# Probiotics, with special emphasis on their role in the management of irritable bowel syndrome

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**Keywords:** probiotics, irritable bowel syndrome, IBS

## Abstract

Probiotics are live microorganisms, and when administered in adequate amounts, bestow beneficial effects on the host. The therapeutic and preventative application of probiotics in several disorders is receiving increasing attention, and this is especially true when gastrointestinal microbiota is thought to be involved in their pathogenesis, as in irritable bowel syndrome (IBS). Given the increasingly widespread use of probiotics, a thorough understanding of their risks and benefits is important. The purpose of this review is to update healthcare professionals on current probiotic information, and provide an overview of probiotic treatment approaches, with special emphasis on IBS.

Ⓟ **Peer reviewed. (Submitted: 2010-12-19, Accepted: 2011-05-15). © SAJCN** **S Afr J Clin Nutr 2011;24(2):63-73**

## Introduction

The scientific literature on probiotics commences with the Russian Nobel laureate, Elie Metchnikoff, who suggested that ingestion of lactic acid-producing bacteria, such as that found in yoghurt, was a protective factor, enhancing longevity and potentially beneficial in treating digestive diseases.[1] Probiotic research is a relatively young, but rapidly expanding field. By mid-2010, there were 7 180 publications in the PubMed database, of which 26% (1 863) were reviews. By comparison, the search term "antibiotics" yielded 509 728 publications, of which 8.5% (43 515) were reviews. Therefore, it can be concluded that the field of probiotics does not suffer from too few reviews, but rather from insufficient original research.[2]

The term "probiotic" is derived from the Latin "pro" (meaning for) and the Greek "bios" (meaning life). The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) of the United Nations have defined probiotics as "live microorganisms, that when administered in adequate amounts, have beneficial effects for the host."[3] Some definitions have also changed the word "administered" to "consumed."[4] Although this is the acknowledged scientific definition, there is no legal definition for the term "probiotic". Unfortunately, the definition is often used by industry, even when the minimum scientific criteria for probiotics are not met.[5]

## Colonisation and diversity of gut microbiota

The gut microbiota comprises a complex ecological system, consisting of at least 500 different bacterial species, yeasts, protozoa, viruses and fungi, and this microbiota plays an integral part in the digestive and metabolic processes that are essential for general well-being.[6] The bacterial microbiota is the most reported and researched.[7] Inherent colonisation of microbiota occurs at birth with organisms that inhabit the skin, oral cavity, vagina and gastrointestinal tract.[8] This colonisation is influenced by the route of delivery (vaginal vs. Caesarean section), gestational age (prematurity vs. full term), and use of antibiotics in the perinatal period, especially in the neonatal intensive care unit setting. For example, vaginal births are associated with a greater intestinal colonisation by bifidobacteria, but not lactobacilli, compared to Caesarean section deliveries.[9] In comparison, Caesarean section births are associated with increased colonisation by *Klebsiella, Enterobacter* and *Clostridium*. These organisms are common in hospital settings.[10] Early feeding practices also influence microbial colonisation. Breastfed infants have less intestinal permeability, compared to formula-fed infants.[11] Formula feeding is associated with an increased presence of both *Clostridium* and *Bacteroides* in the intestinal tract.[10] Poor microbial variety in infancy seems to be related to a greater risk of atopic disease later in childhood.[12] The initial acquisition of intestinal microbiota plays a key role in the development of immune processes and protection against pathogens. A reduction in the variety of the gut microbiome often occurs in a number of conditions that are potentially related to dysbiosis, including inflammatory bowel disease and chronic diarrhoea.[13]

## Dysbiosis

Disturbances in the sensitive balance between the host and the intestinal microbiota (dysbiosis) can lead to changes in the mucosal immune system that range from obvious inflammation, as seen in Crohn's disease, to low-grade inflammation, evidenced in a subset

of irritable bowel syndrome (IBS) patients.[14] Research verifies the significance of the colonising microbiota in determining the equilibrium of proinflammatory to regulatory cells in the gut.[15,16] Variations in the intestinal microbiota balance have been associated with obesity,[17,18] Crohn's disease, ulcerative colitis and coeliac disease.[19-21] These conditions have been linked to less species variation and abnormal immune responses to intestinal bacteria.

The faecal microbiota of IBS patients differs significantly from that of healthy subjects.[22] Balsari studied stool samples of 20 IBS patients and noted a decrease in coliforms, lactobacilli and bifidobacteria, compared to that in healthy individuals.[23] Similar results have been found in other studies.[24,25] A further study that divided IBS patients according to subtype, showed that diarrhoea-predominant IBS (D-IBS) patients had lower numbers of lactobacilli, while constipation-predominant IBS (C-IBS) patients had increased numbers of *Veillonella* spp.[26] Despite the fact that dysbiosis has progressively become better documented in various intestinal diseases,[27,28] it remains to be seen whether this is, in fact, a cause-and-effect relationship.

