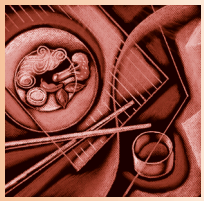

Inulin and Oligofructose

New Scientific Developments

Glenn R. Gibson, PhD
Nathalie Delzenne, PhD

This article explores the potential role of inulin-type fructans in the human diet, focusing on scientific developments presented at the 5th Orafti Research Conference held at the Harvard Medical School in 2006, with special emphasis on the effects of inulin and oligofructose on the modulation of the gut microbiota and their effects on human health.
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For more than a decade, there has been a rapid increase in the use of functional foods and ingredients in the Western diet, such as prebiotics, probiotics, long-chain n-3 fats, and polyphenols.[1] Functional food ingredients are those that possess physiological food values over and above their normal nutritional properties. They offer a user-friendly approach toward improving health. Many have attracted support from the scientific literature, notably the inulin-type fructans, inulin and oligofructose, which are indigestible carbohydrates originating from plant material. Inulin and oligofructose ingredients from chicory roots have been developed for human and animal nutrition by the Orafti/Palatinit ingredients unit of the Sudzucker group. The company's research strategy has contributed in a major way to current knowledge that exists on the effects of inulin and oligofructose on human and animal health and well-being. This research builds upon previous in vitro animal and human studies and provides evidence of diverse health benefits, which has been disseminated in research conferences on inulin and oligofructose, which are sponsored by the company.

What Are Prebiotics?

Prebiotic was defined more than a decade ago as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon, and thus improves host health."[2] Later, 3 major criteria were identified that must be met before an ingredient could be defined as a prebiotic,[3] namely, that it should

1. be *nondigestible*, that is, after ingestion, it should resist the acidity of the stomach and the effects of digestive enzymes in the small intestine, thus entering the colon intact;
2. be *fermented* by bacteria in the colon; and
3. *selectively stimulate* the growth and/or metabolic activity of beneficial bacteria indigenous to the colon. Bifidobacteria and lactobacilli are the usual target genera, usually classified as dietary fibers. Major food sources are onions, garlic, leeks, bananas, artichoke, and asparagus. The daily per capita intake of inulin and oligofructose in the United States is estimated to range from 1 to 4 g, whereas in Europe, intakes range from 3 to 11 g, depending on the geographic, demographic, and other related parameters (age, sex, season, etc).[4]

Prebiotics, probiotics, and synbiotics are all now being marketed in the United States.

The term *synbiotic* has been coined to describe combinations of prebiotics and probiotics. Probiotics are live beneficial bacteria that improve the gut flora composition. Synbiotics can be used to improve the survivability of live probiotic bacteria by providing a selective growth substrate in tandem. However, the use of probiotics in food is somewhat limited by their vulnerability to cooking and storage, which might lessen viability of the probiotic bacteria. Hence, they are most often added to dairy products. Concerns about probiotic survivability not only during food manufacturing and preparation but also after ingestion[5] have stimulated interest in prebiotics because their inert nature ensures resistance to processing and

digestion. Examples of prebiotic products include yogurts, cereals, infant feeds, breads, drinks, table spreads, snack products, sauces, and confectionery.

Focus on Inulin-type Fructans

Inulin and oligofructose are linear polymers consisting of fructose monomers linked to each other by β-(2→1) bonds (Figure 1). These bonds are resistant to mammalian digestive enzymes and extremes of pH found in the human gastrointestinal tract. Therefore, inulin and oligofructose escape hydrolysis in the upper intestine and reach the colon intact, where they are selectively fermented by indigenous bacteria.

The selectivity of the colonic fermentation by bifidobacteria and lactobacilli provides the mechanism underpinning the proposed health benefits associated with inulin-type fructans. The gut is in the vanguard of bodily defenses against potentially harmful microorganisms originating from food, the environment, or the gut itself. Central to this defense system is the composition of the microflora that naturally inhabit the intestinal tract. These are thought to play an active role in promoting resistance to colonization, and beneficial species may also inhibit the establishment of potentially harmful species.

The composition of the diet plays an important factor in this process because dietary components that arrive in the colon are metabolized by the microflora, and therefore, they can influence the overall balance of different microbiological species. For example, low-fiber and high-protein diets induce proteolysis and can encourage the growth of proteolytic bacteria,

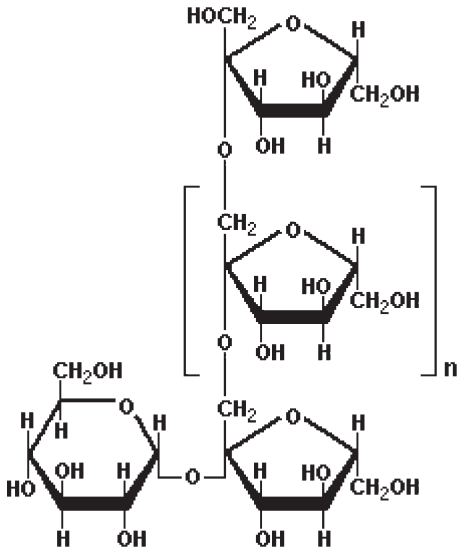

Figure 1. Chemical structure of inulin-type fructans.

