PROBIOTICS FOR GASTROINTESTINAL AND RELATED CONDITIONS

Introduction
The progressive westernisation of diets and lifestyles of South Africans is likely to be associated with an increase in gastrointestinal conditions such as constipation, colorectal cancer, functional abdominal pain and irritable bowel syndrome (IBS). The latter is a complex condition and its pathogenesis differs from individual to individual. It is characterised by recurrent abdominal pain associated with alterations in bowel habits. Modifications in the gut microbiota and immunomodulation are linked to IBS symptom development.

KEY RECOMMENDATIONS FOR CLINICAL PRACTICE

- Probiotic use reduces the risk of antibiotic-associated diarrhoea in children and adults
- Probiotic use may reduce the incidence of Clostridium difficile-associated diarrhoea
- Probiotic use significantly reduces the risk of hepatic encephalopathy
- Probiotic use increases remission rates in adults with ulcerative colitis
- Probiotic use improves abdominal pain and global IBS symptoms
- Probiotic use reduces the incidence of necrotising enterocolitis and mortality in preterm infants.

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Prevalence of IBS in South Africa

A very recent study of work-related stress, burn-out and self-reported illness among some 8000 employees from various economic sectors in South Africa illustrates the growing prevalence of IBS among South Africans. The study included an equal number of black people (42%) and white people (42%) working in the financial, government and health sectors providing data that are relevant to our demographic situation. Fifty-five percent were women and 45% men; the majority were in the age group of 30-49 years.

The incidence of self-reported health conditions is summarised in Table 1, indicating that IBS ranked third after hypercholesterolaemia and hypertension.3 Burn-out and stress had a significant relationship with IBS.

<table>
<thead>
<tr>
<th>Health condition</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular conditions</td>
<td>181</td>
<td>2.3</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>629</td>
<td>8.0</td>
</tr>
<tr>
<td>Depression</td>
<td>429</td>
<td>5.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>324</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1026</td>
<td>13.0</td>
</tr>
<tr>
<td>IBS</td>
<td>527</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Overview of probiotics and their function

Major micro-organisms considered to be probiotics

Lactic acid bacteria are the major group of bacteria suitable for use as probiotics. They are Gram-positive and catalase-negative, and produce lactic acid as the main end-product from the fermentation of carbohydrates. The most important genera are Lactobacillus and Bifidobacterium, which are used in food products and nutraceuticals. Enterococcus is also an important lactic acid bacterium, which is often used in combination with either Lactobacillus or Bifidobacterium.

Table 2 provides a list of species used and cited in clinical research.4

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. acidophilus</td>
<td>B adolescentis</td>
</tr>
<tr>
<td>L. casei</td>
<td>B animalis</td>
</tr>
<tr>
<td>L. crispatus</td>
<td>B bifidum</td>
</tr>
<tr>
<td>L. gallinarum (Mainly used by animals)</td>
<td>B breve</td>
</tr>
<tr>
<td>L. gasseri</td>
<td>B infantis</td>
</tr>
<tr>
<td>L. johnsonii</td>
<td>B lactis (Recently reclassified as B animalis subsp. lactis)</td>
</tr>
<tr>
<td>L. paracasei</td>
<td>B longum</td>
</tr>
<tr>
<td>L. plantarum</td>
<td></td>
</tr>
<tr>
<td>L. reuteri</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td></td>
</tr>
</tbody>
</table>
A South African-produced probiotic containing two lactic acid bacteria (*L. plantarum* and *Enterococcus mundtii*) has been shown to prevent *Listeria monocytogenes* from colonising the gastrointestinal system of mice. This is a particularly interesting finding in view of the recent listeriosis outbreak and deaths in South Africa.

**Essential probiotic properties**

Probiotics need to be able to withstand the harsh gastric environment to reach the intestine and adhere to the mucosal and epithelial surfaces. *In vitro* tests are used to determine the following desirable properties:

1. Acid and bile tolerance; essential for oral administration
2. Adhesion to mucosal and epithelial surfaces to compete with and exclude pathogenic bacteria from the receptor
3. Production of antimicrobial activity against pathogenic bacteria (so that the probiotic can compete even more successfully with pathogenic bacteria)
4. Bile salt hydrolase activity
5. Resistance to certain antibiotics, so that the probiotic is able to restore the microbial balance and prevent antibiotic side-effects
6. Quantity of viable micro-organisms, although not precisely defined, should reach a minimum total of $10^8$-$10^9$ colony-forming units (CFUs). Viability should also be maintained under normal storage conditions.

