Evidence-based Pharmacy Practice (EBPP):

PROBIOTICS AND PREBIOTICS

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Terminology
Microorganisms living within the body can either be probiotic, pathobiotic or eubiotic. A **probiotic** is a microorganism that contributes positively to the body’s health. These “friendly” bacteria are also called flora. A **pathobiotic**, on the other hand, harms or impedes the body in one way or another. A **eubiotic** can be either harmful or helpful to the body, depending upon their colony size and location. A healthy body contains a substantially greater number of probiotics than pathobiotics.

**Probiotics** are designed for, and most effective in the small intestine. **Prebiotics** are specifically targeted to act on the flora of the large intestine. **Synbiotics** are a combination of a prebiotic and a probiotic in a single product. The rationale is that the product contains a beneficial agent in the small intestine (the probiotic) and one in the large intestine (the prebiotic), and that the two therefore act synergistically (hence the name “syn”-biotics).

There is growing public and scientific interest in probiotics and prebiotics. Researchers are studying whether these products taken as foods or supplements can help treat or prevent illness. Probiotics will be discussed first, followed by a discussion on prebiotics.

PROBIOTICS

A probiotic is defined as a live microbe that protects its host and prevents disease. A probiotic is therefore a living microorganism that, when administered in sufficient numbers, is beneficial to the host and exerts health benefits beyond inherent basic nutrition. The best-known probiotic is *Lactobacillus acidophilus*, found in yoghurt. Probiotics include foods, medicines and dietary supplements. Probiotics may be added to dairy products as a culture concentrate, or are available as dietary supplements. Species of *Lactobacillus* and *Bifidobacterium* are most commonly used as probiotics (the acidophilus-bifidus (AB) products are the most widely consumed probiotics intended for humans), but the yeast *Saccharomyces cerevisiae* and some *E. coli* and Bacillus species are also used as probiotics. Lactic acid bacteria (LAB), including species of *Lactobacillus*, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents of food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term “probiotic” should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit.

The positive role of certain nonpathogenic bacteria was first noted by the Russian scientist and Nobel laureate Elie Metchnikoff. He suggested that it would be possible to modify the gut flora and to replace harmful bacteria by useful bacteria. He observed that some Russians who lived largely on milk fermented by lactic-acid bacteria were exceptionally long-lived. Subsequently, Henry Tissier from the Pasteur Institute isolated a bifidobacterium from a breast-fed infant and claimed that bifidobacteria can displace the proteolytic bacteria that cause diarrhoea in infants. Thereafter, the centre of probiotic activity moved to the United States and in the 1970s the dairy industry began to promote fermented milk products containing *L. acidophilus*.

Probiotics help maintain the natural balance of organisms (microflora) in the intestine. The normal human digestive tract contains approximately 400 types of probiotic bacteria that reduce the growth of harmful bacteria and promote a healthy digestive system. Probiotics are used to treat conditions in the digestive tract, but only certain strains have been shown to work in the digestive tract. More research to prove exactly which probiotics (alone or in combination) work best to treat diseases need to be conducted.

A report on “Guidelines for the Evaluation of Probiotics in Food” considered more fully what minimum assessments a probiotic must undergo. The findings were:

- A probiotic must be identified at the genus, species and strain level, using appropriate molecular and physiological techniques.
- The strain should be deposited in an internationally
Conditions treated
In most circumstances, probiotics are used to prevent diarrhoea caused by antibiotics. Antibiotics kill “good” (beneficial) bacteria along with the bacteria that cause disease. A decrease in beneficial bacteria may lead to diarrhoea. Taking probiotic supplements (as capsules, powder or liquid extract), in combination with antibiotics may therefore help to replace the lost beneficial microbes and help prevent diarrhoea. The yeast *Saccharomyces boulardii* and three strains of *Lactobacillus* have been shown to be effective in this regard. Various mechanisms of action can be summarised as follows:

- Produce antimicrobial substances, such as organic acids or bacteriocins.
- Upreregulate immune response (for example, secretory IgA) to possible pathogens or to vaccines.
- Downregulate inflammatory response.
- Assist in early programming of the immune system to result in a more balanced immune response and reducing risk of development of an allergy.
- Improve gut mucosal barrier function.
- Enhance stability or promote recovery of commensal microbiota when disturbed.
- Modulate host gene expression.
- Deliver functional proteins (for example, lactase) or enzymes (natural and cloned).
- Decrease pathogen adhesion.

