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Probiotics: Mechanisms and Immunomodulatory Effects

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ABSTRACT

Probiotics give immunological protection to the host by regulating, activating, and modifying immune responses. Researchers are now focusing their efforts on better understanding the immunomodulatory effects of probiotics, which have the potential to prevent or ameliorate some diseases for which there is now no effective medical treatment. Immune cells (T- and B-cells) promote adaptive immunity and give immunological protection by developing pathogen-specific memory, according to scientific evidence. However, the purpose of this review is to highlight the most recent research on mechanism of probiotics and their immunomodulatory effects. It has been reported that a number of Lactobacillus and Bifidobacterium species have important roles in innate immunity by boosting natural killer cell cytotoxicity and macrophage phagocytosis, as well as mediating adaptive immunity by interacting with enterocytes and Th1, Th2, and Treg cells. Finally, the immunomodulatory effects of probiotics on the generation of proinflammatory and anti-inflammatory cytokines in various animal models have been thoroughly examined. Finally, this research goes through the immunomodulatory effects of probiotics on proinflammatory and anti-inflammatory cytokine production in several animal models. Isolating new probiotic strains and studying their immunomodulatory effects on cytokine profiles in people is therefore still a hot topic.

Keywords: cytokine production, immunomodulatory effects, T- and B-cells, mechanism of probiotics, IgA and IgM secreting cells.

1. INTRODUCTION

1.1 Probiotics

Probiotics are flora/living microorganisms (such as bacteria and yeasts) that are non-pathogenic and beneficial to human health. There are good microorganism and bad microorganism everywhere in the food supply. Probiotics are "live bacteria that, when provided in suitable proportions, confer a health benefit to the host," according to an **FAO/WHO** report. Probiotics are normally present as inhabitants of the intestine and are mainly found in healthy gastrointestinal tract of human beings. The term 'probiotic' is used to describe food supplementations especially manufactured for the improvement of health. In 1974 Parker defined "probiotics" as 'microbial organisms which put up the microbiome balance in intestines.'

1.2 Mechanism of Probiotics:

The general mechanism of probiotics is the conquest of helpful bacteria in gastrointestinal tract, aids systematic

digestive functions, helps in the prevention of stomach upsets and stimulation and maintenance of the body's immune system. **(Food Microbiology, Frazier and Westhoff, 5e)**. There are diverse mechanisms of probiotics which endeavor numerous health benefits to the host organism by influencing the composition or functioning of the symbiotic micro-flora, by altering the epithelial system and immune system of the host **(Hyland *et al.*, 2014)**, by combating the toxic products of microorganisms, food particles or host origination which may have damaged outcome on the health of the host organism **(Rupa and Mine, 2012; Sanders *et al.*, 2013).**

1.2.1 Enhancement of gastrointestinal epithelial barrier: The gastrointestinal barrier performs an important part in an etiology of various gastro-intestinal ill-health **(Blaut and Clause, 2012)** Thus probiotics help to strengthen the gut barrier and become preventive for various types of diseases **(van Hermert *et al.*, 2013)**.

1.2.2 Degradation of toxin receptors: Probiotics help in the modification of toxin receptors by enzymatic mechanism, conquering of toxic metabolites, reduced pH of intestinal tract, debilitation of acidity and so on **(Bermudez-Brito *et al.*, 2012).** Probiotic organisms also help in the advancement of non-specified spur of the immune system of host organisms, which includes intensification of immune cells, enhancement of endocytic functions of macrophages and high-rate construction of immunoglobulins namely IgM and IgA **(Kaur *et al.*, 2009).**

1.2.3 Competition for Nutrients: Probiotics present in the gastro intestinal tract use up high amount of nutrients thus a very little nutrients are left for infective bacteria which lead them to starve and death. There are two competitive pathways for nutrients by probiotics, one is utilizing the nutrients for pathogens thus inhibiting the proliferation and grown of pathogens, other one is lowering the gastrointestinal pH (which is essential for pathogens) due to the production of various fatty acids and organic acids by metabolic reactions and fermentative functions in the intestinal tract **(Kumar Bajaj *et al.*, 2015).**

1.2.4 Production of anti-microbial agents: Probiotics provide some anti-bacterial effects to some infective bacteria by the manufacture of antimicrobial metabolites namely H2O2, organic acids, bacteriocins etc. and help in the growth inhibition of pathogenic bacteria **(Arauz et al., 2009; Razdan *et al.*, 2012; Bajaj *et al.*, 2014; Bajaj *et al.*, 2014a; Dec *et al.*, 2014)**.

