Prebiotics and on Their Health Effects

Subjects: Others
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Prebiotic compounds were originally defined as “a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health”; however, a significant modulation of the definition was carried out in the consensus panel of The International Scientific Association for Probiotics and Prebiotics (ISAPP), and the last definition states that “prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit”.

Keywords: prebiotics ; health ; outcomes ; human ; pathologies

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1. Colorectal Cancer

Prebiotics could modify and positively affect the intestinal microbiota in patients affected by colorectal cancer (CRC). Inulin alone and in combination with GOS increased the production of SCFA [1][2][3], which probably determined a reduction (49.9%) in the number of colon polyps [2].

COS (chitosan depolymerised oligomers) had a positive influence on CRC, through an increase of *Akkermansia* (butyrate-producing microorganism) and *Cladosporium* spp. and a reduction in *Escherichia*, *Shigella, Enterococcus,* or *Turicibacter* levels [4].

Ohara et al. [5] observed the synergistic effect between FOS and *B. longum* which led to an increase in SCFA content and a suppressive effect on *Bacteroides fragilis* enterotoxin (ETBF) and on putrefactive bacteria.

In addition, marked anti-cancer properties were shown also by complex matrices with prebiotic action, such as Acacia gum with *Lpb. plantarum* [6], Yacon (known as the potato of diabetics) [7], seeds of Jabuticaba (an exotic fruit tree native to Brazil also known as grape tree) with *Lactobacillus delbrueckii* subsp. *bulgaricus* [8], jujube polysaccharides [9] and polysaccharides isolated from Nostoc commune Vaucher [10].

2. Psychological and Neurological Conditions

2.1. Cognitive Functions

Several researchers reported a possible effect of prebiotic compounds on stress and cognitive functions. Berding et al. [11] studied the effects of the consumption of vegetables, fermented foods, and prebiotics in adult subjects through Cohen’s scale and found a reduction in perceived stress, while Mysonhimer et al. [12] only found a positive reading of *Bifidobacterium* spp. after the consumption of FOS without a clear connection with mental health.

Prebiotics could also affect cognitive functions. For example, Azuma et al. [13] studied the effect of a beverage containing inulin on Japanese women or men (50–80 years) and assessed biochemical and immunological parameters, the quali-quantitative composition of the microbiota of fecal samples, the cognitive functions through Cognitrax (a computer-based battery of cognitive function tests), and quality of life on eight scales (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health); the results revealed the improvement in the scores of three domains of cognitive functions (attention, flexibility, and executive functions), probably linked to an increase in bifidobacteria and to a slight modulation of some inflammatory markers.

A possible effect on attention and on some other cognitive functions (including flexibility) was also found by Berding et al. [14], who studied the effect of polydextrose. These authors concluded that the improvement in the cognitive functions could be the result of the modulation of *Ruminococcus* 5, which in turn could be responsible for the decrease in some inflammatory markers.

2.2. Stress, Anxiety, and Depression

Prebiotics could also play a role on stress, anxiety, and depression, probably linked to a reduction in perceived stress [14], as a result of the modulation of *Bifidobacterium* spp. or of other taxa of gut microbiota [12].

Leo et al. [15] used α-lactalbumin (ALAC, a seroprotein with high biological value) combined with sodium butyrate (NaB), a postbiotic, to evaluate the effects on anxiety and depression on mice. This combination resulted in a valuable aid against depressive phenomena and anxious states by relieving symptoms and by reducing intestinal inflammation; in fact, the administration of both compounds resulted in behavioral improvements (improved sociability and memory and reduction in repetitive behavior) and increased motility [15]. According to the authors, ALAC would act on the intestinal composition and NaB would show a direct effect on the brain; moreover, NaB is a histone deacetylase inhibitor (hdaci) playing a role in neurodegenerative and neurological developmental diseases including epilepsy.

The role of prebiotics on depression is controversial, although preliminary data suggest the existence of possible correlation, as hypothesized by Tarutani et al. [16], who reported an improvement in the self-efficacy scores after the consumption of galactosylsucrose in patients with depressive episodes.

2.3. Autism

nother effect resulting from the use of GOS combined with *Limosilactobacillus reuteri* and *B. longum* was a higher survival of probiotic strains, suggesting that GOS exerts a protective effect [17].

