Original Communication

# Healthy Effects Exerted by Prebiotics, Probiotics, and Symbiotics with Special Reference to their Impact on the Immune System

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**Abstract:** Pre-, pro-, and symbiotics are endowed with a broad spectrum of beneficial effects when administered to animals and humans. A series of experimental and clinical studies have clearly demonstrated that prebiotics, probiotics, or their combination are very effective in attenuating chronic inflammatory conditions such as inflammatory bowel disease or obesity. In addition, these natural products are able to prevent or arrest tumor development, acting on the intestinal microbiota as well as potentiating the immune response.Aging is characterized by a dramatic reduction of both innate and adaptive immune responses, the so-called immunosenescence. This leads to an increased incidence of infections, autoimmune diseases, and cancer in the elderly. Pre-, pro-, and symbiotic administration has been shown to ameliorate the immune response in aging. In particular, administration of a symbiotic to free-living elderly was able to potentiate the release of interleukin-8, thus increasing neutrophils in the host, perhaps explaining the reduced frequency of winter infections in the elderly.

**Key words:** aging, inflammation, prebiotics, probiotics, symbiotics

## Introduction

The intestinal microbiota or microflora [1] consists of several bacterial species with a very broad amount of strains [2]. In fact, microbiota encompasses more than 400 different bacterial species and strains per individual, in a total concentration up to $10^{11}$ or $10^{12}$ cells/g luminal content [3]. Metagenomic analyses have demonstrated that in adults the major constituents of the intestinal microbiota are represented by the phyla *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* [4].

Intestinal microbial homeostasis contributes to the maintenance of a healthy status mediated by a dynamic equilibrium between host and microorganisms. This is attained on a daily basis by virtue of the gut-associated lymphoid tissue function and, mostly, of Peyer's patches, which represent the major site of intestinal immune responsiveness [5]. The equilibrium between microbiota and the host contributes to

 DOI 10.1024/0300–9831/a000112

a healthy status throughout life. However, in aging, a decrease in *Anaerobes* and *Bifidobacteria* with an increase in *Enterobacteria* [6] has been demonstrated, a transition which is dependent on dietary changes, increased incidence of infectious events, and drugs administered for concomitant diseases.

The microbiota is in close contact with the intestinal mucosa or epithelial interface, forming the so-called mucosal barrier, a protective defense system against potentially immunogenic or pathogenic luminal agents.

The main functions of the microbiota are listed in Table I.

*Table I:* Major functions exerted by the intestinal microbiota.

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|---|
| – participation on the formation of intestinal wall |
| – production of short-chain fatty acids (SCFA) |
| – production of vitamins (especially B and K groups) |
| – interaction with the mucosal immune system |
| – degradation of xenobiotics |

Over recent years, dietary modulation of the composition and function of the intestinal microbiota has been attained by pre-, pro- and symbiotic administration [7–9]. Their potential health effects can be classified as alteration of the host immune response and of the colonic microbial ecosystem metabolism. Dietary factors may prevent the colonization of harmful or pathogenic bacteria such as *Clostridia*, sulfate-reducers, and certain *Bacteroides* species, thus establishing a predominance of potentially beneficial or health-promoting bacteria, *e.g., Lactobacilli* and *Bifidobacteria.* [10].

This review will focus on the modifications of intestinal microbiota with pre-, pro-, and symbiotics with the aim of preventing or ameliorating inflammatory chronic diseases, cancer, and age-related diseases.

# Dietary intervention

## Prebiotics

The term "prebiotic" means "a non-digestible food ingredient that selectively stimulates growth and/or activity of one or a limited number of bacteria in the colon, thereby improving host health" [11].

Inulin and oligofructose (or fructo-oligosaccharides), galacto-oligosaccharides, and lactulose are the major prebiotic compounds [12,13]. Plants containing inulin-type fructans are the Liliales, *e. g.,* leek, onion, garlic and asparagus or the Compositae, such as Jerusalem artichoke (*Helianthus tuberosus*), dahlia, and chicory (*Cichorium intybus*) [14,15].

