A Symphony of Bacteria: The Role of Probiotics and Prebiotics

Minha Faran[1,*], Afsheen Zainab[2], Aqsa Batool[2], Muhaddisa Laraib[3], Savera Nashin[4] and Rameen Nawaz[5]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]Department of Microbiology, University of Jhang, Jhang, Pakistan
[3]Department of Biochemistry, University of Jhang, Jhang, Pakistan
[4]National Institute of Food Sciences and Technology (NIFSAT), University of Agriculture, Faisalabad, Pakistan
[5]Centre of Agricultural Biochemistry and Biotechnology (CABB), University of Agriculture, Faisalabad, Pakistan
*Corresponding author: minhafaran67@gmail.com

Abstract

The human body is inhabited by a vast array of microorganisms, with the gut microbiome playing a pivotal role in maintaining overall health and well-being. The intricate interplay between probiotics and prebiotics creates a harmonious symphony within the microbial world, profoundly influencing host health and disease resistance. Probiotics, beneficial live microorganisms, and prebiotics, the non-digestible compounds fostering their growth, work synergistically to maintain gut homeostasis and enhance immune functionality. This chapter explores the mechanisms sustaining this relationship, exploring their roles in shaping the gut microbiota, combating pathogenic microbes, and promoting metabolic health. The chapter highlights innovative applications of probiotics and prebiotics in therapeutic strategies, ranging from gastrointestinal disorders to mental health. By unraveling this symphony of bacteria, we underscore the potential of leveraging probiotics and prebiotics to pioneer novel approaches in nutrition and medicine.

Keywords: Prebiotics, Probiotics, Gastro-intestinal tract, Micro-flora, Strains

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Introduction

For eons, there has been a curiosity about the microorganisms especially bacteria. Seemingly containing a simple cell, they can work wonders. It was only the dawn of the twentieth century when Nobel Prize laureate Metchnikoff (1907) discovered how fermented milk was beneficial to the ecosystem of the human gut but also accelerated the digestion of lactose. The term probiotic was first introduced by Lilly and Stillwell in 1965. In modern terminology, probiotics are defined as small microorganisms which are beneficial to health when consumed (Pandey et al., 2015). These probiotics usually have bacterial strains and flourish in the gastrointestinal tract of the host animal. Examples of frequently used strains in probiotics are *Lactobacillus*, *Bifidobacteria,* and *Saccharomyces boulardii* (fungi) (Figure 1). On the other hand, prebiotics are indigestible feed ingredients generally an insoluble fiber that are used for bacterial fermentation in the gut (Gibson and Roberfroid, 1995). Together both probiotics and prebiotics are called synbiotics.

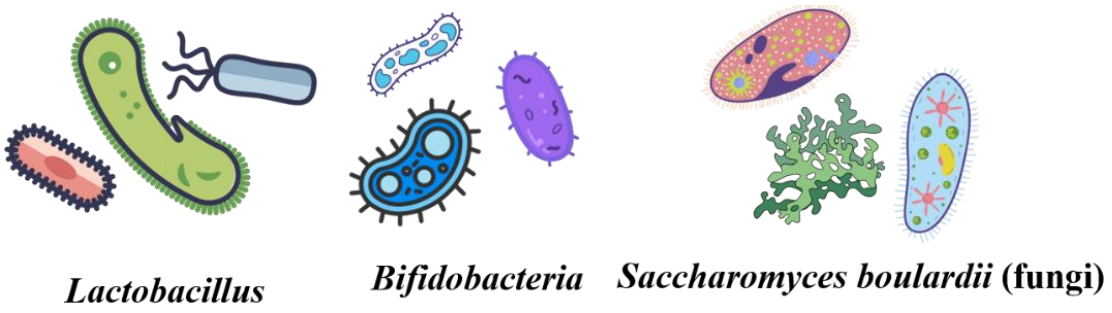

Fig. 1: Probiotic Strains

Probiotics

Henry Tissier was a French pediatrician who observed that the stool of children having diarrhea had few strains of bacteria that were preeminently present in the stool of healthy individuals. That's why he recommended giving infants milk fermented with *Bacillus acidiparalectici* to prevent pathogens responsible for diarrhea. Metchnikoff also noticed the benefits of bioactive components of milk laced with *Lactobacilli*, hence he stated that not all microorganisms are harmful. According to the FAO/WHO (2001) report on probiotics the characteristics

that contribute to the usefulness of the strains are:

1) Their beneficial effect has been proved beforehand.

