Probiotics, prebiotics and gastrointestinal health

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Probiotics can lessen the severity of several conditions and may also enhance immunity and the general health of people requiring gastrointestinal and immune support. Prebiotics support the growth of probiotics.

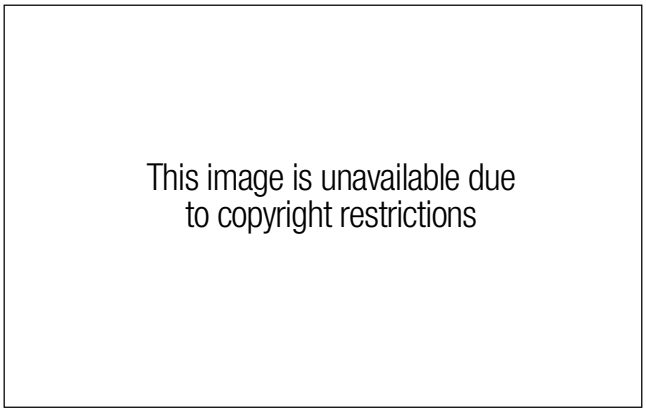

Figure 1. *Lactobacillus acidophilus* (coloured TEM), strains of which are used as probiotics.

Fermented dairy products such as yoghurts and other soured milk products have been consumed for hundreds of years in the belief that they provide health benefits beyond basic nutrition. This therapeutic use evolved well before the existence of micro-organisms was recognised and the bacteria that later became the basis of probiotic supplements were isolated.

Research has shown that probiotic and prebiotic dietary supplements can influence the microflora of the digestive tract and may have very important roles to play in human health.[1] Although scientific understanding of probiotics and their potential for preventing and treating health conditions is in its infancy, evidence-based research on efficacy and tolerability is rapidly accumulating. The terms probiotic, prebiotic and symbiotic are defined in the box on this page.

Functionality of the GI tract

The microflora of the human gastrointestinal tract is complex and comprises about 400 to 500 different species of bacteria, of which about 30 to 50 species predominate.[2] The human gastrointestinal tract is sterile at birth but soon becomes colonised by bacteria, mainly through feeding. These bacteria soon become an essential and functional part of the human organism.

The intestinal microflora makes a significant contribution not only to the healthy functioning of the gastrointestinal tract but also to various other metabolic activities, including immune function, cholesterol metabolism and hormone metabolism.[2] Various factors, such as poor diet, alcohol intake, excessive stress and the use of certain medications (for example, antibiotics), may contribute to changes in the make-up of this ecosystem. Such shifts in the balance of the intestinal flora have long been considered to have significant health effects.[3-6]

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What are probiotics, prebiotics and synbiotics?

Probiotics
A probiotic is a preparation or product containing a defined single or mixed culture of live micro-organisms that is believed to exert beneficial effects on health by altering the intestinal microflora and which, when ingested, improves the health of the host beyond that of basic nutrition.

Prebiotics
A prebiotic is a nondigestible food ingredient that is of benefit to the host by selectively promoting the growth and activity of a limited number of bacteria in the gastrointestinal tract. While a probiotic provides bacteria to the gut, a prebiotic provides a food source for the growth of bacteria already in the gut.

Synbiotics
A synbiotic is a product that contains both a probiotic component and a prebiotic component. The combination enhances the survival of the probiotic during transit through the proximal gastrointestinal tract and improves its colonisation of the large intestine, and also has a stimulating effect on the growth of the endogenous intestinal microflora.

History of probiotics

For hundreds of years before the discovery that micro-organisms were responsible for the fermenting of food, soured milk and other fermented dairy products had been consumed in the belief that they exerted health benefits.

Metchnikoff was the first to suggest, in 1907, that consuming certain bacteria could have a beneficial effect on health, proposing that lactobacilli consumed in yogurt reduced the numbers of toxin-producing bacteria in the gut.[6] Since then certain micro-organisms, mainly belonging to the lactic acid bacteria family, have been used for the prevention or treatment of several pathological conditions – either as probiotic supplements or probiotic foods.