## Probiotic organisms

In the stomach, small numbers of probiotic organisms [0-$10^3$ colony-forming units (CFU) per gram] are found, consisting mainly of lactobacilli, streptococci, staphylococci, enterobacteriacae and yeasts. These small numbers are primarily because of the low intragastric pH. Subsequently, there is an increase from 0-$10^5$ CFU per g in the duodenum, to $10^8$ CFU per gram in the ileum, and $10^{10}$-$10^{12}$ CFU per gram in the colon because of the neutral intestinal pH, a slower transit time and the availability of nutrients. In the colon, > 99% of the microorganisms are strictly anaerobic, such as bifidobacteria, *Bacteroides* spp., *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp. and peptostreptococci.[6,29] As part of the normal microflora, *Lactobacillus* and *Bifidobacterium* genera vary from $10^6$-$10^{10}$ in different individuals. For probiotic bacteria to be effective, they need to transit through the gastrointestinal tract that contains gastric juices, bile and pancreatic juice. Adhesion to the intestinal mucosa is considered to be a prerequisite for interaction with the immune system.[30]

## Nomenclature of probiotics

Probiotics need to be classified according to their genus (e.g. *Lactobacillus*), species (e.g. *rhamnosus*) and strain (e.g. GG). This level of specificity in describing a probiotic is important, as effects can be and are, strain-specific. For example, *L. plantarum* 299v may have a different mechanism of action and effect to *L. plantarum* MF1298. It is important to look for probiotics that are supported by strain-specific research.[4,5]

## Clinical application of probiotics

Probiotic usage is likely to attract the interest of two groups of people: healthy people who are interested in probiotics to keep them that way, and people with specific health concerns, about which evidence of probiotic efficacy is available. The second group is motivated and has a measurable outcome: symptom improvement.[5] Several functions of the gut microbiota may be influenced by probiotics beneficially. Probiotics have been studied in a number of diseases, especially when intestinal bacteria are thought to be involved in their pathogenesis.[2] The main study areas and application of probiotics are a direct result of their mechanisms of action. The clinical benefits of probiotic usage include those related to improvement of the gut epithelial or mucosal layer, strengthening of the immune response, and prevention of diseases later in life, e.g. eczema, atopic eczema, allergic rhinitis and cancer. The consensus recommendations for the correct clinical use of probiotics in various scenarios, as well as examples of probiotic strains and their associated published benefits, are tabulated in Table I.

**Table I:** Examples of probiotic strains and their associated published benefits[5,31]

| Indication | Genus, species, strain |
|---|---|
| Infant diarrhoea | *Lactobacillus rhamnosus* GG<br>*L. casei* DN-114001<br>*L. reuteri* |
| Inflammatory bowel conditions (primary evidence in pouchitis) | Multistrain probiotic containing three *Bifidobacterium* strains, four *lactobacillus* strains, and *Streptococcus thermophilus* (VSL#3)<br>*Escherichia coli* Nissle |
| Antibiotic-associated diarrhoea, (*Clostridium difficile)* | *Saccharomyces boulardii*<br>*L. rhamnosus* GG<br>*L. casei* DN-114011<br>*L. acidophilus* CL1285 plus *L. casei*<br>*L. bulgaricus* |
| Gut transit time | *Bifidobacterium animalis* DN-173 010 |
| Keeping healthy | *L. reuteri* ATCC 55730<br>*L. casei* DN-114001 |
| Atopic dermatitis | *L. rhamnosus* GG<br>*B. lactis* |
| Lactose intolerance | Most strains<br>*L. bulgaricus* and/or *S. thermophilus* |
| Colic in infants | *L. reuteri* ATCC 55730 |
| Immune support | *B. lactis* HN019<br>*B. lactis* Bb12<br>*L. casei* DN-114001<br>*L. rhamnosus* GG<br>*L. plantarum*<br>*L. acidophilus*<br>*B. lactis*<br>*L. johnsonii* |
| Vaginal applications | *L. rhamnosus* GR1 plus *L. reuteri* RC14<br>*L. acidophilus* |
| Irritable bowel syndrome | *L. plantarum* 299v<br>*B. infantis* 35264 |

