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A Review on Immunomodulatory Effects of Probiotics.

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ABSTRACT

Probiotics are live microbes which when ingested in sufficient amount confer health benefits to their hosts. The science of probiotics have come of age since its inception by ElieMetchinkoff. A number of different studies have suggested critical role of probiotics in maintaining human health and well-being. This review focusses on studies pertaining to cellular, humoral and preventive effects of probiotics in stimulating the immune system and their therapeutic applications in several diseases and syndromes including aging and senescence.

Keywords: Probiotics, Immunomodulation, Cellular response, Humoral response

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INTRODUCTION

Probiotics are referred to as certain commensal microbes which have been implicated in several health beneficial effects in humans. Recent research has established that probiotics can not only influence the composition of gut microbiota but are also capable of stimulating both specific and nonspecific components of the immune system, which could be responsible for several health beneficial aspects of probiotics. As a result, several therapeutic applications of the probiotics can be cited, including the prevention of inflammatory disorders, protection against infections, diarrhea, reduction of hypercholesterolemia, protection against cancers, and food allergy [1-4]. The gastrointestinal tract is the main entry site of bacteria and other pathogens through foods and drinks and thus is a potent antigen-presenting region made of gut-associated lymphoid tissue with an abundance of immunoglobulin-producing cells. Probiotics interact with these cells of lymphoid tissue, which finally culminates in downstream activation of various immunological pathways. This results in multi-faceted effects of probiotics on human health which have gained attention of immunologists and nutritionists in development of probiotic based food strategies for healthy living.

PROBIOTICS AND THE IMMUNE SYSTEM

Effects on Cellular Immune response:

Indeed, several studies have reported enhanced phagocytosis and macrophage production, increased secretion of lysosomal enzymes, increased reactive oxygen species, and modified cytokine production in peritoneal and pulmonary macrophages on oral administration of probiotics in both animal models and human trials [5–11].

Studies in rats and mice have revealed that oral administration of lactic acid bacteria increased the numbers of T lymphocytes, CD4+ cells, and antibody-secreting cells in the intestinal mucosa and enhanced lymphocyte proliferation [12–14] Supplementation of probiotic *Lactobacillus casei*–and *Lactobacillus acidophilus*–fermented milk in mice have been reported to increase resistance against *Shigella*infection mediated by high titers of anti-*Shigella*antibodies in serum and intestinal secretions [15].Similarly, inoculation of *Lactobacillus casei*stimulated the production of specific antibodies against *Pseudomonas* antigens by increasing circulating immunoglobulin M (IgM) antibodies [16]. Similarly, various reports regarding protective effects of probiotics against gut infections and tumors can be cited [17–19].

Because cell-mediated immunity forms the basic and immediate protection against pathogens, many reports have targeted the innate immune response for validating antiimmunosenescence effects of probiotics. Using a senescence-accelerated mice model, a recent study[20] has reported a significant increase in cytotoxic activity of natural killer cells after oral administration of heat-killed Lactobacillus gasseri TMC0356. The mRNA expression of interleukin (IL)-2 and interferon-α and -β receptor were found to be significantly up-regulated, which may have contributed to the increased activation of natural killer cells. These results suggest that probiotic supplementation enhance cell mediated immune response by modulating cytokine expression in immune compromised aged individuals. Another study[21] has observed an increase in cytotoxicity and phagocytosis of peripheral blood mononuclear cells in elderly individuals on account of dietary supplementation with probiotic cheese containing Lactobacillus rhamnosus HN001 and Lactobacillus acidophilus NCFM. These results further concluded that daily consumption of the probiotic cheese enhanced parameters of innate immunity in elderly volunteers.

Administration of Lactobacillus plantarum CECT 7315 and Lactobacillus plantarum CECT 7316 in elderly subjects resulted in significantly increased percentages of activated T-suppressor (CD8+CD25+) cells, natural killer (CD56+CD16+) cells, T-helper lymphocytes (CD4+CD25+), B lymphocytes (CD19+), and antigen-presenting cells [22]. Whereas low doses of probiotic resulted in enhanced humoral immune response, higher doses were effective in generating an enhanced immediate cytotoxic immune response. The rates of infection and mortality in probiotic-fed subjects were also significantly lowered as compared with placebo-fed subjects. Administration of probiotic dahi-containing Lactobacillus acidophilus and Bifidobacteriumbifidum resulted in immune-enhancing benefits on aging mice. Feeding of probiotic dahi for four months significantly increased phagocytosis and cytokine production in macrophages and an enhanced in vitro proliferative capacity and interleukin production in lymphocytes [23]. Furthermore, the alleviation of age-inflicted oxidative stress in tissues and improvement in expression of biomarkers of aging, including senescence marker protein-30 and

klotho in hepatic and kidney tissues in old mice, corroborated the anti-immunosenescence effects of probiotic dahi[24]. Similar to these investigations, Gill et al.[25] observed that administration of milk supplemented with Bifido bacteriumlactis HN019 and Lactobacillus rhamnosus HN001 in elderly subjects resulted in increased proportions of T lymphocytes, natural killer cells, and their increased phagocytic activity.

