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THE BENEFITS & POTENTIAL HEALTH HAZARDS POSED BY THE PREBIOTIC INULIN – A REVIEW

Piotr Hołownia[1], Barbara Jaworska-Łuczak[1], Iwona Wiśniewska[1], Przemysław Biliński[1,2], Andrzej Wojtyła[1,3]*

[1]Chief Sanitary Inspectorate, Warsaw, Poland; [2]Institute of Haematology and Transfusion Medicine, Warsaw, Poland; [3]Institute of Agricultural Medicine, Lublin, Poland

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The prebiotic inulin is a non-digestible carbohydrate which occurs naturally throughout the normal human diet. Following passage through the gastro-intestinal tract inulin ultimately becomes metabolised to fructose by colonic bacteria, especially the beneficial species, whose growth are also promoted at the expense of the harmful types. There has been much recent attention by industry and the general public in the EU concerning inulin and prebiotics, especially in the marketing of their derived/supplemented products that includes the Central & East European region, (CEE) [Halliday, 2008]. Major benefits to human health have been reported variously worldwide and chiefly consist of maintaining healthy microbial gut homeostasis, reducing gut inflammation and infection, preventing colonic cancer, increasing mineral reabsorption, decreasing cholesterol, improving bowel habits, being of use in diabetic treatments and enhancing immune function. Inulin can thus be of great potential benefit to public health not just through these physiological effects but also in helping to reduce weight by replacing fat and digestible carbohydrate in food products. It is also important however to recognise the likely hazards of inulin arising mainly from fructose intolerance and rare cases of allergy. In addition under certain medical conditions it is possible that the growth of other harmful gut bacterial species may become stimulated with a potential but as yet unproven link to autoimmune disease. This article aims to review and discuss the scientific evidence as well as addressing general concerns raised by consumers and the general public alike. Recommendations based on current knowledge are suggested at the end.

INTRODUCTION

Inulin and the closely related oligofructoses are naturally occurring oligosaccharides found in significant amounts of about 36,000 plant species that include common root/bulb vegetables, cereals and fruit (Table 1), [Davidson & Maki, 1999]. These substances act as a plant energy store and afford protection against cold through osmoregulation. Some plants that contain inulin do not have starch. Inulin is composed of mixtures of 10-65 linear fructose residues linked at the beta-2-1 position usually with a terminal glucose whereas oligofructoses are a mixture of shorter fructose chains with a degree of polymerisation (DP) of <10 that may terminate in glucose or fructose [Niness, 1999]. After starch, they are the most plentiful carbohydrates occurring in the plant kingdom and are classed as soluble fibres in the diet as well as being osmotically active in the human gut. A physiological definition of dietary fibre combines the nutritional criteria of non-digestibility with the physiological effects that are associated with the regular intake of dietary fibre [Cherbut, 2002]. Because of resistance to enzymatic hydrolysis in the human digestive tract, (due to the β-configuration of the anomeric C2 in the fructose monomers), they arrive intact in the large bowel and are eventually fermented mainly by the native bifidobacteria and lactobacillus species of beneficial bacteria in the colon that possess the β-fructofuranosidase enzyme. In contrast to other dietary fibres, inulins also reduce potentially harmful species of bacteria [Gibson *et al*., 1995; Kleessen *et al*., 1997; Roberfroid 2007a; Kolida & Gibson, 2007] by lowering the pH through the production of short chain

TABLE 1. Inulin content (% fresh weight) in some edible plants (source: Franck [2006]).

Food source	Edible parts	Inulin (g/100 g)	Oligofructose (g/100 g)
Chicory	Root	35.7-47.6	19.6-26.2
Jerusalem artichoke	Tuber	16.0-20.0	12.0-15.0
Dandelion	Leaves	12.0-15.0	9.6-12.0
Garlic	Bulb	9.0-16.0	3.6-6.4
Leek	Bulb	3.0-10.0	2.4-8.0
Globe artichoke	Leaves/heart	2.0-6.8	12.0-15.0
Onion	Bulb	1.1-7.5	1.1-7.5
Asparagus	Leaves	2.0-3.0	2.0-3.0
Wheat	Cereal	1.0-4.0	1.0-4.0
Barley	Cereal	0.5-1.5	0.5-1.0
Rye	Cereal	0.5-1.0	0.5-0.9
Banana	Fruit	0.3-0.7	0.3-0.7

