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Rohit Sharma [a], Rajeev Kapila [a] & Suman Kapila [a]
[a] Animal Biochemistry Division, National Dairy Research Institute, Karnal, India

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# Probiotics as Anti-immunosenescence Agents

ROHIT SHARMA, RAJEEV KAPILA, AND SUMAN KAPILA

Animal Biochemistry Division, National Dairy Research Institute, Karnal, India



*Immunosenescence is an inevitable, gradual decline in functions of the immune system during aging. The process affects all cells of the immune system and hence contributes to increased risk of infections and disorders in the elderly. Dietary consumption of probiotics has long been considered beneficial for health mostly because of its immunomodulatory attributes. Recent advances in understanding the effects of probiotics on the aging immune system have begun to unfold their potent anti-immunosenescence attributes. A better understanding of these effects may help devise a probiotic-based anti-immunosenescence strategy for a healthy elderly life.*

**Keywords** Aging, Immunity, Immunomodulation, Immunosenescence, Probiotics

## Introduction

The increase in life expectancy in the past century has led to a dramatic expansion of aging population throughout the globe. As a result, the percentage of elderly (>60 years) population has increased from 8% in year 1950 to an expected 20% in year 2050.[1] This longevity subsequently has led to an increased rate of morbidity and mortality particularly in the elderly in response to infectious agents and autoimmune and neurodegenerative diseases.[2,3] As a whole, these diseases threaten the quality of life of the elderly and present a challenge to public health systems. An important reason for age-associated increase in infections and chronic disorders is the dysregulation of the immune system during aging, commonly referred to as immunosenescence. This term was first introduced by Dr. Roy Walford[4] and refers to the immune system's impaired function with age.[5] In fact, declines in immune function are a hallmark of aging and result in decreased ability of the elderly to both resist infection and respond to vaccination.[6] The beneficial effects of probiotics in human health have created interest among scientists since the observations by Ellie Metchinkoff[7] in his book *The Prolongation of Life*, which highlighted the potential of lactic acid bacteria in maintenance of healthy gut and promoting longevity in humans. The term "probiotics" was introduced in 1965 by Lilly and Stillwell as "Substances produced by microorganisms which promote the growth of other microorganisms." They showed that several species of protozoa, during their logarithmic phases of growth, produce substances that prolong the logarithmic phase in other species.[8] Probiotics are currently defined by the World Health Organization as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[9] Over the last century, several different microorganisms have been identified as probiotics and their role in the prevention and cure of diseases is widely purported.[10,11] The established probiotics are generally lactic acid bacteria, most commonly *Lactobacillus* and *Bifidobacterium* species, but microorganisms

Address correspondence to Rajeev Kapila, Animal Biochemistry Division, National Dairy Research Institute, Karnal, India. E-mail: rkapila69@rediffmail.com

belonging to other genera and species such as *Pediococcus acidilactici*, *Bacillus coagulans*, *Enterococcus faecium*, nonpathogenic strains of *Escherichia coli*, and some yeast strains are also categorized as probiotics. Today, probiotics have become very common in use and consumption of various probiotic-based dairy products has claimed to boost immune response and gastrointestinal health. A number of different studies have been performed pertaining to the beneficial and immunomodulatory effects of probiotics. Thus, in this review we first provide an overview of various immune-enhancing and immune-protective effects of probiotics and then focus on different aspects of anti-immunosenescence potential of probiotics as purported by various experimental animals as well as human studies.



## Immunomodulatory Effects of Probiotics

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, thereby conferring health benefits to the host. As a result, several therapeutic applications of the probiotics can be cited, including the prevention of urogenital diseases, alleviation of constipation and lactose intolerance, protection against diarrhea, reduction of hypercholesterolemia, protection against colon and bladder cancers, and prevention of osteoporosis and food allergy.[12–15] 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. 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.[16–22] 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.[23–25] 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.[26] Subcutaneous inoculation of *Lactobacillus casei* stimulated the production of specific antibodies against *Pseudomonas* antigens by increasing circulating immunoglobulin M (IgM) antibodies.[27] Similarly, various reports regarding protective effects of probiotics against gut infections and tumors can be cited.[28–30]

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.[31] 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.[32]

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.[33,34] Hence, to fully comprehend the efficacy of probiotics, it is imperative to carefully select probiotic strain of choice depending on study design.

