



Active Food Scientific Monitor



Interview

with
Dr. Francisco
Guarner

In this issue we present an
interview with Dr. Francisco

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Dr. Francisco Guarner is Consultant of Gastroenterology and Head of the Experimental Laboratory of the Digestive System Research Unit, Hospital Vall d'Hebron, in Barcelona. He studied at the School of Medicine of the University of Barcelona and the University of Navarra, Pamplona. He is a member of the Board of Directors of the International Scientific Association for Probiotics and Prebiotics (ISAPP) and of the editorial board of *Gastroenterología y Hepatología*, *Experimental and Clinical Gastroenterology*, and a reviewer of *Gut*, *Gastroenterology*, *American Journal of Gastroenterology*, *European Journal of Clinical Investigation*, *Scandinavian Journal of Gastroenterology*, *Journal of Nutrition* and *American Journal of Clinical Nutrition*.

His main research interests concern inflammatory bowel diseases, intestinal immunity, colonic microflora and prebiotics. In winter, Dr. Guarner likes to go skiing. "We are very lucky to live in Barcelona as the mountains are very close. So, during the week-ends we go often skiing with the children. On the other hand, Barcelona is also very close to the sea. This gives us the opportunity in summertime to go sailing. We have a small sailing boat and in the summer we spend most week-ends on the sea."

The role of prebiotics in the management of inflammatory bowel diseases

Why are prebiotics so important to maintain digestive health?

The human gut is the natural habitat for a large and dynamic bacterial community. The relevance and effect of resident bacteria on host's physiology and pathology have been well documented. Major functions of the gut microflora include metabolic activities that result in salvage of energy and absorbable nutrients, important trophic effects on the intestinal epithelium, regulation of immune structure and function, and protection of the colonised host either against invasion by foreign microbes or against overgrowth by indigenous species with potential pathogenicity.



P R E F A C E

by Dr. Anne Franck



ORAFTI's 4th Research Conference on 'Inulin and Oligofructose: Feelgood Factors for Health and Well-being' has demonstrated once again, the extraordinary

potential for chicory inulin and oligofructose to make a real impact on our health and well-being.

The Conference, which took place in February at the Cité des Sciences et de l'Industrie in Paris, France, gathered together the world's experts in prebiotics and gastrointestinal health, and an invited audience of around 200 scientists from the fields of food, nutrition and health.

Papers were presented on subjects as varied as inulin, oligofructose and gastro-intestinal health and well-being, resistance to gastro-intestinal infections, immune system modulation, mineral absorption and bone health, lipid metabolism, modulation of gut hormones, or application in infant foods.

One of the highlights of the conference was a report of the latest results from the SYNCAN project, an EU-sponsored research programme co-ordinated by ORAFTI. The aim of the project was to investigate whether pro-, pre- and synbiotics can reduce the risk of colorectal cancer. A key part of the project is a human volunteer study. The double-blind, placebo-controlled study involved 80 human volunteers receiving a synbiotic treatment (consisting of Raftilose®Synergy1 and two probiotic bacteria) or a placebo which was administered each day for 12 weeks. The results, presented for the first time at this conference, are extremely interesting. Several bio-markers for colon cancer risk were positively modulated by the synbiotic treatment, which suggests that the consumption of synbiotics may provide a protective effect against colorectal cancer in humans.

This issue of our Scientific Monitor will give you more detailed information on the several presentations which were given during this successful conference.

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The use of prebiotics targets the 'good' bacteria of the intestinal microflora in order to improve the relationship between these bacteria and the host. Many studies have shown that prebiotics like inulin and oligofructose can improve metabolic functions of the flora, such as the absorption of calcium and other minerals. The fermentation of inulin improves lipid metabolism in the liver and may prevent dysfunctions related to the metabolic syndrome and non-alcoholic steatohepatitis.

In newborn babies, we have shown that these prebiotics increase bifidobacteria in the flora and prevent gastrointestinal infections, particularly diarrhoea, but also other infections such as necrotising enterocolitis.

You also did a lot of research on the potential role of prebiotics in the prevention and treatment of inflammatory bowel diseases in adults.

This is indeed a fascinating subject. A lot of evidence nowadays indicates the link between the intestinal bacteria and chronic inflammatory processes in the gut, such as Crohn's disease and ulcerative colitis. These diseases are characterised by lesions in the intestinal mucosa that do not heal spontaneously. The current therapies mitigate the severity of the acute inflammatory phase of the intestinal mucus membrane, but there is no treatment capable of eradicating these diseases.

Epidemiological observations suggest that the establishment of the intestinal microflora plays an important role in the risk of developing an

inflammatory bowel disease. In fact, there is a remission of the lesions and of the inflammatory activity in germ-free animals or when bacteria are removed from the gut lumen with broadspectrum antibiotics. We thus believe that the intestinal flora is essential to these conditions. Patients suffering from inflammatory bowel disease (IBD) present an abnormal reaction to commensal bacteria of the intestinal microflora. Constant activation of the intestinal immune system against these bacteria seems to be responsible for the relapses characteristic of this type of illness.

The challenge now is to select those bacteria that do not stimulate the inflammatory processes. Studies have shown that bifidobacteria and lactobacilli have a less severe stimulatory effect on the immune system in comparison to the other commensal bacteria. This leads us to suppose that we could offset these inflammatory reactions by selectively stimulating the growth and/or activity of these beneficial intestinal bacteria. The ingestion of prebiotics could be a convenient way to achieve this.

Our studies with prebiotics in animal models that resemble human Crohn's disease and ulcerative colitis have shown very good results. Also the first results of prebiotic use in patients with ulcerative colitis and pouchitis are very encouraging. So we hope that this will open new perspectives to prevent and control these inflammatory bowel diseases. Moreover, the gut microflora might also be an essential factor in other pathological disorders, including multisystem organ failure and colon cancer.



The 4th ORAFIT Research Conference

Inulin and Oligofructose: Feelgood Factors for Health and Well-being



At the 4th ORAFIT Research Conference (Paris, February 12-13, 2004) leading scientists from Europe and the United States presented the most recent data on the (potential) health benefits of inulin (Raftiline®), oligofructose (Raftilose®) and the combination of both (Raftilose® Synergy1).

New evidence was presented on the potential of inulin-type fructans in the prevention and improvement of gastrointestinal infections and inflammatory diseases, in the stimulation of a breastfed-like microflora in formula-fed infants, in weight control and the management of hyperglycaemic syndromes and obesity, on the positive effects

on calcium absorption and bone health, and on lipid metabolism and lipogenesis. A first human study also showed promising effects on colon carcinogenesis in people at risk for colon cancer.

4th ORAFIT
Research Conference
Paris
February 12-13, 2004



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A new concept: Optimum nutrition

Until recently, nutrition science was mainly concerned with the concept of a balanced diet: essential nutrients and nutrition standards that aimed at recommending intakes (RDA's) to support growth, maintain body weight and prevent the development of deficiency diseases. Since a few years, nutrition science became aware of the diet as a risk factor in the etiology of chronic diseases (cardiovascular disease, cancer, diabetes, osteoporosis...). Now, instead of avoiding deficiencies, the challenge becomes to correct excesses in order to prevent disease and enhance well-being.

This led Roberfroid to the introduction of a new concept: optimum nutrition. Optimum nutrition will help each individual to improve his/her physiological functions by matching his/her unique biochemical needs with selected nutrient intakes.

Functional foods are central to this concept. Functional food is conventional or everyday food consumed as part of the normal diet, enriched with naturally occurring components to increase their concentration or to add them to foods that would not normally supply them. These components have scientifically demonstrated positive effects on target functions beyond their basic nutritional necessity, they enhance the state of well-being and health and/or

they are able to reduce the risk of disease.

