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Probiotics: Role in immunomodulation and consequent effects

Jubeda Begum [1]*, Bidyarani Buyamayum [2], Madhu C. Lingaraju [3], Kapil Dev [3], Avishek Biswas[4]

[1] Govind Ballabh Pant University of Agriculture & Technology, College of Veterinary & Animal Sciences, Pantnagar-263145, India
[2] Jawaharlal Nehru Institute of Medical Science, Porompat, Manipur-795004, India
[3] Indian Veterinary Research Institute, Izatnagar-243122, India
[4] ICAR Central Avian Research Institute, Izatnagar- 243122, India

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** Corresponding author: Jubeda Begum*

Email: jubedavet@gmail.com

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Central Avian Research Institute, Izatnagar, India

Abstract

Microbiologically gastrointestinal tract (GIT) is one of the most active ecosystems with rich diversity of microflora and this gut microbial ecosystem is very crucial for the development and maturation of the GIT associated immune system. The probiotics mediate their effects by regulating various immune cells, such as T regulatory cells, effector lymphocytes, natural killer T cells, B cells, dendritic cells, and epithelial cells. Gut microbiota is very instrumental in the development and immunomodulation of mucosal immune system and any sort of impairment might result in development of microbiota-related diseases. There are two major mechanisms underlying the immunomodulatory actions of probiotics – regulation of gene expression and signalling pathways in the host cells. The immunomodulatory effects are achieved by: a) direct stimulation of residing immune cells in the GIT, which results in macrophage activation and enhanced phagocytosis, b) modulation of enzyme activity by changing the microbial metabolism. On exposure to any foreign antigen an immune response is initiated by host gut mucosal immune system to maintain the homeostasis partly by adaptive immune response and partly by inducing inflammation. The advancement in the knowledge of intestinal microbiota as a result of metagenomics strategies has provided us a greater understanding of underlying mechanisms of how gut microorganisms affect the body functions. Significant amount of encouraging data pertaining to studies on humans and animal models show that supplementation of probiotics are promising approaches for prevention and treatment of GIT and immune disorders. The effects of probiotics have been observed beyond GIT and the interaction between GIT and central nervous system have revealed the role of neurochemical signalling in gut homeostasis and mental health. However, there is uncertainty in reproducibility of the effects of probiotic supplementation in animal or human nutrition and also there is no information whether the probiotics used in animal nutrition enter the human food chain or not.

1. Introduction

Microbiologically gastrointestinal tract (GIT) is one of the most active ecosystems with rich diversity of microflora and this gut microbial ecosystem is very crucial for the development and maturation of the of GIT associated immune system. The GIT microbiota is known to interact indirectly with intestinal epithelial cells and immune cells associated with the lamina propria to exert the immunomodula-tory effects (Hooper et al. 2012; Kemgang et al. 2014). The intestinal epithelium serves to deliver the stimulus to the underlying immune cells through the metabolites produced by the GIT microbiota to elicit a targeted immune response (Hooper et al. 2012; Okumura and Takeda 2017). The use of antimicrobials as feed additives in animal nutrition is highly questionable because of the risk of drug residue carry-over through meat, milk, and eggs along with the emergence of drug resistant pathogens in veterinary as well as medical settings (Begum et al. 2018). Therefore, the use of probiotics as a replacement of antimicrobials have gained a considerable success (Gadde et al. 2017). The application of probiotics helped reduce the pathogen load and spread in livestock as well as improved the nutrient utilization and gut health (Ding et al. 2021).

