



JOURNAL ON COMMUNICATIONS

ISSN:1000-436X

REGISTERED

Scopus®

www.jocs.review

Importance of probiotics for human health: A critical review

B Stany¹Anushka Das¹ Shatakshi Mishra¹

Vellore institute of technology

School of biosciences and technology

Abstract

Probiotics, prebiotics, and synbiotics have been studied for decades for their health benefits. Probiotics are live microorganisms known to confer a health benefit when administered in adequate amounts. The most common prebiotics are FOS, GOS, XOS, Inulin, and fructans. Synbiotics, nondigestible fibres, selectively increase particular microbe species' growth and activity, improving host health. Postbiotics are beneficial microbes or metabolites that induce T regulatory cell differentiation and synthesize anti-inflammatory cytokines, killing bacteria chemically and mechanically. Probiotic strains must pass multiple testing rounds to prove pathogen causation and monitor and investigate the illness. In vitro investigations for stomach acidity, bile acid resistance, antibacterial activity, and pathogen adhesion are recommended. Manufacturing and storage should include quality control and assurance, and effectiveness studies should focus on humans. These beneficial groups of microorganisms are a great boon to human health and are recommended for use in various prophylactic measures. This paper discusses the uses, properties, and functions of some probiotic strains used widely after confirmation with clinical trials. Next-generation probiotics production is one of the few advancements in the field of biology and has significant prospects.

Introduction

The health advantages of probiotics, prebiotics, and synbiotics have been extensively researched over the last few decades. These dietary supplements, functional meals, have been shown to change, modify, and restore pre-existing gut flora (Pandey et al., 2015). They also help the digestive environment run smoothly. Bifidobacterium, Lactobacilli, S. boulardii, and Bifidobacterium coagulans are the most often utilized probiotic strains. Prebiotics such as FOS, GOS, XOS, Inulin, and fructans are the most frequently used fibres that, when combined with probiotics, are referred to as synbiotics and can boost probiotic viability (Pandey et al., 2015). The current review concerns the composition and functions of Probiotics, Prebiotics, and Synbiotics in human health. Additionally, additional health advantages such as immunological modulation, cancer prevention, inflammatory bowel disease, and so on are highlighted.

Probiotics have been utilized to aid in the prevention and treatment of various medical disorders. Some of their health benefits have been validated, while insufficient data back others. Probiotic effects are strain-specific, and probiotic products may differ, with more advantages found with one lot of probiotics vs. another due to the challenge of quality control with living microorganisms (Figure 1). Furthermore, combination agents might make it difficult to assess specific therapeutic advantages (Senok et al., 2005; Surawicz, 2008; Wald & Rakel, 2008). Probiotics have traditionally been used to treat gastrointestinal disorders, owing to their antimicrobial properties and capacity to repair gut flora. The most compelling evidence for probiotic usage is treating certain diarrheal illnesses, particularly rotaviral diarrhea in children. Clinical research has also shown probiotics to be effective in treating pouchitis (Pham et al., 2008; Vanderhoof & Young, 2008). Data on the effectiveness of probiotics for antibiotic-associated diarrhea (AAD) and travellers' diarrhea are inconclusive (Pham et al., 2008; Senok et al., 2005). Despite inconsistent clinical trial outcomes, probiotic medication may effectively treat Crohn's disease, ulcerative colitis (UC), irritable bowel syndrome (IBS), and Helicobacter pylori infection (Macintyre & Cymet, 2005; Pham et al., 2008; Santosa et al., 2006; Scarpellini et al., 2008).

Prebiotics are primarily nondigestible fibres that benefit the host's health by selectively boosting certain microbe species' development and activity (Figure 1) (Gibson & Roberfroid, 1995). Lactobacilli and bifidobacteria are commonly found in the colon (Gibson & Roberfroid, 1995). An excellent prebiotic

should be resistant to the effects of stomach acids, bile salts, and other hydrolyzing enzymes in the gut; the upper gastrointestinal system should not absorb it and be readily fermentable by intestinal microorganisms (Gibson & Roberfroid, 1995). WHO defines Prebiotics as a non-viable dietary component that confers health benefits to the host through microbiota regulation. Prebiotics are a varied category of substances like carbohydrate components with unknown origins, fermentation characteristics, and doses necessary for health effects. Prebiotics can be found in breast milk, soybeans, raw oats, unprocessed wheat, unrefined barley, bacon, non-digestible carbs, and especially non-digestible oligosaccharides. However, only bifidogenic, non-digestible oligosaccharides (especially inulin, its hydrolysis product oligofructose, and (trans) galactooligosaccharides (GOS)) meet all prebiotic categorization requirements (Gibson & Roberfroid, 1995). Prebiotics such as inulin and pectin provides various health advantages, including reducing the frequency and length of diarrhea, relieving inflammation, and alleviating other symptoms linked with diarrhea, intestinal bowel disease, and preventive properties against colon cancer (Gibson & Roberfroid, 1995). They are also related to improved mineral bioavailability and absorption, decreased risk factors for cardiovascular disease, and promoted satiety and weight reduction, hence avoiding obesity (Pokusaeva et al., 2011).

A synbiotic product benefits the host by increasing the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively expanding the development and activating the metabolism of one or a small number of health-promoting bacteria (Figure 1). Because synbiotics imply synergism, they should be reserved for products in which the prebiotic compounds specifically benefit the probiotic organisms (Cencic & Chingwaru, 2010). Synbiotics were created to help probiotics survive. The justification for using synbiotics is based on findings demonstrating improved probiotic bacteria survival during transit through the upper digestive system. More efficient embedding in the colon and a stimulating influence on the growth of probiotics and ubiquitous bacteria help maintain intestinal homeostasis and a healthy body (Peña, 2007).

Postbiotics are either metabolites or fragments of microorganisms that positively affect the host (Figure 1). The structural variability of postbiotics suggests a plethora of approaches for postbiotic acquisition. Chemical and mechanical approaches can be used to kill bacterial cells. Enzymatic extraction, solvent extraction, sonication, and heat are examples of these procedures. Extraction, dialysis, and chromatography isolate and identify desired compounds (Zolkiewicz et al., 2020). SCFA stands for short-chain fatty acids.

Postbiotics exhibit pleiotropic characteristics. Postbiotics restore the balance between the two primary arms of the immune system, represented by Th1 and Th2, by inducing differentiation of T regulatory cells and synthesizing anti-inflammatory cytokines (Zolkiewicz et al., 2020). Th2 lymphocytes are white blood cells. The balance of Th1 and Th2 cells is critical for immunoregulation, and its disruption causes various immunological illnesses, including atopic dermatitis. Antibacterial action is most likely mediated by postbiotics' influence on the molecular structure of enterocytes, which results in the intestinal barrier being sealed. Postbiotics' "statin-like" action and potential therapeutic use in metabolic and associated illnesses are significantly expected (Zolkiewicz et al., 2020).

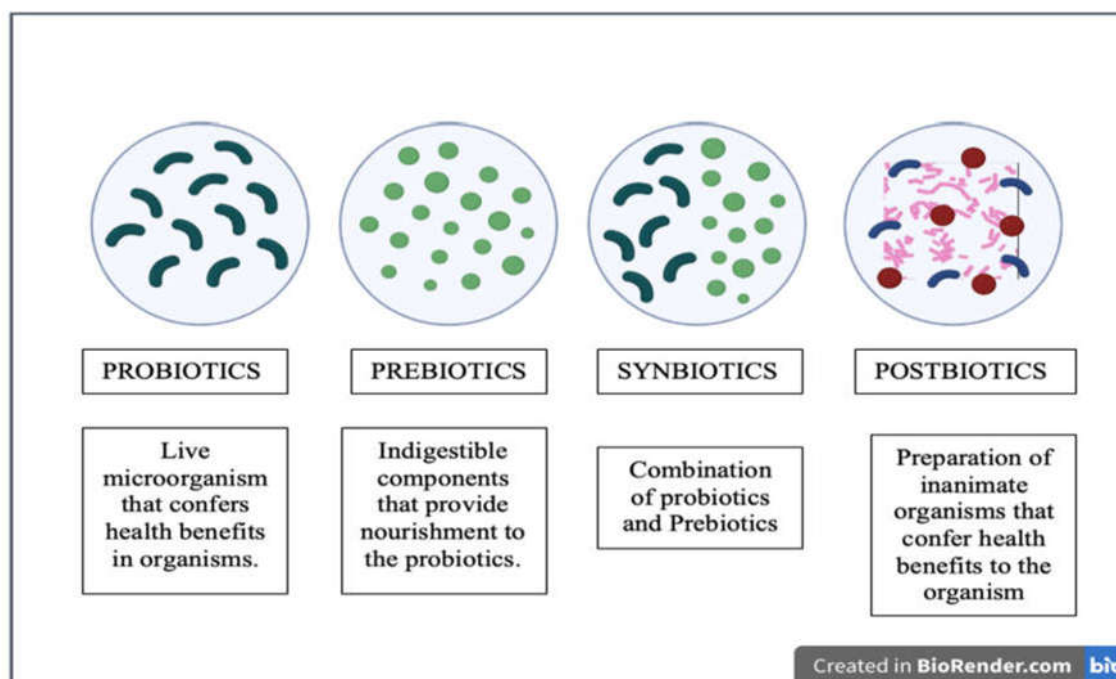


Figure 1: Diagrammatic representation of Probiotics, Prebiotics, Synbiotics and Postbiotics (Using BioRender).