The term 'probiotic', meaning 'for life', was first used in 1960s to mean a substance secreted by one micro-organism that stimulates the growth of another (as opposed to an 'antibiotic', a substance secreted by a micro-organism that inhibits the growth of another). The definition has since been broadened to its present day meaning – 'a defined single or mixed culture of live micro-organisms that are believed to exert beneficial effects on health by altering the intestinal microflora and which upon ingestion improve the health of the host beyond that of basic nutrition'.

Probiotics

Probiotics are preparations or products containing a defined single or mixed culture of live micro-organisms that are believed to exert beneficial effects on health by altering the intestinal microflora (especially that of the large intestine) and which, upon ingestion, improve the health of the host beyond that of basic nutrition.[7] It is further proposed that probiotics are bacteria and other organisms that when ingested may treat or prevent disease. Probiotics have also been called friendly bacteria, or good bacteria.[7] A brief history of probiotics is given in the box above.[6]

Probiotic cultures appear to modulate the innate immune system, improve lactose intolerance, resolve some bacterial and viral diarrhoeal diseases and reduce symptoms associated with inflammatory bowel disease. These effects may be due to various mechanisms of action, including suppressing growth of pathogenic bacteria, blocking gut epithelial cell attachment by pathogens, enhancing mucosal function, and modulating host immune responses.[3,8,9]

Supplementation with probiotics can contribute to disease prevention by maintaining a balanced gastrointestinal bacterial ecosystem.

Probiotic supplementation

Probiotic supplements are widely used in clinical practice in a bid to promote a healthy balance in the intestinal flora, and numerous products are available in Australia. Supplements are generally recommended for people who have a poor diet, are taking certain medications or exhibit digestive symptoms.

Probiotic supplements may also be recommended as therapy for specific conditions. Gastrointestinal conditions such as irritable bowel syndrome, inflammatory bowel disease and gastritis are suspected to be associated with a disruption of the intestinal microflora. Immune hypersensitivity-based conditions such as eczema (atopic dermatitis), allergic conjunctivitis, allergic rhinitis and asthma have also been linked with intestinal microflora imbalances.

Low dose (nonviable) probiotic preparations can have similar effects to probiotic preparations with bacterial loads. A standard yoghurt containing low doses of probiotic strains can still demonstrate efficacy.

Probiotic supplements generally contain a more concentrated load of viable bacteria than do probiotic foods, and are therefore more effective in producing a therapeutic effect.

Probiotic bacteria

Various species of bacteria that are known to colonise the human intestines are used in probiotic supplements. Lactobacilli and bifidobacteria are most commonly used, such as specific strains of *Lactobacillus acidophilus, L. casei, L. plantarum, L. rhamnosus, L. fermentum, Bifidobacterium bifidum, B. lactis* and *B. infantis*. Other bacteria used include strains of *Streptococcus thermophilus*. The fermented milks that have been consumed for thousands of years in the belief that they have health benefits contain *S. thermophilus* and *L. bulgaricus*.

S. thermophilus is used to enhance digestion of lactose in people who are lactose-intolerant.[9] It does this by producing the enzyme lactase, which breaks down the lactose.

Probiotic bacteria exhibit strain-specific differences in their resistance to stomach acid and bile, ability to colonise the gastrointestinal tract, and clinical efficacy.[10]

Probiotic yeast

Saccharomyces boulardii, a nonpathogenic yeast, has been used as a dietary supplement in both animal studies and human clinical trials. This yeast is thought to promote the growth of beneficial bacteria without itself colonising the gastrointestinal tract. Moreover, *S. boulardii* has been shown to have many different mechanisms of activity in different settings.[11]

Clinical use of probiotics

Probiotic supplementation has immense potential for protecting against intestinal colonisation by pathogenic bacteria, reducing gastrointestinal inflammation and preventing infections.

Probiotic bacteria such as *L. rhamnosus* GG and certain strains of *L. acidophilus, L. casei, L. fermentum, L. plantarum, L. reuteri, B. lactis* and *Enterococcus faecium* and the probiotic yeast *S. boulardii* have been investigated with regard to their medicinal use, either as single strains or in mixed-culture probiotics. Clinical uses and the levels of evidence supporting these uses are listed in Table 1.