*In vitro* and *in vivo* studies have clearly demonstrated that the colonic fermentation of inulin-type fructans enhances the production of butyrate, the so-called "butyrogenic effect" [16,17]. In *in vitro* fermentation studies, butyrate-producing bacteria (e. g., *A. caccae* and *R. intestinalis*) were shown to be unable to degrade oligofructose. By contrast, in the presence of *Bifidobacteria* and/or fermentation metabolites (acetate) or breakdown products, degradation occurred with corresponding butyrate production [18]. In particular, carbohydrate fermentation leads to the generation of SCFA, predominantly acetate, propionate, and butyrate [19]. Most of the SCFAs are absorbed and metabolized, thus providing energy to the host. Butyrate is mainly oxidized by the colonic epithelium and increased SCFA synthesis creates a more acidic environment in the gut [20]. This enhances the colonization resistance against pathogens [21], reduces the formation of secondary bile acids [22], and impairs the activity of specific enzymes such as proteases. Another important role of SCFAs on colonic physiology is their trophic effect on the intestinal epithelium, thus leading to epithelial cell proliferation and differentiation in the large and small bowel [23]. In addition, butyrate inhibits cell proliferation and stimulates cell differentiation in epithelial cell lines of neoplastic origin *in vitro* [24]. SCFAs possess anti-inflammatory capacities, affect satiety hormones, and mitigate insulin resistance [25]. There is emerging evidence that SCFAs not only exert effects in the colonic epithelial cells but also enter the circulation, thus influencing metabolic processes in other tissues and organs [26].

The effects exerted by prebiotics are illustrated in Table II.

## Probiotics

Probiotics are defined as "live bacteria which when administered in adequate amounts confer a health benefit to the host" [27]. These bacteria are devoid of any virulence properties or antibiotic resistance, while creating an unfavorable environment for pathogens [28].

Health benefits related to probiotic administration are illustrated in Table III.

In general, probiotic health benefits can be divided into three levels [29]. Probiotics can directly interact with the intestinal microbiota (level 1). They can act

*Table II:* Effects exerted by prebiotics within the host.

– stimulation of growth and/or metabolic activity of intestinal bacteria that are associated with health and well-being
– improvement and/or stabilization of gut microbiota composition
– improvement of intestinal functions (stool bulking, stool regularity, stool consistency)
– increase in mineral absorption and improvement of bone health (bone Ca content, bone mineral density)
– modulation of gastrointestinal peptide production, energy metabolism, and satiety;
– initiation (after birth) and regulation/modulation of immune functions
– improvement of intestinal barrier functions
– reduction of metabolic endotoxemia
– reduction of risk of intestinal infections
– reduction of risk of obesity, type 2 diabetes, metabolic syndrome
– reduction of risk and/or improvement in the management of intestinal inflammation
– reduction of risk of colon cancer

upon the intestinal mucus layer and epithelium (level 2), thus modulating both the intestinal barrier function and the mucosal immune system. Finally, probiotics can affect remote organ function outside the gastrointestinal tract, such as the peripheral immune system, the liver, and the brain (level 3). When compared to a single strain, probiotic mixtures seem to possess a wider range of health benefits even if they might also result in reduced efficacy. In fact, individual strains may exert opposite effects or even inhibit each other. However, more *in vivo* studies are needed to sustain the above contention.

## Symbiotics

Symbiotics result from the combination of pre- and probiotics. For instance, regular, long-term intake of various symbiotics has been shown to improve adult health by reducing the incidence and severity of respiratory diseases during the cold season [30], suggesting a synergistic effect of both probiotic and prebiotic ingredients. Symbiotics have also been suggested to alter the composition of the colonic microbiota, reduce inflammatory processes in the gut mucosa, and to have the potential to induce disease remission in inflammatory bowel disease (IBD) [31].

## Effects of pre-, pro-, and symbiotics on chronic inflammatory status

The colonization of the human intestine with the microbiota begins at birth [7], and breast-feeding represents one route for oral access of microbes and antigens. In addition, human milk provides to the newborn molecules with antimicrobial activity (e.g., lactoferrin) [32] as well as probiotics such as *Lactobacillus gasseri* and *Lactobacillus fermentum* [33]. In experimental models, prebiotics such as inulin and oligofructose have been associated with reduced mucosal inflammation and may offer an opportunity to prevent IBDs and other mucosal inflammatory disorders [34, 35]. IBDs are characterized by an impairment of both the epithelial mucosal barriers and the innate and acquired

*Table III:* Main effects exerted by probiotics within the host.

– promotion of the integrity of the gut defense barrier by normalizing intestinal permeability
– modulation of intestinal secretory immunoglobulin function
– control of intestinal inflammatory responses by balancing the release of cytokines
– maintenance of normal microecology of the gastrointestinal flora and antimicrobial effects mediated by nutrient competition
– alteration of local pH
– production of bacteriocins
– modification of pathogen-derived toxins
– stimulation of epithelial mucin production.

host immune responses, which facilitate penetration of luminal contents into underlying tissues. Consequently, the impaired clearance of foreign material from the bowel wall may lead to a chronic inflammatory response, thus provoking the characteristic IBD lesions [36]. The intestinal microbiota is important in the pathogenesis of IBD. In fact, it has been shown that intestinal inflammation does not develop in a germ-free environment [37]. Moreover, experimental colitis can be successfully treated with antibacterial agents [38]. Also diversion of intestinal contents improves the inflammatory pattern in IBD. Finally, in patients with Crohn's Disease (CD), systemic antibodies against microbial antigens have been detected [39].