Requirements for a strain to qualify as a source of probiotics

The test probiotic strain has to undergo various levels of testing to qualify as a potential probiotic strain; these are achieved in multiple steps, which include characterization of the strain, safety level tests for intended use, usage of clinical trials on humans, delivery requirements to enter into the host, determining the dosage and also enhancement of the shelf life. In case the probiotic stain stands out with the characteristics mentioned. It is safe for humans and a prophylactic element for preventing many health conditions. ICMR-DBT has incorporated several guidelines to satisfy the above screenings, which are discussed below (Council & Icmr, 2015);

- Identification of the strain is crucial for establishing causality between a pathogen and a particular health outcome and for conducting effective monitoring and investigations of the spread of disease (epidemiological). Phenotypic and genetic testing should adhere to established protocols.
- PCR-based methods, 16S rRNA sequencing, and DNA fingerprinting are currently employed molecular approaches for identification, including ribotyping and PFGE (pulsed-field gel electrophoresis).
- In vitro tests are recommended to screen potential probiotic strains for resistance to gastric acidity, bile acid resistance, antimicrobial activity, and ability to reduce pathogen adhesion.
- These in vitro assays are predicated on the idea that the circumstances in the gut are unfavorable. These tests, taken together, determine which cultures are effective in the role of probiotics. And should be tested first on suitable animal models to ensure safety before being tried on humans in clinical trials.
- Evaluation of the acute, subacute, and chronic toxicity of exceptionally high doses of probiotics should be conducted for all possible strains. This evaluation may not be essential for strains with a documented usage history. This category comes under the in vivo tests dealing with safety levels.

- To verify in vitro effects, proper, validated animal models must be utilized before human testing. This category deals with the in vivo tests to determine the efficacy level.
- Probiotics for human use should be evaluated with the following tests: determination of antibiotic resistance patterns, assessment of undesirable side-effects, and assessment of toxin production and hemolytic activity. Assessment of lack of infectivity by a probiotic strain in immunocompromised individuals is also an added measure.
- Humans should be the primary focus of probiotic efficacy research because of the potential for similar health benefits. Improvements in condition, symptoms, signs, health, or quality of life; decreased risk of disease; an increased time before the subsequent incidence of sickness; or accelerated recovery from illness, all of which are statistically and clinically significant in studies. Every metric must be statistically significant while testing probiotics.
- The probiotic strain's cfu/ml/day minimum effective dosage or quantity of viable cells in the carrier. Foods that exhibit functions that promote general health, overall wellness or specific health claims in the target group should be clearly labeled.
- Essential details on a label (Gregor Reid et al., 2001; Saldanha, 2008) should be the genus, species, and strain names, minimum viable numbers of each probiotic strain, health claims, recommended serving size, and proper storage conditions. These details should be included in addition to the general information required by food legislation.
- Quality control and assurance measures should be in place throughout production and storage. It is recommended that all factories follow GMPs. Guidelines for using hazard analysis and critical control points (HACCP), as outlined by the Codex General Principles of Food Hygiene, should be implemented.

Probiotics used as an aid for irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most common digestive tract disease caused by an altered intestinal flora, the so-called dysbiosis. The intestinal flora consists of more than 2000 different types of bacteria belonging to the four main strains *Bacteroides*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* (Qin et al., 2010). Environmental and genetic factors determine the proper functioning of the intestinal flora (Wilson et al., 2019). It has various effects, such as abdominal pain and bloating, and is caused by loose stools accompanied by diarrhoea and/or constipation, ranging from mild to severe (El-Salhy et al., 2014; Schuster, 2001). Although irritable bowel syndrome does not result in increased mortality (Wu et al., 2022), it does have several extraintestinal symptoms, including headache, fatigue, fibromyalgia, poor social functioning, and emotional well-being (Böhn et al., 2013). This can sometimes lead to a reduction in a person's quality of life in daily work, leading to a financial burden on society (Hahn et al., 1999; Patrick et al., 1998). The main challenge in choosing a probiotic strain is the lack of clarity about the pathogenesis of IBS; However, several factors are responsible for the pathogenesis of IBS, mainly altered gut microbiota (dysbiosis) (Hong & Rhee, 2014), alternative enteroendocrine cells, previous infections, genetics, and diet (Mazzawi, 2022).

Probiotics are essential in maintaining gut dysbiosis (Tamboli et al., 2004). IBD patients have increased intestinal permeability, which causes the invasion of pathogenic bacteria. A defective mucosal barrier promotes light exposure and triggers a sustained immune activation (Cain & Karp, 2011; Gersemann et al., 2012; Seksik et al., 2008). This leads to a decrease in protective bacteria, such as *Bifidobacterium* and *Lactobacillus*, and an increase in the number of pathogenic bacteria, such as *Escherichia coli* and *Clostridium* species (Di Cagno et al., 2011; Macfarlane et al., 2004). It also reduces the synthesis of short-chain fatty acids (acetates, butyrate, and propionates) (Cain & Karp, 2011). It increases the synthesis of toxins and the production of pro-inflammatory cytokines that cause inflammation and symptoms. On the contrary, probiotics offered a therapeutic treatment for these enteropathies (Vanderpool et al., 2008). The mechanism by which probiotics alter the gut microbiota includes a

reduction in luminal pH, competitive adhesion, secretion and induction of antimicrobial compounds (bacteriocins and defensins), changes in nitrogen metabolism, and cellular avoidance (Ng et al., 2009; Scott et al., 2015). The significant effect of these probiotics are analysed in the table 1. Pharmacological treatment of IBS has been observed as predominantly symptomatic and short-lived (Rao & Weber, 2014; Tack et al., 2016). Therefore, researchers have focused on nutritional management and probiotics to treat IBS over the past decade.

Table 1: Multivariant probiotics strains and its mode of action.

Strains	Mechanism of action	Reference
<i>Lactobacillus paracasei subsp. Paracasei B21060</i>	Inhibiting blood CD4 ⁺ T-cell proliferation in patients with IBD.	(Peluso et al., 2007)
<i>B. breve</i> and <i>Bifidobacterium bifidum</i> strains	Reduction of proinflammatory cytokines (IL-8). Increases the IL-10 synthesis in peripheral blood mononuclear cells.	(Imaoka et al., 2008)
<i>B. breve</i> , <i>B. longum</i> and <i>L. casei</i>	Improvement of symptoms, such as diarrhoea and abdominal pain.	(Fujimori et al., 2007)
<i>L. salivarius</i> , <i>L. acidophilus</i> and <i>B. bifidum</i> strain <i>BGN4</i> .	Disease activity index improvement. Reduction in the recovery time.	(Palumbo et al., 2016)
<i>Lactobacillus delbruekii</i> and <i>Lactobacillus fermentum</i>	Improvement of mucosal inflammation and lesion.	(Hegazy & El-Bedewy, 2010)

Probiotics used as an aid for Alzheimer's and Parkinson's Disease

Neurogenerative disorders have proven to spread widely throughout the world (Bulck et al., 2019). Some of them are curable, while certain disorders remain to be uncured. Multiple factors lead to the development of such disorders. Environmental, genomic, and metabolic are some of the factors that lead to the development of these disorders. The two most common neurogenerative disorders include Alzheimer's and Parkinson's disorder (Bulck et al., 2019). Alzheimer's is usually characterized by memory impairment, primarily due to the presence of neurofibrillary fibers and A β (Naomi et al., 2022). Modern-day treatments use probiotics to treat this disorder in humans, and it has been observed that changes in gut microbial diversity also adversely affect Alzheimer's in humans (Naomi et al., 2022). Parkinson's is the second stage of Alzheimer's. It is progressive and has been characterized by both motor and non-motor nerves (Gazerani, 2019).

Among the reports made, certain strains of probiotics, such as **SLAB51** (Bonfili et al., 2018), which contains species of *Lactobacillus* and *Streptococcus*, regulated glucose and brain metabolism when it was injected into an animal model. The table 2 lists other prominent strains and their mechanism of the action below.

Table 2: Probiotics strains and its mode of action for Alzheimer's and Parkinson's disease.

