ORIGINAL ARTICLE

Probiotics and Gastrointestinal Health: Mechanism of Gastrointestinal Immunomodulation and Neuromodulation

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ABSTRACT The microbial population in the gastrointestinal tract is well known as gastrointestinal microbiota. The gastrointestinal tract contains 3.8×10^{13} microbes whose main metabolism and activities are completed in this part of the human body. The probiotic bacteria are a family of gastrointestinal microbiota which are usually administrated orally from the external environment by the foods. Probiotics have various functional activities in the gastrointestinal tract. Digestion and absorption of undigested long-chain polysaccharides, which are known as prebiotics, help to increase the probiotic bacterial ecosystem in the gastrointestinal tract, whose main activity is to ferment foods and produce short-chain fatty acids which have a positive impact on the proliferation of epithelial cells and pancreatic secretion. By the production of interleukin-10 and interleukin-12, probiotics prevent damage to the intestinal host cell, reduce inflammation and limit the host immune response. These have a functional activity on modulation of immune cell function and inducing the hypo-responsiveness of T cells and B cells. In this way, probiotic bacteria can apply immunomodulation activity to the gastrointestinal tract. The neural interaction between the gastrointestinal tract and central nervous system is sometimes maintained by the probiotic bacteria. Probiotics help submit and transmit the neural signals between the gastrointestinal tract and central nervous system. Various evidence demonstrated that probiotics may reduce anxiety and depression behaviour and also it improves brain function. In this review, discussion has been done regarding gastrointestinal health, related to immunomodulatory and neuromodulatory functions by the activity of the probiotics, the life-saving components of nature

Keywords: Anxiety, Brain function, Depression, Gastrointestinal tract, Immune cell, Immunomodulation, Life-saving medicine, Long chain polysaccharide, Microbiota, Neuromodulation, Prebiotic probiotics

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INTRODUCTION

The word "probiotics" is a Greek language meaning "for life". Now various types of probiotic bacteria have become increasingly famous during the last two decades resulting in scientists continuously working on this for their beneficial effects on human health.[1] Probiotics are harmless, non-pathogenic living microorganisms that have a beneficial property on human health.[2] According to the World Health Organisation (WHO) and the Food and Agriculture Organisation (FAO) of the United Nations, probiotics are the "live microorganisms which when administrated in adequate amount confer a health benefit on the host". The lactic acid bacteria are the most common probiotics and they also include species from *Lactobacillus pedicoccus* and *Bifidobacterium* genera. The representative species like

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Lactobacillus casei, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Bifidobacterium longum* are also probiotics.[3, 4] Probiotics have major health benefits on the gastrointestinal tract. Probiotics improve the gastrointestinal microflora. It also reacts with the immune system, reduces serum cholesterol and improves the lactose metabolism of lactose intolerance patients.[5, 6]

Nowadays, probiotics are used as neuromodulators and immunomodulators. Various probiotics modulate the gastrointestinal defence system by some secretions and production of metabolites which affects the active function of gastrointestinal epithelial and immune cell.[7] The human gastrointestinal tract has a complex enteric nervous system, whose main function is the regulation of physiological activity of the gastrointestinal tract (GIT) and modulating communication between the gastrointestinal tract and central nervous system (CNS). The gut microbes may help to communicate between the gut-brain-axis.[8, 9] Some probiotic mixture helps to modulate the neural signalling activity and reduce the psychological problem which is induced by the gastrointestinal tract such as stress, depression, anxiety, etc.

