The role of probiotics in the prevention of disease

Abstract

Health care is rapidly changing, and a key focus of this evolution is preventative medicine, as opposed to treatment and curative options once disease has been established. This focus on prevention is aimed at reducing the overall health-care burden through better education, improved lifestyle choices and, in some cases, specific therapy to avoid disease. Natural supplements have been used in various forms for centuries, and increasingly they are undergoing vigorous scientific research in order to explore their various associated claims. Of these, probiotics are some of the most extensively investigated, and they potentially represent a safe and viable option for the prevention of certain conditions. The volume of research into probiotics has increased in parallel with the search for alternative, natural therapies with fewer side effects and clinical implications. This is reflected by the development of medicinal probiotics with extensive pre-clinical and clinical research to support their use. This review article will introduce some of the basic concepts related to probiotics, the human bacterial population (microbiome) and some of the evidence available to support their use in preventing disease.

It is important to have a basic understanding of the relationship humans have with the bacterial population found within the body. The most important of these various bacterial groups is the microbiota of the gastrointestinal (GI) system, which can contain up to 1000 bacterial species (Aziz et al, 2013), outnumbering the cells of the human body, and with a collective weight of up to 1.5 kg, similar to that of the human liver (Bengmark, 1998; Hawrelak and Myers, 2004). In addition, the collective genetic information of the gut microbiota contains over 100 times the number of genes in the human genome (Biagi et al, 2012) and as such has a multitude of functions that contribute to overall health. As with any organ system, a disturbance in the function of this 'bacterial organ' can have dramatic effects on one's health and the development of disease. As a result, any measures taken to help restore the balance can potentially have a positive effect on health.

Probiotics

The current accepted definition of probiotics is 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (Food and Agriculture Organization (FAO)/World Health Organization (WHO), 2002: 8). These benefits have historically been associated with the general function of the gut, but as more research is carried out into the actions of probiotics, more specific clinical benefits are being identified. These range from general improvements in disease status to specific improvements in measurable biomarkers. As a result, the term 'pharmabiotic' is becoming more commonplace and recognises their clinical potential.

Mechanisms of action

Different species of probiotics exhibit different properties and, in fact, there is widespread diversity even between different strains of the same species. Their actions are complex in

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nature and they not only have effects on the human body, but also on other bacteria present within the local environment. They can broadly be categorised into three main areas where they have an effect:

- Effects on the local environment
- Effects on the immune system (local and systemic)
- Effects on the surrounding bacterial population.

Within each category there are numerous mechanisms by which they exhibit their effects, some of which are summarised in *Figure 1*.

Different probiotic species will exhibit different combinations of the above traits, while others will have a completely unique profile. There is evidence that demonstrates that probiotic bacteria can work synergistically to potentiate each other's properties and exert a greater effect than the individual strains (Chapman et al, 2011). This translates to much improved clinical benefit seen with the use of a multi-strain formulation (Timmerman et al, 2004). This is true of more generalised effects of probiotics on the immune system, health and wellbeing. However, when trying to isolate a specific action of a bacterial strain (for example, to reduce hepatic inflammation), it is seen to be more effective as a single-strain preparation (Cani et al, 2015).

Evidence base

The multiple properties of probiotic bacteria result in multiple therapeutic areas where they can be used. In preventative medicine they can be classified broadly into their ability to modulate the immune system (allergic disease) and their ability to influence the human microbiome (infectious disease). There are ongoing studies looking at their ability to prevent metabolic disorders such as gestational diabetes (Isolauri et al, 2015) and non-alcoholic fatty liver disease (Shavakhi et al, 2013; Eslamparast et al, 2014). There is growing evidence for their use in helping to manage these conditions, but the evidence for their use in prevention is poor or non-existent.

