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MIRACULOUS HEALTH BENEFITS OF PREBIOTICS

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ABSTRACT

A prebiotic is a living microorganism that, when administered in sufficient numbers is beneficial to the host and exerts health benefits beyond inherent basic nutrition. Prebiotics include foods, medicines and dietary supplements. In general, the benefits of the regular consumption of prebiotics include enhanced immune function, improved colonic integrity, decreased incidence and duration of intestinal infections, down-regulated allergic response, and improved digestion and elimination. Pharmaceutical and nutritional industries are exploring more natural treatments for health conscious consumers as natural treatments have been effective since immemorial and are staging a comeback and natural 'renaissance' is happening all over the globe.

INTRODUCTION: Prebiotics are defined as "selectively fermented ingredients that allow specific changes, both in the composition and or activity in the gastrointestinal microflora that confer benefits upon host well-being and health [1].

Prebiotics are also defined as non-digestible to low-digestible food ingredients that benefit the host organism by selectively stimulating the growth or activity of one or more than but limited number of probiotic bacteria in the colon [2, 3, 4, 5]. This role is played by Fermentable carbohydrates, which are not digested or poorly digested in the small intestine and stimulate, preferentially, the growth of bifidobacteria and some Gram-positive bacteria, belonging to the probiotic bacteria administered to humans play this role.

Complex carbohydrates traverse through the small intestine to the lower gut where they become available for some colonic bacteria but are utilized by only certain microbial types out of the majority of the bacteria present in the colon.

Lactulose, galactooligosaccharides (GOS), Fructooligo saccharides (FOS), inulin and its hydrolysates, maltooligo-saccharides, and resistant starch are the prebiotics commonly used in human nutrition. The main end products of carbohydrate metabolism by the way of fermentation by enzymes of Probiotic origin are short-chained fatty acids, namely acetate, butyrate and propionate, which are further used by the host organism as an energy source. In practice, the most common oligosaccharides are inulin and its hydrolysates and oligofructans.

The majority of studies have so far focused on inulin, FOS and GOS [6, 7]**.** These saccharides have now a long history of safe use and are generally regarded as safe, although there is some concern over increased gas production with some compounds, particularly when ingested in higher amounts or during the first few days of intake. They can be found in chicory, topinambuco, onion, garlic, asparagus, artichoke, leek, bananas, tomatos and many other plants.

Prebiotic oligosaccharides can be produced in three different ways: by extraction from plant materials, microbiological synthesis or enzymatic synthesis, as well as by enzymatic hydrolysis of polysaccharides [2, 8]. In practice, combined mixtures of probiotics and prebiotics are often used because their synergic effects are conferred onto food products. For this reason, such mixtures are called synbiotics. In conclusion, prebiotics are dietary substances (mostly consisting of nonstarch polysaccharides and oligosaccharides poorly digested by human enzymes) that nurture a selected group of microorganisms living in the gut. They favor the growth of beneficial bacteria over that of harmful ones.

Prebiotics

History: The term "prebiotic" was coined in 1995 by Gibson and Roberfroid [9], although prebiotics were recognized as early as the 1950s when György and coworkers described "bifidus factor", a bifidogenic substance that selectively promoted the growth of bifidobacteria (called *Lactobacillus bifidus* at that time) [10, 11]. Human milk and colostrum were found to contain large amounts of "bifidus factor". Multiple substances in human milk were found to be bifidogenic and were shown to stimulate the growth of bifidobacteria when administered to bottle-fed infants [12, 13]. In the 1970s and '80s, Japanese investigators pioneered the use of digestion-resistant saccharides to favorably modify the intestinal microbiota using fructooligosaccharides, galactooligosaccharides, and lactulose [14, 15]. Prebiotics offer the ability to enhance the healthful strains of bacteria including beneficial strains not available as probiotics, such as *Eubacterium* species[16].

Types of Prebiotics: Most prebiotics are used as food ingredients- in biscuits, cereals, chocolate, spreads, and dairy products, for example. Commonly known prebiotics are:

- Oligofructose
- Inulin
- Galacto-oligosaccharides
- Lactulose
- Breast milk oligosaccharides

Lactulose is a synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy.

The prebiotic oligofructose is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, and leeks. Oligofructose can also be isolated from chicory root or synthesized enzymatically from sucrose.

Fermentation of oligofructose in the colon results in a large number of physiologic effects, including:

1. Increasing the numbers of bifidobacteria in the colon
2. Increasing calcium absorption
3. Increasing fecal weight
4. Shortening gastrointestinal transit time
5. Possibly, lowering blood lipid levels

The increase in colonic bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

Major Prebiotics and their characteristics: Prebiotics can be classified as a type of digestion-resistant carbohydrate or dietary fiber [17, 18]. Like all fibers, prebiotics resist breakdown by human digestive secretions and arrive relatively unchanged in the lower regions of the intestinal tract where they can be utilized as an energy source by the resident microflora. What distinguishes prebiotics from other fibers is that prebiotics by definition selectively stimulate the growth of only beneficial microfloral organisms such as lactobacilli and bifidobacteria. Prebiotic properties have been ascribed to many types of carbohydrates, but they have been best documented for digestion-resistant oligosaccharides (DGOs) [19, 9].