The gastrointestinal physiology and functioning are obvious key targets for the development of such functional foods. The gastrointestinal tract serves at the digestion of food, the absorption of nutrients and certain non-nutrient compounds and the elimination of residues. It also acts as a barrier against deleterious compounds and micro-organisms. The intestines contain 70 to 80% of the immune cells of the body, about the same number of neurons as in the spinal cord. Messages departing the gut outnumber the messages coming from the brain (Cherbut), which may explain why nutrition influences our state of mind and, vice versa, why our state of mind determines our food choices.

Eating breakfast improves mood, enhances memory and, taken on a regular basis, makes one feel better and can reduce minor illnesses such as the common cold (Smith). The consumption of a high fibre cereal breakfast reduces fatigue, increases energy and induces a more positive mood compared to normal breakfast. This effect may be due to improved bowel function as well as to the fermentation and subsequent release of short chain fatty acids by the gut microflora.

The addition of Raftilose®Synergy1 (at the doses of 5% and 10%) to the diet of rats caused relaxing-like

effects, stimulated and increased the general activity and the interest of the rats to explore the test environment and improved their cognitive performances (using the light extinction test) and well-being (using functional observational battery items) (Messaoudi).

Delzenne presented the results of animal studies showing that inulin (Raftiline®), oligofructose (Raftilose®) and Raftilose®Synergy1 modulate the secretion of three endogenous intestinal peptides (the incretins GLP-1, PYY and ghrelin) involved in insulin and glucagon secretion and appetite regulation. The control of gluco-incretin secretion represents a major goal for new therapeutic strategies in weight control, the treatment of hyperglycaemic syndromes and obesity, and the improvement of well-being.

Moreover, the incretin GLP-1 is also involved in cognition and memory and acts as a neuroprotector dimin-

ishing cell death through apoptosis (Burcellin).

Impaired intestinal functioning leads to numerous disorders and diseases which have a major impact on the quality of life. Furthermore, alimentary security depends partly on the integrity of the intestinal mucosa and on the gut microbiota balance, whereas food allergy is related to the intestinal barrier. There may be also a relationship of the gut microflora with rheumatoid arthritis and even with autism. Therefore, optimisation of the balance and the activity of the gut microbiota through pro- and pre-biotics, is a promising way to influence gut functions and to improve wellness beyond the gut (Cherbut).

According to Roberfroid, a prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity of the gastrointestinal microflora, that confer benefits upon host well-being and health. Food ingredients

The prebiotic index

Roberfroid introduced a new concept, the prebiotic index: the increase in bifidobacteria expressed as the absolute number (N) of 'new' cfu per g of faeces divided by the daily dose (in g) of prebiotic ingested in each human nutrition trial.

The prebiotic index of inulin-type fructans is of the order of a few (average = 4.00 ± 0.82) 10^8 . The prebiotic index correlates with the initial number of bifidobacteria ($r=+0.55$, $p<0.01$) in the gut microflora.



meeting these criteria are inulin (Raftiline®), oligofructose (Raftilose®) and galacto-oligosaccharides. Beyond their basic properties as dietary fibres (increased stool volume and frequency) and as prebiotics (selective stimulation of bifidobacteria), the inulin-type fructans have additional beneficial effects on well-being and health, such as the improved absorption of minerals, the maintenance of lipid homeostasis, the stimulation of the body's defence mechanisms and the modulation of gastrointestinal regulatory peptides secretion.

Gastrointestinal health

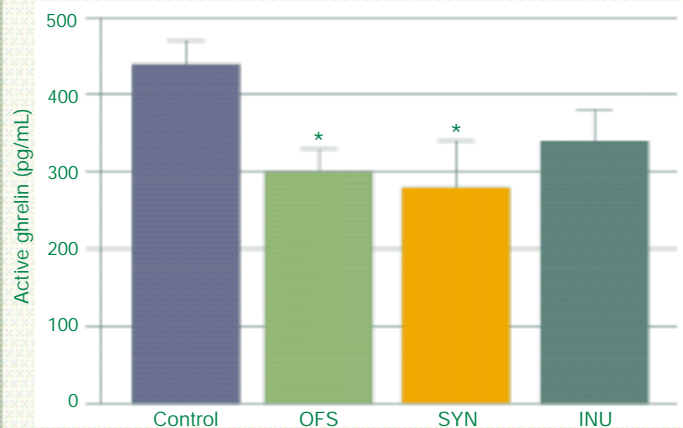
Inulin and oligofructose beneficially affect a series of gastrointestinal functions by modulating the structure, the composition and the metabolic activity of the intestinal mucosa and the gut microflora. They modulate the immune response of the gut-associated lymphoid tissue (GALT), they increase colonisation resistance and decrease translocation, they reduce the risk and shorten the inflammatory period in inflammatory bowel diseases (IBD), they reduce the risk of colon cancer and slow down the growth of transplanted tumours (Roberfroid). A number of studies demonstrate that prebiotics are useful in the prevention and treatment of acute gastrointestinal infections, often trans-

mitted through food or water, such as travellers' diarrhoea.

Oligosaccharides have a direct antimicrobial action by preventing the adhesion of pathogens to intestinal cells. They also exert an indirect antimicrobial activity as prebiotics, since they selectively stimulate the growth of bifidobacteria and lactobacilli, two species that attenuate the virulence of pathogens.

The inulin-type prebiotics selectively stimulate the growth of bifidobacteria and lactobacilli in vitro and in vivo. The long chain inulins, in Raftiline®HP and Raftilose®Synergy1, have been demonstrated to be beneficially fermented (partly) in the distal colon, the site at which most gut disorders occur. The metabolic end products of prebiotic fermentation, such as short chain fatty acids and lactate, lower the gut pH to levels below those at which pathogens are able to effectively compete with the resident microflora. Lactobacilli and bifidobacteria also excrete peptides acting as natural antibiotics with a broad spectrum of activity. They improve immune stimulation, compete for nutrients and block pathogen adhesion sites in the gut. Many intestinal pathogens utilise oligosaccharides receptor sites in the gut. In stimulating such receptor sites by prebiotics, the pathogen is decoyed into not binding at the host-mucosal interface. This anti-adhesive action was confirmed in a

Plasma active ghrelin levels



Plasma levels of active ghrelin (pg/mL), a recently identified modulator of appetite and regulator of body weight, in rats fed a control diet or a diet supplemented with 10% oligofructose (OFS), inulin (INU) or Synergy 1 (SYN) (*P<0.05).

primate model. Gibson concluded that several mechanisms of effects are feasible to explain the prophylactic management of acute intestinal infections through prebiotics and that a combination of influences may be preferable.

Inulin-type fructans seem not only to change the composition and the activity of the microflora in the gut, but also in the mucosal biofilm present. Wistar rats associated with a human faecal flora (HFA) received either a standard diet or a diet supplemented with 5% Raftilose®Synergy1. Changes in luminal and mucosa-associated bacterial population groups were investigated by fluorescent in situ hybridisation (FISH). The inulin diet resulted in significant higher numbers of bifidobacteria on the colonic mucosa, whereas no change was

seen in bacterial numbers of total bacteria, bifidobacteria or bacteroides in the lumen. Morphological measurements of distal jejunal and colonic tissue showed an increase in villus height and crypt depth, a higher number of goblet cells per crypt and a thicker epithelial mucus layer with inulin.

