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The relationship between probiotics and digestive health: A critical mechanism of gastrointestinal neuromodulation and immunomodulation

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Abstract
The term "gastrointestinal microbiota" refers to the microbial population in the gastrointestinal system. The gastrointestinal tract contains 3.8×10^{13} microorganisms, most of which carry out their primary functions here. The gastrointestinal microbiota family known as probiotic bacteria is administered orally from the outside environment through food. Probiotics function in a variety of ways in the digestive system. Probiotics contribute to an expansion of the prebiotic bacterial ecosystem in the gastrointestinal tract, which aids in the digestion and absorption of undigested long-chain polysaccharides. Their primary function is to ferment those foods and create short-chain fatty acids, which have a favourable effect on pancreatic output and epithelial cell growth. Probiotics minimise damage to the intestinal host cell, lessen inflammation, and restrict the host immune response by producing the cytokines interleukin-10 and interleukin-12. These have the ability to modulate immune cell activity and cause T cells and B cells to become less sensitive. Probiotic bacteria can influence the digestive tract's immune system in this way. Probiotic bacteria can occasionally keep the neuronal connection between the central nervous system and the gastrointestinal tract functioning. Probiotics aid in the submission and transmission of neural impulses between the central nervous system and the gastrointestinal tract. Numerous studies have shown that probiotics may boost brain function and reduce anxiety and depressive symptoms.

Keywords: Probiotics, prebiotics, long-chain polysaccharide, microbiota, immunomodulation, depressive symptoms, neuromodulation, pancreatic output and epithelial cell growth, nervous system, gastrointestinal tract, digestive health, T cells and B cells,

Introduction
Probiotics is a Greek word that means "for life." Since different probiotic bacteria have grown in popularity over the past 20 years, researchers have been studying them in order to understand how they can improve human health (Kechagia *et al*., 2013) [27]. Probiotics are living microorganisms that are beneficial to human health and are non-pathogenic and nontoxic (Shi *et al*., 2016) [51]. Probiotics are defined as "live microorganisms that, when administered in suitable amounts, impart a health benefit on the host" by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations (Food and Agricultural Organization of the United Nations *et al*., 2006) [18]. The most prevalent probiotics are lactic acid bacteria, which also include species from the Lactobacillus pedicoccus and Bifidobacterium families. Probiotics include representative species such Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium lactis, and Bifidobacterium longum (Kailasapathy and chini, 2000; Ishibashi and Yamazaki, 2001) [26, 23]. Probiotics provide significant gastrointestinal tract health advantages. The gut microbiota is improved by probiotics. Additionally, it influences the immunological system, lowers serum cholesterol, and enhances people with lactose intolerance's lactose metabolism (Saarela *et al*., 2000; Nagpal *et al*., 2012) [45, 41].

Probiotics are now utilised as immuno- and neuromodulators. Different probiotics alter the gastrointestinal defence system by secreting substances and metabolites that have an impact on the immunological and epithelial cells' ability to work actively (Preidis and Versalovic, 2009). A complex enteric neural system exists in the human gastrointestinal tract, and its primary job is to regulate the GIT's physiological activity and regulate communication between the GIT and the central nervous system (CNS). The gut flora may facilitate communication along the gut-brain axis (Bienenstock *et al*., 2010; Forsythe *et al*., 2009) [6, 19]. A probiotic combination can assist to regulate neuronal signalling activity and lessen psychological issues brought on by the digestive tract, such as stress, depression, and anxiety.