Age-associated immunosenescence is a very complex process and mechanisms of its inevitable manifestation still remain to be completely deciphered. Due to its widespread effects, the individual factors contributing to immunosenescence are many and varied (Figure 1). As a result, it is often difficult to conclude whether changes in a particular cell characteristics or function are intrinsic to it or caused by another cell type(s) or both. The multifaceted therapeutic and immunomodulatory benefits of probiotics indicate promising implications in developing anti-immunosenescence strategies. However, there is a need for distinctive evaluation of immunomodulatory effects of probiotics in the elderly because the effects of probiotics have been shown to vary according to different population groups.[35] Therefore, to understand and implicate probiotics in combating immunosenescence, it is essential to design studies based on the elderly population only rather than extrapolating the results of studies carried out in young and adult populations. The diverse consequences of age-associated immunosenescence on various components of the immune system are well documented and supplementation of probiotics has been reported not only to counteract these deleterious effects but also to boost immune response in a variety of ways for maintaining the efficacy of general immunity in the elderly.

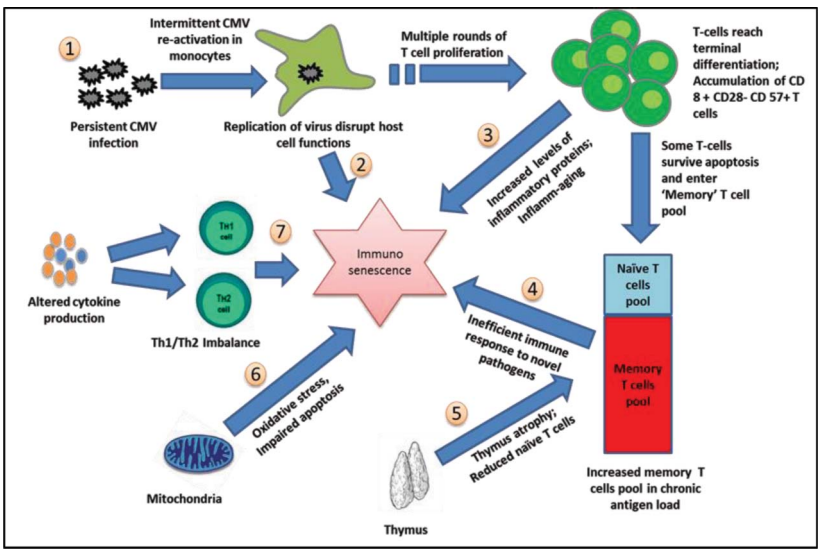


**Figure 1.** Factors contributing to immunosenescence (color figure available online).

## Amelioration of Cellular Immune Response

The dysregulation of the immune system during aging is widespread and is observed for both the innate and adaptive arms of the immune system. Innate immunity is a key element of the immune response; it eliminates pathogens that gain access into the body's tissues and guides the adaptive immune system to mount pathogen-specific humoral and cellular immune responses. The innate immune system includes several cellular components such as macrophages, natural killer cells, neutrophils, and dendritic cells, which provide first-line cellular defense against bacterial and viral infections. Although no significant variations in the number of cells of the innate immune system during aging are reported, different functional changes suggesting reduced efficacy of immune response have been described.[36,37] A growing body of data has indicated a decrease in phagocytic ability of macrophages and neutrophils in the elderly.[38–41] This is corroborated with impaired oxidative burst capacity and production of reactive oxygen intermediates in phagocytes that are prerequisites for an effective phagocytic action.[42,43] Furthermore, the decreased capacity of neutrophils and macrophages to migrate in vitro in response to chemotactic agents such as granulocyte-macrophage colony-stimulating factor (GM-CSF) or the *N*-formyl-Met-Leu-Phe (FMLP) peptide indicates suppressed in vivo activation of phagocytes in old age.[44] These functional discrepancies in the cells of the innate immune system could be attributed to the increased risk of bacterial and viral infections as commonly observed in the elderly. Indeed, greater numbers of neutrophils were reported to be required in a wound repair process in old mice compared with young adult mice owing to reduced neutrophil function.[45] Similarly dendritic cells, which are major antigen-presenting cells responsible for stimulating adaptive immune response, have been reported to show decreased phagocytosis, chemotaxis, and maturation as a result of immunosenescence.[46] In addition to cells of innate immune response, progressive aging results in involution of thymus leading to decreased production, activation, proliferation, and antigen presentation of naïve T cells and a gradual shift towards memory phenotype T cells that constantly fills up the immunological space.[47] As a result, T cells of the elderly exhibit distinct combinations of cell surface markers (CD 28,[48,49] CD 154,[50,51] CD 57,[52,53] and CD 95[54,55]) that are considered as hallmarks of immunosenescence. Hence, the impaired functional properties of the cells of the innate immune system coupled with the reduced generation of downstream response by the cells of the adaptive immune system may offer an explanation for the increased frequency, severity, persistence, and generation of poor immune response against various infectious agents in the elderly.