Author's address for correspondence: Piotr Holownia, Chief Sanitary Inspectorate, ul. Długa 38/40, 00-238 Warsaw, Poland; tel.: (48 22) 536 14 62; fax: (48 22) 635 61 94; e-mail: p.holownia@gis.gov.pl

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fatty acids (SCFA) such as acetic, lactic, butyric and propionic acids during fermentation [Topping & Clifton, 2001]. This produces a powerful antimicrobial and inhibitory effect on many species of harmful bacteria particularly by the undissociated form of acetic acid which competitively favours lactic acid bacteria for active sites on the colonic epithelial wall [Kleessen *et al*., 1997; Fooks & Gibson, 2002]. In addition production of bacteriocins, (*e.g.* Lactacins and Lactocin), and antibiotics, (*e.g.* acidolin, acidophilin, lactocidin and bulgarican), occurs which are targeted against the pathogenic species [Gibson & Wang, 1994; Gibson & Roberfroid, 1995]. By such means a selective enhancement of the activity and growth of the beneficial gut bacteria, bifidobacteria, lactobacili, bacteriodes and eubacterium [*ibid* Gibson & Roberfroid, 1995] occurs and hence the effect is officially classified as being nutritionally prebiotic, (*defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health*). Gut bacteria are comprised of over five hundred different species [*ibid* Kolida & Gibson, 2007] that include both beneficial and potentially deleterious bacteria in a balance that affects how food is digested and energy obtained. It should be however pointed out that some studies have shown that other bacterial species in the intestine can also ferment, in various degrees, inulin and oligofructoses including *Klebsiella*, E. coli and many Clostridium species which are considered less-friendly bacteria in the gut [Ochuba & von-Reisen, 1980; Roberfroid *et al*., 1998; Valyshev *et al*., 2000; Macfarlane & Macfarlane, 2006]. These studies were however performed *in-vitro* and mostly used the shorter and more fermentable chained substrates. Colonic species of bacteria are also mainly responsible for gas formation, (hydrogen and carbon dioxide), which especially occurs after ingestion of oligofructoses [Topping & Clifton, 2001]. Most people can eat 5-10 gram/day without gaseous discomfort, whereas others already have problems with just 1 gram. Industrially inulin and oligofructoses are extracted from chicory root or synthesized from sucrose and are increasingly used by manufacturers in foodstuffs and processed foods to replace fat, flour and sugar, improve taste and texture or to confer advantageous technological properties such as gelling [Franck, 2002]. For example isolated inulin is added to replace fat in products, such as salad dressing while sweet-tasting oligofructose is added to products, such as fruit yogurts and desserts *etc*. [Kaur & Gupta, 2002; *ibid* Franck, 2002]. They are also used in fibre supplements which may offer more health benefits than other fibers such as bran or cellulose. From a nutrition labelling perspective, inulin and oligofructoses are not only prebiotic dietary fibres they are also low-calorie carbohydrates 6.3 kJ/g (1.5 kcal/g) resulting from their fermentation in the colon [Roberfroid, 1999].