2) They must resist physiological stresses (biliary salts, gastric juice and acidity of stomach) during ingestion that they can reach easily to their site of action.

3) They should not impose any harm to the host.

All these features must remain intact throughout their journey from processing to ingestion. The edibles having bioactive components in it i.e. probiotics are called functional foods. The most used bacterial strains are *Lactobacillus* (often referred to as LABs) and *Bifidobacterium* (Figure 2).

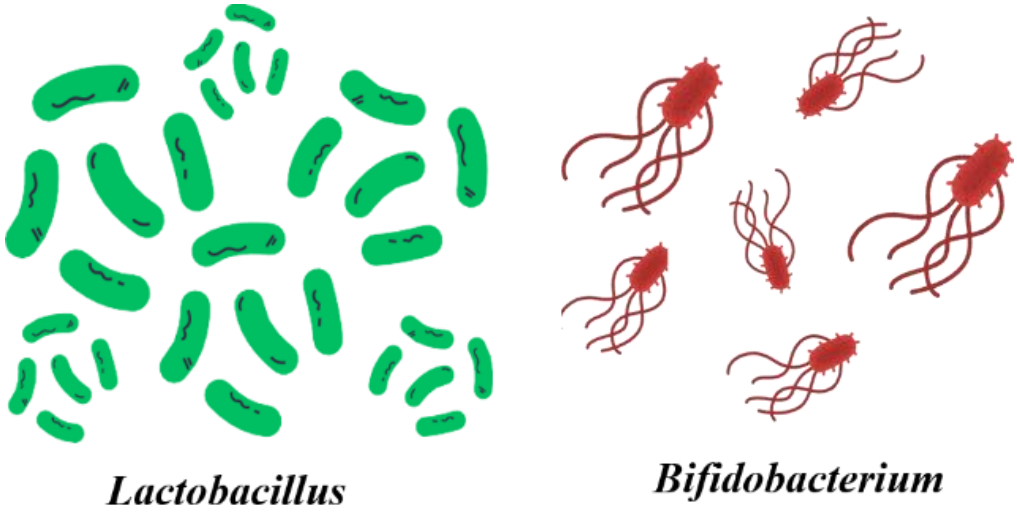

Fig. 2: Popular bacterial strains *Lactobacillus* and *Bifidobacterium*

Prebiotics

Prebiotics are non-living and indigestible food ingredients. They are favorable to the host and the associated microflora in the gut (FAO, 2008). The food we eat has both digestible and indigestible fibers, later being the prebiotics. Since probiotics are dependent on these prebiotics therefore their required features are: 1) suitable for bacterial activities 2) resilient towards gastric fluids, and 3) safe to arrive in the colon without being absorbed in the stomach (Butel and Dupriet, 2016). Fructo-oligosaccharides (FOS), trans-galacto-oligosaccharides (TOS), galacto-oligosaccharides, and inulin (Figure 3). A mixture of FOS/GOS (10/90) by percentage, mimics the molecular distribution of oligosaccharides present in human milk hence induced in formula milk for infants. For adults, a 50/50 combination of inulin-oligofructose is used. The natural origin of oligosaccharides and inulin are breast milk, bananas, garlic, wheat, oats, onion, soybean, and asparagus. Oligofructose is commonly used as the substitute of sucrose but it provides less energy and is less sweet. Some other molecules like wheat dextrin, whole grain wheat, whole grain corn, polydextrose, psyllium, and lactulose have prebiotics.