Strains	Mechanism of action	Reference
<i>Lactobacillus plantarum</i>	Regulates brain and glucose metabolism. Regulates neuronal activity. Regulates brain metabolism. Promotes the production of neurotransmitters like acetylcholine and acetylcholinesterase. Activates immune cells that leads to the stimulation of microbiota-gut-brain axis.	(Bonfili et al., 2018)
<i>Bifidobacterium longum</i>	Regulates metabolic abnormality. Regulates metabolic abnormality and oxidative stress. Regulates presynaptic neurotransmitters in the brain. Regulates brain metabolites. Regulates serum metabolites.	(Rezaei Asl et al., 2019; Rezaeiasl et al., 2019)
<i>Lactobacillus acidophilus</i>	Regulates brain and glucose metabolism. Regulates neuronal activity. Activates immune cells leading to stimulation of microbiota gut brain axis. Regulates brain metabolism and the intestinal microbiome. Regulates presynaptic neurotransmitters in the brain.	(Abraham et al., 2019; Leblhuber et al., 2018; Rezaeiasl et al., 2019)
<i>Clostridium butyricum WZMC1016</i>	Regulates brain metabolites.	(Bonfili et al., 2018)
<i>Lactobacillus helveticus IDCC3801</i>	Regulates brain metabolites.	(Bonfili et al., 2018)

To summarize, this study shows various evidence-based studies that have proven to help effectively in treating neurodegenerative disorders in humans. Clinical trials associated with humans have shown that Alzheimer's and Parkinson's can be treated by the usage of probiotics (Figure 2). In addition, various other clinical trials are being conducted to detect the specific changes in the gut flora. This interdisciplinary approach can effectively help treat and prevent various neurodegenerative disorders in humans.

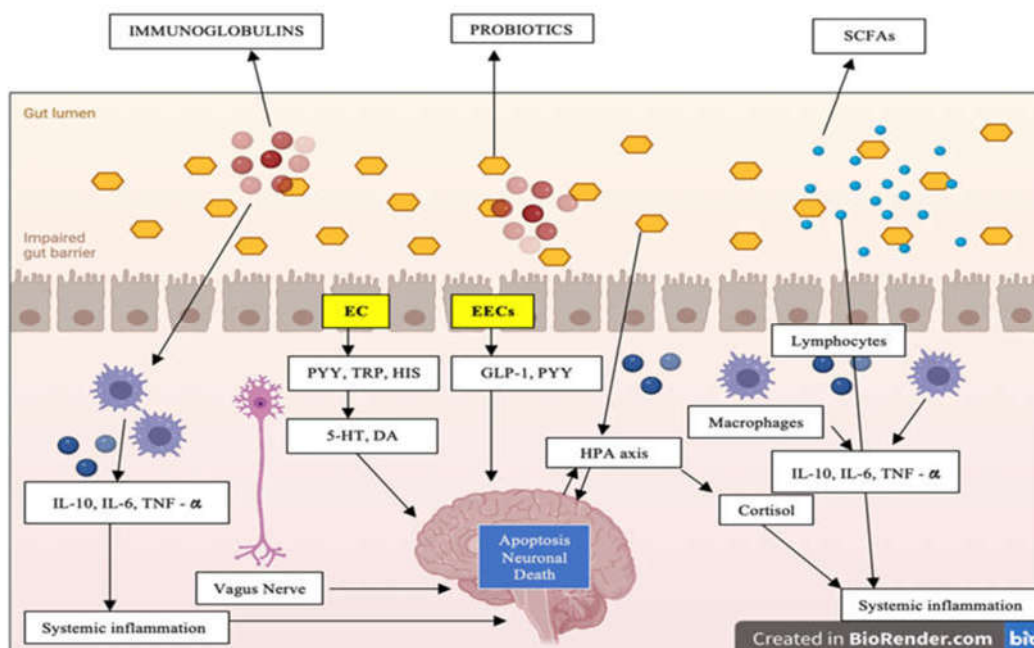


Figure 2: Mode of action of Probiotics in Alzheimer's disease (Using BioRender).

Probiotics used as an aid for food Hypersensitivity

The ingestion of a particular food or food additive that causes an immunogenic response in the body is known as food hypersensitivity or food allergy (Isolauri et al., 2002). This is mainly caused due to the release of IgE and other chemical mediators in the body that might lead to a classic allergic reaction or allergic anaphylaxis in the body. Allergies are primarily concerned with small children, and it has been noted that the gut flora of typical children is different from that of an allergic child (Isolauri et al., 2002). Most commonly, *Lactobacillus* and *Bifidobacterium* are the genera highly concentrated in humans' guts. After the first week of birth, infants compromise on various probiotics. Probiotics are maintained in the body with the help of prebiotics, the indigestible fibres that help nourish probiotics. Breast milk is said to be loaded with many prebiotics (Isolauri et al., 2002). Food hypersensitivity can be very well controlled by certain strains which are listed below in table 3.

Table 3: Probiotics strains and its mode of action for food hypersensitivity.

Strains	Mechanism of action	Reference
<i>Lactobacillus rhamnosus</i> + <i>Bifidobacterium lactis</i>	Helps in decreasing atopic dermatitis or eczema in children with food allergy.	(Santos et al., 2020)
<i>Lactobacillus rhamnosus GG</i>	Decreases allergic asthma Increases fecal IgA levels	(Pessi et al., 2000)
<i>Lactobacillus casei</i>	Decreases allergic rhinitis	(Santos et al., 2020)
<i>Lactobacillus reuteri</i>	Increases the Th1 and Th2 balance in the body and the Th2 cytokines	(Santos et al., 2020)

<i>Bifidobacterium longum</i>	Decreases IL 10 production in the body	(Santos et al., 2020)
-------------------------------	--	-----------------------

This topic remains controversial as few clinical trials have been conducted to check the probiotic's action in treating food hypersensitivity. Mixing one strain of probiotics with either a prebiotic or a mixture of whey can also affect the mode of action of these probiotics in the body. Probiotics must not be supplied to immunocompromised children, even though they are prone to specific food allergies and atopic dermatitis (Kilpi et al., 2002). To conclude, there is not much evidence to prove that probiotics help effectively treat and prevent food allergies in humans.

Probiotics used as an aid for Oral Health

Oral health has gotten much attention in the last decades. A pleasant and valuable dental structure that enables an individual to lead a fulfilling social life (Meurman & Stamatova, 2007). On the other hand, oral health is the state of being comfortable and pain-free, having a socially acceptable dentofacial profile, being able to chew and eat a wide variety of diet-related foods, speaking clearly, and having fresh breath (Meurman & Stamatova, 2007). Oral health can be controlled by certain strains which are listed below in table 4.

Table 4: Probiotics strains and its mode of action for Oral health.

Strains	Mechanism of action	Reference
<i>Lactobacillus rhamnosus</i> GG + <i>Lactobacillus casei</i>	Hamper the growth of <i>Streptococcus</i> which are associated with the development of dental caries in the mouth.	(Ahola et al., 2002; Busscher et al., 1999; Hatakka et al., 2001; Meurman et al., 1994)
<i>S. salivarius</i>	Reduction in volatile sulphur compounds	(Burton et al., 2005)
<i>Lactobacillus sp</i>	Helps to form a barrier to stop the colonization of pathogens due to the production of inhibiting substances	(Boris et al., 1997; G Reid et al., 1988)
<i>Lactobacillus reuteri</i> ATCC 55 730	Reduction in the level of <i>Streptococcus mutans</i>	(Caglar et al., 2006)
<i>W. cibaria</i>	Reduction in volatile sulphur compounds	(Kang et al., 2006)

It has been demonstrated that the oral cavity contains strains specifically designated as probiotics with its diverse microbial species (Meurman et al., 1994). More research is needed to identify the mouth's resident probiotics, delineate the process they colonize, and determine how they ultimately affect the oral environment. More research would be needed to determine how probiotics affect the harmony of the oral ecosystem. Studies on the combined effect of multiple probiotics used concurrently, examining the potential additive, cumulative, or competing modes of action in the oral environment may be of particular interest. The studies on the safety of probiotics mentioned here can be used as a starting point for further, in-depth research. The basic requirements for a strain to be classified as an oral probiotic may also change depending on its intended indications. Compared to the standards appropriate for the relevant strains in other regions of the gastrointestinal system, oral applications may need to be adjusted (Meurman et al., 1994). In other words, requirements for an oral probiotic may differ from those for other health purposes. To find the best candidate probiotics for oral and dental illnesses, systematic screening and identification of latent or resident probiotic microbes is required. Investigating probiotic

therapy's role in managing oral symptoms of various diseases, such as cutaneous disorders, is critical for understanding the mechanisms by which probiotic species modify oral immunity (Meurman et al., 1994). There is no evidence that probiotics have any effect on autoimmune disease oral symptoms. Studies on people with lichen planus, pemphigus vulgaris, cicatricial pemphigoid, or aphthous stomatitis may be useful in this area. Probiotics have traditionally been administered through dairy products, the vast majority of which are produced through lactic acid fermentation. Species that ferment sugar and reduce oral pH harm the teeth (Meurman et al., 1994).

