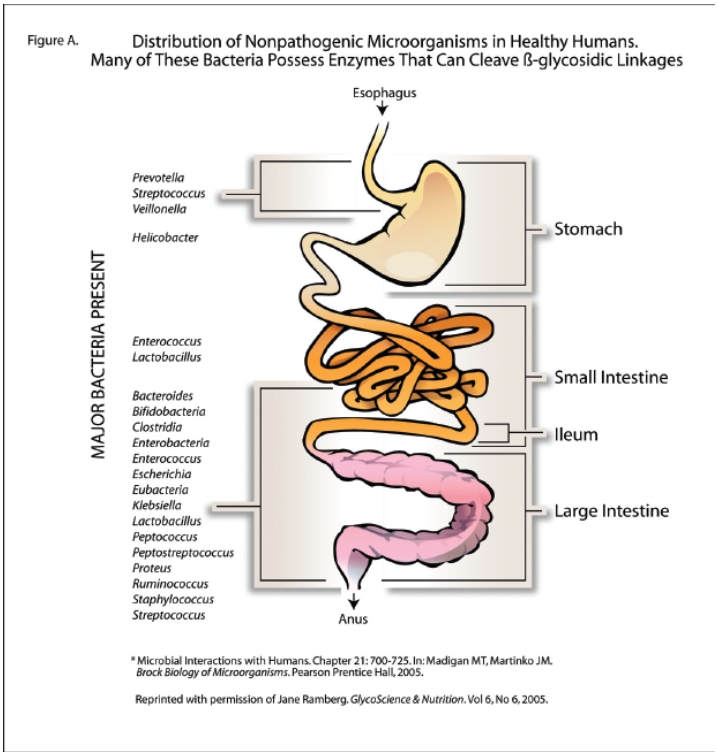
Bugs in Our Guts – Not All Bacteria Are Bad: How Probiotics Keep Us Healthy

By Leila Kiani

What is Probiotics?

At birth, the gastrointestinal tract is sterile and incapable of digesting food. Within hours, bacteria ingested during the birthing process rapidly colonize the gut. The gastrointestinal tract soon contains about 10 times as many bacteria as there are cells in the body. Hundreds of species are present, many of which are uncultivable and remain unidentified. It is these bacteria that are responsible for priming the gastrointestinal immune system (1). This gut flora includes 100 trillion bacteria, some three pounds, which are intimately linked to the body's natural defense system (12).

Probiotics are defined as live microbial food ingredients that benefit human health. Most probiotics fall into the group of organisms known as lactic acid-producing bacteria and are normally consumed in the form of yogurt, fermented milks or other fermented foods (2). The concept of probiotics arose at the turn of the 20th century from a hypothesis first proposed by Noble Prize winning Russian scientist Elie Metchnikoff, who suggest that the long, healthy life of Bulgarian peasants resulted from their consumption of fermented milk products. He believed that when consumed, the fermenting Bacillus (Lactobacillus) positively influenced the microflora of the colon, decreasing toxic microbial activities (3, 4). The historical association of probiotics with fermented dairy products, still true today, stems from these early observations. Investigations in the probiotics field during the past several decades, however, have expanded beyond bacteria isolated from fermented dairy products to those of intestinal origin (3, 4).



Distribution of Nonpathogenic Organisms in Healthy Humans
http://www.mercola.com/2003/oct/18/bacteria_gut.htm
Dr. Joseph Mercola

There is some debate about whether or not yogurt starter bacteria should be considered probiotics. The yogurt starter cultures *Lactobacillus bulgaricus* and *Streptotoccus ther-*

mophilus are used to ferment milk and turn it into yogurt. But these cultures are not very resistant to conditions in the stomach and small intestine and generally do not reach the gastrointestinal tract in very high numbers. Therefore, they cannot mediate some probiotic effects. But these starter bacteria have been shown to improve lactose digestion in people lacking lactase and have demonstrated some immunity enhancing effects. For these reasons, they are often considered 'probiotic' (6).

Most gastrointestinal organisms are relatively benign. Some are potentially more pathogenic; however, many are actually beneficial; it is these beneficial organisms that have attracted attention as possible probiotics (1).
The table below lists some suggested health benefits of consuming probiotics. Those that have significant research to back up the claims are discussed in more depth later in this article (15).

Possible health effects of probiotics

Intestinal effects

- Relieve effects, promote recovery from diarrhea (rotavirus, travelers' and antibiotic-induced)
- Produce lactase, alleviate symptoms of lactose intolerance and malabsorption
- Relieve constipation
- Treat colitis

Immune system effects

- Enhance specific and nonspecific immune response
- Inhibit pathogen growth and translocation
- Stimulate gastrointestinal immunity
- Reduce chance of infection from common pathogens (Salmonella, Shigella)

Other effects

- Reduce risk of certain cancers (colon, bladder)
- Detoxify carcinogens
- Suppress tumors
- Lower serum cholesterol concentrations
- Reduce blood pressure in hypertensives
- Treat food allergies
- Synthesize nutrients (folic acid, niacin, riboflavin, vitamins B6 & B12)
- Increase nutrient bioavailability
- Improve urogenital health
- Optimize effects of vaccines (e.g. rotavirus vaccine, typhoid fever vaccine)

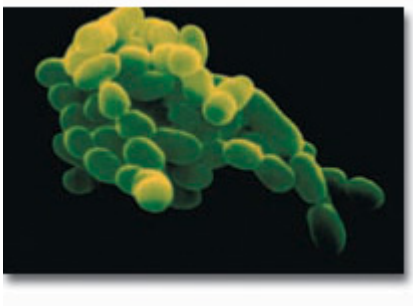
http://www.dairycouncilofca.org/PDFs/probiotics.pdf
Probiotics - Friendly Bacteria with a Host of Benefits (Dairy Council of California, 1101 National Dr. Ste. B, Sacramento, CA 95834-1901)

Microflora in the Intestinal tract
Considering the high number of microbes in the intestinal tract, what are their effects?

