

## THE ROLE OF PROBIOTIC SUPPLEMENTATION ON THE IMMUNE SYSTEM IN ELDERLY

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### Abstract

Elderly tends to be more susceptible to infections and chronic diseases. Malnutrition, immunosenescence, and changes in the gut microbiota affect susceptibility to the elderly. Several studies have shown that there is a change in the composition and variability of gut microbiota as we grow older. These changes are considered to increasing the risk of infection and play a role in the pathogenesis of various diseases in elderly. Supplementation of probiotics is expected to overcome the microbiota changes in the elderly and therefore improve the health of the elderly.

In this review we will discuss about normal gut microbiota, changes in gut microbiota in the elderly, and effects of probiotics, prebiotics and synbiotics supplementation in the elderly. We will also review recent studies on the health benefits of probiotics for the elderly immune system as a new strategy for healthy aging. Recent data suggests that supplementation of probiotics can increase the immunity of the elderly.

Further research is needed so that probiotic supplementation can be applied in clinical setting as a supporting therapy to improve the health of the elderly.

**Keywords:** Elderly, geriatric, gut microbiota, prebiotic, probiotic, synbiotic.

### INTRODUCTION:

Human life expectancy is increasing recently, reaching 72 years old in 2016. Globally, there is an increase of life expectancy by 5,5 years from 2000 until 2016.<sup>1</sup> The increase of life expectancy also lead to increase in age-related diseases with the growing of elderly population. The elderly is more vulnerable to get infections and chronic diseases such as cancer and heart disease because there is a decrease in their immune system, called "*immunosenescence*".<sup>2</sup> Studies show that aging is followed by changes of composition and variability of gut microbiota. These changes raise the vulnerability, the risk of infection, and play a role in the pathogenesis of various diseases in elderly. Diet plays a big role on elderly's immune system because of the reduction of amount and variety of fibers that elderly consumed and the risk of malnutrition.<sup>3</sup> Supplementation of probiotic, prebiotic, and synbiotic is expected to restore the composition of microbiota to "ideal" composition in elderly's gut, so this can be a new intervention to improve the health status of the elderly.<sup>4</sup>

In this review we will discuss about normal gut microbiota, changes in gut microbiota in the elderly, and effects of probiotics, prebiotics and synbiotics supplementation in the elderly. We will also review recent studies on the health benefits of probiotics for the elderly immune system as a new strategy for healthy aging.

### Microbiota in Gastrointestinal Tract

Human gastrointestinal tract is sterile in newborn and will start to colonize during the delivery process. In vaginal birth, the infant is inoculated by bacteria that came from mother's vaginal microbiota or surrounding environment. This bacteria is a mixture of gram negative and gram positive bacteria, aerobes and anaerobes. resembling their mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* spp.. Whereas in C-section infants, inoculated bacteria similar to those found on the skin surface, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp (Figure 1).<sup>5,6</sup>

At first, there was unstable colonization of gut bacteria. As time goes by, with consumption of breast milk or infant formula, the gut microbiota became stable. In breast-fed babies, *Bifidobacteria* became the most dominant microbiota. In babies that consume infant formula, there is a different microbiota population that dominates the gut. Changes in the variety of food that babies eat will lead to changes in microbiota and gut microbiota becomes stable at the age of 2 years.<sup>7</sup>

Colon is the main site for microbiota colonization, containing about 1,5 kilograms of bacteria, which is equivalent to  $10^{14}$  microorganism. The majority of microbiota species are anaerobic (97%) and facultative aerobics (3%). Most bacteria in adults gut are nonsporing anaerobes, which include *Firmicutes*, *Bacteroides* spp., *Bifidobacterium* spp., *Eubacterium* spp., and other gram positive cocci.<sup>8</sup>

There are 3 main functions of gut microbiota. First, microbiota as a protective agent. Resident bacteria in the gut inhibit the growth of pathogen bacteria by direct or indirect mechanism. Directly, microbiota produces antimicrobial factor, such as bacteriocin and lactate. Indirectly, resident bacteria compete with pathogen bacteria to get nutrition and they prevent colonization of pathogen by inhibiting pathogen to bind to gut mucosal. Pathogens mucosal binding can induce the activation of host immune system.<sup>9</sup>