Health benefits of inulin; in summary

The positive effects of inulin in the human diet, [Macfarlane *et al*., 2006b; Wong & Jenkins, 2007; Leenen & Dielemen, 2007; Guarner, 2007; *ibid* Roberfroid 2007a; *ibid* Kolida & Gibson, 2007] and in animal models [Loh *et al*., 2006; Scholz-Ahrens & Schrezenmeir, 2007] are many and have been widely documented in the scientific literature although in some cases the health benefits have yet to be convincingly demonstrated [*ibid* Macfarlane *et al*., 2006b]. As mentioned previously inulin and oligosaccharides produce a bifidogenic effect in the intestine by providing substrates for beneficial bacteria, (bifidobacteria & lactobacilli), to thrive on which result in many benefits to health seen both in human and animal studies. One of these is safeguarding against gastrointestinal and systemic infection. This is achieved by effects on the intestinal mucosa where deepened crypts, higher villi and more goblet cells are observed together with a thickening of the colonic epithelial mucus. In addition it is likely that, through inulin, the antagonistic and competitive action of the bifidobacteria and lactobacilli with pathogens coupled with a trophic effect on the intestinal lining could be responsible for securing against intestinal infection [Topping & Clifton, 2001; *ibid* Guarner, 2007]. Indeed, many recent studies of critical health conditions have investigated the effect of inulin and oligosaccharides on preventing bacterial translocation [Rayes *et al*., 2002a; Anderson *et al*., 2004; *ibid* Roberfroid, 2007a]. Other frequently reported health benefits consist of improving bulk and gut motility *i.e.* bowel habits and constipation [Kleessen *et al*., 1997], (through increasing faecal biomass and water content of the stools), prevention of colonic cancer through SCFA [Emenaker *et al*., 2001; Miyauchi *et al*., 2004] treatment of Chronic Inflammatory Bowel Disease [Leenen & Dieleman, 2007], regulation of appetite through modulating the secretion of gastrointestinal peptides [*ibid* Roberfroid, 2007a], increased mineral absorption of calcium, iron & magnesium [Weaver, 2005], reducing lipogenesis and occasionally cholesterol especially in hyperlipidaemic subjects [*ibid* Davidson & Maki, 1999; Letexier *et al*., 2003] although the precise mechanism remains unclear, replacing sugar in the treatment of diabetes [Wong & Jenkins, 2007] and enhancing immune system function, particularly during its development in infants [Veereman, 2007]. In other recent studies on infants, prebiotics have been effective in reducing atopic dermatitis and other allergies through apparently modulating post-natal immune development [Moro *et al*., 2006; Arslanoglu *et al*., 2008] and are well tolerated in full term infants [Rao *et al*., 2009]. Furthermore due to the detrimental changes in the gut bacteria of elderly people, where the mortality of GI infections are 400 times higher than in younger people, the effect of a diet containing prebiotics has seen some reduction in disease [Tuohy, 2007]. Inulin is thus regarded as a "functional food" *i.e.* "*a food when consumed in the course of the daily diet, that has specific physiological benefits"*. However, much further research is necessary for the understanding of the mechanisms underpinning some of these effects [*ibid* Roberfroid, 2007a]. Another beneficial and fairly recent use of inulin is as a constituent of products termed synbiotics [Bengmark & Martindale, 2005]. These are composed of both probiotic bacteria and prebiotic sugars thereby in effect providing the combined advantages of added beneficial bacteria and increased amounts of endogenous beneficial bacteria. These can be found in various foods such as yogurts, milk, cream cheeses as well as supplements [Crittenden *et al*., 2001; Boehm *et al*., 2002; Casiraghi *et al*., 2007]. Indeed this strategy has also been shown to be an effective clinical treatment in various inflammatory diseases of the large bowel such as ulcerative colitis and others [Furrie

et al., 2005; *ibid* Guarner 2007; Olah *et al*., 2007; Haskey & Dahl, 2009], in trauma patients [Kotzampassi *et al*., 2006], and elderly people more at risk of gut infection [Bartosch *et al*., 2005]. Mixtures of these probiotics and prebiotics have also significantly reduced the rate of postoperative infections in liver transplant patients and those after abdominal surgery [*ibid* Rayes *et al*., 2002a,b]. A study on patients in intensive care with sepsis showed that there were no differences in gut permeability in patients receiving symbiotics and controls but that the incidence of pathogenic bacteria had decreased significantly in the former [Jain *et al*., 2004]. Another useful and related role for inulin, (and other undigestible oligosaccharides), is as an inert coating in the delivery of drugs targeted to the colon [Chourasia & Jain, 2004].

