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Review Article

Effect of Prebiotics on Gastrointestinal System

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Abstract

Prebiotics are selectively fermented ingredients that allow beneficial changes in the gut microbiota and, according to their definitiononly two food carbohydrates can be considered as prebiotics: inulin-type prebiotics andGalacto-oligosaccharides. Recent studies suggest an anti-inflammatory action and an antioxidant capability of inulin, which is resistant to cooking and digestion.The interaction between dietary intake,microbiota and gastro-intestinaldisease is now emerging, and prebiotics,such as inulin,represent a novel treatment option thanks to their beneficial properties.

Keywords: Prebiotics;Inulin; Microbiota; Diet; Inflammatory Bowel Disease

Prebiotics and gastrointestinal disorders: role of antioxidant activity

Prebiotics were defined by Gibson and Roberfroidin 1995 as "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host wellbeing and health"[1]. The introduction of the concept of prebiotics augmented the number of scientific studies as well as industrial interest, even if the prebiotic activity has been associated to many oligosaccharides and polysaccharides (including dietary fiber) without considering the right criteria[2]. Indeed, according to their definition, prebiotics must fulfill the following criteria, which are to be proven by in vitro and in vivo tests in the targeted species (i.e., humans, livestock, or animals):

1. resistance to gastric acidity, hydrolysis by digestive enzymes and Gastro-Intestinal (GI) absorption;
2. fermentation by intestinal microflora which can be measured in vitro by adding the respective carbohydrates to suspensions of colon contents, or pure or mixed bacteria cultures in an anaerobic batch or continuous culture fermentation system[3];
3. Stimulation of the growth and/or activityof intestinal bacteria beneficially associated with health and well-being[4].In vivo studies have also confirmed the bifidogenic effect of prebiotics [2,5].

Until now, it must be emphasized that only two food carbohydrates, essentially non-digestible oligosaccharides, fulfill the criteria of prebiotic classification: inulin-type prebiotics andGalacto-oligosaccharides. Data are promising for other substances, but more studies are still required[4]. Inulin-type prebiotics are members of a larger group called "fructans." Fructansinclude all oligo- and polysaccharides in which one or more fructosyl-fructose linkages incorporate the majority of glycosidic bonds. Fructans can have at least one fructosyl-glucose linkage and, when present, this bond is typically the first in the polymer chain[6]. Fructanscan also be described by their Degree of Polymerization (DP) which refers to the number of repeat units in an oligomer or polymer chain, so DP of an individual fructan would be its number of repeating fructose units[6].

Inulin-type prebiotics have beta (2-1) fructosyl-fructose glycosidic bonds[2]whichgive them their unique structural and physiological properties. In the human intestine the enzymes that hydrolyze the polymer bonds of these prebiotics are lacking so they can resist to small-intestinal digestion and reach the colon intact where

they undergo fermentation by bacteria[6]. Inulin-typeprebiotics can be extracted from a food source,or synthesized from sucrose. In either case, the resultant prebiotic consists of mixtures of inulin-type fructan molecules with varying DP; most frequentare inulin, oligofructose, and FructoOligoSaccharides (FOS)[6].

Many prebiotic carbohydrates are present in the normaldiet. For example, inulin-type fructans are found in a relativelylarge amounts in chicory root,Jerusalem artichoke and garlic, but they are also present in smaller amounts incereals such as wheat[7]. The ingestion of oligofructose or inulin in a solid or liquid meal seems to have no side-effects[8,9].Modest daily intake (2.5-5 g) of inulin-type prebiotics can have a bifidogenic effect in adults[9,10]. Bouhnik et al.[11]conducted a dose-response trial of FOS supplementation to a group of healthy volunteers and concluded that the minimum dose of prebiotics able to induce a bifidogenic effect in healthysubjects consuming their usual diet is 10 g/daily. However, the ingestion of higher quantities of prebiotics in healthy individuals may lead to flatulence, abdominal pain and diarrhea, sincetheir fermentation takes place mostly in the colon[12].

Unlike healthy human subjects,patients experience a number of issues that may alter theirmicrobiota (disease, use of antibiotics and inflammation) and themanipulation of the microbiota as a therapymay not have the same effects in patients as they do inhealthy people. The interaction between dietary intake,microbiota and GI disease (i.e irritable bowel syndrome, inflammatory bowel diseases) is now emerging, in part due to the development of more scientific approaches to examine dietary intake, complex microbial community and disease outcomes. Prebiotics,such asinulin, exhibit several health benefits likereducing the prevalence and duration of diarrhea, relief from inflammation and other symptoms associated with intestinal bowel disorder and protective effects to prevent colon cancer[13]. Irritable Bowel Syndrome (IBS) is a disorder in whichthe microbiota is thought to play an important role and, in particular, the relative lower numbers ofbifidobacteria in diarrhea-predominant IBS has suggestedthe use of prebiotics in its management[14]. The obtainedresultsshowed that both the type and doseof prebiotic is important in determining any clinical benefitin IBS, with some evidence that higher doses may have anegative impact on symptoms[14-17].

