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Research Article

PROBIOTICS: IN SICKNESS AND IN HEALTH

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ABSTRACT

Most medications and supplements including probiotics have both desired clinical outcomes and undesired side effects, which play a role when considering them as a modality for treatment. This review is an update about the advantages and disadvantages associated with the use of probiotics as part of a therapeutic armamentarium in health and in disease. Advantages of probiotics run across multiple organ systems and a wide age spectrum. They promote cardiovascular health, accelerate recovery from diarrhea, decrease risk of necrotizing enterocolitis, limit inflammation in IBD, and promote wound healing. Additionally, probiotics serve in combating chronic diseases for patients with type 2 diabetes and HIV/AIDS. Moreover, probiotics play a significant role in the treatment and/or prevention of cancers, especially those of the colon and bladder. On the other hand, probiotics pose serious threats to immunocompromised, genetically predisposed individuals, children and infants. Using probiotics can lead to bacteremia, fungemia or septicemia. Also, probiotics can cause pneumonia, abdominal abscesses, increase platelet aggregation and trigger antibiotic resistance among others. In conclusion, in vitro and in vivo data from our laboratory and others support the selective evidence based use of probiotics. Actually, a huge number of organisms inhabit the human gut and consequently cause a complex network of the interactions of those organisms with each other and with the host cells, which stresses on the necessity of extra care in the use of probiotics as therapy.

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INTRODUCTION

Historical background

The word 'probiotic' is derived from the Greek word meaning 'for life'. It is considered as the antonym of the term antibiotics and has had different meanings over the years. The term was first introduced in 1953 by Werner Kollath and used by Lilley and Stillwell in 1965 describing it as substances secreted by one microorganism which stimulated the growth of another.¹⁻³

However in 1971, the word probiotics was described differently; as tissue extracts which stimulated microbial growth and in 1974, Parker defined Probiotics as "Organisms and substances which contribute to intestinal microbial balance". This definition related probiotic use to the intestinal

microflora, however, the inclusion of 'substances' gave it a wide connotation which would include antibiotics. In order to improve the definition, Fuller in 1989 redefined probiotics as "Alive microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance".⁴⁻⁵ Ten years later in 1998 Salminen *et al* suggested a more modern definition and defined probiotics as "foods that contain live bacteria which are beneficial to health". At the turn of the millennium, in 2002, Marteau *et al* defined them as "microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being".⁵ However, recently probiotics were broadly defined as live microbial food components that can confer beneficial effects on host's health.¹ In addition, an expert panel commissioned by FAO and WHO defined probiotics, in 2014, as "Live microorganisms which

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when administered in adequate amounts confer a health benefit on the host".¹ However this definition was not acceptable to the European Food Safety Authority (EFSA) due to the fact that it may embed a health claim that is not measurable.² Consequently, the panel identified three categories of probiotics or microbial species used in a food or food supplement; (1) without a specific health claim, (2) with a specific health claim or (3) used as a probiotic drug.²

On the other hand, a thorough look into literature showed that the origin of probiotics precedes recorded history. Actually, Probiotics in fermented milk have been consumed by humans for thousands of years. However, in 1907, Dr. Elie Metchnikoff, a Russian Scientist and Nobel laureate, also regarded as the grandfather of modern probiotics, published "The Prolongation of Life" in which he gave a special attention to exceptionally long-lived Bulgarian peasants who consumed large quantities of sour milk containing *Lactobacillus Bulgaricus*. He specified that four out of every thousand people lived beyond 100 years of age.³ Metchnikoff also wrote, "The dependence of the intestinal microbes on the food intake makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes". He believed that, when consumed, *Lactobacillus Bulgaricus* can positively influence the microflora of the colon by decreasing toxic microbial activities.¹ Again, early in the 20th Century, in 1916, Nissle was the first to recommend reducing risk and managing infections by probiotics; he proved that by transferring human gut microbiota to healthy typhoid carriers resulted in *Salmonella* being cleansed from their intestines. Moreover, foods containing strains of probiotic microbes for human consumption have been marketed in Japan since the 1920s.⁶

In addition, at that time, Henry Tissier as mentioned in Dash *et al* 2015, recommended the administration of bifidobacteria to infants suffering from diarrhea. This was based on an observation that children with diarrhea had in their stools a low number of this bacterium as compared to healthy children. In this case, bifidobacteria would displace the proteolytic bacteria that cause diarrhea.³

METHODOLOGY

PubMed, Medline, Google Scholar, Scopus and UpToDate were searched from 1994 to 2018 for articles with no language restriction. Secondary and hand searches of reference lists, authors, reviews, commentaries, associated diseases, books, and meeting abstracts were also conducted. Search terms for this review article were probiotics AND bacteremia, cancer, lactobacillus, opportunistic infections, microbiota, pregnancy, history, cardiovascular health, digestive system, oral health, animal production, animal health, side effects, inflammatory bowel diseases, irritable bowel syndrome, colorectal cancer. Search strategies were broad-based initially, then narrowed to the disease of interest. Around 150 articles were found with these search terms; 70 of them were compatible with our review. Information on study design, methods, interventions, outcomes, adverse effects, and treatments were extracted from each article.

Available Probiotics

Various bacterial genera and species are considered as potential probiotics; they include those derived from the *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Bacillus*, *Clostridium*, *Bifidobacterium* species, *E. coli* Nissle, *Saccharomyces*, *Propionibacterium* yeasts (e.g. *Saccharomyces cerevisiae* and *Saccharomyces Boulardii*) and filamentous fungi (e.g. *Aspergillus Oryzae*). Most of probiotic bacterial strains are lactic acid producing bacteria which are isolated from traditional fermented products, the gut, the faeces and the breast milk of human subjects. Molecular tools based on 16S ribosomal DNA sequences and PCR techniques have been developed for identifying probiotics strains or species, they include:

1. **Lactobacillus sp.:** *L. acidophilus*, *L. casei*, *L. delbrueckii* ssp., *L. cellobiosus*, *L. curvatus*, *L. fermentum*, *L. lactis*, *L. plantarum*, *L. reuteri*, *L. brevis*
2. **Bifidobacterium sp.:** *B. bifidum*, *B. adolescentis*, *B. animalis*, *B. infantis*, *B. thermophilum*, *B. longum*
Enterococcus sp: *Ent. faecalis*, *Ent. Faecium*
3. **Streptococcus sp:** *S. cremoris*, *S. salivarius*, *S. diacetylactis*, *S. intermedius*³

