Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health?

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Colonic microflora are important to health. The growth and metabolism of the many individual bacterial species inhabiting the large bowel depend primarily on the substrates available to them, most of which come from the diet.[1,2] This has led to attempts to modify the structure and metabolic activities of the community through diet—using probiotics and prebiotics. Probiotics are live microbial food supplements. The best known are the lactic acid bacteria and bifidobacteria, which are widely used in yogurts and other dairy products. These organisms are nonpathogenic and nontoxigenic, retain viability during storage, and survive passage through the stomach and small bowel. Prebiotics are nondigestible food ingredients that selectively stimulate the growth, activity, or both, of lactobacilli or bifidobacteria in the colon, thereby improving health.

Bacteria and yeasts used as probiotics

Bifidobacterium longum
B breve
B infantis
B bifidum
B adolescentis
Lactococcus cremoris
L lactis
Enterococcus faecium
Lactobacillus rhamnosus
L acidophilus
L casei
L bulgaricus
L gasseri
Saccharomyces boulardii
S cerevisiae

The probiotic concept

Since probiotics do not permanently colonize the host, they need to be ingested regularly for any health-promoting properties to persist. Most studies on probiosis have been observational rather than mechanistic, and thus the processes responsible for many probiotic phenomena are seldom explained. Some probiotics are members of the normal colonic microflora and are not viewed as being overtly pathogenic. These organisms have occasionally caused infections in people whose health is compromised in other ways, however.[3,4]

Commercial probiotic preparations are usually mixtures of lactobacilli and bifidobacteria, although yeasts such as saccharomyces have also been used (see box). Bifidobacteria are of particular interest. These are anaerobic pleomorphic rods or club-shaped organisms (Figure 1) that normally have an important role in breaking down dietary carbohydrate and interact directly with the host metabolism.[5] Bifidobacteria also synthesize and excrete water-soluble vitamins, but there are considerable differences in species and strains.[6] These organisms predominate in the colons of breast-fed babies; they account for up to 95% of all culturable bacteria and protect against infection.[7] Bifidobacteria do not occur in such high numbers in adults.

Adherence

Attachment of probiotics to the gut epithelium is an important determinant of their ability to modify host immune reactivity, but this is not a universal property of lactobacilli or bifidobacteria and is not essential for successful probiosis.[8] Adherence of *Lactobacillus acidophilus* and some bifidobacteria to human enterocyte-like CACO-2 cells prevents binding of enterotoxigenic and enteropathogenic *Escherichia coli*, as well as *Salmonella typhimurium* and *Yersinia pseudotuberculosis*.[9,10] *Bifidobacterium infantis* and some strains of *B breve* and *B longum* attach strongly, although other *B breve* and *B longum* isolates are poorly adherent. Thus there are species and strain variations in this probiotic attribute.

Nineteen strains of lactobacilli (each 5×10^6/ml) were fed to healthy volunteers in 100 ml of fermented oatmeal soup.[11] Biopsy specimens showed that the organisms colonized jejunal and rectal mucosas. Adherent lactobacilli were recovered from jejunal samples 11 days after the probiotic was stopped, while mucosal clostridia decreased up to 100-fold in some volunteers. In rectal tissue, anaerobes and enterobacteria were reduced.

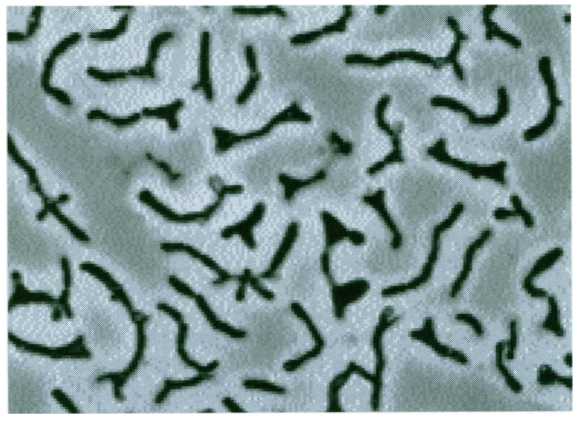

Figure 1 *Gram-stained preparation of Bifidobacterium adolescentis showing club-shaped cells and other pleomorphic forms*

Probiotics and gut infection

Colonic microflora normally present a barrier to invading organisms, but pathogens often become established when

Table 1 *Chemical composition and characteristics of candidate prebiotic carbohydrates*