A second study investigated the efficacy of 5% Raftilose®Synergy1 in reducing or preventing the colonisation of Salmonella thyphimurium in HFA-rats. Inulin inhibited the survival of salmonella in the intestinal content but did not markedly reduce its mucosal translocation, although lower numbers of this organism were found in the Peyer's patches (PP) of the rats. Luminal bifidobacteria count was not affected by the diet, but fructans increased the numbers of bifidobacteria on the

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mucosal surface. The author concluded that inulin could be of benefit for both the protection of an intact intestinal epithelium as for the therapy of a disturbed mucosal barrier (Kleessen).

Probiotics and prebiotics also have been used successfully to preserve barrier function in critical disease states where translocation of gut bacteria is associated with septic complications. Recent trials suggest that pro- and prebiotics can reduce the rate of post-operative infections in liver transplant patients and the occurrence of septic complications in severe acute pancreatitis (Guarner).

Modulation of the trophic functions of the intestinal flora by prebiotics could help in the control of inflammatory disorders. In IBD, an exaggerated immune response against commensal bacteria has been demonstrated. Bacteria locally influence innate responses and cytokine signalling of the mucosa. Stimulation of indigenous lactic acid bacteria by inulin/oligofructose offers an opportunity to down-regulate mucosal inflammation.

The effect of inulin was tested in a rat model of distal colitis induced by DSS that histologically resembles human ulcerative colitis, and in the TNBS model that resembles human Crohn's disease. Inulin prevented mucosal inflammation as evidenced by lower colonic lesion scores, lower

release of inflammatory mediators and lower tissue myeloperoxidase activity in test rats compared with controls (Guarner).

Interesting results were also obtained in humans. After only one month, ulcerative colitis patients treated with a synbiotic, consisting of a probiotic (2 x 10¹¹ Bifidobacterium longum, 2 times/day) combined with a prebiotic (2 x 6g Raftilose®Synergy1), showed significant reductions in the expression of pro-inflammatory cytokines (IL-1 alfa, TNF alfa, HBD2-4, C-reactive protein), reductions in sigmoidoscopy scores and clinical activity rates compared with the placebo group (Macfarlane).

Inulin has also been tested in patients with pouchitis, which is the inflammation of the ileal pouch-anal anastomosis in people who have undergone a total colectomy.

Compared to placebo, three weeks of dietary supplementation with inulin reduced endoscopic and histological parameters of inflammation of the mucosa of the ileal reservoir. This was associated with an increase in faecal butyrate and a decrease in bacteroides counts (Guarner).

The effects of Raftilose®Synergy1 alone and in combination with probiotics (Bifidobacterium lactis Bb12 and Lactobacillus rhamnosus LGG) on the systemic and local immune system (GALT) of rats fed a high-fat (40% of energy) Western diet were

tested. After 4 weeks, the prebiotic supplementation in combination with probiotics resulted in increased secretory IgA (sIgA) production in the ileum, while prebiotic treatment alone also enhanced the production of sIgA in the caecum. Prebiotic supplementation stimulated the production of interleukin-10 (IL-10) in the Peyer's patches (PP). Prebiotic supplementation thus primarily affects the GALT, while only minor effects

are observed at the level of the systemic immunity (Watzl).

Colon cancer

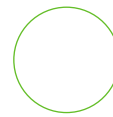
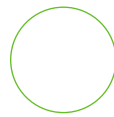
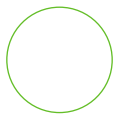
The preventive effect of inulin-type fructans on colon cancer risk was confirmed in a study in rats treated with the colon carcinogen azoxymethane (AOM). The long-term (33 weeks) prebiotic supplementation (Raftilose®Synergy1), alone and in combination with probiotics, pre-

The SYNCAN project

Of particular importance are the first human results of the EU-funded SYNCAN project in which 37 colon cancer patients who had undergone curative resection and 43 polypectomised subjects were studied. Half of each group received a placebo, the other half a synbiotic composition (12 g/day Raftilose®Synergy1 and 10¹⁰ cfu probiotics Bb12 and LGG) during a period of 12 weeks. Especially in the polypectomised patients receiving the synbiotic preparation, mucosal markers indicated an increased protection against carcinogenesis. Immunological markers were also affected. Moreover, an important protective effect on DNA damage and a reduction of cell proliferation rate were observed in the synbiotic group.

An additional long-term rat chemoprevention trial showed a significant reduction in tumour incidence in rats receiving Raftilose®Synergy1 and the synbiotic preparation, whereas no effects were seen in rats receiving only probiotics. The reduction in tumour incidence correlated with increased short chain fatty acids (particularly butyrate).

Supporting in vitro studies revealed that faecal slurry fermentations of Raftilose®Synergy1 led to a reduced genotoxic potential on various cancer cell lines.



vented the suppressive effect of AOM on the lytic activity of natural killer (NK) cells from spleen and PP. It also enhanced the NK cell activity and the IL-10 secretion in the GALT (PP) and reduced significantly the numbers of tumours in the colon (Watzl).

An overview of new studies with AOM-treated rats revealed that animals which received Raftilose® Synergy1 (10% of the diet for 31 weeks), with or without probiotics (Bb12 and LGG), had a significantly lower number of tumours than rats without Raftilose® Synergy1, whereas only a slight, non-significant anti-carcinogenic effect was observed after feeding probiotics alone. The prebiotic treatment reduced faecal genotoxicity and thus reduced exposure to genotoxins. This effect was confirmed in recent human studies with probiotic yoghurts containing 1% oligofructose, bread supplemented with 4% inulin and a preparation of Raftilose® Synergy1 in combination with probiotics (Bb12 and LGG).

In addition to this anti-genotoxic mechanism, new studies in human cell systems also showed that inulin-type fructans inhibit growth, modulate the differentiation and reduce the metastatic activities of colon tumour cells. This is mainly due to the short chain fatty acids butyrate and propionate produced during the gut flora-mediated fermentation of the fructans, and less so to other fermen-

tation products. Sodium butyrate suppresses the survival of human colon adenoma cells, which is very important as these cells are often seen in older people and are very close to cancer cells (Pool-Zobel).

Baby food

The intestinal mucosal immune system is developed after a full-term birth, but the actual protective function of the gut requires the microbial stimulation by initial bacterial colonisation.

This initial colonisation is influenced by a number of factors such as the passage of maternal bacteria during delivery, contacts with the surrounding environment and the type of feeding.

Breast milk contains oligosaccharides which are fermented in the colon by resident bacteria, stimulating the proliferation of specific commensal bacteria, especially bifidobacteria and lactobacilli. These bacteria are important for the development and sustainment of intestinal defence mechanisms. They stimulate for instance the synthesis and secretion of polymeric IgA, the antibody that protects mucosal surfaces against harmful bacterial invasion, they stimulate a balanced T-helper cell response and they prevent an imbalance which leads to clinical diseases (such as atopic disease, Crohn's disease...). Furthermore, a series of pattern recognition recep-

tors, toll-like receptors on gut lymphoid and epithelial cells, interact with bacterial molecular patterns and help modulate intestinal innate immunity (Walker).

Although the vast majority of babies are initially breast-fed, the duration of exclusive and even partial breast feeding is often limited to a few months. In order to obtain a bifidogenic effect and the advantages of a 'breast-fed-like' flora, most starter formulae are today supplemented with either pre- or probiotics.

The bifidogenic effect of inulin-type fructans has been repeatedly demonstrated in animals and in human adults. Veereman presented a review of studies in term and preterm infants, showing that the bifidobacteria patterns and short chain fatty acids profiles of infants fed prebiotic formulae are comparable to those of breast-fed babies. Prebiotics also soften stools. No significant side effects were seen with formulae containing 0,8 g/dL inulin-type fructans and galacto-oligosaccharides.

