyond basic nutrition – are emerging as important dietary ingredients in functional foods. The majority of probiotics are lactic acid bacteria, especially lactobacilli, and bifidobacteria. In the U.S., food products containing these “friendly” probiotic bacteria are almost exclusively dairy products, such as yogurt and cultured dairy drinks.

Additional possible health benefits attributed to probiotics include a decrease in colon cancer risk; enhancement of the immune system; reduction in symptoms of inflammatory disorders such as inflammatory bowel diseases (i.e., ulcerative colitis, Crohn’s disease, and pouchitis); alleviation of some symptoms of irritable bowel syndrome; and prevention of allergic symptoms, among other benefits.

Although findings are promising, further research is needed to substantiate many of probiotics’ health benefits. Numerous factors influence probiotics’ therapeutic or preventive effects. *In vitro*, experimental animal, and human studies have used different bacterial strains or combinations of strains at different doses, each of which offers a greater or lesser health benefit. Additional research is needed to determine the optimal intake, duration of treatment, and selection of probiotic strains for a specific outcome, the best way to deliver probiotics, and their mechanisms of action.

Dairy products, which are nutrient rich foods, are a desirable natural vehicle to deliver probiotic bacteria into the intestine. Investigators are exploring potential synergistic effects between components in dairy foods and probiotic cultures, as well as the ability of components in milk or fermented milks to trigger beneficial genes in probiotic cultures. Identification of the genetic characteristics of specific probiotics may lead to the development of probiotics with unique or enhanced characteristics. Before probiotics can be recommended in clinical practice or health claims can be made, their efficacy in enhancing health or reducing the risk of disorders needs to be confirmed by rigorous clinical trials in humans.



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PROBIOTICS: CONSIDERATIONS FOR HUMAN HEALTH

Interest in the role of probiotics in human health is not new. However, only in recent years has considerable progress been made in identifying potential health benefits of specific probiotics or foods containing probiotics. Intake of yogurt, particularly with live, active cultures, and specific probiotic bacteria in adequate amounts has been demonstrated to alleviate symptoms of intolerance in lactose maldigesters. This beneficial effect is largely due to the digestion of lactose by the lactase enzyme released from yogurt cultures in the intestine. Additional mechanisms may also be involved.

A substantial body of evidence supports a beneficial role for specific probiotics in reducing the duration and/or severity of a variety of diarrheal diseases, such as acute diarrhea caused by rotavirus infections in infants and young children, antibiotic-associated diarrhea, and travelers’ diarrhea. Probiotics or dairy foods such as yogurt containing probiotics may also help to protect against infectious diseases, such as decrease the growth of *Helicobacter pylori* (a bacterial pathogen responsible for type B gastritis, peptic ulcer, and perhaps stomach cancer).

INTRODUCTION

Over the past decade, there has been considerable progress in identifying potentially beneficial roles for probiotics in human health (1). Probiotics are defined as “live microorganisms administered in adequate amounts that confer a health effect on the host” (2). Interest in the role of probiotics for human health dates back to the beginning of the 20th century (1908) when the Nobel Prize winning Russian scientist, Elie Metchnikoff, linked the long, healthy life of Bulgarian peasants to their high intake of fermented milk products containing lactic acid producing microorganisms (2,3). He theorized that the lactic acid bacteria in fermented milk displace undesirable bacteria normally present in the intestine, resulting in a healthier life. In recent years, there has been a plethora of published scientific studies examining the health attributes of probiotics, especially those related to gastrointestinal health and immune system modulation.

The human gastrointestinal tract contains an extremely complex and diverse microbial population of more than 400 different species of bacteria. While the majority of these bacteria are non-pathogenic, some may potentially cause disease. In healthy individuals, there is a balance of bacteria. Disrupting this balance in the gastrointestinal tract (e.g., by stress, infection, antibiotic therapy) can lead to proliferation of undesirable or pathogenic microbes and increased risk of clinical disorders such as inflammatory diseases, infectious illnesses, and others (4). Increasing scientific evidence indicates that consumption of probiotics can help maintain a healthy microbial population, resulting in several therapeutic benefits (5,6).

For a microorganism to achieve probiotic status, it must have a demonstrable benefit for the host, be alive when administered, and be non-pathogenic (2,3,5). The majority of probiotics are strains of different species of *Lactobacillus* and *Bifidobacterium* (1,4). In the U.S., food products containing probiotic bacteria are almost exclusively dairy products, such as yogurt, Sweet Acidophilus® milk, kefir, and some cottage cheeses (2,3,7). Yogurt is the



Although interest in probiotics (health-promoting bacteria) dates back to the beginning of the 20th century, only in recent years has considerable progress been made in identifying their potentially beneficial roles in human health.

most popular dairy product containing probiotics (7). In addition to the yogurt starter bacteria, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, probiotics such as *Lactobacillus acidophilus* and bifidobacteria, are frequently added to yogurt to confer unique characteristics (7). Dairy foods containing probiotics are a major and growing segment of the world's market for functional foods (i.e., foods fortified with ingredients capable of producing health benefits) (8,9).