Allergic conditions

The gut bacterial population has a complex relationship with the gut-associated lymphoid tissue (GALT) through its interactions with specific immunomodulatory cells. These cells are able to influence the innate and adaptive immune response through up-regulation and down-regulation of specific cytokines, inflammatory markers and other immune cells (Vitaliti et al, 2013). In this way, they act as primers for the immune system and can therefore heighten or dampen allergic hypersensitivity reactions.

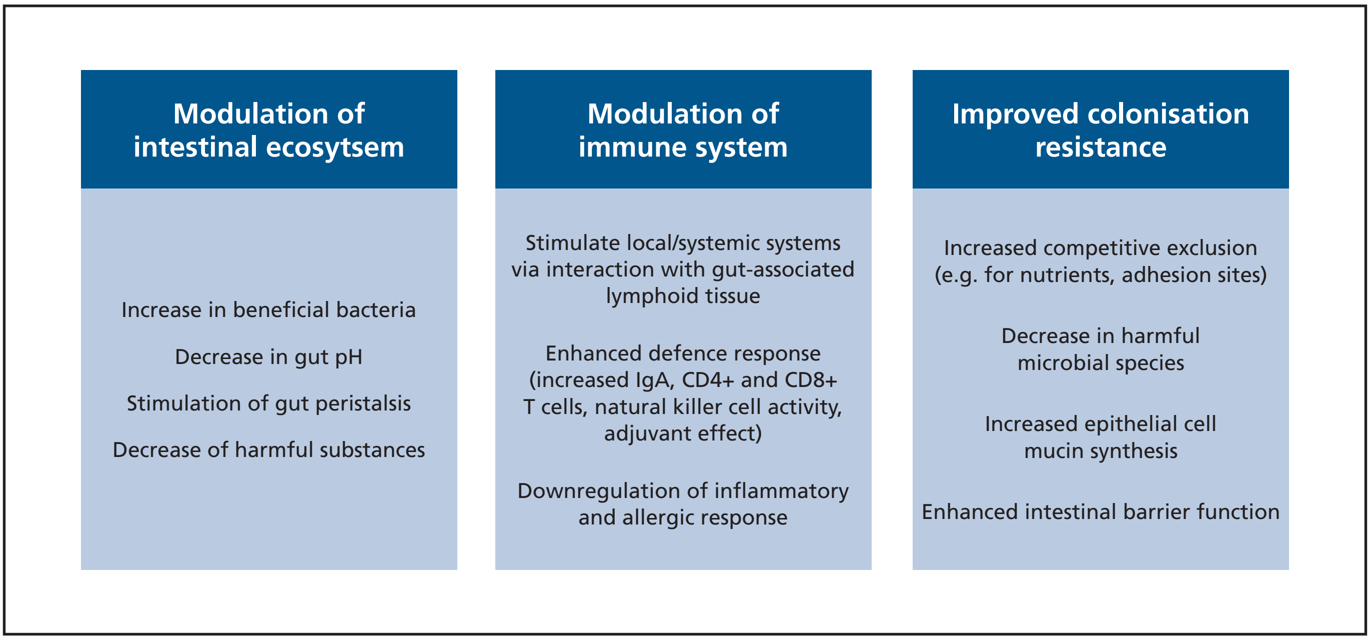

Figure 1. Summary of mechanisms by which probiotics influence normal bowel function (adapted from Baker et al, 2009)

It is this complex relationship with the immune tissue in the gut that forms the basis for the use of probiotics in the prevention and management of certain allergic conditions. The strength of the evidence varies between allergic conditions, and this is likely to do with the various mechanisms of action for probiotics and the heterogeneity of probiotic mixtures that have been investigated.