The gut flora seems to contribute to the development of inflammation through secretion of quorum-sensing molecules or by direct damage to the epithelium *via* definable virulence properties of the bacteria. In particular, bacterial DNA can be an immunomodulatory component of healthy gut flora or can lead to persistent inflammation of the intestine. Of note, the mucosal-associated bacterial flora seems to be more pathogenically important than the luminal flora in IBD [40].

Patients with IBD lack their normal tolerance to commensal intestinal flora and bacterial components are recognized by Toll-like receptors (TLRs), thus contributing to the inflammatory response [41]. Moreover, mucosal bacterial concentration is abnormally increased in IBD, with concentrations correlating with severity of disease but not the extent of inflammation [42]. Microbially derived proteolytic degradation of the extracellular matrix may also contribute to the pathogenesis of IBD [43].

The effect of inulin-type fructans in modulating the IBD process has been repeatedly demonstrated in experimental models in which inflammation was induced by chemical agents such as dextran sodium sulfate [44] or trinitrobenzenesulfonic acid [45], or in the HLA-B27 transgenic rat, which spontaneously develops colitis. In each of these models, administration of inulin-type fructans (alone or as a symbiotic) reduced cytokines and improved clinical and histological markers. In humans affected by ulcerative colitis (UC), *Bifidobacteria* are about 30-fold lower compared to healthy individuals. Supplementation of oligofructose-enriched inulin together with a probiotic (*Bifidobacterium longum*) to UC patients for 1 month resulted in a dramatic increase in *Bifidobacteria* in mucosal biopsies. In addition, some patients showed improvement of the clinical course as evidenced by a decrease in sigmoidoscopy scores, proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1α, and increase in regeneration of the epithelial tissue [46]. In another clinical trial in patients with UC, oligofructose-enriched inulin decreased the levels of fecal calprotectin, thus improving response to therapy [44].

In patients with active CD, administration of a combination of inulin and oligofructose improved disease activity markers (reduction in Harvey Bradshaw Index), while enhancing lamina propria dendritic cell IL-10 production and TLR2 and TLR4 expression [47].

Obesity is a chronic inflammatory status characterized by an abnormal microbiota. In the obese, lower levels of *Bacteroidetes* and higher levels of the phylum *Firmicutes* in the colonic microbiota have been found [48]. Also, feeding high-fat diets induced a dramatic alteration of the microbiota composition in mice [49] with a metabolic shift towards a pro-inflammatory phenotype, weight gain, and impaired glucose metabolism. There is evidence that in high-fat feeding endotoxemia may account for some of the observed changes and, moreover, levels of endotoxemia negatively correlated with *Bifidobacterium spp.* Restoration of *Bifidobacteria* at gut level in mice following oligofructose supplementation reduced endotoxemia and improved mucosal barrier function [50]. Furthermore, levels of IL-1β, TNF-α, and plasminogen activator inhibitor type-1 in adipose tissue were reduced in comparison with unsupplemented, high-fat fed mice.

The above-described healthy effects are summarized in Table IV.

## Effects of pre- pro- and symbiotics on ageing

The decline of immunity in the elderly, the so-called immunosenescence, seems to account for an increased incidence of infection, cancer, and autoimmunity [51]. In aged people, immune deficits are very often combined with an involvement of both innate and adaptive immunity [52]. In elderly, T-cell receptors such as CTLA-4 and PD-1 deliver signals that deactivate T cells, thus accounting for increased chronic infections and tumor growth [53].

The effects of nutrients on the enhancement of immune function in the elderly have been studied, demonstrating that supplementation of zinc, vitamin E, and β-carotene led to an improvement of depressed immunity [54]. Furthermore, evidence has been provided that the host-intestinal microbiota alteration may account for so-called "inflammaging" [54]. In fact, a decline in viable counts of *Bacteroides* with increas-

*Table IV:* Effects of pre-, pro-, and symbiotics on the chronic inflammatory status.