Probiotics should not be confused with prebiotics or synbiotics. Prebiotics are non-living, non-digestible food ingredients such as oligosaccharides (e.g., inulin) that stimulate the growth or activity of health-promoting lactobacilli and bifidobacteria (1,5,10). A synbiotic is a combination of prebiotics and probiotics (10). This combination can have an additive or synergistically beneficial effect on the host by improving the survival and/or persistence of the probiotic in the intestinal tract.

This *Digest* reviews potential health benefits of probiotics and discusses factors influencing probiotics' effects in various disorders, as well as the benefits of dairy foods as probiotic delivery vehicles. For more information about probiotics (as well as prebiotics and synbiotics), readers are referred to numerous reviews (1-7,11-25), proceedings of symposia (26-28), and books on this topic (29,30). Also, a Web site, <http://www.usprobiotics.org>, provides up-to-date information on probiotics and dairy foods in the U.S.

POTENTIAL HEALTH BENEFITS OF PROBIOTICS

Research indicates that probiotics confer a variety of health benefits. However, when drawing conclusions regarding this research, it is important to recognize that different strains, species, and genera of bacteria may have unique effects. In *vitro*, experimental animal, and human studies of probiotics have used different bacterial strains and combinations of strains at different doses (3). Because human health issues are very difficult to study directly, different end points (e.g., blood cholesterol as an indicator of heart disease risk) are employed. Also,

the mechanisms by which probiotics exert their effects are largely unknown (3,11,18,23). For the above reasons, generalizations about the health effects of probiotics can be misleading (2). Nevertheless, some promising health benefits (e.g., alleviation of lactose intolerance symptoms, anti-diarrheal effects, and immune stimulation) are attributed to specific strains of probiotics consumed at adequate levels (10,22,25).

Alleviation of Lactose Intolerance Symptoms. Individuals with low levels of the intestinal enzyme lactase (i.e., lactose maldigesters) have a limited ability to digest lactose (milk sugar), which can result in gastrointestinal symptoms or lactose intolerance (31). Studies demonstrate that intake of yogurt and some probiotics can improve lactose digestion and alleviate symptoms of intolerance (3,5,7,12,18,21,31).

Lactose maldigesters generally tolerate lactose from yogurt with live, active cultures better than from milk mainly due to the digestion of lactose in the gut lumen by lactase contained in yogurt starter cultures and released in the small bowel where these bacteria are lysed by bile acids (3,12,21,31). This benefit is substantially reduced if yogurt is heated after inoculation, which inactivates bacteria and its lactase enzyme (7,12,31). Compared to milk, yogurt delays gastric emptying and slows intestinal transit which prolongs the action of lactase in the small intestine and decreases the osmotic load of the lactose (5,31). Yogurt and probiotics may also improve tolerance to lactose by their positive effects on intestinal function and colonic microflora and/or by reducing individuals' sensitivity to symptoms (31).

A variety of probiotic bacteria such as *L. acidophilus* and bifidobacteria improve digestion of lactose in lactose maldigesters, although the effects are less consistent than those achieved for yogurt with live, active cultures (3,31). The finding that some fermented dairy products formulated exclusively with probiotic bacteria, such as Sweet Acidophilus® milk, are ineffective in improving tolerance to lactose may be explained by the low level of probiotics in the product (3).

Anti-diarrheal Effects. An extensive body of research supports a beneficial

Consuming yogurt, particularly with live, active cultures, allows many lactose maldigesters to comfortably include dairy products and their accompanying nutrients in their diet.

role for probiotics in the prevention and treatment of a variety of diarrheal illnesses, such as acute diarrhea caused by rotavirus infections, antibiotic-associated diarrhea, and travelers' diarrhea (6,11,12,17,19-21,32). Specific strains of lactobacilli, such as *Lactobacillus rhamnosus* GG and a combination of *Lactobacillus rhamnosus* 190702 and *Lactobacillus reuteri* DSM 12246, as well as fermented dairy foods such as yogurt, have been shown to reduce the severity and duration of acute diarrhea caused by rotavirus infections in infants and young children (32-36). According to a meta-analysis of randomized controlled studies, therapy using lactobacilli offers a safe and effective means to treat acute infectious diarrheal diseases in children (37).

