Prebiotic (nutrition)

Prebiotics are food ingredients that induce the growth or activity of beneficial microorganisms (e.g., bacteria and fungi).[1] The most common example is in the gastrointestinal tract, where prebiotics can alter the composition of organisms in the gut microbiome.

Dietary prebiotics are typically non-digestible fiber compounds that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them.[1] They were first identified and named by Marcel Roberfroid in 1995.[1][2] As a functional food component, prebiotics, like probiotics, are conceptually intermediate between foods and drugs. Depending on the jurisdiction, they typically receive an intermediate level of regulatory scrutiny, in particular of the health claims made concerning them.

Definition

The definition of prebiotics and the food ingredients that can fall under this classification, has evolved since its first definition in 1995.[3] In its earliest definition, the term prebiotics was used to refer to non digestible food ingredients that were beneficial to the host through their selective stimulation of specific bacteria within the colon.[3][4] As a result of research suggesting that prebiotics could impact microorganisms outside of the colon, the International Scientific Association for Probiotics and Prebiotics (ISAPP) produced the current, 2016 definition of prebiotics: a substrate that is selectively used by a host microorganism to produce a health benefit.[3]

Compounds that can be classified as prebiotics must also meet the following criteria:[3][4]

- non-digestible and resistant to breakdown by stomach acid and enzymes in the human gastrointestinal tract
- selectively fermented by intestinal microorganisms
- selectively target and stimulate the growth and activity of beneficial bacteria

Thus, consumption of prebiotics must result in an improvement of the health of the host.[5] Based on the previous classifications, plant-derived carbohydrate compounds called oligosaccharides are the main source of prebiotics that have been identified.[4][6][7]Specifically, fructans and galactans are two oligosaccharide sources which have been found to stimulate the activity and growth of beneficial bacterial colonies in the gut.[5][7][3] Fructans are a category of carbohydrate consisting of fructooligosaccharides (FOS) and inulins, while galactans consist of galactooligosaccharides (GOS).[3] Other dietary fibers also fit the definition of prebiotics, such as resistant starch,[8] pectin,[9] beta-glucans,[10] and xylooligosaccharides.[11]

The European Food Safety Authority (EFSA), the regulatory agency for product labeling, differentiates between "prebiotic" and "dietary fiber", stating that "a cause and effect relationship has not been established between the consumption of the food constituents which are the subject of the health claims and a beneficial physiological effect related to increasing numbers of gastrointestinal microbiota".[12] Consequently, under EFSA rules individual ingredients cannot be labeled as prebiotics, but only as dietary fiber and with no implication of health benefits.[12]

Function

Most prebiotic research has focused on the effects that prebiotics confer on *Bifidobacteria* and *Lactobacillus*.[3][4][13] These bacteria have been highlighted as key probiotics and beneficial gut bacteria as they may have several beneficial effects on the host in terms of improving digestion (including but not limited to enhancing mineral absorption)[14] and the effectiveness and intrinsic strength of the immune system.[15] Both *Bifidobacteria* and *Lactobacillus* have been shown to have differing prebiotic specificity and selectively to ferment prebiotic fiber based on the enzymes characteristic of the bacterial population.[16] Thus, *Lactobacilli* prefers inulin and fructooligosaccharides, while *Bifidobacteria* displays specificity for inulin, fructooligosaccharides, xylooligosaccahrides and galactooligosaccharides.[16] A product that stimulates bifidobacteria is described as a bifidogenic factor, a concept that overlaps, but is not identical with, being prebiotic.[17] Studies have also shown that prebiotics, besides stimulating the growth of beneficial gut bacteria, can also inhibit the growth of detrimental and potentially pathogenic microbes in the gut,[6][4] such as clostridia.[4]

Mechanism of action

Fermentation is the main mechanism of action by which prebiotics are used by beneficial bacteria in the colon.[7][5][4] Both *Bifidobacteria* and *Lactobacillus* are bacterial populations which use saccharolytic metabolism to break down substrates.[4] Research shows that the bifidobacterial genome contains many genes that encode for carbohydrate-modifying enzymes as well as genes that encode for carbohydrate uptake proteins.[7] The presence of these genes indicates that *Bifidobacteria* contain specific metabolic pathways specialized for the fermentation and metabolism of plant-derived oligosaccharides, or prebiotics.[7] These pathways in *Bifidobacteria* ultimately produce short chain fatty acids,[7][4][5] which have diverse physiological roles in body functions.[18][3]