Additional studies are needed to show if prebiotics can primarily or secondarily stimulate intestinal host defences.

Bone health

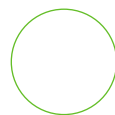
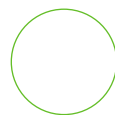
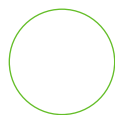
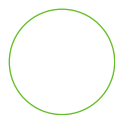
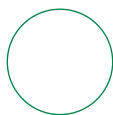
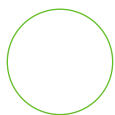
Of the bone-building nutrients, calcium (Ca) is the most likely to be inadequate in terms of dietary intake. Calcium is critical to achieve optimal peak bone mass in adolescence and

to modulate the rate of bone loss associated with ageing (Coxam). A large number of experimental studies have consistently shown an increased mineral absorption in animals after ingestion of inulin and/or oligofructose. Some studies also reported an enhanced bone mineral density and bone mineral content or improved bone structure. Several mechanisms may explain the improved Ca absorption in the lower gut: the increase of short chain fatty acids which reduces the pH and increases the solubility of calcium, the hypertrophy of the intestinal mucosal cells, and the increased paracellular Ca diffusion.

Although all inulin-type fructans are effective, it has been shown that Raftilose® Synergy1 is more active than oligofructose (Raftilose® P95) or inulin (Raftiline® HP) used separately (Abrams).

Weaver presented new evidence on the positive effect of Raftilose® Synergy1 (5.5% of the diet during 21 days) on calcium and bone metabolism in 6-month old ovariectomised rats: calcium absorption, femoral calcium content, bone mineral density and calcium retention were all significantly increased, whereas bone turnover rate was decreased.

In humans, the most convincing data have been obtained in adolescents and in post-menopausal women. Abrams presented the results of a



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study with 59 healthy girls aged 11-13 years with a daily calcium intake of 1500 mg. One group received either 8g/day Raftilose® Synergy1 or placebo for periods of 21 days, a second group received either 8g/day oligofructose (Raftilose® P95) or placebo (sucrose). Ca absorption was measured with the dual stable isotope technique. A relative increase in calcium absorption of about 20% was observed with Raftilose® Synergy1, even in volunteers with an average daily calcium intake above the recommended daily allowance (RDA), whereas no significant effect was seen with Raftilose® P95.

According to Weaver, the effect of inulin-type fructans on calcium absorption could be life-stage dependent, or vary according to the calcium/inulin ratio in the diet or the state of oestrogen. Studies also have shown an inverse correlation between the relative increase in calcium absorption by inulin-type fructans and the basal absorption capacity, which indicates that consuming them would benefit more to adolescents who have a low level of absorption capacity. Since genetic polymorphisms do account for differences in Ca absorption, some genotypes could be more likely to benefit from inulin or oligofructose supplementation (Abrams).

Reviewing the existing evidence on calcium absorption in adults, Coxam concluded that in late post-

menopausal women, inulin and oligofructose seem able to improve calcium (and magnesium) absorption, leading to a better calcium status. A mixture of both (Raftilose® Synergy1) is more efficient, mainly because fermentation takes place in both proximal and distal colon.

For the prevention of post-menopausal osteoporosis, Coxam presented experimental data showing that inulin-type fructans can exacerbate the bone sparing effect of isoflavones by modulating their bio-availability and improving equol production in ovariectomised rats and mice. Phyto-oestrogens such as daidzein, mainly found in soy, occur in plants bound as glycosides that have to be hydrolysed for intestinal

absorption. Bacterial glucosidases from the gut microflora are involved in this process. A dietary combination of prebiotic oligofructose and isoflavones may thus be useful for maintaining or improving bone mass in post-menopausal women.

Lipid metabolism

Beylot reviewed animal and human studies with inulin-type fructans on lipid metabolism.

Animal studies clearly indicate that inulin (Raftiline® HP) and oligofructose (Raftilose®) can reduce plasma levels of cholesterol and triglycerides in rodents. Inulin also induced a moderate decrease of plasma triglycerides but not of cholesterol in dogs. Moreover, inulin-type fructans

can oppose the accumulation of triglycerides in the liver and thus have favourable effects on hepatic steatosis. The decrease in plasma triglycerides is related to a reduction in hepatic de novo lipogenesis, the re-esterification of fatty acids, the modified secretion and concentration of intestinal peptides (GIP and GLP-1) and decreased concentrations of glucose and insulin.

The repression of lipogenesis is not observed in adipose tissue, and this selective effect on liver lipogenesis could be explained by the increased production of propionic acid in the large intestine, resulting in a selective exposure of the liver to increased amounts of this short chain fatty acid. This may also contribute to a decrease in plasma cholesterol since propionic acid could inhibit HMG-CoA reductase activity and thus hepatic cholesterol synthesis.

In humans, the studies have yielded less clearcut results with either a decrease or no effects on plasma lipids levels. The effect was more important on triglycerides than on cholesterol, and inulin (Raftiline® HP) was more effective than oligofructose (Raftilose® P95). The benefits are more consistent in (slightly) hyperlipidemic subjects than in healthy volunteers.

The diet also plays a role since reductions in plasma triglycerides and in hepatic lipogenesis were observed mainly after a rather high carbohydrate diet.

What consumers tell us

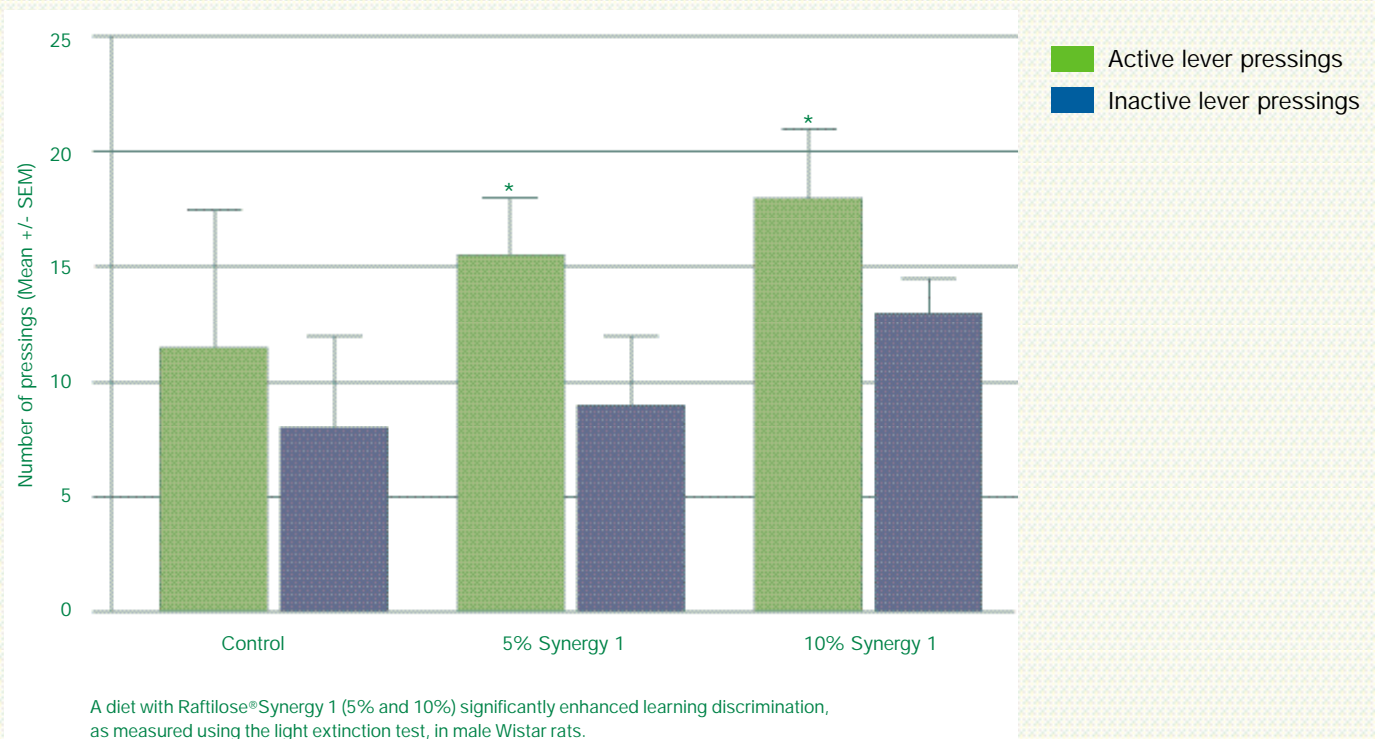
Every year, thousands of new food and drink products are launched onto the market. The chances of success can be dramatically improved by listening carefully to consumers and measuring their interest in new products.

