Probiotics and its health benefits

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### PROBIOTIC

Hippocrates famous statement, *“Let food be thy medicine and medicine be thy food”,*' embodies the fundamental philosophy embraced by health-conscious individuals. The term 'probiotic' originates in Greek, derived from 'pro' (for) and 'biotic' (life), signifying its relation to promoting life. In the late 19th century, microbiologists made noteworthy observations regarding the disparities in gut flora between healthy and diseased individuals. Nobel laureate Elie Metchnikoff reported the advantageous role of selective bacteria in the gastrointestinal tract. Probiotic organisms are pivotal in enhancing the body's natural defence mechanisms (Getahun *et al.,* 2017). The term 'Probiotics' was initially introduced by Vergin, who was investigating the detrimental effects of antibiotics and similar agents on gut microflora. He observed that 'probiotika' exhibited favorable attributes for the gut microbiota. Fuller (1989) postulated that "probiotics" encompass live microbial feed supplements that exert advantageous effects on the host by ameliorating its microbial equilibrium. The Food and Agriculture Organization (FAO) presents the official elucidation of 'probiotic' as living microorganisms that, when ingested in specific quantities, confer advantageous effects on the consumer's health (FAO/WHO, 2002). For a food product to be classified as 'probiotic,' it is essential to maintain a microbial count of ≥6 log CFU (Colony Forming Units) per milliliter or gram at the end of its shelf-life to ensure the claimed health benefits (Ganguly *et al.,* 2019). Recent recommendations propose that a concentration of 8 log CFU/g of product is necessary to claim health-promoting effects on the host (ICMR-DBT, 2011). The utilization of probiotics for disease management and the preservation and enhancement of health is not a novel concept. Nonetheless, there has been a resurgence in interest regarding their application as biotherapeutic agents, primarily driven by consumer demand and media influence. Subsequent research in this domain has unveiled that regular consumption of these beneficial bacteria can impart various health advantages.

Consumers are now looking for products that offer value addition, meet health requirements beyond nutrition, and can be used as a value addition to food products for specific health benefits like lowering the risk of developing diseases, overall well-being, along with plenty of health benefits in the age of the rapidly expanding population and changing lifestyle (Singh *et al*., 2021). Incorporating probiotics into various food items has led to the popularization of a novel category of functional foods known as 'probiotic products.' Bacteria from the *Bifidobacterium and Lactobacillus* genera are considered safe and commonly recognized as probiotics. They exert positive effects on gut health. (Kimoto-Nira *et al.,* 2007). Among the frequently utilized *lactobacilli* strains are *L. acidophilus, L. casei, L. rhamnosus, L. reuteri, L. delbrueckii ssp. bulgaricus, L. plantarum, L. johnsonii, L. brevis, L. cellobiosus, L. fermentum,* and *L. gasseri* (Meurman and Stamatova, 2007). The employed *bifidobacteria* species include *Bifidobacterium* *breve, B. animalis subsp lactis*, formerly known as *B. lactis* (Masco *et al.,* 2004), as well as *B. longum* *biotypes infantis* and *longum* (Masco *et al.,* 2005). Other LAB encompassed within the probiotic family are *Streptococcus, Lactococcus, Enterococcus, Leuconostoc, Propionibacterium*, and *Pediococcus* (Power *et al.,* 2008). Some non-related microbial species, have been identified as probiotics, comprised of non-pathogenic *Escherichia coli strain Nissle* 1917 and *Clostridium butyricum* (Harish and Varghese, 2006), yeast species (*Saccharomyces boulardii*), filamentous fungi (*Aspergillus oryzae*), and certain spore-forming *bacilli* (Gibson *et al.,* 2003). To confer health benefits to the host, probiotic organisms must successfully withstand the challenges posed during their passage through the gastric system, including resistance to gastric acid, bile, and gastric enzymes, followed by adequate adherence and colonization within the intestinal epithelium (Huang and Adams, 2004).

 Foods with a high buffering capacity as well as appropriate pH can elevate the gastric pH, thereby promoting the stability of probiotics. The viable count of probiotic bacteria present in a food product during consumption is a critical factor influencing their efficacy. The survival of probiotics in food products is influenced by various factors, such as post-acidification during storage (in the case of fermented products), product pH, susceptibility to oxygen toxicity, and storage temperatures (Shah, 2000).

 As per the study conducted by the World Health Organization in 2018, a population greater than 300 million people worldwide suffer from depression and other mental health issues. Anxiety and depression are the two most prevalent mental health issues in the world. People who suffer from mental illness experience a decline in their health and in the quality of their lives. Recently, scientific interest has been increasing in focusing on the gut microbiome to determine how it positively affects our brain and behavior. The use of psychobiotics in treating anxiety and depression is thought to be very promising.

####  Probiotic organisms

Numerous strains have been recognized as probiotic microorganisms exhibiting advantageous health effects, primarily characterized by their capacity to reside within the human gastrointestinal (GI) tract naturally. Essential prerequisites for probiotic strain include its capacity to endure the challenging conditions of the gastric environment, such as stomach acidity, and to withstand the bile present within the small intestine, thus enabling the exertion of favorable influences on the host.

##### Lactic acid bacteria (LAB) as probiotic

LAB include a diverse array of genera, comprising a substantial number of species. These bacteria are Gram-positive and typically lack catalase activity. They thrive in environments ranging from micro-aerophilic to strictly anaerobic conditions, and they do not produce spores. The most notable genera among LAB include *Lactococcus,* *Lactobacillus, Pediococcus, Enterococcus, Leuconostoc, Streptococcus, Carnobacterium* and *Bifidobacterium*. Various species from these genera can be found in the gastrointestinal tracts of both humans and animals as well as in fermented foods. Notably, strains utilized as probiotics are predominantly affiliated with the genera *Lactobacillus*, *Enterococcus*, and *Bifidobacterium*.