However, the most important and intriguing aspect of probiotic application in human and animal nutrition is its ability to modulate the GIT associated mucosal immune system at local as well as systemic levels. This immunomodulation is a highly complex process resulting from the interaction between probiotics, intestinal microbiota, GIT epithelium, and GIT associated immune cells (Jhonson and Klaenhammer 2014). The probiotics mediate their effects by regulating various immune cells, such as T regulatory cells, effector lymphocytes, natural killer T cells, B cells,

dendritic cells, and epithelial cells (Hooper et al. 2012; Galdeano et al. 2019). Most of the established probiotics belong to genera *Lactobacillus* and *Bifidobacterium*. However, many bacteria belonging to genera *Enterococcus*, *Leuconostoc*, and *Streptococcus* and yeast belonging to genus *Saccharomyces* have been used as probiotics in animal and human nutrition (Silva et al. 2012; Georgieva et al. 2015; Al-Shawi et al. 2020). It has been observed in studies of recent years that probiotics simulate the activities of commensal gut bacteria, particularly the immunomodulatory activity (Georgieva et al. 2015).

2. Role of gut immune cells

Intestinal immunity is an indispensable barrier which protects the body from foreign antigens and pathogens. This barrier constitutes a mass of dispersed innate and adaptive effector cells collectively called as gut-associated-lymphoid tissues (GALT) (Mowat and Agace 2014). The effector immune cells of GALT are comprised of antigen presenting cells – M-cells, T-cells, B-cells, dendritic cells, and macrophages (Ding et al. 2021) which maintains a balance between tolerance and immunity to prevent the intestinal inflammation (Kamada et al. 2013; Ding et al. 2021). The gut microbiota and GALT immune cells are separated physically by intestinal epithelial layer which compartmentalises microbes and foreign antigens from the host immune cells on one hand and deliver signals to immune cells on the other hand in response to metabolites produced by the gut microbiota to invoke an immune response (Al-Shawi et al. 2020).

The gut barrier performs its protective barrier function by the production of mucus and secretory immunoglobulin A (sIgA). The mucus acts as a physical barrier to the gut microbiota and other antigens, whereas, sIgA is a major functional component of mucosal humoral adaptive immune system. The sIgA is contributed by plasma cells of lamina propria and transported into intestinal lumen where it binds to pathogens, toxins, and other antigens resulting in their immune exclusion by a non-inflammatory process (Galdeano et al. 2019). In addition to this, sIgA has also been reported to preserve the local homeostasis by translocating to payer's patches via M cells (Favre et al. 2005).

3. Probiotics: Development of gut immune cells and interaction with them

On exposure to any foreign antigen an immune response is initiated by host gut mucosal immune system to maintain the homeostasis partly by adaptive immune response and partly by inducing inflammation. The immune signals from gut microbiota in maintaining this homeostasis and eliciting protective responses is very significant (Yan and Polk 2011). The presence of gut microbiota has been reported to be very instrumental in increasing the size and number of germinal centres in Payer's patches, IgA producing plasma cells, CD4+ T cells in lamina propria, and αβ T cell receptor-expressing intraepithelial CD8αβ+ T cells (Galdeano et al. 2019). Therefore, alterations in the gut microbiota is a promising approach to favourably modulate the host immune system and dietary supplementation of probiotics is the most convenient way of altering the gut microbiota. The dietary probiotic supplementation reprogrammes the gut microbial composition which fosters the development of intestinal epithelial cells and GALT, favourably affects the properties of mucous layer, and production of IgA and antimicrobial peptides (Bai et al. 2019; Sanchez et al. 2017). The probiotic supplementation has been reported to increase the IgA producing plasma cell concentration not only in lamina propria of intestines but also in bronchi and mammary glands which indicates the positive effects of probiotics at places away from the gut as well (Galdeano et al. 2019).

