Comprehensive REVIEWS in Food Science and Food Safety

Significance of Inulin Fructans in the Human Diet

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Abstract: This paper reviews the physicochemical properties and nutritional significance of inulin fructans (oligofructose and inulin). These compounds are naturally present in a large number of food crops and serve in our diet as dietary fiber. Inulin fructans can be isolated and purified from the chicory root and used as ingredients in a large range of foods to improve structure and/or taste and to increase the intake of dietary fiber. Inulin fructans have a low caloric value, are safe, and generally well tolerated up to a level of 20 g/d. They exert a range of effects, which can be differentiated into direct effects on the gut and the intestinal flora and indirect systemic effects. Direct effects on the gut include prebiotic (bifidogenic) effects, improvement of bowel habits and bowel function in constipated subjects, increased colonic absorption of minerals (Ca and Mg), and secretion of satiety hormones. Indirect effects are on blood lipids, bone mineral content, the immune system, and energy homeostasis. These issues are discussed and it is argued that promising avenues for research are particularly in the areas of energy homeostasis and systemic low-grade inflammation in relation to changes in the composition of the intestinal microbiota.

Keywords: dietary fiber properties, gut health, inulin fructans, nutritional significance, review

Introduction

Inulin, a polydisperse energy storage polymer in plants of the Compositae and Lilialiaceaes families, is a fructan consisting almost entirely of linearly beta-1,2-linked fructose units with a terminal alpha1-beta2- linked glucose molecule. The inulin molecules in chicory roots have a degree of polymerization (DP) of 3 to over 60 units and are indicated with the formula $GF_{n,}$ whereas hydrolysis products are indicated with the formula $F_{m,}$ with $n \geq 2$ and $m \leq 7$. Inulin molecules with a DP of 3 to 10 are called oligofructose or fructo-oligosaccharides (FOS).[1] Inulin belongs to the so-called nondigestible oligosaccharides (NDOs), which are carbohydrates that after ingestion enter the colon where they are fermented by the microbiota. In foods they thus serve as a source of soluble dietary fiber, providing less energy than digestible carbohydrates. Inulin and oligofructose are isolated and purified from the chicory root, in a way comparable to that of sucrose from sugar beet (Boeckner and others 2001). They are widely used as ingredients with specific physicochemical and nutritional capabilities in a wide range of foods and drinks. FOS can also be synthesized industrially from sucrose using specific enzymes. This paper reviews the current knowledge on the nutritional significance of inulin and oligofructose.

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[1]In this paper, the word oligofructose is used for chicory-derived fructo-oligosaccharides, whereas the term FOS is used for sucrose-derived fructo-oligosaccharides.

Intake from Natural Sources

Historically, the intake of inulin from plants has been in the order of 25 to 32 g/d (Roberfroid 1993). Because of a shift from plant to animal foods and because of refinement of the western diet, the intake from natural sources nowadays is in the range of 2 to 11 g/d in most European countries and 2 to 8 g/d in the United States (van Loo and others 1995; Moshfegh and others 1999). Most of the inulin intake from our diet (>90%) originates from wheat and onions. In southern European countries (such as Spain), the intake of inulin has been reported between 5 and 18 g, due to consumption of relatively high amounts of garlic. Table 1 shows inulin- and oligofructose contents of various foods.

Physicochemical Properties

The physicochemical properties of inulin and oligofructose have been reviewed by Niness (1999) and Franck (2002). Inulin is moderately soluble in water (up to 10% at room temperature), producing a low-viscosity solution. At higher concentrations, a tridimensional microcrystalline gel network with a creamy structure and a fat-like mouthfeel can be formed. The sweetness of inulin is about 10% of that of sucrose. By removing the smaller inulin molecules, the sweetness is eliminated and the gel-forming capabilities are enhanced. Inulin finds extensive applications as a low-calorie fat replacer in spreads, dressings, dairy products, bakery foods, and ice cream.

Oligofructose has a higher solubility in water than inulin (up to 80% at room temperature). Its sweetness is about 35% of that of sucrose and it has a balanced profile. This makes oligofructose very suitable in mixtures with intensive sweeteners like aspartame, acesulfame K, or steviol glycosides. Oligofructose reduces the unpleasant aftertaste of these intensive sweeteners. Inulin and oligofructose are stable to heat at pH >5. At pH values of <4,

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Table 1–Contents of inulin and oligofructose (g/100 g; midpoint of reported ranges) in various foods

Food item	Inulin	Oligofructose (as fraction of inulin)
Banana (fresh)	0.5	0.5
Asparagus (fresh)	2.5	2.5
Chicory root (fresh)	17.5	9.6
Garlic (fresh)	12.5	5.0
Jerusalem artichoke (fresh)	18.0	13.5
Leeks (fresh)	6.5	5.2
Onions (fresh)	4.3	4.3
Wheat bran (fresh)	2.5	2.5
Wheat flour (baked)	2.4	2.4
Barley(fresh)	0.8	0.8
Rye (baked)	0.7	0.7

Taken from Boeckner and others 2001 and personal communication with Dr. D. Meyer, Sensus, Roosendaal, the Netherlands.

hydrolysis occurs depending on temperature and heating time (Glibowski and Bukowska 2011).