Negative aspects; in summary

The disadvantages in taking inulin are several and in the first instance relate to fructose malabsorption [*ibid* Davidson & Maki, 1999; Shepherd & Gibson, 2006;], leading to somewhat uncomfortable symptoms *e.g.* gas, bloating, cramps, abdominal pain, diarrhoea. This condition affects 30-40% of the population but can be alleviated in various ways such as by limiting the intake of inulin to 0.5 g/meal, gradually increasing intake or consuming roughly equimolar amounts of glucose with fructose. Human tolerance to inulin depends on chain length and dosage taking into account the ambient levels of the bacterial colonic population. It is seen that the adverse abdominal symptoms increase with increasing dose and decreasing chain length [Rumessen & Gudmand-Hoyer, 1998; Rossi *et al*., 2005; Stewart *et al*., 2008] as a result of more rapid fermentation of the shorter chain oligosaccharides [*ibid* Roberfroid *et al*., 1998; Stewart *et al*., 2008]. Studies in normal individuals have generally indicated 20 g/day inulin is well tolerated with DPs ranging from 10-60 [Carabin & Flamm, 1999; Bruhwyler *et al*., 2008] and that a 50% effective dose in causing diarrhoea is 30 g/day [Briet *et al*., 1995]. Certainly there seems to be no problem at 10 g/day [Bouhnik *et al*., 1999]. There also appears to be little difference between the sexes. Furthermore it is suggested [Coussement, 1999] that human tolerance to inulin can be classified into 3 groups; non-sensitive persons tolerating 30 g/day and higher, sensitive persons with some undesirable symptoms at 10-20 g/day and very sensitive persons experiencing undesirable symptoms at <10 g/day. Set against this background it is generally accepted that 5-8 g/day of inulin is sufficient for a desired bifidogenic effect [*ibid* Kolida & Gibson, 2007]. There have also been a few recent reports of allergic actions to inulin in food and it is generally regarded possible that in time these may increase as awareness of this likelihood grows. It should also be mentioned that another potential, (and controversial), but still unproven association exists in the form of the aforementioned *Klebsiella* gut bacteria. It has been demonstrated in some studies, (see introduction) that inulin and other indigestible oligosaccharides may provide a rich nutrient source for *Klebsiella* as well as other types although this has really only been demonstrated *in vitro*. It has also been long recognised that other pathogenic bacteria, such as Salmonella, Shigella, Clostridia, Staphylococcus aureaus, Candida albicans, Campylobacter jejuni, Escherichia coli, Veillonella, as well as *Klebsiella*, possess a potential ability of causing disease and detrimental local and systemic effects if allowed to overspread due to imbalances of gut microflora [Elmer *et al*., 1996]. Extensive research demonstrates the benefits of bifidobacteria and lactobacilli in maintaining control over, disease-causing organisms thus preventing dysbiosis and any resulting disease in the large bowel [*ibid* Kolida & Gibson, 2007]. However in cases of gut infection, the *Klebsiella* bacteria has been for some time now linked by association to ankylosing spondylitis (AS) through a possible mechanism of cross-reaction with antigens present on this bacterial strain [Rashid & Ebringer, 2007a]; AS being an arthritic autoimmune disease of the spine, (due to its response to immuno-suppressive medication), of as yet unknown aetiology but with a strong genetic component. Its frequency is approximately 0.1-0.2% of the population. A more general concern sometimes opined on various nutrition websites, [Crow, 2001; Gottschall, 2005; Donovan, 2007], is that changing the bacterial composition of the gut by artificial means, (*i.e.* through supplements), to favour a particular group over others may be potentially dangerous as the intestinal bacterial population and their interactions are very complex and still relatively poorly understood.

GENERAL DISCUSSION

Clearly inulin has therefore many advantageous and significant actions. Inulin and oligofructose are an important part of the daily diet of most of the world's population today and indeed since time immemorial they have been consumed in foods with no human awareness of there being any specifically related problems. The average daily consumption for inulin and oligofructose is estimated to be between 1 and 4 g in the USA [Moshfegh *et al*.,1999], with a higher intake of 3 to 11 g seen in Europe [Van Loo *et al*., 1995]. However historically, the dietary intake of inulin has been significantly higher than current-day consumption estimates. This can be compared to the total fibre intakes in the United States & Europe of approximately 12-25 g/day where most individuals consume far less dietary fibre than the recommended daily value (DV) set at 25 g [*ibid* Carabin & Flamm, 1999]. For example in the UK the average figure is 9.7-15.2 g [British Nutrition Foundation, 2007], whereas in Poland according to data available from a comprehensive survey demonstrated levels of 27.1 g for males and 23 g for females [Szponar *et al*., 2003]. Because both inulin and oligofructose are macroingredients, it is difficult to apply classical toxicology tests [*ibid* Coussement, 1999]. Some high dose animal tests have been performed however none revealed any toxic effects. These included assessing mortality, morbidity, target organ toxicity, reproductive or developmental toxicity and carcinogenicity [*ibid* Carabin & Flamm, 1999]. Several *in vitro* studies have also shown the absence of mutagenic or genotoxic potential [Clevenger *et al*., 1988]. The safety of inulin and oligofructose for use in foods has been positively evaluated by a plethora of clinical studies [*ibid* Guarner, 2007] and authorities worldwide [FDA, 2002] and as a result, both inulin and oligofructose are defined as food ingredients by most countries, where in food products their use is unrestricted and where they are labelled as dietary fibres [*ibid* Coussement,

1999]. A food (ingredient) is regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body beyond adequate nutritional effects and it is clear that inulin and oligofructose fulfill these criteria many times over. However for the purposes of food safety, the discussion is now mainly focused on dealing with the negative aspects as described above together with some marketing issues relevant to safety. According to conventional wisdom gastrointestinal intolerance to inulin and oligofructoses, are really the only convincingly proven basis for limiting the use of such fibre in the human diet. However in addition there are other potentially possible and perhaps serious problems referred to in the literature which this review is thereby behoved to discuss.