Intestinal microflora are important for maturation of the immune system, the development of normal intestinal morphology, and maintenance of a continued and immunologically balanced inflammatory response. The microflora reinforce the barrier function of the intestinal mucosa, helping it to prevent attachment of pathogenic microorganisms and the entry of allergens. Some members of the microflora may contribute to the body's requirements for certain vitamins, including biotin, B-complex vitamin and vitamin B_{12}. Alteration of the microbial flora of the intestine, such as may occur with antibiotic use, disease, and aging, can reduce its beneficial role (5).

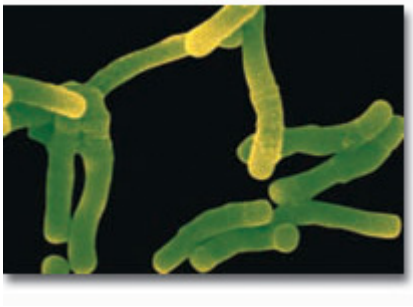
A close up photo of some of these species (14)

Lactobacillae:



Lactobacillae are located throughout the digestive tract but are especially abundant in the small intestine. Some of the main human varieties are:
Lactobacillus acidophilus,
Lactobacillus rhamnosus,
Lactobacillus plantarum,
Lactobacillus brevis and
Lactobacillus salivarius.

Bifidobacterium:



Bifidobacteria are located in the entire digestive tract but are especially abundant in the large intestine. The system's first inhabitants, these species evolve according to age, diminishing progressively towards the end of life. Some of the main varieties are:
Bifidobacterium breve,
Bifidobacterium infantis and Bifidobacterium longum in children, and Bifidobacterium bifidum and Bifidobacterium longum in adults.

http://www.florahealth.com/Flora/Home/canada/Products/TG8_More.asp?CategoryID=&ImageFlag=
Intestinal Flora: A Complex and Diverse Universe (FloraHealth.com; Post Office Box 73, 805 E. Badger Road Lynden, Washington 98264)

It is known that microbes in the large intestine complete the digestion process on any food components that were not digested in the small intestine, such as lactose in lactose intolerant people or fibers resistant to the enzymes they encounter in the small intestine.

There is evidence of non-digestive microbial activities as well. Certain intestinal microbes are known to produce vitamins. Also, in studies done with special microbe-free laboratory animals, evidence is strong that without normal microbial populations, the immune system functions poorly, and resistance to pathogenic bacteria is greatly reduced. Other evidence suggests that intestinal microbes might act on pre-carcinogenic or mutagenic (capable of inducing genetic mutation) compounds. Depending on the specific microbe, mutagenic or carcinogenic activity can be either increased or decreased (5).

There are obvious advantages in skewing the balance of bacteria toward beneficial ones. Both *lactobacilli* and *bifidobacteria* are normal inhabitants of the healthy intestine. Although they are not the dominant genera in either the small or large intestine of adults (bifidobacteria are generally the dominant flora of breast-fed infants), they are non-pathogenic and their presence is correlated with a healthy intestinal flora. The metabolic end products of their growth are organic acids (lactic and acetic acids) that tend to lower the pH of the intestinal contents, creating conditions less desirable for harmful bacteria (5).

The probiotics that are marketed as nutritional supplements and in functional foods, such as yogurts, are principally the *Bifidobacterium* species and the *Lactobacillus* species. Probiotics are sometimes called colonic foods. Most of the presently available probiotics are bacteria. *Saccharomyces boulardii* is an example of a probiotic yeast (5).

Some beneficial effects of lactic acid bacteria consumption include: (i) improving intestinal tract health; (ii) enhancing the immune system, (iii) synthesizing and enhancing the bioavailability of nutrients; (iv) reducing symptoms of lactose intolerance; (v) decreasing the prevalence of allergy; and (vi) reducing risk of certain cancers (2).

The following describe the various bacteria and yeasts used as probiotics (5):

- ***Bifidobacterium***

Bifidobacteria are normal inhabitants of the human and animal colon. Newborns, especially those that are breast-fed, are colonized with bifidobacteria within days after birth. Bifidobacteria were first isolated from the feces of breast-fed infants. The population of these bacteria in the colon appears relatively stable until advanced age, when it seems to decline. They are saccharolytic organisms that produce acetic and lactic acids without generation of CO_2, except during degradation of gluconate. They are also classified as lactic acid bacteria (LAB).

- ***Lactobacillus, Lactococcus and Streptococcus thermophilus***

Lactobacilli are normal inhabitants of the human intestine and vagina. *Lactococcus lactis* (formerly known as *Streptococcus lactis*) is found in dairy products and is commonly responsible for the souring of milk. *Steptococcus thermophilus* is also found in milk and milk products. It is a probiotic and used in the production of yogurt. *Streptococcus sali-*

varus subspecies *thermophilus* type 1131 is another probiotic strain. These are all classified as LAB.

- ***Enterococcus***

Enterococci are part of the intestinal microflora of humans and animals. *Enterococcus faecium* SF68 is a probiotic strain that has been used in the management of diarrhea illnesses.

