Handbook of Prebiotics and Probiotics Ingredients
Health Benefits and Food Applications
Susan Sungsoo Cho, E. Terry Finocchiaro

Inulin and Oligosaccharides A Special Focus on Human Studies

Publication details
Damien Paineau, Frédérique Respondek, Yoram Bouhnik
Published online on: 19 Nov 2009

How to cite :- Damien Paineau, Frédérique Respondek, Yoram Bouhnik. 19 Nov 2009, Inulin and Oligosaccharides A Special Focus on Human Studies from: Handbook of Prebiotics and Probiotics Ingredients, Health Benefits and Food Applications CRC Press
Accessed on: 06 Jan 2019

PLEASE SCROLL DOWN FOR DOCUMENT

Full terms and conditions of use: https://www.routledgehandbooks.com/legal-notices/terms

This Document PDF may be used for research, teaching and private study purposes. Any substantial or systematic reproductions, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The publisher shall not be liable for an loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
CHAPTER 3

Inulin and Oligosaccharides
A Special Focus on Human Studies

Damien Paineau, Frédérique Respondek, and Yoram Bouhnik

CONTENTS

3.1 Introduction ....................................................................................................44
3.2 Characteristics and Physiological Effects of Fructans ...................................44
  3.2.1 Effects of Fructans on Intestinal Microflora Composition ........................45
    3.2.1.1 Bifidogenic Effect ................................................................ 45
    3.2.1.2 Effect on Other Intestinal Bacteria ................................. 48
    3.2.1.3 Limits ...................................................................................49
  3.2.2 Effects of Fructans on Intestinal Functions ........................................49
    3.2.2.1 Stool Weight.........................................................................49
    3.2.2.2 Fermentation and Production of Short-Chain Fatty Acids ............50
    3.2.2.3 Epithelial Cell Growth and Differentiation .............................51
    3.2.2.4 Immunity ............................................................................. 51
  3.2.3 The Barrier Effect............................................................................... 52
3.3 Effects of Fructans on Gastrointestinal Disease ............................................ 53
  3.3.1 Infectious Diarrhea ........................................................................ 53
  3.3.2 Inflammatory Bowel Disease ......................................................... 53
  3.3.3 Irritable Bowel Syndrome ............................................................. 56
  3.3.4 Colonic Tumors ............................................................................ 56
3.4 Effects of Fructans on Metabolism of Minerals and Vitamins ......................59
  3.4.1 Fructans and Calcium Absorption ............................................... 59
  3.4.2 Fructans and Absorption of Magnesium, Copper, Selenium, and Zinc ............................................................62
  3.4.3 Fructans and Isoflavone Metabolism ............................................ 62
  3.4.4 Fructans and Vitamin Production ............................................... 63
  3.4.5 Fructans and Absorptive-Productive Functions ................................. 63
3.1 INTRODUCTION

The intestinal habitat, mainly the large intestine of an individual, contains 300 to 500 different species of bacteria, and the number of microbial cells within the gut lumen is about 10 times larger than the number of eukaryotic cells in the human body (Salminen et al., 1998; Segain et al., 2000; Guarner and Malagelada, 2003). In this complex and dynamic microbial ecosystem, living bacteria achieve concentrations of up to $10^{11}$ to $10^{12}$ per gram of luminal content (Guarner and Malagelada, 2003). This ecosystem interacts with the host health, in various domains including the protection against pathogens (barrier effect), inflammatory bowel diseases, colonic cancers, and others (Guarner and Malagelada, 2003). Some gut bacteria, including subspecies of *Clostridium perfringens*, sulfate-reducing and amino acid fermenting species are considered harmful. On the other hand, others are considered as beneficial. The main potentially health-enhancing bacteria are the bifidobacteria and lactobacilli, both of which belong to the lactic acid bacteria group (Salminen et al., 1998). These two genera do not include any significant pathogenic species and their potentially prophylactic and therapeutic beneficial effects are now well demonstrated in human and animal studies (Picard et al., 2005).

Modulation of the microflora composition by “functional foods” with the objective to improve the colonic environment is a challenge. A prebiotic is defined as a “nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or the activity of one or a limited number of bacteria in the colon” (Gibson et al., 2004; Macfarlane et al., 2006). They have been widely tested, in animal and human studies, for their beneficial actions in the prevention or treatment of a broad spectrum of gastrointestinal disorders, from impairment of colonic transit to colonic carcinogenesis (Macfarlane et al., 2006). Probiotics are defined as “live microorganisms, which confer a health benefit on the host when administered in adequate amounts” (Guarner and Schaafsma, 1998). Synbiotics are products in which both a probiotic and a prebiotic are combined.

The aim of this chapter is to focus on the physiological effects of oligosaccharides and inulin (fructans) in the gastrointestinal tract, with a special focus on human studies.

3.2 CHARACTERISTICS AND PHYSIOLOGICAL EFFECTS OF FRUCTANS

The only known components for which convincing evidence in favor of a prebiotic effect has been reported are carbohydrates that resist digestion in the upper
INULIN AND OLIGOSACCHARIDES

Table 3.1 Fructans Used as Prebiotics

<table>
<thead>
<tr>
<th>Name</th>
<th>Composition</th>
<th>Method of Manufacture</th>
<th>Degree of Polymerization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-chain fructo-oligosaccharides</td>
<td>(\beta(2\rightarrow1)) linear fructans</td>
<td>Tranfructosylation from sucrose, or hydrolysis of chicory inulin</td>
<td>3–5</td>
</tr>
<tr>
<td>Fructo-oligosaccharides</td>
<td></td>
<td>Tranfructosylation from sucrose, or hydrolysis of chicory inulin</td>
<td>2–10</td>
</tr>
<tr>
<td>Inulin</td>
<td></td>
<td>Hydrolysis of chicory inulin</td>
<td>2–60</td>
</tr>
<tr>
<td>Long-chain inulin</td>
<td></td>
<td>Hydrolysis of chicory inulin</td>
<td>10–60</td>
</tr>
</tbody>
</table>

gastrointestinal tract (nondigestible carbohydrates or NDCHs), but that are hydrolyzed and fermented in the large bowel. Three types of carbohydrates, essentially nondigestible oligosaccharides, fulfill the criteria for prebiotic classification: fructans (inulin and fructo-oligosaccharides (FOS)), \((trans)\)-galacto-oligosaccharides (TOS or GOS), and lactulose (Macfarlane et al., 2006). The aim of this chapter is to focus on fructans (Table 3.1); TOS, GOS, and lactulose are presented in other chapters.

3.2.1 Effects of Fructans on Intestinal Microflora Composition

3.2.1.1 Bifidogenic Effect

Over the past decade, it has emerged that some NDCHs have the potential to increase the concentration of bifidobacteria in the colon (Bornet and Brouns, 2002). The intensity of this bifidogenic effect depends on the chemical structure of the prebiotic, leading to differences in efficient doses. The results of the main human studies carried out to assess bifidogenic properties of fructans are summarized in Table 3.2.