Nutritional Significance

Dietary fiber properties

According to EU Commission Directive EC/2008/100 (European Commission 2008), dietary fiber includes a wide variety of nondigestible carbohydrates with a DP of 3 or more (plus lignin). These compounds traditionally originate from plant materials, including fruits, cereals, pulses, seeds, nuts, legumes. The main types of dietary fiber are nonstarch polysaccharides (cellulose, hemicellulose, pectins, gums, mucilages, and beta-glucans), resistant oligosaccharides (inulin, oligofructose, FOS, galactooligosaccharides), resistant starch, and lignin (associated with resistant polysaccharides). Average dietary fiber intake in adults in European countries ranges between 15 and 30 g/d (European Food Safety Authority 2010). This level of intake is lower than 3.4 g/MJ (14 g per 1000 kcal), as recommended by official bodies (Institute of Medicine of the National Academies 2001; Health Council of The Netherlands 2006). Dietary fiber may have direct effects on the gut and/or the microbiota. It may also have indirect effects which are mediated through changes in the composition and/or metabolic activities of the microbiota. The Health Council of the Netherlands (2006) evaluated the health benefits of dietary fiber, merely on the basis of food consumption data and health outcomes, and arrived at the conclusions that dietary fiber decreases transit time and reduces constipation; a high-fiber diet (particularly whole grain and fruits) reduces the risk of coronary heart disease and may help to prevent overweight. Because of the molecular heterogeneity, different types of dietary fiber do not display identical physiological effects and, therefore, effects of the intake of inulin and oligofructose must be considered specifically. They can be differentiated in intestinal and systemic effects (Figure 1).

Safety, tolerance, and caloric value

In general, there are no safety concerns with the ingestion of nondigestible oligosaccharides, but excessive intake can cause undesirable side effects, such as flatulence, bloating, rumbling, cramps, and liquid stools, caused by gas formation and osmotic effects of certain fermentation products. These are short-chain fatty acids (SCFA) and lactate and they are formed in the cecum and colon. Distribution of the intake over the day and ingestion with solid foods (meals), as well as adaptation of a disirable intestinal flora, may decrease such side effects, although interindividual variability in response exists (Marteau and Florié 2001). Side effects will be less with long-chain inulin molecules, since these are fermented at a rate which is about 50% lower than that of short-chain inulin molecules (Roberfroid and others 1998; Coussement 1999). Havenaar (2000) reviewed studies in humans and concluded that in adults up to 20 g/d of inulin with an average DP of 9 does not cause serious adverse side effects, except mild to moderate discomfort such as flatulence in some individuals. In the large majority of studies on the nutritional significance of oligofructose and inulin, intake levels were below 20 g/d. In 2 recent randomized controlled trials (RCTs; Bonnema and others 2010; Holscher and others 2014), the tolerance of moderate doses (5 to 10 g/d) of chicory oligofructose, chicory inulin, and agave inulin was confirmed. Only mild gastrointestinal side effects (flatulence and bloating) were observed and these effects were less with native inulin than with oligofructose. If not given in excess (over 80 g/d; see Clausen and others 1998), inulin is completely fermented in the colon, resulting in the production of SCFA (mainly acetic acid, propionic acid, butyric acid) and lactate.

On the basis of biochemical balance charts for carbon atoms, metabolic pathways, and energy yields to the host, Roberfroid (1999) calculated for inulin a caloric value of 25% to 35% of that of fully digested and absorbed fructose. Similar as for other indigestible carbohydrates that are more or less completely fermented by the intestinal flora, Roberfroid (1999) proposed an energy value of 1.5 kcal/g for inulin and oligofructose for food labeling purposes. The European Union adopted in 2008 an energy value of 2 kcal/g for all dietary fibers (European Commission 2008; European Food Safety Authority 2010). Also, Health Canada (2012) adopted this value and in the recently proposed rules to adapt nutritional information, the US FDA proposed this value (Food and Drug Administration 2014).

Oral health

Inulin and oligofructose are not broken down by salivary enzymes, but may be fermented by the oral streptococci. In response to ingestion of oligofructose or inulin, fructanases are induced and acid is formed. It was found by Hartemink and others (1995) that oligofructose is fermented by *Streptococcus mutans* and forms plaques at a rate comparable to that of sucrose, indicating that oligofructose could be as cariogenic as sucrose. However, since in many cases, inulin or oligofructose will be present in the oral cavity at the same time as glucose or sucrose and since fermentation of inulin and oligofructose is subject to catabolite suppression, cariogenic effects probably are relatively small. Doran and Verran (2007) investigated the possibility that inulin, by stimulation of oral acidogenic microorganisms, could reduce oral malodor, and concluded that sucrose and inulin have comparable effects in reducing the tongue pH.

Composition of the intestinal microbiota

The number of microbial cells in the intestine is about 10^{14} and outnumbers the body cells by a factor of 10. More than 1000 different species are recognized worldwide with hundreds in 1 individual (Rijkers 2014). The microbiota can be considered as an ecosystem which provides colonization resistance against pathogens and which interacts intensively with the host, by modulating both the innate and adaptive immune responses and by producing metabolites which affect the body. The composition and metabolic activities of the microbiota are influenced by genetic host factors and by external influences, including diet composition and intake of drugs, especially antibiotics. The intestinal microbiota displays an impressive impact on human health. Research