Second, commensal bacteria is important for the growth of gut mucosal immune system. Gut mucosal is the largest surface in human body. There are *Gut Associated Lymphoid Tissue* (GALT) in gut mucosal. It contains *dendritic cells* that protect gut from pathogens. GALT is a center of immunomodulating effects from commensal or probiotic bacteria.<sup>10</sup> Commensal microbiota stimulates secretion of immunoglobulin A (IgA), humoral immune system and immunomodulation process. The mechanisms include mucus production, macrophage activation by lactobacilli, neutrophil stimulation and inhibition of inflammatory cytokines.<sup>9</sup>

In addition to its role in protection and immunomodulation function, microbiota also has metabolic functions. It plays a role in fibers degradation, fat metabolism and storage, increase ion absorption, and synthesize vitamin K, biotin and folic. Gut microbiota also produces *short-chain fatty acid* (SCFA) that helps in epithelization of colon epithelium.<sup>9</sup>

Several studies had showed that gut microbiota had beneficial effects on human health and changes in the gut microbiota composition can cause a variety of metabolic and inflammatory disorders.<sup>6</sup>

### Changes of Microbiota Composition in Elderly

Aging is an increase of age followed by a decrease in physiological function. Aging causes changes in structure and composition of elderly microbiota. Some of the factors that responsible in changing gut microbiota composition are physiological changes in gastrointestinal tract, diet changes in elderly, and immune system changes in elderly (*immunosenescence*). These changes lead to decreased immune system and/or increased vulnerability to pathogens invasion. There is a decrease in humoral immune response (mediated by B cells). *Immunosenescence* decreases naïve T cells which reducing the adaptive immune system ability in elderly.<sup>4,11</sup>

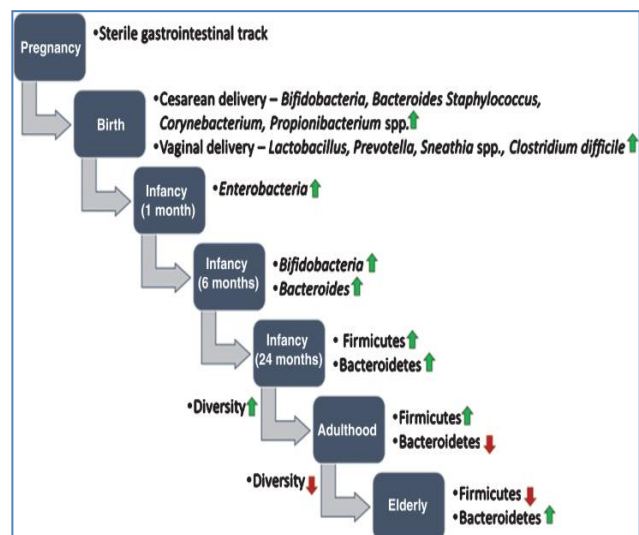


Figure 1: Development of human gut microbiota from prenatal to elderly.<sup>6</sup>

Diet plays a big role on elderly's immune system because of the reduction of amount and variety of fibers that elderly consumed and the risk of malnutrition. These changes increase vulnerability, comorbidities, and affect nutritional status, inflammation and metabolism in elderly. Gut microbiota homeostasis is crucial in healthy aging process.<sup>4</sup>

There is a reduction of gut microbiota variety and species in elderly. In 2010, there is a first report on microbiota composition in very old individuals. It compared microbiota composition in "centenarians", which is, people who have lived for over 100 years

with microbiota composition in young adults and 70 year old people.<sup>12</sup> It showed that their microbiota composition differed significantly. The centenarians microbiota was characterized by rearrangement in the *Firmicutes* population and an enrichment in facultative anaerobes. *Faecalibacterium praunitzii* is one of *Firmicutes* species and showed a marked decrease. On the other hand, there was a decreasing amount of *Bacteroidetes*, *Lactobacillus*, *Bifidobacterium*, and *Proteobacteria*. There is also an increase in gram negative bacteria, such as *Enterobacteriaceae* and other pathogen in elderly. Gram negative bacteria has lipopolysaccharide (LPS), an endotoxin that cause inflammation in the gut.<sup>6</sup>