Because cell-mediated immunity forms the basic and immediate protection against pathogens, many reports have targeted the innate immune response for validating anti-immunosenescence effects of probiotics. Using a senescence-accelerated mice model, a recent study[56] 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 immunocompromised aged individuals. Another study[57] 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.[58] 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 *Bifidobacterium bifidum* 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.[59] 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.[60] Similar to these investigations, Gill et al.[61] observed that administration of milk supplemented with *Bifidobacterium lactis* HN019 and *Lactobacillus rhamnosus* HN001 in elderly subjects resulted in increased proportions of T lymphocytes, natural killer cells, and their increased phagocytic activity.

## Improvement in Expression of Toll-Like Receptors

The innate immune system detects pathogens using 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.[62–65] 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.[66] 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.[67,68] 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.

## Preservation of Inflammatory Homeostasis

Increase in longevity results in an increased exposure of the immune system to pathogens and antigens. As a consequence of this chronic exposure, there is progressive activation of macrophages and related innate immune system cells in most organs and tissues of the body, creating an imbalance between inflammatory and anti-inflammatory networks. The net result is a low-grade chronic proinflammatory status referred to as "inflamm-aging" in the elderly.[69] Thus, although the immune system itself is dysregulated, leading to an impaired host defense, the system is in a constant hyperactivated state owing to infamm-aging. This scenario is commonly considered to be an immunological paradox. As a result, increased concentrations of classic proinflammatory cytokines such as TNF-α, IL-1, and

IL-6 and acute-phase proteins such as C-reactive protein (CRP) and monocyte chemotactic protein have been reported in the elderly.[70–73] This chronic systemic inflammation can be self-destructive which might explain the increased risk of inflammatory and autoimmune disorders such as Alzheimer's, lupus, diabetes, and rheumatoid arthritis as observed in the elderly.[74,75]

Probiotics are known to induce synthesis of anti-inflammatory cytokines in the gut microenvironment and studies have indicated their ability to down-regulate potent systemic inflammatory markers. It has been reported that consumption of a milk-based drink containing *Lactobacillus rhamnosus* GG, *Bifidobacterium animalis* sp. *lactis* Bb12, or *Propionibacterium freudenreichii* sp. *shermanii* JS by healthy adults led to a significant decrease in the levels of serum CRP and proinflammatory cytokines in peripheral blood mononuclear cells, suggesting a strain-dependent anti-inflammatory effect of probiotics.[76] Similarly, consumption of probiotic yoghurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium animalis* Bb12 by pregnant women resulted in significantly decreased levels of serum CRP with no effect on serum TNF-α.[77] These anti-inflammatory effects of probiotics can be linked to their production of short-chain fatty acids, which have been shown to reduce systemic levels of blood lipids via a liver-dependent pathway.[78] Short-chain fatty acids can enter the blood circulation and act on liver enzymes that may be responsible for the observed decrease in various inflammatory molecules. The ability of probiotics to increase the levels of systemic polyamines has led to another novel hypothesis in alleviating inflamm-aging.[79] Polyamines, including putrescine, spermidine, and spermine, are involved in regulating inflammation by inhibiting synthesis of proinflammatory cytokines in macrophages[80,81] and modulating the NFκB activation pathway.[82] The levels of these polyamines decrease in aging mammalian cells and organs,[83,84] thereby creating an imbalance in inflammatory and anti-inflammatory networks ultimately contributing to inflamm-aging. Matsumoto et al.[85] have reported that dietary consumption of yogurt containing *Bifidobacterium lactis* LKM512 increased the levels of polyamines (putrescine, spermidine, and spermine) in elderly volunteers, which negatively correlated with a significant decrease in the level of a fecal inflammatory marker (haptoglobin), suggesting possible inflammation-alleviating effects of probiotics. Although more studies are required to corroborate the effects of probiotics in regulating liver enzymes and polyamine contents, especially in old age, it seems plausible that probiotics have the potential to counteract inflamm-aging in at least more than one way of action.