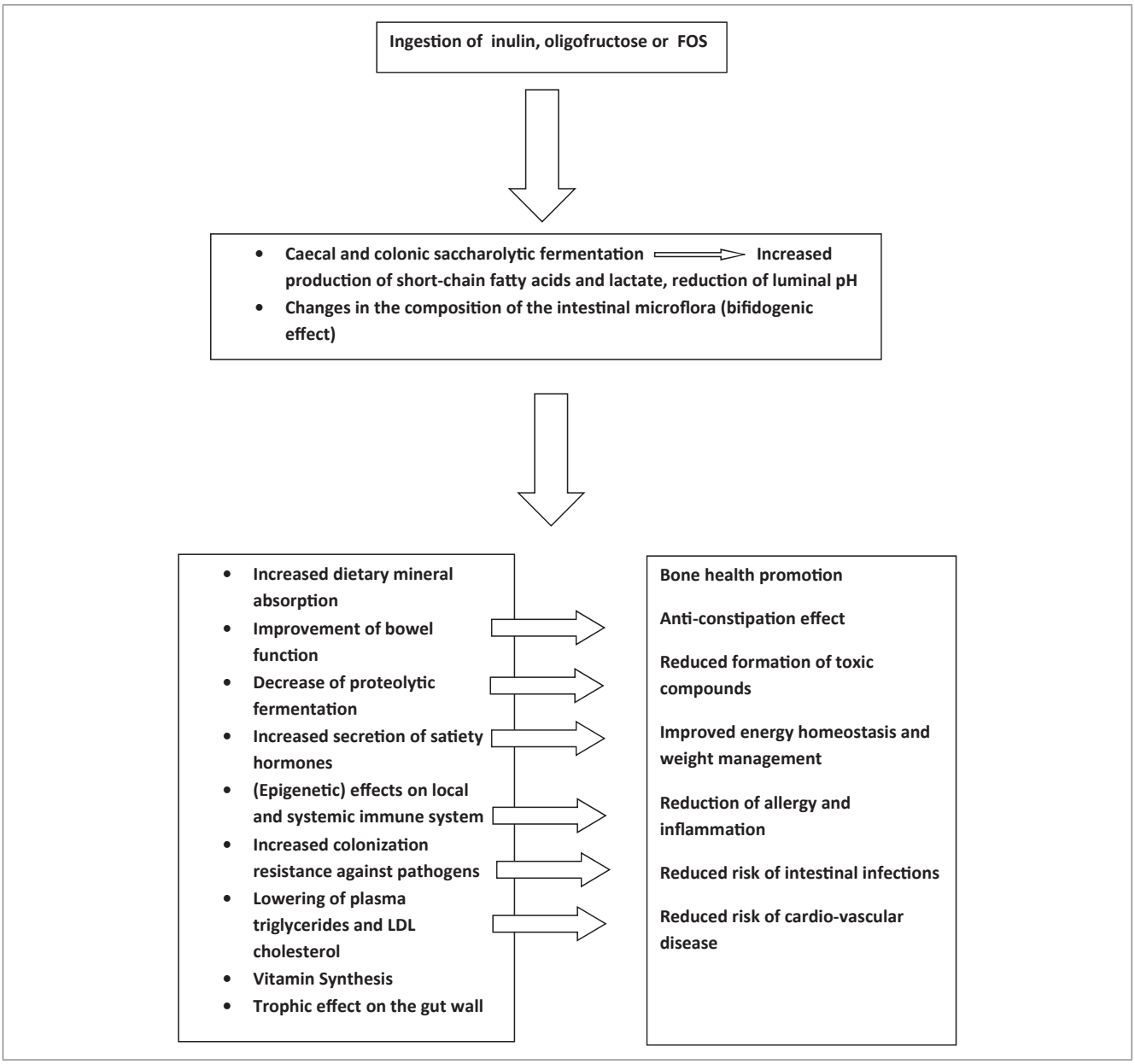

Figure 1–Intestinal and systemic effects of ingestion of inulin, oligofructose or FOS, as reported in experimental animals and/or humans.

of the last decade has shown that changes in the microbial composition are associated with specific diseases, including allergies, celiac disease, obesity, anorexia, inflammatory bowel disease, and type 2 diabetes (Clemente and others 2012).

Together with trans-galacto-oligosaccharides, inulin and oligofructose are "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confer benefits upon host well-being and health"; therefore, they are called prebiotics (Roberfroid 2007). It is well established through *in vitro* studies, in animal experiments and studies in humans, including formula-fed infants, that inulin and oligofructose stimulate the growth of bifidobacteria (Roberfroid 2007; Meyer and Stasse-Wolthuis 2009; Roberfroid and others 2010). Bifidobacteria dominate the intestinal flora in breast-fed infants and constitute one of the major organisms in the colonic flora of healthy children and adults. *Bifidobacteria* are considered to play an important role in the maintenance of a healthy and stable microbial ecosystem. Their numbers are generally low in various disease conditions and their reduction or disappearance from the human intestine would indicate an "unhealthy" state (Mitsuoka 1990). Gibson and Wang (1994a) showed that Bifidobacteria, in addition to production of acetic acid and lactic acid, excrete an antimicrobial substance with a broad spectrum of activity against pathogenic bacteria. More recently, it was demonstrated, in both *in vitro* and animal experiments, that distinct strains of bifidobacteria influence maturation- and cytokine-production patterns of dendritic cells of the intestinal mucosa (Menard and others 2008; Dong and others 2010; Lopez and others 2011). Dendritic cells sample antigens from food and bacteria and modulate the immune system. Through secretion of cytokines they control B- and T-lymphocytes, which may have consequences for development of tolerance and inflammation. Recent information

from *in vitro* trials suggests that inulin and oligofructose may also interact directly with the immune system through the Toll-like Receptor 2, which mediates cell activation (Vogt and others 2013, 2014). *Bifidobacteria* are not the only species that are stimulated by oligofructose or inulin. Also butyrate-producing *Faecalibacterium prausnitzii* and *Eubacterium* spp. increase in response to inulin or oligofructose ingestion (Ramirez-Farias and others 2009; Louis and others 2010).

Metabolic activities of the intestinal microbiota

From reviews by Cummings and Macfarlane (1997), Macfarlane and Macfarlane (1997, 2011), and van Loo and others (1999), the metabolic activities of the intestinal flora in the large intestine are summarized as follows. The activities of the anaerobic microorganisms can conveniently be differentiated into saccharolytic- and proteolytic activities, whereby the 1st occur mainly in the proximal bowel and the latter mainly in the distal bowel. The metabolic potential of the colonic microbiota is comparable to that of the liver in number of biochemical reactions and transformations.

The total amount of fermentable carbohydrates in the western diet delivered from the ileum has been estimated at 30 to 40 g/d. Cecal and colonic carbohydrate fermentation result in the production of SCFA, lactate, gasses (hydrogen, carbon dioxide, and methane) and in a reduction of the luminal pH. The SCFA are largely (95% to 99%) absorbed, covering about 10% of human energy requirement. Butyrate is used directly by the colonic cells, exerting a trophic effect on these cells. SCFA stimulate salt and water absorption and epithelial growth. The saccharolytic activities increase biomass, fecal bulk, stool weight, and stool frequency. For inulin the increase in stool weight in adults is relatively small (1.5 to 2 g per g ingested inulin). *In vitro* fermentation of inulin-type fructans with human cecal or fecal microbiota indicates a typical increase in the production of acetate and butyrate. Since *Bifidobacteria* do not produce butyrate, this indicates that other bacteria than just *Bifidobacteria* also benefit from this substrate or that cross-feeding may occur (Belenguer and others 2006).