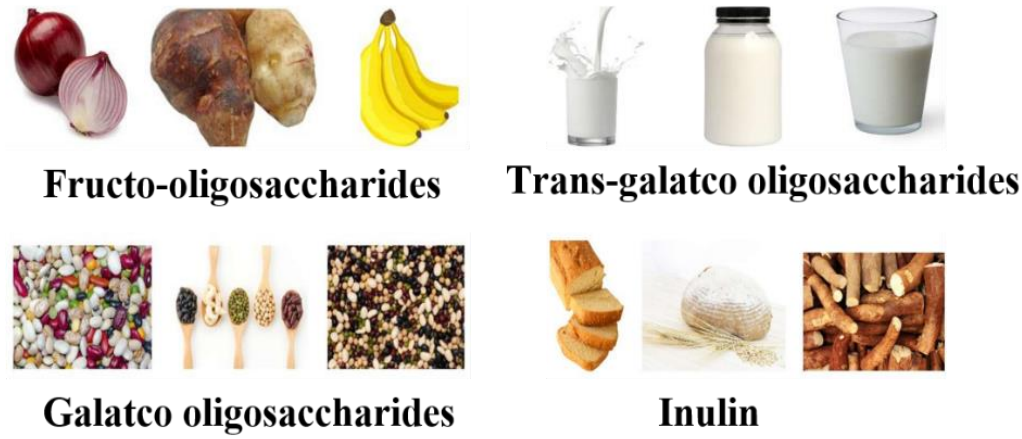

Fig. 3: Examples of prebiotic

Action Mechanism of Probiotics

The action mechanism of probiotics is rather unknown to some degree. Their biological function can be described under different terms i.e. modulation of microbes in the gut, resistance to bacterial colonization (Barrier effect), and exclusion through competition (Figure 4). The inhibition of Colonization of exogenous, aerobic bacteria is implied by releasing certain antimicrobial metabolites like short-chain fatty acids or bacteriocins which ultimately lower the pH and hence make it unfavorable for bacteria to grow. The barrier effect is also promoted by competition with other microbes but occupying the binding spaces and stopping the adhesion. The mucosal layer enhancement is another method. There are junctions present between the epithelial cells of the intestine. The tighter the junction the better it is. The paneth cells

present there release peptides (defensins or lysozyme) having antimicrobial properties, hence the proliferation of a protective mucosal layer. Probiotics are also responsible for activating the signals for the mucus layer, defensins, and the proteins of the junction.