Relationship Between Gut Microbiota and Probiotic Species

In human gastrointestinal tract contain trillions of microbes mostly in the large intestine and small intestine. If a 70 kg man is a reference, 3.8×10^{13} microorganisms are reported to have a total weight of 0.2 kg.[12] The gastrointestinal microbiota includes fungi, bacteria, protozoa, viruses, and archaea which affect the physiology and health of the host.[13] The gut microbiota has a significant role in human health influencing the improvement of digestion and promotion of angiogenesis vitamin-B synthesis and also nerve function.[14]

A type of gastrointestinal microbiota can ferment non-digestible carbohydrates such as fructo-oligosaccharide, oligofructose, inulin, and xylose, which are well known as prebiotics. The symbiotic, have a systemic function like vitamin synthesis, modulation of gastrointestinal hormone-releasing,

Table 1: Report on the Self Analysis of Health Care Practices/Awareness of the Respondents

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

Note: [a]Mainly used for animals; [b]Recently reclassified as *Bifidobacterium animalis* subspecies lactis.11; and [c]Very few probiotics properties are found.

brain behaviours regulation and also neuronal signalling.[15, 16, 17, 18, 19, 20] Numerous research studies suggest that the probiotic species alter the microorganism's population in the gastrointestinal tract and improve the function of the ecosystem of the microbiota species.[21]

Modulation of Properties of Mucus Layer by Probiotics

The gastrointestinal epithelium is a physical barrier between the external environment and the host immune system. This barrier helps in nutrient absorption and protects from entering the pathogenic substances from gut microbiota.

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.[22, 23, 24.]

The mucus layer reduces the interaction and also penetration of bacteria and bacterial toxins. A healthy mucus layer prevents inflammatory and infectious diseases. The mucus, which is composed of mucin, is produced by the goblet cell of the intestinal epithelium. Mucus is a glycoprotein with a higher molecular weight substance that is divided into two subgroups: secret music which is coded by MUC 2, MUC 5 AC, MUC 5B, and MUC 6 genes, that are involved in the mucus layer formation and other is transmembrane mucin, like as MUC 1, MUC 4, MUC 13, MUC 16, they are responsible in the signalling pathway.[22, 25, 26]

Numerous research study suggests various specific probiotic bacteria species regulate mucin expression. And also influence the function of the mucus layer and improve the regulation of the gastrointestinal immune system. *Lactobacillus planetarium* strain 299V was shown to interrupt adherence of enteropathogenic *Escherichia coli* (*E. coli*) to gastrointestinal epithelial HT-29 cell line. *Lactobacillus Plantarum* stain 299V and HT-29 increase the expression of mRNA of the MUC 2 and MUC 3 genes under incubation conditions. These probiotics regulate epithelial cells to secrete mucin which reduces the binding capability of bacteria in mucosal epithelial cells.[26]

Effects of Probiotics on Gastrointestinal Health

Probiotics bacteria are a crucial component of the gastrointestinal tract. It may help to increase nutrient absorption, increase the gut microbiota and prevent various pathogenic and genetic diseases like diarrhoea and lactose intolerance.[27, 28, 29]

Improvement of Gastrointestinal Health by Nutrient Absorption and Regulation

The gastrointestinal tract is a major way for digestion and absorption of foods. In the gastrointestinal tract, mainly in the small intestine, large doses of nutrients absorption have occurred.[30, 31]

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.[32]

Probiotics may also facilitate the digestion of lipids and proteins with the help of digestive enzymes and produce a simple form for absorption.[33] Protein absorption affects in metabolic and physiological functions of the host.[34] Probiotic bacteria have higher fermentation activity that causes intestinal digestion to improve greatly and intestinal enzyme production and enzymatic activity are also increased.[35]

The study of Al-Khalaifa *et al.* (2019) in their study "Effects of dietary probiotics and prebiotics on the performance of broiler chickens", suggests that 1 gm/kg of Bacillus coagulations or *Lactobacillus* supplement in the broiler diet for 35 days, inhibits the *Escherichia coli* and Salmonella species growth and cecum's pH value changes in acidic nature.[36] The acidic pH nature of the cecum increases the production of antimicrobial substances which eliminate the variety of pathogens.[37]

Probiotics Change the Composition of Gut Microbes and Improve Gastrointestinal Health

For improvement of the gastrointestinal health status of the targeted population, probiotics enhance the cell barrier of the intestinal epithelium, regulate the immune system and reprogramme the composition of gut microbiota.[38, 39] The intestinal microbiota is a functional component of increasing the intestinal epithelial cell barrier and immune system. This microbiota enhances the improvement of the lymphoid structure, affects the mucous layer functions and balance the production of IgA.