A restriction diet (free of gluten and casein, responsible for inflammation phenomena), associated with the intake of B-GOS, was administered to autistic children with positive effects on sociality and behavior. In addition, the prebiotic acted as a growth stimulator of *Faecalibacterium prausnitzii*, an anaerobic butyrate-producing microorganism in the human colon [18].

2.4. Schizophrenia and Parkinson

Prebiotics were also studied as active components in controlled trials on patients affected by schizophrenia and Parkinson. The data should be carefully confirmed and corroborated by other studies, due to the complexity of these pathologies and to the high number of variables playing a role, but there are some promising results, which suggest the possibility of using prebiotics as co-adjuvants to ameliorate the symptoms.

In particular, the consumption of raw materials with prebiotics (green leafy vegetables, high-fiber fruit, whole grains) improved the general cardio-metabolic profile in patients with schizophrenia spectrum disorders [19], while inulin, resistant starch, resistant maltodextrin, and rice bran played an active role in reducing the markers of inflammation (plasma zonulin and stool calprotectin), positively affected gut microbiota composition with an increase in SCFA, had a clinical impact leading to reduced severity of motor and non-motor Parkinson's disease symptoms and improved gastrointestinal function [20].

3. Intestinal Diseases

3.1. Inflammatory Bowel Disease

About 25 years ago, Kennedy et al. [21] demonstrated the effectiveness of inulin in relieving inflammatory bowel disease (IBD) through a study conducted on mice with colitis provoked by dextran sodium sulfate (DSS); the daily oral administration of the prebiotic led to an increase in indigenous lactobacilli in the cecum and to a reduction in the pH of the colon. Moreover, the mucosal inflammation and histological damage scores were reduced as well as a lower degree of mucosal damage was observed [21]. Several years later, Koleva et al. [22] combined inulin with FOS to feed transgenic rats and observed a reduction in intestinal inflammation and increased levels of intestinal bifidobacteria and lactobacilli. They also found a decrease in mucosal proinflammatory cytokines.

Similar effects were observed by using resveratrol, in mice with DSS-induced colitis [23]; in fact, increased levels of *Bifidobacterium* and *Lactobacillus* were observed, along with lower amounts of *E. coli* and Enterobacteriaceae.

Other human studies showed the ability of inulin and FOS in combination with *Bifidobacterium* to reduce inflammation and TNF (Tumor Necrosis Factor) and IL-1a (Interleukine-1a) [24].

Valcheva et al. [25] fed 25 ulcerative colitis (UC) patients with 7.5 or 15 g/day of fructans for 9 weeks. Patients in the high-dose group showed a significant increase in colon butyrate production and improvement of colitis. Moreover, inulin and FOS improved clinical symptoms and *Bifidobacterium* population even in patients with Crohn's disease who were exposed to these prebiotics for four weeks [26].

Lindsay et al. [27] studied the effects of FOS in patients with Crohn's disease: 15 g of FOS were administered for 3 weeks in 10 patients. FOS supplementation reduced the HBI score (HBI, index assessing the degree of disease activity), increased fecal *Bifidobacterium* concentrations, and increased the percentage of IL-10-positive dendritic cells (DCs).

3.2. Irritable Bowel Syndrome

GOS, oligosaccharides, inulin, and fructans are the main prebiotics often involved in ameliorating irritable bowel syndrome (IBS) symptoms, although the results are controversial [28][29]. Azpiroz et al. [30] described the influence of prebiotics on anxiety level of IBS individuals and concluded that FOS significantly reduced anxiety scores and increased fecal bifidobacteria. Wilson et al. [31] concluded that prebiotics did not lead to an improvement in the symptoms of the disease but rather favored the increase in bifidobacteria. However, when 44 patients received GOS as prebiotic, not only was an increase in the number of bifidobacteria observed, but also some symptoms, such as flatulence, abdominal pain, and discomfort resulted improved [32].

3.3. Enteric Syndrome

Prebiotics positively affect enteric syndrome, a severe congenital enteropathy, characterized by intractable diarrhea in the first month of life, associated with growth retardation, facial dysmorphism, hair abnormalities and, in some cases, immune system disorders and intrauterine growth restriction [33]. It could be treated with antibiotics, but as reported by Ayala-Monter et al. [34], their improper use can cause bacterial resistance; thus, prebiotics and probiotics appear to be valid alternatives.