## Mechanism of action

The microbiota performs many significant functions for the host. These include the production of vitamins, degradation of bile acids, conversion of (pro)carcinogenic substances and digestion of nutrients.[30] Anaerobic bacteria are of benefit to the host by performing metabolic functions, such as fermentation, providing

short-chain fatty acids (SCFAs), producing vitamins, adding to the trophic action of the epithelium, and aiding in the development of the immune system.[32] Saccharolytic fermentation of unabsorbed and indigestible carbohydrates by intestinal bacteria occurs mainly in the colon. This is essential, as SCFAs (i.e. acetate, propionate and butyrate) are produced.[33] Butyrate, a major energy source for intestinal epithelial cells, affects cell proliferation and differentiation, increases mucus secretion and decreases inflammation.[34] Proteolytic bacterial fermentation usually takes place in the more distal colon, where carbohydrates are no longer available, and results in the production of toxic compounds like ammonia, phenols, cresols and paracresols.[35]

The exact mechanism by which probiotics exert their favourable effect has not been fully elucidated. Different strains of organisms have very diverse and specialised metabolic activity. Proposed mechanisms include those responsible for the manipulation and regulation of the intestinal microbial balance, those that protect the mucosa against pathogenic invasion (adhesion and translocation), and those that modulate an appropriate immune response.[36,37]

In the gastrointestinal tract, probiotics can aid with the following:

- The secretion of antibacterial substances, e.g. bacteriocins and acids, which result in a reduction in the luminal pH, with decreased growth ability of the pathogens.
- The production of intestinal mucin, which influences bacterial colonisation, and human β-defensins (peptides with antibacterial properties), which affect mucosal adherence, and inhibit pathogenic bacteria adherence.
- The expression of receptors (toll-like receptors 2 and 4), that sense bacterial components and trigger an appropriate immune response through the release of protective cytokines (IL-6).
- An increased release of secretary IgA that can protect the microflora against bacterial attachment.
- The regulation of epithelial cell apoptosis.
- The acidification of the colon by nutrient fermentation.[36-39]

The immune response is modulated by controlling levels of circulating inflammatory cytokines (NF-κB and TGF-β), restoring the imbalance between Th1 and Th2 responses, and increasing the expression of heat-shock proteins which are essential for the maintenance of the epithelial barrier function. Through an appropriate pro- and anti-inflammatory response, the immune function is regulated suitably for each condition in a strain-specific manner.[36,37,39,40] Certain probiotic strains also exhibit anticarcinogenic effects by increasing faecal mutagen excretion, and inhibiting the conversion of precarcinogens to carcinogens by reducing the enzyme β-glucuronidase.[39] Indirectly, this anticarcinogenic effect is seen by an increased immune response (as discussed previously).

## Dose

Dose levels of probiotics should be based on levels that are found to be efficacious in human studies.[41] The necessary amount and duration of use depends on the specific strain and the health condition being studied. Studies demonstrating beneficial results at levels < 100 million ($10^8$) CFU/day are uncommon in published literature. For example, the efficacy of *Bifidobacterium infantis* 35264 has been documented at $10^8$ CFU/day,[42] whereas the recommended dose of VSL#3 is 1.8 x $10^{12}$CFU/day (a four-log-cycle difference).[43] This disparity underlines the inaccuracy in making general dose recommendations.[5]

## Single- vs. multiple-strain vs. multi-species products

The value of using a single-strain probiotic over a combination of probiotic strains or species is a topic of ongoing debate. Microorganisms may behave differently when administered in combinations, compared to in isolation. The use of combinations or cocktails concerns some investigators because attempts to classify the mechanism of action are then difficult to define.[13] Within a product containing eight to 20 strains or even more, it may be fair to say that a few dominant strains will exert a greater effect, or discount the effects of others. Uncertainty exists as to whether the correct strain will be effective at the right time, and in the correct location. Each strain within a probiotic cocktail has been selected for a specific characteristic, such as the induction of a certain immune parameter. However, the same strain may have another immune modulating parameter that is not desired in the concerned application. These disadvantages do not mean that cocktails are undesirable, the so-called multistrain (containing more strains of the same genera, e.g. several *Lactobacillus* spp.) and multi-species (containing strains of different genera, e.g. lactobacilli, bifidobacteria, streptococci) may be more advantageous over mono-strain probiotics, particularly in people who are interested in probiotics to keep them healthy, and not aid management of a specific health concern.