In vitro fermentation of oligofructose showed that 40 mol% is SCFA, 15% is lactate, 5% carbon dioxide, and 40% of the C-atoms may be used for biomass synthesis (Havenaar and Petitet 1996). According to Morrison and others (2006), bifidobacteria and lactobacilli produce acetate and lactate from oligofructose. Subsequently, extracellular acetate is converted to butyrate and extracellular lactate to acetate, propionate, and butyrate with a major role for butyrate-producing bacteria related to *F. prausnitzii* and *Roseburia spp*. (Duncan and others 2004).

The ileal delivery of protein in adults has been estimated at 12 to 18 g/d and is derived from undigested dietary protein and endogenous digestive enzymes. The nitrogen is partly used for microbial biomass synthesis. The rest of the protein is fermented. This results in a variety of products, including branched-chain fatty acids (BCFA; from the branched-chain amino acids valine, leucine, and isoleucine), in ammonia (from deamination of amino acids), in indoles and phenols (from aromatic amino acids), and in amines (from decarboxylation of amino acids). Sulfides are formed from sulfate by sulfate-reducing bacteria. The extent of protein fermentation depends on a number of factors, including transit time, the amount of protein in the colon and the amount of protein used for biomass synthesis. Ammonia, sulfides, indole, and phenols are considered toxic to the colonic epithelium. Van Nuenen and others (2003) demonstrated in a colon model with a human flora that inulin inhibited the formation of ammonia, phenolic compounds, and BCFA, indicating that stimulation of saccharolytic activities and biomass production reduced protein fermentation. In a trial with humans, Swanson and others (2002) showed that a small amount of FOS (3 g/d for 4 wk) reduced fecal protein ammonia ($P < 0.07$) and isovaleriate ($P < 0.11$). De Preter and others (2008) showed that both lactulose and oligofructose-enriched inulin in a dose of 10 g/d for 4 wk significantly reduced urinary excretion of paracresol and colonic ammonia formation.

Regulatory and epigenetic effects of butyrate

Recent studies have indicated that, beyond being an energy source, SCFA and particularly butyrate may exert a range of beneficial effects, both at the intestinal and extra-intestinal levels by acting on leucocytes, intestinal cells, and endothelial cells through inhibition of histone deacetylase (Gao and others 2009; Canani and others 2011, 2012) and metabolic regulation by signaling through guanosine nucleotide-binding proteins (G-proteins), which are activated by protein-coupled receptors (GPCRs), such as GPR41 or GPR43 (Vinolo and others 2011). G-proteins regulate metabolic enzymes and ion channels, controlling cell functions as transcription, motility, contractility, and secretion. They serve as molecular switches. Histone deacetylases regulate gene transcription through modification of chromatin structure by deacetylation of proteins, including histone proteins and transcription factors. It has been shown that sodium butyrate induces peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) activity in skeletal muscles and brown fat in mice (Gao and others 2009). PGC-1 is a transcription coactivator of PPAR-γ (peroxisome proliferator-activated receptor).

The epigenetic effects of butyrate on leukocytes result in changes in the production of cytokines and chemokines and may result in anti-inflammatory effects, promotion of cell growth and differentiation, reinforcement of the intestinal barrier function, enhancement of intestinal motility, inhibition of intestinal cholesterol synthesis, reduction of obesity by enhancing mitochondrial function, and increase of insulin sensitivity in type 2 diabetes (Canani and others 2012; Tremaroli and Bäckhed 2012). The anti-inflammatory effect of butyrate is probably related to the reinforcement of the intestinal barrier against the transport of lipopolysaccharides (LPSs) and peptidoglycan from the lysis of Gram-negative bacteria). These compounds are known to trigger the production of pro-inflammatory cytokines and cause systemic inflammation. Oral administration of butyrate was reported to reduce the production of macrophage chemoattractant protein (MCP-1) in adipose tissue; MCP-1 is involved in the recruitment of macrophages in adipose tissue and is relevant for the development of insulin resistance through inflammatory mediators, produced by activated macrophages, in obese subjects (Vinolo and others 2011).

Bowel habit

The increase of saccharolytic activities of the intestinal flora, in response to the ingestion of oligofructose or inulin, increases biomass, fecal bulk, stool frequency, and leads to softer stools and is thus associated with an anticonstipation effect or mild laxative effect, without affecting transit time. The effect of completely fermentable fibers, like inulin and FOS, on fecal bulk is known to be less than that of fibers with strong water-holding capacity that reach largely intact the cecum, like wheat fiber (FAO 1998). Den Hond and others (2000) observed increased stool frequency and increased fecal bulk (1.5 g per 2 g of ingested inulin) in subjects with a low stool frequency pattern, ingesting for 2 wk 15 g of inulin per day (average DP of 25). An anticonstipation effect in controlled studies in subjects with low stool frequency was also reported for

FOS (3 g/d: Tominaga and others 1999) and for inulin (12 to 20 g/d: Kleessen and others 1997; Tomono and others 2010; Marteau and others 2010). Such data clearly show the dietary fiber features of inulin-type fructans. Recently Dahl and others (2014) confirmed the dietary fiber property on stool frequency of oligofructose in an RCT with a parallel design. Ninety-five healthy young adult volunteers with habitual fiber intakes below 20 g/d (mean: 12.1 g/d) ingested daily, as part of their diet, 16 g oligofructose via 2 snacks for 8 wk. This increased their mean fiber intake from 12.1 to 24.3 g/d. Oligofructose increased mean stool frequency from 1.3 to 1.8 and from 1.0 to 1.4 defecations per day in males and females, respectively. Symptoms of Intestinal discomfort, particularly flatulence, remained moderate, except for a few subjects on a few days, with no adaptation over time. Only 1 subject experienced enough discomfort to stop the study.