- ***Saccharomyces***

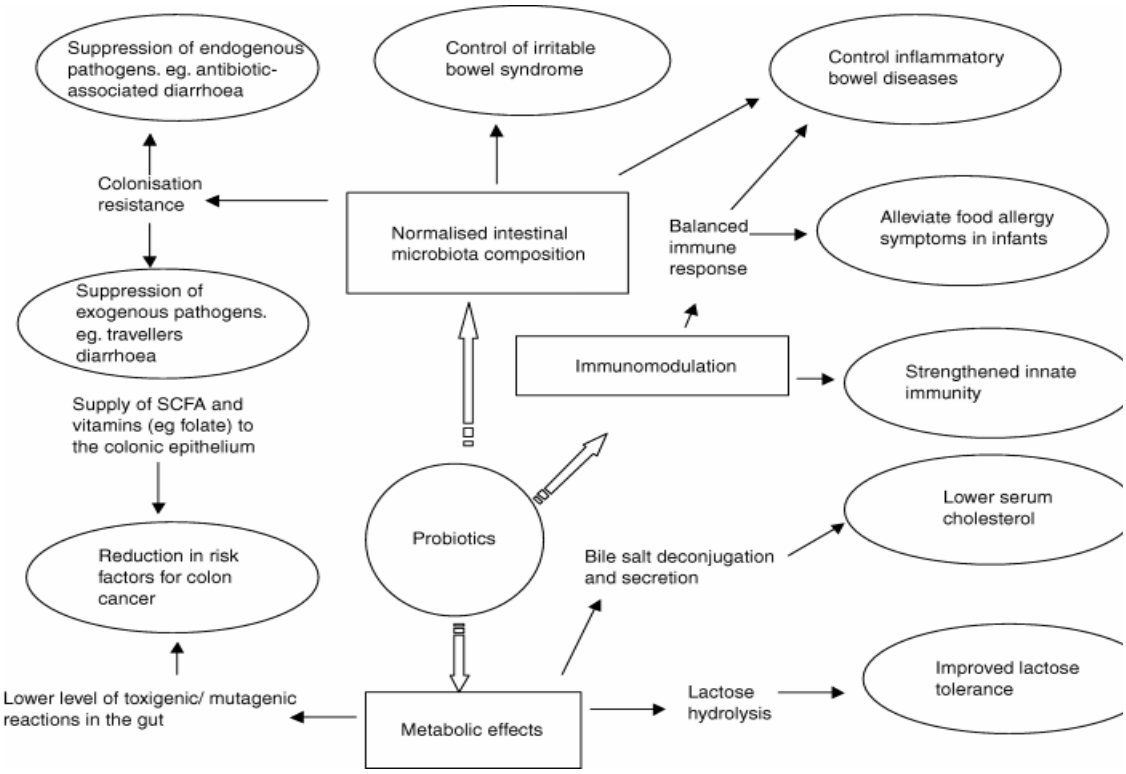
Saccharomyces belongs to the yeast family, which include *Saccharomyces cerevisiae*, also known as bakers' yeast. The principal probiotic yeast is *Saccharomyces boulardii*. *S. boulardii* is normally a nonpathogenic yeast, which has been used to treat diarrhea associated with antibiotic use.

Probiotics Disease and Health Effects

Élie Metchnikoff, the father of modern immunology, spoke optimistically about the possible health benefits of lactic acid-bacteria (LAB) (5). For centuries, folklore suggested that fermented dairy products containing live active cultures are healthful. Recent controlled scientific investigation supports these traditional views, suggesting that probiotics are a valuable part of a healthy diet (6). Research suggests that probiotic bacteria may mediate a variety of health effects through numerous proposed mechanisms (Fig. 1). Alleviation of lactose intolerance symptoms and anti-diarrhea effects are the best substantiated effects. Anticancer and immune modulation effects are encouraging, but need more through substantiation in humans.

Modulation of the gut microflora (populations and activities) and influence on mucosal immunity are mechanisms of probiotic function with potential to broadly influence human physiology (2, 3). For example, the ability of probiotic bacteria to support the immune system could be important to the elderly or other people with compromised immune function. (It is important that immune compromised individuals ask their doctor before taking any dietary supplement, including probiotics) (6). Much active research focuses on the development of target-specific probiotics containing well-characterized bacteria that are selected for their health-enhancing characteristics. These new probiotics are entering the marketplace in the form of nutritional supplements and functional foods, such as yogurt products (5).

A brief assessment of probiotics effects targeted toward several endpoints, with emphasis on results from human studies where possible, follows (3, 6, 2):



Various Health Benefits from Probiotics Consumption
http://www.blackwell-synergy.com/doi/full/10.1111/j.1365-2672.2006.02963.x?cookieSet=1
Parvez S., Malik K.A., Ah Kang S. and Kim H.Y. (Probiotics and their fermented food products are beneficial for health. Journal of Applied Microbiology 100: 6: 1171-1185, 2006)

- ***Diarrhea***

Many types of diarrheal illnesses, with many different causes, disrupt intestinal function. The ability of probiotics to decrease the incidence or duration of certain diarrheal illnesses is perhaps the most substantiated health effect of probiotics. Probiotics can prevent or ameliorate diarrhea through their effects on the immune system. Moreover, probiotics might prevent infection because they compete with pathogenic viruses or bacteria for binding sites on epithelial cells (2 and 16).
In the pediatric population, probiotics appear to benefit viral diarrhea, possibly by increasing the antibody secretory IgA and decreasing viral shedding, suggesting an immunological mechanism (2).

Studies evaluating the effect of probiotics on travelers' diarrhea are equivocal. Traveler's diarrhea (3 times or more) occurs in residents of developed countries after traveling to subtropical and tropical zones. Drinking Lactobacillus GG strain significantly decreased the incidence of diarrhea in travelers. Studies with more reliable results are still needed through appropriate selection of traveling regions (7).

- ***Inflammatory Bowel Disease***

Inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are serious intestinal disorders that can ultimately necessitate the surgical removal of the colon. The causes of such diseases are unknown, but it has been hypothesized that an intolerance to the normal flora (bacteria) in the gut leads to inflammation and resulting pathology. The role of gut flora in the progression of these diseases has led some researchers to study the impact certain probiotic bacteria might have on maintaining the state of reduced inflammation that occurs during the diseases' remission stages. Several controlled clinical trials have shown that high levels of certain probiotic strains can extend the disease-free remission period. Additional research in this area is progressing in Europe and the US (6).

Probiotics bacteria have been shown to improve the clinical outcome in many intestinal disease targets (table) (3).

Table 4 Targets and postulated mechanisms of probiotic influence on abnormal gastrointestinal conditions. Many studies were designed as pilot studies (small numbers of subjects, not blinded) and results have not been confirmed in large trials

Intestinal Conditions Mediated by Probiotic Bacteria	Reference
Antibiotic-associated diarrhea	Orrhage et al., 1994
Toxic amines in blood stream of chronic kidney and liver disease patients with small bowel bacterial overgrowth	Muting et al., 1968 Simenhoff et al., 1996
Inflammatory bowel diseases	Kruis et al., 1997
Lactose intolerance symptoms	Suarez et al., 1995
Rotavirus or other pediatric diarrhea	Belloma et al. 1980 Majamaa et al., 1995 Saavedra, et al., 1994 Vanderhoof and Young, 1998
Intestinal permeability to antigens (rats)	Isolauri et al., 1993a, b
Travellers' diarrhea	Oksanen et al., 1990
Irritable bowel syndrome	Gade and Thorn, 1989
Neutralization of cholera toxin (rats)	Dias et al., 1995
Clostridium difficile pseudomembranous colitis	Rolfe, 1995