Probiotic preparations can be found in the form of powders, tablets, capsules, pastes, sprays or fermented foods, such as yoghurts, buttermilk, sour poi (a starchy paste made from the corm of taro plants) and miso (fermented soybean paste). The method of delivery, e.g. yoghurt vs. milk, may have an impact on the viability of the bacterial colonies. The probiotic product needs to have a good taste and smell, and an acceptable shelf-life.[30]

## Storage

Environmental conditions, such as moisture, oxygen, acid and heat, affect susceptible probiotic strains in different ways. Micro-encapsulation or coating technologies (e.g. enteric coating) have been developed by manufacturers to ensure that a live probiotic, in the correct quantities, is delivered on ingestion. However, once a probiotic package is opened, these barriers are compromised. Generally microbes survive better at lower temperatures, but properly stabilised non-refrigerated products can retain potency at room temperature. Refrigerated products are also not necessarily of a better quality than non-refrigerated probiotics. Products need to be chosen from reputable companies that are labelled to reflect viability "through the end of shelf-life" and not "at time of manufacture". Some products contain dried probiotics, and if these bacteria have been dried and stabilised properly, they remain alive,

although dormant, and start to grow again after they reach the moist environment inside the body.[5] By definition, the term "probiotic" can never be used to describe products comprising dead bacteria primarily, even though in some cases, dead bacteria or bacterial cell products have been shown to have physiological effects.[44] For example, the administration of heat-killed *Enterococcus faecalis* to healthy dogs increased neutrophil phagocytes. These dead cells exert an anti-inflammatory response in the gastrointestinal tract. The variable amounts of dead cells found in probiotic products might contribute to the variation in response that is often seen with probiotic cultures.[44]

## Adverse effects and safety issues

Although probiotics are generally considered to be safe, some research has revealed that probiotics may be inappropriate in specific populations. Probiotics have the potential to result in bacterial translocation across the gastrointestinal mucosa, and to transfer antibiotic resistance to other microorganisms. For these and other reasons, some adverse events have been linked to the use of probiotics in certain clinical settings.

Patients receiving nutritional support have been studied extensively with regard to the use of probiotics in various scenarios, e.g. antibiotic-associated diarrhoea and *Clostridium difficile*-associated diarrhoea. Conditions where gastric pH is increased through medications, or where the stomach is bypassed, i.e. jejunal feeding, result in the increased survival of probiotics in the small bowel. Patients with a central venous catheter (CVC) are also a known risk category.

In one study, the efficacy of a multi-species probiotic was tested in patients with severe pancreatitis in an ICU setting. A significantly increased risk of death was reported in the group receiving the probiotic. The patients who died had evidence of necrotising jejunitis. In this study, a multi-species probiotic of various strains, previously not tested, was administered nasojejunally.[45] This finding raised the possibility of an impaired splanchnic circulation that was further compromised by direct delivery of a high concentration of microorganisms into the proximal intestine. To date, this is the only study to associate probiotic use with increased risk of death in a clinical setting. However, Oláh et al did show that early nasojejunal feeding with a symbiotic preparation may prevent organ dysfunction in the late phase of severe acute pancreatitis, highlighting once again how much research still needs to be carried out in this area.[46]

A recent systematic review evaluated the safety of probiotic administration to patients receiving nutritional support (either enteral or parenteral nutrition).[47] Bacteraemia (n = 5), fungaemia (n = 27) and endocarditis (n = 2) were reported, and the causative strains were *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. The risk factors identified for these adverse events were patients receiving antibiotics with a CVC in situ, those at increased risk of bacterial translocation (i.e. with colitis or sepsis), and those with immune suppression [sepsis, human immunodeficiency virus (HIV) and necrotising enterocolitis]. It is argued that the two strains identified are the most commonly used in an ICU setting, and thus the reason for being cited. Similarly, the identified risk factors are general factors that are prevalent in most ICU patients, i.e. patients with a CVC and those receiving antibiotics. This systematic review evaluated studies published between 1996-2009, and only identified 32 cases of adverse events out of a total of 4 131 patients receiving probiotics.

As a result of the reported side-effects, the recommendations for the use of probiotics in various clinical settings are unclear. According to some, caution must be exercised when prescribing probiotics in newborns, immunocompromised patients, patients with pancreatitis, those with short-bowel syndrome, with a CVC in situ, and those with severe underlying illness.[4] Others propose classifying the risk factors responsible for probiotic sepsis into major and minor categories. A major risk factor includes immunocompromised patients. Minor risk factors include a CVC, jejunal administration of probiotics, impaired intestinal epithelial barrier function, cardiac vascular disease *(Lactobacillus* only), and administration of a broad-spectrum antibiotic to which a probiotic is resistant.[48] Finally, some advocate that it is not contraindicated to prescribe probiotics to patients receiving various forms of nutrition support, or those that are immunocompromised, provided that it is done under proper medical supervision and with good monitoring systems in place.[31,47]

