

Probiotics: which, when and why?

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The normal gut microflora, aside from aiding digestion, provides protection against pathogenic organisms. Probiotics have been manufactured with the idea of maximising the effect of gut microflora, also known as “good bacteria”, thus reducing the risk of infection. This theory has proved scientists right on several occasions however stronger evidence is necessary to establish the efficacy, safety and cost-effectiveness of these products.

Introduction

The World Health Organisation (WHO) has defined probiotics as ‘live microorganisms which when administered in adequate amounts confer a health benefit on the host’.¹ Most often, the bacteria come from two groups, *Lactobacillus* or *Bifidobacterium*. Within each group, there are different species (for example, *Lactobacillus acidophilus* and *Bifidobacterium bifidus*), and within each species, different strains (or varieties).² Locally as in the rest of Europe, probiotics are available in foods such as milk, yoghurts and butter, combined with vitamins and minerals or sold alone. In recent years consumption of probiotics has been attributed to a multitude of benefits ranging from the treatment of diarrhoea to anticancer effects. Although such claims are in abundance, evidence from clinical trials to support such claims is lacking.

Claim 1: Prevention

and treatment of diarrhoea

a) Treatment of *Clostridium difficile*-associated colitis in adults

Mechanism: probiotics restore the microbial balance of the gastrointestinal tract altered by infection with *C. difficile*.

Studies: Four studies have evaluated the use of probiotics in conjunction with conventional antibiotics (e.g. metronidazole and vancomycin) for the treatment of recurrence or an initial episode of *C. difficile* colitis in adults. Only one study has demonstrated significant benefits in patients receiving *S. boulardii*.³

Conclusion: The evidence to support the use of probiotics with conventional treatment for *C. difficile* colitis is scanty and there is no evidence at all to support the use of probiotics as monotherapy for the treatment of *C. difficile* colitis.³

b) Probiotics for the prevention of antibiotic-associated diarrhoea (AAD)

Mechanism: antibiotics alter the microbial balance within the gastrointestinal tract and probiotics work via restoration of the gut microflora. It is also thought that probiotics release inhibitory substances that stall the growth of pathogenic bacteria responsible for the diarrhoea.

Studies: there are ten studies conducted on around 2000 children who were receiving short-term probiotics co-administered with antibiotics to prevent AAD. These trials included treatment with various probiotics including *Saccharomyces boulardii*, *Lactobacilli spp.* and *Bifidobacterium spp.* Results of these studies show statistically significant results favouring probiotics over controls.⁴ There are only two small studies conducted in adults, and only one of these utilising the *Lactobacillus* strain has shown some efficacy.⁵

Conclusion: Although results are very promising, the routine use of probiotics for the prevention of paediatric AAD is not recommended until further trials determine the strain and dose required.⁴ In adults the evidence is very limited because the group sizes of the trials were small and significant effects could have been missed.

c) Traveller’s diarrhoea

Mechanism: probiotics restore the gut flora.

Studies: three studies investigated whether *Lactobacillus* strains can prevent traveller’s diarrhoea. In one of the studies treatment with probiotics reduced the incidence of diarrhoea significantly from 40% to 24%. In the other study the incidence of diarrhoea was not statistically significant between the probiotic group and the placebo group. A double-blind placebo controlled study using *L. acidophilus* strains showed no difference in the incidence of traveller’s diarrhoea.⁵

Conclusion: the effect of probiotics on the incidence of traveller’s diarrhoea seems to depend on the bacterial stain and the destination of the travellers and needs further study.⁵

d) Diarrhoea caused by rotavirus

Mechanism: rotavirus infection causes gastroenteritis characterised by acute diarrhoea and vomiting and is a leading cause of death and disease among children worldwide. Probiotics are thought to restore the gut microflora following rotavirus infection.

Studies: Several studies have shown that consumption of *Lactobacillus* GG shortened the duration of diarrhoea from 3.5 to 2.5 days in children. *B. bifidum* and *S. thermophilus*, also reduced the incidence of diarrhoea in a double-blind, placebo-controlled trial in 55 hospitalised infants.⁵ Studies with *Enterococcus* species also showed beneficial effects however *L. acidophilus* failed to show significant differences in recovery times in diarrhoea caused by rotavirus.⁵

Conclusion: The strongest evidence for shortening of the diarrhoeal phase of rotavirus infection was with the consumption of *Lactobacillus* GG.^{2,5}

Claim 2: Treatment of *Helicobacter pylori* Infection

Mechanism: Probiotics may compete directly with *H. pylori*, possibly through the inhibition of adherence, as well as produce

metabolites and antimicrobial molecules such as bacteriocins, which inhibit *H. pylori* growth. Only animal and *in vitro* data has supported these properties.²

Studies: Seven of nine human studies showed an improvement of *H. pylori* gastritis and decrease in *H. pylori* density after administration of probiotics.⁶ The addition of probiotics to standard antibiotic treatment improved *H. pylori* eradication and reduced treatment associated side effects. This success however seems to be attributed to the fact that more patients completed the eradication treatment rather than because of eradication *H. pylori* infection by probiotic treatment alone.⁶⁻⁸

Conclusion: Based on current data, even though an effect against *H. pylori* has been described, probiotics cannot be considered as an alternative to standard anti-*H. pylori* treatment. Nevertheless, their use in association with standard anti-*H. pylori* treatment may be advisable, as they are able to improve patient compliance by reducing antibiotic-related adverse events, thus increasing the number of patients completing the eradication therapy.