Atopic dermatitis

A Korean population-based study showed that the administration of probiotics pre and postnatally significantly reduced the risk of developing atopic dermatitis (AD) in the first year of life (Kim et al, 2010). This effect was particularly pronounced in those infants that were identified as high risk for the development of allergic disease. An extensive meta-analysis of data available for the use of probiotic supplementation in the prevention of AD in children was performed in 2012. The researchers were able to show that the use of probiotics significantly reduced the occurrence of AD, particularly in children administered probiotics perinatally (Kim and Ji, 2012). There is further evidence that supports the use of probiotics perinatally to prevent the development of AD in later life, with no probiotic specific safety concerns identified (Kalliomäki et al, 2001; Kukkonen et al 2007; Pelucchi et al 2012). Kalliomäki and colleague's (2001) were able to demonstrate a reduction in AD from 46% in the placebo group to 23% in the treatment group (*Lactobacillus rhamnosus GG*). Kukkonen et al (2007) demonstrated a relative risk reduction of 36% with the use of a multi-strain probiotic formulation, while Pelucchi et al's (2012) meta-analysis revealed an overall relative risk reduction of 21% in 18 different publications looking at various probiotic formulations.

Allergic rhinitis

There is some evidence to suggest that probiotics can be used in the prevention of allergic rhinitis, or hayfever. A 2013 review paper demonstrated that probiotics have been shown to have a beneficial effect in the treatment and prevention of allergic rhinitis in both children and adults (Kim et al, 2013). They also found that these improvements correlate to improvements in blood markers of inflammation and allergy. They found evidence to show that probiotics improved the nasal symptoms of allergic rhinitis. These findings further backed up a study by Wassenberg et al in 2011, which found that *Lactobacillus paracasei* taken for a month actually reduced symptoms of nasal congestion and itching in allergic rhinitis sufferers. In addition, they showed that the probiotics reduced specific immune markers, suggesting that there was a systemic effect. The 2013 review by Kim et al suggested that the evidence points towards the use of probiotics in an ongoing fashion to confer a baseline protective effect in order to prevent acute episodes. However, they concluded that there is little or no evidence to show that taking probiotics in early life can actually prevent the development of allergic rhinitis later on in life.

Other atopic conditions

There is further, less compelling evidence to suggest that probiotics may have a role to play in the prevention of asthma and food allergy (Chen et al, 2010; Castelazzi et al 2013; Van der Aa et al, 2011). However, the evidence is scarce and their use must be investigated further before probiotics can be considered as an effective preventative therapy.

Infectious disease

Probiotics' ability to modulate the human microbiome is well established, and for that reason research has shown that they are particularly effective at preventing infectious conditions. This is largely due to their ability to counteract and compete with pathogenic bacteria, thereby reducing their numbers and their ability to cause disease.

Antibiotic-associated diarrhoea

There have been hundreds of clinical trials studying the effect of probiotics in the prevention and management of antibiotic-associated diarrhoea (AAD) making the case for their use much stronger than other, less well-investigated conditions. With such a large body of work, the most useful information is usually obtained through systematic reviews and meta-analysis of the overall data. Two of the more comprehensive meta-analyses by Hempel et al (2012) and Johnston et al (2012) have shown that probiotics can reduce the relative risk of AAD by 42% and 66% respectively. The Cochrane Database of Systematic Reviews also contains a meta-analysis and systematic review of the use of probiotics specifically to prevent *Clostridium difficile* (*C. diff*)-associated diarrhoea following the use of antibiotics, again demonstrating a beneficial effect by reducing incidence by 64% (Goldenberg et al, 2013). The Cochrane review also used a 'numbers needed to treat' analysis to demonstrate that 29 patients would need to be treated in order to prevent one case of *C. diff*-associated diarrhoea, which would represent a saving when considering the cost of a course of probiotics and the cost of treating one case of *C. diff*-associated diarrhoea in hospital. These results, along with the excellent safety record of probiotics, mean that their use can and should become more widespread. It is worthwhile mentioning that not all tested probiotic preparations have been demonstrated to be effective in reducing the risk of AAD, as seen in the Probiotic *Lactobacilli* and *Bifidobacteria* in Antibiotic-associated Diarrhoea and *Clostridium difficile* Diarrhoea in the Elderly (PLACIDE) study (Allen et al 2013a; 2013b). However, given the strain-specific properties of probiotics, it is possible that the bacterial strains used in some unsuccessful studies do not have the necessary characteristics to prevent the development of AAD. It is likely that this type of heterogeneity between probiotics influenced the cautious recommendation from the Cochrane review:

'Based on this systematic review and meta-analysis of 23 randomised controlled trials including 4213 patients, moderate quality evidence suggests that probiotics are both safe and effective for preventing *Clostridium difficile*-associated diarrhea.' (Goldenberg et al, 2013).