## Irritable bowel syndrome

The definition of IBS, according to the Rome III criteria, is that of a chronic disorder characterised by abdominal pain or discomfort associated with disordered defecation, either C-IBS, D-IBS, or mixed and alternating symptoms of constipation and diarrhoea.[49] The patient group is heterogeneous. It is estimated that IBS affects 3-25% of the general population.[50] The prevalence of IBS in South Africa is unknown. However, the progressive Westernisation of diets and lifestyles of less privileged populations is likely to be associated with an increased incidence of bowel disease and IBS. IBS patients can account for up to 30-50% of gastroenterology clinic visits.[50] Various factors have been linked to the pathophysiology of IBS. These include altered bowel motility, enhanced visceral sensitivity, neurotransmitter imbalances, low-grade inflammation of the gastrointestinal mucosa, altered microflora and increased proinflammatory cytokine secretion.[40,51-53] Elevated levels of cytokines IL-6, IL-6R, IL-1$\beta$ and TNF-$\alpha$,[54,55] and a lower IL-10/IL-12 ratio,[56] have been reported in IBS patients vs. controls.

There is no single curative treatment, and therapy is aimed at reducing the symptoms, often with very little success.[50] Pharmacological treatment comprises the use of bulking agents, antispasmodics, dopamine antagonists and antidepressants. The handful of therapeutic agents that were previously useful in the management of global IBS symptoms have either been removed, or limited, due to adverse side-effects.[57] Current treatment aims at strengthening or improving gastrointestinal epithelial function, and

improving the host's immune ability. This has led to numerous clinical trials investigating the therapeutic benefit of probiotics in IBS.

## Clinical trials involving probiotics and irritable bowel syndrome

Many of the clinical trials on probiotics and IBS have important weaknesses in trial design, study execution and data analysis. These weaknesses include not using the intention-to-treat group for analysis, involving only a specific group (e.g. C-IBS), while others have included both C-IBS and D-IBS, not stipulating whether C-IBS or D-IBS patients are being used, and using a crossover design where the treatment may "wash over" into the non-treatment period. There is a wide variety in dosing regimens, species used, and clinical end-points in probiotic or IBS clinical trials. Guidelines have been developed for clinical trials involving functional gastrointestinal disorders (including IBS).[58] Recently, there have been two systematic reviews[40,59] and four meta-analyses, one with particular emphasis on *S. boulardii*.[50,60-62]

Twenty-eight double-blind, placebo-controlled, randomised trials were identified for the purposes of this review. Only those trials where the strain of the probiotic was clearly identified were used, regardless of type, dose and duration of treatment. The probiotics varied from one to multiple strains, and no symbiotic preparations were included.[63,64] In the clinical trials, there had to be clear primary end-points. Single-blinded studies,[65,66] those not using a control,[63] and non-randomised trials[67] were excluded. To date, there have been two clinical trials that have focused on children aged six to 20 years[68] and six to 16 years.[69] However, in this review, only those

**Table II:** Clinical trials with probiotic use in IBS

| Author | n | Probiotic preparation | Treatment duration | Results |
|---|---|---|---|---|
| O'Sullivan and O'Morain[70] (2000) | 24 | *Lactobacillus casei* GG | 20 weeks | No significant differences between the two groups. |
| Nobaek and Johansson[71] (2000) | 60 | *L. plantarum* 299v = DSM 9843 | 4 weeks | Reduction in flatulence and pain. |
| Niedzielin and Kordecki[72] (2001) | 40 | *L. plantarum* 299v | 4 weeks | Pain resolution and improvement in [a]GSS. |
| Sen and Mullan[73] (2002) | 12 | *L. plantarum* 299v | 4 weeks | No significant difference between the two groups. |
| Kim et al[74] (2003) | 25 | VSL#3 (*Bifidobacterium longum, B. infantis, B. breve, L. acidophilus, L. plantarum, L. casei, L. bulgaricus, Streptococcus salivarius* spp. *thermophilus*) | 8 weeks | Improvement in abdominal bloating, but no significant difference between the two groups. |
| Kim et al[75] (2005) | 48 | VSL#3 | 4-8 weeks | Significant reduction in flatulence. |
| Saggioro[76] (2004) | 70 | *L. plantarum* LP01 and *B. breve* BR03 or *L. plantarum* LP01 and *L. acidophilus* LA02 or placebo | 4 weeks | Significant decrease in GSS and abdominal pain with probiotic combinations, compared to placebo. |
| Kajander et al[77] (2005) | 103 | *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, *Propionibacterium freudenreichii* spp. *shermanii* JS | 6 months | Significant reduction in GSS (abdominal pain, distension, flatulence, and borborygmi). |
| Lyra et al[78] (2010) | 42 | *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, *Propionibacterium freudenreichii* spp. *shermanii* JS | 6 months | Significant decrease in stool *Bifidobacteria* spp. in probiotic group. |
| Kajander and Kroglus-Kurikka[79] (2008) | 86 | *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. animalis* spp. *lactis* Bb12, *P. freudenreichii* spp. *shermanii* JS | 5 months | Significant reduction in GSS. |
| Niv et al[80] (2005) | 54 | *L. reuteri* ATCC 55730 | 6 months | No significant differences between groups. Trend towards improvement in constipation and flatulence in treatment group. |
| O'Mahony et al[56] (2005) | 80 | *L. salivarius* UCC4331 or *B. infantis* 35624 | 8 weeks | *B. infantis* reduced GSS, while *L. salivarius* reduced abdominal pain and discomfort, bloating and straining. |
| Whorwell et al[42] (2006) | 362 | *B. infantis* 35624 in three different doses | 4 weeks | With $10^8$ CFU, significant improvement in abdominal pain, bloating, bowel movement satisfaction, straining, passage of gas and evacuation. |