The metabolic attributes of these LAB are primarily chemo-organotrophic, and they ferment carbohydrates into lactic acid as a primary end product. Key physiological characteristics that render them suitable as probiotics include their capacity to survive in the gastrointestinal tract, resistance to low pH and/or bile, and their temperature growth ranges (Fuller, 1989). For taxonomic considerations, the most significant physiological and biochemical features are related to carbohydrate fermentation patterns, resistance to different salt concentrations, growth on various nutrient media, growth at defined temperatures, and resistance to antibiotics. These traits are essential for identifying and classifying LAB species accurately.

In diverse ecosystems, lactic acid bacteria (LAB) provide advantageous effects by inhibiting the proliferation of pathogenic bacteria via the synthesis of antimicrobial agents like organic acids, hydrogen peroxide, and bacteriocins (Reid *et al.,* 2001). Bacteriocins are compact proteins with bactericidal or bacteriostatic properties (Klaenhammer et al., 1988). Lactobacilli that produce bacteriocins, for example, can function as safeguarding cultures to improve the microbiological safety of food items (Olasupo *et al.,* 1997). Furthermore, bacteriocins demonstrate antagonistic actions against spoilage microorganisms in food (Barbuti et al., 2008), primarily focusing on microbes like *Pseudomonas*, *Staphylococcus aureus*, *Salmonella sp*., and *Listeria monocytogenes.* (Chinang *et al.,* 2000). Consequently, bacteriocins hold considerable potential as bio-preservatives for food (Arokiyamary and Sivakumar, 2011).

##### Genus *Bifidobacterium*

In 1899-1990, Tisser isolated Y-shaped bacteria belonging to the *Bifidobacterium* genus from infant feces, which he named *Bacillus bifidus*. Before this discovery, *bifidobacteria* were classified as subspecies of *Lactobacillus*, but in 1924, they were reclassified as a separate genus, *Bifidobacterium*. These microorganisms are characterized as obligate anaerobes, displaying Gram-positive properties, lacking spore formation, being catalase-negative, and non-motile. Some *bifidobacteria* can tolerate oxygen as such or in the presence of carbon dioxide (Talwalkar and Kailasapathy, 2004). Morphologically, they exhibit pleomorphic shapes, appearing as short, curved rods, club-shaped rods, and bifurcated Y-shaped rods. Numerous species of *Bifidobacterium* have been identified and isolated from various sources, including humans, animals, and insects. These microorganisms thrive under ideal conditions, with a temperature range of 37-41°C and a pH range of 6-7. Their growth is entirely inhibited below pH 4.5 and above pH 8.0.

##### Genus *Lactobacillus*

Genus *Lactobacilli* comprises non-flagellated rods or coccobacilli with characteristics of being gram-positive, catalase-negative, non-sporing, microaerophilic or anaerobic, and strictly fermentative (Salvetti *et al.,* 2012). Presently, approximately 70 species of *lactobacilli* have been characterized. Among these, the most commonly employed *lactobacilli* in dietary formulations are *L. acidophilus, L. casei, L. paracasei, L. plantarum,* and *L. rhamnosus* (Tannock, 2002). For commercial food products, particularly in yogurt production, commonly used *lactobacilli* strains include *L. acidophilus La-5* (Christian Hansen) and *L. acidophilus* LAFTI L10 (DSM Food Specialties) (Talwalkar and Kailasapathy, 2004). *Lactobacilli* possess several essential probiotic features, such as the production of digestive enzymes, synthesis of vitamins, breakdown of bile salts, enhancement of immunity, and inhibition of pro-inflammatory mediators. The regular consumption of exogenous *Lactobacillus spp*. through the diet can establish colonization in the intestine, in addition to the indigenous *Lactobacillus spp*. Figure 1.1 illustrates common *lactobacillus* species used as probiotics. *Lactobacillus acidophilus* is a prevalent dietary supplement due to its inherent probiotic potential among the various *lactobacillus* species. *L. acidophilus* is a non-spore-forming, gram-positive microorganism occurring as non-flagellated rods singly, in pairs, and in short chains. It predominantly thrives in a microaerophilic environment, and anaerobic conditions support its growth on suitable media. *Lactobacillus acidophilus* thrives within an ideal temperature range of 35°C to 40°C, with the ability to withstand temperatures as high as 45°C. Its preferred pH range for growth is between 5.0 and 5.6, and it demonstrates tolerance to acidity levels ranging from 0.3% to 1.9% titratable acidity. Liong and Shah (2005a) have demonstrated that *L. acidophilus* 33200 displays superior resistance to bile salts and acidic conditions compared to other organisms. Additionally, this strain effectively facilitates the removal of cholesterol from fermentation broths (Liong and Shah, 2005b). Various strains of *L. acidophilus* are commonly incorporated into food products such as yogurt and buttermilk. These strains include MUH-41, O-61, L-1, 43121, and La-5 (Nighswonger *et al.,* 1996). Moreover, in commercial food products, other frequently used *L. acidophilus* strains are La-5 (Christian Hansen) and *L. acidophilus* LAFTI L10 (DSM Food Specialties) (Talwalkar and Kailasapathy, 2004).

Figure 1. 1 *Lactobacillus* species used as probiotics

Source: Sanders and Klaenhammer (2001)

#### Selection criteria for probiotic organisms

The probiotic microorganism must possess the following desirable properties:

1) High acid and bile salt tolerance to ensure its viability and survival in the gastrointestinal tract.

2) The ability to adhere to mucosal and epithelial surfaces helps provide health benefits to the host.

3) Exhibiting antimicrobial activity against harmful organisms, thereby contributing to the maintenance of gut health.

4) Exhibiting bile salt hydrolase activity, which contributes to the degradation of bile salts and promotes various digestive processes.

5) Demonstrating specific cell surface properties that promote probiotic adhesion to host tissues, including cell surface hydrophobicity, aggregation, and adhesion mechanisms.