Sources

Prebiotic sources must be proven to confer a benefit to the host in order to be classified as a prebiotic.[3] Fermentable carbohydrates derived from fructans and xylans are the most well documented example of prebiotics,[3] and galactooligosaccharides are enzymatically synthesized from lactose. However, there are additional endogenous prebiotics and exogenous food sources that can be classified as prebiotic sources.[7][6][13][3] Additionally, functional foods containing prebiotic food ingredients serve as an additional prebiotic food source.[5] However, the FOS and inulin content in food sources is very low, meaning it is difficult to consume sufficient prebiotics from food alone.

Endogenous

An endogenous source of prebiotics in humans is human breast milk, which contains oligosaccharides structurally similar to GOS, referred to as human milk oligosaccharides (HMOs).[6][16][3] These HMOs were found to increase the *Bifidobacteria* bacterial population in breastfed infants, and to strengthen the infant immune system.[3][6] Furthermore, HMOs play a role in the establishment of a healthy intestinal microbiota composition of newborns.[3][7]

Exogenous

Indigestible carbohydrate compounds classified as prebiotics are a type of fermentable fiber, and thus can be classified as dietary fiber.[4] However, not all dietary fiber can be classified as a prebiotic source.[4] In addition to the food sources highlighted in the following table, raw oats,[13] unrefined barley,[13] yacon,[13] and whole grain breakfast cereals,[4] are also classified as prebiotic sources.

Top 10 Foods Containing Prebiotics	
Food	**Prebiotic Fiber Content by Weight**
Gum Arabic	85%
Raw, Dry Chicory Root	64.6%
Raw, Dry Jerusalem Artichoke	31.5%
Raw, Dry Dandelion Greens	24.3%
Raw, Dry Garlic	17.5%

Raw, Dry Leek	11.7%
Raw, Dry Onion	8.6%
Raw Asparagus	5%
Raw Wheat bran	5%
Whole Wheat flour, Cooked	4.8%
Raw Banana	1%
Source:[19]	

While there is no broad consensus on an ideal daily serving of prebiotics, recommendations typically range from 4 to 8 grams (0.14–0.28 oz) for general digestive health support, to 15 grams (0.53 oz) or more for those with active digestive disorders. Given an average 6 grams (0.21 oz) serving, below are the amounts of prebiotic foods required to achieve a daily serving of prebiotic fiber:

Food	Amount of food to achieve 6 g serving of fructans
Raw Chicory Root	9.3 g (0.33 oz)
Raw Jerusalem Artichoke	19 g (0.67 oz)
Raw Dandelion Greens	24.7 g (0.87 oz)
Raw Garlic	34.3 g (1.21 oz)
Raw Leek	51.3 g (1.81 oz)
Raw Onion	69.8 g (2.46 oz)

Cooked Onion	120 g (4.2 oz)
Raw Asparagus	120 g (4.2 oz)
Raw Wheat Bran	120 g (4.2 oz)
Whole Wheat Flour, Cooked	125 g (4.4 oz)
Raw Banana	600 g (1.3 lb)
Source[19]	

Functional food applications

The use of prebiotics, specifically GOS, as a fundamental ingredient in the creation of functional foods has been seen in the following food sources:[5]

- fermented milks/yogurts
- sports/health drinks
- energy bars
- baby foods
- sugar-free candy/chewing gum
- breakfast cereals
- bread/baked goods
- meat products
- pet foods

Research

Preliminary research has demonstrated potential effects on calcium and other mineral absorption,[20] immune system effectiveness,[21][22] bowel acidity, reduction of colorectal cancer risk,[23] inflammatory bowel disease (Crohn's disease or ulcerative colitis)[24]hypertension[25] and defecation frequency.[26] Prebiotics may be effective in decreasing the number of infectious episodes needing antibiotics and the total number of infections in children aged 0–24 months.[22]

While research demonstrates that prebiotics lead to increased production of short-chain fatty acids (SCFA),[27] more research is required to establish a direct causal connection. Prebiotics may be beneficial to inflammatory bowel disease or Crohn's disease through production of SCFA as nourishment for colonic walls, and mitigation of ulcerative colitis symptoms.[28]