In a recent randomized controlled study, Bouhnik et al. (2004) found that lactulose, long-chain inulin, and isomalto-oligosaccharides (IMO) were not bifidogenic at 10 g/day for 7 days on the contrary to short-chain fructo-oligosaccharides (sc-FOS), soybean oligosaccharides (SOS), and galacto-oligosaccharides (GOS). The three nonbifidogenic substrates were further studied in a dose–response relationship using higher doses (Bouhnik et al., 2004). In the study, 80 volunteers were randomized in three groups of 24 subjects who received one of the three nonbifidogenic NDCHs at a dose of 10, 15, and 20 g/day for 7 days (8 volunteers per dose) and a fourth group of 8 subjects who received the placebo. Bifidobacteria counts increased when using lactulose at 20 g/day \((P < 0.05)\) and inulin at 15 g/day \((P < 0.01)\) and 20 g/day \((P < 0.05)\) (Table 3.2). A dose relationship was demonstrated for sc-FOS (Bouhnik et al., 1999, 2004, 2006), but not for other bifidogenic substrates.

When focused on the fructans, sc-FOS were found bifidogenic at doses ranging from 2.5 to 10 g/day (Bouhnik et al., 1999, 2004, 2006), and inulin at doses ranging from 5 to 15 g/day (Bouhnik et al., submitted (a); Gibson and Roberfroid, 1995;
Table 3.2 Selection From Our Randomized Controlled Trials Using Fructan Prebiotic for Evaluation of Bifidogenic Effect in Healthy Adults

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study Design</th>
<th>Prebiotic Type, Consumption</th>
<th>Method/end Points</th>
<th>Main Results</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| n = 200  | Double-blind parallel-group study (n = 64) | Prebiotic at 10 g/d for 7 days  
- sc-FOS  
- SOS  
- GOS  
- Type III resistant starch  
- Lactulose, long-chain inulin, IMOS  
- Placebo | Fecal bacterial count at d0 and d8 | Increase of bifidobacteria  
- \( P = 0.008 \)  
- \( P = 0.006 \)  
- \( P < 0.0001 \)  
- \( P = 0.02 \)  
- NS, NS, NS | Bouhnik et al., 2004 |
|         | Double-blind parallel-group, dose–response relation (DRR) study (n = 136) | Prebiotic at dose of 2.5, 5.0, 7.5, and 10 g/d vs. placebo for 7 days  
- sc-FOS  
- SOS  
- GOS  
- Type III resistant starch | DRR between scFOS and fecal bifidobacteria counts | DRR found for scFOS  
- No DRR for SOS, GOS, type III resistant starch  
- A low baseline bifidobacteria count was associated with the bifidogenic response to treatment (\( P < 0.001 \)) | |
| n = 40   | Double-blind, parallel-group, DRR study | sc-FOS at dose of 2.5, 5.0, 7.5, and 10 g/d or placebo for 7 days | DRR between the sc-FOS and fecal bifidobacteria counts | DRR bifidogenic effect from dose of 2.5 g/d | Bouhnik et al., 2006 |
| $n = 80$ | DRR study of NDCH at higher doses than 10 g/d | Prebiotic at dose of 10, 15, and 20 g/d vs. placebo for 7 days:  
  - Lactulose  
  - Inulin  
  - IMOS | Fecal bacterial count at d0 and d8 | Increase of bifidobacteria  
  - Lactulose at 20 g/d ($P < 0.05$)  
  - Inulin at 15 g/d ($P < 0.01$) and 20 g/d ($P < 0.05$)  
  - No linear DRR  
  - A low baseline bifidobacteria count was associated with the bifidogenic response to treatment | Bouhnik et al., submitted (a) |
| $n = 50$ | Randomized, double-blind, controlled study | Prebiotic for 15 days:  
  - sc-FOS 10 g/d  
  - Inulin 10 g/d | Fecal bacterial count at d0, d8, and d15 |  
  - At d8, bifidobacteria counts were higher in sc-FOS than in Inulin group ($P = 0.04$).  
  - At d15, bifidobacteria counts increased in both groups ($P < 0.01$) | Bouhnik et al., submitted (b) |
Bouhnik et al., 2004). Experimental data suggested that the importance of bifidogenic effects of sc-FOS and inulin could be related to their chain length. *In vitro* studies reported a difference in fermentation profile according to the chain length (Hidaka, 1986; Wang and Gibson, 1993). Moreover, a study performed in rats found that modifications in the fructan chain length could modulate the composition of the intestinal microflora (Kleessen, 2001). Therefore, a head-to-head comparison of sc-FOS and long-chain (lc) inulin (without small molecules) was performed in a randomized control trial including 50 volunteers (Bouhnik et al., submitted (b)). Bifidobacteria counts increased in both groups ($P < 0.01$), but the effects appeared quickly in sc-FOS group, probably because the fermentation was slower in lc inulin group.

### 3.2.1.2 Effect on Other Intestinal Bacteria

Even if the effects of fructans on the human gut microbiota were mainly investigated to search for a selective stimulation of bifidobacterial growth, other bacteria have been studied, such as lactobacilli, eubacteria, enterobacteria, enterococci (Kleessen, 2001; Apajalahti et al., 2002; Macfarlane et al., 2006; Louis et al., 2007). It has also been reported that FOS increased the colonization and translocation of *Salmonella* in an animal model (Ten Bruggencate et al., 2004). This was not observed, however, in human volunteers on a regular diet (Scholtens et al., 2006).

In another study, Kleessen et al. (2001) investigated changes in bacterial species in human flora associated rats fed on diets containing various mixtures of short- and long-chain fructose polymers. Bacteria were enumerated using FISH (fluorescent *in situ* hybridization) with group-specific probes. They showed that a mix of FOS and lc inulin or inulin alone enhanced the numbers of the clostridial cluster XIVa group, which was unaffected by FOS alone.

A recent human study using analysis by temporal temperature-gradient gel electrophoresis (TTGE) and fluorescent *in situ* hybridization also showed changes in the diversity and composition of dominant bacterial communities in response to dietary supplementation with hormone-related compounds combined with sc-FOS (Clavel et al., 2005). Overall, different groups of bacteria may be stimulated by fructans (Louis et al., 2007). For instance, fructan consumption may stimulate growth of *Roseburia inulinivorans*, which is a butyrate-producing inulin degrader belonging to clostridial cluster XIVa. The increased production of butyric acid from FOS, therefore, may be attributed in part to direct stimulation of butyrate-producing species (Manderson et al., 2005). It has also been recently shown that two distinct mechanisms of metabolic cross-feeding between *Bifidobacterium adolescentis* and butyrate-forming bacteria may operate in gut ecosystems, one due to consumption of fermentation end products (lactate and acetate) and the other due to cross-feeding of partial breakdown products from complex substrates (Belenguer et al., 2006).
3.2.1.3 Limits