#####  Contribution of probiotics in human health

##### Synthesis and bioavailability of nutrients

Probiotic microorganisms have been noted for their positive impact on nutrient availability and digestibility in the fermentation and absorption of fermented foods. Yogurt and other fermented dairy products also play a role in providing folic acid. Additionally, research indicates that yogurt, following fermentation, exhibits higher levels of niacin and riboflavin compared to non-fermented counterparts (Alm, 1982). The release and production of a variety of enzymes and vitamins into the intestinal lumen are pivotal in the process of digestion, mitigating problems related to malabsorption (Mack *et al.,* 1999). Probiotic bacteria produce enzymes that facilitate the hydrolysis of proteins and fats, consequently enhancing the bioavailability of these essential nutrients (Fernandes *et al.,* 1987). Furthermore, the fermentation process increases the production of functional components, such as free amino acids, short-chain fatty acids (SCFA), lactic acid, and propionic acid, among others. In the context of lactose intolerance, the presence of lactase, produced by milk *Lactobacilli* during fermentation, aids in lactose degradation, thus preventing symptoms associated with lactose intolerance (Martini *et al.,* 1991).

##### Management of diarrhea

Lactic acid, a metabolic product synthesized by probiotic organisms, exerts a regulatory effect on the intestinal pH, inhibiting growth for invasive pathogens, including *Salmonella spp*. and various strains of *Escherichia coli* (Mack *et al.,* 1999). Probiotics are widely recognized for their efficacy in the prevention and management of acute viral and bacterial diarrhea and their ability to mitigate antibiotic-associated diarrhea. Several specific probiotic strains have been documented to provide substantial benefits in the treatment of diarrhea, notable examples being *Lactobacillus GG, Lactobacillus reuteri, Saccharomyces boulardii,* and various *Bifidobacteria spp*. (Benchimol and Mack, 2004). These strains have shown particular effectiveness in managing rotavirus-induced diarrhea in young children (Vanderhoof, 2000). Noteworthy *lactobacilli* species, such as *L. reuteri, L. casei, S. boulardii, B. bifidum, and S. thermophilus,* are established for their therapeutic potential in the treatment of diarrheal diseases among children (Gorbach, 2000; Solga and Diehl, 2003). The ingestion of probiotics represents a promising approach for addressing antibiotic-associated diarrhea and infections caused by *Clostridium* *difficile* (McFarland, 2009).

The potential mechanism underlying the regulation of diarrhea involves the secretion of diverse enzymes into the intestinal lumen, promoting effective digestion and reducing malabsorption. In pediatrics, probiotics have been observed to confer benefits in cases of viral diarrhea. This is achieved through an augmented production of secretory IgA, which decreases viral shedding and enhances the body's immune response. Moreover, probiotics provide a preventive effect against infections by competitively inhibiting pathogens from accessing nutrients and attaching them to the epithelial cells of the intestines. Moreover, probiotics stimulate intestinal mucin production, further inhibiting enteropathogenic organisms' attachment.

##### Alleviation of lactose intolerance

Probiotics have been demonstrated to alleviate the symptoms of lactose intolerance in individuals with lactase deficiency. This beneficial effect is attributed to the potential of certain probiotic bacteria to enhance lactase activity within the small intestine (Marteau *et al.,* 1990), thereby improving lactose digestion and alleviating intolerance symptoms (Sanders, 1993).

Milk is renowned for its high calcium content, vital for fulfilling the body's calcium requirements. Researchers have verified that lactose deficiency can impair calcium absorption, potentially resulting in osteoporosis. The mechanism behind calcium malabsorption may involve the avoidance of milk consumption due to complications arising from lactose intolerance. Notably, higher calcium absorption occurs in an acidic environment; therefore, lactic acid leads to a decrease in gut pH, favoring calcium absorption.

In individuals afflicted with lactose intolerance, the supplementation of probiotics stimulates the enzymatic breakdown of milk lactose by probiotic species, thereby facilitating efficient lactose assimilation and calcium absorption. This mechanism effectively counteracts calcium malabsorption, consequently contributing to the fulfillment of the body's calcium demands.

#####  Hepatic disease

Hepatic encephalopathy (HE) is a severe liver disorder, yet its precise pathogenesis remains unknown. Probiotic microorganisms, including *Bifidobacteria, L. plantarum, L. casei, L. acidophilus,* have demonstrated diverse preventative and therapeutic properties, exerting their effects through various mechanisms to impede the pathogenesis of Hepatic disease (Solga, 2003).

#####  Inflammation/arthritis

Probiotic microorganisms have effectively mitigated inflammation by regulating inflammatory mediators, including cytokines. The inflammatory reactions within the gastrointestinal (GI) tract can be controlled by regulating immune markers. The utilization of probiotics has shown potential in the modulation of rheumatoid arthritis (Marteau *et al.,* 2001).

##### Allergies/eczema

Probiotics contribute to the amelioration of allergic reactions by bolstering the functionality of the mucosal barrier and activating the immune system (MacFarlane and Cummings, 2002). Hypersensitivity reactions, often associated with inflammation in individuals with atopic eczema, and food allergies, can be effectively managed by administering probiotic bacteria (Isolauri, 2004). The administration of Lactobacillus rhamnosus GG to infants at risk of eczema resulted in a noteworthy 50% reduction in the incidence of eczema. (Isolauri *et al.,* 2000). In the early stages of life, the colonization of probiotic organisms in the previously sterile gut of newborns has long-term effects on immunoregulation and the development of atopic disorders. Probiotics play a crucial role in enhancing the endogenous barrier mechanisms of the gut, thus mitigating intestinal inflammation.

Consequently, they represent a valuable therapeutic approach in treating food allergies (MacFarlane and Cummings, 2002). Furthermore, probiotic organisms have shown efficacy in alleviating symptoms associated with milk protein-related food allergies. This outcome is ascribed to the breakdown of milk proteins into smaller peptides and amino acids, which subsequently alleviates symptoms of atopic dermatitis (Majamaa and Isolauri, 1997).

##### HIV and immune function

The utilization of probiotics represents a promising approach for improving the immune system in individuals with compromised immunity, as they exhibit the potential to modulate immune responses. Consuming a combination of probiotic organisms in synergy may further enhance the immune response (Cunningham-Rundles *et al.,* 2000). Evidence from studies conducted in vitro, in vivo, and on humans suggests that probiotics can augment specific and nonspecific immune responses (McNaught *et al.,* 2005). These positive effects are thought to occur through a range of mechanisms, including the activation of macrophages, modulation of cytokine levels, augmentation of natural killer cell activity, and increased production of immunoglobulins (Ouwehand *et al.,* 2002).