Research has shown that certain probiotics may restore normal bowel function and may therefore help to reduce:

- Diarrhoea that is a side effect of treatment with certain antibiotics.
- Certain types of infectious diarrhea. The use of probiotics in gastroenteritis is generally safe and may have some benefit in relieving symptoms. They can be given in the form of yoghurt with active cultures.
- Inflammation of the ileal pouch (pouchitis) that may occur in people who have had surgery to remove the colon.

Results also suggest that eventually probiotics may be used to:

- Help with other causes of diarrhoea.
- Prevent and treat vaginal yeast infections and urinary tract infections.
- Help prevent or shorten the duration of infections in the digestive tract.
- Help control immune response (inflammation), such as in inflammatory bowel disease (IBD). Probiotics assist with the correction of a dysfunctional imbalance in the intestinal microflora (with subsequent effects on motility, sensitivity and gas production) and the suppression of low-grade mucosal inflammation or immune activation (which alters pro-inflammatory cytokines).
- Reduce bladder cancer recurrence.
- Prevent eczema in children.

The use of probiotics is also studied for use in colon cancer.

Studies suggest that probiotics found in yoghurt help to prevent diarrhoea caused by antibiotics. More studies, however, are needed to confirm that yoghurt is effective. Also, the yoghurt must contain active cultures. Most yoghurt containers indicate whether active cultures are present. Probiotics are also found as dietary supplements and in foods such as fermented and unfermented milk, some juices and soy drinks.

Safety
Probiotic bacteria are part of the normal digestive system and are considered safe. They are classified as dietary supplements. More research, however, is needed especially on their safety in young children, the elderly and in those with compromised immune systems. Generally, the side effects of probiotics are mild and digestive (for example, flatulence and bloating).

Patients should always tell their health care practitioner if they are using dietary supplements such as probiotics, and must remember that:

- Dietary supplements may, similar to conventional medicine, cause side effects, trigger allergic reactions or interact with other medicines or supplements they are taking.
- Dietary supplements may not be standardised in their manufacturing, therefore how well they work or side effects may differ among products and even within different batches of the same products.
- The long-term effects of most dietary supplements are not known.

Evidence
Probiotics, such as *lactobacillus*, are generally safe and may have some benefit in relieving symptoms of gastroenteritis. They can be given in the form of yoghurt with active cultures. Various nonpathogenic microorganisms (for example, commensal *E. coli*, *Lactobacillus* species and *Saccharomyces*) administered daily serve as probiotics and may be effective in pouchitis, but other therapeutic roles have yet to be clearly defined.

Commerially available probiotic products usually contain in excess of 10^6 colony-forming units (CFUs) of viable organisms, but the
Probiotic dose for specific clinical disorders is not well established. Probiotics are widely used and have had a good safety record, but several reports of sepsis have been attributed to the Lactobacillus species. There have not been reports of sepsis related to Bifidobacterium, most likely because of its lower pathogenicity.

Studies that have evaluated probiotics in patients with irritable bowel syndrome (IBS), found the results of these studies difficult to evaluate because most studies were small and under-powered. In addition, results were difficult to compare because of the differences in study design as well as in probiotic strains and dosages. Probiotic dosages varied from as little as 10⁶ CFUs of viable organisms to 10¹², and mixtures of probiotic strains made it impossible to determine which the active moieties were.