Human studies performed to investigate the effects of fructans on faecal microflora present two main limits. The first one is that the initial level of bifidobacteria may have an impact on the microbiological results, as we recently demonstrated that a low baseline bifidobacteria count was an independent factor significantly associated with an increased count after treatment (Bouhnik et al., 2004). The second is the variability and the specificity in bacteria counting methods. This is a major point because proving the selective stimulation of growth and/or activity of bacteria by prebiotics is contentious and difficult to fulfill (Gibson et al., 2004). In recent years, the development of molecular methods helped to overcome limitations of microbiological plating methods (Tannock, 2002; Gibson et al., 2004; Mai and Morris, 2004; Zoetendal et al., 2004; Egert et al., 2006). Based on 16S rDNA sequence similarities, these methods indeed allow for gender and even species-specific bacteria counts (Matsuki et al., 2004). The main molecular methods are FISH, denaturing gradient gel electrophoresis (DGGE), quantitative dot-blot hybridization, restriction fragment length polymorphism (RFLP), and large-scale rDNA sequencing. Although these methods provide an advanced tool for accurate microbiota characterization, some shortcomings can be underlined: some predominant species—including bifidobacteria—may not be detected due to imperfect DNA denaturation (Wilson and Blitchington, 1996; Suau et al., 1999). Moreover, these methods are still limited by the relative paucity of sequenced gene fragments and the use of fecal biota as a surrogate for the entire gut microflora. Overall, a combination of conventional and molecular microflora analysis tools will help to better define the complexity of human microbiota and the effects of prebiotic candidates on it (Mai and Morris, 2004).

3.2.2 Effects of Fructans on Intestinal Functions

3.2.2.1 Stool Weight

In adults, nondigestible oligosaccharides may increase stool weight through an increase in bacterial biomass (Gibson and Roberfroid, 1995; Cummings et al., 2001; Cummings and Macfarlane, 2002; Marteau and Boutron-Ruault, 2002), leading to a reduction in transit time (Cummings et al., 1992; Spiller, 2003). This effect depends on the dose ingested and the polymerization degree of the oligosaccharide (Cummings et al., 2001; Marteau and Seksik, 2004). Another property of nondigestible oligosaccharides that may contribute to their effect of transit time is their gasogenic effect, which is supposed to trigger the acceleration of transit (AFSSA, 2005). In two studies (Gibson and Roberfroid, 1995; Den Hond et al., 2000), the increase in stool wet weight corresponded to 1.5 to 2.0 g per gram of FOS or lc inulin fed. This is less than that seen with nonstarchy polysaccharide sources, such as wheat bran (5.4 g) or fruit and vegetables (4.7 g), but similar to that produced by more rapidly fermented polysaccharides (soluble fibers), such as pectin, guar gum, and acacia gum (Cummings, 1993; Cherbut et al., 2003b). Three other human experiments did not
show any increase in stool weight after ingestion of fructans (Ikeda et al., 1994; Alles et al., 1996; Bouhnik et al., 1997), but in none of these studies was the subjects’ diets controlled, which would tend to mask a small effect.

3.2.2.2 Fermentation and Production of Short-Chain Fatty Acids

A major metabolic function of colonic microflora is the fermentation of nondigestible dietary residue, such as fructans. Fermentation of carbohydrates is a major source of energy in the colon. The metabolic end point is generation of short-chain fatty acids (SCFA: acetate, propionate, and butyrate; Salminen et al., 1998). All these fatty acids have important functions in host physiology, but butyrate seems to be the most interesting. First, its oxidation makes up for more than 70 percent of the oxygen consumption by the human colonic tissue, indicating that butyrate is the prime energy substrate of the colonocyte (Cummings and Macfarlane, 2002). Acetate and propionate are found in portal blood and are eventually metabolized by the liver (propionate) or peripheral tissues, particularly muscle (acetate). Acetate and propionate might also play a role as modulators of glucose metabolism: Absorption of these short-chain fatty acids would result in lower glycemic responses to oral glucose or standard meal—a response consistent with an ameliorated sensitivity to insulin. In fact, foods with a high proportion of nondigestible carbohydrates all have a low glycemic index (Thorburn et al., 1993; Englyst et al., 1999).

Each prebiotic may be characterized by its fermentation profile, for example, the relative proportion of acetate, propionate, and butyrate resulting from its fermentation. Among fructans, sc-FOS presents a high level of butyrate production during bacterial fermentation, as shown both in vitro (Wang and Gibson, 1993; Luo et al., 1996) and in vivo in animals (Le Blay et al., 1999; Pierre et al., 1999) and humans (Boutron-Rouault et al., 2005).

SCFAs are also able to modulate intestinal and colonic motility (Cherbut et al., 1997; Fich et al., 1998). They may stimulate contraction in the terminal ileum and shorten ileal emptying, which could protect the ileal mucosa against the potentially harmful effects of reflux of the colonic contents (Cherbut et al., 1996, 1997). Mechanisms of action of SCFA on gastrointestinal motility may involve systemic humoral and neural pathways (Cherbut et al., 1998) as well as reflexes and myogenic responses (Cherbut et al., 1996).

Colonic microorganisms also play a part in vitamin synthesis and in absorption of calcium, magnesium, and iron. Absorption of ions in the cecum is improved by carbohydrate fermentation and production of SCFAs (Guarner and Malagelada, 2003). Much research in experimental animals has shown positive effects of nondigestible oligosaccharides on calcium, magnesium, iron, and zinc absorption (Scholz-Ahrens et al., 2001). The mechanism underlying these positive effects is most likely related to increased solubility of these minerals in the cecum and the colon as a consequence of increased microbial fermentation and lower luminal pH.
3.2.2.3 Epithelial Cell Growth and Differentiation

Possibly, the most important role of SCFAs on colonic physiology is their trophic effect on the intestinal epithelium. The rate of production of crypt cells is reduced in the colon of rats bred in germ-free environments, and their crypts contain fewer cells than do those of rats colonized by conventional flora, suggesting that intraluminal bacteria affect cell proliferation in the colon (Guarner and Malagelada, 2003). Differentiation of epithelial cells is greatly affected by interaction with resident microorganisms. All three major SCFAs stimulate epithelial cell proliferation and differentiation in the large and small bowel in vivo. However, among the SCFAs produced by fermentation, butyrate has specific biological activities in the colon. Butyrate stimulates proliferation and differentiation in normal epithelial cell lines and has the opposite effects in transformed cell in vitro. Moreover, butyrate promotes reversion of cells from neoplastic to nonneoplastic phenotypes (Guarner and Malagelada, 2003). In pig also, FOS has been shown to stimulate SCFA production: a test diet containing FOS (10 percent) ad libitum for 10 days led to a significant increase in the concentration of SCFA, especially for n-butyrate (Tsukahara et al., 2003). sc-FOS, which presents a high level of butyrate production during bacterial fermentation (Tsukahara et al., 2003), thus may modulate cell proliferation in a beneficial manner.