Qualitative research in 8 countries (Belgium, the United Kingdom, Germany, France, Spain, Australia, Brazil and Thailand), and quantified studies in 3 countries (United Kingdom, Germany, France) showed that consumers expect to feel better if they eat more healthily (Currie).

They consider the digestive system to be a very important contributor to their sense of well-being. Benefits to be emphasised in the communication to consumers are that inulin (Raftiline®) and oligofructose (Raftilose®) are natural food ingredients from chicory to make well-balanced food products that stimulate your digestive health and make you feel good..



Effects of Raftilose® Synergy1 (5% and 10%) on learning discrimination in rats



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Walker W.A., The role of GALT and mucosal defences.

Watzl B., Inulin, oligofructose and immunomodulation.

Weaver C., Inulin, oligofructose and bone health: experimental approaches and mechanisms.

FREQUENTLY ASKED QUESTIONS

Can inulin and oligofructose be used in a low carb diet?

Dr. Atkins is the most famous promoter of a low carb diet. His diet is often perceived as a food pattern rich in proteins and devoid of any carbohydrate. The actual nutritional recommendations of the Atkins diet are more balanced, however. The low carb diet advises to restrict/exclude processed and refined carbohydrates. This type of carbohydrates, as is found in sugar, white bread,

white pasta and in most starchy foods, is readily available for uptake by the human body. It is digested and taken up in the small intestine, thereby rapidly increasing blood sugar levels and stimulating insulin secretion. On the other hand, the intake of fibre-rich foods and non-starchy vegetables is encouraged. The Atkins diet uses subsequent phases to cut down on refined carbo-

hydrates (sugars and starch) and to increase the intake of fibres. Dietary fibres slow down nutrient uptake, blunt the rise in blood glucose levels after a meal and induce satiety.

Non-digestible carbohydrates such as inulin and oligofructose are metabolised by bacteria in the large bowel and they contribute to stool regularity, weight maintenance and health. It is obvious that inulin and

oligofructose, which are both non-digestible and selectively fermented carbohydrates, do not induce a rise in glycaemia or insulin and that they do have an important role to play in a low carb diet, such as the Atkins diet.

Reference: Dr. Atkins – The diet revolution (book).

Why is Raftilose® Synergy1 such a unique product?

Chicory inulin and oligofructose are both non-digestible carbohydrates composed of $\beta(2-1)$ bound fructose units and selectively fermented by the beneficial bacteria in the gut, i.e. bifidobacteria and lactobacilli.

Although the metabolism is similar for both inulin and oligofructose, the fermentation pattern in vivo is distinctively different. Chicory oligofructose, as is the short-chain FOS synthesised from sucrose, consists of short fructose chains (DP 2-10) that are easily accessible for the bifidobacteria and hence rapidly fermented. Therefore, most of the short-chain oligosaccharides are completely metabolised in the proximal part of the colon. Chicory inulin is a mixture of $\beta(2-1)$ fructose polymers

that contains longer chains (up to DP 60-65), which are more difficult to be broken down by the gut bacteria. Because this metabolism requires more time, the fermentation of the long chains takes place in more distal parts of the colon.

Raftilose® Synergy1 is a unique patent-pending product that combines in a specific ratio both short (oligofructose) and long (inulin) chains of fructans. As a result, the rapid fermentation of the short chains promotes the selective growth of a healthy gut flora in the proximal colon, the presence of which is maintained by providing them enough long-chain substrates to make them grow and survive throughout the whole colon. In this

way, a healthy gut flora extends towards the distal parts of the colon, the site where most gut disorders and diseases (e.g. colon cancer) occur and where the presence of a beneficial flora is mostly wanted. Thanks to its unique chain length distribution and consequent fermentation pattern, Raftilose® Synergy1 is an effective prebiotic throughout the whole length of the colon and it has been shown to have enhanced nutritional and health benefits towards its separate components inulin and oligofructose used alone. So, Raftilose® Synergy1 is more efficient than other fructans in increasing calcium and magnesium absorption in both animals and humans.

DP = degree of polymerisation.



MONITOR

Prebiotics and synbiotics stimulate gut-associated immunity

This study investigated whether the effects of probiotics and prebiotics on the immune system vary among different immune compartments and whether the combined application of probiotics and prebiotics in a synbiotic has a greater effect than either of its components alone.

The probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12, the prebiotic Raftilose®Synergy1, and the synbiotic composed of this pro- and prebiotic combination were fed to F344 rats for 4 weeks as supplements to a high fat Western-type diet.

Functions of immune cells isolated from peripheral blood mononuclear cells, spleen,

mesenteric lymph nodes and Peyer's patches were measured.

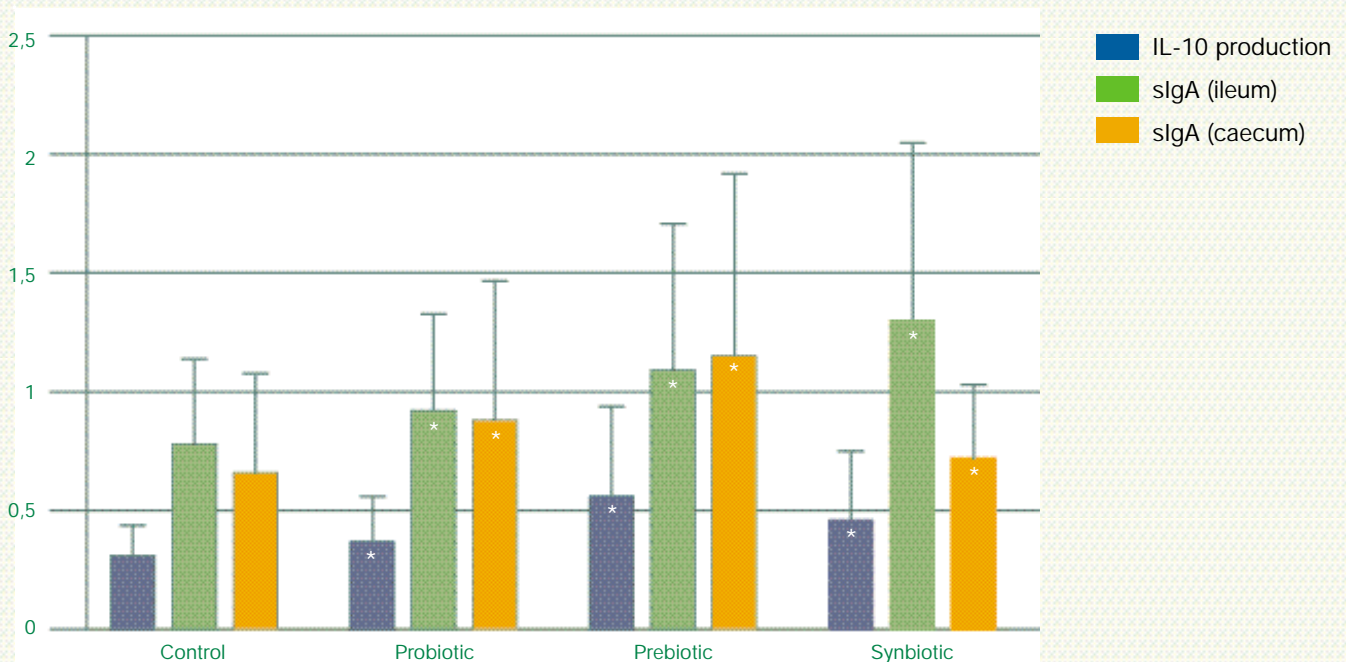
Prebiotics showed to specifically act on peripheral blood mononuclear cells and Peyer's patches. The prebiotic supplement enhanced the production of interleukin-10 in Peyer's patches as well as the production of secretory immunoglobulin A (sIgA) in the caecum. The results indicate that the prebiotic thus primarily acted at the level of the gut-associated lymphoid tissue (GALT).