Dysbiosis causes “inflamm-aging”, which increases proinflammatory cytokines such as IL-6 and TNF- $\alpha$  in blood plasma. In common conditions, after infection or tissue injuries, the proinflammatory factors will be eliminated and inflammatory response changes into balanced state, which is called resolving inflammation. However, under dysbiosis, loss of

intestinal barrier integrity may lead to leakage of various microbial and/or microbial components through the gut barrier that initiate hyper-inflammatory responses. Inflammation fails to change into a steady state and continues to nonresolving inflammation state. This inflamm-aging related to chronic inflammation in elderly (Figure 2).<sup>13,14</sup>

Reduction in microbiota variation is related to a decrease in the microbiota metabolic capacity. It causes a decrease in *short chain fatty acid* (SCFA) production. This is thought to be related to the reduced population of *Faecalibacterium praunitzii* and other bacteria that produce SCFA, such as *Bacteroides* and *Bifidobacteria* in elderly. Decreased production of SCFA related with mucin secretion in gut epithelium and it increases pathogen on gut mucosal. It also related with irregular gut transit, loss of appetite, immune system disturbance, weight loss, hypertension, vitamin D deficiency, diabetes, arthritis, and sarcopenia.<sup>4</sup>

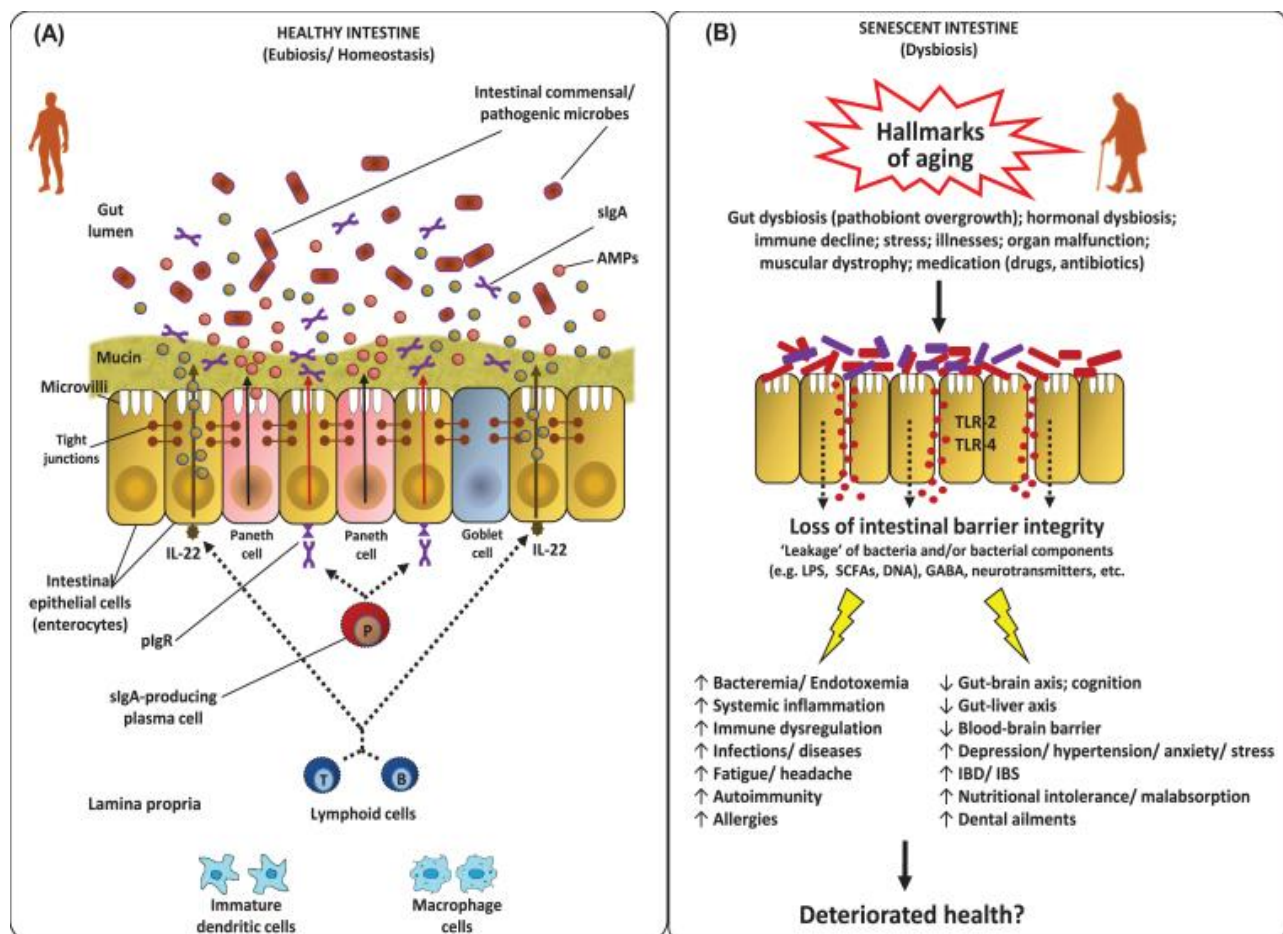


Figure 2: Homeostatic intestinal environment (eubiosis) (A) and gut dysbiosis in elderly (B).<sup>14</sup>

### Role of Gut Microbiota on Immune System

Gut microbiota stability is important in maintaining epithelial barrier integrity and immune homeostasis. Instability results in a dysbiotic condition which is associated with inflammation and compromised barrier function that allow the pathogens (microbiota components with the potential to cause significant disease) to pass through the epithelium and spread to the other body parts that can have a fatal consequences.<sup>15</sup>