Inulin/Fructose intolerance

Intolerance to fructose consists of either of two separate disorders of metabolism known as Fructose Malabsorption (FM), (approx. 1:3 frequency) or the quite rare, but serious condition of Hereditary Fructose Intolerance, (HFI), with an approximate frequency of 1:20,000. In the latter [Yasawy *et al*., 2009] the liver enzyme fructose 1-phosphate aldolase is absent and causes a build up of fructose-1-phosphate which, through product inhibition, then inhibits the breakdown of glycogen and synthesis of glucose thus resulting in acute hypoglycemia after fructose has been consumed. Accompanying symptoms consist of severe abdominal pain and vomiting and in infants suffering from this condition, hepatic and renal failure leading to death is seen when fructose is consumed in a sustained fashion. HFI is treated by strictly removing fructose from the diet. This requires considerable self-discipline and would obviously include all inulins and oligofructoses but sufferers can lead a normal life, nevertheless fructose can always be consumed accidentally. Fructose malabsorption occurs when there is a defect in a specific transport protein in the intestinal enterocytes either through its absence or inactivation [Helliwell *et al*., 2000]. The condition can be inherited or acquired or result from an impairment of the intestinal lining due to disease, (*e.g.* Coeliac) [Born, 2007]. Fructose is therefore not absorbed and passes to the large bowel and if inulin is present it will add to the fructose load [Shepherd & Gibson, 2006] which is rapidly fermented by the intestinal bacteria to short chain fatty acids and gases, predominantly hydrogen, carbon dioxide and methane. The physiological outcome of these changes consist of increasing the osmotic load, providing substrate for rapid bacterial fermentation, changing gastrointestinal motility, promoting mucosal biofilm and altering the profile of bacteria. This can be of clinical significance in subjects with existing disorders of the bowel such as irritable bowel syndrome where these effects become more readily pronounced. The gases formed cause the main problems; flatulence, bloating, diarrhoea and abdominal pain. Also if the initial bacterial population of the colon is unbalanced, (*i.e.* dysbiosis), then the worse the symptoms of intolerance will be although this may be ameliorated by taking probiotics. The condition is unpleasant but is nowhere near as serious or life threatening as HFI. The threshold in sensitivity varies widely among individuals *e.g.* 1-20 g and also depend on the type of food in which inulin or oligofructose is incorporated. Its treatment is to limit fructose/oligofructose by adopting special diets tailored to the individual [*ibid* Shepherd & Gibson, 2006]. This would therefore apply to inulin where various recommendations have been made; the chief being to limit inulin intake to <0.5 g per serving. Various categories of sensitivity have also been proposed [*ibid* Coussement, 1999] as defined previously in the 'negative aspects ' section however it is important to always take into account the amounts and types of flora initially present in the colon [Roberfroid, 2007b] where this should be analysed prior to assigning any classification. An alternative treatment for fructose malabsorption that is effective in some cases [*ibid* Shepherd & Gibson, 2006] is to select those foods that contain an equimolar ratio of fructose and glucose or those in which fructose is given as sucrose [Rumessen, 1992], where the presence of the latter stimulates the activity of the fructose intestinal carrier GLUT-5 [Truswell *et al*., 1988]. Alleviation of many of the symptoms in some patients with FM can thus be achieved [*ibid* Born, 2007].

Inulin allergy

There have been only a few documented cases of anaphylactic reaction to inulin arising from dietary sources [Bacchetta *et al*., 2008] which also includes processed foods [Gay-Crosier *et al*., 2000], where the presence of anti-inulin IgEs have been confirmed [Franck *et al*., 2005]. There is a possibility that more cases may arise with a wider use of inulin in food especially when processed or in the form of supplements. There have also been a few cases of an allergic response [*ibid* Bacchetta *et al*., 2008] in circumstances where inulin is injected into the circulation when used as a clinical marker in the standard clinical chemistry method of measuring glomerular filtration rate [Tsinalis, 2009].