The ones used commercially in probiotic foods are predominantly bacteria from the genera *Lactobacillus* and *Bifidobacterium*, for two reasons: (1) Both having a long history of safe use and are considered as GRAS (generally recognized as safe), (2) *Lactobacillus* is a dominant inhabitant in the small intestine and *Bifidobacterium* in the large intestine.⁷

On the other hand, it is worth noting that (1) bacterial probiotics have been effective in chickens, pigs and pre-ruminant calves; (2) Yeasts and fungal probiotics (such as *Saccharomyces Cerevisiae* and *Amaferm: Aspergillus Oryzae*) have given better results in adult ruminants (Fuller, 1999); (3) The composition of the probiotic containing one strain of microorganism differs from those containing many strains; (4) Multi-strain probiotics can act in a broad spectrum and be active in different species of host animals; and also (5) Combinations of probiotics strains could increase the beneficial health effects compared with individual strains because of their synergistic adhesion effects.⁷

It is important to note that the range of food products containing probiotic strains is wide and still growing. The main products existing in the market are dairy-based ones including fermented milks, cheese, ice cream, buttermilk, milk powder, and yogurts, the latter accounting for the largest share of sales. Nondairy food applications include soy based products, nutrition bars, cereals, and a variety of juices as appropriate means of probiotic delivery to the consumer.⁸ Additionally, the unique physiology of plants as well as fat constituents of meat are also able to protect probiotic bacteria from different stresses. Several traditional non-dairy fermented foods used as vehicles for probiotics delivery are presented in Figure 1.⁹

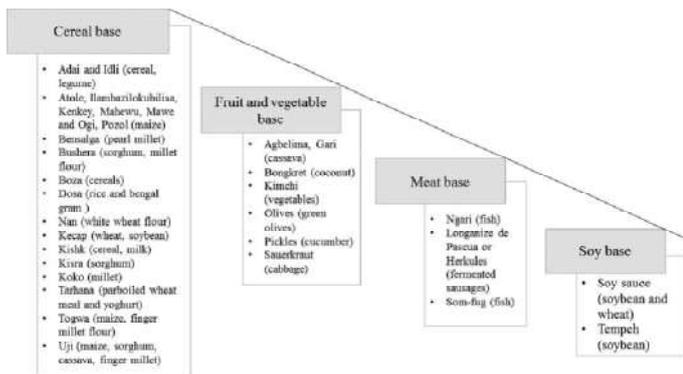


Figure 1 Traditional fermented foods that may contain potential probiotic bacteria⁹

1. pH and acidity: favorable conditions have high pH (low acidity)
2. Storage temperature: favorable temperature is in the range of 37-43 °C
3. Oxygen levels: high levels of oxygen lead to loss of viability of oxygen sensitive bacteria
4. Presence of competing microorganisms and inhibitors (protective agents)
5. Microencapsulation: to preserve them from detrimental factors during processing and storage such as low pH and high acidity

In brief, quality control of production, packing and storage is of primordial importance to maintain the efficacy of the products.

Table 1 Best probiotic supplements ranked for year 2018.¹⁰

Supplements	Probiotics
1 Renew Life Ultimate Flora Critical Extra Care	50 billion active cultures in each capsule (Bifidobacterium species and Lactobacillus species) Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus plantarum, Lactobacillus casei,
2 Now foodsprobiotic-10	Lactobacillus rhamnosus, Lactobacillus paracasei, Bifidobacterium breve, Streptococcus thermophilus, Lactobacillus salivarius, Bifidobacterium longum
3 Healthy Origins Probiotic	Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus casei, Bifidobacterium breve, Lactobacillus salivarius, Lactobacillus plantarum, Bifidobacterium longum, Lactobacillus rhamnosus
4 DR. Mercola Complete Probiotics	Lactobacillus acidophilus DDS-1, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Lactobacillus rhamnosus, Lactobacillus brevis, Bifidobacterium lactis, Bifidobacterium longum, Bifidobacterium bifidum, Streptococcus thermophilus
5 Nutrition NOW PB8	Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus plantarum
6 Sedona Labs iFlora Multi-Probiotic	Lactobacillus salivarius, Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus rhamnosus, Lactobacillus casei
7 Culturelle Digestive health Probiotic	Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium lactis HN019, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus gasseri, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus salivarius, Lactococcus lactis, Streptococcus thermophilus
8 GNC Ultra 50 Probiotic Complex	Active probiotic cultures of lactobacillus GG
9 Puritan's Pride Premium Probiotic 10	Lactobacillus acidophilus, Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium lactis, Fructooligosaccharides
10 Bio-Kult Probiotic	Lactobacillus acidophilus, Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium animalis var. lactis, Lactobacillus Plantarum, Lactobacillus salivarius (CUL61), Streptococcus thermophilus
	Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus delbrueckii ssp. bulgaricus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus salivarius, Lactococcus lactis ssp. lactis, Streptococcus thermophilus

Criteria for selection

Based on multiple observations and studies, multiple criteria are to be considered in selecting the appropriate probiotics. They have to be: (1) safe (non-toxic and non-pathogenic) probiotic strains that contain the adequate dose of the appropriate probiotic organisms at the time of consumption; (2) having an excellent viability during the processing operations and during storage as frozen or dried cultures; (3) having an excellent survival during the intestinal transit and during food processing operations; (4) having the ability to colonize human intestine and stabilize the intestinal microflora; (5) having the ability to exert potential health benefits on host or consumer; (6) having the ability to produce antimicrobial substances towards the pathogens; and (7) having to be technologically suitable for a large-scale industrial process.^{7,11,12}

Probiotic viability in the food matrix

Probiotic activity and viability in the food matrix for extended periods of time depend on processing operations (drying, freezing and thawing), Packaging and storage conditions, such conditions include¹³:

Probiotics in health: Advantages

The human body is a complex ecosystem containing trillions of bacteria (skin, genital areas, mouth and especially intestines). It is well known that the microbiota of the human gastrointestinal tract plays a key role in nutrition and health. It comprises approximately 300-500 bacterial species and nearly 2 million genes (the "microbiome"). Indeed, the number of bacteria within the gut is about 10 times that of all of the cells in the human body. These Microbes not only threaten us but would offer vital help with basic physiological processes; from digestion to growth to immunity and self-defense. Normally, a balance is maintained between beneficial and pathogenic bacteria. Dysbiosis occurs when there is an alteration in the normal balance of the micro-flora or organisms of the human body. Thus, it becomes imperative to control dysbiosis by providing the body with "good bacteria", known as Probiotics.³ Four different mechanisms of action have been considered for probiotics: (1) antagonism through the production of antimicrobial substances; (2) competition with the pathogen for adhesion sites or nutritional sources; (3) Immunomodulation of the host; and (4) inhibition of the production of bacterial toxins

(Metabolism). However, it is worth noting that: the first three are attributed to lactic acid bacteria, while the fourth is attributed to yeast.¹⁴

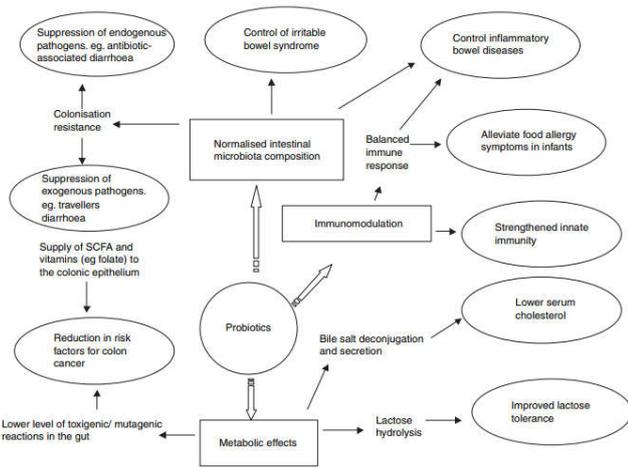


Figure 2 Various health benefits from probiotics consumption¹⁵

Probiotics with potential cardiovascular health benefits

Accumulating evidence shows that probiotics reduce blood serum cholesterol levels significantly by drinking yogurt fermented with wild strains of *Lactobacillus* sp.¹⁶ Moreover, Harrison, Peat, and de Heese (1975) reported decreased levels of serum cholesterol by consuming infant formula added with cells of *Lactobacillus acidophilus*.¹⁷ They also referred lower low density lipoproteins (LDL)-cholesterol and improve the LDL/high density lipoproteins (HDL) ratios, as well as lower blood pressure, inflammatory mediators, blood glucose levels and body mass index (Harison et al., 1975). Thus, probiotics could be considered as dietary supplements with multiple potential cardiovascular health benefits, see figure 3.¹⁸

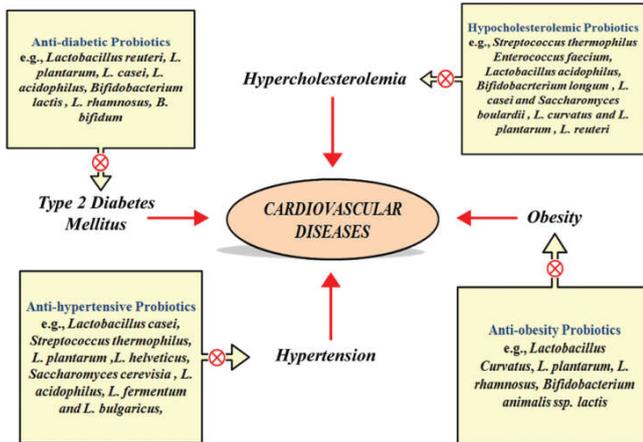


Figure 3 Schematic representation of the cardiovascular benefits of probiotics¹⁸

Probiotics and the digestive system

Antibiotic-associated diarrhea (AAD) is defined as unexplained diarrhea that occurs in association with antibiotic therapy. Probiotics could accelerate recovery from this diarrhea. Moreover, *Lactobacillus reuteri* DSM 17938 administration could prevent diarrhea and antibiotic-associated diarrhea (AAD) in children: children who receive *L. reuteri* DSM 17938 during the antibiotic therapy will have a lower risk of AAD than children receiving a placebo.¹⁹

Acute diarrhea is the most studied disease for which bifidobacteria are applied with great success; *Bifidobacterium longum* and *Bifidobacterium breve* being the most utilized species.²⁰ In addition, probiotics reduce the risk of necrotizing enterocolitis (NEC) in the newborns. High-quality meta-analyses show that probiotics like Bifidobacteria prevent, treat, and reduce the incidence of NEC pathologies.²¹

A recent Cochrane review calculated a relative risk (RR) of 0.43, 95 % confidence interval (CI) 0.33 to 0.56 for the efficacy of probiotics supplementation in reducing incidence of severe NEC (stage II or more), and mortality RR of 0.65, 95 % CI 0.52 to 0.81.²² The number need to treat (NNT) was approximately 33. The evidence is sufficiently strong enough to support a change in practice. In brief, probiotics with documented efficacy may be considered for prevention of NEC, particularly where incidence is high.²

Furthermore, microbial colonization of the infant gut plays a key role in immunological and metabolic pathways impacting positively human health.