The gut microbiota is established since birth along with the immune system. At birth, the microbiota and immune system still immature, then become fully established to be able to provide effective T and B cell responses. Important factors that play a role in the development of the gut microbiota and the immune system are early life nutrient and breast milk that help in establishing beneficial Bifidobacteria which can modulate the immune system.<sup>15</sup>

Propionic acid, acetic acid and butyric acid are SCFAs that are produced in large amount by microbiota and have beneficial effects on health. Propionic acid is absorbed and metabolized in liver, and play a role in cholesterol synthesis inhibition. Acetic acid is absorbed and metabolized by various tissues such as the brain, kidneys, and heart. Butyric acid is used as an energy resource for colon epithelial cells and play a role in cells growth and differentiation. Butyric acid is thought to reduce the risk of colon cancer by activating the apoptotic pathway.<sup>6</sup>

Some studies showed butyric acid also has an anti-inflammatory effect with immunomodulating effects on macrophages by decreasing IL-6. The reduction in inflammation is followed by a decrease in permeability of the intestinal mucous membrane, so that harmful molecules such as LPS cannot infiltrate. This finding shows that the presence of butyrate has a positive effect on the immune system.<sup>6</sup>

### Potential Benefits of Probiotic Supplementation in the Elderly

In modulating the intestinal microbiota there are 3 types of supplementation that can be done. First, supplementation of probiotics that according to WHO defined as live microorganisms, which when administered in adequate amounts can give health benefits to the host. Second, prebiotics which are defined as selectively fermentable ingredients that allow specific changes in the composition and/or activity of the GI microbiota that give benefits to the

host. And the last is synbiotics, which are combined supplementation of probiotics and prebiotics.<sup>8</sup>

Microbiota modulates the immune system in humans by stimulating the immune system either the nonspecific (innate) or the selective (adaptive), or both. Probiotics can also stimulate directly into the humoral or cellular immune system.<sup>4</sup>