The immediate addition of substantial quantities of prebiotics to the diet may result in an increase in fermentation, leading to increased gas production, bloating or bowel movement.[29] Production of SCFA and fermentation quality are reduced during long-term diets of low fiber intake.[30] Until bacterial flora are gradually established to rehabilitate or restore intestinal bacteria, nutrient absorption may be impaired and colonic transit time temporarily increased with an immediate addition of higher prebiotic intake.[29][31]

Genetic modification

Genetically modified plants have been created in research labs with upregulated inulin production.[32][33]

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Probiotic

Probiotics are microorganisms that are claimed to provide health benefits when consumed.[1][2][3] The term came into more common use after 1980. The introduction of the concept (but not the term) is generally attributed to Nobel laureate Élie Metchnikoff, who postulated that yogurt-consuming Bulgarian peasants lived longer lives because of this custom.[4] He suggested in 1907 that "the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes".[5] A significant expansion of the potential market for probiotics has led to higher requirements for scientific substantiation of putative benefits conferred by the microorganisms.[2]

Although there are numerous claimed benefits of using commercial probiotics, such as reducing gastrointestinal discomfort, improving immune health, relieving constipation, or avoiding the common cold, such claims are not backed by scientific evidence[2][6][7] and are prevented as deceptive advertisements in the United States by the Federal Trade Commission.[8]

Probiotics are considered generally safe, but may cause bacteria-host interactions and unwanted side effects in rare cases.[9][10][11]

Etymology

Some literature gives the word a full Greek etymology,[12][13] but it appears to be a composite of the Latin preposition *pro* ("for") and the Greek adjective βιωτικός (*biōtikos*), "fit for life, lively",[14] the latter deriving from the noun βίος (*bios*, "life").[15] The term contrasts etymologically with the term *antibiotic*.

Definition

The World Health Organization's (WHO) 2001 defines probiotics as live micro-organisms that, "...when administered in adequate amounts, confer a health benefit on the host."[16] Following this definition, a working group convened by the FAO/WHO in May 2002 issued the “Guidelines for the Evaluation of Probiotics in Food”. This first global effort was further developed in 2010; two expert groups of academic scientists and industry representatives made recommendations for the evaluation and validation of probiotic health claims.[17][18] The same principles emerged from those groups as the ones expressed in the Guidelines of FAO/WHO in 2002. This definition, though widely adopted, is not acceptable to the European Food Safety Authority because it embeds a health claim that is not measurable.[2]

A consensus definition of the term *probiotics*, based on available information and scientific evidence, was adopted after a joint Food and Agricultural Organization (FAO) of the United Nations and World Health Organization (WHO) expert consultation. In October 2001, this expert consultation defined probiotics as live micro-organisms that "...when administered in adequate amounts, confer a health benefit on the host.”[3] The FAO/WHO consultation was also a first effort towards the assessment of probiotics efficacy and resulted in May 2002 in a document named *Guidelines for the Evaluation of Probiotics in Food*.[19] This effort was accompanied by local governmental and supra-governmental regulatory bodies requirements to better characterize health claims substantiations.

A group of scientific experts assembled in London, UK, on October 23, 2013, to discuss the scope and appropriate use of the term probiotic. The meeting was motivated by developments in the field since 2001. The panel's conclusions were published in June 2014.[1]

Probiotics must be alive when administered.[20][21][22] One of the concerns throughout the scientific literature resides in the viability and reproducibility on a large scale of the observed results, as well as the viability and stability during use and storage, and finally the ability to survive in stomach acids and then in the intestinal ecosystem.[2] Probiotics must have undergone controlled evaluation to document health benefits in the target host. Only products that contain live organisms shown in reproducible human studies to confer a health benefit can actually claim to be probiotic.[2][23][24] The correct definition of health benefit, backed with solid scientific evidence, is a strong element for the proper identification and assessment of the effect of a probiotic. This aspect represents a major challenge for scientific and industrial investigations because several difficulties arise, such as variability in the site for probiotic use (oral, vaginal, intestinal) and mode of application.[20]

The probiotic candidate must be a taxonomically defined microbe or combination of microbes (genus, species, and strain level). It is commonly admitted that most effects of probiotics are strain-specific and cannot be extended to other probiotics of the same genus or species.[21] This calls for a precise identification of the strain, i.e. genotypic and phenotypic characterization of the tested microorganism.[17]

