Chapter

Probiotic: An Uprising Human Health Concept

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Abstract

Most of our gut microbiota live with us in a mutually beneficial life-long relationship. The gut microbiota plays a vital role in the host's overall health through its metabolic activities. Human microbiota might be supported by consuming friendly bacteria (probiotics) and consuming foods to improve the microbiota (prebiotics). During the last two decades, probiotics' interest has increased with rising scientific shreds of evidence of benefits on human health. Hence, they have been exploited as various food products, mainly fermented foods. Probiotics as a treatment modality may restore normal microbiota and functioning of the gastrointestinal (GI) tract. Strong scientific evidence is associating these bacteria with the prevention and therapy of various GI disorders. (In light of the ongoing trend of probiotics, further research is needed to obtain the perspective of potential applications for better health. Probiotic applications have been extended from health applications to food and agricultural applications. The benefits of probiotics led to its applications in probiotic 'health food' industries and agricultural sectors.

Keywords: Probiotics, Prebiotics, Food products, Gut microbiome, Benefits

1. Introduction

The human body exists in close relation with numerous structurally and functionally diverse microbes inhabiting different parts of the body. The mouth, the gastrointestinal tract (GIT), and the vagina are most heavily populated. This composition is known as microbiota which is acquired soon after birth [1]. The microbiota that is exclusively found in GIT is referred to as 'Gut microbiota.' Gut microbiota is primarily non-pathogenic and plays a vital role in conferring health benefits to the host [2]. Through metabolic activities and physiological regulation such as resistance to pathogens, improvement of intestinal barrier function, promotion of nutrient absorption, formation of bioactive compounds [2]. It may also influence the physiology, biochemistry of the host [3].

The idea that bacteria can confer health benefits to humans was postulated 100 years ago by Elie Metchnikoff. The 'probiotic' word is derived from the Greek word, meaning "for life" and has had several different meanings over the years [4]. The increase in evidence of the benefits of probiotics and prebiotics, especially in health improvement, led to its applications in various food industries. This book chapter highlights the significance of gut microbiota and the emergence of probiotic concepts to benefit human health. In this chapter, we have made a little attempt to introduce the concept of probiotics and prebiotics, their benefits to humans' health, and their probability of being applicable in various fields.

2. Gut microbiota

The human body harbors a complex ecosystem that includes more than 1000 various microorganisms [5, 6]. It means the number of bacteria within the gut is about ten times that of eukaryotic cells in the human body. In a healthy animal, the internal tissues such as blood, brain, muscle, etc. in a healthy animal are usually free of microorganisms. However, the surface tissues, such as skin and mucous membranes, are constantly in contact with environmental organisms and become readily colonized by various microbial species. The microbiota extends from mouth to anus and into the vaginal tract of women. In the healthy host, enteric bacteria colonize the alimentary tract soon after birth, and the composition of the intestinal microbiota remains relatively constant [7]. The normal flora of humans consists of a few eukaryotic fungi and protists, but bacteria are the most numerous and obvious microbial components of the normal flora. The total genomic content of microbiota is referred to as a microbiome that inhabits a specific anatomical site of the body [8]. The mixture of organisms regularly found at any anatomical site is referred to as the "normal flora". However, researchers in the field who prefer the term "indigenous microbiota," which includes resident microbiota, transient microbiota, and opportunistic microbiota.

The gut microbiome exhibits various interactions with the human body. It may be mutualistic or pathogenic. The interactions between the gut microbiome and host have evolved into symbiotic relations. It confers various benefits to the human body, significantly strengthens the host's immune system, and protects against various diseases caused by harmful pathogens. Hence, it is helpful to study the symbiotic relationship of the gut microbiome with the host and its influence on the host's overall health.

2.1 Composition of gut microbiota

The gut microbiota is composed of four main phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Predominantly, anaerobic bacteria colonize the Gastrointestinal tract (GIT) [9].

GI tract consists of the stomach, small intestine, and large intestine. Various parts of the GI tract differ in their environmental characteristics, chemical compositions, and physiological properties. Therefore types and numbers of microbiota vary in different parts. In general, microorganisms increase in numbers from the stomach to the small intestine to the large intestine.

2.1.1 Microbiota of stomach

The microbes in the stomach are primarily of similar types that are present in the mouth and throat. Generally, aerobic microbes inhabit the stomach, and that too in a lesser amount than the population of mouth and stomach. The stomach receives many microbes from the mouth through food and water, but most of them are killed due to hydrochloric acid (HCl). Thus, few microorganisms that can tolerate high pH can form normal resident flora of the stomach.

Organisms generally found in the stomach are – *Lactobacillus, Enterococcus, Streptococcus, Staphylococcus, Peptostreptococcus, Candida, Helicobacter pylori,* etc. [10, 11]. Some of them are hazardous to health, such as *Helicobacter pylori, which* can cause chronic gastritis and peptic ulcers.

2.1.2 Microbiota of small intestine

The small intestine is a tube about 6 meters long-running from the stomach to the large intestine. The small intestine usually has three sections: duodenum, jejunum, and ileum. Each section reflects slightly different functions. The microbiota of the small bowel is the least well understood due to its inaccessibility for study.