##### Immuno-modulatory activity

Zoumpopoulou et al. (2009) demonstrated that probiotic microorganisms manifest inhibitory actions on inflammatory responses in various experimental colitis models. These probiotic organisms hold potential for application in treating chronic bacterial infections, as indicated by the same study. The activation of gut immunity by probiotic microorganisms encompasses vital mechanisms, including the expansion of immunoglobulin-producing cells, enhancement of the immune response, and the initiation of either upregulation or downregulation of the innate immune response. Galdeano *et al*. (2007) discussed that these processes collectively contribute to preserving intestinal homeostasis. Furthermore, the impact of probiotic organisms on cytokine production also plays a significant role in modulating immune responses*.* It's important to recognize that the impact of probiotic microorganisms on the immune system may display strain-specific attributes and the possibility for synergistic interactions*.*

#####  Control of blood cholesterol and hyperlipidemia

Cholesterol plays a critical role in human physiology, serving as a crucial precursor for numerous hormones and vitamins. Additionally, it constitutes an integral part of cell membranes and the nervous system. Increased levels of total blood cholesterol have been associated with a higher risk of coronary heart disease. The regulation of serum cholesterol levels is significantly influenced by dietary factors. The ingestion of probiotics has been linked to beneficial effects on blood lipid profiles. In an animal model with elevated cholesterol levels, the administration of a low dose of *L. reuteri* for seven days resulted in a substantial reduction of both total cholesterol and triglyceride levels, with decreases of 38% and 40%, respectively. Additionally, this treatment demonstrated a significant 20% increase in the high-density lipoprotein (HDL) to low-density lipoprotein (LDL) ratio. (Taranto *et al.,* 1998).

#####  *Helicobacter pylori* infections

In laboratory experiments, the significant production of lactic acid by *Lactobacillus salivarius* was demonstrated to be highly effective in inhibiting the growth of *Helicobacter pylori* (Ai-ba *et al.,* 1998). Conversely, *Lactobacillus acidophilus, Lactobacillus casei,* and *Lactobacillus salivarius* exhibited poor colonization and growth in the stomach, leading to lower lactic acid production and an inability to inhibit the growth of *H. pylori* (Bazzoli *et al.,* 1992). Probiotic bacteria have been observed to hinder the colonization and activity of H. pylori, particularly in conjunction with the management of gastric or peptic ulcers. Both laboratory (in vitro) and live (in vivo) studies have showcased *L. salivarius* capability to prevent the colonization of *H. pylori* (Aiba *et al.,* 1998; MacFarlane and Cummings, 2002). Given the potential advantages, the use of probiotics has been proposed to enhance eradication rates, enhance tolerability, and decrease the necessity for multiple antibiotic treatments in cases of *H. pylori* infections. (Bazzoli *et al.,* 1992). Additionally, the consumption of *Lactobacillus johnsonii* has also exhibited inhibitory effects against *H. pylori* (Marteau *et al.,* 2001).

##### Inflammatory bowel disease (IBD)

Specific strains of lactobacilli have shown positive effects in relieving symptoms linked to Inflammatory Bowel Disease (IBD), pouchitis, and ulcerative colitis (Schultz and Sartor, 2000). Probiotic bacteria have exhibited the capability to enhance intestinal motility and relieve constipation, which is likely achieved by lowering the pH in the gut (Sanders and Klaenhammer, 2001). The combination of probiotic treatments has demonstrated benefits for individuals with Inflammatory Bowel Disease (IBD) (Schultz and Sartor, 2000; Shanahan, 2001). *S. boulardii* and *LGG* have both been noted to elevate secretory IgA levels in the gastrointestinal tract, offering advantages in cases of Inflammatory Bowel Disease (IBD)..

##### Irritable bowel syndrome (IBS)

Probiotic treatment has shown positive outcomes in the management of inflammatory and functional bowel disorders. In a clinical study, the effects of *L. plantarum* 299 v and DSM 9843 strains on patients with irritable bowel syndrome (IBS) were examined, revealing their efficacy in reducing symptoms like abdominal pain, bloating, flatulence, and constipation (MacFarlane and Cummings, 2002). Another probiotic, *Saccharomyces boulardii*, effectively reduced diarrhea in IBS, but did not show significant control over other symptoms associated with the syndrome (Marteau *et al.,* 2001). Recent studies have illuminated the possible involvement of gut microbiota in diminishing inflammation within both the intestines and joints. The interplay between intestinal microbes and gastrointestinal (GI) tissues plays a vital role in regulating regular gut functions, affecting processes like motility, absorption, secretion, and intestinal permeability (Verdu and Collins, 2005).

Many probiotics have undergone scrutiny for their efficacy in the management of IBS, and among these, *Bifidobacterium infantis* has been identified as notably effective (Brenner *et al.,* 2009; Niedzielin *et al.,* 2001).

##### Colon cancer

Cancer stands as the primary cause of death in industrialized nations and holds the second-highest position in terms of mortality in developing countries, according to the World Health Organization's 2008 report. As reported by Jemal *et al*. (2011), colorectal cancer (CRC) ranks as the third most prevalent cancer in men worldwide and the second most common in women. The development of colon cancer exhibits a strong correlation with dietary patterns and environmental factors. Huycke and Gaskins (2004) observed that significant colorectal neoplasms develop sporadically from adenomatous polyps due to the gradual accumulation of mutations in oncogenes such as APC, K-ras, and TP53. The current management of CRC entails a combination of surgical interventions, chemotherapy, and radiation therapy, but these approaches often lead to a notable decline in the patient's quality of life. In recent studies, probiotic therapy has shown considerable promise in the context of colorectal cancer, as outlined in Table 1. 1.

The mechanisms involving the preventive effects of CRC encompass several aspects:

1. The modulation of intestinal micro-ecology,
2. A reduction in the production of carcinogenic enzymes within the fecal matter
3. The attenuation of toxigenic and mutagenic reactions within the gut, iv
4. Protecting against DNA damage by generating short-chain fatty acids (SCFA) by Park *et al*. in 2005.