- **Cancer**

In general, cancer is caused by mutation or abnormal activation of genes that control cell growth and division. Many processes or exposures can increase the occurrence of abnormal cells, among them chemical exposures. Cancer-causing chemicals (carcinogens) can be ingested in a normal diet or generated by metabolic activity of microbes that live in the gastrointestinal system. It has been hypothesized that probiotic cultures might decrease

the exposure to chemical carcinogens by (a) detoxifying ingested carcinogens; (b) altering the environment of the intestine and thereby decreasing populations or metabolic activities of bacteria that may generate carcinogenic compounds; (c) producing metabolic products (e.g., butyrate) which improve a cell's ability to die when it should die (a process known as apoptosis or programmed cell death); (d) producing compounds that inhibit the growth of tumor cells; or (e) stimulating the immune system to better defend against cancer cell proliferation (6).

Research suggests that the consumption of probiotic cultures may decrease cancer risk. Researchers testing the effect of the consumption of fermented milks, probiotic bacteria, and components or extracts of bacteria have found (6):

- A reduction in the incidence of chemically induced tumors in rats.
- A reduction of the activity of fecal enzymes, postulated to play a role in colon cancer in human and animal subjects.
- Degradation of nitrosamines.
- A weakening of mutagenic activity of substances tested in the laboratory.
- Prevention of damage to DNA in certain colonic cells.
- In vitro binding of mutagens by cell wall components of probiotic bacteria.
- Enhancement of immune system functioning.

Taken together, these results suggest that probiotic cultures may positively influence the gastrointestinal environment to decrease the risk of cancer. However, more studies are

Table 3 Activities of probiotics or probiotic-containing products that may play a role in reducing risk of cancer

Activity Suppressed	Reference
Cell growth and differentiation of tissue culture cells	Baricault et al., 1995
Aberrant crypt foci in colonic tissue of animals	Rowland et al., 1998; Rao et al., 1999.
Tumors in mice (colon, liver, mammary)	Reddy and Rivenson, 1993; Goldin et al., 1996; Adachi, 1992.
Recurrence of superficial bladder cancer in humans	Aso and Akazan, 1992
Enzyme activities (nitroreductase, b-glucuronidase, azoreductase, 7-a-dehydroxylase, glycocholic acid hydrolase) involved in conversion of procarcinogens into carcinogens in feces of laboratory animals and humans; not all parameters positively influenced in all studies.	Ling et al., 1994; McConnell and Tannock, 1993; Goldin et al., 1980
Mutagenic activity	Renner and Munzner, 1991
Genotoxicity	Venturi et al., 1997

http://members.ift.org/NR/rdonlyres/702F0C70-6A78-4278-9717-E0D0ADA9FD06/0/probiotics.pdf
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needed to confirm cancer reduction in humans, and conducting these would be very expensive. Only one study has done so, in this case the effect of consumption of *Lactobacillus casei* fermented milk on recurrence of superficial bladder cancer. The recurrence-free period for the *Lactobacillus*-consuming group was found to be almost twice as long as the control group.

- ***HIV and Immune System Stimulation.***

The immune system provides the primary defense against microbial pathogens that have entered our bodies. The immune system is extremely complex, involving both cell-based and antibody-based responses to potential infectious agents. Immunodeficiency can result from certain diseases (e.g., cancer, AIDS, leukemia) or, to a lesser extent, from more normal conditions such as old age, pregnancy, or stress. Autoimmune diseases (e.g., allergies, rheumatoid arthritis, inflammatory bowel diseases) also can occur due to misdirected immune system activity (6).

Probiotic cultures have been shown in a variety of test systems to stimulate certain cellular and antibody functions of the immune system. Animal and some human studies have shown an effect of yogurt or lactic acid bacteria on enhancing levels of certain immunoreactive cells (e.g. macrophages, lymphocytes) or factors (cytokines, immunoglobulins, interferon)]. In addition, some studies have shown improved survival of pathogen-infected laboratory animals consuming probiotic cultures as compared to animals consuming a control diet. Results accumulated so far suggest that probiotics may provide an additional tool to help your body protect itself (6).

Animal models and human studies (table 3) provide a baseline understanding of the degree and type of probiotic-induce immune response. From these studies, it appears that probiotic bacteria are able to enhance both non-specific and specific immune responses by activating macrophages (3).

- **Allergy.**

Allergy is on the rise in industrialized nations (see.CSA's "ABC's of Allergies" (http://www.csa.com/discoveryguides/allergy/review.php for more information). It is estimated that the incidence of asthma in the United States doubled between 1980 and 2000. Scientists have proposed the ‘hygiene hypothesis’ to explain the rise in allergic conditions such as asthma and eczema. This hypothesis is based on observations that lower allergy incidence is associated with environments that have greater numbers of microbes, such as day care centers, farms, or in homes with siblings or pets. Sanitary living environments and the consumption of processed foods have limited the number of microbes in the diet. The hypothesis suggests that the exposure of infants to microbes before the age of six months helps the immune system mature to better tolerate allergens later in life (6).

Table 5 Immune effects evoked by probiotic bacteria or yogurt in immunocompetent humans