Duodenum is adjacent to the stomach, and it is slightly acidic. The duodenum includes similar types of organisms that are found in the stomach. It mainly acquires acid-resistant organisms such as Lactobacillus and Enterococcus. The intestine becomes less acidic from the duodenum to the ileum; hence, the microbial population increases. In the jejunum, prominently, lactobacillus, Enterococci, *Candida albicans*, etc., are found. In ileum microbial population resembles that of the large intestine. It mainly includes obligate anaerobes such as *Clostridium perfringes*, anaerobic *E. coli*., Bacilli, Streptococcaceae. Actinomycinaeae and Corynebacteriaceae are abundant in the duodenum, jejunum, or ileum [12, 13].

2.1.3 Microbiota of large intestine

The large intestine follows on from the small intestine. The large intestine receives remains of food that enzymes have not digested. The chyme, on entering the large intestine, is referred to as feces. The large intestine is divided into three distinct parts: caecum, colon, and rectum. About 1100 different species of microbes are present in the large intestine [14].

The large intestine harbors obligate anaerobes and facultative anaerobes. The more common genera include Bacteroides, *Clostridium*, *Eubacterium*, *Roseburia*, *Faecalibacterium*, and *Ruminococcus* [15, 16]. The large bowel includes increased Lachnospiraceae (Firmicutes) proportions, and Bacteroidetes are found in the colon [13]. It also inhibits *E.coli, Lactobacillus, Bifidobacterium, Enterococcus* in smaller numbers.

2.2 Benefits of gut microbiota

Earlier, the gut microbiota was thought to be commensals whose only benefit was controlling the abundance of pathogenic bacteria. However, as the knowledge about these symbionts increased, their essential roles, such as aiding digestion and various metabolites, were also known to improve the immune system [17, 18]. The gut microbiota plays a crucial role in immunomodulation and the nervous system and intestinal mucosal system development. In addition, gut microbiota plays a crucial role in synthesizing essential vitamins such as vitamin B12, vitamin K, nicotinic acid, pyridoxine, thiamine [19]. The gut microbiota generates short-chain fatty acids (SCFAs) by fermenting complex carbohydrates. These SCFAs play a significant role in inflammatory response and regulation of immune response. The gut microbiota also influences epithelial homeostasis [19].

There are pieces of evidence that gut microbiota provides extra nutrition. It could be due to the digestion by enzymes of the resident microbiota. Another benefit of gut microbiota is a defense against a range of pathogens, including *Listeria cytogenes, Clostridium botulinum*, and *Cryptosporidium parvum*. The gut microbiota provides a hostile environment, produces antimicrobial substances, and strengthens the human body's defenses to defend against pathogens. It also stimulates peristalsis, so gut contents are moved more quickly, making it more difficult for newly-arrived pathogens to be established.

2.3 Disturbance of gut microbiota

The composition of gut microbiota may vary between individuals though some key bacterial species are typically present in most. Diet is thought to explain over 50% of these microbial structural variations in mice and 20% in humans, signaling the potential for dietary strategies in disease management through gut microbiota modulation [20]. The gut microbiota shows drastic changes in infants with lactation followed by an introduction to solid food. The mode of intake, medication dosage may influence the gut microbiota. Gut microbes are regularly purged and have the ability to double in specific time intervals. The short-term and long-term dietary changes and modification in micronutrient intake can significantly change gut microbiota composition. The experiment conducted by Wu et al. showed a dramatic shift in the fecal microbiota of the participants due to high fat/low fiber and low fat/high fiber. Fiber content and type were thought to be primer determinants of the composition of the microbiota of the gut.

Through antibiotics, improvement in human health is achieved through the drugs have negative consequences also. Antibiotic drugs control the infections caused by pathogens, but other beneficial bacteria are also harmed. A disturbed microbiota may not function well against infections caused by new pathogens, resulting in the overgrowth of pathogens such as *Clostridium difficile* [21]. Several factors may influence the disturbance of gut microbiota caused by antibiotics: (i) the dose and duration of the drug (ii) the range of microbes affected by antibiotics (e.g., broad-spectrum or narrow-spectrum) (iii) the proportion of antibiotic that is being absorbed into the body or resides in the intestine.

Most antibiotics are taken orally, and some are given intravenously. The latter type has a significant influence to disturb microbiota. Different antibiotics have different effects, e.g., penicillin has minor effects on the gut microbiota, while ampicillin causes significant disturbance to the gut microbiota. Thus, there is a need to develop an alternative that is safer and effective for use. Increasing knowledge of probiotics and their efficacy against pathogens can aid the recovery of gut microbiota. Probiotics may be suitable to take after or simultaneously as antibiotics to reduce the risk of disease from disturbance of microbiota.

3. Probiotics

Probiotics are live organisms which when administered in an adequate amount, confers health benefits to the host (FAO and WHO, 2002). The characteristics of effective probiotics are their ability to survive the passage through the digestive tract and utilize the nutrients and substrates in a normal diet. Probiotics are healthy gut flora and thereby improve digestion. Several criteria have been used to prove any strain as novel probiotic strains, categorized into two groups: safety and functionality. The concept of probiotics deals with the constant introduction of the new microbes beneficial to the human host as an attempt to change the indigenous microbial population equilibrium to increase overall health [22].