Vaginal probiotics are being developed and trialled to reduce bacterial vaginosis, a condition characterised microbiologically by replacement of the lactobacilli predominant in the vaginal microbiota.

**Mechanisms of action**

Probiotics have various mechanisms of action. These include the production of bacteriocins (antibacterial peptides) and short-chain fatty acids, lowering of gut pH, stimulation of mucosal barrier integrity and immunomodulation. There is considerable evidence that probiotics influence the acquired and innate immune response by inducing phagocytosis and IgA secretion, modifying helper T-cell response and the release of cytokines in a strain-specific manner.

**Link between gastrointestinal flora and immune function**

Probiotics maintain the balance of gastrointestinal microbiota and help to prevent invasion of the epithelium by pathogenic bacteria. The body’s immune system is associated with the intestinal epithelial barrier and its mucosal lining. Disruption of the healthy, indigenous microbiota by pathogens leads to a dysfunctional innate immune system and increases the risk of developing disease, including IBS (Figure 1).

**Safety of probiotic use**

Probiotics are generally considered to be safe but caution is advised in immunologically vulnerable populations. Available evidence from randomised clinical trials (RCTs) does not indicate an increased risk, but very rare adverse events (bacteraemia/fungaemia/positive blood cultures, five cases in 1557 participants) have been identified in patients with cancer.

**Specific conditions that benefit from probiotic use**

While a RCT among free-living older adults was negative for benefit from three months use of probiotics, other RCTs have provided a clearer idea of which patients/people in particular circumstances will benefit from probiotic supplements.
Probiotics for gastrointestinal and related conditions

Pregnant and lactating women
A RCT of high-dose probiotic supplementation of women during late pregnancy and lactation has shown that breast-milk cytokines and secretory IgA production in newborns are beneficially modified by therapy. This improves the overall gastrointestinal function in infants of treated mothers with a reduction of colic symptoms.

Antibiotic-associated diarrhoea
A Cochrane analysis of available clinical trials suggests a positive outcome with regard to the reduction of antibiotic-associated diarrhoea in children with a number needed to treat (NNT) of 10. Among the various probiotics evaluated, L. rhamnosus or Saccharomyces boulardii at 5-40 billion CFUs/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. Although no serious adverse events from probiotic usage have been observed among otherwise healthy children, adverse events have been observed in severely debilitated or immune-compromised children with underlying risk factors, including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in paediatric populations at risk for adverse events.

In healthy adults, a randomised, double-blind placebo-controlled trial of two lactobacilli (L. helveticus (R0052) and L. rhamnosus R0011), taken for one week with the antibiotic and one week after completion, showed that supplementation significantly reduced the duration of diarrhoea-like symptoms.
IBS

According to the most recent guideline from the American College of Gastroenterology on the management of IBS, probiotics improve global symptoms, bloating and flatulence in IBS based on meta-analyses of more than 23 RCTs involving 2500 patients. This guideline acknowledges that recommendations concerning which species, preparations or strains to use are difficult because of insufficient and conflicting data.

Patients on aspirin to reduce small bowel injuries

A very recent prospective randomised double-blind placebo-controlled trial showed that a lactobacillus (L. gasseri OLL2716 (LG)) given daily for six weeks reduced aspirin-induced small bowel injuries and mitigated gastrointestinal symptoms.

Patients/people vulnerable to adverse effects of respiratory tract infections (RTIs)

In the elderly population, upper RTIs can have severe implications. A RCT of people aged 60-74 years, healthy and not living in retirement homes, showed that a Bacillus subtilis CU1 probiotic decreased the frequency of respiratory infections compared to placebo.

Probiotic usage in vulnerable children/immunocompromised children is not recommended to prevent RTIs; however, Cochrane analysis has shown the value of probiotics in otherwise healthy children in reducing the occurrence of RTI’s.

Athletes in training

Trained athletes benefit from probiotic usage as prolonged intense exercise is associated with the suppression of immune function and an increased risk of infections. A randomised, double-blind placebo-controlled trial conducted among Austrian athletes showed that a multi-species probiotic given for 12 weeks reduced exercise-induced drops in tryptophan levels and reduced the incidence of upper RTIs without enhancing athletic performance.

Conclusion

Probiotic use can be beneficial, particularly to a subset of patients with gastrointestinal problems and can significantly improve the immune status during treatment.
References

5. Van Zyl WF, Dean SM, Dicks LM. Enterococcus mundtii ST4SA and Lactobacillus plantarum 423 excludes Listeria monocyctogenes from the GIT as shown by bioluminescent studies in mice. Microbes 2016, 7(2): 227-235.