Test product	Effect	Reference
Fermented milk (ST) with *Lactobacillus johnsonii* La1 (10^8/d or 10^9/d)	↑ phagocytic activity + respiratory burst of peripheral blood leukocytes no effect seen at 10^8/d	Donnet-Hughes et al., 1999
Yogurt (10^{11} each ST with LB/d) (control: milk)	↑2′-5′ A synthetase activity in BMC (as more stable indicator of IFN) in yogurt group; no effect on IFN-g, IL-1b, or TNF-a	Solis-Pereyra et al., 1997
Lactobacillus GG capsules (dose not specified); placebo: sucrose	↑ serum IgA response to *Salmonella typhi* lipopolysaccharide vaccine (adjuvant effect)	Jung, 1999
Lactobacillus GG powder capsules (5×10^{10}); placebo: microcrystalline cellulose	↑ IgM secreting cells against rotavirus vaccine	Isolauri et al., 1995
Fermented milk (10^{11}/d *Lactobacillus casei* Shirota) (control: milk)	No effect on natural killer cell activity, phagocytosis or cytokine production	Spanhaak et al., 1998
Fermented milk with *L. johnsonii* La1 (7×10^{10}) or *Bifidobacterium bifidum* Bb12 (10^{10}); no placebo	No effect on lymphocyte subsets, but ↑ phagocytosis of *Escherichia coli* compared to pre-feeding levels	Schiffrin et al., 1995
Lactobacillus brevis subsp. *coagulans* (Labre) tablet, live, and heat-killed, 1.5, 3, and 6×10^8/d	↑a-IFN (as measured by 2′-5′ A synthetase activity) in 3 and 6×10^8/d test groups	Kishi et al., 1996
Yogurt (10^{11} each ST + LB/d) (control: milk)	↑2′-5′ A synthetase activity in BMC	Solis-Pereyra and Lemonnier, 1993
Fermented milk with $4 \times 10^{9\text{-}10}$/d *L. johnsoni* La1 and *Bifidobacterium*; control: diet with no fermented foods	↑ serum IgA response to *Salmonella typhi* vaccine (adjuvant effect)	Link-Amster et al., 1994
Yogurt with 3×10^{12}/d ST and LB	↑ serum IFN-g, B lymphocytes and NK cell subset	De Simone et al., 1993
Lactobacillus GG ($2 \times 10^{10\text{-}11}$)	↑ rotavirus specific IgA antibody secreting cells in rotavirus-infected infants	Kaila et al., 1992, 1995
2×10^{10} CFU/day dried *Lactobacillus* GG	↑ IgA secreting cells; no change in clinical status of Crohn's disease patients.	Malin et al., 1996
Bifidobacterium lactis formula	↑ IgA	Fukushima et al., 1998

ST, *Streptococcus thermophilus*; LB, *Lactobacillus delbrueckii* subsp. *bulgaricus*; LA, *Lactobacillus acidophilus*; B, *Bifidobacterium* spp.; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; Ig, immunoglobulin; BMC, blood mononuclear cells

http://members.ift.org/NR/rdonlyres/702F0C70-6A78-4278-9717-E0D0ADA9FD06/0/probiotics.pdf
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Of course, increasing exposure to microbes must be done safely. This hypothesis led researchers in Finland to conduct a study evaluating the effects of a *Lactobacillus* strain on incidence of atopic eczema in 132 infants at high risk of developing eczema. The study was double-blinded and placebo-controlled. Pregnant mothers two-to-four weeks before

delivery and newborn babies through six months of age were given *Lactobacillus rhamnosus* GG. Infants were followed through two years of age and incidence of recurring atopic eczema was recorded. The study reported a 50% drop in incidence of recurring atopic eczema in the group receiving the probiotic supplement. A follow up study of these same children indicated that these trends were still present at 4 years of age. These results suggest that exposure to the right types of microbes early in life may decrease allergy risk (6).

Other Health Effects

- ***Lactose Intolerance.***

The inability of adults to digest lactose, or milk sugar, is prevalent worldwide. People of northern European descent are unique in retaining the ability to produce the lactose-digesting enzyme, lactase, into adulthood so they can continue to drink milk. Consumption of lactose by those lacking adequate levels of lactase produced in the small intestine can result in diarrhea, bloating, abdominal pain and flatulence. These symptoms are due to the undigested lactose reaching the large intestine and being fermented by the colonic microbes, which can produce gases and products that lead to watery stool (6).

The consumption of dairy products – important for supplying calcium and preventing osteoporosis – by people with lactose intolerance can be facilitated by probiotic bacteria (6).

It has been documented scientifically that many lactose intolerant individuals are better able to consume fermented dairy products, such as yogurt, with fewer symptoms than the same amount of unfermented milk, even though yogurt contains about the same amount of lactose as milk. Yogurt was found to aid digestion of lactose because the lactic acid bacteria used to make yogurt produce lactase and digest the lactose before it reaches the colon. In addition to yogurt starter bacteria, *L. acidophilus* and bifidobacteria have been shown by several studies to improve digestion of lactose, although generally to a lesser extent than the yogurt starter cultures, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (6).

- ***Hypertension.***

About 50-60 million people in United States are estimated to have hypertension, or elevated blood pressure. Antihypertensive effects have been documented in animal models and in mildly hypertensive adults for three compounds derived from the growth of certain lactobacilli: i) fermented milk containing two tripeptides derived from the proteolytic action of L. helveticus on casein in milk; ii) bacterial cell wall components from cell extracts of lactobacilli; and iii) fermented milk containing fermentation-derived gamma amino butyric acid. Systolic blood pressure was decreased on the order of 10-20 mm Hg. These results suggest that consumption of certain lactobacilli, or products made from them, may reduce blood pressure in mildly hypertensive people. Viability of the lactoba-

cillus is not required for the effect. Such fermentation-derived, but nonprobiotic, products have been developed (6).

- ***Antibiotic therapy disease***

One group assessed for the impact of probiotics is people on antibiotic therapy. The purpose of antibiotics is to kill harmful bacteria. Unfortunately, they frequently kill normal bacteria as well, often resulting in disruption of the bacterial flora, leading to diarrhea and other intestinal disturbances. Replenishing the flora with normal bacteria during and after antibiotic therapy seems to minimize disruptive effects of antibiotic use. Studies show that probiotics can prevent antibiotic associated diarrhea, but that no strong effect on the ability of probiotics to treat diarrhea exists. Not all studies have shown positive results in the prevention of antibiotic associated diarrhea or other symptoms associated with antibiotic therapy (6).

- ***Vaginosis***

The vagina and its microbiota form a finely balanced ecosystem. Disruption of this ecosystem can lead to a microbiological imbalance and symptoms of vaginosis. Vaginosis used to be considered a mere annoyance, but now is being examined for a role in serious conditions including pelvic inflammatory disease, pregnancy-related complications (low birth weight babies, etc.), and increased susceptibility to AIDS infection. Vaginosis can be caused by several different organisms, and in many cases, the causative agent may not be identified. What is known is that lactobacilli predominate in the healthy vagina, and a lack of lactobacilli (especially those producing hydrogen peroxide) is a risk factor for vaginosis. The lactobacilli are thought to maintain a favorable vaginal pH in the acidic range and to inhibit pathogens, possibly through the production of hydrogen peroxide and other antimicrobial factors. Intravaginal applications of lactobacilli have been somewhat effective in treating bacterial vaginosis. One study done with 13 women showed that consumption of yogurt containing *L. acidophilus* decreased the incidence of *Candida* yeast infections. Research suggests that lactobacilli may be helpful in controlling the incidence and duration of vaginal infections, but larger, controlled studies are needed (6).