Probiotics as an aid for child health

Probiotics are bacteria that are advantageous to the host's health. Hypothesized processes include raising the mucosal barrier's resistance to the migration of bacteria and their toxins by strengthening intestinal cell junctions, modifying the host's response to microbial products, and boosting immunoglobulin levels. A mucosal response, enteral nutrition improvement to avoid pathogen growth, Competitive exclusion of potential pathogens, and antimicrobial protein production. In published meta-analyses and systematic reviews, the effects of probiotics on essential neonatal clinical outcomes are discussed (Szajewska, 2016). Human health and the activity and makeup of the gut microbiota are becoming increasingly linked to intestinal and systemic illnesses. In full-term newborns with mild hypoxia on the first day of life, Lachnospiraceae and Clostridia predominate, related to decreased brain development and communication at 6 months (Szajewska, 2016). Antibiotic-resistant bacteria in preterm neonates increase the risk of infection and negatively impact neonatal growth and development (Bresesti et al., 2022). Probiotics have increased intestinal Bifidobacteria and the functional capacity to utilize human milk oligosaccharides while reducing enteric inflammation and antibiotic resistance. To investigate gut microbiota as a predictive biomarker and develop targeted therapies, it must be known if dysbiosis causes or results from significant disorders. Probiotic strains such as *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*, *Lactobacillus reuteri* DSM 17938, *Bifidobacterium animalis* subsp. BB12, *E. coli* nissle 1917, and *Bifidobacterium lactis* DN173, along with rehydration therapy, are used frequently in neonatal treatments and for the prevention of conditions like acute gastroenteritis, antibiotic-associated diarrhea, nosocomial diarrhea, allergies, inflammatory bowel disease in the children (Szajewska, 2016).

Probiotics as an aid for cancer

Probiotics improve apoptosis in cancer patients (Śliżewska et al., 2020). In mouse and human colon cancer, HGC-27 and colitis *Lactobacillus rhamnosus* GG suppresses proliferation and promotes apoptosis in Caco-2, DLD-1, and HT-29 cells (Orlando et al., 2012). Probiotics and their metabolites, such as butyrate and pyridoxine, may fight cancer in preclinical trials (figure 3). SCFAs provide colon cells with energy, keep the gut acidic, restrict secondary bile acid generation, and promote cancer cell acidosis and death (Kahouli et al., 2013). Butyric acid balances colon cell growth, division, and apoptosis. Colorectal cancer patients have lower stool butyrate levels than healthy persons because colon cell metabolism produces 70%–90% of it (Macfarlane & Macfarlane, 2003).

Due to individual variances, gut flora may not create enough SCFAs to prevent colorectal cancer. Thus, probiotics boost SCFA production. SCFAs suppress pathogen development. In vitro, propionic acid and butyric acid prevented *Salmonella typhimurium* from attacking healthy cells by inhibiting its invasive genes (Gantois et al., 2006). SCFAs also modulate systemic and intestinal immunity. SCFAs cause intestinal epithelial cells to generate antimicrobial peptides and tight junctions to sustain intestinal barrier function. SCFAs interact with intestinal G protein-coupled receptors to balance inflammation and immunological response (Soel et al., 2007). Both conjugated linoleic acid (CLA) and LA can stimulate apoptosis genes, including Bcl-2, caspase 3, and caspase 9, preventing colon cancer cell spread (Lu et al., 2021). According to previous research, *Lactobacillus*, *Bifidobacterium*, *Streptococcus salivarius*, and *Propionibacterium freudenreichii* subspecies can create CLA in the terminal ileum, which colonic cells can absorb or interact with to benefit (Śliżewska et al., 2020). These strains can be

used alone or alongside cancer drugs. Immune surveillance against cancer achieved therapeutic goals(Zhang et al., 2019). It is also observed that TGF- β receptor blockers and probiotics enhanced the antitumor immune response, decreasing tumor development (Shi et al., 2019). Probiotics' anticancer mechanisms include positive control of intestinal flora, metabolic activity, binding and degradation of carcinogenic chemicals, immunomodulation to reduce chronic inflammation, decreasing intestinal pH, and inhibiting enzymes that create potential carcinogens (Molska & Reguła, 2019; Reis et al., 2019). In animal models, probiotics cure cancers (Li et al., 2016; Ranji et al., 2019). Abnormal gut flora increases colorectal cancer risk (Fong et al., 2020). Colorectal cancer patients have more gut bacteria that induce gastrointestinal inflammatory disorders and create toxins and carcinogenic compounds (Yang et al., 2017). SCFA-producing bacteria and probiotics decrease. Inflammation increases cancer risk. Under the colon mucus layer, *Clostridium* spp. invaded the submucosa and caused chronic local inflammation (Molska & Reguła, 2019). Colorectal cancer tissues had elevated *Clostridium* spp. and a profile of inflammation-related genes and proteins, such as COX-2, NF- κ B, TNF- α , IL-6, IL-8, and IL-12, and matrix metalloproteinases 3 and 9, which contributed to tumor development and transfer (Reis et al., 2019). It's been discovered that *Lactobacillus rhamnosus* GG, *acidophilus*, or celecoxib decreased NF- κ B, COX-2, b-catenin, and K-ras carcinogenic indicators in a colorectal cancer animal model (Chandel et al., 2019). Colorectal cancer patients have a distinct microbial structure and lower diversity than noncancer individuals. Probiotics boosted mucosal bacteria diversity and structure. Pyrosequencing showed that probiotics reduced *Fusibacter* genus abundance, previously linked to cancer. Another preclinical investigation suggested that *Bifidobacterium bifidum* and *L. acidophilus* might change gut microorganisms to prevent colon cancer. Probiotics may prevent or treat colorectal cancer in high-risk individuals (Lu et al., 2021).

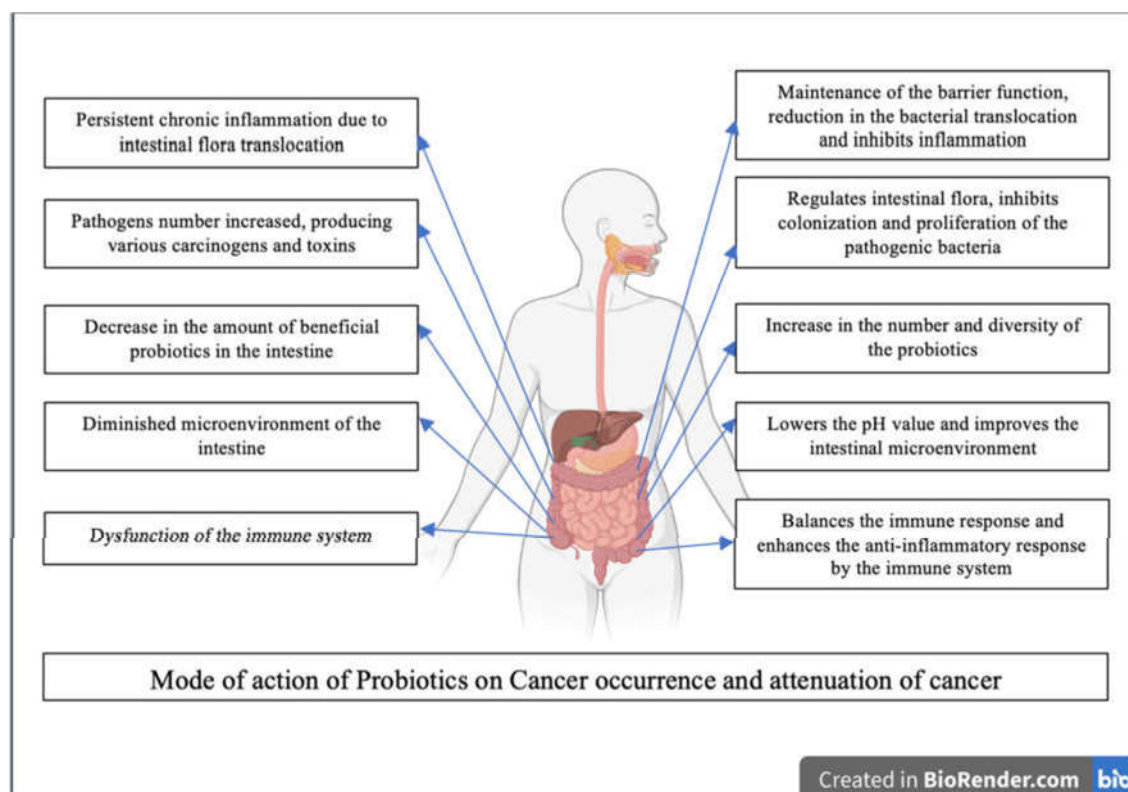


Figure 3: Mode of action of probiotics on cancer occurrence and attenuation of cancer.

Next generation probiotics

Over the past decade, gut commensal bacteria research has outpaced pathogen research. Many researchers have examined gut microbiota dysbiosis. Chronic inflammation causes intra- and extra-intestinal chronic inflammation-related illnesses, including colitis, obesity/metabolic syndromes, diabetes mellitus, liver diseases, cardiovascular diseases, cancer, and neurodegenerative diseases (Chang et al., 2019). Altering gut microbiota structure has been extensively investigated to overcome these hurdles. It has revealed more about treating inflammation-related illnesses (Chang et al., 2019). Next-generation probiotics are showing promise as preventive and therapeutic agents, whereas conventional probiotics frequently have relatively moderate advantages. *Prevotella copri* and *Christensenella minuta* regulate insulin resistance. *Parabacteroides Goldstein*, *Akkermansia muciniphila*, and *Bacteroides thetaiotaomicron* reverse obesity and insulin resistance, *Faecalibacterium prausnitzii* protects mice from intestinal diseases, and *Bacteroides fragilis* reduces inflammation and fights cancer (Chang et al., 2019). New anti-inflammatory drugs will be released soon. Intestinal integrity and homeostasis depend on next-generation probiotics and gut microbiota necrobiosis.