The meta-analysis identified 26 studies that reported adverse events, 7 of which reported no adverse events in the whole study (both interventional and control groups). Four of the studies reported serious adverse events, none of which were attributed to the probiotics used.

The recommendations for paediatric AAD are less conclusive, with only two probiotics identified as being moderately beneficial (*Lactobacillus rhamnosus* or *Saccharomyces boulardii*) at a dose of 5 to 40 billion colony-forming units (Goldenberg et al, 2015). It was also noted that, while serious adverse events were not observed in otherwise healthy children, they were reported in those that were severely debilitated or immune-compromised with underlying risk factors. The meta-analysis of the safety data demonstrated no statistically significant differences in the incidence of adverse events, but the overall quality of the evidence was classified as low. For this reason, the authors concluded that 'until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events. Future trials would benefit from a standard and valid outcomes to measure AAD.' (Goldernberg et al, 2015).

Recurrent urinary tract infections

Urinary tract infections (UTIs) are among the most commonly occurring bacterial infections, with an estimated one in three women experiencing a UTI by the age of 24 years, and 25–30% of adult women with a first episode of UTI will have a recurrence (Barrons and Tassone, 2008). *Escherichia coli* is the predominant pathogen causing UTIs; other common causative microorganisms are *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and occasionally *Klebsiella pneumoniae* and *Proteus mirabilis*. The use of prophylactic antibiotics to reduce recurrence has previously been effective, although side-effect profiles and the increase in bacterial resistance have seen the efficacy of treatment fall. Studies involving probiotics in recurrent UTIs have had variable effects, but with more research into the specific mechanisms of action and strain-specific clinical trials, evidence is building for the use of probiotics in UTI prevention. There are many studies that have shown impressive results using probiotics to prevent recurrence. Reid et al (2001a), Kontiokari et al (2003) and Stapleton et al (2011) all showed significant reduction in UTI recurrence with the use of a prophylactic probiotic.

It is important to note that acute UTIs should be treated with antibiotics, and the role of probiotics is mainly to help prevent further recurrence.

Vulvovaginal candidiasis

Vulvovaginal candidiasis (VVC) is another common urogenital infection in women, with one survey reporting up to 8% of women over the age of 18 years experiencing between one and four episodes per year. In the US alone, treatment for VVC accounted for $1.8 billion in terms of health-care costs (Falagas et al, 2006). Antibiotic therapy, spermicide use, oral contraceptives, oestrogen therapy, diabetes mellitus, and frequent sexual intercourse are factors that increase the risk for development of VVC. All of these factors influence the microflora of the vagina, altering the balance of the bacterial species.

There are few studies that do not support the use of probiotics in the prevention of VVC, and the most impressive study showed that the administration of an intravaginal probiotic was almost as effective at preventing episodes of VVC as a prophylactic antifungal. The relative risk for developing VVC was 0.4 in the antifungal group and, incredibly, 0.5 in the probiotic group (Falagas et al, 2006). Several studies have shown that oral administration of *Lactobacilli* probiotics can influence and modulate the vaginal microflora in patients with recurrent VVC, reducing the ability of *Candida albicans* to translocate to and colonise the vagina (Hilton et al, 1995; Reid et al, 2001a; Reid et al, 2001b; Reid et al 2003).