Each prebiotic compound can stimulate the growth of lactobacilli and bifidobacteria in the gut. For inulin, significant increase in the percentage of basophils, improvement in the body's immune response, and significant reduction in diarrheal phenomena were also observed, while catechins showed a marked ability to stimulate SCFA production [33][35]. A synbiotic action of inulin + *Lcb. casei*, compared to the sample treated only with inulin, favored the increase in lactobacilli and the reduction in total coliforms, improving the use of nutrients introduced with the diet [34].

4. Obesity

A common effect of flavanols, decaffeinated green and black tea polyphenols, aqueous extracts of tea, marc, cinnamon, inulin, vanillin, and lignans is the reduction in the Firmicutes/Bacteroidetes ratio [36][37][38][39][40][41]. This ratio is considered as a possible hallmark for obesity, as it is high in obese people and tends to decrease following weight loss. In fact, Magne et al. [42] observed the increased abundances of Firmicutes in obese animals and humans, due to the fact that they are more efficient in extracting energy from food than Bacteroidetes, thus promoting a higher calorie absorption and a consequent weight gain. However, in the case of following a low-calorie diet for 12 months, Bacteroidetes increased, with the consequent normalization of the Firmicutes/Bacteroidetes ratio, along with weight loss [42]. *Bacteroides* can reduce serum triglyceride levels, improve glucose intolerance, and counteract body weight gain [36].

Flavanols and aqueous extract of tea were also able to promote the growth of *A. muciniphila* [36][38] and similarly did other potential prebiotic compounds, such as cranberry extract, apple procyanidins, aqueous tea extracts, resveratrol, pterostilbene, and catechins [43][44][45][46][47].

The role of inulin-type fructans (ITF) (carbohydrates consisting of β-(2-1)fructosyl-fructose units) is also important, as they can modulate the intestinal microbiota composition in obese women by stimulating the growth of *F. prausnitzii* [48].

ITF, resveratrol, catechins, flavanols, promote the growth of bifidobacteria, which play an essential role in fighting obesity [43][45][48][49] as they modulate the secretion of ghrelin, a hormone that regulates the sense of appetite in vitro, highlighting their therapeutic potential [17].

A positive effect on *Bifidobacterium* spp., also linked to a modulation of fecal calprotectin and to an increase in rumenic and linolenic acids, was evidenced by Neyrinck et al. [50] during a 3-month, multicentric, single-blind, placebo-controlled trial. The most important outcome was the strong reduction in calprotectin, thus emphasizing the potential interest of prebiotic intake to combat gut inflammatory disorders occurring with obesity.

This effect on inflammation was also reported by Crovesy et al. [51], who combined FOS with a probiotic (*B. animalis* subsp. *lactis*), and by Lyon et al. [52], who studied the effect of a combination of inulin from chicory with a complex mixture of probiotic microorganisms (lactobacilli, bifidobacteria, *Bacillus*, *Streptococcus*, *Saccharomyces*).

Other compounds (soy isoflavones, pomegranate extract, arctic berries, pollen extract, and genistein) positively affected gut microbiota composition and favored weight loss [53][54][55][56][57][58].

Positive effects of prebiotics on obese patients also include a reduction in the levels of cortisol with a direct effect on sleep quality [59], a significant decrease in plasma triglycerides [60], and a reduction in waist and hip circumferences [57].

5. Diabetes

COS and ITF were the most used prebiotics in diabetes; these compounds, alone or combined with probiotics, exert various beneficial effects. Some studies on mice highlight that COS reduces hyperglycemia and hyperlipidemia and prevents obesity. In addition, it positively affects the composition of the gut microbiota; in fact, it favors the abundance of Firmicutes, Bacteroidetes and Proteobacteria [61], as well as Actinobacteria and Lachnospiraceae populations [62]. In addition, COS reduces blood glucose levels (BGLs) [62].

Just like COS, ITF also promotes a reduction in BGL; other effects are a reduction in fasting blood glucose (FBG), a lower Firmicutes/Bacteroidetes ratio, and increased levels of *Phascolarctobacterium*, *Lachnoclostridium* [63], *F. prausnitzii* and bifidobacteria [64].

In particular, Birkeland et al. [64] found that ITFs are responsible for the production of acetic and propionic acid; in fact, patients with diabetes have lower levels of butyrate-producing intestinal microorganisms and often occurs that the severity of the disease intensifies.