One of the best ways to treat diseases caused by leaky gut syndromes is with the help of probiotic drugs. The main reasons why probiotics are given may include making the intestinal epithelial layer stronger, boosting IgA production to its highest level, controlling the production and release of homeostatic bile acids, and making more antimicrobial peptides (Oliveira & González-Molero, 2016). Generally, well-known conventional probiotics like *Bifidobacterium* spp., *Lactobacillus* spp., and many others were chosen by chance or by putting together personal experiences. But the overall effects and functions on improving illness are statistically insignificant, even if most are safe for biological use. Some may work to improve the condition. Traditional probiotics, however, don't treat any particular diseases. Because of this, it is essential to find and describe new NGPs specific to the disease (Bottacini et al., 2017). In addition to safety concerns, the NGP will need to know a lot about the conditions they are trying to treat and the genetic and physiological aspects of bacteria, such as how they grow and respond to antibiotics.

Also, it's essential to understand the molecular pathways that lead to improvement. To do this, cutting-edge NGS (next-generation sequencing) and bioinformatics technology platforms must be used to screen and isolate the NGP and then do strict functional validation of the novel probiotics. In terms of how they work, these methods are very different from those usually used alone or with traditional probiotics. To choose good probiotics, it would be necessary to do cross-sectional (or even longitudinal) studies and more in-depth bioinformatics analysis of the microbiota composition, metagenomics, and the host's responses, such as the metabolites/metabolomes that are made. After that, potential probiotics or the consortium could be chosen based on the analysis done by the many multi-omics big data groups. After that, the selected probiotics are tested to make sure they work. This can be done with in vitro cell lines, ex vivo animal models, in vivo animals, or even clinical trials with people. Also, it may be necessary to improve the quality of the samples to be analyzed to get more valuable and relevant results. These samples could come from nearby mucosa loci or feces that are easy to get. It is important to stress that strict design and execution of standardized processing processes for sample collection, ideal storage conditions, and complete sequencing and bioinformatics analysis will be needed. To get a biochemical result that looks at the big picture, different extensive data findings from studies of large amounts of blood/serum, tissues, urine, and feces samples under other environmental conditions, such as different diets and drug treatments, must be combined. Then, these results can be used to show how the host and bacteria interact in more realistic ways (Hiippala et al., 2018).

Some of the prominent examples suitable for next-gen probiotics include *Bacteroides fragilis*, *Faecalibacterium prausnitzii* (Duncan et al., 2002; Park et al., 2018; Wrzosek et al., 2013), *Akkermansia muciniphila* (P D Cani et al., 2014; Patrice D Cani & de Vos, 2017; Everard et al., 2013; Plovier et al., 2017; Wang et al., 2018), *Prevotella copri* (Fu et al., 2005; Hu et al., 2009), *Bifidobacterium* spp (Bilen et al., 2018; Delcenserie et al., 2007; Russell et al., 2011). Several techniques, such as bioinformatics,

computational biology, 16srna sequencing, biochemical characterization, strain improvement techniques, and genetic engineering, could be followed and practiced to work the next generation of probiotics successfully.

Risk factors involved in the use of probiotics as health supplements

Probiotics are widely considered to be safe (GRAS) and are added to a variety of meals, primarily yoghurts, as well as beverages and other common food supplements (Floch, 2013). They are often offered over the counter and are not regulated beyond the control of marketing claims. However, there are potential infection risk factors that should be considered prior to probiotic administration, such as immunocompromised and preterm infants (Floch, 2013). Minor risk factors for heart valve dysfunction include the presence of central venous catheters, impaired intestinal epithelial barriers, administration of probiotics via jejunostomy, concurrent administration of broad-spectrum antibiotics to which probiotics are resistant, properties of high mucosal adhesion of known pathogens, and cardiac valve disease. Boyle et al., 2006 and his colleagues found that these risk variables were substantial despite their limited prevalence. Whelan & Myers, 2010 conducted a systematic analysis of case reports, randomised controlled trials, and nonrandomized studies, and found that the extremely low frequency of problems in individuals receiving nutritional assistance did not constitute a contraindication for their usage. Prior to administration, probiotics should be subjected to a risk-benefit analysis and regular adverse event monitoring should be performed. There is a long history of safe use of probiotics in meals and as supplements, and the Food and Drug Administration and EFSA generally consider them to be safe (Ferreira et al., 2010).

Conclusion

Probiotics, prebiotics, and synbiotics have been studied for their health benefits, and this paper discusses the uses, properties, and functions of some probiotic strains. Next-generation probiotics production is one of the few advancements in biology and has significant prospects. Probiotics are GRAS and are often offered over the counter, but there are potential infection risk factors such as immunocompromised and preterm infants. Risk factors for heart valve dysfunction include central venous catheters, impaired intestinal epithelial barriers, administration of probiotics via jejunostomy, concurrent administration of broad-spectrum antibiotics, and cardiac valve disease. Prior to administration, probiotics should be subjected to a risk-benefit analysis and regular adverse event monitoring.

References

- Abraham, D., Feher, J., Scuderi, G. L., Szabo, D., Dobolyi, A., Cservenak, M., Juhasz, J., Ligeti, B., Pongor, S., Gomez-Cabrera, M. C., Vina, J., Higuchi, M., Suzuki, K., Boldogh, I., & Radak, Z. (2019). Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: Role of microbiome. *Experimental Gerontology*, 115, 122–131. <https://doi.org/10.1016/j.exger.2018.12.005>
- Ahola, A. J., Yli-Knuuttila, H., Suomalainen, T., Poussa, T., Ahlström, A., Meurman, J. H., & Korpela, R. (2002). Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors. *Archives of Oral Biology*, 47(11), 799–804. [https://doi.org/10.1016/s0003-9969\(02\)00112-7](https://doi.org/10.1016/s0003-9969(02)00112-7)
- Bilen, M., Dufour, J.-C., Lagier, J.-C., Cadoret, F., Daoud, Z., Dubourg, G., & Raoult, D. (2018). The contribution of culturomics to the repertoire of isolated human bacterial and archaeal species. *Microbiome*, 6(1), 94. <https://doi.org/10.1186/s40168-018-0485-5>
- Böhn, L., Störsrud, S., Törnblom, H., Bengtsson, U., & Simrén, M. (2013). Self-Reported Food-Related Gastrointestinal Symptoms in IBS Are Common and Associated With More Severe Symptoms and Reduced Quality of Life. *Official Journal of the American College of*

Gastroenterology | *ACG*, 108(5).

https://journals.lww.com/ajg/Fulltext/2013/05000/Self_Reported_Food_Related_Gastrointestinal.2.aspx

- Bonfili, L., Cecarini, V., Cuccioloni, M., Angeletti, M., Berardi, S., Scarpona, S., Rossi, G., & Eleuteri, A. M. (2018). SLAB51 Probiotic Formulation Activates SIRT1 Pathway Promoting Antioxidant and Neuroprotective Effects in an AD Mouse Model. *Molecular Neurobiology*, 55(10), 7987–8000. <https://doi.org/10.1007/s12035-018-0973-4>
- Boris, S., Suárez, J. E., & Barbés, C. (1997). Characterization of the aggregation promoting factor from *Lactobacillus gasseri*, a vaginal isolate. *Journal of Applied Microbiology*, 83(4), 413–420. <https://doi.org/10.1046/j.1365-2672.1997.00250.x>
- Bottacini, F., van Sinderen, D., & Ventura, M. (2017). Omics of bifidobacteria: research and insights into their health-promoting activities. *The Biochemical Journal*, 474(24), 4137–4152. <https://doi.org/10.1042/BCJ20160756>
- Boyle, R. J., Robins-Browne, R. M., & Tang, M. L. K. (2006). Probiotic use in clinical practice: what are the risks? *The American Journal of Clinical Nutrition*, 83(6), 1256–1257. <https://doi.org/10.1093/ajcn/83.6.1256>
- Bresesti, I., Salvatore, S., Valetti, G., Baj, A., Giaroni, C., & Agosti, M. (2022). The Microbiota-Gut Axis in Premature Infants: Physio-Pathological Implications. *Cells*, 11(3). <https://doi.org/10.3390/cells11030379>
- Bulck, M. Van, Sierra-Magro, A., Alarcon-Gil, J., Perez-Castillo, A., & Morales-Garcia, J. A. (2019). Novel approaches for the treatment of alzheimer's and parkinson's disease. *International Journal of Molecular Sciences*, 20(3). <https://doi.org/10.3390/ijms20030719>
- Burton, J. P., Chilcott, C. N., & Tagg, J. R. (2005). The rationale and potential for the reduction of oral malodour using *Streptococcus salivarius* probiotics. *Oral Diseases*, 11 Suppl 1, 29–31. <https://doi.org/10.1111/j.1601-0825.2005.01084.x>
- Busscher, H. J., Mulder, A. F., & van der Mei, H. C. (1999). In vitro adhesion to enamel and in vivo colonization of tooth surfaces by *Lactobacilli* from a bio-yoghurt. *Caries Research*, 33(5), 403–404. <https://doi.org/10.1159/000016541>
- Caglar, E., Cildir, S. K., Ergeneli, S., Sandalli, N., & Twetman, S. (2006). Salivary mutans streptococci and lactobacilli levels after ingestion of the probiotic bacterium *Lactobacillus reuteri* ATCC 55730 by straws or tablets. *Acta Odontologica Scandinavica*, 64(5), 314–318. <https://doi.org/10.1080/00016350600801709>
- Cain, A. M., & Karpa, K. D. (2011). Clinical utility of probiotics in inflammatory bowel disease. *Alternative Therapies in Health and Medicine*, 17(1), 72–79.
- Cani, P D, Geurts, L., Matamoros, S., Plovier, H., & Duparc, T. (2014). Glucose metabolism: focus on gut microbiota, the endocannabinoid system and beyond. *Diabetes & Metabolism*, 40(4), 246–257. <https://doi.org/10.1016/j.diabet.2014.02.004>
- Cani, Patrice D, & de Vos, W. M. (2017). Next-Generation Beneficial Microbes: The Case of *Akkermansia muciniphila*. *Frontiers in Microbiology*, 8, 1765. <https://doi.org/10.3389/fmicb.2017.01765>
- Cencic, A., & Chingwaru, W. (2010). The role of functional foods, nutraceuticals, and food supplements in intestinal health. *Nutrients*, 2(6), 611–625. <https://doi.org/10.3390/nu2060611>
- Chandel, D., Sharma, M., Chawla, V., Sachdeva, N., & Shukla, G. (2019). Isolation, characterization and identification of antigenotoxic and anticancerous indigenous probiotics and their prophylactic potential in experimental colon carcinogenesis. *Scientific Reports*, 9(1), 14769. <https://doi.org/10.1038/s41598-019-51361-z>