Probiotics must be safe for their intended use. The 2002 FAO/WHO guidelines recommend that, though bacteria may be generally recognized as safe (GRAS), the safety of the potential probiotic should be assessed by the minimum required tests:[25]

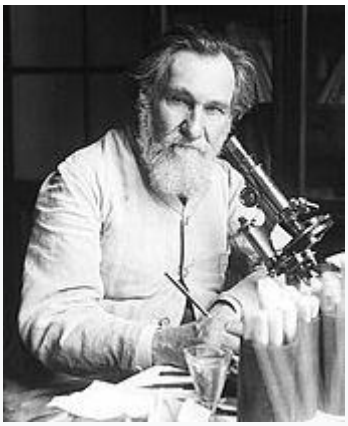
- Determination of antibiotic resistance patterns
- Assessment of certain metabolic activities (e.g., D-lactate production, bile salt deconjugation)
- Assessment of side effects during human studies
- Epidemiological surveillance of adverse incidents in consumers (after market)
- If the strain under evaluation belongs to a species that is a known mammalian toxin producer, it must be tested for toxin production. One possible scheme for testing toxin production has been recommended by the EU Scientific Committee on Animal Nutrition[26]
- If the strain under evaluation belongs to a species with known hemolytic potential, determination of hemolytic activity is required

In Europe, EFSA has adopted a premarket system for safety assessment of microbial species used in food and feed productions, to set priorities for the need of risk assessment. The assessment is made for a selected group of microorganisms, which if favorable, leads to the "Qualified Presumption of Safety" status.[27]

Finally, probiotics must be supplied in adequate numbers, which may be defined as the number able to trigger the targeted effect on the host.[*citation needed*] It depends on strain specificity, process, and matrix, as well as the targeted effect. Most of reported benefits demonstrated with the traditional probiotics have been observed after ingestion of a concentration around 10^7 to 10^8 probiotic cells per gram, with a serving size around 100 to 200 mg per day.[17][*not in citation given*]

History

Probiotics have received renewed attention in the 21st century from product manufacturers, research studies, and consumers. The history of probiotics can be traced to the first use of cheese and fermented products, that were well known to the Greeks and Romans who recommended their consumption.[28] The fermentation of dairy foods represents one of the oldest techniques for food preservation.[29]



Élie Metchnikoff first suggested the possibility of colonizing the gut with beneficial flora in the early 20th century.

The original modern hypothesis of the positive role played by certain bacteria was first introduced by Russian scientist and Nobel laureate Élie Metchnikoff, who in 1907 suggested that it would be possible to modify the gut flora and to replace harmful microbes with useful microbes.[5] Metchnikoff, at that time a professor at the Pasteur Institute in Paris, proposed the hypothesis that the aging process results from the activity of putrefactive (proteolytic) microbes producing toxic substances in the large bowel. Proteolytic bacteria such as clostridia, which are part of the normal gut flora, produce toxic substances including phenols, indols, and ammonia from the digestion of proteins.

According to Metchnikoff, these compounds were responsible for what he called *intestinal autointoxication*, which would cause the physical changes associated with old age.[30]

It was at that time known that milk fermented with lactic-acid bacteria inhibits the growth of proteolytic bacteria because of the low pH produced by the fermentation of lactose. Metchnikoff had also observed that certain rural populations in Europe, for example in Bulgaria and the Russian steppes, who lived largely on milk fermented by lactic-acid bacteria were exceptionally long lived. Based on these observations, Metchnikoff proposed that consumption of fermented milk would "seed" the intestine with harmless lactic-acid bacteria and decrease the intestinal pH, and that this would suppress the growth of proteolytic bacteria. Metchnikoff himself introduced in his diet sour milk fermented with the bacteria he called "Bulgarian Bacillus" and believed his health benefited. Friends in Paris soon followed his example and physicians began prescribing the sour-milk diet for their patients.[31]

Bifidobacteria were first isolated from a breast-fed infant by Henry Tissier, who also worked at the Pasteur Institute. The isolated bacterium named *Bacillus bifidus communis*[32] was later renamed to the genus *Bifidobacterium*. Tissier found that bifidobacteria are dominant in the gut flora of breast-fed babies and he observed clinical benefits from treating diarrhea in infants with bifidobacteria. The claimed effect was bifidobacterial displacement of proteolytic bacteria causing the disease.[*citation needed*]