A common side-effect of antibiotic therapy is diarrhea, usually caused by the growth of pathogenic bacteria, specifically *Clostridium difficile* (4). Several placebo-controlled clinical trials have demonstrated that *L. rhamnosus* GG, *L. acidophilus* LA1, and *Saccharomyces boulardii*, as well as yogurt, reduce the incidence of or lessen the severity of antibiotic-associated diarrhea (32,38-41). Two meta-analyses of placebo-controlled clinical trials support a strong benefit of probiotics in reducing the risk of antibiotic-associated diarrhea (40,41). Probiotics such as *L. rhamnosus* GG or specific mixtures of probiotics (e.g., *L. acidophilus*, *L. bulgaricus*, *B. bifidum*, and *S. thermophilus*) have been used to reduce the incidence of travelers' diarrhea among adults (3,4). However, the role of probiotics in the prevention of travelers' diarrhea varies with the probiotic strain used and the travel destination.

Protection Against Infections.

Probiotics may help prevent or treat infections such as postoperative infections (11), respiratory infections (42,43), and the growth of *Helicobacter pylori*, a bacterial pathogen responsible for type B gastritis, peptic ulcers, and perhaps stomach cancer (44-48). A 7-month randomized, double-blind, placebo controlled study of more than 570 healthy children aged 1 to 6 years in day care centers found that intake of a probiotic milk containing *L. rhamnosus* GG reduced the number and severity of respiratory infections and the need for antibiotics (42). Regular intake of probiotics (i.e., a fermented milk drink

containing a mixture of *L. rhamnosus* GG, *Bifidobacterium*, *L. acidophilus*, and *S. thermophilus*) has been demonstrated to reduce potentially pathogenic bacteria in the upper respiratory tract of humans (43).

Some *in vitro*, experimental animal, and limited human studies indicate that probiotics, especially lactic acid bacteria, may inhibit the growth of *H. pylori* (4-7,12,18,44-48). Probiotics such as *Lactobacillus casei* strain *Shirota*, bifidobacteria, and *Lactobacillus salivarius* have been shown to inhibit the growth and/or colonization of *H. pylori* in *in vitro* and experimental animal studies (4,5,46,48). According to an *in vitro* study, yogurt containing *Bifidobacterium lactis* Bb12 reduced the growth of *H. pylori*, whereas *L. acidophilus* La5 did not (47). When 59 adults with *H. pylori* infection consumed a mixture of these two probiotics in yogurt twice daily after a meal for 6 weeks, *H. pylori* was suppressed, but only when the probiotic yogurt was consumed regularly, whereas *H. pylori* continued to increase in the subjects consuming a placebo (47). Other human studies show that intake of fermented milks containing *Lactobacillus johnsonii* with or without antibiotics suppresses *H. pylori* infection or diminishes the severity and activity of gastric inflammation caused by *H. pylori* (44,45). Although these preliminary findings in humans indicate that some specific probiotic strains may help control *H. pylori* infection, there is no evidence that they can kill this pathogen *in vivo* (7).

Reduced Risk of Colon Cancer.

Some evidence, primarily from *in vitro* and experimental animal studies, indicates that probiotics may have the potential to reduce colon cancer risk (3-5,29a,49-53). In experimental animals, intake of yogurt and specific probiotic cultures has been shown to reduce the development of precancerous lesions (aberrant crypts) and chemically-induced tumors, although the findings appear to be both species- and strain-dependent (50,52). Epidemiological studies in humans link intake of yogurt or other fermented milk products to decreased cancer risk, however, the findings are



Emerging scientific evidence indicates that specific probiotics may reduce the risk of certain diarrheal diseases, infections, and colon cancer; enhance immune function; and alleviate symptoms of inflammatory disorders, among other benefits.

inconsistent (3,7,12,49). Although human intervention studies demonstrate the ability of specific probiotics to inhibit biomarkers of colon cancer risk, such as bacterial enzyme activities, there is no direct evidence that probiotics reduce colon cancer incidence in humans (5). Based on a recent review of the evidence, researchers conclude that the protective role of milks fermented with probiotic cultures in colon cancer risk reduction is promising, but as yet inconclusive (49).

Immune Enhancement. Findings from experimental animal and mostly short term human studies indicate that yogurt and probiotics such as lactobacilli and bifidobacteria stimulate certain cellular and antibody functions of the immune system, which in turn may increase resistance to immune-related diseases (e.g., infections, gastrointestinal disorders, cancer, allergies) (29b,54-58). Secretory immunoglobulin A, which helps to protect against microbial antigens at the intestinal mucosal surface, has been shown to be increased in mice fed *L. acidophilus*, *L. casei* or yogurt, and in humans consuming fermented milk containing *L. acidophilus* (4,7,56). In mice fed fermented milk with *L. casei*, *L. acidophilus*, or both, macrophages (i.e., one of the first lines of nonspecific defense against bacterial invasion) increased (7). Consumption of yogurt or lactic acid bacteria (e.g., *L. casei*, *L. rhamnosus* GG, and other strains) also modulates the production of several cytokines, which have diverse roles in regulating immune functions (7,56).