3.1 History of Probiotics

The concept of using microbes to improve health is a hundred years old. During the twentieth century, probiotics gained much interest due to an increase in scientific evidence proving the beneficial effects of probiotics. The idea that bacteria could benefit human health was postulated almost 100 years ago by Elie Metchnikoff while working at the Pasteur Institute in Paris. Metchnikoff's adoption of an idea to use beneficial bacteria to improve the bacterial population of the intestine arose from his inquiries into how old age could be delayed and life prolonged. Metchnikoff concluded that fermented milk drank by peasants of Bulgaria has a key role (Metchnikoff 1907) [21] in their longevity. He found a bacterium from peasant's milk and named it *Bacillus bulgaricus.* He explained that the production of lactic acid by a bacterium reduces the harmful effects of other microorganisms. It is not sure which bacterium was found by Metchnikoff. It may be *Lactobacillus bulgaricus,* a strain that is commonly used in yogurt.

The term probiotic literally means 'for life is derived from the Greek language. Lilly and Stillwell first coined this term in 1965 to describe "substances secreted by one microorganism which stimulates the growth of another" and thus was contrasted with the term antibiotic [23]. Parker modified this definition to "organisms which contribute to intestinal microbial balance" [24]. The concept of probiotics became weak after the early death of Metchnikoff and the development of antibiotic drugs. Though, interest in the general public did not fall entirely. One of the factors that gained the popularity of probiotics towards the end of the century is the rise of resistant strains of pathogens against different antibiotics.

3.2 Mechanism and action of probiotics

The mechanisms of probiotic action are diverse. The activities of these strains can influence other factors such as the presence of other bacteria in the intestinal environment or even the disease setting in which the strain is being used [25]. The characteristics of effective probiotics are their ability to survive the passage through the digestive tract and utilize the nutrients and substrates in a normal diet. However, some mechanisms have been reported for most of the probiotic strains, which include: colonization resistance, antimicrobial activity, antimutagenic effects, antigenotoxic effects, influence on enzyme activity, etc.

The probiotic bacteria have antagonistic effects on different microorganisms and competitive adherence to mucosa and epithelium. These characteristics also work as antimicrobial activity. By decreasing luminal pH, they are inhibiting other bacterial adherence, translocation, and secretion of antimicrobial substances such as antimicrobial peptides (e.g., bacteriocin), organic acids (lactic and acetic acid), hydrogen peroxide (in environments in which oxygen is present), diacetyl, β-hydroxypropionaldehyde [26–30]. The probiotics are also capable to modulate cell proliferation and apoptosis. Polysaccharide fermentation by probiotic strains increases the availability of short-chain fatty acids (SCFAs), which felicitate repair of epithelial damage. Some strains also produce mucus excessively, which enhances the intestinal barrier. It can separate bacteria from the lumen and prevent the colonization of the epithelium [31]. Probiotics can exert control over epithelial cells, dendritic cells, monocytes, macrophages, lymphocytes, IgA through different mechanisms for the stimulation of the human immune system; increased IgA decreases the number of pathogens, thus improving gut health [32, 33]. **Figure 1** shows various mechanisms by which probiotics benefits health of host.

3.3 Types of probiotic microbes

There is a growing number of microorganisms described as probiotics. Among the various types of microbes, bacteria are used as probiotics mainly. The potential of intestinal and dairy species Lactobacilli and Bifidobacteria as probiotics was postulated over a hundred years ago. At that time, the yearning to understand the microbial ecology of these groups in the human intestine was linked to the aspiration to manage and maintain human health. The link between Lactobacilli and human health was first proposed in the late 1800s by Metchnikoff [34].