During an outbreak of shigellosis in 1917, German professor Alfred Nissle isolated a strain of *Escherichia coli* from the feces of a soldier who was not affected by the disease.[33] Methods of treating infectious diseases were needed at that time when antibiotics were not yet available, and Nissle used the *E. coli* Nissle 1917 strain in acute gastrointestinal infectious salmonellosis and shigellosis.[*citation needed*]

In 1920, Rettger and Cheplin reported that Metchnikoff's "Bulgarian Bacillus", later called *Lactobacillus delbrueckii* subsp. *bulgaricus*, could not live in the human intestine.[34] They conducted experiments involving rats and humans volunteers, feeding them with *Lactobacillus acidophilus*. They observed changes in composition of fecal microbiota, which they described as "transformation of the intestinal flora".[34] Rettger further explored the possibilities of *L. acidophilus*, and reasoned that bacteria originating from the gut were more likely to produce the desired effect in this environment. In 1935 certain strains of *L. acidophilus* were found very active when implanted in the human digestive tract.[35] Trials were carried out using this organism, and encouraging results were obtained, especially in the relief of chronic constipation.[*citation needed*]

Contrasting antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other microorganisms. In 1989 Roy Fuller suggested a definition of probiotics that has been widely used: "*A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance*."[20] Fuller's definition emphasizes the requirement of viability for probiotics and introduces the aspect of a beneficial effect on the host.

The term "probiotic" originally referred to microorganisms that have effects on other microorganisms.[36] The conception of probiotics involved the notion that substances secreted by one microorganism stimulated the growth of another microorganism. The term was used again[37] to describe tissue extracts that stimulated microbial growth. The term probiotics was taken up by Parker,[38] who defined the concept as, "Organisms and substances that have a beneficial effect on the host animal by contributing to its intestinal microbial balance." Later, the definition was greatly improved by Fuller,[20] whose explanation was very close to the definition used today. Fuller described probiotics as a "live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance." He stressed two important claims for probiotics: the viable nature of probiotics and the capacity to help with intestinal balance.

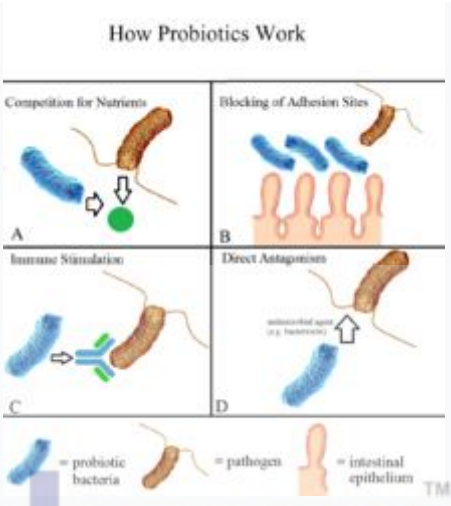
In the following decades, intestinal lactic acid bacterial species with alleged health beneficial properties were introduced as probiotics, including *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Lactobacillus johnsonii*.[39]

Scientific reviews and regulatory actions

The European Food Safety Authority has rejected all petitions by commercial manufacturers for health claims on probiotic products in Europe due to insufficient research, and thus inconclusive proof of effectiveness.[2][40] Occurring over many years, the scientific reviews established that a cause-and-effect relationship had not been sufficiently proven in the products submitted.[40]

In the United States, where food product labeling requires language approval by the FDA, probiotic manufacturers have received warning letters for making disease or treatment claims.[7][41] The Federal Trade Commission has taken punitive actions, including a US$21 million fine coordinated across 39 state governments against a major probiotic manufacturer, for deceptive advertising and exaggerated claims of health benefits for a yogurt and probiotic dairy drink.[8]

Research



Four different mechanisms under research by which probiotics may defend against pathogens in the intestine. Probiotics may compete against pathogens for the same essential nutrients, leaving less available for the pathogen to utilize (A). They may bind to adhesion sites, preventing pathogen attachment by reducing the surface area available for pathogen colonization (B). Signaling of immune cells by probiotics may result in the secretion of cytokines, targeting the pathogen for destruction (C). Finally, probiotics may attack pathogenic organisms by releasing bacteriocins, killing them directly (D).[42]