Claim 3: Managing Lactose Intolerance

Mechanism: microbial β -galactosidase in live yoghurt hydrolyses lactose allowing

better digestion and absorption of glucose and galactose thus reducing the symptoms associated with lactose intolerance.^{2,9,10}

Studies: A large number of human studies in which consumption of fresh yoghurt with live cultures was compared with consumption of a pasteurised product with heat killed bacteria demonstrated better lactose digestion and absorption as well as reduction of gastrointestinal symptoms with the fresh yoghurt.² The efficacy of probiotics is dependent on the ability of lactobacilli to release β -galactosidase and this is limited by the fact that not all lactobacilli have the same ability to release this enzyme.^{2,10}

Conclusion: Some probiotics maybe effective in alleviating the signs and symptoms of this condition, although further trials of specific strains and concentrations are necessary.

Claim 4: Lowering of blood cholesterol

Mechanism: Probiotic bacteria ferment food-derived indigestible carbohydrates to produce short-chain fatty acids in the gut, which can then cause a decrease in the systemic levels of blood lipids by inhibiting hepatic cholesterol synthesis and/or redistributing cholesterol from plasma to the liver. Other bacteria may interfere with

Table 1. Summary of evidence for the use of probiotics

Claim	Evidence
Prevention of Clostridium difficile-associated colitis in adults	No evidence for monotherapy with probiotics
Prevention of antibiotic-associated diarrhoea	Evidence limited but very promising
Prevention of traveller's diarrhoea	Insufficient evidence
Treatment of diarrhoea caused by rotavirus	Strong evidence especially in paediatrics
Treatment of Helicobacter pylori infection	Good evidence for use in conjunction with standard anti- <i>H. pylori</i> treatment
Managing lactose intolerance	Strong evidence in favour of probiotics in alleviating signs and symptoms of lactose malabsorption
Lowering of blood cholesterol	Insufficient evidence
Treatment of vaginal infections	Insufficient evidence
Anticancer effects	Insufficient evidence
Management of inflammatory bowel disease	Good evidence for pouchitis and maintenance of remission but larger trials are needed to assess their value in other inflammatory bowel disorders
Prevention and treatment of atopic diseases	Strong evidence for probiotic use in high risk infants
Enhancement of the immune function	Strong evidence for shortening duration of common colds
Prevention of preterm labour	Insufficient evidence

cholesterol absorption from the gut.¹¹

Studies: In 1974 a paper published in the American Journal of Clinical Nutrition reported that consumption of probiotics in the form of fermented milk was associated with reduced serum cholesterol in the Maasai people.¹² Other studies in 1970's have utilised inadequate sample sizes and excessive quantities of the product thus producing equivocal findings.¹³ More recent studies, which are of better quality with redesigned standards, have failed to provide convincing and consistence evidence that strains of *L. acidophilus* and *L. bulgaris* have lowering-cholesterol efficacy in man.⁵ A meta-analysis of controlled short-term studies has shown that consumption of yoghurt containing *Enterococcus faecium* is effective in reducing both total and low-density lipoprotein (LDL) cholesterol by 4% and 5% respectively. Whether the effects are sustained over time remains to be proven.² Consumption of food products containing *L. plantarum* 299v has also been reported to lower total and LDL cholesterol in subjects with moderately raised cholesterol levels. Additionally subjects consuming 200ml of milk fermented with *L. casei* TMC0409 and *S. thermophilus* TMC 1543 daily showed significant increases in high density lipoprotein after four and eight weeks of supplementation.²

Conclusion: The lasting effect of probiotics on serum cholesterol is inconclusive.

Claim 5: Treatment of vaginal infections

Mechanism: lactic acid bacteria predominate in the normal vaginal flora, generating an acidic pH, which inhibits the growth of other organisms that can cause vaginal infections.⁹

Studies: Over the years there have been a number of clinical trials evaluating the ability of orally or intravaginally administered lactobacilli to inhibit the vaginal colonization by yeasts and prevent the recurrence of vulvovaginal candidiasis. In most of these studies the difference in risk of developing vaginal candidiasis in patients on probiotics compared to those who took placebo was small and not significantly different. Additionally a study investigating the use of lactobacilli in the prevention of post-antibiotic vulvovaginitis

failed to show any significant advantage of using probiotics in conjunction with antibiotics.¹⁴

Conclusion: Although several studies have shown that oral consumption of probiotics can alter vaginal microflora, most of these had either a flawed methodology or a very small sample size thus providing limited evidence to support the effectiveness of probiotic preparations.