– inulin-type fructans are able to improve histological, immunological, and clinical markers in experimental model of inflammatory bowel disease

– in humans with ulcerative colitis, supplementation with symbiotics could increase the number of Bifidobacteria and improve disease activity markers

– in high-fat fed mice, restoration of the intestinal levels of Bifidobacteria with oligofructose supplementation diminished endotoxemia and proinflammatory cytokine levels

ing age, mostly magnified by antibiotic therapy, has been reported [55]. Also, the species diversity within the genus *Bacteroides* is reduced in elderly compared with young counterparts [56]. *Bacteroides* species are responsible for the majority of polysaccharide digestion in the colon and changes at the species level could account for considerable consequences in the elderly host. Reduction in amylolytic activity in the healthy elderly population, and to a lesser extent, in antibiotic-treated elderly patients seems to correlate with the nutritional importance of *Bacteroides spp.*

*Fusobacteria* are known to ferment amino acids, resulting in the production of several detrimental endproducts such as ammonia and indoles [57]. A rise in these proteolytic bacteria as well as of *Clostridia* has been reported in elderly populations [58]. The decline in *Bifidobacteria* species diversity in elderly people seems to rely on the reduced adhesion to the intestinal mucosa, because of changes in the bacteria, and/or in the chemical composition and structure of intestinal mucus [59]. Such a decline may lead to a reduced immune responsiveness in the gut, and an increased susceptibility to gastrointestinal infections.

The immunostimulatory effects of probiotic preparations seem to occur through the regulation of pro- and anti-inflammatory cytokines [60]. Probiotics have also been shown to increase humoral immune responses, to enhance the intestinal immunological barrier [61, 62], thus facilitating immune elimination. Probiotics also downregulate reactions of hypersensitivity [63], such as food intolerance [64] and atopic eczema [65]. Vulevic *et al.* [66] reported an increased phagocytosis of *Escherichia coli* following probiotic administration to elderly volunteers for 10 weeks.

All the above-cited properties of probiotics may be advantageous in elderly people [67]. In fact, T-lymphocytes and natural killer (NK) cells were increased in elderly subjects by supplementation with *Bifidobacterium lactis* HN019 [68]. The *ex vivo* phagocytic capacity of mononuclear and polymorphonuclear phagocytes and the tumoricidal activity of NK cells were also elevated. Moreover, a double-blind feeding trial in elderly individuals, with a symbiotic containing *B. lactis* BL-01 and *B. bifidum* BB-02, used in association with inulin, led to a [55] significant increase in *B. bifidum*, total *Bifidobacteria***,** and total *Lactobacilli* numbers compared with the placebo. This dietary regimen led to a reduction of winter infections since normalization of the microbiota could likely prevent severe alterations of immunocompetent cells.

Finally, administration of a symbiotic [fermented cow milk containing *Lactobillus rhamnosus* GG (LGG) and oligofructose as a prebiotic] for one month to free-living elderly people led to an increase in serum levels of IL-1β, IL-6, and IL-8, while values of other cytokines such as IL-12, IL-10, and TNF-α were not affected by this dietary approach. Of note, baseline values of IL-12 and IL-10 were undetectable in these subjects, thus indicating a condition of impaired inflammatory/anti-inflammatory mechanisms. According to our data [69], it is reasonable to postulate that the symbiotics used may enhance innate immunity, mostly *via* IL-8 release, which is a chemoattractant for neutrophils. Influx of neutrophils to organs such as lungs may offer protection to the elderly host in the course of winter infections.

The above healthy effects on ageing are listed in Table V.

*Table V:* Effects of pre-, pro-, and symbiotics on ageing.

– Probiotics are able to increase innate and adaptive immunity when administered to elderly people

– Symbiotics are able to increase Bifidobacteria and Lactobacilli in aged people and enhance serum levels of IL-1β, IL-6, and especially IL-8

– Pre-, pro-, and symbiotics administration has been shown to reduce incidence of winter infections in the aged

## Conclusion

Taken together, the bulk of experimental and clinical data discussed support the beneficial effects exerted by the intestinal microbiota, mostly *via* communication with the epithelium and the innate and adaptive immune effectors. Alteration of this equilibrium in genetically susceptible hosts leads to a chronic inflammatory status and/or cancer of the bowel. Therefore, further investigations on those microbial species of the microbiota that are preferentially involved in the maintenance of gastrointestinal health seem to be necessary. This may provide useful information on the design of innovative dietary interventions with pre-, pro-, and symbiotics in disease-prone individuals.

### Acknowledgements

Paper supported by a grant from University of Bari, Italy (ex 60 %).

### Abbreviations

**ACF:** Aberrant crypt foci;
**CD:** Crohn disease;
**IBD:** Inflammatory bowel disease;
**IL:** Interleukin;
**LGG:** Lactobacillus *rhamnosus* GG;
**NK:** Natural killer;
**SCFA:** Short fatty acids;
**TLR:** Toll like receptor;
**TNF:** Tumor necrosis factor;
**UC:** Ulcerative colitis

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