Oligosaccharide (example)	Chemical composition
Fructo-oligosaccharides (Raftilose P95)	95% oligosaccharides β (2-1) fructan; 60% glucose, fructose$_{(n)}$, 40% fructose$_{(n)}$ dp 2-8, average dp 4-5
Inulin	>99% oligosaccharides β (2-1) fructan; average dp 10-12
Pyrodextrins	Complex mixture of glucose-containing oligosaccharides
Transgalactosylated oligosaccharides (Oligomate 55)	Mainly 6′ galactosyllactose, dp of oligosaccharide fraction 2-5 (primarily dp 3); 55% pure
Galacto-oligosaccharides	Oligogalactose (85%), small amounts of glucose, galactose, and lactose
Soy oligosaccharides	Stachyhose (fructose, galactose, galactose, glucose) and raffinose (fructose, galactose, glucose), dp 3-4
Xylo-oligosaccharides	β (1-4) linked xylose; 70% pure, dp of oligosaccharide fraction 2-4
Isomalto-oligosaccharides	Mixture of α (1-6)-linked glucose oligomers (isomaltose, panose, isomaltotriose)
Lactulose	Galactose and fructose-containing disaccharide

dp = degree of polymerization.

the integrity of the microbiota is impaired through stress, illness, antibiotic treatment, changes in diet, or physiological alterations in the gut. Bifidobacteria are known to be involved in resisting the colonization of pathogens in the large bowel.[12] Feeding *B breve* to children with enteritis eradicated *Campylobacter jejuni* from their stools, although less rapidly than in patients treated with erythromycin.[13] Supplementation of infant formula milk with *B bifidum* and *Streptococcus thermophilus* reduced rotavirus shedding and episodes of diarrhea in children in the hospital.[14]

Lactobacilli have been widely used in treating diarrheal diseases such as pseudomembranous colitis, but the results have been mixed.[15] Feeding freeze-dried powders of *L acidophilus* NCDO 1748 had no effect on patients with pseudomembranous colitis,[16] but lactobacillus GG successfully eradicated *Clostridium difficile* in five patients with relapsing colitis.[17] Viable lactobacilli (approximately 10^{10}) were fed daily in skimmed milk. Diarrhea was immediately relieved in four patients, and there were concomitant reductions in titers of *C difficile* toxin in stools. The other patient also improved after further antibiotic and probiotic treatment. Lactobacillus GG had previously been shown to colonize the gut and secrete an antimicrobial product that was active against *C difficile* and a range of other micro-organisms.[18]

Not all lactobacilli are effective in combating enteric pathogens, however. Twenty-three healthy volunteers were given a commercial product containing *L acidophilus* and *L bulgaricus* and were then challenged with enterotoxigenic *Escherichia coli*.[19] They did not differ in respect of attack rate, incubation period, or duration of illness from control subjects given a placebo.

The yeast *Saccharomyces boulardii* has also been used in studies of the prevention and treatment of diarrhea associated with *C difficile* infection.[20] Of 180 patients in a double-blind controlled study, 9.5% of those receiving the probiotic had diarrhea compared with 22% of the controls given placebo. The authors concluded that prophylactic use of the probiotic reduced the incidence of diarrhea associated with *C difficile* infection, although *S boulardii* did not prevent acquisition of the pathogen.

Traveler's diarrhea

Lactobacilli, bifidobacteria, enterococci, and streptococci have been used prophylactically to prevent traveler's diarrhea caused by enterotoxigenic *E coli*. Neither *L acidophilus* nor *Enterococcus faecium* had any probiotic effect on groups of Austrian tourists,[21] and no differences were observed in healthy volunteers given either placebo or lactobacilli, who were then challenged experimentally with virulent enterotoxigenic *E coli*.[19] The incidence of diarrhea was reduced from 71% to 43%, however, in tourists going to Egypt who were given capsules containing *S thermophilus*, *L bulgaricus*, *L acidophilus*, and *B bifidum*.[22]

Prebiotics

To be effective, prebiotics should escape digestion in the upper gut, reach the large bowel, and be utilized selectively by a restricted group of micro-organisms that have clearly identified, health-promoting properties. The food ingredients most likely to meet these criteria at present are oligosaccharides, including inulins, and their derivatives, the fructo-oligosaccharides (see Table 1). These low-molecular-weight carbohydrates occur naturally in artichokes, onions, chicory, garlic, leeks, and, to a lesser extent, cereals. Other oligosaccharides such as raffinose and stachyose are the major carbohydrates in beans and peas. These simple molecules can also be produced industrially, and a number of new potential prebiotics are being developed for this market (see below). The degree of polymerization of these substances (Table 1) refers to the number of individual monosaccharides in the molecule.