Moreover, the most recent updates are in favor of the use of bifidobacteria for the prevention and treatment of many pathologies such as necrotizing enterocolitis, colics, and streptococcal infections. In addition, a number of not strictly enteric pathologies have in recent years evidenced a strict correlation with an aberrant gut microbiota in infants, in particular showing a reduced level of bifidobacteria.¹⁸

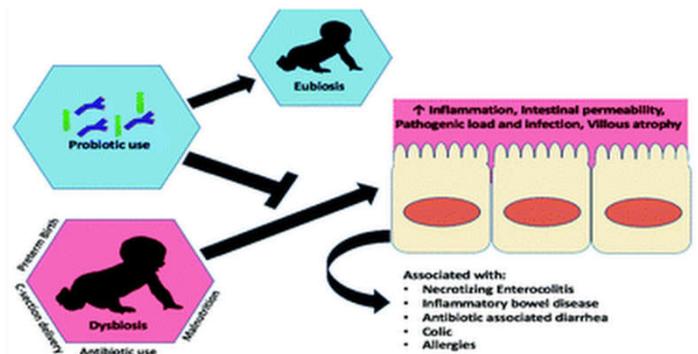


Figure 4 Probiotic use and the Gastrointestinal tract.²³

In 2014, the European Society for Paediatric Gastroenterology Hepatology and Nutrition published an evidence-based position paper with a conclusion supporting the efficacy of the use of probiotics. Actually, the use of the following probiotics may be considered as adjuncts to standard oral rehydration therapy for reducing diarrhoea duration: LGG or the yeast species *Saccharomyces boulardii* (low quality of evidence for both strains; strong recommendation); and *Lactobacillus reuteri* DSM 17938 (low quality of evidence; weak recommendation). However, there was insufficient evidence to recommend any of the many other probiotics that have been studied.²

Table 2 The various effects of probiotics: ¹

Intestinal effects	Immune system effects	Other effects
Relief effects: accelerated recovery from diarrhea	Enhanced specific and non specific immune response	Reduction of certain cancers: colon, bladder Detoxifying carcinogens Suppressing tumors Control of Inflammatory Bowel diseases (IBD), Irritable Bowl Syndrome

Production of lactase, alleviation of symptoms of lactose intolerance and mal-absorption (metabolism)	Inhibition of pathogen growth and translocation	Reduction of serum cholesterol concentration Reduction of blood pressure Increasing of nutrient bioavailability
Relief of constipation symptoms	Stimulation of Gastrointestinal immunity Reduction in chances of infections from common pathogens	Ameliorating food allergies: alleviate food allergy symptoms in infants.
Treatment of colitis		Optimizing effects of vaccines

Inflammatory Bowl Diseases

Crohn’s disease (CD) and ulcerative colitis (UC), collectively referred to as IBD, are chronic aggressive disorders with a prevalence of 0.1-0.5%. Genetic factors, immune system responsiveness, and environmental factors (such as the composition and metabolic activity of the gut flora) are all believed to play a role in the progression of these inflammatory states. Clinical observations suggest that certain intestinal and extraintestinal bacterial infections sometimes precede or reactivate chronic intestinal inflammation. The most compelling evidence for the interactive role of genes, bacteria, and immunity has been derived from experimental animal models of both spontaneously occurring or genetically engineered (KO or transgenic) animal models of IBD and Crohn’s-like.²⁴

Lactobacillus reuteri (*L. reuteri*) was used to prevent colitis in IL-10 knock-out (KO) mice and to increase the number of lactobacilli in the gastrointestinal tract: The normalization of *Lactobacillus* levels was obtained by oral administration of a prebiotic and rectal swabbing with *L. reuteri* to neonatal IL-10 KO mice. In addition, in a placebo-controlled trial, orally administered *L. salivarius* UCC118 reduced prevalence of colon cancer and mucosal inflammatory activity in IL-10 KO mice by modifying the intestinal microbiota in these animals with reduction in *C. perfringens*, coliforms, and enterococcus levels in the probiotic fed group. The administration of yoghurt, with potential probiotic strains, decreased the inflammation by modulation of the host immune response in a trinitrobenzenesulphonic-induced mouse model of IBD.²⁵

However, for inducing or maintaining remission in Crohn’s Disease or for preventing postoperative relapse trials have found LGG and other *lactobacilli* not superior to placebo as an additive to standard care.

Several published Randomized controlled trials have shown benefit of probiotics in the management of Ulcerative Colitis. These studies have examined *induction of remission* and *maintenance of remission* typically by comparing the probiotic with oral mesalamine or adding the probiotic to standard therapy. Study conducted in India included 144 adults with relapsing Ulcerative Colitis. They showed that the group that was using probiotics had significantly higher remission rates (42.9% vs 15.9%) and endoscopic healing (32% vs 14.7%). Most patients in both groups remained taking a stable dose of mesalamine therapy.^{24, 26} Certain strains have shown benefit (e.g. *E. coli* Nissle, lactobacilli, bifidobacteria and streptococci) in maintaining remission in UC and acute pouchitis, but there is no reliable evidence for CD yet.²

Supplementation with a mixture of *Lactobacillus casei* and *Bifidobacterium lactis* significantly reduced the inflammation

incolonic mucosa. Moreover, it showed efficacy in reversing malignant changes and in reducing apoptosis exerting a potential role in cancer prevention.²⁷

Irritable Bowel Syndrome

Irritable bowel syndrome is characterized by symptoms of abdominal pain and altered bowel habits which occur over at least 3 months. IBS patients may have subtle differences in their luminal and mucosal-associated intestinal microbiota compared with controls. Small-bowel bacterial overgrowth has been reported in a proportion of IBS patients, and antibiotics offer relief of IBS symptoms in some individuals. Although controversy exists, bacteria likely contribute to at least some symptoms of IBS. A meta-analysis suggests that LGG moderately improves pain symptoms in children with IBS. A *Bifidobacterium infantis* strain was evaluated in 2 clinical trials. One study found significant reductions in pain, bloating, bowel movement difficulty, and composite symptom score vs placebo and a *lactobacillus* species. In a larger follow-up study, reduction in pain and global relief of IBS symptoms were significantly greater in the *B infantis*-treated group compared with placebo. The evidence of benefit is not sufficiently strong to support the general recommendation of probiotics for IBS; however, the benefit appears greatest for *bifidobacteria* species and certain combinations of probiotics which include *bifidobacteria* species rather than single species *lactobacillus* probiotics.²⁶ The rationale for probiotic use in Irritable Bowel Syndrome is based on the role of the gut microbiota in many GI functions and the observation of a disturbed microbiota in patients. However, more research is needed to determine mechanisms of actions, which probiotics are effective and at what dosage and duration such criteria are essential.²

Table 3 Available probiotic Products Specifically Tested for Gastrointestinal Disorders²⁶