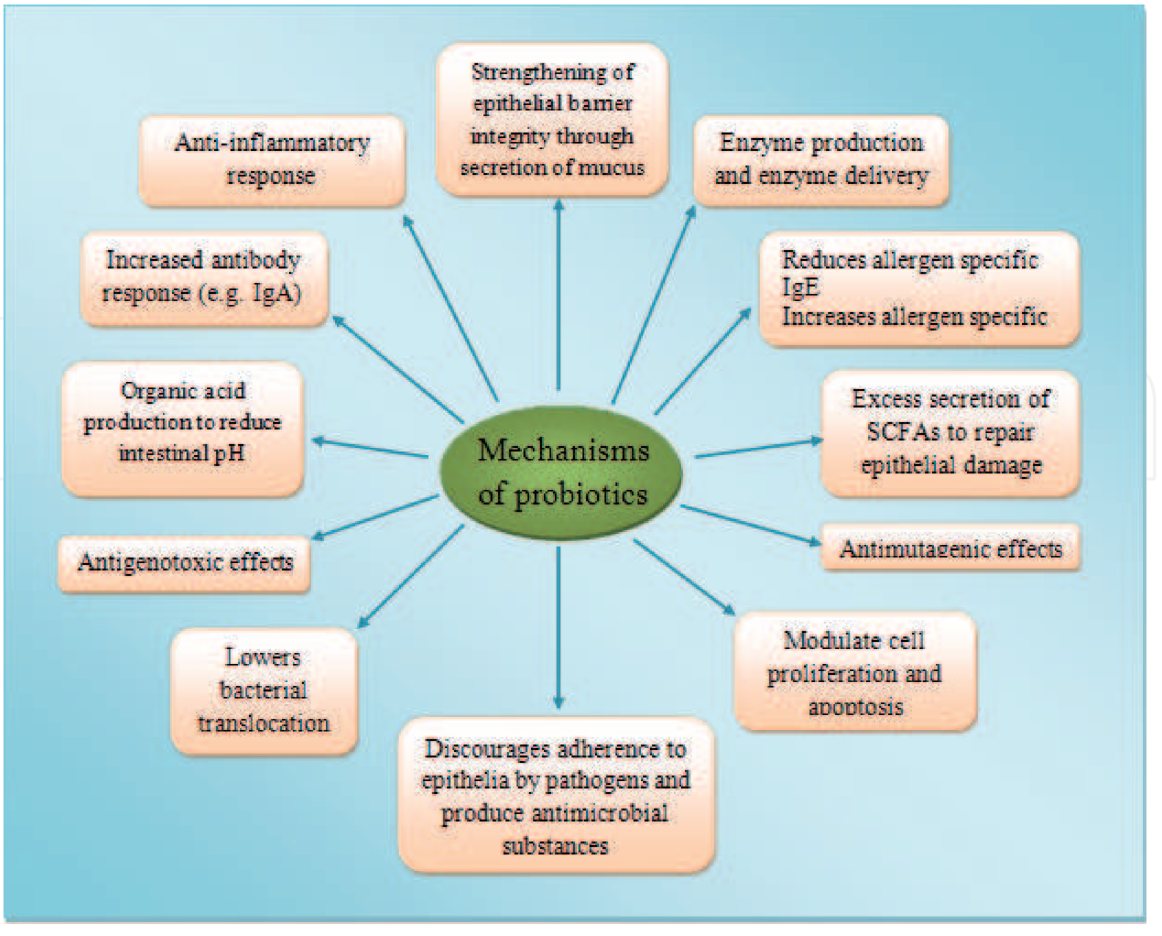

Figure 1.
Mechanism of probiotics.

The majority of the different species included in probiotics belong to the genus *Lactobacillus*. Metchnikoff favored this bacterium. They are normal flora of the small bowel as there is a wide range of food in that part of the small intestine. There are fewer lactobacilli present in the large bowel also. Lactobacilli are easy to grow, which aid as an essential factor in using probiotics at a commercial scale. Other characteristics of lactobacilli are resistance to gastric stress and the ability to grow in a microaerophilic environment that makes them well-suited to live in the gastrointestinal tract. Lactobacilli are heterofermentative and require many micronutrients to grow. The species most commonly used in probiotics are *L. acidophilus, L. casei, L. crispatus, L. johnsonii, L. plantarum, L. reuteri, L. rhamnosus, L. salivarius.* The probiotic effect of lactobacilli is as follow:

- Secretion of lactic acid lowers the pH of GIT and eliminates harmful bacteria. Some lactobacilli produce acetic acid, which gives a more substantial effect than lactic acid against pathogens.

- Lactobacilli produce antibiotic-like compounds referred to as bacteriocins, which restrict the growth of pathogens. Some of them also produce hydrogen, which exerts antibacterial effects.

- Lactobacilli tend to attach to mucosa and form colonies, which is the primary requirement of good probiotics. They block the attachment of pathogens and may also influence the immune cells in the gut wall. Some lactobacilli also produce mucus in excess to discourage attachment of pathogens.

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Probiotic Lactic acid bacteria	
Lactobacillus spp.	*Bifidobacterium spp.*
Lactobacillus rhamnosus	*Bifidobacterium lactis*
Lactobacillus plantarum	*Bifidobacterium bifidum*
Lactobacillusreuteri	*Bifidobacterium animalis*
Lactobacillus acidophilus	*Bifidobacterium breve*
Lactobacillus casei	*Bifidobacterium infantis*
	Bifidobacterium longum
Other lactic acid bacteria	**Non-lactic acid bacteria and yeast**
Lactococcus lactis	*Propionibacterium freudenreichii*
Streptococcus thermophilus	*Saccharomyces cerevisiae*

Table 1.
List of probiotic microorganisms [21, 37–39].

There are other genera of lactic acid-secreting bacteria. One of them is *Enterococcus, which* has species such as *E. faecium* that are used as probiotics. The mechanism is similar to those of lactobacilli.

Bifidobacteria are the second most commonly used type of bacteria in probiotic products. One of the reasons for their less popularity could be their incapability to grow and process commercially. Henry Tissier identified the unusually shaped *Bifidobacterium* from the stool of the baby. A large number of these bacteria in the intestine of the baby reassured that they are probably beneficial. Bifidobacteria reduce lactose intolerance, cholesterol levels, improve the gut immune system, and prevent gut infection in infants. Some of the species frequently used in probiotics are *Bif. adolescentis, Bif. animals, Bif. bifidium, Bif. breve, Bif. longum, and Bif. infantis.*