Zhang et al. [65] evaluated the interactions between plant extracts (bitter gourd extract, BGE and mulberry leaf extract, MLE) and potential probiotics (*Lcb. casei* K11 and *Lacticaseibacillus paracasei* J5) on mice; both extracts provided interesting results. In fact, microbial targets showed a marked vitality in the gastrointestinal tract. In addition, the interactions *Lcb. casei* K11-BGE and *Lcb. casei* K11-MLE significantly reduced BGL and improved insulin resistance in diabetic mice. *Lcb. casei* K11 with both plant extracts also modulated lipid metabolism, proinflammatory cytokine levels and oxidative stress; in addition, it led to an improvement of glucagon-like peptide-1 (GLP-1) secretion, SCFA levels, and free fatty acid receptor 2 (FFAR2) upregulation.

6. Metabolic Syndrome

N acetyl-chitooligosaccharide (NACOS) and proanthocyanidins extracted from grape seeds resulted in a reduction in Firmicutes [66][67][68]; however, most studies with phenolic extracts did not produce definitive clinical evidence, as patients generally involved in the trial are poly-medicated subjects affected by several variables [69].

NACOS improved glucose tolerance and inhibited lipid accumulation in the liver [67]. In addition, by monitoring fasting blood glucose (FBG), mice fed with NACOS actually had lower fasting glucose, and by measuring plasma insulin, it was found that feeding NACOS greatly promoted insulin secretion [66].

Concerning pro-anthocyanidins of grape seeds, they exerted a positive effect on satiety-related enterohormones (glucagon-like-peptide-1, GLP-1; ghrelin) as they led to a significant increase in GLP-1, and, therefore, to an improvement in glucose tolerance, and an induction of satiety, strengthened by the increase in ghrelin [68].

7. Osteoporosis

FOS and GOS were essential to a better absorption of calcium, better density, and resistance to bone wear [70][71][72][73].

In a study conducted on animal models, the treatment with FOS recorded higher levels of serum alkaline phosphatase (ALP a marker enzyme of bone formation, used in the diagnosis of skeletal and liver diseases) and femurs with higher resistance. Increased bone density can lead to greater bone strength, reducing the risk of fracture [70].

Interesting was the study conducted by Johnson et al. [72] who compared antibiotics and prebiotics administered in mice. After 10 weeks of treatment with alendronate (a drug given for osteoporosis, especially in menopausal women), bone mineral density increased by 7.31%. The best results were obtained for FOS + dried prune treatment, which led to an increase of 36%. Hence, the combination of these two compounds has shown results that are equivalent to and can surpass those of conventional drugs [67]. Other data were reported by Wu et al. [74], who studied calcium absorption in premenopausal women with history of RYGB (Roux-en-Y gastric bypass).

8. Immunosenescence

Several articles focused on immunosenescence; it consists of the gradual deterioration of the immune system, due to natural age advancement; it involves both the host's capacity to respond to infections and the development of long-term immune memory.

In immunosenescence, gut microbiota composition is not constant but change with aging, and these changes have been linked to declines in immunity; however, it has been demonstrated that the maintenance of a "youthful" and "healthy" gut microbiota could positively affect by delaying immunosenescence [75]. Therefore, probiotics and prebiotics perform the function of reducing the proinflammatory response and improving innate immune dysfunction in the elderly.

Syringaresinol (SYR), a lignan occurring in plant foods (oilseeds, cereal brans, and various berry seeds) act as antioxidant, antistress, antitumorigenic, and anti-inflammatory compound; although at present the mechanism is not yet well understood, the compound can delay immunosenescence by modulating the immune system and the composition of gut microbiota. Si-Young et al. [75] reported that SYR effectively delayed immunosenescence by increasing the number of total T lymphocytes, which identify the antigen and activate the immune response, by implementing a protection against infections by intracellular microorganisms such as viruses and some bacteria [75]. Moreover, SYR reduced the Firmicutes/Bacteroidetes ratio; furthermore, it markedly increased the *Bifidobacteriium* and *Lactobacillus* (*B. animalis*, *Lactobacillus johnsonii*, *Lim. reuteri*) population, compared to control samples. Conversely, potentially opportunistic genus members, Bacteroidaceae, *Bacteroides vulgatus* and *Staphylococcus lentus*, were adversely affected [75].

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