Brand name (Company)	Bacterial species	Clinical condition	Effectiveness
Activia (Dannon, White Plains, NY)	<i>B. lactis</i> DN-173010 (plus yogurt starters <i>L. bulgaricus</i> , <i>L. lactis</i> , and <i>Streptococcus thermophilus</i>)	IBS	C
Align (Procter and Gamble, Cincinnati, OH)	<i>B. infantis</i> 35624	IBS	B
BioGaia (Everdis Health Sciences, St. Louis, MO)	<i>L. reuteri</i> Protectis SD2112 (ATCC 55730)	Infectious diarrhea treatment IBS	A C
Bio-K+ (Bio-K Plus International, Inc., Laval, QC, Canada)	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> /LBC80R	AAD prevention CDAD prevention	
Culturelle (Valio, Helsinki, Finland); Health, Inc., Cromwell, CT)	LGG (LGG also included in Danimals yogurt; Dannon)	AAD prevention Infectious diarrhea treatment Infectious diarrhea prevention CDAD prevention CDAD prevention of recurrence Crohn’s disease IBS	A A B B/C B/C C B/C (children)
Danactive (Dannon)	<i>L. casei</i> /DN-114001	AAD prevention Infectious diarrhea prevention CDAD prevention	A
Florastor (Biocodex, Inc., Creswell, OR)	<i>Saccharomyces boulardii</i> (yeast)	AAD prevention Infectious diarrhea treatment Infectious diarrhea prevention CDAD prevention CDAD prevention of recurrence Crohn’s disease C	A A B B/C B/C C
Mutaflo (Ardeypharm, Herdecke, Germany)	ECN	UC induction UC maintenance	B A
VSL*3 (Sigma-Tau Pharmaceuticals, Inc., Towson, MA)	Combination probiotic product (<i>Streptococcus thermophilus</i> , <i>B. breve</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. delbrueckii/bulgarius</i>)	IBS UC induction UC maintenance Pouchitis: prevention and maintaining remission	B/C B B A

Effectiveness based on expert panel recommendations where: A - strong, positive, well-conducted, controlled studies in the primary literature; B-some positive, controlled studies but presence of some negative studies or inadequate amount of work to establish the certainty; C -some positive studies but clearly inadequate amount of work to establish the certainty.

Colorectal cancer

Moreover, *Lactobacillus casei* BL23 regulates Treg and Th17 T-cell populations and reduces DMH-associated colorectal cancer. Oral treatment with this probiotic bacterium modulates host immune responses and significantly protects mice against DMH(1,2-dimethylhydrazine)-induced CRC. This protection may be associated with the modulation of regulatory T-cells towards a Th17-biased immune response accompanied by the expression of regulatory cytokines (IL-6, IL-17, IL-10 and TGF- β). It is also coupled with the colonic expression of IL-22 observed in vivo on *L. casei* BL23- treated mice; suggesting the induction of a fine-tune Th17- biased response.²⁸

Additionally, probiotics may decrease the expression of COX-2, an enzyme that catalyzes the production of prostaglandins from arachidonic acid, which has been linked to an increased risk of developing CRC, since it stimulates cell proliferation and the pro-inflammatory process. Another important immunomodulatory pathway consists in the increased production of immunoglobulin A (IgA). It is important to highlight that the immunomodulatory activity of probiotics is dependent on their survival and persistence in the gastrointestinal tract as well as the variety, dosage and frequency used. Besides, their type of interaction with the host immune system can affect their immunomodulatory activity.²⁹

Probiotics and oral health

Oral benefits like prevention and arrest of caries or promotion of optimal remineralization of tooth surface could result from probiotic replacement therapy by the application of a genetically engineered strain of *S. mutans* BCS3-L1 that will replace the cariogenic or wild strain.³

A complex association exists between the periodontal disease and certain systemic disorders such as arteriosclerosis, T2DM, pneumonia, heart disease and premature childbirth. Professor Kuniyasu Ochiai's (Nihon University School of Dentistry, Japan) group are researching into this, focusing on the role of butyric acid (BA), which is produced at high levels by periodontopathic plaque species such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Eubacterium*. BA accumulates in gingival crevices at higher levels in periodontitis cases compared with the healthy and could serve as a promoter of periodontitis. At low concentrations, BA stimulates cell growth, but at higher concentrations it induces apoptosis in neutrophils, T-cells and macrophages. The complex signalling network associated with oral BA shows how it may elicit systemic effects, which could influence ageing and latent infections.²

Place of probiotics in animal production

Reports have documented that the administration of probiotic strains separately and in combination improved significantly feed intake, feed conversion rate, daily weight gain and total body weight in chicken, pig, sheep, goat, cattle and equine. They also reduced leg weakness in broilers, prevented starvation sterility of young sows, had positive effects on various digestive processes, improved disease resistance and reduced risk of allergies. In brief, probiotics increased intestinal IgA secretion both in sows and piglets and IgM levels in turkey; thus protecting the host against a variety of pathogens.¹⁴

Other miscellaneous advantages of probiotics

Other advantages have also been reported for probiotics use in animal and human health. In vivo data showed specific wound healing-accelerating effects of the probiotic *Lactobacillus rhamnosus* GG (LGG) on mucosal physiology, which are achieved through previously established secretion of the proteins P40 and P75 that modulate epidermal growth factor-receptor signaling.² Additionally, probiotics' anti-infective and anti-inflammatory effects can decrease the risk of infection and promote wound healing. Probiotics can be especially used in diabetic patient's local treatment of chronic wounds.³⁰ Probiotics start acting on diabetic wounds by penetrating the inter-cellular lipid matrix into the dermis. Inside the dermis, they activate toll like receptors (TLRs), a type 1 transmembrane protein, which has been found to act as major signaling receptor for pathogen-associated molecular patterns (PAMPs). TLRs are also found on all the epithelia including the mouth, nasal cavity, keratinocytes and Langerhans cells. It is through the TLRs, that the probiotic derived bioactives (PDBs) activate the production of proteins called beta defensins (b-defensins).

