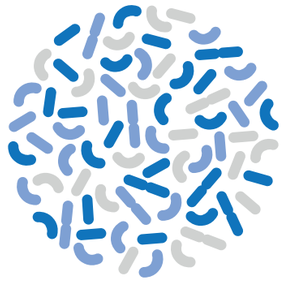
Big benefits from microscopic friends



Probiotics are advocated in the management of dermatitis, IBS and diabetes. This article looks at the evidence

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IN 1907, METCHNIKOFF observed that the consumption of large quantities of fermented milk products containing contributed to the long and healthy lives of Bulgarian peasants[1,2]. The term 'probiotic' was originally proposed as an alternative to the term 'antibiotic', to describe substances secreted from microorganisms that promoted the growth of another rather than retarded it[3]. Probiotics have been defined as "live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the health of the host"[4].

All probiotic products should meet the following guidelines, which were established jointly by the Food and Agriculture Organisation of the United Nations and the World Health Organisation[5]:

- Properly identify, to the level of strain, all probiotics in the product and deposit all strains in an international culture collection.
- Characterise each strain for traits important to its safety and function.
- Validate health benefits in human studies, including identifying the quantity of the microorganism required to provide the benefit.
- Provide truthful and not misleading labelling of efficacy claims and content through to the end of shelf life.

The most widely used and extensively studied probiotic organisms belong to the lactic acid bacteria (LAB) and bifidobacteria, particularly *Lactobacillus spp* and *Bifidobacterium spp*.

Probiotic mechanism of action

In a review[6], the impact of probiotics in gastrointestinal disorders show a diversity of outcomes but there is a growing body of evidence to support the use of probiotics to support intestinal dysbiosis. Probiotics have been shown to have intestinal barrier, immune system stimulation, antibacterial, and motility and sensation effects that may contribute to their effectiveness in various diseases.

Probiotics increase intestinal wall integrity and barrier function by preventing epithelial cell death (apoptosis)[7] and increasing mucin production by the host[8] (epithelial integrity is important in preventing the transmission of pathogens from the gastrointestinal tract to elsewhere in the body). Probiotic bacteria are able to compete for binding sites on epithelial cells, preventing invading pathogens from adhering to the gut wall[9].

Many probiotic bacteria are also able to suppress the growth of pathogens by:

- Producing antimicrobial factors[10]
- Stimulating the host cells to produce their own antimicrobial factors[11,12]
- Lowering the intestinal pH via release of short-chain fatty acids (SFCA) from epithelial cells[11]
- Interfering with the cell-to-cell signalling molecules that allow bacteria to communicate[13].

Any antibiotic treatment may disturb the gastrointestinal microbiota, resulting in a range of symptoms, including antibiotic associated diarrhoea (AAD). Symptoms of AAD include frequent watery bowel movements, urgency and abdominal pain. AAD is associated with altered intestinal microbiota, reduced intestinal-wall integrity and diminished vitamin/mineral metabolism[14]. Administration of aminopenicillins, cephalosporin and clindamycin is most commonly associated with diarrhoea[14,15].

Incidence of AAD is between 5 and 62 per cent, and it may occur at any point from the start of antibiotic therapy to up to two months after the end of treatment[14]. As the 'normal' gastrointestinal microbiota is compromised, the path is opened for the overgrowth of a variety of opportunistic bacterial pathogens. *Clostridium difficile* is commonly associated with AAD, and is also implicated in the most serious adverse events. Probiotics play an important role in the prevention of AAD and *C.difficile* diarrhoea[17].

Probiotics, alone or in combination, have been shown to be effective for the prevention of AAD in the general population[17,18]. In the case of *C.difficile* diarrhoea, a placebo-controlled study monitoring 150 hospital inpatients showed that co-administration of a probiotic containing *L.acidophilus*, *B.lactis* and *B.bifidum* reduced the incidence of *C. difficile* diarrhoea[19].

IBS and probiotics

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain or discomfort and abnormal bowel habit. During recent years the evidence for the involvement of the gut microbiota in the pathogenesis and pathophysiology of IBS has increased and IBS patients have an altered microbiota compared to healthy individuals[20].

A meta-analysis of clinical trials of probiotics in the treatment of IBS with 18 randomised, controlled clinical trials using a variety of probiotic organisms and examining over 1,600 patients, showed a reduction in IBS symptoms in 918 individuals[21]. And 15 trials found probiotics had a statistically significant improvement effect on IBS symptoms compared to placebo[21].

Probiotics, especially bifidobacteria, have been shown to influence host immune system function and are linked to suppression of mucosal inflammation in animal models of IBD[22], but the anti-inflammatory effects of probiotics often observed in *in vitro* and animal studies may not always translate to clinical beneficial effects[6]. Probiotics can improve gut function[23], reduce inflammation[24], and prevent disease progression to ulcerative colitis[25,26]. In humans, the indications are that probiotics are not a therapeutic option for maintenance of Crohn's disease remission[27]. Overall, meta-analyses conclude that the use of probiotics in IBD cannot be routinely recommended at present[28].

Allergic conditions

An increasing number of children (approximately 10-15 per cent of the population) develop allergy in a clinical progression of the so-called 'atopic march' (eczema→rhinitis→asthma). Allergic disorders have been associated with aberrant gut microbiota, and factors associated with allergy such as mode of delivery, antibiotic use in the new-born and infant, and breast-feeding are also associated with shifts in the gut microbiota.