The probiotics modestly affected immune functions, but systemic immuno-modulatory effects were observed in rats fed the synbiotic combination. The synbiotic increased

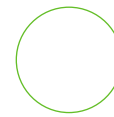
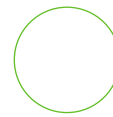
sIgA production in the ileum compared to the control group and decreased the oxidative burst activity of blood neutrophils compared with rats fed the probiotics.

From this study, it is clear that probiotics and prebiotics act on the immune system via different mechanisms. The combined application of probiotics and prebiotics has different effects from those of the individual components, but the outcome is not simply an additive or synergistic effect.

Roller M., Reckemmer G. & Watzl B. (2004). Prebiotic inulin enriched with oligofructose in combination with the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* modulates intestinal immune functions in rats. *J. Nutr.*, 134, 153-156.



Interleukin 10 (IL-10) production in Peyer's patches and secretory immunoglobulin A (sIgA) concentrations in ileum and caecum of rats fed a high fat diet supplemented with a probiotic, a prebiotic or a synbiotic for 4 weeks (* = significantly different from control, $P < 0.05$).



Effects of inulin on calcium bio-availability

Fructans with various degrees of polymerisation have been compared in terms of their impact on calcium absorption, bone density, and excretion of collagen cross-links in young adult male rats. The basal diet given to the rats was a semi-synthetic one containing 0.5% calcium.

The various fructans tested were oligofructose (Raftilose®P95), inulin (Raftiline®HP), and a mixture of 92% inulin and 8% oligofructose, of which 5% was added to the diet for 4 weeks after one week of basal diet. The retention of calcium was evaluated using calcium balance, parathyroid hormone levels and excretion of collagen degradation products in the urine. The bone mineral density (BMD) and bone mineral content (BMC) were measured *ex vivo* in the femur and the spine.

The inulin-fed group had a significantly higher BMD in the femurs, as well as a significantly higher spinal BMC. The excretion of Type-1 collagen fragments decreased in all groups during the 4-week feeding period, but the decrease was most significant in the group fed inulin.

Several mechanisms could explain the effect of the fructans on calcium absorption and retention. The organic acid metabolites, resulting from fermentation in the colon, cause an acidification of the gut lumen which enhances calcium solu-

bility and hence absorption. Another possible mechanism involves the calcium-binding protein calbindin D9k. This study clearly showed that various types of fructans have distinctive effects on calcium bio-availability.

Kruger M.C., Brown K.E., Collett G., Layton L. & Schollum L.M. (2003). The effect of fructo-oligosaccharides with various degrees of polymerization on calcium bioavailability in the growing rat. *Exp. Biol. Med.*, 228, 683-688.

Inulin enhances mineral absorption from infant formulae

By use of an *in vitro* continuous flow dialysis model, the availability of calcium, iron and zinc from dairy infant formulae supplemented with soluble dietary fibre fractions (3% on dry weight) was studied in a controlled and defined environment. The fibres tested were inulin (Raftiline®HP), oligofructose (Raftilose®P95), high and low esterified pectins, locust bean gum, xanthan gum, as well as modified starches (16% pregelatinised rice and corn starches, 1.9% maltodextrin). Pooled mature human milk was used as the reference standard.

The conditions provided by mature human milk proved to be optimal for calcium, iron and zinc availability. The addition of soluble dietary fibres can affect the availability of calcium, iron, and zinc in either a positive or a negative way, depending on the type of fibre used.

Calcium availability from standard formula was increased by 30% after inulin supplementation, whereas locust bean gum and high esterified pectin reduced availability by approximately 10%. The effect of inulin on *in vivo* bio-availability, which takes place during the fermentation process in the colon, may already start during the initial phase of calcium absorption in the upper intestine.

Iron availability from standard formula was increased by rice starch, whereas it was reduced by high esterified pectin, oligofructose, and low esterified pectin.

Zinc availability was highest after the addition of rice starch and lowest with the addition of locust bean gum and maltodextrin.

Bosscher D., Van Caillie-Bertrand M., Van Cauwenbergh R. & Deelstra H. (2003). Availabilities of calcium, iron, and zinc from dairy infant formulas is affected by soluble dietary fibers and modified starch fractions. *Nutrition*, 19, 641-645.

Inulin stimulates NO synthesis

This study examined whether inulin induces NO synthesis and activates NF-kappaB in RAW 264.7 cells, a macrophage-like cell line.

Inulin alone had no effect, whereas inulin with IFN-gamma synergistically increased the NO production and inducible NO synthase (iNOS) expression in RAW 264.7 cells. Synergism between IFN-gamma and inulin was mainly dependent on inulin-induced TNF-alpha secretion.

The synergistic effect was time- and dose-dependent and was always maximal at 1 mg/mL of inulin. Concentrations of less than 0.01 mg/mL were less effective and sometimes ineffective. Also, protein kinase C (PKC)-alpha was involved in the inulin-induced NO production.

Inulin-mediated NO production was inhibited by the protein tyrosine kinase (PTK) inhibitor, tyrphostin AG126. Since iNOS gene transcriptions have been shown to be controlled by the NF-kappaB/Rel family of transcription factors, the effect of inulin on NF-kappaB/Rel was assessed. Inulin produced strong induction of NF-kappaB/Rel binding, whereas AP-1 binding was slightly induced in RAW 264.7 cells. Inulin stimulated phosphorylation and degradation of I-kappaB-alpha.

These results show that in IFN-gamma-primed RAW 264.7 cells, inulin might stimulate NO synthesis via activation of PKC-alpha and PTK, resulting in the activation of NF-kappaB.

It was concluded that inulin could be a new class of activators to stimulate the induction of iNOS and thus the production of NO. NO mediates a number of host-defense functions of activated macrophages, including anti-microbial and tumoricidal activity.

Koo H.N., Hong S.H., Seo H.G., Yoo T.S., Lee K.N., Kim N.S., Kim C.H. & Kim H.M. (2003). Inulin stimulates NO synthesis via activation of PKC-alpha and protein tyrosine kinase, resulting in the activation of NF-kappaB by IFN-gamma-primed RAW 264.7 cells. *Journal of Nutritional Biochemistry*, 14, 598-605.