The probiotics or gut microbiota interact with the intestinal epithelial cells, dendritic cells, macrophages, and lymphocytes of the host gut and pattern recognition receptors are the principal components involved in the interaction and the response from these gut cells (Bermudez et al. 2012; Yan and Polk 2011). This occurs either by direct interaction of microbe with intestinal epithelial cells or by internalisation of microbe/microbial component by M cells via interaction with dendritic cells which initiates the immune response mediated by macrophages and lymphocytes. The probiotics exert their immunomodulatory effects by altering the cytokine production of the gut immune system. Cytokines participate in signal transduction between cells and regulate immune responses (Guan et al. 2019). The cytokine production, particularly IFN-γ and TNF-α, by T cells in lamina propria were elevated in humans by probiotic administration compared to control (Galdeano et al. 2019). Similarly, the dietary supplementation of *L. casei* CRL 431 enhanced the IL-10 production by Th2 lymphocytes and macrophages to maintain the gut homeostasis (Lemme-Dumit et al. 2018; Sichetti et al. 2018). It has been observed that dietary supplementation of *Bacillus amyloliquefaciens* SC06 in piglets down-regulated the expression of nuclear factor (NF) kB-P50, Toll-like receptor (TLR) 6, tumor necrosis factor (TNF), and IL-1α in the intestinal mucosa and IL-4, IL-1β, and IFN-α in serum, whereas, IL-6 and IL-8 were upregulated (Du et al. 2018). This study establishes that by activating TLR signalling pathway *B. amyloliquefaciens* SC06 could modulate the immune function of intestinal epithelial cells. Furthermore, in a study with laying hens the supplementation of *L. acidophilus* enhanced T- and B-lymphocyte proliferation, humoral immunity, cell mediated immunity, and decreased the ratio of heterophils to lymphocytes (Alaqil et al. 2020; Wang et al. 2020). In another study on broiler chicken the supplementation of *L. plantarum* 16 and *Paenibacillus polymyxa* 10 reduced the cell apoptosis and enhanced the intestinal immunity which was evident from up-regulation of gene expression of IFN-γ, IL-6, and IL-10 in jejunum, and reduced serum levels of alkaline

phosphatase and creatine kinase (Wu et al. 2019).

4. Probiotics and GIT disorders

The gut microbiota is very instrumental in the development and immunomodulation of mucosal immune system and any sort of impairment might result in development of microbiota-related diseases (Qin et al. 2010). A number of studies in mice and humans have shown that certain inflammatory diseases are associated with dysbiosis of gut microbiota (Kamada et al. 2013). Studies on germ-free mice testified the role of gut microbiota in the development of mucosal immune system. The significantly poor development and growth of lymphoid system, such as Peyer's patches and mesenteric lymph nodes, were observed in germ-free mice with the consequent reduction of B and T cell immune response as well as lower serum IgG and IgA levels (Georgieva et al. 2015). In these modern times new metabolic disorders such as inflammatory bowel disease (IBD), rheumatoid arthritis, irritable bowel syndrome, colorectal cancer, obesity, cardiovascular diseases, etc. are emerging because of changing food habits of people (Iraniro et al. 2014; Mir et al. 2018). This has led the researchers to investigate the applications of gut microbiota/ mucosal immune system interaction in the treatment and control of these emerging diseases. Various probiotics, either singly or in combinations have been investigated in GIT disorders such as diarrhea, ulcerative colitis, chron's disease, IBD, etc. It has been concluded that probiotics appear to be safe in outpatient settings only and there are the chances of probiotic sepsis in immunocompromised and hospitalized patients (Verna and Lucak 2010). The probiotic supplementation in mice inhibited the tissue damaging pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α which in turn prevented irinotecan induced diarrhea (Lu et al. 2020). The treatment of *E. coli* induced piglet diarrhea by *L. plantarum* ZLP001 reduced the permeability of intestines induced by *E. coli* infection (Wang et al. 2018). They also observed down-regulation of IL-6, IL-8, and TNF-α expression and prevented the increase of tight junction protein expression. The dietary supplementation of *B. amyloliquefaciens* DSM25841 reduced the diarrhea caused by *E. coli* infection in weaned piglets, and favourably affected the mucosal transcriptome profile (Luise et al. 2019). Similarly, in weaned piglets reduction in intensity and duration of *E. coli* induced diarrhea along with an increased serum IgA level and inhibition of *E. coli* colonization of GIT was observed due to *Saccharomyces cerevisiae* supplementation (Trckova et al. 2014).