- ***Small Bowel Bacterial Overgrowth.***

Under certain conditions, such as during the production of low stomach acid or kidney dialysis, microbial populations in the small intestine can increase beyond normal levels. This is termed small bowel bacterial overgrowth. Growth of the misplaced microbes can produce potentially toxic byproducts. Researchers have found that feeding high levels of certain probiotic strains can control the toxic effects of these microbes. This is another example of the ability of probiotic strains fed in high numbers to modulate the activity of other intestinal bacteria (6).

- ***Helicobacter pylori.***

Helicobacter pylori is a bacterium which colonizes the stomach. Its presence is associated with gastric ulcers and gastric cancer, although its role in the etiology of these diseases is still under investigation. The effect of probiotics on *Helicobacter pylori* has been studied. Most evaluations have been done either in laboratory assays or in animal models. These studies show that antibacterial substances including (but not limited to) organic acids produced by some lactobacilli inhibit the growth and survival of this pathogen. Results in animal models demonstrate that some lactobacilli inhibit *H. pylori* attachment and prevent colonization. Results in humans show that milk fermented by a *Lactobacillus johnsonii* strain can help control *H. pylori* gastric infections, but cannot eradicate *H. pylori* from the stomach. These results are preliminary, but suggest that probiotic growth in milk may yield anti-*Helicobacter* substances that may help control this infection (6).

- ***Kidney Stones.***

A high oxalate level in the urine is a risk factor for the development of kidney stones. Use of oxalate by intestinal microbes limits its absorption. A probiotic preparation that contained bacteria able to degrade oxalate in vitro was shown to reduce oxalate fecal excretion in six patients. This study suggests that manipulation of the gut flora with the right probiotic bacteria may improve gastrointestinal tract oxalate levels and may decrease oxalate absorption. These results are intriguing, but preliminary (6).

- ***Elevated Blood Cholesterol.***

Cholesterol is essential for many functions in the human body. It acts as a precursor to certain hormones and vitamins and is a component of cell membranes and nerve cells. However, elevated levels of total blood cholesterol or other blood lipids are considered risk factors for developing coronary heart disease. Although humans synthesize cholesterol to maintain minimum levels for biological functioning, diet also is known to play a role in serum cholesterol levels. The extent of influence varies significantly from person to person. Probiotic cultures have been evaluated for their effect on serum cholesterol levels. Clinical studies on the effect of lowering cholesterol or low-density lipid levels in humans have been inconclusive. Some human studies suggest that elevated blood cholesterol levels can be reduced by consumption of probiotic-containing dairy foods, but the evidence is not overwhelming. It is likely that some strains may demonstrate this property while others do not (6).

The dietary cholesterol absorption is reduced in three ways: assimilating, binding, or degradation. Probiotic strains assimilate the cholesterol for their own metabolism. Probiotic strains can get to the cholesterol molecule, and can degrade cholesterol to its catabolic products. The cholesterol level can be reduced indirectly by deconjugating the cholesterol to the bile acids, thereby reducing the total body pool (4).

Consumer Information

Probiotic bacteria have a long history of association with dairy products. This is because some of the same bacteria that are associated with fermented dairy products also make their homes in different sites on the human body, including the mouth, the gastrointestinal tract and the vagina. Some of these microbes, therefore, can play a dual role in transforming milk into a diverse array of fermented dairy products (yogurt, cheese, kefir, etc.), and contributing to the important role of colonizing bacteria (6).

The consuming public may have a generally negative image of bacteria in foods, but they are aware of "live, active cultures" in fermented dairy foods, and these cultures convey a positive, healthful image. Information about probiotic bacteria can be an extension of the comfortable association of cultures in dairy products, and make it easier to communicate health messages to the public (6).

A dairy product containing probiotics makes a healthy "functional food package." In addition to the vitamins, calcium, other minerals, and protein obtained from milk products, modern research has suggested healthful properties of fermentation-derived peptides and butyric acid found in some dairy products. Dairy products have recently been shown to be important for a healthy diet, doing more than preventing osteoporosis. Consumption of three or more servings of dairy products each day has been associated with lower levels of obesity, and hence lower incidence of diabetes, hypertension and heart disease. The DASH (Dietary Approaches to Stop Hypertension) diet also recommends three servings of lowfat dairy products. Considering all these findings, dairy products combined with probiotic bacteria may translate into improved long-term health (6).

Numerous commercial products containing LAB have been associated with healthy function. Basic conditions for LAB strains to be used as probiotics have been reported to include the following: (a) general recognized as safe (GRAS) (b) able to keep their viability during processing and storage, (c) tolerant to acid and bile, (d) able to adhere to the intestinal epithelium of the hosts, and (e) antagonistic activity against bacterial pathogens (8).

Probiotics are provided in products in one of three basic ways (6):

- as a culture concentrate added to a food (usually a dairy product) at medium levels, with little or no opportunity for culture growth
- inoculated into a milk-based food (or dietary supplement) and allowed to grow to achieve high levels in a fermented food
- as concentrated and dried cells packaged as dietary supplements such as powders, capsules, or tablets

Foods are the best choice for delivering probiotics due to the synergistic effect between components of foods and probiotic cultures. The natural buffering of stomach acid by food also enhances the stability of consumed probiotics. Dairy products containing probiotics provide a number of high quality nutrients, including calcium, pro-

tein, and conjugated linoleic acids. Taking supplements, although convenient, has always posed the problem of long term compliance, whereas incorporating foods containing probiotics into daily food choices can become a lifestyle habit (15).