Effects of inulin measured by metabolic fingerprinting

Metabolic fingerprints are novel measurement tools to evaluate the biochemical status of a living organism by using $[^1\text{H}]$ NMR and multivariate data analysis (MVDA) to analyse biological fluids. NMR provides concurrent detection of all hydrogen-containing molecules in a sample without pretreatment, while MVDA is a powerful technique for the analysis of data sets with a large number of variables. In this way, changes in health or diseased state, as reflected in alterations of metabolic patterns, can be quickly evaluated.

Normally, metabolic fingerprinting is based on in vivo studies, which is a labor-intensive and expensive manner of investigation. In vitro studies are not hampered by these disadvantages, thus constituting an interesting alternative.

This research presents the results of a pilot experiment in which metabolic fingerprinting was combined with an in vitro model. For this purpose, differentiated Caco-2 cells were exposed to inulin and its fermentative metabolites, both dissolved in the culture medium. Cells were incubated for 0 or 48 h. Cell fractions were analysed by NMR, then subsequently analysed with MVDA. It was confirmed that differences in treatment provided detectable variations in the metabolic patterns of cell contents. The data showed that inulin and its metabolites

on Caco-2 cells had an effect on the glucose metabolism linked to glutamate.

Metabolic fingerprinting in combination with an in vitro model appears to be a feasible technique to visualise metabolic patterns of cell contents. It provides an efficient tool to generate hypotheses about the metabolic pathways involved in the relationship between nutrition and health.

Lamers R.J., Wessels E.C., van de Sandt J.J., Venema K., Schaafsma G., van der Greef J. & van Nesselrooij J.H. (2003). A pilot study to investigate effects of inulin on Caco-2 cells through in vitro metabolic fingerprinting. *J. Nutr.*, 133, 3080-3084.

Oligofructose improves folate status and lowers total homocysteine in rats

Low folate status leads to increased total homocysteine (tHcy) concentration, which has been associated with an increased risk of cardiovascular disease, Alzheimer's disease, cancer and certain abnormalities such as neural tube defects.

In this study the effects of diets high in different dietary fibres on folate status were investigated in a rat model, to test the hypothesis that the folate status could be improved by promoting bacterial folate synthesis in the large intestine. To confirm that folate in these experiments arose from bacterial synthesis, a treatment containing a known inhibitor of bacterial folate synthesis (succinylsulfathiazole) was included.

Weanling Sprague-Dawley rats were fed a folate-deficient diet with 5% cellulose for four weeks. Rats were then randomly assigned to one of five folate-adequate (400 micrograms/kg diet) test diets (basal; basal + succinylsulfathiazole; + cellulose; + citrus pectin; and + oligofructose Raftilose®P95) for 24 days. High-fibre diets were formulated by diluting the basal diet such that the final diets contained 10% of the added fibre. Rats receiving the citrus pectin diet had significantly higher folate and lower tHcy concentrations in plasma, erythrocytes and colonic tissue than rats given the cellulose diet. Rats receiving oligofructose had significantly higher plasma folate and lower tHcy concentrations compared to control animals. Folate was detected in the livers of all rats except those receiving succinylsulfathiazole.

This study showed that citrus pectin and oligofructose, but not cellulose, can significantly increase indices of folate status in rats and lower tHcy. It also confirmed the ability of the large bowel to absorb folate.

Thoma C., Green T.J. & Ferguson LR. (2003). Citrus pectin and oligofructose improve folate status and lower serum total homocysteine in rats. *Int. J. Vitam. Nutr. Res.*, 73, 403-409.

Oligofructose does not affect the development of Type-1 diabetes

The diabetes-prone BioBreeding (BB) rat was used to test the hypothesis that an enhanced mucosal barrier

resulting from exposure to oligofructose (Raftilose®P95) might reduce the contact between dietary protein antigens in the gut lumen and the host immune system, which could prevent the induction of the pathogenic process thought to underlie Type-1 diabetes mellitus (T1DM). In addition, oligofructose is documented to lower blood glucose and insulin levels in non-diabetic rats and humans. This reduces the metabolic activity of β -cells, which is associated with a lower expression of auto-antigens and with protection against auto-immune destruction.

Groups of BB rats were fed experimental diets from weaning. The diets were a cereal-based rodent diet (diabetogenic, positive control) and semi-synthetic rodent diets containing hydrolysed casein (non-diabetogenic, negative control), soy or whey as the sole protein source, and either 5% cellulose or 5% oligofructose as fibre source. T1DM incidence up to the age of 160 days was measured by applying biochemical and morphological criteria. Physiological effects of fibres were assessed by the analysis of biochemical parameters in plasma and the protein/DNA ratio in intestinal mucosa.

Cereal-, soy- and whey-based diets were significantly more diabetogenic than the hydrolysed casein-based diet. Oligofructose supplementation did not affect the incidence nor the

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Raftilose® Synergy1 suppresses bone resorption in rats

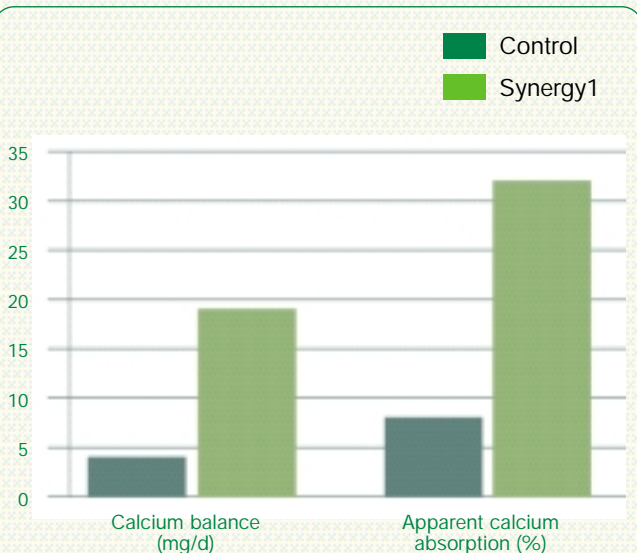
The effect of a mixture of chicory inulin and oligo-fructose (Raftilose® Synergy1) on calcium and bone metabolism in ovariectomised rats, used as a model to mimic post-menopausal women, was investigated. The 6-month old rats were fed a semi-purified diet for 3 months after ovariectomy, followed by either a control or a Synergy1 supplemented diet (55 g/kg) for 21 days. At the end of this period, catheters were placed in their jugular veins and two days later, a [⁴⁵Ca] tracer was administered by gavage or i.v. injection. Blood was sampled for up to 300 min, urine and faecal samples were collected for 4 days after the [⁴⁵Ca] administration. Femurs were measured for bone mineral density, breaking strength and total calcium content.

The rats in the Synergy1 group had comparable body weight, food intake, and total calcium intake, but a lower faecal calcium excretion and they absorbed and retained more calcium than the control group.

Femoral calcium content, bone mineral density and bone balance were all significantly increased in the Synergy1 group, and the bone resorption/ bone formation ratio was significantly lowered by Synergy1.

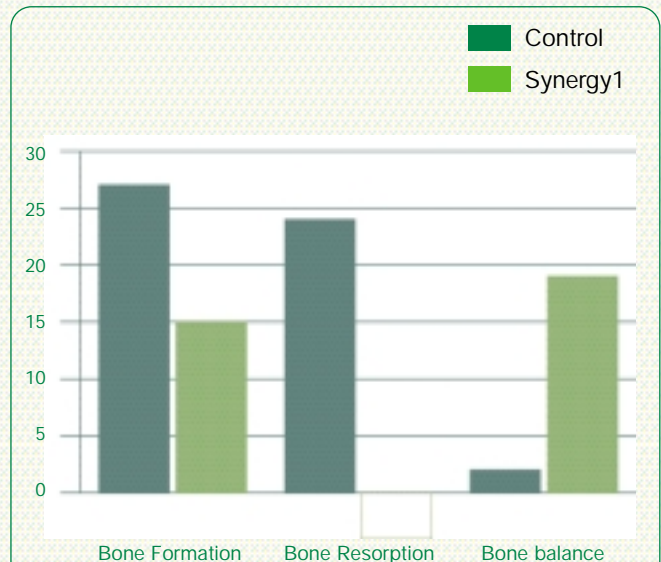
In conclusion, these results demonstrate that the intake of Synergy1 favours the absorption of calcium and its deposition in the bone.