eliciting metabolites such as ammonia, *p*-cresol, and others which are believed by some scientists to have detrimental effects on mucosal cells.[6] In contrast, diets containing fermentable carbohydrates induce a shift toward more saccharolytic fermentation, thereby increasing the levels of organic acids, such as lactic acid, and short-chain fatty acids, such as acetic, propionic, and butyric acids, which scientists believe may be beneficial. Butyric acid has been extensively studied because of its ability to promote normal cell turnover and functioning of the epithelia.[7]

Human intervention trials on the prebiotic effect of inulin-type fructans have consistently shown an increase in the numbers of lactobacilli and bifidobacteria.[3] Both genera are inhibitors of common pathogens and are recognized as important for enhancing gut defenses.[8] Inulin-type fructans therefore modulate gut microbial ecology and induce biochemical, genetic, and physiological changes in the gut that are thought to help maintain overall health and well-being.

Inulin-type fructans are extracted from chicory root, which grows widely in Europe.

Inulin-type fructans are extracted from the chicory root, which is a natural rich source and a ubiquitous crop in Europe. The resulting ingredients resemble a fine powder or syrup and can be used in a wide variety of food and beverage products to deliver functional benefits and as sucrose or fat replacers. Native inulin consists of a range of fructan oligomers or polymers with degrees of polymerization of 3 to 60. Oligofructose is an inulin-type with short chains (degrees of polymerization of 3-8, with an average of 4) and is fermented in the more proximal part of the colon. Long-chain inulin (average chain length of 25) is more slowly fermented and has its bifidogenic effect in the distal colon. This knowledge was the basis for the development of a new oligofructose-enriched inulin, a patented combination of a selected fraction of short and long inulin chains (Synergy1). The combination of short and long inulin chains provides a sustained bifidogenic effect across the entire colon.[9]

Immune Function

As the gut matures during infancy, so does the immune system, and this process is markedly affected by early

diet. Human breast milk is a rich source of prebiotics, including the "bifidus factor." As a result, the gut flora of breast-fed infants is dominated by lactic acid–producing bacteria, such as bifidobacteria and lactobacilli, whereas formula-fed infants have a more complex composition of the colon flora.

Studies have been performed in infants and young children to investigate the ability of inulin and oligofructose to reduce the risk of infection and disease. In children attending day care centers, where the risk of infection is usually high, 21 days of oligofructose supplementation increased the levels of bifidobacteria in feces while decreasing potential pathogens, such as clostridia. The prebiotic group also experienced significantly less flatulence, diarrhea, vomiting, and fever compared with the controls.[10] Similar effects on clinical outcomes have been reported in other studies.[11] In a related study,[12] malnourished Brazilian preschoolers were given a nutritional supplement with or without a synbiotic (oligofructose plus *Lactobacillus acidophilus* and *Bifidobacterium infantis*). After 4 months, the number of sick days in 3- to 5-year-old children was significantly lower in the synbiotic group compared with the controls.

Other aspects of immunity where a well-balanced gut flora might bring relief are "autoimmune" conditions, for example, allergy, asthma, eczema, and inflammatory bowel disease (IBD).[13] The effects of inulin and oligofructose in IBD have been the subject of many investigations in animal models and clinical studies in patients with ulcerative colitis and Crohn's disease. In diverse animal models of IBD, supplementation with oligofructose and inulin has been shown to reduce inflammation (e.g., lower levels of proinflammatory mediators, cytokines, myeloperoxidase activity, etc), with an associated regeneration of epithelia and overall decrease in disease activity.[14] The reduced inflammatory response and decreased severity of the disease induced by the administration of inulin and oligofructose alone or as a synbiotic have been confirmed in clinical trials of patients with pouchitis,[15] active ulcerative colitis,[16] and Crohn's disease.[17]

Obesity and Metabolic Syndrome

The gut acts like an endocrine organ, producing a range of hormones that are devoted to the regulation of behavioral and metabolic function, by sending signals to the brain or other key target organs (eg, liver and pancreas). This can affect appetite, energy, and nutrient metabolism.