Table 1: Collected from Holzapfel *et al*., 2001 [22]

The microorganisms considered as probiotics	
Lactobacillus species	**Bifidobacterium species**
Lactobacillus acidophilus *Lactobacillus casei* *Lactobacillus crispatus* *Lactobacillus gallinaruma* *Lactobacillus gasseri* *Lactobacillus johnsonii* *Lactobacillus paracasei* *Lactobacillus plantarum* *Lactobacillus reuteri* *Lactobacillus rhammnosua*	*Bifidobacterium adolescentis* *Bifidobacterium animalis* *Bifidobacterium breve* *Bifidobacterium infantis* *Bifidobacterium lactis*[b] *Bifidobacterium bifidum* *Bifidobacterium longum*
Other lactic acid bacteria	**Non-lactic acid bacteria**
Enterococcus faecalis[a] *Enterococcus faecium* *Lactobacillus lactis*[c] *Leuconostoc mesenteroids* *Pediococcus acidilactici*[c] *Sporolactobacillus inulinus*[a] *Streptococcus thermophilus*[c]	*Bacillius cereus var. toyoi*[a] *Escherichia coli strain nissle* *Saccharomyces cerevisiae* *Saccharomyces boulardii* *Propionibacterium freudenreichii*

[a] Mainly used for animals
[b] Recently reclassified as Bifidobacterium animalis subspecies lactis (Masco *et al*., 2004) [37]
[c] Very few probiotics properties are found.

1. Relationship Between Gut Microbiota and Probiotic Species

Trillions of bacteria are found in the human gastrointestinal tract, primarily in the large and small intestine. According to reports, 3.8 1013 bacteria have a total weight of 0.2 kg when compared to a 70 kg man as a reference (Sender *et al*., 2016) [47]. Fungi, bacteria, protozoa, viruses, and archaea make up the gastrointestinal microbiota, which has an impact on the host's physiology and health (Claesson *et al*., 2012) [9]. Human health is greatly influenced by the gut flora, which influences digestion, angiogenesis, vitamin B production, and neuronal function (Zhang *et al*., 2015) [64].

Fermentation of well-known prebiotics such fructooligosaccharide, oligofructose, inulin, and xylose by a certain type of gut bacteria is possible. Symbiotic organisms serve a variety of systemic purposes, including the manufacture of vitamins, control of gastrointestinal hormone release, regulation of brain behaviour, and neuronal signalling (Backhed *et al*., 2004; LeBlance *et al*., 2013; Endt *et al*., 2010; Roond and Mazmanin, 2009; Collins *et al*., 2012; Bin *et al*., 2017) [4, 30, 17, 44, 10, 7]. Numerous studies have suggested that probiotic species can affect the microbe population in the digestive tract and enhance the functioning of the microbiota species' ecosystem (Azad *et al*., 2018) [3].

2. Modulation of Mucus Layer Properties by Probiotics

Between the host immune system and the outside environment, there is a physical barrier called the gastrointestinal epithelium. This barrier aids in the absorption of nutrients and prevents harmful chemicals from the gut microbiota from entering.

The viscoelastic mucus layer covered the intestinal epithelium. Whose main function is-

a. Passing the food particles
b. Protect epithelium from frictional obstruction by food
c. Prevent the entering a bacterium into lamina propria. (Corfield *et al*., 2000; Derrien *et al*., 2010; De Santis *et al*., 2015) [11, 16, 14]

The mucus layer decreases bacterial contact and bacterial toxin penetration. An effective mucus layer guards against viral and inflammatory illnesses. The goblet cell of the intestinal epithelium produces the mucus, which is made up of mucin. The higher molecular weight substance known as mucus is a glycoprotein that is subdivided into two subgroups: secret music, which is encoded by the MUC 2, MUC 5 AC, MUC 5B, and MUC 6 genes, and is involved in the formation of the mucus layer; and transmembrane mucin, such as the MUC 1, MUC 4, MUC 13, and MUC 16, which is involved in the signalling pathway (Corfield *et al*., 2000; Cornick *et al*., 2015; Mack *et al*., 1999) [11, 12, 36].

Numerous studies indicate that different distinct probiotic bacteria species control the production of mucin. furthermore, affect the mucus layer's functionality, and enhance the control of the digestive immune system. It has been demonstrated that the lactobacillus planetarium strain 299V prevents enteropathogenic Escherichia coli (E. coli) from adhering to the gastrointestinal epithelial HT-29 cell line. Under incubation conditions, the Lactobacillus Plantarum stain 299V and HT-29 promote the expression of the MUC 2 and MUC 3 genes' mRNA. These probiotics control the secretion of mucin by epithelial cells, reducing the ability of bacteria to adhere to mucosal epithelial cells (Mack *et al*.,1999) [36].