- Chang, C. J., Lin, T. L., Tsai, Y. L., Wu, T. R., Lai, W. F., Lu, C. C., & Lai, H. C. (2019). Next generation probiotics in disease amelioration. *Journal of Food and Drug Analysis*, 27(3), 615–622. <https://doi.org/10.1016/j.jfda.2018.12.011>
- Council, I., & Icmr, C. U. (2015). Policy Document ICMR-DBT Guidelines for Evaluation of Probiotics in Food. *Indian J Med Res*, 13(134), 22–25.
- Delcenserie, V., Gavini, F., Beerens, H., Tresse, O., Franssen, C., & Daube, G. (2007). Description of a new species, *Bifidobacterium crudilactis* sp. nov., isolated from raw milk and raw milk cheeses. *Systematic and Applied Microbiology*, 30(5), 381–389. <https://doi.org/10.1016/j.syapm.2007.01.004>
- Di Cagno, R., De Angelis, M., De Pasquale, I., Ndagijimana, M., Vernocchi, P., Ricciuti, P., Gagliardi, F., Laghi, L., Crecchio, C., Guerzoni, M. E., Gobbetti, M., & Francavilla, R. (2011). Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. *BMC Microbiology*, 11, 219. <https://doi.org/10.1186/1471-2180-11-219>
- Duncan, S. H., Hold, G. L., Harmsen, H. J. M., Stewart, C. S., & Flint, H. J. (2002). Growth requirements and fermentation products of *Fusobacterium prausnitzii*, and a proposal to reclassify it as *Faecalibacterium prausnitzii* gen. nov., comb. nov. *International Journal of Systematic and Evolutionary Microbiology*, 52(Pt 6), 2141–2146. <https://doi.org/10.1099/00207713-52-6-2141>
- El-Salhy, M., Hatlebakk, J. G., Gilja, O. H., & Hausken, T. (2014). Irritable bowel syndrome: recent developments in diagnosis, pathophysiology, and treatment. *Expert Review of Gastroenterology & Hepatology*, 8(4), 435–443. <https://doi.org/10.1586/17474124.2014.888952>
- Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J. P., Druart, C., Bindels, L. B., Guiot, Y., Derrien, M., Muccioli, G. G., Delzenne, N. M., de Vos, W. M., & Cani, P. D. (2013). Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences of the United States of America*, 110(22), 9066–9071. <https://doi.org/10.1073/pnas.1219451110>
- Ferreira, C., Magalhães, M., Gueimonde, M., & Salminen, S. (2010). *Probiotics: From Origin to Labeling from a European and Brazilian Perspective* (pp. 75–87). <https://doi.org/10.1002/9781444329384.ch5>
- Floch, M. H. (2013). Probiotic safety and risk factors. *Journal of Clinical Gastroenterology*, 47(5), 375–376. <https://doi.org/10.1097/MCG.0b013e3182840226>
- Fong, W., Li, Q., & Yu, J. (2020). Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene*, 39(26), 4925–4943. <https://doi.org/10.1038/s41388-020-1341-1>
- Fu, G.-F., Li, X., Hou, Y.-Y., Fan, Y.-R., Liu, W.-H., & Xu, G.-X. (2005). *Bifidobacterium longum* as an oral delivery system of endostatin for gene therapy on solid liver cancer. *Cancer Gene Therapy*, 12(2), 133–140. <https://doi.org/10.1038/sj.cgt.7700758>
- Fujimori, S., Tatsuguchi, A., Gudis, K., Kishida, T., Mitsui, K., Ehara, A., Kobayashi, T., Sekita, Y., Seo, T., & Sakamoto, C. (2007). High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. *Journal of Gastroenterology and Hepatology*, 22(8), 1199–1204. <https://doi.org/10.1111/j.1440-1746.2006.04535.x>
- Gantois, I., Ducatelle, R., Pasmans, F., Haesebrouck, F., Hautefort, I., Thompson, A., Hinton, J. C., & Van Immerseel, F. (2006). Butyrate specifically down-regulates salmonella pathogenicity island 1 gene expression. *Applied and Environmental Microbiology*, 72(1), 946–949. <https://doi.org/10.1128/AEM.72.1.946-949.2006>
- Gazerani, P. (2019). Probiotics for Parkinson Disease Marked.Pdf. *International Journal of Molecular*

- Sciences*, 26. <https://www-proquest-com.ezproxy.library.wur.nl/docview/2332370186?accountid=27871>
- Gersemann, M., Wehkamp, J., & Stange, E. F. (2012). Innate immune dysfunction in inflammatory bowel disease. *Journal of Internal Medicine*, 271(5), 421–428. <https://doi.org/10.1111/j.1365-2796.2012.02515.x>
- Gibson, G. R., & Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *The Journal of Nutrition*, 125(6), 1401–1412. <https://doi.org/10.1093/jn/125.6.1401>
- Hahn, B. A., Yan, S., & Strassels, S. (1999). Impact of Irritable Bowel Syndrome on Quality of Life and Resource Use in the United States and United Kingdom. *Digestion*, 60(1), 77–81. <https://doi.org/10.1159/000007593>
- Hatakka, K., Savilahti, E., Pönkä, A., Meurman, J. H., Poussa, T., Näse, L., Saxelin, M., & Korpela, R. (2001). Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ (Clinical Research Ed.)*, 322(7298), 1327. <https://doi.org/10.1136/bmj.322.7298.1327>
- Hegazy, S. K., & El-Bedewy, M. M. (2010). Effect of probiotics on pro-inflammatory cytokines and NF-kappaB activation in ulcerative colitis. *World Journal of Gastroenterology*, 16(33), 4145–4151. <https://doi.org/10.3748/wjg.v16.i33.4145>
- Hiippala, K., Jouhten, H., Ronkainen, A., Hartikainen, A., Kainulainen, V., Jalanka, J., & Satokari, R. (2018). The Potential of Gut Commensals in Reinforcing Intestinal Barrier Function and Alleviating Inflammation. *Nutrients*, 10(8). <https://doi.org/10.3390/nu10080988>
- Hong, S. N., & Rhee, P.-L. (2014). Unraveling the ties between irritable bowel syndrome and intestinal microbiota. *World Journal of Gastroenterology*, 20(10), 2470–2481. <https://doi.org/10.3748/wjg.v20.i10.2470>
- Hu, B., Kou, L., Li, C., Zhu, L.-P., Fan, Y.-R., Wu, Z.-W., Wang, J.-J., & Xu, G.-X. (2009). Bifidobacterium longum as a delivery system of TRAIL and endostatin cooperates with chemotherapeutic drugs to inhibit hypoxic tumor growth. *Cancer Gene Therapy*, 16(8), 655–663. <https://doi.org/10.1038/cgt.2009.7>
- Imaoka, A., Shima, T., Kato, K., Mizuno, S., Uehara, T., Matsumoto, S., Setoyama, H., Hara, T., & Umesaki, Y. (2008). Anti-inflammatory activity of probiotic Bifidobacterium: enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. *World Journal of Gastroenterology*, 14 16, 2511–2516.
- Isolauri, E., Rautava, S., Kalliomäki, M., Kirjavainen, P., & Salminen, S. (2002). Role of probiotics in food hypersensitivity. *Current Opinion in Allergy and Clinical Immunology*, 2(3), 263–271. <https://doi.org/10.1097/00130832-200206000-00018>
- Kahouli, I., Tomaro-Duchesneau, C., & Prakash, S. (2013). Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. *Journal of Medical Microbiology*, 62(Pt 8), 1107–1123. <https://doi.org/10.1099/jmm.0.048975-0>
- Kang, M.-S., Kim, B.-G., Chung, J., Lee, H.-C., & Oh, J.-S. (2006). Inhibitory effect of Weissella cibaria isolates on the production of volatile sulphur compounds. *Journal of Clinical Periodontology*, 33(3), 226–232. <https://doi.org/10.1111/j.1600-051X.2006.00893.x>
- Kilpi, T., Kero, J., Jokinen, J., Syrjänen, R., Takala, A. K., Hovi, T., & Isolauri, E. (2002). Common respiratory infections early in life may reduce the risk of atopic dermatitis. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 34(5), 620–626. <https://doi.org/10.1086/338783>