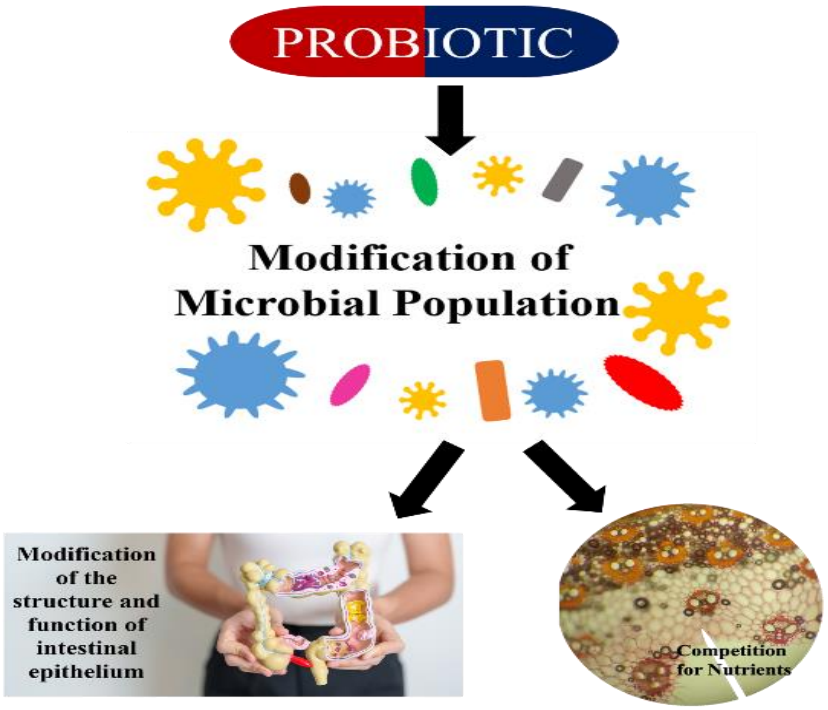

Fig. 4: Action mechanism of probiotics

Safety Protocols Regarding Probiotics

Bifidobacteria and *Lactobacilli* have long been used in foods and fermented milk. Other than that living organisms face continuous exposure to these microbes in their environment. They can be involved in commensal relationships with humans, plants, and animals. Yeast, *Lactobacilli, Lactococci,* and *Bifidobacteria* are usually put in the "Generally regarded as safe" (GRAS) category. But still, there are shreds of evidence of infections in patients with compromised immune systems (Cannon et al., 2005). Some strains of these microbes which are also probiotic are usually not that safe and they share a fair chance of health risks regarding their use (Franz et al., 2011). Hypothetically some risks have been listed. Movement of bacteria from the gastrointestinal lumen to extra-intestinal sites may lead to bacterial translocation which can further cause infections. Some studies have shown if the rate of translocation is reduced it may create a protective effect. Certain strains of *Lactobacillus rhamnosus* have been found to accompany bacteremia, abscesses, and endocarditis (Syndman, 2008). However such cases were observed in patients who were already facing some health problems like short bowel syndrome or subjects who had been implanted with the central venous catheter. The same issues were noticed regarding Fungemia caused by a probiotic strain of *Saccharomyces boulardii* (Lherm et al., 2002). Some toxic metabolites i.e. D-Lactase of these probiotics are also responsible for lactic acidosis. Short bowel syndrome in infants was due to the induction of *Lactobacillus*. However, no evidence of lactic acidosis was found in healthy children (Connolly et al., 2005).

Strain specificity of probiotic benefits is the presumption unless mechanistic and clinical evidence suggests otherwise (Figure 5).