Like lactobacilli and bifidobacteria, other organisms such as *E. coli, Bacillus subtilis, Saccharomyces cerevisiae, S. boulardii*. Most *E. coli* are benign commensals, but some are opportunistic pathogens. *E. coli* Nissle 1971 (EcN) is the best known *E. coli* probiotic [35, 36]. Nissle bacteria are protected from stomach acid by added enteric coating. The coating won't dissolve until it reaches the ileum and caecum. EcN strengthens the barrier function of epithelial cells against pathogens. EcN has been used as an anti-diarrhoeal and to treat constipation and ulcerative colitis [21]. *Bacillus subtilis* is a spore-forming bacterium; the spores protect the cells from gastric acid. Some of the spores germinate in the intestine and influence the gut immune system and stimulate lactobacilli's growth. Some other *Bacillus* species are used as probiotics, such as *B. coagulance, B. licheniformis, B. pumilus,* and *B. clausii*. *Saccharomyces boulardii,* a sub-species of *S. cerevisiae* is used as probiotics. *S. boulardii*is not normal flora of the gut, but it can live there temporarily and gives anti-diarrhoeal effects. Some probiotic organisms with Generally Regarded As Safe (GRAS) status are listed in **Table 1**.

4. Benefits of probiotics

There are certain diseases related to the disturbance of microbiota of the gastrointestinal tract. Some of them are infectious diarrhea, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), lactose intolerance, antibiotic-associated diarrhea, constipation, gastritis, and stomach ulcers. There are evidences available showing influence of probiotics to treat such diseases. Other body parts may benefit from probiotics as microbiota is present in other body parts, not just the intestine. Furthermore, the immune system is connected to all parts of the body, so by influencing one part of the immune system, probiotics may influence others.

4.1 Effect of probiotics on diarrhea

Infectious diarrhea, traveler's diarrhea (TD), antibiotic-associated diarrhea are various types of diarrhea caused by different conditions. Infectious diarrhea is generally caused by pathogenic microbes such as viruses, bacteria, yeast, or protozoan. Generally, normal bowel movements return after about three days, but they may not in children with acute diarrhea. In infants, rotavirus is the most common microbe responsible for diarrhea. Probiotics have been tried in many clinical studies as a supplement for rehydration therapy to treat infectious diarrhea in infants. The results have been positive and consistent [40]. In young children, the probiotics were also found to be effective in preventing the development of infectious diarrhea. The types of probiotic microbes used are lactobacilli, bifidobacteria, *S. boulardii* (yeast).

The traveler's diarrhea may be caused by the water supply being contaminated with fecal matter, contaminated food. In the case of traveler's diarrhea, the use of probiotics is more likely to be considered by adults. Though, the use of probiotics in TD has given a mixed response as the cause of TD differs depending on the local situation [41].

The use of antibiotics has revolutionized the treatment of bacterial infections. However, it promotes the rise of resistant bacteria and disturbs gut microbiota's composition, which makes us vulnerable to pathogenic infection. Such infection of the intestine leads to diarrhea, referred to as 'antibiotic-associated diarrhea (AAD)'. When the gut microbiota is disturbed, *Clostridium difficile* increases to infection level; this bacterium causes about one-fifth of AAD. In several studies, probiotic yeast *S. boulardii* was effective against *C. difficile* when given along with antibiotics [42]. In a number of cases, probiotic microbes such as LAB, *S. boulardii*, *Clostridium butyricum* prevented such diarrhea, although not all studies have shown probiotics to be effective [42–45].

4.2 Effect of probiotics in Irritable Bowel Syndrome (IBS)

The irritable bowel syndrome is a common gastrointestinal disorder. In IBS an abnormal condition of gut contractions (motility) and increased gut sensations (visceral hypersensitivity) characterized by abdominal pain/discomfort, gas, bloating, mucous in stools, and irregular bowel habits with constipation or diarrhea. Several studies show the effect of probiotics on this disease; however, the mechanism by which probiotic organisms affect this condition is still unknown. A review and meta-analysis by Ford et al. concluded the beneficial effects of probiotics as a treatment on IBS symptoms, including RCTs published between 1939 and 2013, and it was emphasized that multi-strain probiotics had a more distinct effect on IBS symptoms [46, 47]. However, *Lactobacillaceae* and *Bifidobacteriaceae* (genus: *Lactobacillus* and *Bifidobacterium*) were the two most common families used in multi-strain probiotic supplements [47].

4.3 Effect of probiotics in inflammatory bowel disease (IBD)

Inflammatory bowel disease is a group of the chronic intestinal disease characterized by inflammation of the large or small intestine. Crohn's disease (CD) and ulcerative colitis (UC) are the most common types of IBD. UC only affects the large bowel, and the inflammation is usually found in the rectum and the sigmoid colon but can be found anywhere along with the large bowel. CD can affect any part of the digestive tube from mouth to the anus but is most often found in the area of the junction of the ileum and caecum. The evidence of benefit from probiotics in UC is strong, while the evidence in Crohn's is weak. There have been eight controlled trials involving people with UC in one study, and seven of them showed significant benefit from probiotics. Use of probiotics extended periods of remission or reduced active disease [48]. Some studies have been conducted with *E. coli* Nissle (EcN), *Saccharomyces boulardii*. These microbes have been reported to have some beneficial effects in IBD [41, 49]. *E. coli* probiotic was found to be as effective as a standard drug used in UC to prevent relapse. In comparison, only a small number of trials showed the benefit of probiotic yeast *S. boulardii* in Crohn's disease.