Beta defensins elevate the skin's immune functions, through its antimicrobial and anti-inflammatory properties. Additionally, TLRs are instrumental in the upregulation of collagen and elastin, increase in cellular respiration and improvement in skin clarity, texture and overall appearance. Gram positive pathogens like *Staphylococcus aureus* and *Enterococcus* and Gram negative bacteria like *E. coli* are a major source of bacterial infection in the diabetic foot ulcer. Lipoteichoic acid (LTA) derived from these microbes are reported to be a ligand of TLR 2. Inflammatory response by membrane lipoproteins from the bacteria are mediated by TLR 2. The host recognizes bacterial components (PAMPs) and regulates cellular responses. Thus, TLR 2 has been shown to play a crucial role in host responses to the microbes.³¹

Probiotics compete with pathogens for binding to adhesion sites at host cell surface. This binding can induce the host cells to secrete anti-inflammatory cytokines, which will reduce the inflammation at surface of the tissue. Further, probiotics can release many types of antimicrobials which can either kill or inhibit the growth of pathogens. Probiotics can enhance the overall body immunity by immunomodulation. During this process, probiotics interact with antigen presenting cells (macrophages and dendritic cells), which have a critical role in wound healing and scar formation.³¹ A reduction of 90% of the area of chronic leg ulcers was observed in 43% of diabetics and 50% of nondiabetic patients after 30 days of topical treatment with *L. plantarum*, as well as a significant decrease in colony-forming units after 5 days.³²

Additionally, probiotics can be used in treatment of burn wounds. Topically applied *L. plantarum* inhibited *Pseudomonas aeruginosa* colonization, improves tissue repair, and enhances phagocytosis in burn wounds in mice. Clinical studies on patients with second- and third degree burns found that the application of *L. plantarum* was as effective as silver sulfadiazine in decreasing bacterial load, promoting the appearance of granulation tissue, and wound healing.³² As reported earlier, there is evidence that *L. reuteri* DSM 17938 has benefits for infantile colic.² In 2015, the World

Allergy Organization published new evidence-based guidelines relating to probiotic use. However, current evidence does not indicate that probiotics reduce the risk of children developing allergy, but, despite very poor quality of evidence, it was recommended that there is a likely net benefit from probiotic use in pregnant women who are at high risk of having an allergic child, in women who breast-feed infants that are at high risk of allergy and in infants who are at high risk of developing allergy. However, it remains unclear which specific probiotic(s) should be used.³³

Furthermore, there is potential for probiotics to enhance microbial production of bioactive flavonoid metabolites in the gut. Several animal studies have also indicated that certain *Lactobacillus* and *Bifidobacterium* probiotic strains can reduce oxidative stress via mechanisms such as reducing hydrogen peroxide and hydroxyl radicals. As reported in 2015, the one human study conducted to date showed a similar positive trend: consumption of a probiotic yogurt improved the antioxidant status of people with Type 2 Diabetes.²

Moreover, gut microbiota also produce metabolites that directly affect many physiological processes, and act as signaling molecules to surrounding microorganisms which subsequently produce different types of metabolites that affect the hosts differently as well. Much has been reviewed in Dinan and Cryan, 2017 on the changes of gut microbiota that ultimately affected brain-related physiology including stress, depression, memory and cognition.^{34,35} Gut-brain axis is a new concept. An application of probiotics to enhance mental health is at its infancy, only few strains of *L. plantarum* have been investigated for this purpose. One of the more prominent strains of *L. plantarum* investigated as a psychobiotic is *L. plantarum* PS128. *L. plantarum* PS128 at a daily dose of 109 CFU/mouse reduced early life stress (ELS) induced depression-like behaviors. Reduced levels of dopamine (DA) and serotonin (5-HT) and increased turnover rates of DA and 5-HT have been observed in the prefrontal cortex (PFC) of ELS mice.³⁵ *L. plantarum* C29 was reported to protect memory deficit induced by scopolamine, D-galactose, aging, and IBD. In review of Zuccato and Cattaneo (2009), the levels of BDNF in brain were decreased in neurodegenerative diseases, Alzheimer disease, Parkinson disease, and Huntington disease.^{35,36}

In addition, certain bacterial species in the colon are able to metabolise daidzein to produce equol which has an anti-androgen activity. This is explained by its ability to bind to oestrogen receptor β and the sex hormone-binding globulin (SHBG), thus inhibiting the growth of sex hormone-dependent tumours such as Prostate Cancer.²

Furthermore, probiotics use is being considered in HIV/AIDS patients also have by a progressive depletion of CD4+ T-cells and a severe impairment of the immune system. This is often accompanied by an alteration of the gut mucosal barrier, which allows translocation of microbes and their products, and provokes a chronic state of inflammation. In view of the immunomodulatory effects reported for probiotics in non-immunocompetent and HIV+ subjects, Dr D'Angelo's group from Italy conducted a pilot study on the effects of *L. casei* Shirota (at 1.3×10^{10} CFU/d for 4 weeks) in clinically stable HIV+ patients on antiretroviral therapy and concluded that this probiotic could improve the management of antiretroviral

therapy-treated HIV+ patients, however, this issue warrants further investigation.³⁷

Disadvantages of probiotics

Introducing probiotics in the human body is a matter of concern and could be a potential threat especially to immunocompromised and genetically predisposed individuals.³⁸ When ingested orally, probiotics are generally considered safe and well tolerated.³⁹ However, studies have reported that subjects receiving probiotics could have some minor gastrointestinal symptoms, such as abdominal cramping, nausea, soft stools, flatulence, and taste disturbance.⁴⁰ Such, these side effects are typically mild and subside with continued use. Constipation and increased thirst have also rarely been associated with *S. boulardii*.³⁹

Two cases were reported about one infant and a child, without any underlying GIT disease or immunocompromised status, they suffered from bacteremia upon lactobacilli supplementation.³⁸

Furthermore, one theoretical concern associated with probiotics includes the potential for these viable organisms to move from the gastrointestinal tract and cause systemic infections.³⁹ Medical reports highlighted that Lactic Acid Bacteria and Bifidobacteria have been associated with human opportunistic infections causing sepsis, bacteremia, pneumonia, abdominal abscesses, peritonitis, rheumatic vascular diseases in immune compromised individuals and patients with allergic sensitization and autoimmune disorders. The incidence of such cases depends very much on probiotic species and strain specificity.³⁸ It is estimated that the risk of developing bacteremia from ingested lactobacilli probiotics is less than 1 per 1 million users, and the risk of developing fungemia from *S. boulardii* is estimated at 1 per 5.6 million users. Bacteremia due to lactobacilli rarely occurs, in the presence of factors which include; immunosuppression, prior hospitalization, severe underlying comorbidities, previous antibiotic therapy, and prior surgical interventions.³⁹