Diarrhoea

L. reuteri, B. bifidum and *S. thermophilus* have been reported to reduce the occurrence of diarrhoea and rotavirus among infants and young children.[12,13] *Lactobacillus* GG has been reported to reduce the incidence of diarrhoea in hospitalised children by 80%.[14] *Lactobacillus* GG has also been used to reduce the incidence of traveller's diarrhoea in adults.[15,16]

Supplementation with *Lactobacillus* GG, *L. acidophilus* or *B. lactis* has demonstrated benefit in reducing the incidence of antibiotic-associated diarrhoea.[17-19]

Allergic diseases

Allergic conditions are caused by abnormal or exaggerated immune reactions and a range of symptoms can be expressed. Probiotics are reported to exert some benefit in asthma and eczema, the most common chronic allergic conditions, and this is thought to be due to the immune modulating effects of the bacteria.

Lactobacillus GG may reduce clinical symptoms, intestinal inflammation and mucosal barrier permeability in infants with allergic dermatitis.[20,21] A recent controlled study reported that long-term consumption of fermented milk containing *L. casei* improved the health status of children with allergic rhinitis but had no effect on the health status of children with asthma.[22]

It has also been demonstrated that probiotics such as *L. rhamnosus* GG contribute to relief of symptoms in and prevention of atopic conditions such as eczema in infants and children.[21,23,24]

Table 1. Clinical uses of probiotic bacteria and levels of evidence

Clinical use – conditions/symptoms	Probiotic strain	Level of evidence supporting use*
Antibiotic–associated diarrhoea	*Lactobacillus rhamnosus* GG, *L. reuteri* MM53	I II
Atopic eczema		
Prevention	*L. rhamnosus* GG	II
Treatment	*L. fermentum* PCC	II
Bacterial gastroenteritis		
Vancomycin-resistant enterococci	*L. rhamnosus* GG	II
Clostridium difficile	*L. rhamnosus* GG	III
Colitis	*L. reuteri* MM53	II
Constipation	*L. casei* Shirota, *Bifidobacterium lactis* Bb12	II II
Decreased immunity – for reducing rates of infection in the immunocompromised	*L. rhamnosus* GG, *L. reuteri* MM53, *L. acidophilus* HN019	II II II
Helicobacter pylori infection	*L. reuteri* MM53, *L. acidophilus* La5 plus *L. acidophilus* Bb12	II III
Inflammatory bowel syndrome	*L. fermentum* PCC, *L. plantarum* 299V, VSL#3†	II II II
Prevention of bladder cancer recurrence (combined with epirubicin)	*L. casei* (Yakult Honsha)	III
Prevention of dental caries	*L. rhamnosus* GG	II
Radiation-induced diarrhoea	VSL#3†	II
Rhinitis	*L. casei*	II
Ulcerative colitis		
Inducing remission	VSL#3†	III
Maintenance/remission	*L. rhamnosus* GG35/VSL#3†	II/III
Prevention	VSL#3†	II
Pouchitis	*L. rhamnosus* GG36	III
Vaginal candidiasis	*L. acidophilus* La5	III
Viral gastroenteritis		
Prevention	*L. rhamnosus* GG, *L. acidophilus* Bb12	II II
Treatment	*L. rhamnosus* GG, *L. reuteri* MM53	I II

* Level I evidence: from a systematic review of all relevant randomised controlled trials (meta analyses). Level II evidence: from at least one properly designed randomised controlled clinical trial. Level III evidence: from one or more well-designed pseudorandomised controlled trials (alternate allocation or some other method).
† VSL#3 is a multistrain probiotic product composed of *B. longum, B. infantis, B. breve, L. acidophilus, L. casei, L. plantarum, L. delbruekii* ssp. *bulgaricus* and *S. thermophilus*.