Not all nondigestible oligosaccharides have prebiotic properties. Inulin, fructo-oligosaccharides, and to a lesser degree, galacto-oligosaccharides dominate the published reports (Table 2). Fructo-oligosaccharides have an energy value of 6 kJ/g; they have no genotoxic, carcinogenic, or toxicological effects; and they are mildly laxative, although flatulence is often a complaint when large doses are taken.[23] In controlled dietary studies with human volunteers, fructo-oligosaccharides (15 g/day) increased fecal bifidobacterial numbers tenfold while reducing clostridia and

enterobacteria counts, showing that the species composition of the microbiota could be selectively manipulated through diet. In vitro, eight different bifidobacterial species that were grown on fructo-oligosaccharides produced inhibitory substances that were antagonistic, to various degrees, against salmonella, listeria, campylobacter, shigella, and vibrio.[24] Feeding fructo-oligosaccharides (8 g/day) to elderly people increased fecal bifidobacteria tenfold,[25] and ingestion of soybean oligosaccharides (10 g/day) resulted in a smaller, though still appreciable, increase in bifidobacteria.[26] Fructo-oligosaccharides do more than promote bifidobacterial growth, however, and several other intestinal bacteria are clearly involved in their metabolism.[27]

Galacto-oligosaccharides are present naturally in human and cow's milk and are also produced from lactose by β-galactosidase. Feeding 2.5 g, 5 g, or 10 g of galacto-oligosaccharides to volunteers resulted in a dose-related increase in fecal bifidobacterial excretion, although stool weight and frequency did not change noticeably.[28] At present, no clinical studies on the use of prebiotics to prevent diarrhea have been reported.

Table 2 *Physiological importance and health benefits claimed for nondigestible oligosaccharides*

Physiological effects	Health factors
Stimulated carbohydrate metabolism in colonic bacteria; increased bacterial cell mass, short-chain fatty acids, and fermentation gases	Through short-chain fatty acids, they provide energy sources for the colonic epithelium and control of differentiation. Flatulence may be a problem. Laxative effects
Selection of bifidobacterial and lactic acid bacterial growth in large bowel	Enhanced resistance to invading pathogens
Not hydrolyzed by oral microorganisms	Protection against caries
Not glycemic	Potentially useful for people with diabetes
Nonspecific stimulation of immune function	Resistance to infection
Modulation of carcinogen metabolism	Anticancer properties
Reduced hepatic synthesis of very low density lipoprotein cholesterol and serum triglycerides	Coronary heart disease
Increased absorption of Mg and Ca	Osteoporosis

Antimutagenic activities

Probiotics and prebiotics seem to be antimutagenic in several ways. Gram-positive and gram-negative bacteria bind to mutagenic pyrolysates produced during cooking at high temperatures, and studies with lactic acid bacteria show that they can be living or dead, since the process occurs by adsorption of mutagen to carbohydrate polymers in the cell wall.[29] Lactobacilli also degrade carcinogens such as *N*-nitrosamines, which may be important if the process occurs at the mucosal surface.[30] Coadministration of lactulose and *B longum* to rats injected with the carcinogen azoxymethane reduced intestinal aberrant crypt foci, which are preneoplastic markers.[31] Purified bifidobacterial cell walls have antitumor activities in that the cell wall of *B infantis* induces activation of phagocytes to destroy growing tumor cells.[32] Bifidobacteria probiotics reduced colon carcinogenesis induced by 1,2-dimethylhydrazine in mice when used with fructo-oligosaccharides[33] and inhibited liver and mammary tumors in rats.[34] When Neosugar (4 g/day; fructo-oligosaccharides) was given to healthy volunteers in the form of chewable tablets, it increased the intestinal bifidobacteria and reduced appreciably the fecal activities of enzymes involved in producing genotoxic metabolites such as β-glucuronidase and glycocholic acid hydroxylase,[35] indicating the potential of prebiotics and probiotics to reduce or prevent carcinogenesis.

Immunity

Colonic microbiota affect mucosal and systemic immunity in the host.[36] Intestinal epithelial cells, blood leukocytes, B and T lymphocytes, and accessory cells of the immune system are all implicated.[37] Bacterial products with immunomodulatory properties include endotoxic lipopolysaccharide, peptidoglycans, and lipoteichoic acids.[38] Lipoteichoic acids of gram-positive bacteria such as bifidobacteria possess high binding affinity for epithelial cell membranes and can also serve as carriers for other antigens, binding them to target tissues where they provoke an immune reaction.[39] Yogurt lactobacilli bind in vitro to peripheral blood CD4 and CD8 T lymphocytes but not to B cells; lactobacilli that adhere to human intestinal epithelial cells are capable of activating macrophages.[40,41]

There are as yet no experimental data to support the immunostimulatory properties of nondigestible oligosaccharides in humans. Probiotic organisms interact with the immune system at many levels, however, including cytokine production, mononuclear cell proliferation, macrophage phagocytosis and killing, modulation of autoimmunity, and immunity to bacterial and protozoan pathogens.[36,37,42,43]