Probiotics have been the subject of research to see whether the health claims made for them have any supporting evidence.[2][43] Scientific demonstration of probiotic effects on health and disease first requires a definition of healthy microbiota as well as an understanding of the complex interactions between microbiota and host, which are not yet well-understood. Recent developments of high-throughput sequencing technology and the consequent progresses of metagenomics represent a new approach for the future of probiotics research.[44]

Studies are examining whether probiotics affect mechanisms of intestinal inflammation,[45] diarrhea,[46] or urogenital infections.[47] As of 2012, however, in all cases proposed as health claims to the European Food Safety Authority, the scientific evidence remains insufficient to prove a cause-and-effect relationship between consumption of probiotic products and any health benefit.[2][40]

Research into the potential health effects of supplemental probiotics has included the molecular biology and genomics of *Lactobacillus* in immune function, cancer, and antibiotic-associated diarrhea, travellers' diarrhea, pediatric diarrhea, inflammatory bowel disease, and irritable bowel syndrome.[48] Testing of a probiotic applies to a specific strain under study.[49] The scientific community cautions against extrapolating an effect from a tested strain to an untested strain.[50][51]

Although research does suggest that the relationship between gut flora and humans is a mutualistic relationship,[52] very little evidence supports claims that probiotic dietary supplements have any health benefits.[6] Improved health through gut flora modulation appears to be directly related to long-term dietary changes.[53]

Claims that some lactobacilli may contribute to weight gain in some humans[54][55] remain controversial.[56]

According to the National Center for Complementary and Integrative Health, "Although some probiotics have shown promise in research studies, strong scientific evidence to support specific uses of probiotics for most health conditions is lacking." [57]

Allergies

Probiotics are ineffective in preventing allergies in children, with the possible exception of eczema.[58]

Antibiotic-associated diarrhea (AAD)

Antibiotics are a common treatment for children, and 20% of antibiotic-treated children develop diarrhea. Antibiotic-associated diarrhea results from an imbalance in the colonic microbiota caused by antibiotic therapy. Microbiota alteration changes carbohydrate metabolism, with decreased short-chain fatty acid absorption and osmotic diarrhea as a result. The Cochrane review (2015) concluded that the evidence gathered suggested a protective effect of some probiotics in this condition in children.[59] In adults, some probiotics showed a beneficial role in reducing the occurrence of AAD.[60]

Probiotic treatment might reduce the incidence and severity of AAD as indicated in several meta-analyses.[61][62][63] For example, treatment with probiotic formulations including *L. rhamnosus* may reduce the risk of AAD, improve stool consistency during antibiotic therapy, and enhance the immune response after vaccination.[64]

The potential efficacy of probiotic AAD prevention depends on the probiotic strains and dosage.[65][66] The Cochrane review (2015) recommends for children *L. rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day, given the modest number need to treat and the likelihood that adverse events are very rare.[59] The same review states that probiotic use should be avoided in pediatric populations at risk for adverse events, for example severely debilitated or immuno-compromised children.

Bacterial vaginosis

Probiotic treatment of bacterial vaginosis is the application or ingestion of bacterial species found in the healthy vagina to cure the infection of bacteria causing bacterial vaginosis. This treatment is based on the observation that 70% of healthy females have a group of bacteria in the genus *Lactobacillus* that dominate the population of organisms in the vagina. Currently, the success of such treatment has been mixed since the use of probiotics to restore healthy populations of *Lactobacillus* has not been standardized. Often, standard antibiotic treatment is used at the same time that probiotics are being tested. In addition, some groups of women respond to treatment based upon ethnicity, age, number of sexual partners, pregnancy, and the pathogens causing bacterial vaginosis.[67] In 2013 researchers found that administration of hydrogen peroxide producing strains, such as *L. acidophilus* and *L. rhamnosus*, were able to normalize vaginal pH and rebalance vaginal flora, preventing and alleviating bacterial vaginosis.[68]

Blood pressure

The consumption of probiotics may modestly help to control high blood pressure.[69]

Cholesterol

Preliminary human and animal studies have demonstrated the efficacy of some strains of lactic acid bacteria (LAB) for reducing serum cholesterol levels, presumably by breaking down bile in the gut, thus inhibiting its reabsorption (where it enters the blood as cholesterol).[70][71]