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.[40] 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.[41, 42]

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.[43, 44]

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.

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.[45, 46, 47]

Piglets may experience diarrhoea when *E. coli* produces enterotoxin in the weaning period.[35] Ell-controlled clinical study showed that probiotic bacteria may create a negative effect of E. coli on weaned piglets.

Lactose Intolerance

For new born 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 the lactose intolerance symptoms.[48]

Probiotics and Gastrointestinal Immunomodulation

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:

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 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.[49] 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.[50]

Active Components of Probiotic and Immuno Response Regulation

In a research study, active components of probiotics defined the effectors of probiotic action. Lactis BB-12 sab species of *Bifidobacterium animalis* secreted protein produce 74 active proteins. Thirty-one proteins such as amino acid and manganese, cell wall mobilizing proteins and solute binding proteins for oligosaccharides are involved in carrying out their physiological role either inside or on its surface. For interaction with extracellular matrix protein or human host epithelial cells, 18 proteins are involved. This protein has potential functions such as fimbriae formation, plasminogen binding, mucin and intestinal cell wall attachment and immunomodulating responses induction. This invention suggests that probiotic bacterial protein modulates the host immune system.[51]

Modulation of Immune Cell Function by Probiotic Reaction

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.[52, 53] 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 factor², cyclooxygenase-2 and indoleamine-2, 3-dioxygenase that promote the formation of CD4+FOX P3+ regulatory T cells (Trags). Hyporesponsiveness 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 CD4+FOX P3+ in the region of inflammation. The probiotics substances induce the formation of regulatory dendritic cells to enhance the activity of Trags, which represent a therapeutic opportunity for the inflammatory disorder.[54]

Intestinal Epithelial Cells as a Physiological Barrier

The intestinal epithelium is well known as a physiological barrier that suppressed the pathogenic microbial activity. This epithelial monolayer is crucial for the disparity of commensal bacteria and pathogens and it is also effectively involved in the intestinal immune response. A recent study suggests that probiotics regulate the intestinal cellular immune response.[55, 56] The probiotics also help in the restitution of damaged epithelial barriers, antimicrobial substance and cell-protective protein production, cytokine-induced intestinal epithelial cell apoptosis blocking and regulate 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.

Intestinal Neuromodulation and Probiotics Activity

The enteric nervous system is a complex neural network scattered throughout the gastrointestinal tract, whose main intention is to maintain the physiological function of the gastrointestinal tract. And it helps in communication between the central nervous system and gastrointestinal tract, in the direction gut to the brain (ascending) and brain to the gut (descending).[57] This interaction system is called gut- brain axis. These systems are composed of intricate loops of neurological reflexes[58] The gut-brain axis modulates the communication between the brain, gastrointestinal tract and endocrine system (Bienenstock and Collins, 2010). This gut-brain axis consists of the Central nervous system (CNS), the Enteric nervous system (ENS), the Autonomic nervous system (ANS), the neuroendocrine and neuroimmune system and also gastrointestinal microbiota.[58, 59] A complex signalling network is formed to submit the neural reflux to the central nervous system from intestinal smooth muscle.[60] Through this bidirectional communication network between the central nervous system and gastrointestinal tract, brain signals can affect the sensory, motor, and gastrointestinal secretary function. In this same way brain function can affect by the gastrointestinal tract signals.[59]

Some analytical studies suggest that, alteration of gastrointestinal microbiota can influence the gut-brain interaction and also affects brain function. Gut-brain-axis modulation is a therapeutic solution for various physiological problems like anxiety and depression. And it has the ability to affect the development of psychiatric disorders. Numerous research studies supported that probiotic have a crucial function in modulation and maintaining the mood, stress response and anxiety signs.[61] An in vivo research study suggests that daily consumption of a mixture of probiotics containing *Lactobacillus helveticus* R0052 and *Bifidobacterium* longum R0175 can significantly decrease the anxiety-like behaviour in rats and in the human subject this mixture reduce the psychological distress.[62] In another study, the mixture of probiotics exhibits therapeutic activity on depressive behaviour by the reduction of pro-inflammatory cytokines which leads to depression.[63]