The hygiene hypothesis, formulated as an explanation for the observed rise in the prevalence of allergic diseases, suggests that increased cleanliness, reduced family size and decreased incidence of childhood infections have lowered our exposure to microbes, which play a vital role in the maturation of our immune systems during the first years of our life[29]. With this in mind, there has been a substantial effort to assess the potential role of probiotics in the prevention and/or treatment of allergic diseases, particularly by the feeding of probiotics to neonates.

Exposure to probiotic bacteria can stimulate the immune system and 'train it to produce an appropriate response to allergens. When *Lactobacillus* GG was administered to high risk infants (those with at least one relative with atopic eczema or asthma), a 50 per cent reduction in the incidence of atopic eczema was observed[30] while the skin condition of children with atopic eczema improved when they were given whey formula supplemented with *Lactobacillus rhamnosus* or *Bifidobacterium animalis* subspecies *lactis* for two months[31].

A systematic review of the effect of nutrient supplementation on atopic dermatitis in children found that the best effects were observed when mothers and infants were supplemented with probiotics[32]. High-risk mothers and babies receiving lactobacilli and bifidobacteria for six months from birth had significantly less atopic eczema and cow's milk/hen's egg sensitisation than those receiving a matched placebo[33].

Obesity and diabetes

Modulation of the gut microbiota has been considered as a potential target in cases of obesity and diabetes. Requena *et al*. extensively reviewed the interaction between the obese human host, food and the gut microbiota[34]. Lactobacilli and bifidobacteria show beneficial effects on molecular markers of obesity[35] and type 2 diabetes[36], and ameliorate the progression of obesity and diabetes in mice and rats, suggesting that modulation of the gut microbiota is a potential therapy for obesity and diabetes[37,38]. In humans, a 12-week, randomised, placebo-controlled intervention trial with participants with a BMI greater than 24 receiving either *Lactobacillus gasseri* in fermented milk, or a control milk, resulted in significant reductions in body weight and abdominal fat tissue in the probiotic group[39] but, in contrast, the administration of *Lactobacillus salivarius* to 25 obese adolescents over a 12-week period did not reduce weight or indicators of metabolic syndrome[40].

A prebiotic is "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health"[41]. Ingredients considered to be prebiotics should not be metabolised by the human host cells, and only be metabolised by members of the gut microbiota considered to be important to gut health, such as the lactobacilli and bifidobacteria. Roberfroid suggested that only two food ingredients, inulin and galacto-oligosaccharides (GOS), fulfil these criteria[41].

Inulin is resistant to low pH, mammalian hydrolysis and absorption, and has been shown, *in vitro* and *in vivo*, to have a growth promoting effect on both bifidobacteria and lactobacilli[42-44]. People with type 2 diabetes (T2D) or obese individuals have a smaller population of bifidobacteria and other bacteria belonging to the firmicutes than lean people[45] or individuals without T2D[46], suggesting the involvement of bifidobacteria in obesity and T2D and their associated gastrointestinal and systemic diseases.

When prebiotic inulin was fed to both obese and diabetic mice the proportion of bifidobacteria increased significantly compared to mice on a standard diet that did not contain prebiotic[47,48]. Inulin has also been linked with a reduction in the expression of several host genes that are related to adiposity and inflammation[49].

GOS is produced from lactose, a sugar found in cow's milk[50]. *In vitro* studies have shown that GOS is able to support the growth of most lactobacilli and bifidobacteria[41]. Human volunteer studies showed that supplementation with GOS resulted in significant increases in faecal bifidobacteria[51] and lactobacilli[52], and significant decreases in potentially harmful bacteroides and candida[52].

Conclusions and perspective

Although long recognized for its importance, the human microbiota has been largely ignored by science because of its complexity and the technical limitations of classic microbiological techniques. Microbial ecologists, clinicians, immunologists, physiologists, nutritionists, and computer scientists are now beginning to work together to build a new science of personalised medicine, and maybe even future biotherapeutics.

Current evidence supports the role of probiotics, prebiotics and synbiotics (probiotic and prebiotic combos) in a broad range of gastrointestinal conditions, particularly antibiotic associated diarrhoea, including that driven by *C. difficile*. Probiotics also appear to effectively ameliorate IBS symptoms, may be effective in the prevention of atopic eczema, whilst reducing sensitisation and symptom load. Unfortunately, IBD continues to be a recalcitrant disease where probiotics, prebiotics and synbiotics have only shown limited efficacy in ameliorating symptoms. However, the benefits shown to date still direct physicians to use probiotics as a part of their treatment profile, as other drug treatments are also of limited effect.

Evidence is also quickly building that probiotics have a consistent and profound effect in promoting general immune function as expressed by reduction in upper respiratory tract infections (coughs and colds). A recent meta-analysis shows an average reduction in days with symptoms of 30 per cent and a recent UK trial has shown 50 per cent reduction in days with symptoms and 30 per cent reduction in incidence of coughs and colds over a six-month period, culminating in a reduction of 30 per cent in total absenteeism from school.

The potential for probiotics to offer benefits in disease prevention/risk reduction in areas such as obesity, metabolic disease and, more recently, even in brain and neural functioning, indicates that the gut has a physiological role that is more profound than simply digesting and assimilating food. And moreover, the microbiome is becoming more widely recognised as an integral and highly active component of the human gastrointestinal tract.

The references for this article can be found on the following page.

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