###  HUMAN GASTROINTESTINAL ECOLOGY

Most of the microbial population inhabits the large intestine or colon of the gastrointestinal (GI) tract in humans. The colonic microflora performs diverse roles in the process of digestion. It's estimated that a person's intestines typically house around 100 trillion live bacteria from over 100 distinct bacterial species. (Mitsuoka, 1982).Microbial colonization of the human intestine begins immediately after birth (Gronlund *et al.,* 2000). The gastrointestinal (GI) tract consists of a varied microbial community that includes both facultative and obligate anaerobic microorganisms. (Tannock, 2001). The primary source of bacteria that colonize a baby's intestine is the vaginal and intestinal flora of the mother. Initially, the colon of a newborn is mainly populated by *Enterobacteriaceae* and enteric *streptococci*. Subsequently, microorganisms such as *Lactobacillus, Clostridium, Bacteroides*, and *Bifidobacterium* genera appear within the first week of life. *Bifidobacteria*, in particular, play a pivotal role in colonizing the infant's gut and typically establish themselves within the first 4-7 days after birth, reaching concentrations of 10 billion colony-forming units per gram of feces in breastfed infants. This colonization becomes stable after the first 6-10 months of infancy. These organisms profoundly influence the normal growth of gut microbiota and gut maturation (Saarela *et al.,* 2000). The indigenous gut flora provides protection to the host against exogenous pathogenic infections and opportunistic bacteria in the gut (Guarner, 2006; Mitsuoka, 1992). Certain inherent colonic bacteria, such as *lactobacilli* and *Bifidobacteria*, are considered beneficial to health. The microorganisms in the colon contribute to promoting health through various mechanisms, such as colonizing the gut, aiding in digestion, generating short-chain fatty acids (SCFA), countering the effects of toxins, and bolstering the immune system (Guarner and Malagelada, 2003).

Table 1. 1 Application of probiotics in colorectal cancer

|  |  |  |
| --- | --- | --- |
| **Diseases** | **Function** | **References** |
| Colon Cancer | Antimutagenic effects | Marotta *et al.,* 2003 |
| Colon Cancer | Diminishing the likelihood of colon cancer by inhibiting the DNA damage induced by carcinogens. | Pool-Zobel *et al.,* 1996 |
| Antimutagenic | Stimulation of immune cells following the oral administration of *L. casei* to mice. | Galdeano andPerdigon (2006) |
| Colon carcinogenesis | The probiotics Lactobacillus rhamnosus GG and Lactobacillus acidophilus effectively restrain pro-carcinogenic fecal enzymes induced by DMH and the development of preneoplastic aberrant crypt foci during the early stages of colon carcinogenesis in Sprague-Dawley rats. | Verma and Shukla, 2013 |
| Colon Cancer | Consumption of probiotic yogurt has been shown to lower the risk of developing large adenomas in human intervention studies within the colon. | Burns and Rowland, 2000 |

#### Therapeutic modulation of gut flora

The normal gut microbiota constitutes a significant and metabolically active component of the intestinal defense system (Isolauri *et al.,* 2001). This gut flora actively prevents the proliferation of potential pathogenic microorganisms within the gastrointestinal tract (Ziemer and Gibson, 1998). Consumption of probiotic foods can introduce novel microbial species into the gastrointestinal tract, leading to the proper maintenance and modulation of the gut microbiota (Kajander *et al.,* 2005). Specifically, the introduction of probiotic strains like *Bifidobacterium* and *Lactobacillus spp*. into the gastrointestinal tract holds considerable potential in promoting human health (Salminen and Gueimonde, 2004). Furthermore, the inclusion of probiotic-rich foods in one's diet has resulted in a decreased occurrence of irregular and imbalanced gut microecology, improved immune barrier functions, and alleviated intestinal inflammatory reactions (Saarela *et al.,* 2000).

**1.2.2 Psychobiotics: Probiotics for mental health**

Psychobiotics are probiotics that, when consumed in sufficient quantities, have a positive impact on mental health. These psychobiotics influence the microbiota-gut-brain axis (MGBA), which governs the two-way communication between the gut microbiota and the central nervous system (CNS). Substantial evidence from animal studies now substantiates the notion that the MGBA's ability to modulate brain chemistry and function is achieved through alterations in factors like intestinal permeability and inflammation, as well as the levels of neurotransmitters and other neurotrophic factors, including serotonin and brain-derived neurotrophic factor (BDNF).. (Cryan & Dinan, 2012)

Psychobiotics are a category of probiotics capable of generating and delivering neuroactive compounds such as gamma-aminobutyric acid (GABA) and serotonin (often referred to as the "happy" chemical), which exert their effects through the brain-gut axis. Additionally, they have the capacity to reduce cortisol (the "stress" hormone) levels and elevate oxytocin levels. Logan and Katzman first suggested using probiotics as adjunct therapy in managing depression. Probiotics act as carriers for neuroactive compounds and can potentially be psychotropic agents. As a result, it is hypothesized that a wide variety of bacteria produce and secrete neurochemicals. Lactobacillus and Bifidobacterium strains secrete gamma-aminobutyric acid (GABA). This neurotransmitter is the primary inhibitory agent in the brain, overseeing a wide range of physiological and psychological functions. Dysfunction of this system has been associated with anxiety and depression. In this article, we will delve into psycho-biotic strains, their mechanisms of action, and their impact on neuropsychological disorders. (by using some studies conducted on animal models). (Barbosa *et al.,* 2020)

**Table: - Pyscobiotics used in different neurological conditions.**

|  |  |  |
| --- | --- | --- |
| **Neurological** **Condition**  | **Gut microbes**  | **Psychobiotic Strains** |
| Anxiety  | *Lactobacillus* spp | *Lactobacillus casei* spp *shirota* |
| *L. helveticus* ROO52 |
| *Bifidobacterium* spp | *B. longum* 1714 |
| *B. breve* 1205 |
| Depression | *Lactobacillus* spp | *L. acidophilus* W37 |
| *L. brevis* W63 |
| *Lactococcus* spp | *L. lactis* W19 |
| *L.lactis* W58 |
| *Bifidobacterium* spp | *B. bifidum* W23 |
| *B. lactis* W52 |
| Stress | *Lactobacillus s*pp | *L. plantarum* PS128 |
| *L. rhamnosus* |
| *Bifidobacterium* spp | *B. infantis* |
| *B. longum* R0175 |