| Author | n | Probiotic preparation | Treatment duration | Results |
|---|---|---|---|---|
| Guyonnet et al[81] (2007) | 274 | *B. animalis* DN-173 010, *S. thermophilus*, *L. bulgaricus* | 6 weeks | Significant improvement in quality of life, bloating and stool frequency in constipated participants. |
| Drouault-Holowacz et al[82] (2008) | 116 | *B. longum* LA101, *L. acid* LA102, *L. lactis* LA103, *S. thermophilus* LA104 | 4 weeks | No significant difference in GSS. |
| Agrawal et al[83] (2008) | 41 | *B. lactis* DN-173 010 | 4 weeks | Significant improvements in objectively measured abdominal girth, gastrointestinal transit time. Reduced symptoms. |
| Sinn et al[84] (2008) | 40 | *L. acidophilus* SDC 2012, 2013 | 4 weeks | Significant improvement in treatment group with abdominal pain, pain while straining to pass a stool, bowel habit satisfaction and sense of incomplete evacuation. |
| Enck et al[85] (2008) | 297 | *Escherichia coli* DSM 17252, *Enterococcus faecalis* DSM 16440 | 8 weeks | Significant reduction in GSS and pain. |
| Enck et al[86] (2009) | 298 | *E. coli* DSM 17252 | 8 weeks | Significant reduction in GSS and pain. |
| Dolin[87] (2009) | 61 | *Bacillus coagulans* GBI-30, 6086 | 8 weeks | Significant reduction in number of bowel movements in D-IBS participants. |
| Hun[88] (2009) | 44 | *Bacillus coagulans* GBI-30, 6086 | 8 weeks | Significant improvement from baseline abdominal pain and bloating to end-point scores. |
| Williams et al[89] (2009) | 52 | *L. acidophilus* CUL60, CUL21, *B. lactis* CUL34, *B. bifidum* CUL20 | 8 weeks | Significant improvement in GSS, quality of life, days with pain and bowel habit satisfaction. |
| Hong et al[90] (2009) | 70 | *B. bifidum* BGN4, *B. lactis* AD011, *L. acidophilus* AD031, *L. casei* IBS041 | 8 weeks | Significant reduction in abdominal pain. |
| Ligaarden et al[91] (2010) | 16 | *L. plantarum* MF 1298 | 2 x 3 weeks | Significantly higher symptomatic relief satisfaction while on placebo. |
| Simrén et al[92] (2010) | 74 | *L. paracasei* ssp. *paracasei* F19, *L. acidophilus* La5, *B. lactis* Bb12 | 8 weeks | Significant improvement in GSS in both groups. |
| Søndergaard et al[93] (2011) | 64 | *L. paracasei* ssp. *paracasei* F19, *L. acidophilus* La5, *B. lactis* Bb12 | 8 weeks | No significant improvement in abdominal pain. |
| Guglielmetti et al[94] (2011) | 122 | *B. bifidum* MIMBb75 | 4 weeks | Significant improvement in GSS and quality of life in probiotic group. |
| Choi et al[95] (2011) | 67 | *S. boulardii* | 4 weeks | Significant improvement in quality of life, but not symptoms. |

a = global symptom score

studies involving adults are presented. This review covers the important clinical studies over the past ten years. An overview of studies carried out on the use of probiotics in IBS is given in Table II, in which the main benefits (if found) are given in the results column.