- Leblhuber, F., Steiner, K., Schuetz, B., Fuchs, D., & Gostner, J. M. (2018). Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Current Alzheimer Research*, 15(12), 1106–1113. <https://doi.org/10.2174/1389200219666180813144834>
- Li, J., Sung, C. Y. J., Lee, N., Ni, Y., Pihlajamäki, J., Panagiotou, G., & El-Nezami, H. (2016). Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. *Proceedings of the National Academy of Sciences of the United States of America*, 113(9), E1306-15. <https://doi.org/10.1073/pnas.1518189113>
- Lu, K., Dong, S., Wu, X., Jin, R., & Chen, H. (2021). Probiotics in Cancer. *Frontiers in Oncology*, 11(March). <https://doi.org/10.3389/fonc.2021.638148>
- Macfarlane, S., Furrie, E., Cummings, J. H., & Macfarlane, G. T. (2004). Chemotaxonomic analysis of bacterial populations colonizing the rectal mucosa in patients with ulcerative colitis. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 38(12), 1690–1699. <https://doi.org/10.1086/420823>
- Macfarlane, S., & Macfarlane, G. T. (2003). Regulation of short-chain fatty acid production. *The Proceedings of the Nutrition Society*, 62(1), 67–72. <https://doi.org/10.1079/PNS2002207>
- Macintyre, A., & Cymet, T. C. (2005). Probiotics: the benefits of bacterial cultures. *Comprehensive Therapy*, 31(3), 181–185. <https://doi.org/10.1385/comp:31:3:181>
- Mazzawi, T. (2022). Gut Microbiota Manipulation in Irritable Bowel Syndrome. *Microorganisms*, 10(7). <https://doi.org/10.3390/microorganisms10071332>
- Meurman, J. H., Antila, H., & Salminen, S. (1994). Recovery of lactobacillus strain GG (ATCC 53103) from saliva of healthy volunteers after consumption of yoghurt prepared with the bacterium. *Microbial Ecology in Health and Disease*, 7(6), 295–298. <https://doi.org/10.3109/08910609409141368>
- Meurman, J. H., & Stamatova, I. (2007). Probiotics: Contributions to oral health. *Oral Diseases*, 13(5), 443–451. <https://doi.org/10.1111/j.1601-0825.2007.01386.x>
- Molska, M., & Reguła, J. (2019). Potential Mechanisms of Probiotics Action in the Prevention and Treatment of Colorectal Cancer. *Nutrients*, 11(10). <https://doi.org/10.3390/nu11102453>
- Naomi, R., Embong, H., Othman, F., Ghazi, H. F., Maruthey, N., & Bahari, H. (2022). *Probiotics for Alzheimer's Disease : A Systematic Review*. 1–24.
- Ng, S. C., Hart, A. L., Kamm, M. A., Stagg, A. J., & Knight, S. C. (2009). Mechanisms of action of probiotics: recent advances. *Inflammatory Bowel Diseases*, 15(2), 300–310. <https://doi.org/10.1002/ibd.20602>
- Olveira, G., & González-Molero, I. (2016). An update on probiotics, prebiotics and symbiotics in clinical nutrition. *Endocrinología y Nutrición : Organo de La Sociedad Espanola de Endocrinología y Nutrición*, 63(9), 482–494. <https://doi.org/10.1016/j.endonu.2016.07.006>
- Orlando, A., Refolo, M. G., Messa, C., Amati, L., Lavermicocca, P., Guerra, V., & Russo, F. (2012). Antiproliferative and proapoptotic effects of viable or heat-killed Lactobacillus paracasei IMPC2.1 and Lactobacillus rhamnosus GG in HGC-27 gastric and DLD-1 colon cell lines. *Nutrition and Cancer*, 64(7), 1103–1111. <https://doi.org/10.1080/01635581.2012.717676>
- Palumbo, V. D., Romeo, M., Marino Gammazza, A., Carini, F., Damiani, P., Damiano, G., Buscemi, S., Lo Monte, A. I., Gerges-Geagea, A., Jurjus, A., & Tomasello, G. (2016). The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, 160(3), 372–377. <https://doi.org/10.5507/bp.2016.044>
- Pandey, K. R., Naik, S. R., & Vakil, B. V. (2015). Probiotics, prebiotics and synbiotics- a review.

- Journal of Food Science and Technology*, 52(12), 7577–7587. <https://doi.org/10.1007/s13197-015-1921-1>
- Park, Y.-J., Kuen, D.-S., & Chung, Y. (2018). Future prospects of immune checkpoint blockade in cancer: from response prediction to overcoming resistance. *Experimental & Molecular Medicine*, 50(8), 1–13. <https://doi.org/10.1038/s12276-018-0130-1>
- Patrick, D. L., Drossman, D. A., Frederick, I. O., Dicesare, J., & Puder, K. L. (1998). Quality of Life in Persons with Irritable Bowel Syndrome (Development and Validation of a New Measure). *Digestive Diseases and Sciences*, 43(2), 400–411. <https://doi.org/10.1023/A:1018831127942>
- Peluso, I., Fina, D., Caruso, R., Stolfi, C., Caprioli, F., Fantini, M. C., Caspani, G., Grossi, E., Di Iorio, L., Paone, F. M., Pallone, F., & Monteleone, G. (2007). *Lactobacillus paracasei* subsp. *paracasei* B21060 suppresses human T-cell proliferation. *Infection and Immunity*, 75(4), 1730–1737. <https://doi.org/10.1128/IAI.01172-06>
- Peña, A. S. (2007). [Intestinal flora, probiotics, prebiotics, symbiotics and novel foods]. *Revista espanola de enfermedades digestivas*, 99(11), 653–658. <https://doi.org/10.4321/s1130-01082007001100006>
- Pessi, T., Sütas, Y., Hurme, M., & Isolauri, E. (2000). Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology*, 30(12), 1804–1808. <https://doi.org/10.1046/j.1365-2222.2000.00948.x>
- Pham, M., Lemberg, D. A., & Day, A. S. (2008). Probiotics: sorting the evidence from the myths. *The Medical Journal of Australia*, 188(5), 304–308. <https://doi.org/10.5694/j.1326-5377.2008.tb01627.x>
- Plovier, H., Everard, A., Druart, C., Depommier, C., Van Hul, M., Geurts, L., Chilloux, J., Ottman, N., Duparc, T., Lichtenstein, L., Myridakis, A., Delzenne, N. M., Klievink, J., Bhattacharjee, A., van der Ark, K. C. H., Aalvink, S., Martinez, L. O., Dumas, M.-E., Maiter, D., ... Cani, P. D. (2017). A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nature Medicine*, 23(1), 107–113. <https://doi.org/10.1038/nm.4236>
- Pokusaeva, K., Fitzgerald, G. F., & van Sinderen, D. (2011). Carbohydrate metabolism in *Bifidobacteria*. *Genes & Nutrition*, 6(3), 285–306. <https://doi.org/10.1007/s12263-010-0206-6>
- Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D. R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., ... Consortium, M. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*, 464(7285), 59–65. <https://doi.org/10.1038/nature08821>
- Ranji, P., Agah, S., Heydari, Z., Rahmati-Yamchi, M., & Mohammad Alizadeh, A. (2019). Effects of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* probiotics on the serum biochemical parameters, and the vitamin D and leptin receptor genes on mice colon cancer. *Iranian Journal of Basic Medical Sciences*, 22(6), 631–636. <https://doi.org/10.22038/ijbms.2019.32624.7806>
- Rao, S., & Weber, H. C. (2014). New treatment targets for the management of irritable bowel syndrome. *Current Opinion in Endocrinology, Diabetes and Obesity*, 21(1). https://journals.lww.com/co-endocrinology/Fulltext/2014/02000/New_treatment_targets_for_the_management_of.4.aspx
- Reid, G., McGroarty, J. A., Angotti, R., & Cook, R. L. (1988). *Lactobacillus* inhibitor production against *Escherichia coli* and coaggregation ability with uropathogens. *Canadian Journal of Microbiology*, 34(3), 344–351. <https://doi.org/10.1139/m88-063>
- Reid, Gregor, eng Fao, R., Fao, J., & eng Who, G. (2001). *Regulatory and clinical aspects of dairy*

probiotics.