Inflammatory Bowel Disease (IBD) is chronic, relapsing, multi-factorial disorder causing inflammation of the gastro-intestinal tract and affects both the colon and small intestine,including Ulcerative Colitis (UC) and Crohn's Disease (CD)[13].The pathogenesis of IBD has not been fully clarified, but both genetic and environmental factors, including gut microbiota, seem to be involved[17]. Indeed, there is growing interest in the hypothesis that gut dysbiosis can result in the immune impairmentassociated with IBD. It has been shown that commensal microbiota protects the mucosa from inflammation by decreasing intestinal permeability and increasing epithelial defense mechanisms[17-19].It is well known that the drugs conventionally usedto induce and maintainremission in IBD (such as aminosalicylates, corticosteroids, immunesuppressantsand biologics) suppress theimmune response and have no effect on the microbiota[20].Antibiotic-mediated microbial manipulation hassome efficacy, especially in active CD and pouchitis, butcannot be used to maintain remission because of lack oflong-term efficacy and side effects[18,21,22].Therapies such as prebiotics andprobiotics that selectively manipulate the gastrointestinalmicrobiotarepresent a novel treatment option.In patients with chronic pouchitis, treated with 24g per day of inulin,a significant reduction in the number of bacteriodetes was reported [23].In another randomized study involving 103 Crohn's Disease patients who received FOS 15g/day, no clinical improvementwas reported, but a reduction of IL-6 of lamina propria dendritic cells though no change in IL-12 was observed[24].

Toll like receptor-4 (TLR-4) is an important receptor of bacterial endotoxin and it has been shown to play a pivotal role in the gut-liver axis: modulation of gut microbiota, using probiotics, prebiotics and antibiotics, to reduce the amount of TLR-4 ligand, produces beneficial effects on the liver, at least in the context of NAFLD[25]. The current most popular targets for prebiotic use are lactobacilli and bifidobacteria because of their spread use in the probiotic area[5]. However, as our knowledge of the gut microbiotaimproves, it may become apparent that other microorganisms could benefit from their use, such as ClostridiumcoccoidesorEubacteriumrectale cluster that includes bacteria producing butyric acid, a beneficial metabolite for gut functionality and potentially protective against bowel cancer[5,26].

Food additives and oxidative stress

At high levels,Reactive Oxygen Species (ROS) exert oxidative stress on cells by inducing harmful effects and significant changes in gene expression. Intracellular oxidative stress can provoke a significant damage to DNA, RNA and proteins thus affecting the normal cellular metabolism and, eventually,can lead to programmed cell death[27].In the last years an increasing amount of data support the hypothesis that different oligosaccharides or purified vegetable, fungal and animal polysaccharides exert an antioxidant activity[28,29].

A recent study suggested that synthetic oligosaccharides have free radical scavenging activity;sincetheirintraperitoneal administration significantly decreased the lipid peroxidation in a dose-dependent manner[30]. In this study,oligosaccharides were synthesized using glucose as reactant and their antioxidant activity was evaluatedin vivo and in vitro. Oligosaccharides exhibited antioxidant activity in vitro when compared to standard antioxidants such as Butylated Hydroxyl Toluene (BHT), and alpha-tocopherol. In addition, increased endogenous lipid peroxidation and decreased

Total Antioxidant Capacity (TAOC) were observed in aged mice; in this animal's model, thirty-day intraperitoneal administration of oligosaccharides significantly decreased the lipid peroxidation in a dose-dependent manner. Moreover, oligosaccharides treatment increased TAOC and the activity of Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSH-Px) in all organs tested in aged mice, suggesting that the synthetic oligosaccharides can play an important protective role for their significant free radical scavenging activity[30]. It was already known, from previous studies, that simple sugars such as Mannitol(Mit), Raffinose(Raf) and Galactinol (Gol) are recognized as antioxidants in plants and that the inulin is the most promising scavengers of O2 [31]. Stoyanova et al. have shown that inulin, together with other sugars (stevioside, trehalose and malic acid) has a strong in vitro scavenging activity to the radical O2[29]. The addition of these sugars to the diet should ensure a rapid response against oxidative stress, exerting a protective role in the critical period preceding the activation of the other (classic) antioxidant systems[32].