## Regulation of Skewed T-Helper (Th) Response

On appropriate encounter with an antigen, the naïve T cells are stimulated to expand and form antigen-specific effector T cells, which either stimulate cellular immune response (Th1) or humoral immune response (Th2). A Th1 proinflammatory response activates cellular defense and thus provides the host an advantage of surviving in an infectious environment, while a Th2-type response is generally humoral and anti-inflammatory in nature. In case of an antigenic encounter, the Th1 and Th2 immune responses are antagonist to each other and overall remain in a balanced immunological state. A number of studies have suggested an imbalance in Th1/Th2 ratio resulting in a skewed and exaggerated immune response in aging.[86–88] A skewed Th1 response makes the elderly more prone to autoimmune disorders, whereas an increased Th2 response is generally favorable for allergic disorders.

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.[89–91] 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.[92,93] 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.[59] 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 during Vaccination

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,[94] decrease in antigen-specific antibody production,[95] and impaired antibody affinity maturation in B cells during age-associated immunosenescence.[96]

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.[97] Several reports have shown decreased antibody response to various vaccines in old age, including influenza vaccine,[98] hepatitis B vaccine,[99] and pneumococcal polysaccharides.[100] Furthermore, the antibody responses have been reported to be of shorter duration in the elderly as compared with young adults.[101] 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.[102,103] These data suggest that consumption of probiotics can help generate an adequate immune response to vaccination in the elderly.

## Resisting Infections and Infectious Agents

The overall compromised immune system during aging results in increased incidence, duration, and persistence of infections in the elderly. Probiotics have been reported to both resist and boost immune response against various infections and pathogens in the elderly. A report by Guillemard et al.[104] on an elderly population in a multicentric, double-blind controlled trial has indicated immune-protective attributes of probiotics against infections. Consumption of fermented dairy product containing probiotic *Lactobacillus casei* DN-114001 in an elderly free-living population resulted in a reduced duration of common infectious diseases (CIDs) of the airways and gastrointestinal tract. Furthermore, administration of probiotics significantly reduced both the average duration per episode of CID and cumulative duration of CID. In a similar study,[105] dietary consumption of yogurt fermented with *Lactobacillus delbrueckii* sp. *bulgaricus* OLL1073R-1 resulted in significantly decreased incidence of common cold (2.6 times lower) in probiotic-fed elderly subjects as compared with the control group. This was corroborated with increased natural killer cell activity in the probiotic-fed group as compared with the control group. Fukushima et al.[106]

investigated the effects of enterally fed fermented milk containing probiotic *Lactobacillus johnsonii* La1 (NCC533) in hospitalized, bed-ridden elderly suffering from dysphasia with dementia. In this double-blind trial, probiotic intervention resulted in a significant decrease in the number of days with infections, enhanced blood phagocytic activity, increased blood hemoglobin and albumin levels, decreased levels of the proinflammatory cytokine TNF-α, and suppressed the fecal antibiotic-resistant strain methicillin-resistant *Staphylococcus aureus.* In another study, dietary interventions of *Lactobacillus acidophilus* NCFM and lactitol in healthy elderly resulted in increased numbers of total intestinal microflora, including *Bifidobacterium* and *Lactobacillus*, and increased fecal prostaglandin $E_2$ ($PGE_2$) levels.[107] Similarly, consumption of kefir, a stirred beverage made from milk fermented with a complex mixture of bacteria, including lactobacilli and lactococci, has been reported to increase levels of serum anticholera toxin IgA antibody and IgA-secreting cells in gut-associated lymphoid tissue of old rats, indicating immune-protective effects of probiotics mediated by enhanced humoral immunity.[108]

## Cytomegalovirus-Mediated Immunosenescence: Role of Probiotics

Lifelong chronic antigenic load in the elderly not only poses a constant infectious threat but may also be responsible for shaping up the immune system for aging. The case of cytomegalovirus (CMV) infection is of particular interest in understanding the effects of persistent antigens in modeling the immune response during aging. Human CMV is a persistent β-herpesvirus and its infection is extremely common, with an estimated seroprevalence of approximately 50% in the adult population and more than 90% of the elderly worldwide.[109,110] The virus persists in a latent state in monocytes and myeloid progenitor cells of the immune system and establishes a chronic infection with intermittent reactivations.[111,112] The immune system itself thus plays a crucial role in persistence of CMV in the infected host. In immunocompetent individuals, the primary CMV infection is clinically insignificant, but in cases of immunocompromised or aged individuals, the effects of CMV infection become more dramatic. Persistent CMV infection and its intermittent reactivations constantly stimulate T cells, which over a period of time accumulate and become monoclonal for CMV, exhaust their proliferative capacity, and result in premature senescence. Indeed, it has been estimated that CMV-specific T cells nearly occupy up to 50% of the CD8 and 10–30% of the CD4 T-cell pool in elderly individuals.[113–115] Furthermore, CMV-specific CD8 T cells have been shown to produce high levels of interferon (IFN)-γ and TNF-α, indicating that CMV infection might contribute for the propagation of low-level chronic inflammation (inflamm-aging) as commonly observed in the elderly.[116] Moreover, this accumulation of CMV-specific T cells results in gradual reduction of prevailing levels of immunity to other antigens, thereby resulting in a poor immune response in case of infection.[117] CMV can also induce additional immunosuppression because replication of the virus also takes place in cells of the immune system, that is, in polymorphonuclear leukocytes, which may result in impairment of their functions. In addition to CMV, human T-cell leukemia virus and Epstein-Barr virus may also contribute to immunosenescence owing to their persistent and widespread occurrence in human population.