Effects of *Klebsiella*

It is well recognised in certain examples of disease, *e.g.* Acute Disseminated Encephalomyelitis (ADEM), Guillain-Barré Syndrome, Graves Disease *etc*., that bacterial/viral infections may act as environmental triggers inducing or promoting autoimmune disease in genetically predisposed individuals [Strieder *et al*., 2003; Tenembaum *et al*., 2007; Berlin *et al*., 2007]. It is also suspected that other common autoimmune diseases of unknown aetiology may also have a close association with infection, *e.g.* Rheumatoid Arthritis [Hvatum *et al*., 2006; Rashid & Ebringer, 2007b], Multiple Sclerosis [Ascherio & Munger, 2007], Kawasaki Disease [Rowley *et al*., 2008] *etc*. but definitive evidence is still lacking. A possible mechanism for inducing an immune response could be through molecular mimicry of microbial peptides to self tissues [*ibid* Berlin *et al*., 2007] which is a commonly seen phenomenon. This may be the case in the autoimmune disease Ankylosing Spondylitis (AS) of as yet unknown aetiology however it has been proposed for some time now that an infection by the opportunistic *Klebsiella* bacterium and perhaps others may be a cause or a factor perpetuating this condition [Schwimmbeck *et al*., 1987; Pollanen *et al*., 2009]. AS is a chronic, painful, degenerative inflammatory arthritis primarily affecting the spine and sacroiliac joints. AS is a member of the group of the autoimmune spondyloarthropathies with