In experimental animals (healthy rats fed normal or high-fat diets), the addition of inulin-type fructans has been found to normalize blood lipid and glucose levels and reduce food intake and body weight, with a concomitant modulation of the levels of blood hormones involved in appetite regulation, for example, glucagon-like peptide-1 (GLP-1) and ghrelin.[18] The beneficial effects of oligofructose have also been seen in animals genetically "at risk" of the development of obesity and diabetes.[19] By using genetically modified (GLP-1 receptor knockout) mice, it was possible to elucidate the mechanism behind the observed effects of oligofructose. This stems from its selective fermentation in the bowel and the corresponding formation of end-products, which in turn increase the expression of GLP-1 in the colon and its subsequent release in the portal vein. Glucagon-like peptide-1 is strongly involved in glucose homeostasis and affects appetite by increasing satiety.[20] Also, in human studies, inulin and oligofructose have had a favorable impact on lipid and glucose metabolism.[20] In a recent randomized and placebo-controlled study, healthy adults were supplemented with 8 g of oligofructose twice a day for a period of 2 weeks. Volunteers felt more satiated and had a lower energy intake (by almost 10%) when they received oligofructose in their diet compared with the control diet (Figure 2).[21]

Bone Health

Osteoporosis is a global health problem that takes on increasing significance as life expectancy increases. Although physical activity, vitamin D, and calcium are key preventative measures, there is emerging evidence for a positive impact of inulin-type fructans and, more particularly, oligofructose-enriched inulin. A study in adolescents[22] found improvements in calcium absorption, bone mineral content, and bone

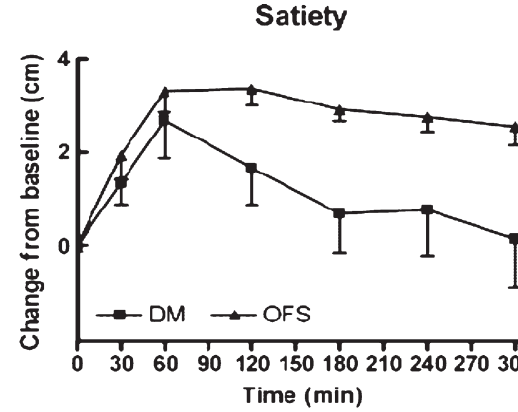

Figure 2. Changes in reported satiety postmeal (n = 10). Adapted from Cani et al.[21] DM indicates maltodextrin; OFS, oligofructose.

mineral density after 1 year of supplementation with 8 g/d of oligofructose-enriched inulin. The difference between intervention and control groups translated into an extra 31 mg of calcium per day assimilated into bones.

Animal models of the menopause (ovariectomized rats) have been used to determine the likely impact of inulin and oligofructose on osteoporosis risk. Studies have revealed improvements in calcium absorption, bone mineral content, and bone mineral density and reduction in ovariectomy-induced bone loss after supplementation with inulin-type fructans.[23] In growing rats, oligofructose was seen to improve markers of biomechanical strength, implying enhanced resistance to fracture.[24] In these studies, the best calcium absorption and retention results were seen with oligofructose-enriched inulin, rather than oligofructose or inulin alone, possibly because of a different fermentation pattern of the former.[25] The mechanisms underlying the role of inulin and oligofructose in mineral absorption are still being investigated but are thought to involve the production of organic acids as an end-product of inulin and oligofructose fermentation by gut bacteria. These acids lower pH, which increases mineral solubility and hence improves colonic absorption.[23]

Colorectal Cancer

Colorectal cancer is the third most common cancer, accounting for around 12% of cancer deaths worldwide. It is believed that colon cancer develops because of interactions between diet, other environmental and disease factors, gut microflora, and immune system. It is estimated that altering the gut microbiota through diet towards a predominance of beneficial species could help in the prevention of the disease. The roles of short-chain fatty acids, for example, acetate, propionate, and butyric acid, are being extensively studied because they have shown to inhibit the growth of colon tumor cells, encourage cell turnover, and support normal gene expression.[26]

Animal studies are promising in colon cancer, but human trials are still in early stages.

Although data from animal studies support a role of inulin and oligofructose in the prevention of the disease (not only aberrant crypt foci but also colonic tumor formation),[27] trials on human beings are still in the early stages. In 1 large multicenter European study (called SYNCAN), biomarkers of colonic cancer risk, such as cell proliferation and toxicity of feces (fecal water), improved when participants were given a synbiotic (oligofructose-enriched inulin plus *Lactobacillus rhamnosus* and *Bifidobacterium lactis*) for 12 weeks.[28] A study is now underway at the National Cancer Institute, National Institutes of Health, Division of Cancer Prevention (United States), in which diets of patients with increased risk of sporadic colorectal neoplasia are being supplemented with oligofructose-enriched inulin or placebo and followed up for many months. Chemoprevention efficacy of the oligofructose-enriched inulin on the development and biomarkers of colorectal cancer will be thoroughly studied.