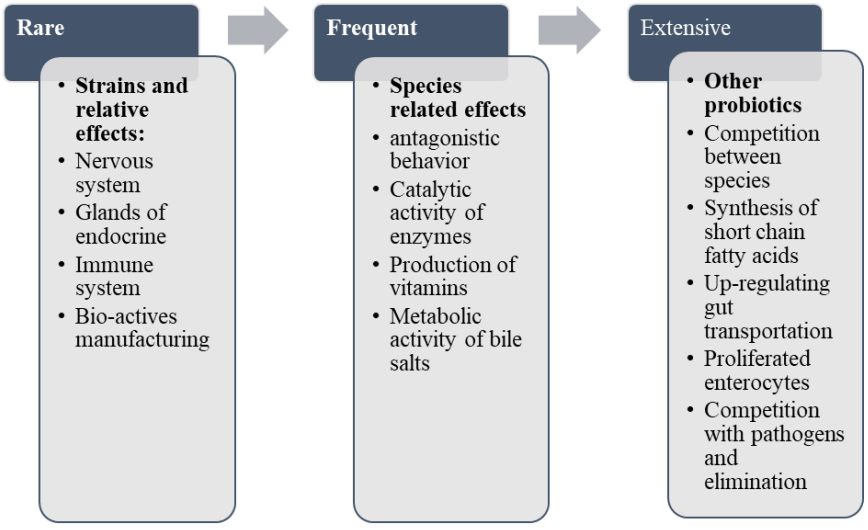

Fig. 5: Impacts of probiotic strains

Prebiotic: A Curious case of Bacterial Fermentation

The colon is the part of the gastrointestinal tract where fermentation takes place. The dietary fibers AKA prebiotics escape acidic digestion in the stomach reside in the colon and host bacterial fermentation. These fibers (oligosaccharides and polysaccharides) are converted into short-chain fatty acids by the acidification process. Human gut enzymes i.e. salivary amylase, disaccharidases, sucrose, and maltase can only degrade a few glycosidic linkages (Cantarel et al., 2012). The microbes in the gut help in the conversion of polysaccharides into monosaccharides through different metabolic pathways regulated by their enzymes. The end products of these fibers are usually SCFAs namely butyrate, acetate, and propionate accompanied by H_2 and CO_2 (Holscher, 2017). SCFAs are important metabolites that help to regulate the cellular processes and maintain the health of the host. Butyrate provides energy to enterocytes and colonocytes. Meanwhile, propionate has been found to regulate gluconeogenesis in certain ruminants by diffusing into the hepatic portal vein. These SCFAs also influence blood sugar regulation, lipid metabolism, and immunity and maintain gut epithelial integrity (Figure 6). The by-products of these fermenting probiotics also provide substrate for other non-probiotic microbes. This phenomenon is called as cross-feeding. SCFAs are a sign of bacterial fermentation in the gut and their concentration changes in proximal and distal areas of the colon (Scott et al., 2014).

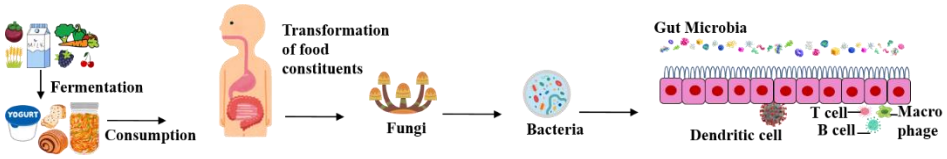

Fig. 6: Probiotic action on prebiotics

The beneficial effects of fermented foods on human health are observed when food ingredients, fermentation products, and live microorganisms are consumed and enter the gastrointestinal tract. These components, along with the resident gut microflora, are transformed into bioactive substances, such as peptides, bacteriocins, amino acids, conjugated linoleic acids, short-chain fatty acids (SCFAs), and other organic acids. Furthermore, microorganisms and their byproducts related to fermentation have the potential to interact with the natural gut microflora, epithelial cells in the intestines, and the immune system of the host.

Synbiotics

A synbiotic is a harmonious combination of prebiotics and probiotics that amplifies their benefits (Figure 7). Synbiotics help in the implantation of micro-organisms in gastrointestinal tract through edible supplements as the growth of certain bacteria is stimulated by up-regulating their metabolism (Cencic and Chingwaru, 2010).

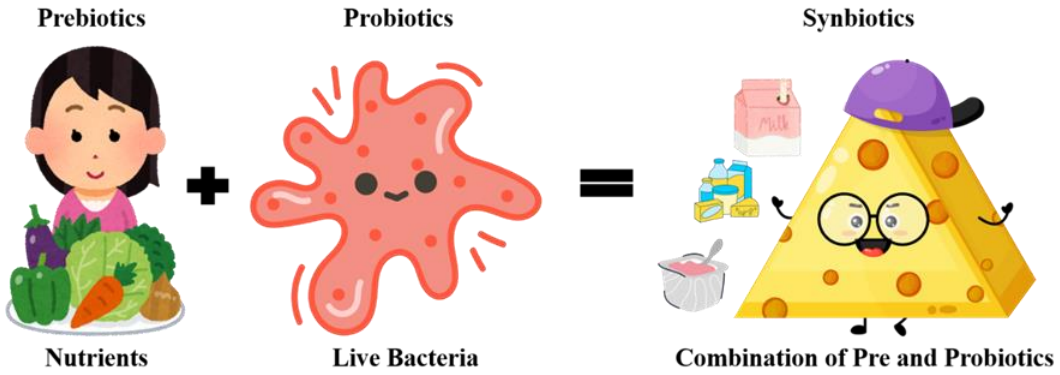

Fig. 7: A sneak peek into synbiotics

Clinical Importance of Probiotics and Prebiotics

There are several clinical benefits of probiotics but the most noticed are prevention against constipation, and diarrhea, changes in conjugation of bile salts, and proliferation of anti-inflammatory and antibacterial activities. Moreover, they enhance the bioavailability of nutrients and also act as anti-oxidative agents. They are known to ease the symptoms of allergy, AIDS, cancer, and infection of the respiratory and urinary tract. Some reports also point toward their favorable impacts on autism, obesity, fatigue, osteoporosis, and type-2 diabetes (Harish and Varghese, 2006). The effects of probiotics on certain diseases and disorders are given below:

1. Diarrhea

World Health Organization (WHO) defines diarrhea as abnormal stools having watery consistency usually more than 3 within 24 hours. Several trials on animals and in vitro investigations have shown that probiotics have validated impacts against different types of diarrhea (Narayan et al., 2010).