1.2.5 Anti-propagative effects: Probiotic organisms possess anti-cancer activity and anti-tumor activity by various mechanisms which include metabolic inactivation of mutagenic substances and binding with HCAs and NOC compounds, thus reduce the levels of carcinogenic compounds and decrease destruction of DNA molecules **(Geier *et al.*, 2006).** Another mechanism states about the amplification of immune response to the tumor tissues by modulated production of cytokines and modulated functional properties of T cells **(Hirayama and Rafter, 2000).**

1.2.6 Blockage of adhesion sites: Probiotics adhere to the gastro intestinal epithelial surfaces thus blocking the adhesion sites and preventing the intestinal accumulation of infective bacteria **(Ohland and MacNaughton, 2010).** It is also beneficial for the immune system modulation and provides hostility against pathogenic organisms present in the gut.

1.2.7 Alteration of gastrointestinal micro flora: Probiotics helps in combating the chronic inflammatory and immunity related disease thus possess the maintenance of optimal gastrointestinal health **(Lin *et al.*, 2014).** Probiotic organisms provide gut health well-being through probiotic cell effectiveness, cell constituent secretion, metabolism, fecal tenacity and cell-cell interaction. Probiotic treatment provides improvement for the various gastrointestinal diseases by stabilizing the gut microorganisms **(Ceapa *et al.*, 2013).**

1.2.8 Modulation of systemic and mucosal immune system: Generally, probiotics help to mature the humoral immune response specially improve the circulation of IgA and IgM secreting cells. Probiotics present in the GI tract beneficially provide interaction with epithelial and mucosal immune apparatus against potentially injurious antigens by various sub-mechanisms like lymphocyte activation and antibody production. **(Hemaiswarya *et al.*, 2013; Kumar Bajaj *et al.*, 2015)**

1.3 Immune modulation and probiotics

Probiotic microorganisms have been found to have a variety of immunological and health-promoting properties. They are important in regulating the bacterial environment and module immune cells

(Dargahi *et al.*, 2019), as well as enhancing the bioavailability of nutrients and maintaining reasonable health. In a healthy gut, dendritic cells (DC) play an important role in immunological homeostasis. DCs are important antigen-presenting cells that take up antigens (such as viruses or tumors) and deliver tiny antigenic peptides on their surface to stimulate T cells to become pro-inflammatory (Th1) or anti-inflammatory (Th2). T cells can be deleted or regulatory T cells can be stimulated when DC is immature **(Foligne *et al.*, 2007)**. DC can be induced to prime these cells by the gut microbiome. Indeed, L. L. reuteri and reuteri casei, triggering the production of IFN gamma and activating pro-inflammatory Th1 cells **(Roock *et al.*, 2011)**. Similarly, B. administrations by mouth have been found to be effective. In mice, infantis stimulates DCs, which decrease Th2-biased responses and activate a Th1 pro-inflammatory response, which is necessary for viral clearance **(Fu *et al.*, 2017)**.

Monocytes are the first cells to come into touch with bacteria and viruses and are found in the peripheral circulation. They differentiate into tissue macrophages, which interact with the gut microbiota or ingested probiotics to release a variety of cytokines. Macrophages release the pro-inflammatory cytokine IL-12, which stimulates natural killer cells and CD4+ Th1 cells to generate IFN-gamma, which is essential for viral eradication **(Kitazawa *et al.*, 1994)**. In addition, probiotic strains of *L. gasseri, L. delbrueckii ssp. bulgaricus, B. bifidum, and L. acidophilus* cause monocytes to produce IFN-alpha. TNF-alpha, IL-6, and IL-8 of human monocyte cell line THP-1 are increased by the probiotic L. paracasei DG **(Balzaretti *et al.*, 2017)**. Similarly, *S. thermophilus* was recently found to elicit a TNF-alpha, IL-6, and IL-8 profile that is necessary for antiviral effects **(Dargahi *et al.*, 2020; Dargahi *et al.*, 2018; Dargahi *et al.*, 2020)**. NK cells play a critical role in the early immune response to viral infections, especially in the clearance of virus-infected cells. *Lactobacillus* probiotic strains can stimulate DCs to secrete IL-12, which then activates NK cells to secrete IFN gamma, an important cytokine for bacterial (*S. aureus*) and viral (HIV) clearance in the lungs (**Roock *et al.*, 2011**); **(Kudva *et al.*, 2011)**. Probiotics, such as *L. casei*, can interact with Toll-like receptors (TLR) on epithelial cells, increasing the production of cytokines that improve epithelial cell productivity and inhibit apoptosis, hence promoting their survival and proliferation during restoration **(Chung *et al.*, 2008); Zendeboodi *et al.*, 2020)**. Understanding immune cell activation, cytokine profiles, and immunological regulation is critical for establishing a clear roadmap for viral infection management.