Conclusion

Inulin and oligofructose seem to modulate a variety of body functions that are associated with health and well-being. They may have a potential in reducing the risk of developing osteoporosis, acute and chronic inflammation of the bowel, colorectal cancer, and some of the metabolic disorders associated with obesity (all chronic conditions with high prevalence in Western world). A common mechanistic thread is the beneficial impact that inulin and oligofructose have on gut microflora and metabolism. The gut microbial ecology has been described as the "the forgotten organ," referring to its ability to influence various parts and functions of the body, such as immune function, hormone release, and even possibly mineral absorption. The prevention and/or reduction in the progression of certain disease states observed with inulin and oligofructose administration, in animal models or human intervention trials or both, can be ascribed to some extent on a well-balanced intestinal microflora and intestinal metabolism and its interactions with host physiology.

Glossary

Gut microbiota: groups of bacteria living naturally in the lower human gut.

Prebiotic: a nondigestible food ingredient, usually a carbohydrate, that beneficially affects the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon and thus improves host health. Examples include inulin and oligofructose.

Probiotic: a preparation of live beneficial microbes, often delivered as a chilled dairy product or dried

compound. Examples include *L. acidophilus* and *Bifidobacterium longum*.

Synbiotic: a supplement containing both probiotic bacteria and prebiotic fibers. These can act in synergy to promote colon levels of beneficial gut bacteria.

Bifidogenic: the induction of a selective increase in gut levels of bifidobacteria.

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This paper represents an overview of the scientific presentations given by independent academics at the conference on ''Inulin and Oligofructose: Proven Health Benefits and Claims,'' held at the Harvard Medical School in Boston in September 2006. The conference was organized by Orafti, Tienen, Belgium.

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Antioxidants Do Not Help Children With Down Syndrome Develop

Down syndrome is the most common genetic cause of learning disability in the United Kingdom, affecting approximately 1 in 1,000 newborn babies.

Giving antioxidants and nutrients to children with Down syndrome does not help their condition improve at all. Researchers from the United Kingdom studied the effect of giving such supplements to 156 babies younger than 7 months with Down syndrome over an 18-month period. Previous studies investigated the possibility that giving folate, antioxidants, or both might improve the effects of Down syndrome, particularly on language and psychomotor development.

Although none of these reported any significant effect, use of vitamin and mineral supplements remains widespread in children with Down syndrome in Europe and the United States because of the extensive marketing of commercial preparations claiming substantial benefits.

In this study, the babies, from several sites in England, were split into 4 groups. One group was given a daily dose of antioxidants, one was given folinic acid, one was given a combination of antioxidants and folinic acid, and one was given a placebo. Folinic acids are also known as 5-formyl tetrahydrofolate. In contrast to folic acid, a synthetic form of folate, folinic acid, is one of the forms of folate found naturally in foods. All the supplements were given in powder form that could be mixed with food or drink. After 18 months, the children remaining in the study were assessed for their mental and cognitive development. The researchers found that giving the supplements made no difference to the biochemical outcomes in the children and did not improve their language or psychomotor development.

The authors concluded that this study provides no evidence to support the use of antioxidant or folinic acid supplements in children with Down syndrome. Parents who choose to give supplements to their children need to weigh their hope of unproved benefits against potential adverse effects from high-dose and prolonged supplementation.

Source: *British Medical Journal,* January 2008

Combination of Calcium and Vitamin D Prevents Bone Loss

The combination of calcium and vitamin D is more effective than calcium alone in preventing bone loss in elderly women, according to a new study in the *Journal of Clinical Endocrinology & Metabolism* (*JCEM*).

Previous studies have shown that high-calcium intake can help prevent bone loss. This latest study, however, demonstrated that calcium therapy, although initially successful at preventing bone loss, was no different from placebo after 3 or 5 years.

The researchers evaluated the relative benefits of 5 years of calcium supplementation with or without vitamin D_2 compared to placebo on hip bone mineral density (BMD) and bone-related biochemistry in ambulatory elderly women aged 70 to 80 years.

The combination of 1,200 mg of calcium a day and 1,000 IU of vitamin D maintained hip BMD constant for 5 years, whereas calcium alone after 3 or 5 years was no different from placebo.

The beneficial effect of calcium and vitamin D is considered to be due to reducing bone turnover, the process of old bone constantly being reabsorbed and replaced with new bone. Vitamin D also suppresses parathyroid hormone concentrations in individuals with relatively high parathyroid hormone levels. Parathyroid hormone is a hormone that regulates calcium levels by taking calcium from bones and releasing it into the blood.

Based on the study, the researchers suggest that older women should increase dietary calcium to 2 g/d as well as replace vitamin D that would normally be activated by sunlight, especially if there is evidence of vitamin D deficiency. This amount of calcium is higher than existing recommendations, and more as well as larger studies will be needed before definitive recommendations can be made.

Source: A rapid release version of this article has been published online and will appear in the March 2008 issue of *JCEM*, a publication of The Endocrine Society.