The mechanism of immune system modulation by probiotic organisms is not entirely known, but it is believed that modulation of the immune system is due to competition with pathogens in the colon to obtain nutrients, impaired pathogenic colonization, and competition with pathogens for binding sites on gut epithelial cells, bacteriocin production, and decrease in colonic pH. Probiotics can fight the inflammatory process by stabilizing the gut microbial environment and gut's permeability barrier. Possible mechanisms of action of probiotic organisms include an increase in intestinal immunoglobulin A (IgA), increase in inflammatory responses and by controlling intestinal permeability and altered gut microecology.<sup>10</sup>

Several studies have tried to prove the benefits of probiotics supplementation in improving the immune system, especially in the elderly. The immune system's response may vary in the presence of different probiotic organisms.

Study by Molina et al. showed the benefits of probiotics for the elderly immune system. First, this study showed a significant decrease in phagocytic activity of peritoneal macrophages and IgA cells in the small intestine of elderly rats compared to young mice. Then the elderly mice get *Lactobacillus* (L.) *rhamnosus* CRL1505 supplementation that resulted in an increase in phagocytic activity of peritoneal macrophages and IgA cells with values similar to the young mice.<sup>16</sup>

*Bifidobacterium lactis* is one of the most extensively studied probiotic organism. There are several trials that showed regular intake of *Bifidobacterium lactis* in elderly will modulate cellular immune response with an increase in phagocyte-mediated bacteriocidal activity, increased T cells (CD4 +, CD25 +), and enhance NK cell killing activity.<sup>10,17</sup>

As one of the most popular probiotic with world-wide availability, *Lactobacillus casei* strain Shirota (LcS) also had been studied in several trials. In a study by Gleeson et al., regular consumption of LcS in athletes can reduced cytomegalovirus plasma and Epstein-

Barr virus antibody titers which beneficial for the immune system.<sup>18</sup> This result also supported by Shida et al. that showed daily intake of fermented milk containing LcS reduced the risk of URTIs in healthy middle-aged male office workers. This randomized controlled trial also compared the NK cell activity between control group and intervention group. NK cell activity decreased in the control group, but kept within baseline levels in the intervention group that consume fermented milk containing LcS. NK cells play an important role in the prevention of viral infections, including URTIs.<sup>19</sup>

Another probiotic like *Bacillus* also had been studied. Study by Lefevre et al. showed that the consumption of *Bacillus subtilis* CU1 probiotics for four months in the elderly significantly increased fecal and salivary secretory IgA concentrations compared to the placebo.<sup>20</sup>

### Risk of Probiotic Supplementation

Elderly people that have compromised immune function might benefit the most from probiotic supplementation because of probiotic's immune stimulating effects, but the risk for adverse effects might also be higher. Probiotics are alive when administered and have potential for infectivity or toxin production. The safety of specific microbes that being used must be considered. Probiotic stability, its metabolic activities, and the pathogenicity or toxigenicity effects must be assessed before probiotics are administered.<sup>21</sup>

A few cases of bacteremia and/or sepsis associated with lactobacilli have been reported, but these cases just occurred in patients with underlying diseases, such as HIV, congenital heart disease, or other immunocompromised conditions. Occurrence of sepsis is very unlikely in healthy individuals that ingested probiotics even with the high number of bacteria it contains.<sup>22</sup>

To our knowledge, there are no reports of adverse effects of probiotics in healthy elderly people, but long term studies to assess the safety of probiotic supplementation in these population is needed consider the beneficial effects of probiotic supplementation in these population.

### Conclusions

Aging process leads to the changes in the gut microbiota. Normal gut microbiota responsible in the development and functioning of the immune system

of the gut mucosa. In elderly there is a decrease in variability and changes in the composition of the gut microbiota.

Probiotic supplementation can help to maintain gut microbiota homeostasis. Various studies have shown the role of probiotic supplementation in improving the body's immune system. However, there are some risk with probiotic supplementation in elderly that can lead to unwanted adverse effects, although it considered unlikely to happen in most elderly. Further research is needed so that probiotic supplementation can be applied safely in clinical setting as a supporting therapy to improve the health of the elderly.

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