Some researchers also believe probiotics may improve general health. A study in Sweden in 2005 involving 181 employees in a randomised double-blind trial, found that the group of employees who were given the probiotic Lactobacillus reuteri missed less work due to respiratory or gastrointestinal illness than did employees who were not given the probiotic.⁸

Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of microflora already in the colon, and thereby improve host health.¹² Prebiotics therefore are specifically targeted to act on the flora in the large intestine. They are considered a functional food. Prebiotics were first identified and named by Marcel Roberfroid in 1995. Roberfroid defined a prebiotic as “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”.⁹

Prebiotics are nutrients that support growth and activity of bacteria, historically principally but not exclusively bifidobacteria, and resist absorption in the upper small intestine. Any product that stimulates bifidobacteria is considered a bifidogenic factor. Some prebiotics may therefore also act as a bifidogenic factor and vice versa, but the two concepts are not identical. Prebiotics include indigestible carbohydrates (non-digestible oligosaccharides or short-chain carbohydrates that are not digested in the small intestine and enter the large intestine unaltered), inulins (soluble dietary fibre) and lactulose. Although most potential prebiotics are carbohydrates, the definition does not exclude non-carbohydrates to be used as a prebiotic. In theory, any antibiotic that would reduce the number of potentially harmful bacteria and favour health promoting bacteria, can be considered to be a prebiotic. Currently, two particular fructo-oligosaccharides fully meet the definition of a prebiotic, namely oligofructose and inulin. The others are referred to as possible or likely prebiotics.

The three criteria required for a prebiotic effect are¹⁰:
- Resistance of the prebiotic to degradation by stomach acid, mammalian enzymes or hydrolysis.
- Fermentation (breakdown and/or metabolism) of the prebiotic by intestinal microbes.
- Selective stimulation of the growth and/or activity of possible microorganisms in the gut.

Effects of prebiotics

The definition for a “prebiotic” states that a change in the metabolic activity may result in an improvement of the host health. This means that no specific group of bacteria has to be stimulated, but that the metabolic activity of the intestinal flora as a whole has to be modified. This generally means an increase in carbohydrate fermentation and a decrease in protein degradation and fermentation. Carbohydrate fermentation generally results in harmless end products, whereas protein fermentation results in the production of potential harmful products (see Figure 1).

![Figure 1: Fermentation of protein and carbohydrates by the intestinal microflora](image)
The gas H₂S is very reactive and can have negative effects on the intestine.¹¹ The other gases (hydrogen (H₂), CO₂ and methane (CH₄)) have no negative effects, except flatulence and bloating.¹¹ SCFA and lactate are beneficial for both the intestinal microflora (lowering of the pH, and making the intestine more acidic) and the intestinal cells (which need SCFA for energy).¹¹ Ethanol is rapidly metabolised by other intestinal bacteria and has no effect on the host. BCFA, ammonia (NH₃), amines, phenols and indoles are irritants to the intestinal cells, possibly mutagenic or may have a negative effect on the immune system in high concentrations.¹¹ It is thus beneficial to increase the carbohydrate fermentation in the intestine and to suppress the protein fermentation. This change in metabolic activity, however, does not necessarily correlate with an increase in the numbers of the possible beneficial bacterial groups.

The main concept of prebiotics therefore is to increase beneficial bacteria and/or increase carbohydrate metabolism. The following effects of prebiotics have been claimed¹¹:

- **Relief of constipation**
  The effect is similar to the effect of dietary fibre. Many prebiotics are carbohydrates, which are fermented in the large intestine. With this fermentation, gases are produced, which increase the volume and reduce the transit time of the contents in the intestine. Constipation is the result of slow intestinal passage, and by reducing the transit time helps for constipation. In addition, many carbohydrates also increase the water content of the intestines and acids produce increased intestinal motility, which also reduces the transit time. The best effects are obtained by carbohydrate mixtures, which include dietary fibres. It is based on a change in metabolism (more carbohydrates) and not on the stimulation of specific bacteria.

- **Reduce intestinal pH**
  This effect is also due to a change in metabolism from protein fermentation (resulting in ammonia and high pH) to more carbohydrate fermentation (resulting in acid). Several intestinal diseases, such as Crohn’s disease and IBS are characterised by a high pH. Reducing the pH reduces the symptoms of the disease, which is beneficial to the patient. A low intestinal pH also increases bowel movement and may protect against pathogenic bacteria. The best effect is obtained by rapidly fermenting carbohydrate mixtures. This effect is also based on a change in metabolism (more carbohydrates) and not on the stimulation of specific bacteria.