Given the vital role of CMV infection in promoting immunosenescence, it becomes essential for any anti-immunosenescence strategy to consider and monitor CMV pathogenesis. Ohashi et al.[118,119] have reported antiviral activity of *Lactobacillus casei* against CMV infection in mice. Treatment of mice with probiotics resulted in decreased titers of infectious CMV in the target organs and enhanced survival ability of mice even after a lethal CMV infection. The increase in cytotoxic activities of natural killer cells on account of

probiotic treatment was hypothesized to be responsible for antiviral effects of *Lactobacillus casei*. However, no further studies regarding the effects of probiotics on CMV infection and persistence in context of immunosenescence have been reported. Nevertheless, it appears that dietary interventions of probiotic bacteria can not only influence the functional aspects of the aging immune system but by possible suppression of persistent pathogens such as CMV, which are critical in genesis of immunosenescence, they can also help reshape the aging immune system for a healthy life.



## Oxidative Stress and Immunosenescence: Case of Probiotics

Disruptions in the cellular oxidative balance due to mitochondrial dysfunctions during aging can trigger oxidative stress in cells, resulting in reduced defense against oxidative damage, making them prone to early senescence. For the cells of the immune system, impaired mitochondrial reactive oxygen species (ROS) production has also been linked to compromised functions characteristic of immunosenescence. Recent studies have shown that bactericidal activities of innate immune cells involve a novel signaling pathway linking TLR activation to recruitment of mitochondria to the phagosome to augment ROS production for aiding the bactericidal activity of macrophages.[120] This implicates mitochondrial ROS production as an important component of antibacterial response of the innate immune cells. Furthermore, because mitochondria are also involved in regulating apoptosis, the normal functioning of the immune system could be affected by alterations in the mitochondrial pathway of apoptosis, which could be triggered due to alterations in ROS production. Additionally, recent studies have shown that mitochondria might play a more direct role in the immune system by activation of the multiprotein immune complex called "inflammasome," which results in the production and release of different proinflammatory cytokines.[121,122] The ROS produced by mitochondria play a critical role in the activation of the inflammasome. Thus, the apparent imbalance in ROS production in mitochondria during aging might result in overactivation of the inflammasome, thereby contributing to the low-grade chronic inflammation (inflamm-aging) as observed in the elderly. Taken together, impaired production of mitochondrial ROS during aging can not only make cells more prone to oxidative damage, but by alterations in mitochondrial processes such as apoptosis and inflammasome activation, it can also directly influence the immunological balance, thereby shaping some of the characteristic attributes of age-associated immunosenescence.

The effects of probiotics in regulating mitochondrial dysfunctions during aging are only partly understood. However, the augmentation in the production of ROS, phagocytic capacity, and tumoricidal activities of various cells of the immune system as purported by dietary interventions of probiotics in several aging groups could be attributed to improved mitochondrial activities.[57–59] Some investigations have also shown that probiotic treatment leads to regulation of apoptosis in both intestinal and peripheral blood lymphocytes by modulating the mitochondrial apoptosis pathway.[123,124] Although research on effects of probiotics in regulating mitochondrial dysfunctions during aging, particularly in the context of immunosenescence, is limited and requires further validation, these data suggest beneficial interactions of probiotics with mitochondria that may help combat some of the deleterious effects of mitochondrial dysfunctions in modeling immunosenescence.

## Conclusions

Aging is an inevitable, multifaceted process and age-associated immunosenescence is one of the foremost reasons of ever increasing rates of infections and mortality in the elderly. The increase in aging global population, persistent and novel pathogens, and

chronic disorders poses a challenge in combating immunosenescence. The science of immunomodulatory effects in the elderly 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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