Inflammatory bowel disease

Inflammatory bowel disease is a complex autoimmune condition in which significant inflammation and ulceration of the bowel causes a myriad of symptoms including diarrhoea, pain and malabsorption, leading to a poor nutritional status.[25] Clinical studies indicate probiotic therapy to be of benefit for some patients with inflammatory bowel disease. Probiotics may contribute to reduced frequency of bowel movements, longer remission periods and a reduced risk of relapse.[26-28] Overall, there is some data for the efficacy of probiotics in ulcerative colitis, but that for Crohn's disease is less.[29]

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is associated with symptoms of abdominal pain and discomfort and recurrent bouts of diarrhoea and/or constipation and abnormal fermentation of food in the gastrointestinal tract. Several clinical trials utilising probiotics have been conducted in people with IBS.[30] Probiotic supplementation results in significant improvement in those patients who most probably have abnormal digestive tract flora. However, probiotics do not assist patients in whom other key factors, such as stress, are responsible for this syndrome.

Helicobacter pylori infections

H. pylori infection is associated with chronic gastritis and peptic ulcers. Probiotic treatment has been reported to reduce the side effects of standard multiple agent antibiotic *H. pylori*-eradication therapy, but no study has demonstrated the eradication of *H. pylori* infection by probiotic treatment.[31,32]

Candida infections

Overgrowth with *Candida albicans* causes symptoms such as thrush and is one of the most common side effects of prolonged antibiotic use. Limited studies demonstrate some benefit with probiotic supplementation in assisting control of the growth of *Candida,* but further research is needed.[33]

Cancer

Recent clinical studies demonstrate that probiotics may have a significant adjuvant role in cancer therapies. A prospective, randomised, controlled trial of the intravesical instillation of epirubicin plus the oral administration of *L. casei* (Yakult Honsha preparation) probiotic after transurethral resection for superficial bladder cancer showed this combination to be a promising treatment for preventing recurrence of this cancer.[34]

In a double-blind, placebo-controlled trial, the high potency probiotic preparation VSL#3 (comprised of *B. longum, B. infantis, B. breve, L. acidophilus, L casei, L. plantarum, L. delbruekii* ssp. *bulgaricus* and *S. thermophilus*) significantly reduced radiation-induced diarrhoea in cancer patients.[35]

Dosage

The minimum dose required to elicit a therapeutic benefit depends on the strain of the probiotic being used. Shornikova and colleagues have reported that 10^7 colony forming units (cfu) of *L. reuteri* MM53 is sufficient to produce a beneficial effect.[12] However, with other bacterial strains, such as *L. rhamnosus* GG (lyophilised), a dose in the order of 10^9 viable bacteria is required.[36]

Research studies have produced conflicting evidence, with some showing a therapeutic benefit with doses of 10^7 to 10^8 cfu per dose,[37] whereas others report success using doses of at least 10^9 cfu.[38]

At present, the best practice is to ensure that supplements contain probiotic strains at concentrations of 10^9 cfu per dose or higher, unless research demonstrates conclusively that efficacy is achieved at lower doses. In preparations with multiple strains, similar strain concentrations should apply for treatment of specific conditions as were used in the published evidence-based data. Probiotic agents are likely to be condition-specific and effective doses may vary.

It is important that probiotic supplements maintain their viability during transit through the acid environment of the stomach. There is some controversy regarding the best time of day for probiotic consumption. Some researchers believe that the best time is with food, while others consider probiotics are best consumed first thing in the morning or last thing at night.

Bacterial strains used as probiotics are known to be sensitive to heat and therefore refrigeration of the preparations is recommended in order to maintain viability. The advent of lyophilised (freeze-dried) probiotic preparations, however, has abrogated the need for refrigeration, and some probiotic preparations are now marketed in lyophilised forms, thereby maintaining viability.[39]

Safety

Food fermentation products have a long history of use, and fermented foods and beverages constitute up to 40% of the current human food supply worldwide.[40] Lactic acid bacteria have a long history of safe use and, in a review of over 140 clinical trials, were associated with no adverse clinical events.[41]

Contraindications, precautions and adverse reactions

Probiotics are generally contraindicated in immunocompromised patients. A recent clinical trial of probiotic prophylaxis (using *L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum* and *B. lactis*) in patients with predicted severe acute pancreatitis concluded that the use of probiotics did not reduce the risk of infectious complications and was associated with an increased risk of mortality.[42] This is most likely explained by a severely compromised cardiovascular system resulting in increased intestinal permeability. On current evidence, therefore, probiotic prophylaxis should not be administered in