Recently, in 2017, one report described a patient with no known probiotic use and no diagnosed intestinal pathology who exhibited recurrent episodes of *Lactobacillus* bacteremia associated with fever and altered mental status. No discrete portal into the bloodstream was ever identified in this patient. The *Lactobacilli* isolated for this patient were susceptible to penicillin and gentamicin. He was thus repeatedly treated with ampicillin-sulbactam and gentamicin. Despite intermittent defervescence and negative blood cultures after treatment, successful eradication of the underlying source was doubtful given his recurrent bacteremia. He continued to be on lifelong oral antibiotic prophylaxis. This approach was finally decided upon, after consultation with infectious disease experts from other tertiary care institutions.⁴¹

There have been also several documented cases of fungemia associated with use of *S. boulardii*. Those at greatest risk include critically ill or highly immunocompromised patients or those with central venous catheters in place. When *S. boulardii* capsules are opened at the bedside for administration through the nasogastric tube, central venous catheters may become contaminated and serve as the source of entry for the organism.

Moreover, there have been infrequent reports of lactobacillemia and fungemia.³⁹

Furthermore, of abdominal abscess, liver abscess is the type most associated with exposure to probiotics. Liver abscess due to the lactobacillus strain is a serious infection. It is generally uncommon and rare, with only 7 reported cases in the literature. Predisposing factors were steroids use, heavy dairy product consumption and intratumoral ethanol injection. The most common underlying diseases were diabetes mellitus (62.5%) and hepatopancreaticobiliary diseases.⁴² It has also been found that certain Probiotic strains can increase platelet aggregation and aggravate hemolytic uremic syndrome. They are also a potential source of toxic metabolites e.g. biogenic amines. Moreover, probiotics may lead to undesirable effects when some silent genes of probiotic bacteria are activated during passage through intestinal tract. Furthermore, certain probiotic strains are implicated in the transfer of genetic information, including antibiotic resistance to pathogens due to the presence of antibiotic resistance plasmids leading to genomic and epigenomic alterations. In addition, *Enterococcus faecium*, known as antibiotic-associated diarrhea preventer, may act as an opportunistic pathogen owing to the presence of a potential reservoir of antibiotic resistance and virulence genes. Septicemia and central nervous system deterioration were also observed in an immunocompromised patient with spores of the probiotic strains of *Bacillus Subtilis*. Some experimental studies highlighted increased bacterial translocation leading to mortality upon *Lactobacillus delbrueckii* UFV-H2b20 and *Bifidobacterium lactis* Bb12 administration in mice with 1,2-dimethyl hydrazine (DMH)-induced injuries. Additionally, some genotoxic effects have also been associated to the presence of *Escherichia coli* Nissle knowing that they possess a set of genes responsible for the induction of double-strand breaks in host cell DNA³⁸ On the other hand, no immunologic phenomenon has been associated with probiotic use in man, except one case of autoimmune hepatitis that might have been enhanced by ingestion of very large doses of yogurt.⁴³

Besides, probiotics can cause metabolic side effects. They are designed to deliver bacteria to the colon; in contrast, they may colonize the small bowel, especially in the presence of dysmotility or low acid conditions that favor bacterial overgrowth.⁴⁴ Bacterial colonization of small bowel can induce diarrhea and intestinal lesions, especially via the deconjugation and dihydroxylation of bile salts.⁴⁵ One study drew attention of the potential risk of excessive deconjugation or dihydroxylation of bile salts in the small bowel by probiotics. Indeed, it showed that patients with ileostomy who ingested LB. acidophilus and *Bifidobacterium* sp. could transform conjugated primary bile salts into free secondary bile salts. Excessive degradation of intestinal mucus layer by probiotics may theoretically be detrimental.⁴⁶

In addition bacteria (*Lactobacilli* and/or *Prevotella* species) colonizing proximal small bowel can likely induce the production of toxic metabolites such as D-lactic acid by bacterial fermentation of carbohydrate substrates. Satish et al. research provided compelling evidence for possible link between brain foginess, SIBO and d-lactic acidosis.⁴⁴ Additionally, one of the studies reported an increased risk of mortality when probiotics were used to prevent infectious

complications in patients with predicted severe course of acute pancreatitis. The authors stated that probiotics should not be routinely given to patients with predicted severe acute pancreatitis and should be used cautiously in critically ill patients or those at risk for nonocclusive mesenteric ischemia.²⁶ In a review of the literature, Boyle et al. identified major and minor risk factors for probiotic associated sepsis. Major risk factors included immunosuppression (including a debilitated state or malignancy) and prematurity in infants. Minor risk factors were the presence of a central venous catheter, impairment of the intestinal epithelial barrier (such as with diarrheal illness), cardiac valvular disease (*Lactobacillus* probiotics only), concurrent administration with broad-spectrum antibiotics to which the probiotic is resistant, and administration of probiotics via a jejunostomy tube (this method of delivery could increase the number of viable probiotic organisms reaching the intestine by bypassing the acidic contents of the stomach). The authors recommended that probiotics could be used cautiously in patients with one major risk factor or more than one minor risk factor.³⁹

Lastly, the traditional way of administering probiotics may not be able to produce the required concentration of the metabolites to produce the desired effect at the target sites *in vivo*. Therefore, to enhance *in situ* production of beneficial metabolites, the administration of either probiotic or specific prebiotic may be useful or these multifunctional metabolites may be given instead of probiotics. Such an issue needs to be thoroughly investigated before implementation.³⁸

Probiotics in pregnancy

Meta-analyses indicate pre and post-natal supplementation with *Lactobacillus* alone or *Lactobacillus* with *Bifidobacterium* appear to be protective.