In the following discussion, the various strains are not discussed individually. Rather, focus is placed on the strains that have provided positive results when treating IBS.

### *L. plantarum* 299v

There are three small studies in which a liquid form of *L. plantarum* 299v was used in the treatment of IBS. Two studies showed some benefit over placebo. One showed improved flatulence,[71] and the other a reduction in abdominal pain.[72] The third trial showed no significant benefit, but it was underpowered.[73] There were differences in enrolled populations, study designs, outcomes and statistical analyses in these three trials. Tolerability and adverse events were poorly recorded. These smaller trials, although showing promising results, have never been followed up with larger, multi-centre clinical studies.

### *L. reuteri* ATCC 55730

A single trial of 54 IBS participants using *L. reuteri* ATCC 55730 over a six-month period, showed an improved global symptom score (GSS) from baseline until the end of the trial in both groups. There was a large placebo effect, and therefore failure in showing benefit over the controls.[80] The study group was small, and was further reduced due to non-compliance during the trial. Compliance and adverse events were well reported.

### *L. salivarius* UCC4331

A single study, carried out by O'Mahony et al, used *L. salivarius* UCC4331 as part of a three-arm study evaluating the efficacy of *L. salivarius* UCC4331 and *B. infantis* 35624 compared to placebo for the treatment of IBS.[56] After a four-week run-in period, 50 participants received either *L. salivarius* or placebo for eight

weeks, followed by a four week washout period. At the end of the trial, a significant reduction in abdominal pain and discomfort was seen at weeks two and seven with *L. salivarius* UCC4331, but this effect was not sustained. This was a well-designed study, and limited only by a lack of statistical power.

***B. infantis* 35624**

In the previously mentioned trial of O'Mahony et al,[56] 77 patients with IBS were randomly assigned *B. infantis, L. salivarius* or placebo. The *B. infantis* (not *L. salivarius*) was shown to reduce pain, bloating and bowel satisfaction scores. The benefit of *B. infantis* has been replicated in a large multicentred research trial in 362 female patients with IBS. Participants were randomised to receive either $10^6$, $10^8$ or $10^{10}$ CFU/day, or placebo.[42] The group taking $10^8$ CFU/day scored significantly better than the placebo in all symptom groups, including global assessment of IBS relief as the primary end-point. The bacteria in the group taking $10^{10}$ CFU/day were found to be nonviable later, perhaps explaining the lack of efficacy.

***B. animalis* subsp. *lactis***

(Sometimes commercially known as *B. lactis* DN-173 010*)*

Several well-designed, large multicentred trials of the use of *B. animalis* subsp. *lactis* in IBS have failed to demonstrate benefit, again often in part as a result of a high placebo response.[63,81] A French multicentre trial of *B. animalis* subsp. *lactis* in 274 patients with C-IBS in primary care, demonstrated symptomatic relief compared with baseline in its primary end-point, but not over placebo.[81] However, subgroup analysis of patients with fewer than three bowel motions a week (n = 19) at baseline showed a significant increase in stool frequency compared with controls (p-value < 0.001). In a single trial carried out by Agrawal et al,[83] 34 IBS patients were randomised to either receive fermented milk containing *B. animalis* subsp. *lactis* or placebo for a four-week period. Compared with the control product, the test product resulted in a significant change in maximal distension [median difference -39%, 95% CI (-78, –5; p-value = 0.02]. An accelerated orocaecal [-1.2 hours (-2.3, 0); p-value = 0.049], as well as colonic [-12.2 h (9-22.8, -1.6); p-value = 0.026] transit, was observed, and overall symptom severity [-0.5 (-1.0, -0.05): p-value = 0.032] also improved. The probiotic resulted in improvements in objectively measured abdominal girth (distension) and gastrointestinal transit, as well as reduced symptomatology.[83]

***Escherichia coli* DSM 17252**

A primary-care-based, placebo-controlled trial[86] was conducted in 298 patients with IBS, diagnosed by a primary care standard (not Rome criteria[96]) and was defined as "clinical remission" with complete resolution of IBS symptoms.[97] In comparison with the placebo, the treatment arm was reported to have achieved complete remission in 18.4% vs. 4.6% (p-value < 0.0004) of the patients studied. In addition, a 50% decrease in abdominal pain scores was recorded (18.9% vs. 6.7% in the treatment and placebo groups, respectively (p-value = 0.001)). This trial was based on a much earlier trial of *E. coli* DSM 17252 in combination with *Enterococcus faecalis* (DSM 16440), originally published in 1993,[98] and more recently reanalysed[85] by redefining the clinical end-points to give a GSS in accordance with modern guidelines. This reanalysis showed a significantly better response rate, defined by a decrease of 50%, in the treatment arm than the placebo (68.5% vs. 37.8%; p-value < 0.001). Although both these arms failed to use Rome II[96] or the definitions of Manning et al[99] as their inclusion criteria, they were otherwise large and well-designed trials. Data from primary care, rather than secondary care patients, are particularly useful, given that the majority of IBS patients are treated by primary care physicians.