Acute Infantile Diarrhea

It is the most studied gastrointestinal disorder and its causative agent is rotavirus. The primary treatment of this condition is repeated hydration by oral passage. Probiotics are quite beneficial when used as a supplement during rehydration. In children, 10 billion CFU is a minimal effective dose within the first 48 hours (Szymański et al., 2006). It was observed in a large experimental study that Colitis induced by

Clostridium difficileis was avoided by the yeast *S. boulardii* in individuals who had recurring episodes of this infection. This yeast releases protease enzymes which break down the toxins of *C. difficileis* and block the receptors thus hindering its toxicity. Moreover, it can stimulate the production of immunoglobulin (antitoxin A) to fight against this bacterial strain (Hord, 2008; McFarland, 2006).

Antibiotics and Diarrhea

It is quite inevitable to face diarrhea after intake of antibiotics. The antibiotics do so resist the gut pathogens thus disrupting its natural microflora. This disturbance further causes variations in bile salts, carbohydrates, and short-chain fatty acids metabolisms (Bartlett, 2002). Different probiotics such as *S. boulardii* (yeast), *L. acidophilus*, *L. fermentum,* etc, have positive effects on diarrhea caused by antibiotics (McFarland, 2006). However, the efficiency and dosage are yet to be confirmed by further clinical trials (Sudha and Bhonagiri, 2012).

Traveller's Diarrhea

According to an estimation about 20-60% of people who travel from developed and industrialized countries to developing countries face diarrhea. The bacteria that are most responsible are *E. coli*, *C. jejuni*, *Salmonella* spp., and *Shigella* spp. The rate of infections caused by viruses is 5% and by parasites is 10% (Hill and Ryan, 2008). Studies showed *S. boulardii* is more effective against bacterial diarrhea and *Lactobacillus GG* are effective against idiopathic and viral diarrhea. *Streptococci*, *Lactobacilli*, *Enterococci,* and *Bifidobacteria* have also been used as preventive measures (McFarland, 2007).

Irritable Bowel Syndrome

Irritable bowel syndrome AKA IBS is a most frequent gut disorder and is a chronic scenario identified by repeated pain and discomfort in the abdomen, bloating, and varied stool patterns without any apparent mucosal disturbances. Psychological and emotional stresses, social factors i.e. family support system and the fostering pattern, and certain biological factors such as GIT motility and sensitivity of viscera play an important role in inciting IBS (Tanaka et al., 2011). A mixture of 8 different probiotics and *Lactobacillus plantarum* known as VSL#3 was found effective in easing up flatulence and bloating (Chapman et al., 2011). *L. rhamnosus GG* was also observed to reduce abdominal pain (Kim et al., 2005). Prebiotic fibers which are non-viscous and soluble have potential benefits in relieving inflammation i.e. IBS. Guar gum under partial hydrolysis was able to alleviate the abdominal pain and normalize bowel pattern as compared to wheat bran and improve the conditions after injury and inflammations in the epithelium (Hardy et al., 2013).

Inflammatory Bowel Disorder (IBD)

It is a gastrointestinal inflammation which is chronic and recurring and different factors are responsible for it. Its symptoms are watery or bloody stool joined by gastric discomfort. Both small intestine and colon are affected by IBD. It is caused by Pouchitis, Ulcerative colitis (UC) and Crohn's Disease (CD). Other factors involved are oxidative stress, dysfunction of immunity, type of gut microflora and genetic and environmental factors (Moeinian et al., 2013). Both Ulcerative colitis and Crohn's Disease are autoimmune inflammatory diseases and are result of disturbance in immune system due to its inadequate adaptations to new environment, also believed to be caused by westernization of cultures (Matsumoto et al., 2005). Health system of different countries is burdened by the individuals affected by these diseases (impact rate: 1-5 out of 1000). Recent studies of genetics and molecular functions of proteins led by genes such as NOD2 and CARD15 have helped in better comprehension of these diseases (Peña, 2007).