3.2.2.4 Immunity

The intestinal mucosa is the main interface between the immune system and the external environment. Thus, it is not surprising that gut-associated lymphoid tissues contain the largest pool of immunocompetent cells in the human body. The colonic microflora, especially bifidobacteria, has been reported to exert a high influence on the immune system of the host, such as mitogenic or adjuvant activities, promotion of macrophages, stimulation of antibody production, and antitumor effects (Salminen et al., 1998; Bornet et al., 2002).

In children, a controlled study showed that a preparation of cereals containing a mixture of inulin and FOS (0.2 g/kg of body weight) increased vaccinal immunoglobulin G (IgG) levels 10 weeks after immunization of the infant against measles (Firmansyah et al., 2001). The level of positive reaction with adequate IgG response was 96 percent in children receiving the prebiotic compared with 88 percent in the control infants. There was no difference in the levels of antimeasles IgM. A recent study (Bakker-Zierikzee et al., 2006) also demonstrated a significant increase in fecal secretory IgA in infants who received a formula enriched with a mix of GOS and FOS (0.6 g/100 mL) compared to a standard group. This mix of prebiotics, which stimulates bifidobacteria and leads to a fermentation profile close to the one found in breastfed children, was often studied and appeared as beneficial for infants (Moro et al., 2003; Boehm et al., 2004; Decsi et al., 2005; Knol et al., 2005).

Atopic diseases, such as atopic eczema, allergic rhinitis, and asthma, are increasing in Western societies, demanding rapid comprehension and prevention. Several
promising studies have been conducted with probiotics (Kalliomaki et al., 2003; Ishida et al., 2005; Weston et al., 2005; Ishida et al., 2006), but the potential effects of prebiotics in children on atopic eczema, either therapeutic or preventive, are little known (AFSSA, 2003). Similarly, no studies are available demonstrating a significant effect of a prebiotic on allergic conditions in adults (AFSSA, 2005). However, in patients with atopic eczema a correlation was shown between the amount of bifidobacteria and the severity of atopic eczema (Bunselmeyer, 2006) and recent studies proved the efficiency of consumption of synbiotics, such as Lactobacillus casei subsp. casei with dextran (Ogawa et al., 2006), on the prevention and treatment of allergic reactions in adults (pollen allergy) or children (atopic dermatitis) (Passeron et al., 2006). On the contrary, two studies reported allergic reactions after consumption of foods containing inulin (Salminen et al., 1998; Gay-Crosier et al., 2000).

### 3.2.3 The Barrier Effect

Resident bacteria are a crucial line of resistance to colonization by exogenous microbes and, therefore, are highly relevant in protecting the internal medium of the host against pathogenic organisms and toxic substances (Cherbut, 2003). It is probably through their effects on the colonic flora that prebiotics are able to reinforce the intestinal barrier as it has been demonstrated that inulin and FOS modify the profile of bacterial biofilms associated with the intestinal mucosa (Cummings and Macfarlane, 2002). Studies in animal models implanted or not with human flora suggested favorable effects of inulin and FOS on intestinal mucosa, e.g., increase of the thickness of the mucin layer and of the number of mucus-containing cells (Hoebler et al., 2002; Kleessen et al., 2003), and modification of the distribution between neutral, acidic, and sulfated mucins in favor of sulfated mucins, possibly more protective (Fontaine et al., 1996). A clinical study conducted in humans failed to show a change in mucin expression (Meijer et al., 2000). Gaudier et al. (2004) suggested that the effects of fructans on mucins could be mediated by the production of butyrate because this SCFA increases the production of certain mucin genes (MUC3) (Gaudier et al., 2004). As mentioned by Fowler et al. (2003), mucins are highly heterogeneous among individuals, so that the effect of fructans could be different depending on the subject.

However, prebiotics also could have deleterious effects on the intestinal barrier. A study found that inulin and FOS increased the hepato-splenic translocation of salmonella in vivo in rats (Ten Bruggencate et al., 2004). In healthy humans, a recent placebo-controlled cross-over study found that FOS consumption (20 g/day over a 2-week period) doubled fecal mucin excretion indicating mucosal irritation (Ten Bruggencate et al., 2006). These results have to be balanced by the fact that overall observed effects were more moderate than those in rats and that the dose ingested was relatively high, especially as it was added in a liquid food (lemonade), leading to increased flatulence and intestinal bloating. Overall, the effect of fructans on the intestinal barrier should be further studied in well-designed clinical trials in humans.
3.3 EFFECTS OF FRUCTANS ON GASTROINTESTINAL DISEASE

3.3.1 Infectious Diarrhea

The efficacy of probiotics in prevention of acute diarrhea in children and in adults has been recently demonstrated in a meta-analysis; even though most pronounced on antibiotic-associated diarrhea, a significant effect was also observed in nonantibiotic-associated diarrhea and nontravelers’ diarrhea (Sazawal et al., 2006).

Prebiotics—either alone or in addition to a probiotic—have been less extensively studied in this situation. The main studies carried out to assess the effects of fructans in the prevention or treatments of acute diarrhea are reported in Table 3.3.

In infants, a mix of a probiotic and oligofructose decreased duration of acute diarrhea compared to control (Ahmas et al., 2000; Agustina et al., 2007). Oligofructose has been recently found effective in preventing intestinal disturbances in very young children (Waligora-Dupriet et al., 2007). In infants living in a community with a high burden of gastrointestinal and other infections, oligofructose failed to show any benefit for prevention of diarrhea (Duggan et al., 2003).

In adults, oligofructose significantly decreased the relapse of diarrhea associated with *Clostridium difficile* (Lewis et al., 2005). In a randomized, double-blind, controlled study, 244 healthy subjects, traveling to high- and medium-risk destinations for travelers’ diarrhea, consumed FOS at 10 g/day during 2 weeks before the trip and during the 2-week trip (Cummings et al., 2001). If there were no significant differences in the primary end points of bowel frequency or consistency between the two groups, as recorded in bowel habit diaries, subjects taking FOS experienced less severe attacks of diarrhea than subjects in the placebo group. These results are indicative of a benefit of prebiotics, but not conclusive.

3.3.2 Inflammatory Bowel Disease

The enthusiasm with which probiotics have been used in inflammatory bowel disease (IBD) and their apparent benefits have led to the suggestion that prebiotics might also be useful (Sartor, 2004). Reports of animal studies are quite numerous, and overall they show a benefit in reducing symptoms, including inflammation, with appropriate increases in bifidobacteria or lactobacilli, and in some reports, in concentrations of butyrate in the gut. These effects are seen across a wide range of models of IBD, and with varying oligofructose (Cherbut et al., 2003a; Moreau et al., 2003).

The main studies carried out to assess the effects of fructans in the prevention or treatments of IBD are reported in Table 3.4.

Two controlled studies that evaluated prebiotics in association with mesalazine or probiotic in ulcerative colitis gave contradictory results (Furrie et al., 2005; Casellas et al., 2007).