4.4 Effect of probiotics in lactose intolerance

The inability of some adults to digest the sugar lactose, which is present in milk, is referred to as 'lactose intolerance. The lactose is hydrolyzed by the enzyme lactase, which is also known as lactose- galactosehydrolase (EC 3.2.1.108). The lactose is digested into glucose and galactose, which is taken up by intestinal cells and transported to the bloodstream. The remaining lactose, which is not hydrolyzed, passes to the colon [36]. The person with lactose intolerance produces less lactase, which is inefficient in digesting much of the milk sugar. The undigested lactose causes intestinal difficulties. When lactose intolerant people consume milk, they may suffer from excess gas, diarrhea, cramps, bloating, abdominal rumblings, and flatulence. One of the reasons for excess gas could be the fermentation of glucose by gut microbiota. As lactose is an active osmotic compound, it causes osmotic pressure, leading to high water content in the feces, causing clinical symptoms as diarrhea [36]. Probiotics have gained attention as an alternative to compensate for the low level of lactase [41, 50]. Probiotic can affect at two levels: (i) By increasing hydrolytic activity in the small intestine (ii) By increasing colonic fermentation [51]. Several studies have shown the effect of probiotic yogurt in better lactose digestion in lactose-intolerant people. The probiotic bacteria used in yogurt (*Lactobacillus bulgaricus* and *Streptococcus thermophilus)* produce a significant amount of their own lactase. Evidence suggests that probiotic organisms can digest lactose in yogurt products and continue digestion in the small intestine when consumed [52]. They prevent excess gas production and reduce or eliminate diarrhea. The yogurt allows more time for lactase to digest lactose as yogurt has a thicker consistency; it takes a longer time to pass through the intestine. There is some evidence showing that Russian fermented milk- kefir or variants of kefir (sugary kefirs, kefir grains) effectively alleviate lactose intolerance [53]. There are probiotic products available in capsule, tablet, or powder form (e.g., *Lactobacillus* and *Bifidobacterium* species used in non-milk products); however, they do not appear to be as effective as yogurt.

4.5 Effect of probiotics in gastritis and stomach ulcers

A bacterium, *Helicobacter pylori,* causes inflammation of the mucosal barrier of the stomach. As well as frequent long-term use of nonsteroidal anti-inflammatory drugs is the major factor involved in gastric ulcer development [53]. Gastric mucosal damage is common; if not treated adequately, it may lead to gastric cancer. To eradicate *H. pylori*, three drugs are used simultaneously: two antibiotics and a proton pump inhibitor [54]. However, this treatment fails in most of the cases due to antibiotic-resistant strains of *H. pylori*; thus, a fourth antibiotic is added to standard triple therapy used previously. The therapy may cause side effects such as diarrhea, taste disturbance, and nausea.

The growing interest in probiotics to prevent or treat gastrointestinal diseases has attracted the attention of many researchers to explore the role of probiotics in the prevention and treatment of gastric ulcers [50]. Some studies have found out that when probiotics are used in conjunction with standard drugs, the rate of eradication was higher than drug therapy or probiotics alone [55]. However, side effects caused by drug therapy were reduced by probiotics. Most of the studies have used lactobacilli, but not all strains showed effects against *H. pylori.* Probiotic yeasts *S. boulardii* also showed potential therapeutic effects in gastric ulcers. *S. boulardii* acquires neuraminidase activity which removes sialic acid, which results in the prevention of binding of *H. pylori* to epithelial cells [53].

4.6 Effect of probiotic in vaginal infections

In a healthy woman, the vagina has a resident microbial population. These resident microbiota live on the lining of the vagina wall. Most of them are lactobacilli. The vaginal lactobacilli have a protective influence against urogenital infections [50]. The vaginal infections are referred to as vaginitis. In which pathogenic infections cause inflammation of the vaginal lining. If a bacterium causes vaginitis, it is known as bacterial vaginosis (BV). If vaginitis is caused by a fungus (generally *Candida- a* type of fungus), it is known as vaginal candidiasis (VC). Both types of vaginitis symptoms are similar, such as burning sensation during urination, itching in the vaginal area, and greyish or white discharge. Antibiotics or antifungals treat the infection. There is evidence that some women have H_2O_2 – secreting lactobacilli in their intestine, which lowers the risk of BV. This suggests that the rectum act as a reservoir supplement vaginal microbiota when it becomes disturbed. This information leads to the development of probiotics to protect the female reproductive system [56, 57]. Though studies have shown mixed responses. In the case of VC, a small number of clinical studies have been undertaken of probiotics against *Candida.* In most of the studies, probiotics didn't show any significant effect. However, when probiotics were taken along with antifungal drugs, they improved the effectiveness of antifungal significantly [58].

4.7 Effect of probiotics in upper respiratory infections

The upper respiratory tract (URT) consists of the nose, throat, and windpipe. The nose and throat have microbiota, and the upper part of the windpipe has a changing microbial population as cilia move mucus upward to the throat. The various diseases associated with URT are common cold, sore throat, pharyngitis, epiglottitis, laryngitis, and diphtheria [29]. Most commonly, viruses such as rhinoviruses, coronaviruses, parainfluenza, and influenza viruses and bacteria such as streptococci, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Corynebacterium diphtheria, Staphylococcus aureus, Haemophilus influenzae* type b, *Streptococcus pyrogens*, and *Streptococcus pneumonia* are associated with URT infection [59, 60]. Infection of URT may spread to the lungs, causing bronchitis and pneumonia. Some studies have shown that probiotics may reduce the severity and duration of the condition. Some probiotic bacteria such as *Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium animals* were beneficial to reduce and prevent URT risks in children and adults [29]. Probiotics may also improve the effectiveness of influenza vaccination in the elderly. This improved immune reaction may enhance protection against acquiring influenza, although it is yet to be confirmed.