Ulcerative Colitis (UC)

The long standing UC largely affects the mucosal lining of the large intestine and the rectum. If long lasting, it can invite colon cancer. Different probiotics like *Bifidobacterium*, *Lactobacillus,* and *S. boulardii* have shown encouraging results when used (Kelesidis and Pothoulakis, 2012).

Crohn's Disease (CD)

This form of IBD can spread its effects from mouth to rectum but usually intestine is affected. It causes soreness and swelling which influences and disturbs the digestion and egestion processes. *Clostridium difficile*, *Salmonella*, *Campylobacter jejuni*, *Adenovirus,* and *Mycoplasma* have been recognized as causative and influential agents of this disease. *Lactobacillus rhamnosus* strain *GG*, *S. boulardii* and *E. coli Nissel*1917 have been found effective in countering this disease in humans (Jonkers et al., 2012). Probiotics also restored the damaged mucosal lining thus preventing the recurring pattern of CD.

Pouchitis

Pouchitis is another form of IBD that is caused by inflammation in the ileo-anal pouch after colectomy. A mixture of VSL#3 probiotics has affected positively and stopped the relapse into chronic pouchitis (Veerappan et al., 2012). Probiotics helped in producing antioxidants like catalase and superoxide dismutase and enhanced the cellular integrity with the help of protein phosphorylation at tight junctions, hence providing a remedy for IBD (Howarth, 2008).

2. Lactose Intolerance

When β galactosidase has low activity, it causes hindrance in lactose digestion hence lactose intolerance is caused. Symptoms are abdominal pain, flatulence, bloating, and diarrhea. The possible treatment for this is oral consumption of lactase in the form of tablets and probiotics such as *Streptococcus thermophiles* and *Lactobacillus bulgaricus*. Milk with additives of *L. acidophilus* and *Bifidobacterium longum* has been proven beneficial because it reduces hydrogen production and flatulence (Vonk et al., 2012).

3. Immunomodulation

Bacterial probiotics play a role in immunomodulation by influencing cell-mediated immunity and humoral immunity. They also show anti-inflammatory properties as well as adjuvant effects. They secrete factors that initiate immunomodulation. An example is secretions from *L. reuteri* reducing gene expression of NF-κB thus, down-regulating cell proliferation and activation of protein kinase which induces apoptosis (Delcenserie et al., 2008). *L. helveticus* (present in fermented milks) causes increased calcineurin expression which enhances mast and goblet cell production in the GIT of the mouse (Isolauri et al., 2002). The exact mechanism of prebiotics is not fully recognized, but some possibilities are:

1) Production of SCFAs like propionate is increased which reduces the activity of enzymes involved in hepatic lipogenesis.
2) Butyrate (an SCFA) production has modulated the acetylation of histone tail which resulted in exposure of more genes to transcription.
3) Mucin production is modulated.
4) Some prebiotics like FOS has shown proliferated numbers of lymphocytes and leucocytes in gut thus strengthening the immunity.
5) Phagocytosis of macrophages (residing between the peritoneal layers) is stimulated in gut-associated lymphatic tissue due to increased immunoglobulin A secretion (Schley and Field, 2002).

Certain data collected from experiments on animals denoted that intake of inulin enhanced the production of short-chain fatty acids in the caecum (Artiss et al., 2006).