Colonization resistance against pathogens

In vitro experiments, animal studies, and human studies demonstrated that the bifidogenic effects of oligofructose and inulin are often associated with suppression of growth of (potentially) pathogenic organisms, such as *Enterobacteriacae, E. coli, Clostridium perfringens, Salmonella, Listeria, Campylobacter, Shigella, Vibrio cholera* (Wang and Gibson 1993; Gibson and Wang 1994b; Gibson and others 1995; Catala and others 1999; Fooks and Gibson 2002). However, such beneficial changes in the microbiota have not always been observed. Thus, in studies with humans, Tuohy and others (2001a, 2001b) observed that the bifidogenic effect of a high-molecular-weight fraction of inulin was associated with a small increase in *Clostridium* and that the bifidogenic effect of oligofructose did not result in changing the numbers of *Clostridium* and *Enterococcus*. Relatively small amounts of FOS in the diet of chickens (0.375 or 0.75%) reduced susceptibility to *Salmonella* colonization (Bailey and others 1991), but in rats 6% of dietary oligofructose or inulin did inhibit the colonization of *Salmonella* in cecal contents but enhanced the translocation of *Salmonella* after a challenge with this pathogen; the effect was partially prevented by increasing the calcium content of the diet (Bovee-Oudenhoven and others 2003; Ten Bruggencate and others 2004). It was indicated that the acid formed by fermentation increased irritation of the lower gut wall and reduced its barrier function. Increasing dietary calcium resulted in higher amounts of calcium phosphate in the lower gut and this would have counteracted acidification of the gut contents. It is possible that differences in dose, background diet, and methodology of measurement of the flora have contributed to the variation of response. Beneficial changes in the composition of the intestinal flora and/or increased colonization resistance against pathogens in response to the bifidogenic effects of oligofructose and inulin can be explained by direct antagonism (acetate and lactate production), competition for nutrients and adhesion sites, and stimulation of immunity (Fuller and Gibson 1997; Corr and others 2007; Fukuda and others 2011).

Mineral absorption, bone health, and vitamin synthesis

Extensive research in animals, mainly rats, has shown consistently that nondigestible carbohydrates that are fermented by the intestinal flora, including oligofructose and inulin, administered in doses of 25 to 150 g/kg diet, increase the cecal and colonic absorption of minerals, particularly calcium and magnesium; this effect is associated with increases in cortical bone mass in growing rats and prevented bone loss in ovarieectomized animals (van den Heuvel and Weidauer 1999; Scholz-Ahrens and others 2007). The effect is dependent on bacterial fermentation, since it cannot be shown in germ-free animals. The mechanism implied is probably related to the formation of SCFA, reduction of the luminal pH, improved mineral solubility, and increased paracellular transport, mediated by osmotic effects and increased luminal fluid volume, which loosens the intercellular tight junctions (van den Heuvel and Weidauer 1999). Another possibility is that the trophic effects of SCFA on cecal and colonic epithelium increase the absorptive capacity of the mucosa.

Results of studies in humans on mineral absorption are less consistent. Table 2 summarizes the studies on the effect of prebiotics on calcium absorption. Using the classical balance technique, Coudray and others (1997) showed that doses of inulin up to 40 g/d increased the apparent absorption and retention of Ca, but not those of Mg, Zn, or Fe in young healthy males. But van den Heuvel and others (1998), using a stable isotope technique, did not find a positive effect on true fractional absorption of Ca and Fe in young healthy men who ingested 15 g/d of inulin, oligofructose, or galacto-oligosacharides. On the other hand, the same group observed a positive dose-related effect on true fractional calcium absorption in postmenopausal women of 10 g/d lactulose (van den Heuvel and others 1999a) and of 20 g/d of trans-galacto-oligosaccharides (van den Heuvel and others 2000). In male adolescents, 15 g/d of oligofructose also increased calcium absorption (van den Heuvel and others 1999b). Griffin and others (2002) showed in girls, who were around the menarche, that a mixture of oligofructose and long-chain inulin at a dose of 8 g/d, but not of oligofructose alone, increased true calcium absorption, while Abrams and others (2005b) showed enhanced calcium absorption by a mixture of short- and long-chain inulin fructans, at a dose of 8 g/d. This resulted in a 35 g higher increment of the bone mineral content after 1 y. Using the classical balance technique, Kim and others (2004) showed that inulin (8 g/d) improved calcium absorption in postmenopausal women. More recently, Martin and others (2010) in a stable isotope study, with girls 11- to 12-y-old, found no effect on either Ca absorption or retention after 3 wk of ingestion of 9 g short- and long-chain inulin. Tahiri and others (2001), also using a stable isotope technique, reported enhanced Mg absorption and urinary magnesium excretion in postmenopausal women, given a dose of 10 g FOS per day for 5 wk.

The positive effects on mineral absorption in humans, although physiologically meaningful, are relatively small (about 10% increase of true fractional absorption) and therefore not easy to detect. This may explain in part the variability of results. Moreover, differences in physiological status, background diet, dose, and way of its administration may play a role. Based on data from their long-term trial in adolescents, Abrams and others (2005a) have suggested that polymorphisms of the specific vitamin D receptor (Fok1) gene directly affect bone mineralization during pubertal growth through an effect on calcium absorption. The Fok1 effect on whole body bone mineral density (BMD) was only significant for those with high calcium intake. In a follow-up study, these investigators evaluated 32 responders and 16 nonresponders to the calcium absorptive benefit of inulin. It was found that responders who increased their calcium absorption by at least 3% after 8 wk of the 1/1 mixture of oligofructose and inulin, had a greater accretion of calcium to the skeleton over a year. There were no differences in habitual dietary calcium intakes between responders and nonresponders (Abrams and others 2007). So far, long-term effects on bone in postmenopausal women have not been assessed.