4.8 Effect of probiotics in constipation

Constipation is quite a common condition that can be acute or chronic. Constipation causes a general feeling of abdominal discomfort. To pass the stool straining may put pressure on the tissues and structures of the anal area with adverse consequences such as hemorrhoids (piles). Other diseases associated with constipation are irritable bowel syndrome and cancer of the large bowel. Several studies have been conducted using *Lactobacillus rhamnosus, Lactobacillus casei, Bifidobacterium animalis,* and probiotic *E. coli.* [61, 62]. Prebiotics also may be effective against constipation as FOS, GOS, and lactulose have mild laxative effects [63]. These laxative effects can be due to osmosis as prebiotics are soluble fibers. Prebiotics also boost bifidobacteria and lactobacilli, and these probiotic bacteria accelerate the transit of large bowel content. However, meta-analyses also indicate that groups of probiotics and synbiotics have more efficiency than individual probiotics [64].

4.9 Other benefits

The list of benefits of probiotics is not limited to the ones mentioned above. However, it includes a range of benefits that need to be explored for further human studies. Some evidences suggest that probiotics may influence cancer incidence [50]. As well as researchers are exploring various alternatives of drugs from probiotics that can be used to treat a disease like cancer and with lesser or no side effects. (i.e., L-asparaginase that is used in cancer treatment from *L. casei, L. reuteri,* etc. is being explored) [43, 65]. Furthermore, evidences suggests that food products with probiotic organisms may reduce serum cholesterol levels and control blood pressure. Probiotics may also prevent coronary heart disease [66, 67]. Several studies examined the effect of probiotics and *pre*biotics to treat allergic conditions. However, studies to prevent allergic conditions like asthma and allergic rhinitis did not show a positive response. However, studies examined that when pregnant women have probiotic intake, it improves the functioning of the mother's immune system and indirectly improves the immature immune system of the infant, reducing the risk of allergies such as eczema and dermatitis [68]. But there are insufficient evidences to recommend probiotics as standard therapy to prevent allergies [44]. There is a close relationship between microbiota and the immune system of the skin. Consumption of probiotics has provided some protection against ultraviolet radiation from the sun. *Vitreoscilla filiformis* showed a beneficial effect on a patient with seborrhoeic dermatitis and atopic eczema [69]. As described earlier, LAB, especially lactobacilli and bifidobacteria, exert a beneficial effect in infants with atopic eczema. A *pre*biotic cream has been developed with encouraging results in controlling acne-associated organism *Propionibacterium acne.* However, much more exploration and research are needed to use probiotics routinely for the skin.

5. Application of probiotics

Due to the health benefits exerted by probiotic organisms, they have a wide range of applications in clinical uses and various industries such as food industries and agriculture industries. Most species of lactobacilli and bifidobacteria are used commercially. Among them *L. rhamnosus, L. plantarum, L. casei, L.paracasei, B. animalis* are widely used. With that in some products organism such as *S. thermophilus* is used.

5.1 Application of probiotics in the food industry

Increasing knowledge of probiotic benefits leads to the development of functional foods. Functional foods, also known as "nutraceuticals" or "designer foods," are ingredients that offer health benefits that extend beyond their nutritional value. Some types contain supplements or other additional ingredients designed to improve health, and they are slowly emerging as 'health food' on supermarket shelves worldwide [70]. A wide variety of dairy products such as milk, yogurt, cheese, ice cream, chocolate mousse, quark, etc., include probiotic organisms to improve their nutrition characteristics [70–74]. Furthermore, whey-based and fortified dairy beverages are also available, including probiotic and *pre*biotic. *L. rhamnosus* GG is widely used in such beverages [75, 76]. The development of non-dairy-based products has gained attention in developed countries as a population

Food product	Probiotic organism used	References
Acidophilus milk	*Lactobacillus acidophilus*	[79]
Yogurt, bio-yogurts	*Streptococcus thermophilus* *Lactobacillus bulgaricus* *Bifidobacterium bifidum*	[76, 80, 81]
Cheese	*Lactobacillus acidophilus* *Lactobacillus paracasei* *Lactobacillus reuteri* *Bifidobacterium infantis*	[81, 82]
Kefir (Fermented milk beverage)	*Lactobacillus kefir* *Lactobacillus paracasei* *Lactobacillus parabuchneri* *Lactobacillus casei* *Lactobacillus lactis* *Lactococcus lactis* *Acetobacter lovaniensis* *Saccharomyces cerevisiae*	[80]
Yosa (oat-bran pudding)	*Lactobacillus acidophilus*	[80]
Uji	*Lactobacillus paracasei*	[80]
Sorghum	*Lactobacillus acidophilus*	[80]
Sauerkraut	*Leuconostocmesenteroides* *Lactobacillus Brevis,* *Pediococcuspentosaceus, Lactobacillus Plantarum* *Lactobacillus sakei*	[80, 83]
Kombucha (Fermented tea beverage)	*Saccharomyces cerevisiae*	[80]
Kimchi (Fermented vegetable dish)	*Lactobacillus sakei, Lactobacillus Plantarum,* *Lactobacillus curvatus,*	[80]
Natto	*Bacillus subtilis*	[84]
Miso	*Aspergillus oryzae* *Saccharomyces cerevisiae*	[80, 83]
Sourdough	*Lactobacillus sanfransiscensis,* *Saccharomyces cerevisiae*	[80, 85]
Bulgarian boza	*Lactobacillus coryniformis*	[35]
Hardline (Grapes)	*Lactobacillus Plantarum,* *Lactobacillus paracasei,* *Lactobacillus casei*	[35]