In a small open-label trial in humans, 10 patients with active ileocolonic Crohn’s disease were given 15 g FOS daily for 3 weeks (Lindsay et al., 2006). A significant
Table 3.3 Main Randomized Controlled Clinical Studies Using Fructan Prebiotic In Prevention Or Treatment Of Acute Diarrhea

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study Design</th>
<th>Prebiotic Type, Consumption</th>
<th>Method/end Points</th>
<th>Main Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesian well-nourished male infants, aged 3–12 months, Acute diarrhea with moderate dehydration n = 58</td>
<td>Randomized double-blind clinical trial</td>
<td>Special infant formula containing probiotic, prebiotic, and supplements vs. control</td>
<td>Duration of diarrhea</td>
<td>Diarrhea significantly shorter in the study group than in the control group (1.63 vs. 2.45 days; p &lt; 0.05).</td>
<td>Agustina et al., 2007</td>
</tr>
<tr>
<td>Infants in a community with a high burden of gastrointestinal and other infections n = 282</td>
<td>Randomized controlled trial 1</td>
<td>Infant cereal supplemented with oligofructose (0.55 g/15 g cereal) or not supplemented</td>
<td>Duration of diarrhea</td>
<td>Mean (± SD) days of diarrhea were 10.3 ± 9.6 in the nonsupplemented cereal group and 9.8 ± 11.0 in the prebiotic-supplemented cereal group (P = 0.66).</td>
<td>Duggan et al., 2003</td>
</tr>
<tr>
<td>Infants in a community with a high burden of gastrointestinal and other infections n = 349</td>
<td>Randomized controlled trial 2</td>
<td>Zinc (1 mg/15 g cereal) added to both oligofructose-supplemented and nonsupplemented cereals</td>
<td>Duration of diarrhea</td>
<td>Mean days of diarrhea were 10.3 ± 8.9 in the group consuming cereal fortified only with zinc and 9.5 ± 8.9 in the group consuming cereal containing both zinc and prebiotics (P = 0.35).</td>
<td></td>
</tr>
<tr>
<td>Consecutive inpatients with C. difficile-associated diarrhea n = 142</td>
<td>Randomly allocation</td>
<td>Oligofructose or placebo for 30 days in addition to specific antibiotic treatment</td>
<td>Prevention of further diarrhea</td>
<td>Relapse of diarrhea was observed in 34% with placebo and 8% with oligofructose (P &lt; .001).</td>
<td>Lewis et al., 2005</td>
</tr>
<tr>
<td>Healthy subjects, traveling to high- and medium-risk destinations for travelers’ diarrhea n = 244</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>10 g FOS or placebo daily for 2 weeks before travel</td>
<td>Prevention of further diarrhea</td>
<td>11.2% in FOS group and 19.5% in placebo (p = 0.08)</td>
<td>Cummings et al., 2001</td>
</tr>
</tbody>
</table>

a Special antidiarrhea infant formula containing probiotic (Lactobacillus rhamnosus LMG P-22799; 5 × 10⁸ colony-forming units/100 mL), prebiotic (inulin 0.15 g/100 mL), fiber (soy polysaccharides: 0.2 g/100 mL), and iron + zinc.
Table 3.4 Main Randomized Controlled Clinical Studies Using Fructan Prebiotic In Patients with Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study Design</th>
<th>Prebiotic Type, Consumption</th>
<th>Method/End Points</th>
<th>Main Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with active ulcerative colitis Mesalazine (3 g/day) n = 21</td>
<td>Randomized, placebo-controlled pilot trial</td>
<td>Oligofructose-enriched inulin (n = 10) or placebo (n = 9) 12 g/day, p.o. 2 weeks</td>
<td>Activity score Fecal calprotectin</td>
<td>• Rachmilewitz score decreased in both groups (P &lt; 0.05) • Reduction of calprotectin in oligofructose-enriched inulin group (P &lt; 0.05)</td>
<td>Casellas et al., 2007</td>
</tr>
<tr>
<td>Subjects with active ulcerative colitis n = 18</td>
<td>Randomized, placebo-controlled pilot trial</td>
<td>Symbiotic(^a) or placebo bid 2 weeks</td>
<td>Clinical activity index (CAI) Intestinal biopsies Inflammatory markers</td>
<td>• CAI (NS) • IB (P = 0.06) trends in favor of symbiotic • Human betadefensin, tumor necrosis factor-α, interleukin-1α β (P &lt; 0.01)</td>
<td>Furrie et al., 2005</td>
</tr>
<tr>
<td>Patients with active ileocolonic Crohn's disease n = 10</td>
<td>Small open-label trial</td>
<td>scFOS 15 g/d for 3 weeks</td>
<td>Activity index Intestinal biopsies</td>
<td>• FOS induced a significant reduction in the Harvey Bradshaw index (p &lt; 0.01) • The percentage of IL-10 positive dendritic cells increased from 30 to 53% (p = 0.06)</td>
<td>Lindsay et al., 2006</td>
</tr>
<tr>
<td>Stable asymptomatic pouchitis n = 24</td>
<td>Randomized double-blind cross-over study</td>
<td>Enteral supplementation of inulin or placebo (24 g/d) for 3 weeks</td>
<td>Pouchitis disease activity index Intestinal flora</td>
<td>Compared with placebo, inulin: • Increased butyrate concentrations • Lowered pH • Decreased numbers of Bacteroides fragilis • Diminished concentrations of secondary bile acids in feces • Decreased inflammation endoscopically and histologically</td>
<td>Welters et al., 2002</td>
</tr>
</tbody>
</table>

\(^a\) Symbiotic combined a probiotic, *Bifidobacterium longum*, isolated from healthy rectal epithelium, and a prebiotic (Synergy 1), a preferential inulin-oligofructose growth substrate for the probiotic strain. Test patients were given 2 × 10\(^{11}\) freeze-dried viable *B. longum* in a gelatin capsule and a sachet containing 6 g of prebiotic fructo-oligosaccharide/inulin mix (Synergy 1; Orafti, Tienen, Belgium) consisting of a probiotic, *B. longum* W11, and the sc-FOS or biotic.
reduction in the Harvey Bradshaw index of disease activity was observed, and fecal bifidobacteria increased from \( \log_{10} 8.8 \) to \( \log_{10} 9.4 \) cells per gram dry feces. The proportion of dendritic cells expressing Toll-like receptors TLR2 and TLR4 also increased (\( p < 0.001 \)).

Patients with pouchitis do well with probiotics, and one successful study has been reported in which prebiotics were used for this condition (Welters et al., 2002). In a randomized double-blind cross-over study, 24 patients with stable asymptomatic pouchitis were given 24 g of inulin or placebo daily, for 3 weeks each. At the end of the prebiotic period, results showed that there was a reduction in the endoscopic and histological pouchitis disease activity index (PDAI) score, together with lower gut pH, and reductions in fecal \( \text{Bacteroides fragilis} \) and secondary bile acids. Butyrate concentrations were increased, while symptom scores were low initially, and were essentially unchanged.

The link between intestinal microflora and IBD is now well established and the use of prebiotics, therefore, might be a promising therapeutic strategy for ameliorating chronic intestinal inflammation (Andoh and Fujiyama, 2006; Ewaschuk and Dieleman, 2006).