5. Probiotics: Immune modulation mechanisms and effects

The advancement in the knowledge of intestinal microbiota as a result of metagenomics strategies has provided us a greater understanding of underlying mechanisms of how gut microorganisms affect the body functions. Gut microbiota dysbiosis has been observed to be linked to the diseases not limited to the GIT (Vujkovic-Cvijin et al. 2013). Hypothetically, all the diseases which are associated with gut microbiota dysbiosis may potentially benefit from the gut microbiota alteration. Even the gut microbiota, be it commensal, probiotic, or pathogen, can potentially activate neural signalling systems in the body. Therefore, in future deciphering the reactor-effector linkage between microbiota, gut, and brain by studies on animal models could potentially lead to treatment of mental problems (Georgieva et al. 2015). Among the gut microbial population a certain set of favourable species is vital for immune regulation and deviations from such favourable populations potentially result in immune dysregulation, rise of pathogenic microbial load, and inflammation. Such favourable populations are restored by probiotic supplementations. The immunostimulatory effect of probiotics is initiated by interaction with intestinal epithelial cells and Payer's patches which stimulates plasma cells, IgA secretion, and migration of intestinal T cells (Silva et al. 2012).

There are two major mechanisms underlying the immunomodulatory actions of probiotics – regulation of gene expression and signalling pathways in the host cells. The immunomodulatory effects are achieved by: a) direct stimulation of residing immune cells in the GIT, which results in macrophage activation and enhanced phagocytosis, b) modulation of enzyme activity by changing the microbial metabolism (Yan and Polk 2011; Silva et al. 2012). It was demonstrated in a study that antigenic fragments of *L. casei* CRL 431 and *L. paracasei* CNCM I-1518 were internalised by intestinal epithelial cells after adhering of whole probiotic cells via TLRs to mediate immune stimulation (Galdeano et al. 2004). Increase in the expression of TLRs results in the release of cytokines such as TNF-α, IL-4, IL-6, and IFN-γ (Ashraf and Shah 2014). The role of TLRs in immune stimulation was ascertained by the fact that feeding of *Bifidobacterium lactis* to TLR-2 knockout mice could not promote IL-6 gene expression. The enhanced IL-6 expression is critical for switching from innate immunity to adaptive immunity, failure of which can potentially promote the onset of chronic inflammatory disorders or autoimmune diseases (Hoebe et al. 2004; Jones 2005). A diet supplemented with a probiotic mixture of *L. casei*, *L. acidophilus*, *Bifidobacterium thermophiles*, and *Enterococcus faecium* increased the concentration of IgM and IgG in turkeys, which conferred them resistance against diseases (Cetin et al. 2005). The supplementation of probiotic *Bacillus cereus* in piglets increased the secretion of intestinal IgA (Scharek et al. 2007) which has the ability to prevent the pathogens and toxins from binding epithelial cells, a mechanism known as immune exclusion (Corthesy 2013). Furthermore, it has been reported that consumption of probiotics down-regulate the immune signalling pathways leading to allergic rhinitis. The consumption of *L. paracasei* strain ST11 significantly decreased production of IL-5, IL-8, and IL-10 by peripheral