Supplements Trade Names (5)

The dietary supplement market for probiotic cultures seems to be a more diverse and more active market than probiotics for dairy. The supplement market contains many different product formats and contents, including capsules, liquids, tablets and even food-like formats. If properly prepared and stored, probiotic bacteria can remain viable in dried form and reach the intestine alive when consumed. A diverse array of bacterial genera and species are represented in these products, including many different lactobacilli, bifidobacteria and less commonly, *Enterococcus, Bacillus, Escherichia coli* and yeast. Dietary supplement products are purchased primarily in health food stores or natural foods grocery stores (6).

Commercial Probiotic Strains

This table lists some commercial probiotic strains currently available. Probiotic species are listed as reported by manufacturer. This speciation may not reflect the most current taxonomy (6)

Strain	Source
L. acidophilus NCFM®	Rhodia, Inc. (Madison, WI)
L. acidophilus SBT-2062[1] *B. longum* SBT-2928[1]	Snow Brand Milk Products Co., Ltd. (Tokyo, Japan)
L. rhamnosus R0011 *L. acidophilus* R0052	Institut Rosell (Montreal, Canada)
L. acidophilus LA-1 *L. paracasei* CRL 431 *B. lactis* Bb-12	Chr. Hansen (Horsholm, Denmark)
L. casei Shirota[1] *B. breve* strain Yakult[1]	Yakult (Tokyo, Japan)
L. casei Immunitas	Danone (Paris, France)
L. fermentum RC-14 *L. rhamnosus* GR-1	Urex Biotech (London, Ontario, Canada)
L. johnsonii La-1 (same as NCC533 and formerly *L. acidophilus* La-1)	Nestlé (Lausanne, Switzerland)
L. plantarum 299V *L. rhamnosus* 271	Probi AB (Lund, Sweden)
L. reuteri SD2112	Biogaia (Raleigh, NC)
L. rhamnosus GG[1]	Valio Dairy (Helsinki, Finland)

L. rhamnosus LB21 *Lactococcus lactis* L1A	Essum AB (Umeå, Sweden)
L. salivarius UCC118	University College (Cork, Ireland)
B. longum BB536[1]	Morinaga Milk Industry Co., Ltd. (Zama-City, Japan)
B. lactis HN019 (DR10) *L. rhamnosus HN001* (DR20)	Fonterra (Wellington, New Zealand)
L. acidophilus LB	Lacteol Laboratory, (Houdan, France)
L. paracasei F19	Medipharm (Des Moines, Iowa)
[1]Strains have been awarded official functional food (FOSHU) status in Japan To have a strain added to this table, please contact *mes@mesanders.com* with information on the strain to justify its inclusion and a contact person	

http://www.usprobiotics.org/products/
usprobiotics.org (California Dairy Research Foundation, 502 Mace Blvd Suite 12 Davis, CA 95616)

Yogurt and milk to which probiotic bacteria have been added, such as acidophilus milk, and fermented milk products, such as kefir, are the primary food sources of probiotics in the United States. Europe and Asia lead the rest of the world in offering a variety of other food products containing probiotics. We will probably see products such as probiotic-fortified energy bars, juices, cereals and cheeses introduced into US over the next few years as well (15)

Some recent moves by U.S. food companies toward a warmer embrace of the probiotic concept are exhibited with the marketing of Lactobacillus as a dietary supplement (Culturelle) by ConA-gra (Omaha, Neb.), the entry of Dannon (Tarrytown, N.Y.) into the dairy beverage market with Actimel (labeled as a dietary supplement, containing yogurt cultures and Lactobacillus casei), and the addition by Stoneyfield Farm (Londonderry, N.H.) of four probiotics to all of its yogurt products. (3)

Safety concept of microorganisms in food and feed

Europe takes a slightly different approach than the United States to issues of microorganisms and food safety. The qualified presumption of safety (QPS) approach of microorganisms in food and animal feed is a system similar in concept and purpose to the Generally Recognized as Safe (GRAS) definition used in the USA, but modified to take account of Europe's different regulatory practices. QPS provides a mechanism to recognize and give weight to prior knowledge when assessing the safety of microorganisms in food and feed production. QPS appears applicable to food, feed and microbial products from the viewpoint of safety assessment; however a number of issues need careful consideration before QPS could be introduced into the European safety evaluation (9).
With the exception of those encompassed, in Europe, by Novel Food Regulation, microorganisms used for fermentation of food are presently not subject to community regulation. In contrast, microorganisms used as feed additives or plant protect products are comprehensively regulated. This has led to illogical situations in Europe where the same strains used freely in human foods have been the subject of stringent safety assessment

when seeking community approval as a feed additive. The QPS approach represents a possible route to harmonization of approaches for the safety assessment of microorganisms used in feed/food production without introducing unnecessary measures in area where there has been no great concern about safety, while allowing more important safety concerns to be addressed. Therefore, QPS is as an operating procedure within EFSA for risk assessment (9).

Many probiotic products are available. These contain various *Lactobacillus* strains, *Bifidobacterium* strains, combinations of lactobacilli and bifidobacteria and combinations of probiotics and prebiotics. Typical doses of probiotics range from one to ten billion colony-forming units (CFU). Probiotics need to be consumed at least a few times a week to maintain their effect on the intestinal microecology (5). Some strains do not lead to adverse events even if administered at a $10^9 – 10^{10}$ level to neonatal patients in a serious state, who appear to be the immunologically weakest of recipients, nor do these strains harm patients after highly invasive surgery on digestive organs (7). Probiotic strains can be administered to the customer in lyophilized form in sealed bags, tables or capsules, or in yogurt, other dairy products or in fruit juices. The storage time for lyophilized products is significantly longer. For each final product, the number of live cells has to be declared and the storage time at different temperature clearly stated. Today, this is the case for but a few products. Since probiotic microbes have different beneficial properties an optional product may need the combination of several strains (10).

In spite of inherent difficulties establishing good measures of probiotic efficacy, studies on lactose intolerance, diarrhea and colon cancer show that a daily dose of lactic acid bacteria is needed for any measurable effect. Unfortunately, the concentration of probiotics in food products varies tremendously and there are currently no national standards of identity for levels of bacteria required in yogurt or other fermented products. Epidemiological data on the safety of dairy products and a thorough review of the safety data suggests no evidence of probiotics being involved with human infections. However, there always remains the possibility that probiotic consumption can cause infection or other side effects and that individuals will respond in different ways to a specific strain. The food industry will need to carefully assess the safety and efficacy of all new species and strains of probiotics before incorporating them into food products (2).