3. Effects of Probiotics on Gastrointestinal Health

The intestinal tract's probiotic bacteria are an essential element. According to Jager *et al*. (2018) [25], Wang *et al*. (2019) [60], and Shin *et al*. (2019) [52], it may aid in enhancing food absorption, improving gut microbiota, and preventing a number of hereditary and pathogenic illnesses like diarrhoea and lactose intolerance.

3.1 Improvement of Gastrointestinal Health by Nutrient Absorption and Regulation

One of the main organs for food digestion and absorption is the gastrointestinal tract. Large dosages of nutrients have been absorbed in the gastrointestinal tract, primarily in the small intestine (Lv *et al*., 2018; Linares *et al*., 2016) [35, 34].

Probiotic bacteria affect the gastrointestinal tract and help in-

a. Digestive enzyme production for the breakdown of carbohydrates
b. Decreasing the cholesterol level in the gut.
c. Gastrointestinal pH changing and minerals absorption.
d. And Some vitamins synthesis (Yoo and Kim, 2016) [63]

With the aid of digestive enzymes, probiotics may also speed up the breakdown of lipids and proteins and create an easy-to-absorb state (Ushakovaa *et al*.,2015) [57]. The host's metabolic and physiological processes are impacted by protein absorption (Jahan-Mihan *et al*., 2015). Intestinal digestion is substantially improved by probiotic bacteria's enhanced fermentation activity, which also increases the generation of intestinal enzymes and their enzymatic activity (Liao and Nyachoti, 2017) [32, 33].

According to Al-Khalifa *et al*study.'s from 2019, "Effects of dietary probiotics and prebiotics on the performance of broiler chickens," adding 1 gm/kg of Lactobacillus or Bacillus coagulations to the broiler diet for 35 days appears to prevent Salmonella and Escherichia coli species growth and acidic pH changes in the cecum (Al-khalifa *et al*., 2019) [1]. The cecum's acidic pH promotes the development of antimicrobial compounds that kill a wide range of bacteria (Wood.1992).

3.2 Probiotics Improve Gastrointestinal Health by Changing the Composition of Gut Microbes

Probiotics strengthen the intestinal epithelium's cell barrier, control the immune system, and change the gut microbiota's composition to improve the targeted population's gastrointestinal health state (Sanchez *et al*., 2017; Bai *et al*.,2019) [46, 5]. The improvement of the intestinal epithelial cell barrier and immune system depends on the gut microbiota. This microbiota influences the functions of the mucous layer, improves lymphoid structure, and balances IgA production.

Various numerous research studies suggest that, the composition of gut microorganisms (commonly known as the microbiota) is changed by the probiotics for maintaining intestinal health. Use of the diet, containing 2 gm/kg of Bacillus amyloliquefaciens in piglets for 28 days of treatment, reduces the jejunal E. coli diversity and increases the quantity of Lactobacillus and Bifidobacterium in the ileum (Li *et al*., 2018) [31]. Additionally, probiotics control gastrointestinal health by fermentation of fibre rich food and proteins to help the production of the advantageous metabolite and help to maintain intestinal health (Underwood.2019; Rios-covian *et al*.,2016) [56, 43].

By the fermentation of carbohydrates (mainly complex carbohydrates) and proteins, probiotics produce short-chain fatty acids such as propionic acid, acetic acid, and n-butyric acid, which may have a positive impact on the epithelial cell's proliferation and also effects on secretary pancreas (Suiryanrayna and Rahamana, 2015; Rios-covian *et al*., 2016) [53, 43].