Studies in older adults have shown that consumption of milk supplemented with a relatively low dose of the probiotic *B. lactis* HNO19 for 3 or 6 weeks enhances some aspects of cellular immunity, including total, helper, and activated T-cells, leukocyte phagocytosis, and tumor-killing cells (59,60). The greatest improvements in *B. lactis*-mediated immunoenhancement occurred in individuals with poorly functioning immune systems (59,60).

Many probiotic effects are mediated by balancing pro-inflammatory and anti-inflammatory cytokines (57). According

to a recent study in 10 healthy adults, cellular immune response to intestinal microorganisms was enhanced following intake of *L. rhamnosus* GG for 5 weeks (61). This probiotic increased the response of peripheral T-lymphocytes to intestinal bacteria and enhanced an anti-inflammatory response by increasing the secretion of suppressive cytokines and decreasing the secretion of pro-inflammatory cytokines (61). Genetically engineering probiotic bacteria with desired functions such as the production of anti-inflammatory cytokines is an active area of research (62).

Anti-inflammatory Effects.

Because probiotics can influence the intestinal flora, they may have beneficial effects for patients with inflammatory bowel disease (IBD), which includes ulcerative colitis, Crohn's disease, and pouchitis (1,5-7,11,29c). Several animal studies and a few clinical trials in humans suggest that specific probiotic bacteria may alleviate or reduce symptoms of IBD (1,5,6,11,18,63,64). Intake of fermented milk for one year helped patients with ulcerative colitis maintain remission and had possible preventive effects, according to a randomized clinical trial in Japan (65). Other studies indicate that a combined probiotic preparation reduces relapses in patients with IBD (5,6,29c, 66). Intake of a combination of eight probiotic strains was effective in maintaining remission in patients with pouchitis (66).

Reduced Symptoms of Irritable Bowel Syndrome. Probiotics may reduce symptoms of irritable bowel syndrome (IBS) (4,6,67). A randomized controlled clinical trial in 25 patients with diarrhea-predominant IBS showed that intake of a probiotic formula twice daily for 8 weeks reduced abdominal bloating (67).

Prevention of Allergic Reactions.

Probiotics may help prevent allergic reactions in individuals at high risk of allergies, such as food allergies (29d,68-71). Results of a randomized double-blind, placebo-controlled study demonstrated that administration of *L. rhamnosus* GG to pregnant mothers 2 to 4 weeks prior to delivery and to their



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newborn babies through 6 months of age led to a 50% decrease in the infants' incidence of recurring atopic eczema (i.e., an indicator of food allergy later in childhood) (69). A follow-up study found that this preventive effect of *L. rhamnosus* GG extended until 4 years of age (70).

Other Potential Health Benefits.

Some experimental animal and human investigations suggest that probiotics may reduce the risk of heart disease by their beneficial effects on blood lipid levels (29e,72-76) and blood pressure (3,4,77). Different strains of lactobacilli and fermented milk products containing probiotic bacteria may help prevent and treat urinary tract infections, bacterial vaginosis, and yeast vaginitis in women (1,3,6,78,79). Probiotics may also help relieve constipation (5,7,80), reduce colic in infants (81), alleviate kidney stones (1), decrease inflammation associated with arthritis (82), and protect against dental caries (1,83).

CONCLUSION

Several potential health benefits of probiotics have been identified, but many must be confirmed by well-controlled human studies (2-7,17,24). Numerous issues remain to be resolved, including the optimal intake, duration of treatment, and selection of probiotic strains for desired outcomes, as well as the best way to deliver probiotics (2,6,18,84).

Probiotic bacteria have long been associated with dairy foods. These foods are considered a desirable natural vehicle to deliver probiotic bacteria such as lactobacilli and bifidobacteria into the intestine (3). Consuming probiotics with dairy foods buffers stomach acid and increases the likelihood that the bacteria will survive into the intestine (18). Dairy products containing probiotics also provide a number of essential nutrients including calcium and protein, as well as other components such as bioactive peptides, sphingolipids, and conjugated linoleic acid. Researchers are investigating the possibility of synergistic effects between components in dairy foods and

probiotic cultures and whether components in milk trigger beneficial genes in probiotic cultures. As a result of new gene technologies, an increased understanding of probiotics' mechanisms and functions and the development of probiotic strains with specific characteristics can be expected (2,18).



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RELATED RESOURCES

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