a strong genetic influence where about 90-95% of patients express the HLA-B27 genotype [Sheehan, 2004], compared to 7% of the general population. Family history of the disease is common. Since only 1% of individuals who have positive findings for HLA-B27 develop the disease, the trigger is likely an unknown environmental factor in patients who are genetically predisposed. Also implicated in AS are cytokines, (*e.g.,* tumour necrosis factor alpha, interleukin-1), CD4+ T lymphocytes as well as two genes ARTS1 and IL23R recently identified to be associated with AS that seem to have an important effect on immune function [Brown, 2008]. Although specific autoantibodies cannot be detected, its response to immunosuppressive medication has prompted its classification as an autoimmune disease. Other alternatives have long been proposed [Edmonds *et al*., 1981; Geczy & Yap, 1982] but have now generally fallen by the wayside and are discussed no further. Current evidence for *Klebsiella* being this unknown environmental factor causing AS [Ebringer, 1992; *ibid* Rashid & Ebringer, 2007a] is really through "guilt by association" and can be summarised as follows; (1) Molecular mimicry of *Klebsiella* with HLA-B27 [Ebringer, 1989; *ibid* Lahesmaa *et al*., 1991; Ebringer & Rashid, 2007a;]; (2) *Klebsiella* microbes can be isolated from patients with AS during the active disease phase [Ebringer, 1978, *ibid* Rashid & Ebringer, 2007a]; (3) elevated titres of anti-*Klebsiella* antibodies can be identified in the sera of active AS patients [Mäki-Ikola *et al*., 1997a; Ahmadi *et al*., 1998; Tiwana *et al*., 1998; Wilson *et al*., 2003]; (4) presence of faecal *Klebsiella* in many AS patients [Hunter *et al*., 1981; Kuberski *et al*., 1983]. This is also supported by studies that have demonstrated an increased intestinal permeability in AS [Wendling *et al*., 1990; Mielants *et al*., 1991] where the associated asymptomatic gut inflammation [Lamarque *et al*., 2003], may be a factor in its pathogenesis especially in cases of fructose intolerance. If this were the case it can thus be argued that an important part of treating AS is to reduce the levels of *Klebsiella* thereby reducing the stimulus for immune cross reactivity and also decrease the gastrointestinal inflammation and the resultant permeability. This could be achieved in part through a diet low in starch and non-digestible carbohydrate [Ebringer & Wilson, 1996] including the prebiotic inulins and oligofructoses, where it is pertinent to again note that inulin and fructo-oligosaccarides can stimulate the production of pathogenic and opportunistic bacteria, such as *Klebsiells*, but only *in vitro* using pure cultures, as opposed to for *e.g.* faecal slurries, where the effects, in the former, of significantly lowering the pH and the release of substances toxic to harmful bacteria by other colonic bacteria are not seen. Moreover it could equally well be argued that *in vivo* these prebiotics could actually be beneficial, in the absence of fructose malabsorption, due to their inherent bifidogenic effect. Many other studies indeed do not confirm the *Klebsiella* hypothesis and the topic remains controversial [Amor & Toubert, 1997; Mäki-Ikola *et al*., 1997b; Spondylitis Association of America, 2009] where it is argued that the evidence for a correlation between *Klebsiella* and AS is circumstantial so far [Ardicoglu *et al*., 1996; Khan, 2002a], no infectious trigger has been established [Khan, 2002b] and that the efficacy of low-starch diets like the Ebringer diet [Ebringer, 1996], has not yet been fully scientifically evaluated [*ibid* Khan, 2002a; *ibid* Spondylitis Association of America, 2009] although some supporting evidence does exist *e.g.* elimination of cow's milk products in the diet was shown to improve the symptoms of AS [Appelboom & Durez, 1994]. Conversely many studies [Sprenkels *et al*., 1996; Toivanen *et al*., 1999; Stone *et al*., 2004; *ibid* Sheehan, 2004] find no support for the role of *Klebsiella* in the aetiology of primary AS. Furthermore the increase in anti-*Klebsiella* antibodies have not been confirmed in other studies [Singh *et al*., 1986; Cameron *et al*., 1987; O'Mahony *et al*., 1992; MacLean *et al*., 1992; Mäki-Ikola *et al*., 1997b; *ibid* Stone *et al*., 2004], nor have increases in faecal *Klebsiella* been seen in patients with AS compared to controls [van-Kregten *et al*., 1991; Toivanen *et al*., 1999; Stebbings *et al*., 2002] and the molecular mimicry between certain *Klebsiella* proteins (*e.g.* nitrogenase, pullulanase) with HLA-B27 has also not been confirmed [Kinsella *et al*., 1984; Georgopoulos *et al*., 1985; de Vries *et al*., 1992; Russell & Suarez Almazor, 1992; Lahesmaa *et al*., 1993]. An important issue is the specificity of antibodies [O'Mahony *et al*., 1992; Russell & Suarez Almazor, 1992] and the non-specific immune response to an underlying inflammatory bowel disease seen in AS and other conditions such as Crohn's disease and rheumatoid arthritis [Cooper *et al*., 1988]. It is seen that current medical opinion on AS does not to regard bacterial infection as a causative agent but does still recognise a possibility of this existing. It is however generally accepted that further and more comprehensive studies are required to resolve this issue [Ebringer, 1992]. Also antibiotic therapy directed against *Klebsiella* in AS patients have to date been equivocal and thus do not firmly support a role of *Klebsiella* in AS [Smieja *et al*., 2001; Ogrendik, 2007] and in fact do not form part of any standard medical treatments currently recommended [Zochling *et al*., 2006; Clegg, 2006, Khan & Akkoc, 2006]. AS associated with immune dysregulation has been linked to other factors such as trauma [Olivieri *et al*., 1991], delayed hypersensitivity. [Kapoor, 1993] and reactive arthritis and Reiter's syndrome following hepatitis B vaccination [Hachulla *et al*., 1990; Hassan & Oldham, 1994]. Another very recent study [Ebringer *et al*., 2007] has also suggested a similar link between the *Klebsiella* and Crohn's disease through molecular mimicry and suggested treatments include antibiotics and low starch diets used in conjunction with traditional treatments. This is however in contrast to the findings of another study where fructo-oligosaccarides supplementation is seen to decrease Crohn's disease activity [Lindsay *et al*., 2006] although admittedly this excluded starch *per se.*

Perceived bacterial imbalances of the GI tract

A number of common concerns regarding inulin supplements can be frequently found on various internet sites related to health and food and so are briefly addressed here, including companies with seemingly likely business interests in either promoting inulin [Starling, 2009] or banning its use in its supplements [Natren, 2003]. Although the health benefits of inulin are generally acknowledged it is recommended that a healthy and natural intake of inulin should be through the diet and not through refined, concentrated forms as found in some supplements. The valid concern is that a large concentrated and purified dose may cause unpleasant side ef-