3.3 Prevention of Gastrointestinal Diseases by Probiotics

Due to various microbial reaction in the gastrointestinal tract various genetic inheritance and immunological imbalance mostly affects the gastrointestinal tract and develop gastrointestinal diseases such as diarrhoea, lactose intolerance etc. Numerous research study suggests that probiotics have an important functional role in the digestive tract that reasons they may minimise the development of various diseases.

Lactose Intolerance

For newborn babies, milk sugar lactose is the main energy source. Lactose molecules are digested to form glucose and galactose by the enzyme lactase in the intestine. Lactose intolerance is a genetically inherited disease caused by the inability and deficiency of beta-galactosidase which is the enzyme of breakdown for lactose to form glucose and galactose. The probiotics have a hydrolytic property that can hydrolyse the lactose and reduce the undigested lactose load in the gastrointestinal tract. The probiotics product increases the hydrolytic capacity in the small intestine. Lactobacillus acidophilus is a bile salt-tolerant bacterium that increases the digestion of lactose. Besides, these probiotic bacteria reduce lactose intolerance symptoms (de Vresa *et al*., 2001) [15].

Diarrhoea

Diarrhoea is a gastrointestinal infectious disease caused by various pathogens such as rotavirus, and Escherichia coli. Infant diarrhoea mostly occurred in the winning period which happened due to rotavirus infection. Escherichia coli is another bacterium that may also cause diarrhoea. A recent study suggests that probiotics

regulate the negative effects on Escherichia coli induced diarrhoea. A clinical study suggests that probiotics such as Lactobacillus reuteri, Lactobacillus rhamnosus GG, Bifidobacterium animalis Bb12, and Lactobacillus casei Shirota can reduce the duration of rotaviral diarrhoea (Shah *et al*., 2007; Szajewska and Mrukowicz, 2001; Isolauri *et al*., 2002) [48, 54, 24].

Piglets may experience diarrhoea when E. coli produces enterotoxin in the weaning period (Liao and Nyachoti, 2017) [32, 33]. A well-controlled clinical study showed that probiotic bacteria may create a negative effect of E. coli on weaned piglets.

3.4 Gastrointestinal Immunomodulation and Probiotics

The immune response started with immunity when our body is exposed to foreign particles. Severe information and uncontrolled tissue damage occurred when the immune response is impaired. The host intestinal mucosal defence system is affected by probiotics. In intestinal epithelium tissue, the probiotics help in blocking the pathogenic bacterial effects by the bactericidal substances producing and competing with pathogens and toxins. For better health, modulation of the immune system is most important which is improved by probiotics. Probiotics enhance innate immunity and reduce microbes induced inflammation. Probiotics modulate the immune system in various ways –

Active Components of Probiotic and Immune Response Regulation

Probiotics substances modulate the activity of macrophages, dendritic cells, and T and B lymphocytes with the regulation of the host's innate and adaptive immune response (Yan and polk,2010; Vanderpool *et al*.,2008). A mixture of probiotics containing Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidium, Lactobacillus casei, and Streptococcus thermophilus stimulate the dendritic cell which expresses a high level of interleukin-10, transforming growth factor β, cyclooxygenase-2 and indoleamine-2,3-dioxygenase that promote the formation of CD $^{4+}$FOX P^{3+} regulatory T cells (Trags). Hypo-responsiveness of T cell and B cell is induced by this probiotic's mixture. A clinical study suggests 2,4,6-trinitrobenzenesulfonic acid-induced inflammation in the intestine is also resisted by this probiotic mixture, that is related to the increment of CD $^{4+}$FOX P^{3+} in the region of inflammation. Probiotics have the potential to treat the inflammatory condition by enhancing the function of Trags by causing the development of regulatory dendritic cells (Kwon *et al*., 2010) [28].

Probiotic Reaction Modulation of Immune Cell Function

Probiotics' active ingredients were used in a study to characterise the effectors of probiotic action. 74 active proteins are produced by the Bifidobacterium animalis Lactis BB-12 sab species. Thirty-one proteins, including those that mobilise cell walls, bind oligosaccharides as solutes, and amino acid and manganese, are engaged in carrying out their physiological functions either within or on the exterior of the cell. 18 proteins interact with human host epithelial cells or extracellular matrix proteins. Fimbriae production, plasminogen binding, mucin and intestinal cell wall adhesion, as well as the activation of immunomodulatory responses, are just a few of this protein's possible uses. According to this discovery, probiotic bacterial protein modifies the immune system of the host (Gilad *et al*., 2011) [20].