- **Restore intestinal bacterial balance**
  Prebiotics may restore intestinal balance after a disturbance due to antibiotics or other medicine, diarrhoea or stress. By selectively stimulating a certain group of bacteria the balance can be restored. This may be possible for different bacterial groups, and can either be by direct stimulation (the selected bacteria grow on the prebiotic) or by indirect stimulation (the bacteria create a favourable environment for other bacteria). Both selective stimulation and changes in metabolism therefore play a role.

- **Effect blood cholesterol level**
  A beneficial effect has been claimed for some oligosaccharides, but it has not been proven.

- **Reduced risk of colorectal cancer**
  This effect has also not been proven. Here are many indications that the products formed by protein fermentation may increase the risk of colorectal cancer. By reducing protein fermentation, the risk will therefore be reduced. In addition, the products from carbohydrate fermentation may reduce the risk of colorectal cancer. The best risk-lowering effect in this case may be due to changes in metabolism, and not by changes in specific groups of bacteria.

- **Effects on the immune system**
  Prebiotics themselves have no effect on the immune system. However, by changing the intestinal flora, the immune system may be influenced. The stimulation may be beneficial (the immune system is activated against possible pathogens) or non-beneficial (allergic reactions are increased due to the stimulation).

- **Better intestinal microflora in infants**
  The intestinal microflora of children under 4 years is unstable and many oral pathogens may disturb the microflora. Substances that stabilise the flora can therefore be considered prebiotics. Several studies have shown that commercial oligosaccharides have a stabilising effect, which is due to a combination of changing the flora and reducing the pH.

**Prebiotic products**

Most commercial prebiotics are oligosaccharides and dietary fibres. Selected non-digestible oligosaccharides will increase the carbohydrate fermentation and therefore be effective for most of the claims made for these products. However, not all oligosaccharides will have a beneficial effect.

There are currently no oligosaccharides that selectively stimulate a certain group of bacteria. It has been claimed that several oligosaccharides selectively stimulate bifidobacteria and lactic acid bacteria, but in vivo and in vitro experiments have shown that all commercial oligosaccharides are fermented by a large number of bacterial species in the intestine. All commercial oligosaccharides therefore act by changing the metabolism, not by selectively stimulating a certain bacterial group.

**Dosage**

According to Roberfroid,⁵ the daily dose of a prebiotic is not a determinant of the prebiotic effect, which is mainly influenced by the number of bifidobacteria per gram in faeces before supplementation of the diet with the prebiotic begins. The ingested prebiotic stimulates the whole indigenous population of bifidobacteria to growth, and the larger that population, the larger is the number of new bacterial cells appearing in faeces. The “dose argument” is thus not supported by the scientific data. Roberfroid proposes a prebiotic index, defined as “the increase in the absolute number of bifidobacteria expressed divided by the daily dose of prebiotic ingested.”⁶
A normal diet provides between 5 and 10 gram of non-digestible carbohydrates per day.11 This includes oligosaccharides from vegetable origin (mainly fructo-oligosaccharides). Effective doses of oligosaccharides are in the range of 5 to 10 gram per day for healthy adults.11 Doses below 5 gram are generally considered ineffective. A daily dose of 5 to 8 g/day of fructo-oligosaccharides (FOS) or galacto-oligosaccharides (GOS) is considered to have a prebiotic effect in adults.

Traditional dietary sources of prebiotics include soybeans, inulin sources (for example, Jerusalem artichoke and chicory root), raw oats, unrefined wheat, unrefined barley, asparagus, garlic and onion. Recently, the prebiotic potential of almonds, has also been publicised.12 However, it will take a large quantity of these foods for their active oligosaccharides to exert a useful prebiotic effect. Some of the oligosaccharides that naturally occur in breast milk are believed to play an important role in the development of a healthy immune system in infants.