### 3.3.3 Irritable Bowel Syndrome

There are currently no published full papers of randomized controlled trials (RCT) concerning the use of prebiotics in irritable bowel syndrome (IBS). A number of studies using probiotics have been carried out with varying benefits, but the pathogenesis of IBS may preclude the use of prebiotics in this condition. In fact, there are several recent reports of low-grade mucosal inflammation in IBS with increased mucosal T lymphocytes in both unselected diarrhea-predominant IBS (Chadwick et al., 2002) as well as those whose IBS begins with an acute episode of bacterial gastroenteritis (Spiller, 2003; Marshall et al., 2007). These results suggest that IBS could be a subclinical inflammatory bowel disease and an intervention on intestinal bacteria could improve symptoms.

The main studies carried out to assess the effects of fructans in the prevention or treatments of IBS are reported in Table 3.5. Only two open-label multicenter studies evaluated the effects of prebiotic in constipation-predominant IBS, with interesting results in term of digestive comfort and stool frequency (Colecchia et al., 2006; Dughera et al., 2007).

### 3.3.4 Colonic Tumors

Intestinal bacteria could play a part in initiation of colon cancer through production of carcinogens, cocarcinogens, or procarcinogens. In healthy people, diets rich in fat and meat, but poor in vegetables, increase the fecal excretion of \( N \)-nitroso compounds, a group of genotoxic substances that are known initiators and promoters of colon cancer (Guarner and Malagelada, 2003). Another group of carcinogens of dietary origin is the heterocyclic aromatic amines that are formed in meat when it is cooked. Some intestinal microorganisms strongly increase damage to DNA in colon cells induced by heterocyclic amines, whereas other intestinal bacteria can uptake
Table 3.5 Main Clinical Studies Using Fructan Prebiotic In Patients With Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study Design</th>
<th>Prebiotic Type, Consumption</th>
<th>Method/End Points</th>
<th>Main Results</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| Patients with constipation-type IBS n = 636 (250 men, 386 women) | Open-label, prospective, uncontrolled, multicenter trial | Synbiotic\(^a\) at a dose of 3 g/d for at least 36 days | Roma II criteria | • In the more severe symptoms classes (moderate-severe), symptom frequency dropped significantly for bloating and abdominal pain  
• Stool frequency significantly increased | Colecchia et al., 2006 |
| Patients with constipation-type IBS n = 129 | Open-label, prospective, uncontrolled, multicenter trial | Synbiotic zir fos\(^b\) 3 g/d for 3 months | Rome II criteria at T0, T1, and T3 | • Total symptom frequency reduction was observed at T1 and T3 vs. T0 (p < 0.0001)  
• An increase of stool frequency (p < 0.0001) | Dughera et al., 2007 |

\(^a\) Synbiotic consisting of a probiotic, *Bifidobacterium longum* W11, and the scFOS or biotic.

\(^b\) A synbiotic drug (zir fos Alfa Wassermann, Alanno Scalo, Pescara, Italy) constituted by a probiotic, *B. longum* W11 (5 × 109 cfu), and by a prebiotic short-chain oligosaccharide, Fos-Actilight\(^b\) (2.5 g).
and detoxify such compounds (Wollowski et al., 2001). Bacteria of the *Bacteroides* and *Clostridium* genera increase the incidence and growth rate of colonic tumors induced in animals, whereas other genera, such as *Lactobacillus* and *Bifidobacterium* prevent carcinogenesis (Pool-Zobel, 2005). Although the evidence is not conclusive, colonic flora seems to be a major environmental factor that modulates risk of colonic cancer in humans (Guarner and Malagelada, 2003).

Numerous studies have shown that inulin-type fructans prevent chemically induced preneoplastic lesions, aberrant crypt foci (ACF), and tumors in the colon of rats and mice (Pierre et al., 1999, 2001; Wollowski et al., 2001; Pool-Zobel et al., 2002, 2005). Contradictory studies have been shown to enhance adenoma growth in mice (Pajari et al., 2003; Misikangas et al., 2005, 2008).

In humans, several trials have been carried out to examine possible effects of prebiotics on colonic carcinogenesis. These trials used fecal butyrate concentration, fecal bile acids, and rectal crypt cell proliferation as promising surrogate markers for the risk of colorectal carcinogenesis (Rafter, 2002). Fecal bacterial enzymatic activities, such as β-glucuronidase, have been extensively studied as they may play a role in the metabolic activation of procarcinogens and deconjugation processes in the colonic lumen (Goldin, 1990). Some trials have been performed in healthy volunteers, with the aim to modify some potential marker of colon carcinogenesis.

Fecal bacterial β-glucuronidase activity is increased in patients on a high meat diet, and this enzyme could act to raise the amount of substances, such as carcinogens, within the colonic lumen (Reddy et al., 1998). In a previous study, we demonstrated that sc-FOS ingestion led to a significant decrease in β-glucuronidase activity (Bouhnik et al., 1996). In a recent RCT, 15-day consumption of 10g/day sc-FOS in healthy subjects has been shown to reduce the activity of β-glucuronidase in fecal samples, whereas consumption of 15 g/day lc inulin over the same period did not change enzymatic activities (Bouhnik et al., 2007). Similar results were found by Kleessen et al., who did not demonstrate changes in β-glucuronidase activity following lc inulin consumption for 19 days at doses ranging from 20 to 40 g/day (Kleessen et al., 1997).

Three interventional studies using fructans or synbiotics in patients with polyps or cancer have been published (Boutron-Rouault et al., 2005; Rafter et al., 2007; Roller et al., 2007) (Table 3.6). In one of them, the effect of a 3-month consumption of 10 g/day sc-FOS on these markers was assessed in subjects with large (>10 mm) or small adenomas (<10 mm), or in healthy subjects (Boutron-Rouault et al., 2005). The butyrate concentration, which was initially significantly lower in subjects with adenomas compared to healthy subjects, significantly increased to the level found in healthy subjects after the 3-month sc-FOS consumption. If there is little doubt that butyrate may exert an effect on colon cancer development, exact mechanisms by which butyrate acts remain unclear. Variable effects could indeed be obtained according to the in vivo or in vitro environments, the timing of butyrate administration in relation to the stage of cancer development, the amount of butyrate administered, as well as an interaction with dietary fat (Lupton, 2004). For example, prebiotics may be protective against the early stages of polyp formation, but not at the stage of transition of polyp to a carcinoma, and low amounts of butyrate may stimulate cell proliferation.
while high amounts may inhibit it (Lupton, 2004). In the study performed by Rafter et al. (2007), the synbiotic intervention resulted in significant alterations in the composition of the colonic bacterial ecosystem, which presumably have consequences for the metabolic activity of this organ. These results also provide indirect evidence that some of the consequences of the synbiotic intervention might be decreased exposure of the epithelium to cytotoxic and genotoxic agents, decreased colonic cell proliferation, and improved mucosa structure. These exciting results suggest that synbiotics may represent a feasible means of chemoprevention of colon cancer in humans.