4. Metabolism of lipids and Cardio-vascular Diseases

It was first suggested by Mann and Spoerry the possibilities of effects of probiotics intake on lipid metabolism. They notified the reduced cholesterol in the serum of Maasai people after consuming fermented milk (Watson and Preedy, 2010). Some probiotic strains were reportedly hypocholesterolemic e.g. *L. reuteri*, *L. bulgaricus* and *B. coagulans*. It was observed that milk laced with *L. acidophilus* reduced serum cholesterol significantly in humans. A depreciation of low-density lipoprotein cholesterol, triglycerides, and total serum cholesterol was observed when yogurt supplemented with *B. longum*BL1 was given to patients with a high cholesterol profile. Also, a 14.5% increment of high-density lipoprotein cholesterol was demonstrated (Homayouni et al., 2012). HDL is good for health and lowers the risk of heart attack. Reasons for hypocholesterolemic activity by probiotics due to,

1) Reduction in hepatic hydroxyl-methyl-glutaryl-Coenzyme-A reductase
2) Cholesterol turning into bile acids, as probiotics assisted the bile salts de-conjugation.

Bile acids are easily absorbed in the intestine after de-conjugation, this further leads to their removal through feces (Teitelbaum and Walker, 2002). Similar activity was also noticed with the prebiotics. According to one study, a decrement of 29% in total cholesterol and 63% in triglycerides was demonstrated in hamsters after inulin intake (Nguyen et al., 2007). 27% of triglycerides were reduced in Sprauge-Dawley rats (40 male) after being treated with xylooligosaccharides (Hsu et al., 2004).

5. Cancer

Lactobacillus delayed the incitation of colon tumor. A demonstration showed consumption of *L. acidophilus* laced colostrum and milk reduced tumor growth by 16-41% (Andrews and Tan 2012). Reportedly, *L. bulgaricus* hindered the sarcoma-180 and Ehrlich ascites tumor activity (Lee et al., 2012). 1 ,2- dimethylhydrazine is carcinogenic to rats and its activity was slowed down by a combination of *Bifidobacteria* with FOS (Fotiadis et al., 2008). A proposal to their anti-tumor mechanism is 1) variations in the immune system relative to the immune response 2) the up-regulation of apoptosis and enhanced cell differentiation against tumor cells 3) the subdued enzymatic production (urease, nitroreductase, azedoreductase) in bad bacteria such as *E. coli*.

Some other benefits are the prevention of obesity, availability of minerals, regulation of stool, and laxation. It was concluded in a study when obese people lost fat, their gut microflora population resembled that of lean people (Ley et al., 2006). Fibers have low energy density and a lower degree of fat that's why they help in weight reduction. Fructans consumption in 100 adult individuals for 12 months up-regulated the Ca absorption (Abrams et al., 2005). Fermentation on prebiotics and reduced pH of the lumen enhanced Ca absorption in the colon (Cashmen, 2003). Retention of fibers in the colon adds up to the overall stool weight hence making defecation easy. Wheat bran is a significant example of such fiber. As probiotics are interjunction between gastro-intestinal physiology, microbiology, and immunology, new advancements are necessary for their better use in medical fields.

Conclusion

The entire chapter gives us a vivid idea of probiotics, prebiotics, and fermentation processes which make their presence so fascinating. Probiotics provide a modern vision of micro-biology and change the viewpoint upheld against microorganisms like bacteria and fungi. Prebiotics not only emphasize the importance of organic food but also push to shed light on successful symbiotic relationships. The evolution of technology, genetics, biochemistry, and bioinformatics has enabled researchers to comprehend in the best way possible the functions of probiotics and prebiotics. The bio-activation and bio-modulation of them have helped treat diseases and the down-regulation of the symptoms of different disorders. The production of short-chain fatty acids, and enzymes, relieves GIT-related issues, these health benefits are just the beginning. Synbiotics is a novel combination, as its design is a statement of the commensalism on a whole other biological stage. The DNA analysis and biochemical processes are especially helpful to observe the activities and plan further modulated bio-activity for these micro-flora. Even though certain strains have beneficial effects we still lack information about their proper mode of action and the selectivity process between probiotics and prebiotics. If we want to expand their clinical and commercial usage advancements through different tools in vitro studies on animals are needed to be done. We have to be certain about the behaviors of strains and fibers, the peculiar frequencies of their interactions, genetic maps, and biochemical processes.

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