Probiotic Genes Regulate Host Immune Response

The probiotic gene is involved in host immune responses. From the environmental human sources, forty-two Lactobacillus plantarum strains are isolated which have a crucial function in the stimulation of interleukin-10 (IL-10) and interleukin-12 with the help of peripheral blood mononuclear cells. In this result, 6 person genes with immunomodulatory capacity were identified (Van Hemert *et al*.,2010) [39, 59]. For the study on gene loci with the help of the same probiotic bacteria and the same method, interleukin-10 and interleukin-12 are regulated by the dendritic cell. Various genes are engaged in the regulation of cytokine formation by the mononuclear cell of peripheral blood. The 6 genes are involved in the production of secretion of bacteriocin. These results suggest that the probiotics gene is specific for the regulation of the different immune cells (Meijerink et a.,2010) [39, 59].

Internal Epithelial Cells as a Physical Barrier

It is common knowledge that the intestinal epithelium acts as a physiological barrier to restrain the action of harmful microbes. The distinction between commensal bacteria and pathogens depends on this epithelial monolayer, which also plays a significant role in the gut immune response. Probiotics may control the intestine cellular immune response, according to a recent study (Yan and Polk, 2010; Vanderpool *et al*.,2008). Probiotics also aid in the repair of damaged epithelial barriers, the creation of cell-protective proteins and antimicrobial substances, the prevention of cytokine-induced intestinal epithelial cell death, and the regulation of cytokine production.

From the above discussion, we come to the conclusion that intestinal epithelial cell is a physiological barrier that provides immunity in our body.

3.5 Probiotics Activity and Intestinal Neuromodulation

The fundamental goal of the enteric nervous system, a vast neuronal network dispersed throughout the digestive tract, is to maintain the physiological function of the digestive tract. Additionally, it facilitates communication between the brain and gastrointestinal tract in both ascending and descending directions, from the gut to the

brain (Sharma *et al*.,2009) [49, 50]. The gut-brain axis is the name of this communication pathway. These systems are made up of complex neurological reflex loops (Mayer, 2011) [38]. The communication between the brain, gastrointestinal tract, and endocrine system is modulated by the gut-brain axis (Bienenstock and Collins, 2010) [6]. The fundamental goal of the complex neural network called the enteric nervous system, which is dispersed throughout the digestive tract, is to preserve the physiological operation of the gastrointestinal tract. Additionally, it facilitates communication between the brain and the gastrointestinal tract in both ascending and descending fashions (Sharma *et al*.,2009) [49, 50]. This method of communication is known as the gut-brain axis. These mechanisms consist of complex loops of neurological responses (Mayer, 2011) [38]. The gut-brain axis controls how well the brain, gastrointestinal tract, and endocrine system communicate (Bienenstock and Collins, 2010) [6].

According to certain analytical research, changes in the gut microbiota may have an impact on how the gut and brain interact, as well as how well the brain functions. Modulation of the gut-brain axis is a treatment approach for a variety of physiological issues, including anxiety and depression. Additionally, it has the power to influence how psychiatric diseases evolve. Numerous studies have shown that probiotics are essential for regulating and maintaining mood, stress response, and anxiety symptoms (Lakhan and Kichyessner, 2010) [29]. A daily dose of probiotics including Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 may dramatically reduce anxiety-like behaviour in rats, according to an *in vivo* study. The mixture may also lessen psychological distress in human subjects (Messaoudi *et al*., 2011) [40]. Another study found that the combination of probiotics has therapeutic effects on depressive behaviour by lowering the pro-inflammatory cytokines that cause depression (Arseneault-Breard *et al*., 2012) [2].