Moreover Kanner et al.[33]have shown that gastric acid secretions can promote the oxidation of lipids and other food constituents. According to their studies, dietary antioxidants (including inulin) may play a role in preventing lipid peroxidation in the stomach. In general, the dietary supplementation with inulin or oligofructose contributes to the protection from oxidative stress, consequently preventing inflammatory reactions associated with OS[34,35]. Furthermore, dietary supplementation with inulin-type prebiotics seems to be effective in preventing hypertension induced by a diet high in fructose; these effects are associated to long-chain polysaccharides (inulin)[36].In addition, these foods are extremely stable to a wide range of pH and temperature[37] and it has been recently shown that they are able to inhibit the degradation of ascorbate (ASC).This evidence are in agreement with the capability of inulin and other "sugar-like" elements to replace the vitamin C as dietary supplement and / or to limit its degradation.

As recently demonstrated, fructans show an antioxidant capability higher than sucrose, glucose and fructose[38], suggesting that the antioxidant feature is typical of FOS. Indeed the fructan antioxidant capability seems also to be influenced by the DP and/or the presence of branches in the molecule. In particular, linear fructans with low DP (i.e inulin Frutafit IQ®) and branched fructans (agavins) seem to have the highest antioxidant capability. Furthermore, the antioxidant capability of inulin IQ appeared resistant to cooking and digestion. Intriguingly this data makes more interesting the antioxidant feature of FOS, being generally the main water-soluble antioxidants quite unstable [38].

Antioxidant activity of inulin and its role in the prevention of human colonic muscle impairment

The antioxidant action of inulin-type fructansisdueto the ability of these compounds to contrast oxidative stress through a removal of direct and / or indirect ROS mechanism. It is believed that these molecules can act indirectly as a scavenger of ROS, thanks to the action of short-chain fatty acids (SCFAs) resulting from their fermentation in the colon; moreover they can also stimulate the activity of antioxidant enzymes Glutathione S-Transferases (GSTs)[27]. Therefore, inulin-type fructans could be partially absorbed by intestinal epithelial cells anddirectlyact as a powerful scavenger of ROS, stunting growth and development of pathogensthat can be stimulated by ROS derived fromgastrointestinal anti-inflammatory responses[29]. Similarly,these fructans could be able to neutralize extracellular ROS produced by the action of NADPH oxidase and other oxidases in the epithelial cell membrane of the colon or arising from the '"oxidative burst" resulting from the activity of blood neutrophils[27]. We recently demonstrated the protective effect of inulin on Lipopolysaccharide (LPS)-induced damage of colonic smooth muscle in an ex vivo experimental model, which seems to be related to the presence of oxidative stress[38]. LPS is known to play an important role during multisystem organ failure and it has been shown, in animal models, that end toxemia results in a significant impairment of intestinal smooth muscle contractility[39,25].

The beneficial effect of inulin on LPS-induced muscle cell impairment is due to the ability of this fructan to contrast the oxidative stress induced by LPS in the human colonic mucosa sincethe level of protein oxidation induced by LPS exposure was significantly reduced by inulin treatment[38]. In addition, in this study it was interesting to observe that the antioxidant capability was significantly higher when the colonic mucosa was exposed to LPS andInu® IQ when compared to the LPS exposure alone. This finding supports the hypothesis that inulin counteracts the release of free radicals (H2O2) and it seems to protect the human colon mucosa from damage induced by LPS. However, the specific mechanisms by which inulin acts on intestinal muscle function and the molecular mechanisms involved in the direct and/or indirect response of colonic mucosa to this prebiotic are not well elucidated.

Data from a recent studyconfirm the protective effect of inulin on the LPS induced colonic mucosal oxidative stress and muscle impairment. UsingTRAQ analysis,it was demonstrated that inulin has restored the level of some important protective

proteins, involved in inflammatory processes and it was able to avoid smooth muscle contraction impairment preventing the LPS-dependent modification of some proteins involved in the intestinal smooth muscle contraction[40].Some of the effects of inulin-type prebiotics are summarized in table 1.

Prebiotic	Effect	Ref.
Inulin-type-fructans	Stimulate the activity of the antioxidant enzymes glutathione S-transferases	27
Inulin	Scavenger activity to the radical O2	29, 32
Inulin	Prevent lipid peroxidation in the stomach	34-35
Inulin and other "sugar-like" elements	Replace the vitamin C as dietary supplement and / or to limit its degradation	37
Inulin-type prebiotics	Inhibit the degradation of ascorbate	37
Inulin	Protective effect on LPS-induced damage of colonic smooth muscle	38,40

Table 1: In vitro effects of inulin-type prebiotics.

Due to their antioxidant and anti-inflammatory action, these moleculescould be used in the prevention and treatment of GI diseases in which oxidative stress plays a pivotal role in their pathogenesis. On this purpose, more in vitro or clinical studies are warranted.

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