Many *Bifidobacteria* strains have the capacity to synthesize and excrete B-vitamins, including thiamine, folate, nicotinate,

Table 2–Studies with humans on the effect of prebiotics on the intestinal calcium absorption

Authors	Technique	Target group	Prebiotic type and dose	Results
Coudray and others (1997)	Classical balance	Young healthy men	Inulin, 40 g/d, 4 wk	Positive
Van den Heuvel and others (1998)	Stable isotopes	Young healthy men	Inulin, oligofructose or galacto-oligosaccharides, 15 g/d, 3 wk	Not significant
Van den Heuvel and others (1999a)	Stable isotopes	Postmenopausal women	Lactulose, 10 g/d, 9 d	Positive
Van den Heuvel and others (1999b)	Stable isotopes	Male adolescents	Oligofructose, 15 g/d, 9 d	Positive
Van den Heuvel and others (2000)	Stable isotopes	Postmenopausal women	Galacto-oligosaccharides, 20 g/d, 9 d	Positive
Griffin and others (2002)	Stable isotopes	Young girls	Oligfructose/inulin mixture, 8 g/d, 3 wk	Positive
Griffin and others (2002)	Stable isotopes	Young girls	Oligofructose, 8 g/d, 3 wk	Not significant
Abrams and others 2005b	Stable isotopes	Adolescents	Mixture of short- and long-chain inulin , 8 g/d, 1 y	Positive
Kim and others (2004)	Classical balance	Postmenopausal women	Inulin 8 g/d, 3 mo	Positive
Martin and others (2010)	Stable isotopes	Young girls	Mixture of short- and long-chain inulin, 9 g/d, 3 wk	Not significant

pyridoxine, and vitamin B12 (Ventura and others 2010). It is not known to what extent B-vitamins are absorbed in the cecum and colon and whether the bifidogenic effects of inulin fructans contribute to the vitamin B-status in humans. Santacruz and others (2010) showed that an increased level of bifidobacteria is associated with an improved folate status in pregnant women.

Intestinal hormones, satiety, and weight management

Studies in rats have shown that 10% dietary inulin-type fructans with different DPs decreases food intake and epididymal fat mass, apparently through increased production of SCFA and stimulated cecal and colonic secretion of the satiety hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) and a decrease in the serum orexigenic peptide ghrelin (Delzenne and others 2005). Oligofructose-enriched inulin supplementation in mice on a high-fat diet reduced weight gain, total body fat and liver fat contents, and these effects were associated with increases in fecal *Bifidobacteria*, *Lactobacillus*, and SCFA. Functional magnetic resonance imaging (MRI) showed an increase in neuronal activation of the arcuate nucleus in the supplemented mice (Anastasovska and others 2012). Short-term studies in humans on the effect of oligofructose, however, have yielded inconsistent results. In a 2-wk study with humans, Cani and others (2006) found that 16 g oligofructose distributed over 2 meal replacement bars increased satiety and reduced food intake. In a carefully controlled crossover study with 31 young adults, Verhoef and others (2011) observed that ingestion of oligofructose (10 or 16 g for 13 d) tended to reduce food intake. With the higher dose, energy intake on day 13 was significantly lower (12%, $P < 0.05$) than with placebo, and this was associated with increased levels of GLP-1 (compared with the 10-g dose) and of PYY compared with the 10-g dose and placebo. In acute (1 to 2 d) experiments, no effects of inulin fructans were observed on appetite or food intake by Peters and others (2009) and Karalus and others (2012). Parnell and Reimer (2009), in a randomized placebo-controlled trial with 48 overweight adults, who consumed 21 g oligofructose per day for 12 wk, found no effects on subjective hunger and on GLP-1. But these subjects reported a lower energy intake, lost significantly more body weight, and had a lower ghrelin concentration and increased PYY levels. In this study, oligofructose supplementation improved blood-glucose control and this was associated with body fat loss, mainly from the trunk.

Evidence is accumulating (Rijkers and others 2012; Clemente and others 2012; Johnson and Olefsky 2013) that the interaction between environmental factors, the host, and its microbiome is involved in the development of such chronic diseases as obesity, type 2 diabetes, and metabolic syndrome. The interaction would involve the immune system with a central role for low-grade inflammation. In obese subjects, a relative abundance in the intestinal flora of *Actinobacteriaceae* and *Firmicutes* compared to *Bacteroidetes* would result in an increased capacity to harvest energy from food and would produce moderate induction of inflammatory cytokines, increase in mast cells, T cells, and macrophages. An imbalance between Th1 and Th2 cells, caused by a disturbed microbiota would be responsible for allergies and autoimmune diseases. A low grade of inflammation is held responsible for insulin resistance. A more diverse microbiota would be related to health, while in disease conditions the diversity often seems to be decreased. An increase in bifidobacteria has also been shown to modulate inflammation in obese mice by increasing glucagon-like-peptide-2 (GLP-2), which reduces intestinal permeability and reduces translocation of bacterial LPS (Cani and others 2009).

Blood lipids and blood glucose regulation

Animal experiments, mainly in rodents, have consistently demonstrated that oligofructose and inulin in doses of 5 to 15 weight% of the diet lower blood triglyceride or cholesterol levels, most probably through inhibition of lipogenic enzymes in the liver following bacterial SCFA production (Delzenne and Kok 1999). Studies in humans have yielded variable results (Williams and Jackson 2002; Beylot 2005). In 2 well-controlled studies with normal subjects (Van Dokkum and others 1999; Pedersen and others 1997) and in 1 comparable study in patients with type 2 diabetes (Alles and others 1999), no significant effects were found on either blood triglyceride, blood cholesterol, or blood glucose regulation when with doses of oligofructose of 14 or 15 g/d for 3 or 4 wk . On the other hand, Causey and others (2000) observed a significant decrease of blood triglyceride levels after 3 wk of ingesting 20 g inulin daily and a trend to cholesterol reduction in hypercholesterolemic men.