Maternal obesity has become highly prevalent worldwide and is associated with an increased risk of maternal pregnancy-related complications and an increased risk of adverse pregnancy outcomes (pregnancy-induced hypertension, preeclampsia and gestational diabetes mellitus (GDM)). Maternal obesity may adversely affect the fetus and fetal growth in the initial stages of life, the risk of pregnancy complications, as well as the child's later development (adiposity in the fetus, macrosomia (a birth weight of over 4000 g) and neonatal hypoglycemia).⁴⁷

The study by Luoto et al. in 2010 was a randomized controlled trial of probiotic intervention with capsules containing *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 in 256 normal-weight pregnant women and reported a reduced risk of gestational diabetes mellitus from 34 to 13 % (P = 0.003) with a combined dietary/probiotic supplementation.⁴⁸

The study by Asemi et al. in 2013 was a randomized controlled trial including 70 pregnant women in their third trimester who were randomly assigned to consume 200 g per day of conventional or probiotic yoghurt containing two strains of lactobacilli (*L. acidophilus* LA5) and bifidobacteria (*Bifidobacterium animalis* BB12) for 9 weeks. Significant differences were found in serum insulin levels: $+1.2 \pm 1.2$ versus $+5.0 \pm 1.1$ μ IU/ml (P = 0.02), and the conclusion was that the consumption of probiotic yoghurt maintains serum insulin levels and might help prevent developing insulin resistance during pregnancy.⁴⁹

Postnatal depression (PND) is associated with persistent depression, and even, in a few cases each year, death from suicide. This disorder may affect a mother's ability to care for and bond with her new infant, as well as her quality of life and daily functioning. In addition, maternal depression can produce long-lasting effects on children's cognitive, social-emotional and health outcomes. There is a growing literature linking the gut microbiota to brain chemistry and behaviour via multiple bi-directional pathways (the microbiome-gut-brain axis), including the immune system, neuroendocrine, hypothalamic pituitary adrenal axis (HPA axis), short chain fatty acids or tryptophan and sympathetic and parasympathetic arms of the autonomic nervous system including the enteric nervous system, the vagus nerve, and the gut microbiota.

In a double blind, placebo randomised controlled trial; healthy subjects were given probiotics (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) or placebo for 30 days. The probiotic group had significantly less anxiety and depression than the controls. Daily intake of a mixture of four probiotic strains (*Bifidobacterium animalis* subsp *Lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and *Lactococcus lactis* subsp *Lactis*) over four weeks reduced brain activity to an emotional attention task in the regions of the brain that influence the processing of sensory information and emotion. Brain activity was assessed using functional magnetic resonance imaging. No changes in commensal bacteria were observed. The authors argued that the probiotics might interact with the host microbiota to alter their metabolic activity resulting in the production of metabolites that influence brain activity.⁵⁰

Slykerman et al. (2017) study demonstrated a significantly lower prevalence of symptoms of depression and anxiety postpartum in women supplemented with the probiotic HN001 during and after pregnancy than in those given a placebo. Furthermore, the number of women reporting clinically significant levels anxiety on screening was significantly lower in the probiotic group.⁵¹

Internationally the prevalence of Bacterial Vaginosis (BV) is high in pregnant women in USA. BV is associated with preterm labour, premature rupture of membranes, spontaneous abortion, and chorioamnionitis.⁵⁰

Probiotics can interfere with the processes that can lead to preterm labour by displacing and killing pathogens, through enhancement of anti-inflammatory cytokines and by reducing the pH to make the vaginal environment friendlier to beneficial bacteria.⁵²

BV treatment study showed that a combination of orally administered *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 and metronidazole doubled the cure rate compared to metronidazole alone. Studies have shown lactobacilli survive passage through the gastrointestinal tract, indicating that oral delivery of lactobacilli is feasible and may be expected to impact the composition of vaginal flora.⁵⁰

There is data that showed that *Lactobacillus rhamnosus* HN001 given daily to mothers from 35 weeks gestation, continuing until 6 months post-partum if breastfeeding and from birth until 2 years in the infant was associated with a significant 50 % reduction in the prevalence of eczema at age 2, 4 and 6 years.

One possible justification for an early probiotic intervention is based on evidence showing that fetal production of IgE antibodies occurs before the end of the first trimester and allergen-specific IgE antibodies towards the end of the second trimester. There is also evidence that maternal allergy alters the regulation of antigen-specific responses during pregnancy, with non-allergic mothers showing down-regulation of their (already lower) Th2 responses to specific allergen from mid to late gestation. The majority of probiotic trials, using a late pregnancy intervention (from 32 to 35 weeks gestation), may therefore have missed the critical window to influence fetal immune responses and thus the later development of allergic disease.⁵⁰

Probiotics in sickness

It has been suggested that probiotics have a significant role in the treatment and/or prevention of cancer, especially colon and bladder, by several mechanisms, such as anticarcinogenic properties.

The mechanisms in which probiotics act may be categorized as:⁵³

- Improving intestinal barrier through improved resistance to colonization by pathogens through lactic microflora production.
- Modulating anticancer drug's pharmacokinetics by altering the composition and metabolic activity of the microflora. This phenomenon may then decrease carcinogen-activating microbial enzymes and has a beneficial effect in the colon, the urinary tract, and the bladder.
- Enhancing production of short-chain fatty acid (butyrate, conjugated linoleic acids) by main energy source for enterocytes to prevent inflammation and increase cancer-preventive properties.
- Modulating the immune system by mucin production through induction of MUC genes in the gut.
- Possible mechanisms for a protective role in carcinogenesis include:⁵⁴
- selectively promoting the growth of bacteria such as bifidobacteria which have a tumour suppressive effect
- the formation of reducing agents, such as glutathione which can inactivate food-borne carcinogens
- decreasing levels of certain bacterial enzymes purported to be involved in activation of carcinogens
- the production of anticancer metabolites such as short chain fatty acids (SCFA), in particular butyrate
- the up-regulation of apoptosis
- causing a decrease in triglycerides, phospholipids and low-density lipoproteins, which are required for tumour growth

CONCLUSION AND FURTHER RESEARCH

In summary, with microbes being such a large physical part of the gastrointestinal tract, as well as other sites, it is vitally important that specialists appreciate their existence, and consciously consider what role they might have in health and disease. The application of probiotics as therapy or health maintenance remedies will require thorough documentation of the strain(s), product formulation and mechanisms of action.

The number of microbial species found in the gut is huge, and the interactions among them and with the host cells need to be further deciphered and explained so that probiotic strains can be used with a rationale.⁵⁵ Microbes have always been a major component of the human body; it's just that humans are finally appreciating their value.⁵⁶

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