According to Bravo *et al.* (2011), in their study "injection of *lactobacillus* stain regulate emotional behaviour and central GABA receptor expression in a mouse via vagus nerve"[61], observed that *Lactobacillus rhamnosus* (JB-1) reduce the stress-induced corticosterone and decrease anxiety and depressive behaviour and via the vagus nerve, it express the regulation dependent alteration in Gamma amino butyric acid receptors (GABAA and GABAB).[64] GABA is a neurotransmitter that is also a main central nervous system inhibitory neurotransmitter. Alteration of the gamma amino butyric acid receptor expression implicates the pathogenesis of depression and anxiety. A specific supplementation of *Lactobacillus rhamnosus* (JB-1) was modulate GABAergic system and alters the anxiety and depressive behaviour in mice.

Consumption of fermented milk which contains some probiotics such as *Bifidobacterium animalis* subspecies lactis, Streptococcus thermophilus, *Lactobacillus bulgaricus*, and *Lactobacillus lactis* subspecies lactis, modulate the brain activity, controlling emotion and sensation and also helps in modulation of gut-brain interaction.[65] Depending on these analytical data, we evaluate those probiotics have neuromodulatory properties that maintain the signalling between the gut and central nervous system and also reduce mental depression, anxiety, stress, psychiatric problems, etc.

CONCLUSION

Nowadays the family of probiotic species has higher acceptability for therapeutic use on human health and their importance is significantly increased all over the world. Various probiotic bacteria have a common role in the human gastrointestinal tract, mainly neurological, immunological and pathological, etc. Probiotic bacteria regulate various enzyme production and help to maintain digestion and absorption of nutrients like long-chain polysaccharides and proteins. Indirectly, by increasing the composition of gut microbiota and also by its own activity, they synthesize B groups vitamin.

The gastrointestinal microbial ecosystem is increased and also maintained by the Probiotics. Probiotic bacteria have functional activity in maintaining the mucus layer activity. This gastrointestinal microflora increases the mucous layer properties and improves the mucus lawyer's health. The gastrointestinal mucus layer restricted the entry of pathogenic toxic substances into the epithelium layer. Various probiotic species such as *animalis reuteri*, *Bifidobacterium animalis*, and *Lactobacillus casei* impedes the rotaviral infection in the gastrointestinal tract and cure the diarrheal disease of infants. Probiotics also interact with the Escherichia coli in the gastrointestinal tract and reduce their activity and pathogenicity. Well-controlled clinical studies suggest that probiotic bacteria have hydrolytic activity and which hydrolyses the lactose and reduces the lactose load of lactose intolerance patients.

Lactobacillus plantarium strain is a probiotic bacterium that has a crucial function in the production of interleukin-10 and interleukin-12 whose main function is limiting the host immune response, anti-inflammatory activity, and preventing the damage of host cells. Active components of probiotic bacteria may modulate the immune cells' function and some of the probiotics mixture induced the hyporesponsiveness of T cells and B cells. These properties indicate that immunomodulatory activity is increased by the probiotic bacterial interaction.

Between the gastrointestinal tract and the central nervous system, a bi-directional neural network is actively worked. Their main function is carrying and transmitting the neural signals from the gastrointestinal tract to the brain and brain to the gastrointestinal tract. Numerous research studies suggest that probiotic bacteria improve brain function and help in the transmission of neural signalling. Recent clinical research studies suggest that the therapeutic use of various probiotics monitors mood, stress response, and anxiety signs. And also, it has functional activity on emotion controlling, brain activity, gut-brain interaction maintaining and mental depression reduction, etc. Some specific probiotics supplement modulates the GABAergic system and alters anxiety and depression.

Depending on the above discussion we have to conclude that probiotics are one of the important therapeutic approaches for maintaining gastrointestinal health and also mental health which is related to gastrointestinal neuro-immunomodulation. And it has become a part of everyday life as a life-saving medicine.

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