Table 2. Clinical uses of prebiotics and levels of evidence

Clinical use – conditions/symptoms	Prebiotic and daily dose	Level of evidence supporting use*
Constipation	Lactulose, 10–40 g† Galacto-oligosaccharides, 9–10 g Fructo-oligosaccharides, 10 g	II II III
Prevention of atopic eczema in infants on formula feeding regimens	Galacto-oligosaccharides and fructo-oligosaccharides, 0.8 g/100 mL of infant formula	II
Decreased immunity – for reducing rates of infection in the immunocompromised	Fructo-oligosaccharides, 2 g for infants/toddlers	II
Enhanced calcium absorption	Fructo-oligosaccharides, 8 g	II
Prevention of urinary tract Infections	Lactulose, about 25 g	III

* Level I evidence: from a systematic review of all relevant randomised controlled trials (meta analyses). Level II evidence: from at least one properly designed randomised controlled clinical trial. Level III evidence: from one or more well-designed pseudorandomised controlled trials (alternate allocation or some other method).
† While this dose of lactulose is likely to have an osmotic softening effect in constipation, this effect may lead to a prebiotic effect with continued use.

patients with severe acute pancreatitis, especially parenterally via nasojejunal tube.

The oral use as probiotics of yeast such as *S. boulardii* has been associated with several cases of *S. cerevisiae* fungaemia.[43] These cases occurred in immunocompromised or critically ill patients. Hence immune competence should be assessed in at-risk patients before dietary supplementation with *S. boulardii*.

General adverse events associated with the use of probiotics include abdominal bloating, excess flatulence, borborygmi and abdominal discomfort.

Prebiotics

Prebiotics are nondigestible food ingredients that are of benefit to the host by selectively promoting the growth and activity of a limited number of bacteria in the gastrointestinal tract. While probiotics provide bacteria to the gut, prebiotics provide a food source for the growth of bacteria already in the gut.

The predominant use of prebiotics is to potentiate the beneficial actions of bacteria in the gut. Prebiotics are generally found in supplements as fructo-oligosaccharides, galacto-oligosaccharides, lactulose and lactitol.[44,45] The various clinical uses of these products and the supporting levels of evidence are listed in Table 2. Fructo-oligosaccharides and galacto-oligosaccharides are derived from plant fibres. Lactitol is a non-absorbable disaccharide (galactose-sorbitol) that has been shown to influence intestinal microflora and hence may be classified as an emerging prebiotic.[46,47]

The use of prebiotic supplements is associated with the same range of adverse events as associated with the use of probiotic supplements, including abdominal bloating, excess flatulence, borborygmi and abdominal discomfort. These effects are dose-dependant, occurring significantly less when smaller doses are prescribed.[48] Patients should be commenced on low doses and the doses increased gradually over a period of three to four weeks.

Synbiotics

Synbiotics contain both probiotic and prebiotic components.[49] The rationale for such products is that the combination enhances the survival of probiotic bacteria in transit through the proximal gastrointestinal tract, improves colonisation of the probiotic in the large intestine and has a stimulating effect on the growth of the endogenous flora.[50]

A recent randomised controlled trial on the safety, tolerance and protective effect against diarrhoea of infant formulas containing synbiotics demonstrated that healthy full-term infants fed formulas containing probiotics or synbiotics showed a similar rate of weight gain as those fed a control infant formula, and tolerated these formulas well.[51] The probiotics used in the trial were *B. longum* BL999 plus *L. rhamnosus* or *L. paracasei*, and the synbiotics were these probiotics plus 90% galacto-oligosaccharide/10% short-chain fructo-oligosaccharide as the prebiotic.

Conclusion

Probiotics have been shown effective in lessening the severity of several conditions. Probiotic supplementation may also enhance immunity and the general health and wellbeing of people requiring gastrointestinal and immune support, such as those with a poor diet and the elderly. Combining probiotics and prebiotics into 'synbiotics' appears to further enhance the immunosupportive effects. There is little evidence that a single-strain-based superprobiotic will be found but combining several specific and defined probiotics and several key plant fibres into multistrain/multifibre synbiotics seems a promising alternative.[50] MT

A list of references is available on request to the editorial office.

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