fects, alluded to previously, or as yet unknown effects when taken long term. As a general principle the opinion is that all ingredients present in whole foods work harmoniously with each other and just as refining a single ingredient and calling it "medicine" or an additive, from past history, often results in adverse effects *e.g*. sucrose, corn syrup *etc*. Another concern about inulin supplements is that they unnaturally alter the balance of microbes in the gut and that as this is a very complex and poorly understood system and changes to promote certain bacteria over others is potentially dangerous. Certainly it is scientifically recognised that the gut microflora is a very complex system [Eckburg *et al*., 2005] however since the advent of prebiotics 12 years ago together with the rapid development of new molecular technologies [*ibid* Eckburg *et al*., 2005] great progress has been made in the understanding of the effects of inulin/prebiotics, gut flora composition, their environment and interactions. Admittedly there is much still to learn and discover but there is little evidence, from a large and growing amount of work to date that conclusively shows any deleterious effects through microbial imbalances. It is also recognised that possible interactions between health promoting and potentially harmful bacteria can in fact be beneficial provided the latter are present in limited amounts [*ibid* Roberfroid, 2007b]. Indeed a new and highly positive perspective has now been proposed to use prebiotics as a research tool to experimentally create specific controlled microflora compositions in the colon of humans or laboratory animal models which can be tested by their effect on various medical conditions/disease states [Rastall *et al*., 2005; *ibid* Roberfroid, 2007a].

Marketing issues

Several points also need to be considered relating to an awareness of misleading claims regarding prebiotics. Contrary to some marketing information the daily dose of prebiotics does not actually determine the prebiotic effect [Tuohy *et al*., 2001]. The major factor that quantitatively controls the prebiotic effect is the number of bifidobacteria per gram of faeces before supplementation of the diet with the prebiotic begins. At the population level it is thus the fecal flora composition (especially the number of bifidobacteria) characteristics of each individual (and thereby the state of colonic health), that determine the efficacy of a prebiotic but not the dose itself. The bigger the population then the greater the effect of prebiotic stimulation. The scientific data are therefore not consistent with this "dose argument" and the consumer is hence misinformed. In healthy subjects a recent study [Kolida *et al*., 2007] has shown that relatively higher doses of inulin (8 g/day) not only exert the expected bifidogenic effect but decrease levels of Clostridium perfringens that is responsible for gas formation and bloating thus explaining why higher doses are better tolerated. One should also be aware that the idea to add the prebiotics inulin/oligosaccharides to probiotic supplements or various yoghurts is not necessarily all due to the potential health benefits but also a marketing strategy to achieve product differentiation. Adding a new claim to an old product adds to consumer interest, thus preventing market stagnation and increasing profits for the manufacturer.

CONCLUSIONS

Inulin is and always has been an major part of the human diet. It is only relatively recently, (last 40 years), that its benefits have been increasingly recognised and promoted. More evidence is constantly emerging of its positive effects through being a prebiotic functional food [Mcfarlane *et al*., 2006]. Inulin is consumed in two ways; either through natural foods rich in inulin or as supplements. The authors suggest that the former is preferred in keeping with the aforementioned general principle that a well balanced and natural diet is inherently the most beneficial and safest way of healthy eating in normal individuals. As described in this review more care is needed over taking supplements primarily to avoid some of the unpleasant effects of fructose intolerance since this condition is so highly prevalent in the human population. For the most part, the other potentially deleterious effects of inulin alluded to in this article remain unproven. The *klebsiella* & AS controversy remains unsolved and one would have expected that after 30 or so years, a definitive link and mechanism would have been elucidated by now – not just an association. This type of evidence is however conspicuous by its absence. Both inulin and oligosaccharides are the only two carbohydrates that can be classified as being prebiotic where for other candidates such as galactooligosaccharides, soyabean oligosaccharides, lactulose, resistant starch and other "colonic foods" [Bengmark, 2000], more data and studies, including reliable human nutrition studies, are required. After ingestion the prebiotic action of inulin is quickly manifest and lasts as long as it is consumed. Most studies to date have been conducted over a limited period of only several months and it would therefore be of interest to see the effects for longer periods of up to a few years. The authors suggest the following recommendations concerning inulin;

RECOMMENDATIONS

– In cases of severe fructose intolerance, (through malabsorption), the dietary intake of inulin should be limited to 0.5 g/day.

– Generally food containing inulin should be spaced over small but regular doses, avoiding large boluses.

– Long chain inulin is preferred with DP >20 (maybe >10) and oligofructoses should be limited if fructose intolerant.

– Patients with AS should be aware of the possible but unproven benefits in low inulin/starch diets.

– Dietary intake through fresh food is preferable to supplements & processed food.

– Awareness of exaggerated marketing claims (applies to all manufactured products).

– If fructose intolerant through malabsorption some additional glucose in the diet may help when fructose is ingested.

– Complete avoidance of inulin, oligofructoses, (& fructose), in cases of the very rare HFI condition.

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