**Conclusion**

Here, we discussed various aspects of probiotics, including their history, classification, benefits, and potential applications in human health. It highlights the function of probiotics in enhancing gut health, improving digestion, maintaining various health conditions such as diarrhea, lactose intolerance, allergies, immune function, and even their potential use in mental health (psychobiotics). It explores the factors considered when choosing probiotic organisms, such as their ability to withstand acidic and bile conditions, adhere to mucosal surfaces, exhibit antimicrobial properties, engage in bile salt hydrolase activity, and possess distinct cell surface characteristics. Furthermore, it highlights the significance of probiotics' ability to modulate the immune system and their role in preserving the balance of the intestinal environment. The chapter also mentions the significant part of the gut microbiota in human health and digestion. It explains how gut flora develops from birth and how introducing probiotics into the diet can help modulate and maintain a healthy gut microbiome. Additionally, psychobiotics is introduced, where certain probiotics are suggested to beneficial affect mental health by influencing the gut-brain axis and affecting neurotransmitter levels. Overall, probiotic bacteria are beneficial for gut health and also help to improve immunity and boost health.

**References**

Aiba, Y., Suzuki, N., Kabir, A. M., Takagi, A. and Koga, Y. (1998). Lactic acidmediated suppression of *Helicobacter pylori* by the oral administration of *Lactobacillus salivarius* as a probiotic in a gnotobiotic murine model. *The American Journal of Gastroenterology*, ***93*(11)**, 2097-2101.

Alm, L. (1982). Effect of fermentation on lactose, glucose, and galactose content in milk and suitability of fermented milk products for lactose intolerant individuals. *Journal of Dairy Science*, ***65*(3),** 346-352.

Arokiyamary, A., and Sivakumar, P. K. (2011). Antibacterial activity of Bacterocin producing *Lactobacillus sp.,* isolated from traditional milk products. *Current Botany,* **2**(3).

Barbosa, M. D. T., Romero, A. H., Amezquita, L. E. G. and Cayuela, T. G. 2020. Psychobiotics: mechanisms of action, evaluation methods and effectiveness in applications with food products. *Nutrients* **12:** 1-31.

Barrett, E., Ross, R. P., O’Toole, P. W., Fitzgerald, G. F. and C. Stanton. 2012. Y-Aminobutyric acid production by culturable bacteria from the human intestine. *J. Appl. Microbiol.* **113**:411–17.

Bazzoli, F., Zagari, R. M., Pozzato, P., Fossi, S., Alampi, G., Scottili, S., Simoni, P., Roda, A. and Roda, E. (1994). 13C-Urea-breath-test to quantify Helicobacter pylori colonization of gastric mucosa and association with severity of inflammation. *Gastroenterology*, **106**, A48.

Benchimol, E. I., and Mack, D. R. (2004). Probiotics in relapsing and chronic diarrhoea. *Journal of Paediatric Haematology/Oncology*. ***26*(8)**, 515-517.

[Burns, A. J.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Burns%20AJ%5BAuthor%5D&cauthor=true&cauthor_uid=11709850), and [Rowland, I. R.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Rowland%20IR%5BAuthor%5D&cauthor=true&cauthor_uid=11709850) (2000). Anti-carcinogenicity of probiotics and prebiotics. *Current Issues in Intestinal Microbiology*, 1(1), 13-24.

Chinang, B. L., Sheih, Y. B., Wang, L. H., Lino, C. K., and Gill, H. S. (2000). Enhancing immunity by dietary optimization and definition of cellular immune responses. *European Journal of Clinical Nutrition*, **54**(11), 849855.

Cryan, J. F., and Dinan, T. G. 2012. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci*. **13**:701–712.

Cunningham-Rundles, S., Ahrne, S., Bengmark, S., Johann-Liang, R., Marshall, F., Metakis, L. and Cervia, J. (2000). Probiotics and immune response. *The American Journal of Gastro-enterology*, ***95*(1),** S22-S25.

Davis, D. J., Doerr, H. M., Grzelak, A. K., Busi, S. B., Jasarevic, E., Ericsson, A. C. and Bryda, E. C. 2016. *Lactobacillus plantarum* attenuates anxiety-related behavior and protects against stress-induced dysbiosis in adult zebrafish. *Scientific Reports* :1-11.

Doron, S. and Gorbach, S. L. (2006). Probiotics: their role in the treatment and prevention of disease. *Expert Review of Anti-Infective Therapy***, 4**(2),261-275.

FAO/WHO. (2002). Guidelines for evaluation of probiotics in food. London, Ontario: Food and Agriculture Organization of the United Nations and World Health Organization Working Group Report Pp:1-34.

from rationale to clinical use. *Current Opinion in Gastroenterology,* **21**(6), 697-701.

Fuller, R. (1989). Probiotics in man and animals. *Journal of Applied Bacteriology,* **66,** 365–78.

Galdeano, C. M., De Leblanc, A. D. M., Vinderola, G., Bonet, M. B. and Perdigon, G. (2007). Proposed model: mechanisms of immunomodulation induced by probiotic bacteria. *Clinical and Vaccine Immunology*. ***14*(5),** 485-492.

Ganguly, S., Sabikhi, L., and Singh, A. K. (2019). Effect of whey-pearl milletbarley based probiotic beverage on Shigella-induced pathogenicity in murine model. *Journal of Functional Foods,* **54**, 498-505.

Getahun, L., Tesfaye, A. and Muleta, D. (2017). Investigation of the Potential Benefits and Risks of Probiotics and Prebiotics and their Synergy in Fermented Foods. *Singapore Journal of Chemical Biology*, ***6*,** 1-16.

Gibson, G. R., Rastall, R. A., & Fuller, R. (2003). The health benefits of probiotics and prebiotics. *Gut flora, nutrition, immunity and health*, 52-76.

Gorbach, S. L. (2000). Probiotics and gastrointestinal health. *The American Journal of Gastroenterology*. ***95***(1), S2-S4.