Zafar T.A., Weaver C.M., Zhao Y., Martin B.R. & Wastney M.E. (2004). Nondigestible oligosaccharides increase calcium absorption and suppress bone resorption in ovariectomized rats. *J. Nutr.* 134, 399-402.



Calcium content (mg) and bone mineral density (BMD) (g/cm²) of the respectively total and distal femur of ovariectomised rats receiving Synergy1 during 21 days in the diet (5.5%) (* = significantly different from control, *P* < 0.05).

(Zafar et al., *Nutr. Met.*, 2004)



Effect of 21 days feeding Synergy1 (5.5% of the diet) on calcium balance (mg/d) [= calcium intake minus faecal and urinary calcium loss measured over 4 days] and calcium absorption (%) in ovariectomised rats (* = significantly different from control, *P* < 0.05).

(Zafar et al., *Nutr. Met.*, 2004)



continuation of page 13

onset of T1DM induced by either soy or whey proteins as compared to cellulose. Unexpectedly, the oligofructose supplementation in the diet of non-diabetic rats did not induce any of the biological effects attributed to a fermentable fibre, such as a trophic effect on the intestinal mucosa and/or modifications of the carbohydrate metabolism, nor did it affect glucose, cholesterol and triacylglycerol plasma levels. The authors concluded that the 5% supplementation level was too low for significant changes.

Perrin I.V., Marchesini M., Rochat F.C., Schiffrin E.J. & Schilter B. (2003). Oligofructose does not affect the development of type-1 diabetes mellitus induced by dietary proteins in the diabetes-prone BB rat model. *Diab. Nutr. Metab.*, 16, 94-1001.

Positive effects of oligofructose and inulin in the diet of healthy dogs

The effects of different concentrations of oligofructose Raftilose®P95 (OFS) and inulin on nutrient intake, nutrient digestibility, stool quality and faecal protein catabolites were investigated in healthy adult dogs fed a meat-based kibbled diet. The dogs received twice daily a diet containing 0, 0.3, 0.6 or 0.9% of either OFS or inulin in a gelatin capsule.

The addition of inulin-type fructans had no effect on the nutrient intake or ileal digestibility of the diet. Total-tract digestibility of dry matter (DM), organic matter (OM), and crude proteins (CP) decreased as a result of dietary OFS and inulin supplementation. Dogs fed the control diet had a

DM total-tract digestibility of 83.0%. Faecal DM of dogs fed the control and 0.3, 0.6, and 0.9% OFS were 36.6, 33.3, 32.8, and 31.7%, respectively. When compared with the control group, OFS and inulin in the diet increased faecal ammonia excretion and short-chain fatty acid (SCFA) concentrations. Total faecal SCFA for dogs fed the control diet and 0.3, 0.6, and 0.9% OFS were respectively 406.4, 529.9, 538.3, and 568.8 micromol/g of faeces, measured on DM basis. Dogs fed 0.3, 0.6, and 0.9% inulin had total faecal SCFA of 472.2, 468.8, and 471.5 micromol/g of faeces (DM basis), respectively. Linear increases were observed in putrescine, cadaverine, spermidine, and total amines in faeces of dogs fed OFS. Lower total and faecal phenol concentrations occurred in dogs fed inulin, along with a linear decrease in total phenols with OFS supplementation. Low-level dietary inclusion of OFS and inulin positively affected indices known to be associated with gut health of the dog without seriously compromising nutrient digestibility or stool quality.

Overall, the treatment with 0.9% OFS resulted in the best responses, including no adverse effect on nutrient intake, ileal digestibility or stool quality, as well as an increase in SCFA and a decrease in phenol concentration in the faeces.

Propst E.L., Flickinger E.A., Bauer L.L., Merchen N.R. & Fahey G.C. (2003). A dose-response experiment evaluating the effects of oligofructose and inulin on nutrient digestibility, stool quality, and faecal protein catabolites in healthy adult dogs. *J. Anim. Sci.*, 81, 3057-3066.

Inulin-type fructans improve colonic microbial ecology in dogs

The effect of low concentrations of inulin-type fructans in the diet of dogs on nutrient digestibility, faecal microbial populations and protein fermentation components in faeces and urine was investigated.

In a first study, eleven adult male beagles were fed a corn-based, kibbled diet supplemented with 0, 0.3, 0.6 or 0.9% oligofructose (OFS). Total-tract digestibility of crude protein tended to be lower in the OFS groups, which is likely due to an increase in bacterial cell synthesis. Surprisingly, the total-tract digestibility of lipid was also decreased. This suggests that OFS may interfere with lipid digestion and absorption, or may have formed a complex with dietary fat during extrusion.

Increasing the concentration of OFS in the diet tended to linearly decrease faecal ammonia concentrations, which may be due to increased ammonia incorporation into bacterial cells. Faecal concentrations of branched-chain fatty acids (BCFA), amines, indoles, or phenols remained unaltered. Total short chain fatty acid (SCFA) concentrations in the faeces tended to be higher in OFS-supplemented dogs, as was the ratio of bifidobacteria to total anaerobes.

In the second experiment, ileally cannulated adult female dogs were fed a meat-based kibbled diet and were assigned to four OFS treatments (0, 1, 2, or 3 g/day). The ileal nutrient

digestibility tended to increase linearly with increasing concentrations of OFS. Also total-tract digestibility of dry and organic matter and total protein was increased, whereas lipid digestibility tended to be lower. On a dry matter intake basis, faecal output tended to decrease linearly in response to increasing OFS supplementation, whereas faecal score exhibited a quadratic response. In general, faecal concentrations of SCFA, BCFA, ammonia, phenols, and indoles were not altered. Supplementation of OFS increased faecal concentrations of total aerobes and decreased concentrations of *Clostridium perfringens*.

These data show that low levels of inulin-type fructans supplemented in the diet of dogs have divergent effects on nutrient digestibility and fermentative end products. From these findings, it is at least clear that OFS does not adversely affect nutrient digestibility or faecal characteristics and may improve colonic microbial ecology in dogs.

Flickinger E.A., Schreijen E.M., Patil A.R., Hussein H.S., Grieshop C.M., Merchen N.R. & Fahey G.C. (2003). Nutrient digestibilities, microbial populations, and protein catabolites as affected by fructan supplementation of dog diets. *J. Anim. Sci.*, 81, 2008-2018.

COLOPHON

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August 25, 2004

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International Symposium on Nutritional Benefits of Inulin and Oligofructose

Content: Nutritional Benefits of Inulin & Oligofructose: latest scientific findings

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Brasil, Sao Paulo

August 31-September 1-2, 2004

Subject: Food Ingredients South America Conferences 2004

Content: Inulin and Oligofructose as FeelGood Factors

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September 22-25, 2004

Subject: VI CONGRESO SOCIEDAD ESPANOLA NUTRICION COMUNITARIA

Content: Nutrition and Immune System

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Belgium, Gimbergen

October 16, 2004

Subject: Symposium on Pro- and Prebiotics

Content: Les Prébiotiques

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