A meta-analysis that included five double-blind trials examining the short-term (2–8 weeks) effects of a yogurt with probiotic strains on serum cholesterol levels found a minor change of 8.5 mg/dL (0.22 mmol/L) (4% decrease) in total cholesterol concentration, and a decrease of 7.7 mg/dL (0.2 mmol/L) (5% decrease) in serum LDL concentration.[72]

A slightly longer study evaluating the effect of a yogurt with probiotic strains on 29 subjects over six months found no statistically significant differences in total serum cholesterol or LDL values. However, the study did note a significant increase in serum HDL from, 50 to 62 mg/dL (1.28 to 1.6 mmol/L) following treatment. This corresponds to a possible improvement of LDL/HDL ratio.[73]

Studies specifically on hyperlipidemic subjects are still needed.

Diarrhea

Some probiotics are suggested as a possible treatment for various forms of gastroenteritis,[74] and a Cochrane Collaboration meta-analysis on the use of probiotics to treat acute infectious diarrhea based on a comprehensive review of medical literature through 2010 (35 relevant studies, >4500 participants) reported that use of any of the various tested probiotic formulations appeared to reduce the duration of diarrhea by a mean of 25 hours (vs. control groups, 95% confidence interval, 16–34 hours), also noting, however, that "the differences between the studies may be related to other unmeasured and unexplored environmental and host factors" and that further research was needed to confirm reported benefits.[75][76]

Eczema

Probiotics are commonly given to breast-feeding mothers and their young children to prevent eczema, but some doubt exists over the strength of evidence supporting this practice.[58]

Helicobacter pylori

Some strains of lactic acid bacteria may affect *Helicobacter pylori* infections (which may cause peptic ulcers) in adults when used in combination with standard medical treatments, but no standard in medical practice or regulatory approval exists for such treatment.[77]

Immune function and infections

Some strains of lactic acid bacteria (LAB) may affect pathogens by means of competitive inhibition (i.e., by competing for growth) and some evidence suggests they may improve immune function by increasing the number of IgA-producing plasma cells and increasing or improving phagocytosis, as well as increasing the proportion of T lymphocytes and natural killer cells.[78][79] LAB products might aid in the treatment of acute diarrhea, and possibly affect rotavirus infections in children and travelers' diarrhea in adults,[78][79] but no products are approved for such indications. A large study demonstrated that probiotics may decrease dental caries in children.[80] Two reviews reported reduction of the incidence of respiratory-tract infections in adults.[81][82]

Inflammation

Some strains of LAB may modulate inflammatory and hypersensitivity responses, an observation thought to be at least in part due to the regulation of cytokine function.[78] Clinical studies are assessing whether they can prevent recurrences of inflammatory bowel disease in adults,[78] as well as affect milk allergies.[83] How probiotics may influence the immune system remains unclear.[84]

Inflammatory bowel disease

Probiotics are being studied for their potential to influence inflammatory bowel disease. There is some evidence to support their use in conjunction with standard medications in treating ulcerative colitis and no evidence of their efficacy in treating Crohn's disease.[85][86][87]

A live formulation of lyophilized *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* (VSL#3) has shown effectiveness in the small clinical trials, some of which were not randomized nor double-blinded, that had been done as of 2015; more high-quality clinical trials are needed to determine safety and effectiveness.[85][86]

Irritable bowel syndrome

Probiotics are under study for their potential to affect irritable bowel syndrome, although uncertainty remains around which type of probiotic works best, and around the size of possible effect.[85][88]

Lactose intolerance

Ingestion of certain active strains may help lactose-intolerant individuals tolerate more lactose than they would otherwise have tolerated.[70]

Necrotizing enterocolitis

Several clinical studies provide evidence for the potential of probiotics to lower the risk of necrotizing enterocolitis and mortality in premature infants. One meta-analysis indicated that probiotics reduce these risks by more than 50% compared with controls.[89]

Recurrent abdominal pain

A 2017 review based on moderate to low-quality evidences suggests that probiotics may be helpful in relieving pain in the short term in children with recurrent abdominal pain, but the proper strain and dosage are not known.[90]

Urinary tract

There is no good evidence that probiotics are of benefit in the management of infection or inflammation of the urinary tract.[91]

Vitamin production

Probiotic treatment has been studied as a means of addressing disorders associated with vitamin deficiencies including those of vitamin K,[92] folic acid,[93] and vitamin B12.[94]