The lipid-lowering effect of inulin fructans is probably related to the production of SCFA. The difference in response between rats and the men could be related to the lower doses used in studies with humans. On a body weight basis, these doses are about 40-fold higher in rats. Since oligofructose and inulin are not digested

in the small intestine and are fermented in the large intestine, they do not contribute to the glycemic response after ingestion. In fact, this feature has now been recognized by the European Food Safety Authority as the basis for a health claim to reduce the postprandial glycemic response (European Food Safety Authority 2014).

Diseases of the gut and allergy

Several diseases of the colon are associated with changes in the composition and/or activity of microbiota. These are inflammatory bowel diseases (IBD, Crohn's disease, and ulcerative colitis), irritable bowel syndrome (IBS), and colon cancer. IBD is the result of an imbalance in the gut-associated lymphoid tissue, resulting in an increased Th1 T-cell-driven inflammatory response. An interaction between the mucosal immune system of the host and the microbiota is probably involved. Higher concentrations of *Bacteroides* and lower concentrations of *Bifidobacteria* have been found in patients with Crohn's disease (Lindsay and others 2006). The immunomodulating effects of *Bifidobacteria* may change the imbalance. In a pilot study with 10 patients having Crohn's disease, Lindsay and others (2006) found that the bifidogenic effect of 15 g of a mixture of oligofructose and inulin (7/3) daily for 3 wk was associated with reduced disease activity and functional changes of dendritic cells. However, in a much larger randomized controlled study with 103 patients, no reduction in the response to disease activity was found after 4 wk administering 15 g daily of a slightly different mixture (oligofructose/inulin, 1/1), although changes in dendritic cell function were noted (Ng and others 2011). In this study no (fecal) bifidogenic effect was seen (Benjamin and others 2011).

In rodent models of ulcerative colitis, several groups of investigators showed reduction of inflammation after administration of FOS, oligofructose, or inulin (Cherbut and others 2003; Winkler and others 2007; Koleva and others 2012). In a pilot RCT in colitis patients, Casellas and others (2007) reported that 12 g of oligofructose-enriched inulin reduced the fecal excretion of calprotectin, a marker of intestinal inflammation. Welters and others (2002) reported that supplementation of 24 g inulin per day for 3 wk in a randomized crossover study with 20 patients with an ileal pouch increased butyrate concentrations, lowered fecal pH and secondary bile acids, and decreased the number of *Bacteroides fragilis* in feces, while it reduced mucosal inflammation.

In rodent models of colon cancer, dietary FOS and inulin also showed favorable results on advanced stages of colon cancer development (Pierre and others 1997), and on the number of aberrant crypt foci, an early preneoplastic marker of malignant potential in colon cancer genesis (Reddy and others 1997; Hsu and others 2004). The proposed involved mechanisms are immunomodulation by the colonic microbial ecosystem and enhanced butyrate formation, associated with growth regulation and differentiation of colon cells (Bornet and Brouns 2002). In humans, no data are available on possible benefits of inulin fructans on colon cancer risk. Only 1 human study with inulin-based synbiotics showed favorable changes in biomarkers related to colon cancer (Rafter and others 2007). In another study (Bouhnik and others 1996), it was found that 12,5 g per day of FOS for 12 wk exerted a strong bifidogenic effect, but did not change the fecal parameters which are suspected to be involved in colon carcinogenesis, including nitroreductase, azoreductase, beta-glucuronidase, concentration of bile acids, and neutral sterols.

In IBS patients, a 2-fold decreased level of fecal bifidobacteria has been reported (Kerckhoffs and others 2009). From this, it might be expected that IBS symptoms could be reduced by supplementation with FOS or inulin. However, results of studies in IBS patients are not consistent. In a multicenter RCT, Olesen and Gudmand-Høyer (2000) found that 20 g/d of oligofructose for 12 wk had no significant effects on symptoms. But in another multicenter RCT (Paineau and others 2008), 5 g/d of FOS for 6 wk suggested improvement in digestive comfort, whereas in an earlier study 6 g/d of oligofructose had no therapeutic value (Hunter and others 1999).

A study in formula-fed infants showed that the bifidogenic effect of a mixture of galacto-oligosaccharides and long-chain inulin in the formula (0.8 g/100 mL) is associated with a significantly reduced incidence of atopic disease after 6-mo intervention in infants at risk of atopy (Moro and others 2006). After 2 y of a follow-up, cumulative incidences of atopic dermatitis, recurrent wheezing, and allergic urticaria were higher in the placebo group. This group also had more episodes of upper respiratory tract infections and antibiotic prescriptions. The benefits of the prebiotic mixture were attributed to its bifidogenic effect (Arslanoglu and others 2008). It is possible that changes in the intestinal flora modulate the immune system by bringing about a shift in the activity of Th-2 cells (predominant atopic activity) to Th-1 cells.

Discussion

It is evident from this paper that application of inulin and oligofructose as food ingredients not just has sensory effects of taste and food structure, but also nutritional benefits. Oligofructose and inulin belong to the wide diversity of heterogenic compounds that occur naturally in our diet and that are collectively called dietary fiber. Each of these compounds has its own specific biological effects. Supplementation of oligofructose and inulin increases fiber intake, but the benefits of this are not necessarily the same as those of an increase of fiber intake from vegetables, fruits, cereals, or other foods. Therefore, it is necessary to specify the fiber effects of inulin fructans.