Safety profile

Probiotics have been used for hundreds of years in the form of fermented foods and drinks with no obvious harmful effect noted. However, with increasing use in clinical practice there is, of course, an increased need to establish the safety profile of the bacteria. This is even more true with the search for new species and strains of bacteria that are constantly sought for their novel properties and potential beneficial effects. Many organisms have been assigned Generally Regarded as Safe or Qualified Presumption of Safety status in the US and Europe respectively, but very few systematic safety studies have been conducted. The safety data that is collected is largely from clinical trial work where safety was a secondary end point.

In 2011, a report published by the Agency for Healthcare Research and Quality (AHRQ) concluded that existing probiotic trials do not reveal an increased risk, but that the literature is not well equipped to answer questions on the safety of probiotics (Hempel et al, 2011). While this conclusion may raise doubts, other researchers have recognised that the most appropriate way to measure safety is based on the 'totality of evidence' (Doron and Snydman, 2015); namely the long history of safe use, animal and in vitro data, as well as clinical studies. They go on to make the point that 'if the AHRQ intended to answer the question 'are apples safe?', it would likely come to the same conclusion, which is that the current literature is not well equipped to answer questions on the safety of apples with confidence.' (Wallace and MacKay, 2011: 1923).

The 2002 joint report released by WHO and the FAO of the US stated that probiotics may theoretically be responsible for four types of side effects (FAO/WHO, 2002):

- Systemic infections
- Deleterious metabolic activities
- Excessive immune stimulation in susceptible individuals
- Gene transfer

Systemic infections have largely been restricted to case studies and have not been shown to be statistically more frequent than infection with commensal organisms, particularly supported by a 6-year Swedish study that showed no change in septicaemia caused by *Lactobacilli* and no cases of probiotic *Lactobacilli* causing sepsis after the introduction of probiotics into the population (Sullivan and Nord, 2006).

One clinical trial looking at pancreatitic patients demonstrated a large increase in mortality attributed to bowel ischaemia with the use of probiotics, and the researchers proposed that the potential metabolic effects of the probiotics triggered an inflammatory reaction resulting in reduced small bowel capillary blood flow (Besselink et al, 2008). However, two other studies in similar groups of patients did not demonstrate any increase in bowel ischaemia, and in fact showed beneficial effects in reducing septic complications, surgical interventions and infected necrosis with the use of a probiotic formulation (Oláh et al, 2002; Oláh et al, 2007).

Due to the ability of probiotics to modulate the immune system, concern has been raised about the potential to overly stimulate the immune response in some individuals, possibly leading to autoimmune phenomena or inflammation. This theoretical concern has not been reported in any human subjects (Doron and Snydman, 2015). Similarly, there are theoretical concerns surrounding the ability of lactic acid bacteria to share DNA (in the form of plasmids), specifically those related to antibiotic resistance. Despite this theoretical possibility, no clinical evidence of antimicrobial resistance gene transfer has been seen.

Overall, the safety of probiotics is well established, with only rare case study reports to suggest any potential harmful effects. Importantly, these effects are not seen as statistically significant compared with the risk of infection with commensal bacteria, and on the whole they are considered safe. However, with increasing use in specific clinical conditions and the ongoing search for medicinal probiotics, there is a recognition that reporting of safety data needs to improve in order to fully establish these medicinal probiotic products as 'safe' for use.

Conclusion

The potential for probiotics to be used in preventative medicine is clear to see, and their use in specific therapeutic areas is certainly increasing, albeit with caution. One of the main problems facing the probiotic industry is that specific data cannot be used in support of different strains of bacteria. Unlike traditional drugs, where a generic formulation can use historical data, the strain specificity of probiotic properties means that there is no generic equivalent and therefore data can only be attributed to the specific formulation being studied. This is true of their safety profile as well as their beneficial properties.

Probiotic research is growing rapidly and this article has introduced some of the basic concepts and evidence for their use. As more companies strive for medicinal licenses, the evidence will become even stronger and the case for their regular use will become more compelling. **GN**

Declaration of interest *Dr Mayur R Joshi is a former employee of Probiotics International Limited, who manufacture both human and animal probiotic products.*

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