Side effects

The manipulation of the gut microbiota is complex and may cause bacteria-host interactions.[11] Though probiotics are considered safe, some have concerns about their safety in certain cases.[11][95] Some people, such as those with immunodeficiency, short bowel syndrome, central venous catheters, cardiac valve disease and premature infants, may be at higher risk for adverse events.[9] In severely ill people with inflammatory bowel disease there is a risk of the passage of viable bacteria from the gastrointestinal tract to the internal organs (bacterial translocation) as a consequence of bacteremia, which can cause adverse health consequences.[11] Rarely, consumption of probiotics by children with lowered immune system function or who are already critically ill may result in bacteremia or fungemia (i.e., bacteria or fungi in the blood), which can lead to sepsis, a potentially fatal disease.[10]

It has been suggested that *Lactobacillus* contributes to obesity in humans, but no evidence of this relationship has been found.[96]

Strains

Live probiotic cultures are available in fermented dairy products and probiotic fortified foods. However, tablets, capsules, powders, and sachets containing the bacteria in freeze-dried form are also available. Probiotics taken orally can be destroyed by the acidic conditions of the stomach. A number of microencapsulation techniques are being developed to address this problem.[97]

There is only preliminary evidence for most probiotic health claims. Even for the most studied strains, few have been sufficiently developed in basic and clinical research to warrant approval for health claim status by a regulatory agency such as the Food and Drug Administration or European Food Safety Authority, and, as of 2010, no claims had been approved by those two agencies.[2] Some experts are skeptical about the efficacy of different strains, and believe that not all subjects benefit from probiotics.[2][98]

Some fermented products contain lactic acid bacteria, including pickled vegetables,[99] tempeh,[100] miso,[101] kefir,[102] buttermilk or karnemelk,[103] kimchi,[99][104] pao cai,[105] sauerkraut,[106] and soy sauce.[107]

Commercial probiotics

Labeling

The US National Yogurt Association gives a *Live & Active Cultures Seal* to refrigerated yogurt products that contain 100 million cultures per gram or frozen yogurt products containing 10 million cultures per gram at the time of manufacture.[108] In 2002, the US Food and Drug Administration (FDA) and World Health Organization recommended that “the minimum viable numbers of each probiotic strain at the end of the shelf-life” be reported on labeling,[109] but most companies that give a number report the viable cell count at the date of manufacture, a number probably much higher than existing at the moment of consumption.[110] Because of variability in storage conditions and time before eating, it is difficult to tell exactly how much active culture remains at the time of consumption.

Due to these ambiguities, the European Commission placed a ban on putting the word "probiotic" on the packaging of products because such labeling misleads consumers to believe a health benefit is provided by the product when no scientific proof exists to demonstrate that health effect.[2][111][112][113]

In the United States, the FDA and Federal Trade Commission have issued warning letters and imposed punishment on various manufacturers of probiotic products whose labels claim to treat a disease or condition.[7][8][41]

History and modern products

Lactic acid bacteria were first cultured in 1930, and a dairy-based product, Yakult, a fermented milk with added *Lactobacillus casei* strain Shirota, was marketed in 1935.[114] Since then many more foods with probiotic properties have come on the market, mostly dairy products. Non-dairy and unfermented probiotics have been produced, including breakfast cereals and snack bars, in addition to traditional fermented products such as kefir, yogurt, kombucha, kimchi, and unpasteurised sauerkraut.[115][116]

Global consumption

Sales of probiotic products have a rising trend from 2010 to 2014, increasing globally by 35% from US$23.1 billion to $31.3 billion.[117] Some regions have increased their use by even more than the average, including Eastern Europe (67%), Asia Pacific (67%), and Latin America (47%), comprising nearly half of probiotics sold globally in 2014.[117] By geographic region, the leading consumers of probiotics in 2014 were Western Europe ($8.3 billion), Asia Pacific ($7 billion), Japan ($5.4 billion), Latin America ($4.8 billion), North America ($3.5 billion), and Eastern Europe ($2.3 billion).[117]

Multiple probiotics

Preliminary research is evaluating the potential physiological effects of multiple probiotic strains, as opposed to a single strain.[118][119] As the human gut may contain several hundred microbial species, one theory indicates that this diverse environment may benefit from consuming multiple probiotic strains, an effect that remains scientifically unconfirmed.

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