Table 1 Different probiotic bacteria and their effects

Probiotics	Mode of action	Effects	Reference
Bacillus amyloliquefaciens SC06	Decreased expression of NF-kB-P50, TLR-6, TNF, and IL-1α. Increased IL-6 and IL-8. Decreased the serum levels of IL-4, IFN-α, IL-1β.	Enhancement of immune function by TLR-signaling pathway	(Du et al. 2018)
Bifidobacterium animalis subsp. lactis BB-12	Secretes 74 distinct proteins which are responsible for binding of plasminogen, formation of fimbriae, adhesion to collagen, attachment to mucin, and intestinal cells to exert immunomodulatory effects	Suggests the role of probiotic proteins in colonization of GIT, adhesion to host tissues, and immunomodulation of the host immune system	(Gilad et al. 2011)
Lactobacillus rhamnosus GG	Secretes soluble protein p40. It prevents dextran sulfate sodium and oxazolone – induced colitis in mice. It also reduced TNF, IL-6, and IFN-γ production	Suggest the role of p40 protein in the regulation of innate immunity and the Th1 immune response	(Yan et al. 2011)
Lactobacillus reuteri RC-14	Produces active cyclic dipeptides. They inhibit the staphylococcal quorum-sensing system agr and decrease the expression of toxic shock syndrome toxin-1 in Staphylococcus aureus MN8	These probiotic- derived active compounds are the potential candidates for clinical applications in disease prevention and treatment	(Li et al. 2011)
Lactobacillus acidophilus NCFM	Deletion of phosphoglycerol transferase gene, which mediates biosynthesis of lipoteichoic acid, downregulated IL-12, TNF and upregulates IL-10, CD4+FoxP3+ T regulatory cells	This mutant bacteria decreased mucosal inflammation	(Mohamadzadeh et al. 2011)
Probiotics mixture (*L. acidophilus*, *L. casei*, *L. reuteri*, *B. bifidium*, and *Streptococcus thermophilus*	Stimulated regulatory dendritic cells with higher expression of IL-10, & TGF-β. It induced both T-cell and B-cell hyporesponsiveness and downregulated T helper (Th) 1, Th2, and Th17 cytokines without inducing apoptosis	Probiotics mixture enhances the generation of regulatory dendritic cells which represent a potential therapeutic approach against inflammatory disorders	(Kwon et al. 2010)
L. rhamnosus Lcr35	Induce an increased production of the pro-Th1/Th17 cytokines, such as TNF, IL-1β, IL-12p70, IL-12p40, and IL-23. Stimulate maturation of the dendritic cell membrane phenotype with an upregulation of the membrane expression of CD86, CD83, HLA-DR, and TLR4, and a downregulation of DC-SIGN, MR, and CD14	Induces a dose- dependent immunomodulation of human dendritic cells and exerts a strong pro-inflammatory effect	(Evrard et al. 2011)
L. plantarum	Modulate the cytokine response (IL-10 and IL-12) of dendritic cells. Six genes (lp_0422, lp_0423, lp_0424a, lp_0424, lp_0425and lp_0429) were involved in bacteriocin secretion and production	Immunomodulatory effects of these genes were confirmed by comparing the cytokine production between targeted gene deletion mutants and wild type strains	(Meijerink et al. 2010)

blood mononuclear cells as well as lowered the serum allergen specific IgG4 (Wassenberg et al. 2011).

6. Conclusions

The family of probiotics is increasing day by day along with its increasing horizon of benefits in animals as well as humans. Significant amount of encouraging data pertaining to studies on humans and animal models show that supplementation of probiotics are promising approaches for prevention and treatment of GIT and immune disorders. Also, the use of probiotics offers a broader choice of antibiotic substitution which prevents the emergence of antibiotic resistance and acts as an effective tool for maintenance of intestinal homeostasis. The intestinal epithelial cells are the main targets of the probiotics which in turn activate the underlying associated immune cells to modulate the mucosal and systemic immunity. The effects of probiotics have been observed beyond GIT and the interaction between GIT and central nervous system have revealed the role of neurochemical signalling in gut homeostasis and mental health (Bercik et al. 2012). However, the futuristic aspect of probiotic application is the evaluation of probiotic bacteria as suitable models for vaccine/drug delivery because of their association with host immunity and immunomodulatory action (Blottiere et al. 2013). Further there is a complete lack of knowledge on whether the probiotics used in animal nutrition enter the human food chain or not and the consequent effects on human health. Another limitation of

probiotic application in animal and human nutrition is the uncertainty in the reproducibility of effects along with the presence of a number of livestock species, probiotic species or potential probiotic species, and varying husbandry practices which result into a complex network of interactions in animal production systems.

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