2. IMMUNOMODULATION OF CYTOKINE PROFILES

Probiotics' immunomodulatory effects and clinical health benefits have made them popular in the treatment of a variety of degenerative disorders. Researchers are now focusing on identifying probiotics' elite properties, which include antipathogenicity, antiobesity, and diabetic effects, as well as anti-inflammatory, anticancer, antiallergic, and angiogenic activities, which result in effects on the central nervous system (CNS), while efficacy is largely dependent on the mechanism of action. Although the immunomodulatory effects of probiotics are not the same in every individual, a number of studies have reported basic molecular mechanisms by which probiotics regulate intestinal epithelial health, such as enhanced IgA secretion, production of cytokines, production of antibacterial substances, enhanced tight junctions of the intestinal barrier against intercellular bacterial invasion, and competition with new pathogenic microorganisms for enterocyte adherence.

Probiotic antigenic fragments, such as cell wall chemicals, have the capacity to penetrate the intestinal epithelial cells and M cells in Peyer's patches and alter the innate and adaptive immune responses in the body **(Galdeano and Perdigon, 2004).**

The release of cytokines such as interleukins (ILs), tumour necrosis factors (TNFs), interferons (IFNs), transforming growth factor (TGF), and chemokines from immune cells (lymphocytes, granulocytes, macrophages, mast cells, epithelial cells, and dendritic cells (DCs)) is thought to be responsible for probiotics' immunomodulatory effect **(Savan and Sakai, 2006; Dewulf *et al.*, 2010).** It has been observed that cell wall components of Bifdobacteria and Lactobacilli, such as lipoteichoic acid, trigger NO synthase, which may be involved in pathogen-induced cell death (NO) provided by macrophages via TNF production. NO also increases the expression of two surface

phagocytosis receptors (Fc RIII and tool-like receptor (TLR)) **(Delcenserie *et al.*, 2008; Schwandner, 1999).** Probiotics have been shown to interact with enterocytes, dendritic cells, T1, T2, and Treg cells in the colon, modulating adaptive immunity into pro- and/or anti-inflammatory responses. Lactobacillus paracasei subsp. paracasei DC412 strain and Lactobacillus acidophilus NCFB 1748 strain induced early innate immune responses and specific immune markers through phagocytosis, polymorphonuclear (PMN) cell recruitment, and TNFalpha (TNF-) production in BALB/c (20–30 g) inbred mice and Fisher-344 inbred rats. TLRs strengthen the immune defence mechanism in terms of pro- and anti-inflammatory cytokine production when foreign items are detected, while CD-206 and TLR 2 cells have a higher number of specific markers **(Galdeano and Perdigon, 2004).**

3. CONCLUSION

Probiotics are harmless microorganisms that, when given to humans in sufficient concentrations and for long enough periods of time, have certain beneficial effects on the host. The mechanisms of action of probiotics include colonization and normalization of disrupted intestinal microbial communities in both children and adults; competitive exclusion of pathogens and bacteriocin production; modulation of enzymatic activities related to the metabolization of a number of carcinogens and other toxic substances; and production of volatile fatty acids, namely SCFAs and BCFAs, which play a role in energy homeostasis and regulation of feces. In addition, probiotics increase intestinal cell adhesion and mucin production and modulate the activity of gut-associated lymphoid tissue and the immune system. Probiotic metabolites, likewise, can interact with the brain-gut axis and influence behavior. Because probiotics, alone or in combination with prebiotics, have the potential to modulate gut microbiota and immune responses in the host, probiotic treatment is a promising research area in the medical sciences. However, when it comes to the significance of probiotics in avoiding obesity, inflammatory illnesses, and cancer, a lot of research papers are nearly identical. Probiotics' immunomodulatory benefits in the treatment of degenerative and other disorders caused by pathogenic bacteria have gotten a lot of attention. Probiotics have a beneficial effect on innate immunity and have antiviral effects. Furthermore, probiotics have been shown to improve gut barrier function by stimulating B cells and influencing cytokine production, which triggers adaptive responses in the host body, though there is a paucity of research on how probiotics induce immunomodulatory effects in the treatment of inflammation. It is also urgent to understand cytokine secretion by Th2 cells, DCs, monocytes, B cells, and Tregs in order to establish new strains of probiotics. Further studies can be suggested to determine the precise action of probiotics on inflammation because these findings will be key routes in the medical sector and for better human health.

Conflict of interest statement

Authors declare that they do not have any conflict of interest.

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