Table 2.
List of probiotic food products.

with vegetarianism and lactose intolerance is higher [77]. Non-dairy based product includes fermented vegetable and fruit-based probiotics. Other non-dairy products such as cereal, soy, and meat-based probiotics such as fermented oats, sourdoughs, sausages, fish are available [78]. Probiotic organisms and substances secreted by them are used to preserve and enhance the quality of food. Various probiotic food products are listed in **Table 2**.

5.2 Application of probiotics in agriculture

Other than human, probiotics application is extended to agriculture as well. One of them is probiotic farming, which is referred to as bio-intensive agriculture that combines various organic farming techniques to make soil healthier. It introduces beneficial microorganisms into the growing environment. The use of probiotics increases crop yield, limits the need for harmful fertilizers and pesticides and depletes damages caused by them. Probiotics also amplify plant's resistance to pests and diseases. Due to antagonistic effects exhibited by probiotic bacteria by 'induced systemic resistance,' plants are protected from pathogenic microorganisms. *Bacillus* spp., LAB, *Actinomycetous,* etc. Protect plants from cropping hazards. Furthermore, plant probiotic microorganisms (PPM) can influence the synthesis of phytohormones and their balance in plants. Some commercial plant products that use probiotic cultures are Kodiak (*Bacillus subtilis* GB03), YiedShield (*B. pumilis* GB34), Rotex (*Phlebiopsisgigantea*) [21]. Probiotics used in animal feed supplements advantageously alter gastrointestinal flora and improve host animals' health and productivity. Probiotic solely or in combination with prebiotic improves the pattern of microbial population in GIT and benefits host's health [86]. Probiotic is generously applied in poultry and aquaculture. Some feed additives can modulate the intestinal milieu and exert beneficial substances in the intestine [87]. Probiotics gained attention to use as an alternative to antibiotics in poultry to get the product with quality and safety [88]. It also reduces their mortality rate and increases bone quality. In ruminants, probiotics increase forage intake, increasing fiber digestion rate, which results in improved weight gain, milk yield, and milk fat content [86]. Probiotic also decreases the prevalence of coliform infection in pre-ruminant calves. The use of probiotics in aquaculture prevents the adhesion of pathogens from fishing intestinal mucus.

5.3 Application of probiotics in clinical use

As described earlier, probiotics prevent or mitigate various diseases and severe symptoms by various mechanisms, but it is advisable to take care when used in immune-compromised patients. Encouraging evidences are emerging for probiotics' efficiency in the management of pouchitis and pediatric atopic diseases. Probiotics are also helpful in preventing postoperative infections [89]. There is strong evidence that some bacterial strains are efficient in enhancing immune function. Probiotics are also beneficial in mental disorders and reduce carcinogenic activity, cholesterol level, and blood pressure [35]. The significance of probiotics in preventing traveler's diarrhea, sepsis-associated with severe pancreatitis, ulcerative colitis, and reduction of hyper cholesterol is unproven [89, 90]. The chemotherapeutic drugs such as L-asparaginase with fewer side effects from probiotic bacteria are still being explored. A study reported the use of kimchi to treat cancer [21]. Furthermore, the development of alternative antibiotics such as lantibiotics, antimicrobial peptides (AMPs) from probiotic bacteria are being explored to reduce side effects caused by traditional drug therapies and as a next-generation drug system against resistant pathogens. LAB bacteriocin- Nisin is commercially used as a food preservative [35]. It also has biomedical applications as it exhibits anti-microbial activity against resistant pathogens and anti-biofilm properties to use in combination with therapeutic drugs [91]. Although probiotics have shown encouraging evidence of efficacy in various diseases, there is much exploration needed for standard clinical practice in humans.

6. Conclusion

Exploration of gut microbiota indicates that beneficial gut microbiota plays a crucial and constructive role in maintaining the health of host (human). The symbiotic relation of gut microbiota with host and benefits exhibited by them leads to the development of probiotics and prebiotics. Studies on various mechanisms of probiotics have shown their abilities to prevent or treat various diseases in human. Due to this efficiency, probiotics and prebiotics and their applications in various fields have shown a substantial increase in the last two decades. Probiotics are mainly applied in the food industry to develop functional foods and supplements to benefit consumers. The applications of probiotics are also extended to the agriculture industry to boost the productivity and quality of crops and animals. The emergence of encouraging evidence has given a sight to use probiotics in clinical practices with minimum side effects. However, clinical use of probiotics as standard practice is under the umbrella of research yet.

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