- Reis, S. A. Dos, da Conceição, L. L., & Peluzio, M. do C. G. (2019). Intestinal microbiota and colorectal cancer: changes in the intestinal microenvironment and their relation to the disease. *Journal of Medical Microbiology*, 68(10), 1391–1407. <https://doi.org/10.1099/jmm.0.001049>
- Rezaei Asl, Z., Sepehri, G., & Salami, M. (2019). Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. *Behavioural Brain Research*, 376, 112183. <https://doi.org/10.1016/j.bbr.2019.112183>
- Rezaeiasl, Z., Salami, M., & Sepehri, G. (2019). The Effects of Probiotic Lactobacillus and Bifidobacterium Strains on Memory and Learning Behavior, Long-Term Potentiation (LTP), and Some Biochemical Parameters in β -Amyloid-Induced Rat's Model of Alzheimer's Disease. *Preventive Nutrition and Food Science*, 24, 265–273.
- Russell, D. A., Ross, R. P., Fitzgerald, G. F., & Stanton, C. (2011). Metabolic activities and probiotic potential of bifidobacteria. *International Journal of Food Microbiology*, 149(1), 88–105. <https://doi.org/10.1016/j.ijfoodmicro.2011.06.003>
- Saldanha, L. G. (2008). US Food and Drug Administration regulations governing label claims for food products, including probiotics. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 46 Suppl 2, S119-21; discussion S144-51. <https://doi.org/10.1086/523328>
- Santos, S. C. dos, Konstantyner, T., & Cocco, R. R. (2020). Effects of probiotics in the treatment of food hypersensitivity in children: a systematic review. *Allergologia et Immunopathologia*, 48(1), 95–104. <https://doi.org/10.1016/j.aller.2019.04.009>
- Santosa, S., Farnworth, E., & Jones, P. J. H. (2006). Probiotics and their potential health claims. *Nutrition Reviews*, 64(6), 265–274. <https://doi.org/10.1111/j.1753-4887.2006.tb00209.x>
- Scarpellini, E., Cazzato, A., Lauritano, C., Gabrielli, M., Lupascu, A., Gerardino, L., Abenavoli, L., Petruzzellis, C., Gasbarrini, G., & Gasbarrini, A. (2008). Probiotics: which and when? *Digestive Diseases (Basel, Switzerland)*, 26(2), 175–182. <https://doi.org/10.1159/000116776>
- Schuster, M. M. (2001). Defining and diagnosing irritable bowel syndrome. *The American Journal of Managed Care*, 7(8 Suppl), S246—51. <http://europepmc.org/abstract/MED/11474909>
- Scott, K. P., Antoine, J.-M., Midtvedt, T., & van Hemert, S. (2015). Manipulating the gut microbiota to maintain health and treat disease. *Microbial Ecology in Health and Disease*, 26, 25877. <https://doi.org/10.3402/mehd.v26.25877>
- Seksik, P., Dray, X., Sokol, H., & Marteau, P. (2008). Is there any place for alimentary probiotics, prebiotics or synbiotics, for patients with inflammatory bowel disease? *Molecular Nutrition & Food Research*, 52(8), 906–912. <https://doi.org/10.1002/mnfr.200700147>
- Senok, A. C., Ismaeel, A. Y., & Botta, G. A. (2005). Probiotics: facts and myths. *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*, 11(12), 958–966. <https://doi.org/10.1111/j.1469-0691.2005.01228.x>
- Shi, L., Sheng, J., Wang, M., Luo, H., Zhu, J., Zhang, B., Liu, Z., & Yang, X. (2019). Combination Therapy of TGF- β Blockade and Commensal-derived Probiotics Provides Enhanced Antitumor Immune Response and Tumor Suppression. *Theranostics*, 9, 4115–4129. <https://doi.org/10.7150/thno.35131>
- Śliżewska, K., Markowiak-Kopeć, P., & Śliżewska, W. (2020). The Role of Probiotics in Cancer Prevention. *Cancers*, 13(1). <https://doi.org/10.3390/cancers13010020>
- Soel, S. M., Choi, O. S., Bang, M. H., Yoon Park, J. H., & Kim, W. K. (2007). Influence of conjugated

- linoleic acid isomers on the metastasis of colon cancer cells in vitro and in vivo. *The Journal of Nutritional Biochemistry*, 18(10), 650–657. <https://doi.org/10.1016/j.jnutbio.2006.10.011>
- Surawicz, C. M. (2008). Role of probiotics in antibiotic-associated diarrhea, *Clostridium difficile*-associated diarrhea, and recurrent *Clostridium difficile*-associated diarrhea. *Journal of Clinical Gastroenterology*, 42 Suppl 2, S64-70. <https://doi.org/10.1097/MCG.0b013e3181646d09>
- Szajewska, H. (2016). What are the indications for using probiotics in children? *Archives of Disease in Childhood*, 101(4), 398–403. <https://doi.org/10.1136/archdischild-2015-308656>
- Tack, J., Vanuytsel, T., & Corsetti, M. (2016). Modern Management of Irritable Bowel Syndrome: More Than Motility. *Digestive Diseases*, 34(5), 566–573. <https://doi.org/10.1159/000445265>
- Tamboli, C. P., Neut, C., Desreumaux, P., & Colombel, J. F. (2004). Dysbiosis in inflammatory bowel disease. *Gut*, 53(1), 1–4. <https://doi.org/10.1136/gut.53.1.1>
- Vanderhoof, J. A., & Young, R. (2008). Probiotics in the United States. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 46 Suppl 2, S67-72; discussion S144-51. <https://doi.org/10.1086/523339>
- Vanderpool, C., Yan, F., & Polk, D. B. (2008). Mechanisms of probiotic action: Implications for therapeutic applications in inflammatory bowel diseases. *Inflammatory Bowel Diseases*, 14(11), 1585–1596. <https://doi.org/10.1002/ibd.20525>
- Wald, A., & Rakel, D. (2008). Behavioral and complementary approaches for the treatment of irritable bowel syndrome. *Nutrition in Clinical Practice : Official Publication of the American Society for Parenteral and Enteral Nutrition*, 23(3), 284–292. <https://doi.org/10.1177/0884533608318677>
- Wang, Y., Ma, R., Liu, F., Lee, S. A., & Zhang, L. (2018). Modulation of Gut Microbiota: A Novel Paradigm of Enhancing the Efficacy of Programmed Death-1 and Programmed Death Ligand-1 Blockade Therapy. *Frontiers in Immunology*, 9, 374. <https://doi.org/10.3389/fimmu.2018.00374>
- Whelan, K., & Myers, C. E. (2010). Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. *The American Journal of Clinical Nutrition*, 91(3), 687–703. <https://doi.org/10.3945/ajcn.2009.28759>
- Wilson, B. C., Vatanen, T., Cutfield, W. S., & O’Sullivan, J. M. (2019). The Super-Donor Phenomenon in Fecal Microbiota Transplantation. *Frontiers in Cellular and Infection Microbiology*, 9. <https://doi.org/10.3389/fcimb.2019.00002>
- Wrzosek, L., Miquel, S., Noordine, M.-L., Bouet, S., Joncquel Chevalier-Curt, M., Robert, V., Philippe, C., Bridonneau, C., Cherbuy, C., Robbe-Masselot, C., Langella, P., & Thomas, M. (2013). *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biology*, 11, 61. <https://doi.org/10.1186/1741-7007-11-61>
- Wu, X., Wang, J., Ye, Z., Wang, J., Liao, X., Liv, M., & Svn, Z. (2022). Risk of Colorectal Cancer in Patients With Irritable Bowel Syndrome: A Meta-Analysis of Population-Based Observational Studies. *Frontiers in Medicine*, 9. <https://doi.org/10.3389/fmed.2022.819122>
- Yang, Y., Weng, W., Peng, J., Hong, L., Yang, L., Toiyama, Y., Gao, R., Liu, M., Yin, M., Pan, C., Li, H., Guo, B., Zhu, Q., Wei, Q., Moyer, M.-P., Wang, P., Cai, S., Goel, A., Qin, H., & Ma, Y. (2017). *Fusobacterium nucleatum* Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating Toll-Like Receptor 4 Signaling to Nuclear Factor-κB, and Up-regulating Expression of MicroRNA-21. *Gastroenterology*, 152(4), 851-866.e24. <https://doi.org/10.1053/j.gastro.2016.11.018>
- Zhang, Z., Tang, H., Chen, P., Xie, H., & Tao, Y. (2019). Demystifying the manipulation of host

immunity, metabolism, and extraintestinal tumors by the gut microbiome. *Signal Transduction and Targeted Therapy*, 4, 41. <https://doi.org/10.1038/s41392-019-0074-5>

Zolkiewicz, J., Marzec, A., Ruszczynski, M., & Feleszko, W. (2020). Postbiotics—A Step Beyond Pre- and Probiotics _ Enhanced Reader. *Nutrients*, 1–17.