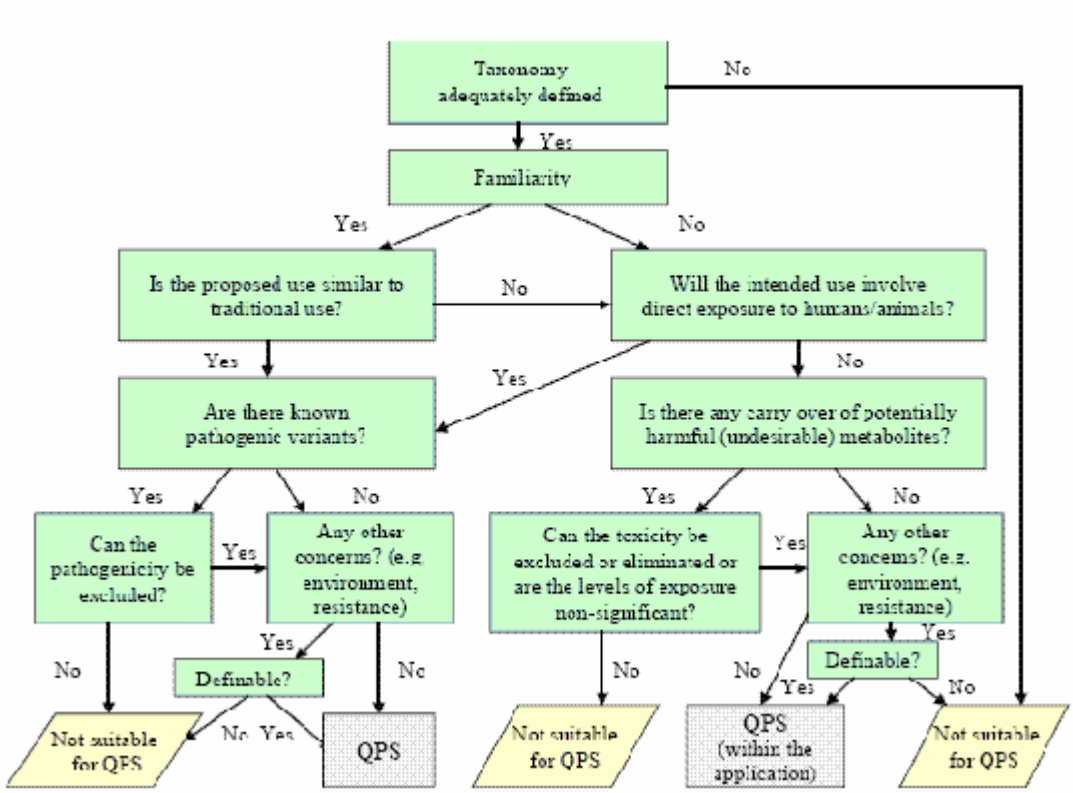
- ✓ ***Contraindications***

Probiotics are contraindicated in those hypersensitive to any component of a probiotic-containing product (5)

- ✓ ***Precautions***

Pregnant women and nursing mothers should only use probiotic nutritional supplements if recommended by their physicians (5)

The use of probiotics for the treatment of any disorder must be medically supervised.



A General Scheme For The Assessment Of Suitability For QPS Status Of Microorganisms
http://ec.europa.eu/food/fs/sc/scf/out178_en.pdf
European Commission, DG Health and Consumer Information (B-1049 Brussels)

- ✓ ***Adverse Reactions***

The most common adverse reactions to probiotics are gastrointestinal and include flatulence and constipation. Probiotics are generally well tolerated. Four cases of *Saccharomyces boulardii* fungemia have been reported. All of the patients had indwelling catheters, and the fungemia was thought to be due to catheter contamination (5).

There are a few reports of *Lactobacillus* bacteremia and endocarditis. In all cases, underlying conditions have been present, including cancer, diabetes mellitus and recent surgery (5).

In the United States, it is essential to have scientific substantiation if a statement (known as a structure/function statement) about the effect of probiotics on the normal functioning of the human body is made on a food or dietary supplement product or during promotion of the product. The burden of proof rests with the manufacturer. Although the Food and Drug Administration (FDA) does not require premarket approval of such statements, the manufacturer must provide scientific justification of any health statements if asked by the FDA (6).

Conclusion

The flora in the human gut constitute “an extremely complex living system that aggressively protects your body from outside offenders” (12). The average American also eats far too many sugars, some 175 pounds per year, feeding the unhealthy bacteria, which stimulate disease. Chemicals can also disrupt the microflora. The "bad" bacteria largely reside in “the intestinal lining (mucosal barrier) that is over 300 square meters, or about the size of a tennis court” (12).

Beneficial bacteria can boost the immune system, prevent allergies, and stop eczema and heal the intestines. A good diet, supplemented with a high-quality probiotic, will improve the balance of good and bad bacteria (12).

In spite of the problems with dosage and viability of probiotic strains, lack of industry standardization, and potential safety issues, there is obviously considerable potential for the benefits of probiotics over a wide range of clinical conditions. Ongoing basic research will continue to identify and characterize existing strains of probiotics, identify strain-specific outcomes, determine optimal doses needed for certain results, and assess their stability through processing and digestion (2).

Gene technology will certainly play a role in developing new strains, with gene sequencing allowing for an increased understanding of mechanisms and functionality of probiotics. In addition to such basic research, industry-centered research will focus on prolonging the shelf-life of probiotic products and likelihood of survival through the intestinal tract, optimizing adhesion capacity and developing proper production, handling and packaging procedures to ensure that the desired benefits are delivered to the consumer (2).

Over time, new food products containing probiotics will emerge, such as energy bars, cereals, juices, infant formula and cheese, as well as disease-specific medical foods. The establishment of standards of identity for probiotic-containing food products will serve to accelerate their development and availability (2).

Available data from traditional medicine and clinical use clearly state that probiotics have great health potential, particularly today with the increasing threat of antibiotic over-usage and prevalence of antibiotic resistant microorganisms (10).

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