Inulin fructans are directly or indirectly responsible for a range of physiological activities (see Figure 1). They stimulate saccharolytic fermentation in cecum and colon. This results in the formation of SCFA, lactate, and gasses (CO_2, H_2, and CH_4), and in a reduction of the luminal pH. SCFA have trophic effects on the mucosa and a low pH inhibits the growth of potentially pathogenic bacteria. Long-chain inulin is more slowly fermented than short-chain FOS, and mixtures of these fructans may contribute to spreading the saccharolytic fermentation throughout the colon. This will help to reduce proteolytic fermentation in the more distal parts of the colon and reduce the formation of toxic compounds, such as phenols, indole, and ammonia. The saccharolytic fermentation increases bacterial mass and defecation frequency and helps to prevent constipation. All these effects are physiological and beneficial, and are typical dietary fiber effects. Undesirable side effects (flatulence, bloating, borborygmus), frequently called intestinal discomfort, may occur at higher doses, but generally do not occur at doses below 20 g/d, when the dose is spread over the day and taken with meals.

Another well-documented effect of inulin fructans is their bifidogenic potential. Because of this potential, oligofructose and inulin are called prebiotics. Although up to now it has been difficult to prove that a bifidogenic effect is beneficial to health, there are indications that this is the case. In fact, in studies with humans, bifidogenic effects of inulin or oligofructose did not decrease numbers of *Clostridia* and *Enterococcus* cells (Tuhohy and others 2001a, 2001b).

Bifidobacteria dominate the flora of breast-fed infants and this, at least in part, is the consequence of the high nondigestible oligosaccharide content of breast milk. Infant formulas with added nondigestible oligosaccharides are also bifidogenic. Bifidobacteria interact with the gut-associated lymphoid tissue and modulate the immune system to reduce allergies. Bifidobacteria contribute to colonization resistance against pathogens by various mechanisms (reduction of pH, formation of acetate or bacteriocins, and competition for nutrients and adhesion sites). Although there is evidence that low numbers of bifidobacteria in the microbiota are associated with an unhealthy state, as yet there is no definite proof that increasing bifidobacteria numbers will improve this state.

The effects of inulin fructans on the intestinal absorption of minerals (such as Ca and Mg) is well documented in rats, but results of studies in humans are variable. The reason for this species difference is probably related to dose levels. When expressed per kg body weight, rats receive doses of about 10 g/kg, whereas the dose in humans is generally below 0.3 g/kg. It is thus possible that the effect on mineral absorption in humans at this dose level is small and not easily detectable. This does not mean that it has no physiological significance. Small but long-term effects could be beneficial for bone development in young individuals, as was demonstrated by Abrams and others (2005a) or reduction of bone loss in later life. So far this latter effect has not yet been demonstrated.

The difference between rats and humans regarding the effect of fructans on food intake, fat mass, blood lipid levels, and blood glucose regulation may also be related to the dose given. Whether ingestion of fructans can help humans in weight management via changes in the microbial composition, secretion of satiety-related gut hormones, or translocation of bacterial LPSs that may cause low grade of inflammation, should be investigated further before any conclusion can be drawn.

The higher dose of fructans given to rats than to humans could explain why in 1 rat study (Ten Bruggencate and others 2003) a decreased colonization resistance against salmonella and increased translocation of this pathogen was detected, particularly in combination with a low-calcium diet. Possibly, osmotic pressure, following heavy caecal and colonic fermentation, decreases the intestinal barrier function and normal colonic physiology. In chickens, lower doses did appear to be protective against *Salmonella* (Bailey and others 1991). In a later study with humans (Ten Bruggencate and others 2006), it was demonstrated in 34 healthy men that, contrary to the rat experiment, no adverse effects on intestinal permeability or cytotoxicity of fecal water were observed with 20 g oligofructose per day. This was confirmed later by Scholtens and others (2006), even with higher intake rates (35 g/d). Regarding IBD and IBS, there is evidence of a disturbed intestinal flora composition with low counts of bifidobacteria, but there is insufficient proof that the bifidogenic effects of FOS, oligofructose, or inulin can help to reduce symptoms of these diseases. There is also not sufficient evidence in humans for benefits of fructans in the prevention of colon cancer. On the other hand, addition of bifidogenic oligosaccharides to infant formula was helpful in the prevention of allergy in children and indicated that oligosaccharides can modulate in a beneficial way the gut-associated immune system.

Overall it can be concluded that, considering their physiological characteristics, inulin fructans are dietary fibers. Supplementing the diet with these compounds can help to increase total fiber intake, which is often far below the recommended levels in western diets. In addition to dietary fiber effects, inulin fructans have proven bifidogenic effects and change the composition of the gut flora in a way that is considered beneficial, but without definite proof for specific well-defined favorable effects on disease or validated health parameters. A possible exception here is allergy reduction in infants and children. Many of the differences in response to fructans between rat and human are attributable to the relatively higher doses given to rats. The human intestinal flora seems to have more impact on the development of several chronic diseases than thought before. The extent to which the effects of inulin fructans on the intestinal flora have a role in prevention of chronic diseases needs to be established (Conterno and others 2011). In addition, the effects of oligofructose and inulin intake on energy balance, mediated via the gut-brain axis, and on low-grade inflammation, associated with the metabolic syndrome and obesity, open new and interesting avenues into health effects of these food ingredients. This fits well in the desire of having more knowledge on the interaction between diet, host, and microbiota that modulates gut permeability and leads to an influx of pro-inflammatory molecules and activation of inflammatory signaling pathways in peripheral tissues that may cause obesity and insulin resistance. Particularly the regulatory and epigenetic effects and potential benefits of butyrate in this regard warrant further studies.

A major problem in research on dietary fiber effects of oligofructose and inulin is the limited availability of validated biomarkers in the field of gut health. A possibility to overcome this problem is the use of the concept of resilience. Resilience can be defined as the ability to cope with stress or to return to a balanced situation after disturbance. Application of this concept, combined with nutrigenomics technology can help to develop new biomarkers and advance further our knowledge on the dietary fiber properties of oligofructose and inulin.

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Author Contributions

G. Schaafsma designed the format, searched and evaluated the literature, and drafted the manuscript. J. Slavin checked the manuscript, reviewed it critically, and accepts responsibility for the contents.

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