Gronlund, M. M., Arvilommi, H., Kero, P., Lehtonen, O. P., & Isolauri, E. (2000). Importance of intestinal colonisation in the maturation of humoral immunity in early infancy: a prospective follow up study of healthy infants aged 0–6 months. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, **83**(3), F186-F192.

Guarner, F. and Malagelada, J. R. (2003). Gut flora in health and disease. *The Lancet*. **361**(9356), 512-519.

Guarner, F., Bourdet-Sicard, R., Brandtzaeg, P., Gill, H. S., McGuirk, P., Van Eden, W., & Rook, G. A. (2006). Mechanisms of disease: the hygiene hypothesis revisited. *Nature Reviews Gastroenterology and Hepatology*, *3*(5), 275.

Harish, K. and Varghese, T. (2006). Probiotics in humans–evidence-based review. *Calicut Medical Journal.* **4**(4),e3.

Hirayama, K. and Rafter, J. (2000). The role of probiotic bacteria in cancer prevention. *Microbes and Infection*, **2**(6), 681-686.

Huang, Y. and Adams, M. C. (2004). In vitro assessment of the upper gastrointestinal tolerance of potential probiotic dairy propionibacteria. *International Journal of Food Microbiology*, **91**(3)**,** 253-260.

Huycke, M. M. and Gaskins, H. R. (2004). Commensal bacteria, redox stress, and colorectal cancer: mechanisms and models. *Experiment Biological Medicine (Maywood)*, **229**, 586-97.

Isolauri, E. T. Y. E. S., Arvola, T., Sütas, Y., Moilanen, E. and Salminen, S. (2000). Probiotics in the management of atopic eczema. *Clinical and Experimental Allergy*, **30**(11), 1605-1610.

Isolauri, E., Salminen, S. and Ouwehand, A. C. (2004). Probiotics. *Best Practice and Research Clinical Gastroenterology*, **18**(2), 299-313.

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E. and Forman, D. (2011). Global cancer statistics. *A Cancer Journal for Clinicians*, **61**(2), 69-90.

Kajander, K., Hatakka, K., Poussa, T., Färkkilä, M., & Korpela, R. (2005). A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6month intervention. *Alimentary Pharmacology and Therapeutics*, ***22***(5), 387-394.

Kimoto-Nira, H., Mizumachi, K., Nomura, M., Kobayashi, M., Fujita, Y., Okamoto, T. and Ohmomo, S. (2007). *Lactococcus sp*. as potential probiotic lactic acid bacteria. *Japan Agricultural Research Quarterly,* **41**(3), 181-189.

Klaenhammer, T. R. (1988). Bacteriocins of lactic acid bacteria. *Biochimie*, **70**(3), 337-349.

 Liong, M. T. and Shah, N. P. (2005b). Acid and bile tolerance and cholesterol removal ability of lactobacilli strains. *Journal of Dairy Science*, **88**(1), 55-66.

Macfarlane, G. T. and Cummings, J. H. (2002). Probiotics, infection and immunity. *Current Opinion in Infectious Diseases,* **15**(5), 501-506.

Mack, D. R., Michail, S., Wei, S., McDougall, L. and Hollingsworth, M. A. (1999). Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. *American Journal of PhysiologyGastrointestinal and Liver Physiology*, **276**(4), G941-G950.

Majamaa, H., and Isolauri, E. (1997). Probiotics: a novel approach in the management of food allergy. *Journal of Allergy and Clinical Immunology*, **99**(2), 179-185.

Marotta, F., Naito, Y., Minelli, E., Tajiri, H., Bertuccelli, J., Wu, C.C., Min, C.H., Hotten, P. and Fesce, E. (2003). Chemoprotective effect of a probiotic preparation on development of preneoplastic and neoplastic colonic lesions: an experimental study. *Hepato-gastroenterology*, **50** (54), 19141918.

Marteau, P. R., Vrese, M. D., Cellier, C. J. and Schrezenmeir, J. (2001). Protection from gastrointestinal diseases with the use of probiotics. *The American Journal of Clinical Nutrition*, **73**(2), 430s-436s.

Marteau, P., Pochart, P., Flourie, B., Pellier, P., Santos, L., Desjeux, J. F. and Rambaud, J. C. (1990). Effect of chronic ingestion of a fermented dairy product containing Lactobacillus acidophilus and Bifidobacterium bifidum on metabolic activities of the colonic flora in humans. *The American Journal of Clinical Nutrition*, **52**(4), 685-688.

Martini, M. C., Lerebours, E. C., Lin, W. J., Harlander, S. K., Berrada, N. M., Antoine, J. M., and Savaiano, D. A. (1991). Strains and species of lactic acid bacteria in fermented milks (yogurts): effect on in vivo lactose digestion. *The American Journal of Clinical Nutrition*, **54**(6), 1041-1046.

Martini, M. C., Lerebours, E. C., Lin, W. J., Harlander, S. K., Berrada, N. M., Antoine, J. M., and Savaiano, D. A. (1991). Strains and species of lactic acid bacteria in fermented milks (yogurts): effect on in vivo lactose digestion. *The American Journal of Clinical Nutrition*, **54**(6), 1041-1046.

Masco, L., Ventura, M., Zink, R., Huys, G. and Swings, J. (2004). Polyphasic taxonomic analysis of *Bifidobacterium animalis* and *Bifidobacterium lactis* reveals relatedness at the subspecies level: reclassification of *Bifidobacterium animalis* as *Bifidobacterium animalis subsp. animalis subsp. nov.* and *Bifidobacterium lactis* as *Bifidobacterium animalis subsp. lactis subsp. nov.* *International Journal of Systematic and Evolutionary Microbiology,* **54**(4), 1137-1143.

McFarland, L. V. (2009). Evidence-based review of probiotics for antibioticassociated diarrhea and Clostridium difficile infections. *Anaerobe*, **15**(6),274-280.

McNaught, C. E., Woodcock, N. P., Anderson, A. D. and MacFie, J. (2005). A prospective randomised trial of probiotics in critically ill patients. *Clinical Nutrition*, **24**(2), 211-219.