Examples of commercial oligosaccharides that are increasingly added to foods for their health benefits (food fortification) are:

- Oligofructose
- Galacto-oligosaccharides
- Breast milk oligosaccharides

FOS is found in foods such as bananas, wheat, honey, onions and tomatoes. These foods are, however, not prebiotics but they contain prebiotics to a greater or lesser extent. Inulin is a natural food fibre found in more than 30 000 plants, including fruits and vegetables.13 Studies have reported that consuming inulin in divided doses of 8 to 10 g per day has the potential to significantly improve health.13

Safety and side effects

Since the commercial oligosaccharides increase carbohydrate fermentation, they also increase gas formation. The main side effects are therefore flatulence and bloating. These effects may be present with the intake of 5 grams in sensitive persons, but may be absent with the intake of 40 grams in tolerant persons. The side effects are therefore due to the type of oligosaccharide and the tolerance of the host.

EVIDENCE FOR PROBIOTICS AND PREBIOTICS AND RECOMMENDATIONS

Table 1 provides a summary of the strength of evidence for the improvement of body functions by probiotics and prebiotics as summarised by Roberfroid.14

The following recommendations are made by the Nutrition Information Centre of the University of Stellenbosch regarding the use of probiotics and prebiotics15:

- Probiotic supplements should be considered in antibiotic treatment to prevent antibiotic associated diarrhoea and further complications, which have cost implications in patient care.
- Infants and young children in daycare centres, who are at greater risk for frequent gastrointestinal infections, might benefit from probiotic supplementation. The available supplemented follow-on milk formulas can be a convenient method to include probiotics in their diets. Bifidobacterium bifidum, given in conjunction with Streptococcus thermophilius in standard milk formula, has been shown to reduce the incidence of diarrhoea caused by the rotavirus.
- Fermented dairy products are a convenient, culturally acceptable and safe method to increase probiotic intake. These products are also good sources of other nutrients such as calcium and protein.
- Good dietary sources of prebiotics include leeks, artichokes, garlic, onions, wheat and wheat products, asparagus and bananas. Prebiotic supplements, if necessary, should not be consumed in excess of the recommended amounts because of their known and unpleasant side effects.

CONCLUSION

Probiotics and prebiotics share a unique role in human nutrition, largely centering on manipulation of the number or activity of the bacteria that colonise the body. Probiotics are live microorganisms contained in food, and they remain intact throughout the digestive process. Since they do not stimulate metabolic activity they provide a different set of benefits than prebiotics. Prebiotics trigger the growth of bacteria having favourable effects on the intestinal flora.

In general, the benefits of the regular consumption of probiotics or prebiotics include enhanced immune function, improved colonic integrity, decreased incidence and duration of intestinal infections, down-regulated allergic response, and improved digestion and elimination. Research has shown that probiotics and prebiotics may be useful in achieving these and other positive effects, provided that proper strain, product selection, and dosing guidelines of commercial products are followed. More research is needed to confirm the effectiveness of these products. There is also a need to consolidate the basic and applied research on probiotics and prebiotics into useful tools for health and nutrition professionals.

<table>
<thead>
<tr>
<th>Functional effects</th>
<th>Strength of evidence*</th>
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<tbody>
<tr>
<td>Lactose intolerance</td>
<td>Strong</td>
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<tr>
<td>Immunostimulation</td>
<td>Preliminary</td>
</tr>
<tr>
<td>Faecal mutagenesis</td>
<td>Preliminary</td>
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<tr>
<td>Hypocholesterolaemia</td>
<td>No effect</td>
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<tr>
<td>Hypolipidaemia</td>
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<tr>
<td>Colonic flora</td>
<td>Preliminary</td>
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<tr>
<td>Calcium bioavailability</td>
<td>Unknown</td>
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</tbody>
</table>

* The classification of evidence is the result of the evaluation, by Roberfroid, of the scientific data reviewed in this article.14 It also relies on previous evaluations of the properties of probiotics and prebiotics quoted in his article.14

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References