The role of probiotics in gastrointestinal disease, and in particular IBS, has clearly not been determined adequately. Although questions exist on the dosage and viability of probiotic strains, lack of industry standardisation and potential safety issues (with specific regard to immunocompromised or seriously ill patients),[100] substantial clinical evidence of the advantageous use of probiotics over a wide range of clinical conditions exists. As there is currently no curative treatment for IBS, the relief that probiotic usage may provide, no matter how small, may motivate patients and caregivers to utilise them. Continuing research will recognise and characterise existing strains, identify specific outcomes, determine optimal doses needed for certain results, and assess their stability through processing and digestion.[56] The heterogeneity of IBS and very high placebo response (up to 50%) are problems that are associated with clinical trials. Inevitably, the low-quality design of the trials on IBS and probiotics has led to concluding statements such as: "Further studies are needed to determine whether the probiotic under study may offer clinical benefits for IBS".

Future studies should use Rome III guidelines for the appropriate design of functional gastrointestinal trials.[101] These guidelines also include sample size calculation, which should be based on the expected behaviour of the primary outcome measure. A study must have sufficient power to detect the minimal clinically important difference.[102] With these data, clinicians will be better able to guide patients to efficacious and safe probiotics. Probiotics may be a safe and effective solution, and are urgently needed in the treatment and management of IBS.

## Regulatory aspects of probiotics

Testing for the probiotic potential of various microorganisms commences at the preclinical level, and includes animal studies and evaluations of antibiotic resistance, safety and potential efficacy.[103] Many studies, both in animal and human clinical trials, report success in reducing the severity of diseases by the use of a certain probiotic strain, but not by the use of others for the same condition. The need for research to determine the underlying mechanisms of action of specific probiotics will help in determining which specific organism is most likely to benefit a specific disease condition.[13] The specific bacterium should be defined by its genus and species, as well as its

strain level. This is not always adhered to in scientific publications.[104]

It is often incorrectly stated that probiotic products are unregulated. The US Food and Drug Administration has regulatory authority over probiotic products and regulates manufacturers' responsibilities, including the labelling and safety of these products, whether in food, supplement or drug form.[41] In South Africa, permissible statements regarding the health benefits of probiotics are included in the regulations governing labelling and advertising in the Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972; www.doh.gov.za). The South African guidelines and regulations need to be revised regularly to accommodate the results of ongoing scientific research in the field of probiotics.[105]

## Conclusion

Effective treatment of IBS is often masked by its various groupings (C-IBS, D-IBS or post-infectious IBS) and their response to a particular treatment. Much of the published data do not differentiate between the groupings or subgroups, making interpretation of reported results difficult. Effective treatment outcomes are further compounded by variations in indigenous microbiota, as observed in stool microbiota, and possible varying aetiology among patients. Specific probiotic strains may work better in patients with either C-IBS or D-IBS. The strains that have shown good results to date include bifidobacteria, lactobacilli, *E. coli* and mixtures of different bacterial strains. Both *B. infantis* 35624 and *L. plantarum* 299v have demonstrated promising initial results in IBS clinical trials as single composites, but as yet, they have not been studied in combination, and a combination or "cocktail" probiotic of these two strains does not exist. It would be beneficial to assess the effects of these two probiotic strains in the treatment of IBS symptoms.

It is important that probiotic clinical findings are not extrapolated to other clinical settings. Knowledge of the various properties of probiotics will prove to be fundamental in improving patient management. To date, it has been difficult to demonstrate a specific mechanism of action via the intestinal immune system, the enteric nervous system, or otherwise.[106] This knowledge would help to answer the question of whether we have the relevant probiotics to manage IBS.

Probiotics and their benefits are an area of intensive research in various domains. Functional foods, with complex modes of action, may provide an alternative to the pharmacological approach in patients who require lifetime probiotic treatment, and/or who suffer from serious side-effects or drug resistance development. It is important to balance the potential benefits against the harms. Probiotics need to be carefully selected in a strain-specific manner. Thoroughly assessed, probiotic strains will possibly present as alternatives to individuals for whom traditional medical therapies have been unsuccessful, and perhaps, in the future, even serve as a first choice of therapy for some patients.

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