Meurman, J. H. and Stamatova, I. (2007). Probiotics: contributions to oral health. *Oral Diseases*, **13**(5), 443-451.

Mitsuoka, T. (1982). Recent trends in research on intestinal flora. *Bifidobacteria and Microflora*, **1**(1), 3-24.

Niedzielin, K., Kordecki, H. and Birkenfeld, B. A. (2001). Controlled, doubleblind, randomized study on the efficacy of *Lacobacillusplantarum* 299V in patients with irritable bowel syndrome. *European Journal of Gastroenterology and Hepatology,* **13**(10), 1143-1147.

Olasupo, N. A., Olukoya, D. K., & Odunfa, S. A. (1997). Assessment of a bacteriocin-producing Lactobacillus strain in the control of spoilage of a cereal-based African fermented food. *Folia microbiologica*, **42**(1), 31.

Ouwehand, A. C., Salminen, S. and Isolauri, E. (2002). Probiotics: An overview of beneficial effects. *Antonie Van Leeuwenhoek,* **82**(1-4), 279–289.

Park, Y., Hunter, D.J. and Spiegelman, D. (2005). Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *Journal of American Medical Association,* **294** (22), 2849–2857.

Pool-Zobel, B.L., Neudecker, C., Domizlaff, I., et al. (1996). *Lactobacillus*- and *Bifidobacterium*-mediated antigenotoxicity in the colon of rats. *Nutrition and Cancer,* **26**, 365–80.

Power, D. A., Burton, J. P., Chilcott, C. N., Dawes, P. J., & Tagg, J. R. (2008). Preliminary investigations of the colonisation of upper respiratory tract tissues of infants using a paediatric formulation of the oral probiotic Streptococcus salivarius K12. *European Journal of Clinical Microbiology and Infectious Diseases*, **27**(12), 1261.

Reid, G. (1999). The Scientific Basis for Probiotic Strains of *Lactobacillus*. *Applied and Environmental Microbiology,* **65** (9), 3763–3766.

Reid, G. (2001). Probiotic agents to protect the urogenital tract against infection. *American* *Journal of Clinical Nutrition*, **73**, 437S - 443S

Saarela, M., Mogensen, G., Fonden, R., Matto, J. and Mattilia-Sandholm, T. (2000) Probiotic bacteria: Safety functional and technological properties. *Journal of Biotechnology,* **84** (3), 197-215.

Salminen, S. and Gueimonde, M. (2004). Human studies on probiotics: what is scientifically proven. *Journal of Food Science*, **69**(5), M137-M140.

Salminen, S., and Von Wright, A. (2004). *Lactic acid bacteria: microbiological and functional aspects*. CRC Press.

Salvetti, E., Torriani, S. and Felis, G. E. (2012). The genus Lactobacillus: a taxonomic update. *Probiotics and Antimicrobial Proteins,* **4**(4),217-226.

Sanders, M. E. (1993). Effect of consumption of lactic cultures on human health. *Advances in Food and Nutrition Research*,**37**, 67-130.

Sanders, M. E. and Klaenhammer, T. R. (2001). Invited review: the scientific basis of *Lactobacillus acidophilus* NCFM functionality as a probiotic. *Journal of Dairy Science*, **84**(2),319-331.

Schultz, M. and Sartor, R. B. (2000). Probiotics and inflammatory bowel diseases. *The American Journal of Gastroenterology*, **95**(1)**,** S19-S21.

Shah, N. P. (2000). Probiotic bacteria: selective enumeration and survival in dairy foods. *Journal of Dairy Science*, **83**(4), 894-907.

Singh, H.K., Puranik, D.B., Poornima and Sain, M. (2021) Process optimisation for the production of papaya leaf extract based therapeutic whey beverage. *Environment Conservation Journal*, **22** (1&2): 153-158.

Solga, S. F. and Diehl, A. M. (2003). Non-alcoholic fatty liver disease: lumenliver interactions and possible role for probiotics. *Journal of Hepatology*, **38**(5), 681-687.

Talwalkar, A. and Kailasapathy, K. (2004). A review of oxygen toxicity in probiotic yogurts: Influence on the survival of probiotic bacteria and protective techniques. *Comprehensive Reviews in Food Science and Food Safety*, **3**(3),117-124.

Tannock, G. W. (2001). Molecular assessment of intestinal microflora. *The American Journal of Clinical Nutrition*, **73**(2), 410s-414s.

Tannock, G. W. (2002). The bifidobacterial and Lactobacillus microflora of humans. *Clinical Reviews in Allergy and Immunology*. **22**(3), 231-253.

Taranto, M. P., Medici, M., Perdigon, G., Holgado, A. R. and Valdez, G. F. (1998). Evidence for hypocholesterolemic effect of Lactobacillus reuteri in hypercholesterolemic mice. *Journal of Dairy Science*, **81**(9), 23362340.

Tisser, H. (1906). Traitement des infections intestinales par la methode de la flore bacterienne de l’intestin. C.R. Soc. Biol, 60, 359-361.

Vanderhoof, J. A. (2000). Probiotics and intestinal inflammatory disorders in infants and children. *Journal of Pediatric Gastroenterology and Nutrition*, **30,** S34-S38.

Verdu, E. F., & Collins, S. M. (2005). Irritable bowel syndrome and probiotics:

Verma, A. and Shukla, G. (2013). Administration of prebiotic inulin suppresses 1, 2 dimethylhydrazine dihydrochloride induced procarcinogenic biomarkers faecal enzymes and preneoplastic lesions in early colon carcinogenesis in Sprague Dawley rats. *Journal of Functional Foods,* **5**(2), 991-996.

Ziemer, C. J. and Gibson, G. R. (1998). An overview of probiotics, prebiotics and synbiotics in the functional food concept: perspectives and future strategies. *International Dairy Journal*, ***8***(5-6), 473-479.

Zoumpopoulou, G., Tsakalidou, E., Dewulf, J., Pot, B., & Grangette, C. (2009). Differential crosstalk between epithelial cells, dendritic cells and bacteria in a co-culture model. *International Journal of Food Microbiology*, **131**(1), 40-51.