In vitro, bifidobacteria induce formation of large amounts of IgA.[44] Of 120 strains tested belonging to a number of species (*B animalis*, *B longum*, *B breve*), three *B breve* strains and one *B longum* isolate induced appreciable synthesis of IgA. This was confirmed in vivo when mice given one of the *B breve* strains together with cholera toxin had augmented immune responses in lymphoid tissue associated with the gut. In mice, *B breve* fed in fermented milk induced macrophagelike cells in Peyer's patches to release a factor that stimulated mitosis in B cells and enhanced production of antibodies against food allergens and pathogens.[45]

L acidophilus and *B bifidum* given in capsule form to elderly people effected appreciable changes in inflammatory and immunological responses.[46] They reduced

colonic inflammatory infiltration considerably but did not affect the numbers of B lymphocytes and T lymphocytes. Study subjects had a greater increase in B cells in peripheral blood than did controls, however. Lactobacillus GG was used to manage an allergy to cow's milk and atopic eczema in 31 infants aged 2 to 16 months.[47] It resulted in a considerable improvement in their condition and reduced fecal excretion of α_1-antitrypsin and tumor necrosis factor-α through "an improvement in antigen elimination by the gut mucosal barrier."[47]

Conclusions

We are entreated to buy the yogurts with live cultures on sale in supermarkets with promises that they will boost our body's natural resistance, promote healthy digestion, and improve the balance of our gut microflora—effects to be achieved thanks to probiotic bacteria. Even more remarkable is the suggestion that some dietary carbohydrates can selectively stimulate growth of these organisms when they occur naturally in our gut and thus produce the same benefits. If true, this is one of the most important stories to emerge in nutrition and gut microbiology since the turn of the century.

Although there are now many published reports on the use of probiotics in humans, information on prebiotics is more limited. Consequently, many of the health claims made in relation to these substances are unsubstantiated. The ability to target specific organisms in the large intestine for defined, health-promoting purposes will clearly be of great value and needs to be developed. There are considerable differences in bacterial carbohydrate utilization patterns, however, between strains as well as species,[48] which is particularly important for the development of prebiotics. A few strains have been identified as having health-promoting potential in vivo, but nonspecific increases in total bifidobacterial or lactobacillus numbers in the large bowel through the introduction of "functional foods" will probably be of questionable benefit to health.

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Complementary and alternative medicine in cardiovascular disease: what is the evidence it works?

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Despite advances in prevention and treatment over the past 20 years, cardiovascular disease remains a leading cause of death and disability. This article reviews coenzyme Q10, hawthorn, complementary chelation, and ginkgo biloba, some of the most common treatments patients ask about and use for cardiovascular diseases.

Summary points

- Coenzyme Q10 and hawthorn merit further investigation to determine what benefits, if any, they offer beyond best present therapies for cardiac ischemia and heart failure.
- The few studies of best design do not support the use of chelation therapy for cardiovascular disease.
- Ginkgo biloba is at least as effective as pentoxifylline for treatment of claudication, and further investigation, perhaps in combination with exercise, is warranted.
- Dietary supplements manufactured in the United States are of inconsistent purity and potency, making it difficult for physicians to advise their patients about how to purchase and use them.

Methods

For Coenzyme Q10 and hawthorn, MEDLINE, BIOSIS and Cochrane databases were reviewed along with references of retrieved articles and personal files of the author. Languages were restricted to English and German. Articles discussed reflect often cited references, not an exhaustive review. The discussion of chelation therapy summarizes a review of studies identified using MEDLINE (1966–1996) and CISCOM (1996) bibliographies of relevant papers and suggestions from six experts and national societies. For the *Ginkgo biloba* for peripheral vascular disease, literature searches located eight randomized placebo-controlled double-blind trials that met inclusion criteria.

Coenzyme Q10

Coenzyme Q10 is used widely in Japan, Europe, and elsewhere for a variety of purposes, but especially for cardiac disease. It is a fat-soluble, vitamin-like substance, structurally similar to vitamins E and K. It is one of many agents called ubiquinones, so named because of their presence in almost all cells of the human body. Its endogenous forms serve as essential cofactors and participate in ATP production within the mitochondria, oxidative phosphorylation, and antioxidation in membranes.[1]

Coenzyme Q10 is undergoing investigation as a treatment for diverse disorders such as Parkinson's disease and mitochondrial myopathies and for its effects on lipoprotein (a).[2-4] One of its most common uses, however, is as adjunctive therapy in the treatment of cardiovascular disease, where it has been studied for improvement of left ventricular pump function and reduction of the signs and symptoms of ischemia. A recent MEDLINE search (July 1999) for the term