Claim 6: Anticancer effects

Mechanism: regular, long-term consumption of probiotics has been suggested to protect against bowel cancer. The basis for this is that the acid pH in the colon generated by probiotics could inhibit the transformation of procarcinogen to active carcinogens and reducing the absorption of mutagens from the intestine.⁹

Studies: consumption of probiotics (*Lactobacillus salivarius*) has been associated with a reduced incidence of colonic adenocarcinoma in mice. Other studies in animal models have also shown probiotics to reduce intestinal inflammation, which has been associated with an increased incidence of colorectal cancer. Human studies have demonstrated the ability of probiotics to decrease the activity of some bacterial enzymes, which play an important role in cancer development as they hydrolyse carcinogenic compounds.^{2,5,15}

Conclusion: Large-scale trials are still required to support the implications of probiotics in the field of colorectal cancer.

Claim 7: Management of inflammatory bowel disease

Mechanism: it is claimed that patients with inflammatory bowel disease such as Crohn's disease and ulcerative colitis may have an abnormal gut microflora in terms of both the organisms and their ability to adhere to the gut wall.⁹ Probiotics can potentially reduce the population of abnormal bacteria and reverse any problems of adhesion. Additionally probiotics may help to improve gut immune function.^{2,9}

Studies: A recent systematic review in ulcerative colitis concluded that significant difference in effectiveness have been reported for different types of strains in species of bacteria and yeasts and it seems that *Bifidobacteria* are likely to give the

best results.¹⁶ There is some degree of evidence that probiotics added to standard therapy may provide modest reduction of disease activity in patients with mild to moderately severe ulcerative colitis.^{16,17}

Seven small studies have investigated the use of probiotics in the induction or maintenance of remission in Crohn's disease. One of the probiotics investigated was VSL#3 a patented combination of eight probiotic strains, including bifidobacteria and lactobacillus. Although outcomes have included an increase in relapse free time and a reduction in inflammation such differences were not statistically significant.¹⁸

Conclusion: Larger trials are needed to assess whether the use of probiotics can reduce the relapse of inflammatory bowel disease and/or maintain patients in remission and to see whether they are safer than the traditional anti-inflammatory drugs.

Claim 8: Prevention and treatment of atopic diseases

Mechanism: it is thought that optimising gut flora might reduce the risk of allergic disease by preventing increase in gut permeability associated with infection or by stimulating anti-allergic immunological responses.

Studies: A randomised double blind, placebo-controlled trial carried out in 54 infants showed no significant benefit for the use of probiotic bacteria in infants with atopic dermatitis. In another similar study 1,233 pregnant women and their babies were evaluated for the cumulative incidence of allergic diseases (eczema, asthma, allergic rhinitis and food allergies). Probiotic treatment compared with placebo showed no effect on the cumulative incidence of allergic diseases by age 2 years but significantly prevented eczema especially atopic eczema.¹⁹

Conclusion: the prevention of atopic eczema in high-risk infants seems possible by modulating their gut microflora of infants with probiotics.¹⁹

Claim 9: Enhancement of the immune function

Mechanism: Specific strains of lactic acid bacteria, when consumed in sufficient

numbers are able to alter some aspects of natural and acquired immune responses.

Studies: A recent double blind randomised controlled trial has studied 479 healthy adults during two winter/spring periods. The patients were supplemented with a daily preparation of vitamins and minerals with or without probiotics lactobacilli and bifidobacteria. Whilst the intake of the probiotic had no effect on the incidence of common colds, it significantly shortened common cold episodes and reduced the severity of symptoms.²⁰

Conclusion: A three-month consumption of probiotics may reduce the severity of common colds and reduce the duration by almost 2 days.²⁰

Claim 10: Probiotics for preventing preterm labour

Mechanism: 30% to 50% of pregnant females who go into labour too soon were found to have an infection and it is thought that this is what stimulates labour.²¹

Studies: there have been two trials involving a total of 108 women. In one trial the probiotics were given orally whereas the other utilised yoghurt used vaginally by

Practice Points

- Probiotics should not be taken with hot beverages. Temperatures above 50°C denature the bacteria rendering the product ineffective.
- There is limited evidence supporting some uses of probiotics. Much more scientific knowledge is needed about probiotics, including about their safety and appropriate use.
- Effects found from one species or strain of probiotics does not necessarily hold true for others.
- Immunocompromised patients should not be exposed to probiotics, as safety in this group of patients has not yet been established.

women diagnosed with bacterial vaginosis in early pregnancy. Pooled results showed an 81% reduction in the risk of genital infection with the use of probiotics.²¹

Conclusion: although probiotics appear to treat vaginal infections in pregnancy there is currently insufficient evidence to justify the use of probiotics to reduce the risk of preterm birth.^{21,22}

Adverse Effects

Probiotics are generally considered to be safe with side effects if any being mild and digestive such as bloating.⁹ However some probiotic species have been rarely isolated

from infectious sites although these appear mainly in patients with serious underlying diseases and/or immunosuppression.²³

They could also cause unhealthy metabolic activities such as over-stimulation of the immune system.²³

Conclusion

It is expected that in the future, new, well characterised, scientifically proven probiotic strains with specific health benefits will be developed. In addition, further well-designed clinical trials should provide health care professionals with sufficient evidence for the rational use of probiotics.

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