Effects on Toll-Like Receptors:

The innate immune system identifies and mounts immune response against pathogens by employing pattern-recognition receptors, such as toll-like receptors (TLRs), which recognize specific molecular patterns present on the surface of pathogens and when activated trigger a variety of signaling pathways, including cytokine production and co-stimulatory molecule up-regulation. Studies in both human trials and experimental animals have indicated reduced TLR expression and function in macrophages and dendritic cells in the elderly as compared with young individuals [26–29]. TLR1/2-induced cytokine production of tumor necrosis factor (TNF)-α and IL-6 has also been reported to be significantly defective in older adults compared with young controls [30].

Studies in adult mice have indicated that administration of probiotics up-regulate the expression of a variety of TLRs, including TLR 2, TLR 4, TLR 5, and TLR 9, in the cells of Peyer's patches in a strain-specific manner, which ultimately helps initiate and boost the immune response [31, 32]. This ability of probiotics to modulate the expression of TLRs is of extreme importance considering the effects of immunosenescence on TLR expression in various cells of the immune system. An enhanced TLR expression and function in aging immune cells by probiotic interventions can increase their potential to respond and mount an effective immune response against invading pathogens.

Effects on Th1/Th2 balance:

Probiotics have been attributed to exert immune-regulatory effects to restore the Th1/Th2 ratio in a balanced state. Previous studies have shown that probiotic interventions may inhibit the development of Th2-related allergic disorders, as confirmed by suppression of IgE levels and increase in cytokines related to Th1 immune response [33–35]. On the other hand, supplementation of probiotics in animal models of arthritis and diabetes has been reported to down-regulate the production of cytokines related to Th1 immune response, thereby suppressing the severity of autoimmune and inflammatory diseases [36,37]. Dietary intervention of probiotic dahi in old mice has been reported to significantly increase the age-inflicted decrease in IL-2 levels of Th1 response in splenic lymphocytes, thereby alleviating the skewness of age-associated Th response. Together, these reports clearly establish that probiotics can intervene to normalize the skewed Th immune response in allergic or autoimmune disorders, but similar detailed studies are required in aging population to implicate the effects of probiotics in regulating the Th1/Th2 immune response for maintaining a balanced immunological state.

Augmentation of Humoral Immune Response:

The changes in the humoral immune response with age are both qualitative and quantitative, as affinity, specificity, and class of antibody produced are affected. Studies have indicated shrinkage of B-cell repertoire diversity, decrease in antigen-specific antibody production, and impaired antibody affinity maturation in B cells during age-associated immunosenescence [38]. Due to decreased antigenic stimulation and proliferation of B cells, the efficacy of vaccines is also greatly compromised in the elderly, rendering them more susceptible to severity and duration of infections. Several reports have shown decreased antibody response to various vaccines in old age, including influenza vaccine, hepatitis B vaccine,and pneumococcal polysaccharides [39]. Furthermore, the antibody responses have been reported to be of shorter duration in the elderly as compared with young adults [40].

However, the evident modulation of the immune system in the elderly by dietary interventions of probiotics suggests their possible role in boosting immune response to vaccines. Indeed, studies in aged volunteers have indicated that dietary consumption of probiotic lactobacilli stimulated the production of specific IgA and IgG antibodies in response to influenza vaccination. These data suggest that consumption of probiotics can help generate an adequate immune response to vaccination in the elderly.

Mechanism of Probiotics action:

The beneficial effects of probiotics in maintaining health, enhancing immunity, and fighting infections have long been investigated. However, the exact mechanisms underlying these effects of probiotics are incompletely understood. Production of antibiotics, competition for adhesion, and acidification of their microenvironment by secreting short-chain fatty acids are some of the methods adopted by probiotics in resisting harmful commensal organisms. The immunomodulatory effects of probiotic bacteria are based on their ability to interact through M cells in the Peyer's patches of intestinal epithelial lining [41]. These mucosal epithelial cells are critical in coordinating the defense mechanisms. They release cytokines in response to external signals and recruit cells from both the innate and adaptive immune responses. Once inside the lamina propria, the probiotic bacteria interact with dendritic cells and macrophages, stimulating them to produce downstream effector cytokines, which finally results in immunomodulatory effects of probiotics, including increased proliferation of CD4 T cells, enhanced IgA production, and altered cytokine synthesis favoring anti-inflammatory response [42]. It is peculiar to note that the various immunomodulatory effects of probiotics appear to be strain dependent and it is not necessary that these effects are common for all strains of a particular probiotic species. As a result, the downstream activation or suppression of cytokines through modulation of pathways such as nuclear factor kappa B (NFκB), signal transducers and activators of transcription (STATs), or peroxisome proliferator-activated receptor γ (PPARγ) is a highly strain-dependent phenomenon and may account for the lack or minimum effects of probiotics as reported in some studies. Hence, to fully comprehend the efficacy of probiotics, it is imperative to carefully select probiotic strain of choice depending on study design.

CONCLUSION

The science of immunomodulatory effects by dietary interventions of probiotics is still in a budding stage. As the mechanisms of action of probiotics with respect to senescent immune cells are better understood, more avenues arise in exploring their anti-immunosenescence effects. However, many experimental and clinical studies have indicated that dietary consumption of probiotics may offer health benefits to elderly consumers in not only combating some of the deleterious effects of immunosenescence but also as preventive measure against infectious diseases. This makes probiotic bacteria potent candidates for developing anti-immunosenescence strategy for the elderly. Especially, a milk-based probiotic product could be more effective owing to its wide reach amongst the general population. As we better understand the anti-immunosenescence effects of probiotics, it may ultimately help devise a probiotic-based anti-immunosenescence strategy to live a long and healthy life.

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