### 3.4 EFFECTS OF FRUCTANS ON METABOLISM OF MINERALS AND VITAMINS

Demonstrating an effect of a given food factor on mineral bioavailability in humans is difficult for methodological reasons (Guéguen and Pointillart, 2000; Scholz-Ahrens et al., 2001). The choice of relevant biological markers is essential. Abrams et al. (1994) showed that calcium absorption can be correctly measured using either the chemical balance or the dual-stable-isotope methods. But the site (serum or urines samples) as well as the timing (e.g., urine collected less or more than 24 hours after tracer administration) for markers measurement chosen can also induce various interpretations of results as observed on trials dealing with nondigestible oligosaccharides (Coudray and Fairweather-Tait, 1998).

#### 3.4.1 Fructans and Calcium Absorption

A review on calcium (Ca) consumption in France revealed that a large part of the population consumes less than two-thirds of the recommended dietary allowance (RDA), the critical threshold for defining groups at risk (Guéguen, 1996). Therefore, there is real public health interest in studying the impact of prebiotics, such as fructans, on Ca absorption, especially for prevention of osteoporosis.

In adolescents, van den Heuvel et al. (1998) found that 15 g/day inulin, FOS, or GOS had no effect on the intestinal absorption using the dual-stable-isotope method. Griffin et al. (2003) showed that the main determinant of the effect of fructans in preadolescents was “Ca absorption during the placebo period.” In fact, individuals with lower Ca absorption during the placebo period had the greatest increase in Ca absorption. Regarding the nature of the prebiotic tested, a study in adolescent girls demonstrated that 8 g/day of a mixture of inulin and oligofructose significantly increased Ca absorption while 8 g/day of oligofructose alone had no effect (Griffin et al., 2002), confirming previous findings in animals (Coudray et al., 2003; Kruger et al., 2003).

In young men, Coudray et al. showed that 40 g inulin per day increased Ca absorption using the chemical balance (Coudray et al., 1997). In postmenopausal women, Holloway et al. (2003) tested a mixture of inulin and oligofructose for 6 weeks (Holloway et al., 2003), showing no effect of prebiotics on Ca absorption, but a great variation in individual responses to the treatment. Interestingly, the efficacy
Table 3.6 Main Randomized Controlled Clinical Studies Using Fructan Prebiotic For Effect In Patients With Colonic Polyps And/Or Cancer

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study Design</th>
<th>Prebiotic Type, Consumption</th>
<th>Method/end Points</th>
<th>Main Results</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| Colon cancer with “curative resection” (n = 34) Polypectomized patients (n = 40) | Randomized double-blind, placebo-controlled trial | Encapsulated bacteria and 10 g of inulin enriched with oligofructose (SYN group) or placebo once daily | Modulation of immune functions | • In the cancer group, SYN resulted in an increased capacity of PBMC to produce interferon-gamma ($P < 0.05$)  
• In the polyp group, IL-2 secretion by activated PBMC increased ($P < 0.05$) | Roller et al., 2007 |
| Colon cancer (n = 37) Polypectomized (n = 43) | Randomized, double-blind, placebo-controlled trial (phase 2 study) | Symbiotic food composed of the prebiotic SYN1—a mixture of short-chain and long-chain inulin (SYN1)—and probiotics LGG and BB12 vs. placebo for 12 weeks | Reduction in cancer risk biomarkers in stools and intestinal mucosa | In all patients:  
• Increase of Bifidobacterium and Lactobacillus  
• Decrease of Clostridium perfringens  
• Reduction in colorectal proliferation and the capacity of fecal water to induce necrosis in colonic cells  
In polypectomized patients:  
• Improvement of epithelial barrier function  
• Decreased exposure to genotoxins  
• Prevention of an increased secretion of IL-2 by peripheral blood mononuclear cells  
In cancer patients:  
• Increase in interferon-gamma production | Rafter et al., 2007 |
<table>
<thead>
<tr>
<th>Subjects with small colorectal adenoma(s) (n = 26)</th>
<th>Interventional study sc-FOS 10 g/d for 3 month</th>
<th>Reduction in cancer risk biomarkers in stools</th>
<th>The mean fecal butyrate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With large adenoma(s) (n = 18)</td>
<td></td>
<td></td>
<td>• Was lower at baseline concentration in the adenoma groups than in the adenoma-free group</td>
</tr>
<tr>
<td>With no adenoma (n = 30)</td>
<td></td>
<td></td>
<td>• Was increased in this group after 3-mo ingestion of sc-FOS (P = 0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In subjects without adenoma:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• sc-FOS ingestion was associated with a decrease in fecal lithocholic acid (P = 0.02) and an increase in cholic acid (P = 0.02), chenodeoxycholic acid (P = 0.04), total primary bile acids (P = 0.03), and ursodeoxycholic acid (P = 0.05)</td>
</tr>
</tbody>
</table>

*Boutron-Rouault et al., 2005*

---

\(a\) 1 × 10^{10} colony-forming units of *Lactobacillus rhamnosus* GG (LGG) and 1 × 10^{10} colony-forming units of *Bifidobacterium lactis* Bb12.

\(b\) Peripheral blood mononuclear cells.

\(c\) Synbiotic preparation-oligofructose-enriched inulin (SYN1) + *L. rhamnosus* GG (LGG) and *B. lactis* Bb12.
of the treatment seemed to be higher in women with lower initial bone density of the spine (Coxam, 2005). In addition, genetic factors (such as vitamin D receptor gene polymorphism) may also be associated with differences in sensitivity to the effects of fructans (Abrams et al., 2005).

A physiological retro-control mechanism provides good intestinal regulation of Ca absorption, thanks to the calcium-binding protein. As it is highly regulated, a high impact of fructans on this absorption is not expected. Overall, the increase of Ca absorption under fructans would only have weak amplitude and few long-term nutritional consequences.

### 3.4.2 Fructans and Absorption of Magnesium, Copper, Selenium, and Zinc

Positive effects of fructans on magnesium (Mg) absorption were naturally expected in humans because, in contrast to Ca, Mg absorption occurs mainly passively and is not regulated depending on intakes and requirements. First results from animal models indicated stimulant effects of fructans on Mg absorption (Rémésy et al., 2002). This has been confirmed for sc-FOS and Mg absorption in a recent study in humans: An increase of 11 percent of relative magnesium absorption was observed after administration of 7 to 10 g/day sc-FOS during 5 weeks in postmenopausal women (Tahiri et al., 2001). Even on Mg, only a weak effect (increase by 10 to 20 percent) can be induced by FOS. However, about 20 percent of the population has Mg intakes lower than two-thirds of RDA. This property of FOS, therefore, could have an impact, even if small, on subjects with insufficient food Mg intakes.