In their study "injection of lactobacillus stain regulate emotional behaviour and central GABA receptor expression in a mouse via vagus nerve," Bravo *et al*. (2011) [8] reported that Lactobacillus rhamnosus (JB-1) was found to reduce stress-induced corticosterone, reduce anxiety and depressive behaviour, and express regulation-dependent alteration in Gamma amino butyric acid receptors ($GABA_A$ and $GABA_B$) via the vagus nerve (Bravo *et al*., 2011) [8]. GABA is a neurotransmitter that serves as the primary inhibitory neurotransmitter in the central nervous system. Changes in the expression of the gamma amino butyric acid receptor are linked to the pathogenesis of anxiety and depression. A particular Lactobacillus rhamnosus (JB-1) supplement was found to modify the GABAergic system and change the anxiety and depression behaviour in mice.

Consuming fermented milk with probiotics like Bifidobacterium animalis subspecies lactis, Streptococcus thermophilus, Lactobacillus bulgaricus, and Lactobacillus lactis subspecies lactis helps to regulate gut-brain communication and regulates brain activity, mood, and sensation (Tillish *et al*., 2013) [55]. Using these analytical results, we determine which probiotics have neuromodulatory capabilities that preserve the signalling between the gut and central nervous system and also lower mental depressive symptoms, anxiety, stress, and other psychiatric issues.

Conclusion

The probiotic species family has a higher acceptance rate for therapeutic application on human health nowadays, and its significance has grown dramatically over the globe. In the human gastrointestinal system, different probiotic microorganisms play a common role, mostly in neurological, immunological, and pathophysiological processes. The creation of different enzymes is controlled by probiotic bacteria, which also aid in the preservation of protein and long-chain polysaccharide digestion and absorption. They produce B group vitamins indirectly by altering the composition of the gut bacteria and also through their own activity.

The probiotics increase and sustain the gut microbial environment. Probiotic microorganisms are useful in preserving the function of the mucus layer. The mucus lawyer's health is improved and the gastrointestinal bacteria increases the mucous layer's characteristics. Pathogenic poisonous chemicals couldn't enter the epithelial layer because of the gastrointestinal mucus layer. Numerous probiotic species, including Lactobacillus reuteri, Bifidobacterium animalis, and Lactobacillus casei, prevent rotaviral infections in the GI tract and treat newborn diarrhoea. Additionally, Escherichia coli in the gastrointestinal tract interacts with probiotics to lessen its activity and pathogenicity. Probiotic bacteria may exhibit lactolytic activity, which hydrolyzes lactose and lowers the lactose burden in patients with lactose intolerance, according to well-controlled clinical research.

A probiotic bacterium known as Lactobacillus plantarium strain plays a key role in the synthesis of interleukin-10 and interleukin-12, which are primarily responsible for controlling the host immune response, acting as anti-inflammatory agents, and reducing host cell damage. Some of the probiotic mixture's active ingredients made T cells and B cells less sensitive, which may influence the activity of immune cells. These characteristics suggest that the probiotic bacterial interaction results in an increase in immunomodulatory function.

A bidirectional neural network that communicates with the central nervous system and gastrointestinal tract is actively used. Their primary job is to transport and transmit neurological impulses from the digestive system to the brain and from the brain to the digestive system. Probiotic bacteria are thought to enhance brain function and aid in the transmission of neuronal signalling, according to a number of studies. Recent clinical research investigations indicate that the therapeutic use of different probiotics keeps an eye on indicators of anxiety, tension, and mood. Additionally, it has beneficial effects on regulating emotions, brain function, preserving gut-brain connectivity, reducing mental depression, etc. Some particular probiotic supplements affect anxiety and depression by modulating the GABAergic system.

According to the explanation above, we must draw the conclusion that probiotics are an essential treatment strategy for preserving both mental and gastrointestinal health, which are connected through gastrointestinal

neuro-immunomodulation. And as a drug that can save lives, and it has become a part of everyday life as a Life-saving medicine.

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