A randomized double-blind, placebo-controlled trial showed that feeding 10 g of FOS per day for 5 weeks increased the absorption of copper in healthy postmenopausal women (Ducros et al., 2005). However, no effects were seen in relation to zinc and selenium uptake. This selectivity would suggest that factors other than simple acidification of luminal contents were involved.

### 3.4.3 Fructans and Isoflavone Metabolism

Fructans may have a beneficial effect on the metabolism of isoflavones, which have been shown to prevent postovariectomy bone loss in rats and mice (Tokunaga, 2004; Coxam, 2005). In ovariectomized mice (Ohta et al., 2002) or rats (Mathey et al., 2004), two experimental models for postmenopausal osteoporosis, oligofructose (sc-FOS) consumption has been shown to increase the bone-sparing effect of isoflavones by improving equol production. However, opposite results were reported in the study of Zafar et al. (2004) as isoflavones enhanced Ca absorption without synergy from inulin, and inulin decreased equol production in rats. In humans, a 2-month intervention trial on 39 postmenopausal women showed that addition of prebiotics (sc-FOS) or probiotics, by partially modulating the bioavailability of soy isoflavones, improved parameters of bone turnover (Coxam, 2005).
3.4.4 Fructans and Vitamin Production

As mentioned by Gibson and Roberfroid (1995), bifidobacteria produce vitamins, mainly from the B-complex (Gibson and Roberfroid, 1995). In an in vitro study, Noda et al. (1994) emphasized the fact that bifidobacteria strains, such as B. bifidum, produced biotin (vitamin B₈) extracellularly. Folic acid and vitamin K are also produced by bifidobacteria. Therefore, it could be thought that consumption of prebiotics, thanks to their stimulation on bifidobacteria growth, could have beneficial effects for subjects deficient in vitamin K or B. However, quantities of vitamins produced by bifidobacteria are very limited compared to dietary allowance (RDA), suggesting that prebiotic stimulation of bifidobacteria is not sufficient to exert significant effects on vitamin status.

3.4.5 Fructans and Absorptive-Productive Functions

Although the number of studies on the effect of nondigestible oligosaccharides on mineral metabolism in humans is limited, so far, positive effects on Ca absorption seem to occur under conditions of increased Ca requirements (e.g., adolescence and postmenopause). The extent of the effect seems to be specific for the type of carbohydrate. Contradictory results on the effect of prebiotics in the literature may be due to differences in the experimental design. Several experimental conditions promoted the stimulation of Ca absorption and retention by nondigestible oligosaccharides, such as high dietary Ca, an optimum dose of prebiotics, sufficient duration of administration, and the age of subjects (Scholz-Ahrens et al., 2001).

Despite the belief that Ca absorption is thought to occur in the proximal gut in humans, a colonic phase may exist. Ellegard et al. (1997) showed that neither inulin nor FOS when fed to ileostomy subjects had any effect on ileostomy excretion of Ca, Mg, zinc, or iron. Because prebiotic carbohydrates pass through the small bowel unchanged, but are fermented in the cecum or colon, a large bowel effect on absorption is possible (Macfarlane et al., 2006).

3.4.6 Metabolic Parameters and Satiety

Recent research has been reported concerning the effect of fructans on satiety and control of energy intake. The available data suggest a beneficial effect of inulin and FOS in modulating energy balance in humans consuming diet ad libitum. In a recent pilot study (Cani et al., 2006), 10 healthy volunteers were included in two 2-week phases during which they received twice a day either 8 g oligofructose or 8 g placebo (maltodextrin), with each phase separated by a 2-week wash-out period. It appeared that oligofructose treatment increases satiety following breakfast and dinner and reduces hunger and prospective food consumption following dinner. However, total energy intake per day was only 5 percent lower during the oligofructose than the placebo periods, what should not have a high impact on the body mass index of subjects.
3.5 DIGESTIVE TOLERANCE OF FRUCTANS

Fermentation of NDCHs in the colon by the microflora produces gases (H\textsubscript{2}, CH\textsubscript{4}, and CO\textsubscript{2}), which may cause flatulence, abdominal pain, or osmotic diarrhea. It appears that digestive tolerance thresholds for prebiotics are clearly influenced by the chemical nature of the prebiotic, the administered dose, and individual factors (Marteau and Seksik, 2004). The individual factors include visceral sensitivity and differences in bacterial profile of the colonic flora (Cherbut, 2003); it has been seen that populations of lactate-utilizing bacteria in subjects reporting the highest number of symptoms of discomfort following consumption of FOS were different from subjects reporting no disturbance (Cherbut, 2003). Digestive tolerance is also influenced by the type of food (differing mainly between solid and liquid food) and the way of consumption (isolated consumption outside meal times favors symptoms) (Absolonne et al., 1995). Overall, it is important to note that digestive tolerance thresholds for NDCHs are significantly higher than efficient doses, which supports the interest in prebiotics as a safe and beneficial modulation of gut microflora.

Besides the evaluation of digestive tolerance of fructans, an increased interest in their impact on the quality of life of subjects is to be noted. In a recent study, it appeared that the regular consumption of sc-FOS at moderate doses (5 g/day over 6 weeks) can improve digestive comfort and daily quality of life in a working and nonmedically treated population suffering from minor functional bowel disorders (Paineau et al., 2008). This was the first study to assess the effects of prebiotics on quality of life with the use of relevant evaluation methods. A quality-of-life questionnaire was completed at the start and end of the treatment period to assess potential effects on well-being and social performance. At the end of the consumption period, the intensity of digestive disorders decreased by 43.6 percent in the sc-FOS group versus a 13.8 percent increase in the placebo group ($P = 0.026$). Expressed as change in quality of life (improvement, worsening, or unchanged), daily activities were significantly improved in the sc-FOS group ($P = 0.022$).

3.6 CONCLUSIONS

Prebiotics are widely available food ingredients that may exert a number of beneficial effects on human health. Most of these effects are mediated through their bifidogenic properties. Promising effects include a benefit in different situations in gastroenterology, such as infectious diarrhea, IBS, IBD, and colonic carcinogenesis. Objectives of future studies must investigate mechanisms in humans to define the optimal consumption of prebiotics. Well-controlled clinical trials in humans are needed especially in IBS, IBD, and prevention of colonic polyps, which are all major and increasing health problems in industrialized countries.
ACKNOWLEDGMENTS

Competing interests: DP and YB have no competing interests; FR is affiliated with Beghin-Meiji, Marckolsheim, France. Author’s contribution: All authors participated in the manuscript writing. All authors read and approved the final manuscript.

REFERENCES


Bouhnik Y, Paineau D, Attar A, Andrieux C, and Bornet F. Influence of fructans chain length on the capacity to stimulate bifidobacterial growth in humans: Comparison between short-chain fructooligosaccharides and long chain inulin. Submitted (b).


Ellegard L, Andersson H, and Boseus L (1997) Inulin and oligofructose do not influence the absorption of cholesterol or the excretion of cholesterol, Ca, Mg, Zn, Fe or bile acids but increase energy excretion in ileostomy subjects. *Eur J Clin Nutr* 51, 1–5.