DGOs include inulin-type fructans, galactooligo saccharides, lactulose, isomaltooligo saccharides, xylooligosaccharides, soyoligosaccharides, gentiooligo saccharides and nigeroligo saccharides [1]. They may be found naturally occurring in foods or milk or they may be synthesized. Most DGOs are composed of 3 to 10 sugar moieties, although the number of linked sugar molecules (degree of polymerization) varies. Chicory inulin may have up to 60 linked fructose molecules while lactulose, a synthetic prebiotic, consists of only galactose linked with fructose [20].

DGOs do not have uniform chain length, but are a mix of oligosaccharides with variable degrees of polymerization. They generally have glycosidic bonds in the β configuration and resist hydrolysis by human salivary and pancreatic digestive enzymes which are specific for α glycosidic bonds [18]**.** Ingested DGOs reach the colon largely intact where they are fermented by specific colonic microbial strains possessing a wide assortment of carbohydrolytic enzymes [21]**.** The rate of fermentation is strongly influenced by the constituent monomeric sugars, the degree of polymerization, type of linkage between monomeric units, and the general complexity of the molecule. Of the many forms of DGOs, only inulin-type fructans, galactooligo saccharides, and lactulose fully meet the criteria established for classification as prebiotics [22, 23].

Inulin-type Fructans: Inulin is arbitrarily defined as a mixture oligosaccharides with chain lengths of 2-60 fructose molecules [24] with or without an initial glucose.Inulin-type fructans are storage carbohydrates commonly found in wheat, onions, asparagus, bananas, garlic, artichokes, and leeks [25].

Galactooligosaccharides- Galactooligosaccharides: Galactooligosaccharides are digestion-resistant oligosaccharides naturally found in both human and cow's milk [19]. They can also be derived from specific microbial fermentation of lactose or synthesized using the enzyme β galactosidase and lactose syrup. Galactooligosaccharides selectively augment *Bifidobacterium* and *Lactobacillus* numbers within the human intestinal microbiota. Prebiotic applications of galactooligosaccharides are of great interest because of their natural occurrence in human milk.

Administration of galactooligosaccharides to formula fed infants has been shown to engender an intestinal flora similar to that of breast-fed infants Bifidobacteria populations are enhanced, pathogen numbers decrease; short-chain fatty acid production increases, fecal pH decreases, and stool characteristics such as frequency and consistency are improved. Galactooligosaccharides appear to offer well-documented prebiotic support, especially in infants, and are only now in the early stages of clinical acceptance.

Lactulose: Lactulose is synthetic galacto-fructose made by the isomerization of lactose [26]. Although technically a disaccharide, lactulose is generally grouped together with the DGOs. Lactulose is not usually present in nature although very small amounts may be found in heat-treated milk products as a result of non-catalyzed isomerization. Use of lactulose as a prebiotic dates to the late 1950s when it was found to be bifidogenic and for a time was dubbed "the bifidus factor" [27]**.** Lactulose cannot be split by human intestinal enzymes and is preferentially metabolized by colonic lactic acid bacteria with lactate and short-chain fatty acids as major end products. Human studies reveal prebiotic effects at daily doses of 3 grams with significant increases in *Bifidobacterium* and *Lactobacillus* numbers and reductions in *Clostridium perfringens*, *Bacteroides*, *Enterobacteriaceae*, and *Streptococcus* populations [28, 22]**.**

Mechanisms of Action: Prebiotics affect intestinal bacteria by increasing the numbers of beneficial anaerobic bacteria and decreasing the population of potentially pathogenic microorganisms. Probiotics affect the intestinal ecosystem by stimulating mucosal immune mechanisms and by stimulating nonimmune mechanisms through antagonism/competition with potential pathogens. These phenomena are thought to mediate most beneficial effects, including reduction of the incidence and severity of diarrhea, which is one of the most widely, recognized uses for probiotics. Probiotics reduce the risk of colon cancer in animal models, probably due to their role in suppressing the activity of certain bacterial enzymes that may increase the levels of procarcinogens, but this has not been proven in humans. Well-designed, randomized clinical studies are still required in order to define the role of probiotics as therapeutic agents in inflammatory bowel disease.

Mechanism of Prebiotics:

MECHANISMS OF PROBIOTIC/HOST INTERACTION. SYMBIOSIS BETWEEN MICROBIOTA AND THE HOST CAN BE OPTIMIZED BY PHARMACOLOGICAL OR NUTRITIONAL INTERVENTIONS IN THE GUT MICROBIAL ECOSYSTEM USING PROBIOTICS OR PREBIOTICS

	Prebiotics
Metabolic effects	• Production of short chain fatty acids, fat metabolism, absorption of ions (Ca, Fe, Mg).
Immunity effects	• Enhancing host immunity (IgA production • cytokine modulation, etc).

Health Benefits of Prebiotics:

Promotion of Normal Colon Transit Time: Constipation is an exceedingly common clinical problem affecting large segments of the population including the elderly, pregnant and nursing women, people on weight loss diets, and people with disrupted daily schedules such as variable shift workers and business travelers [29, 30]**.** Prebiotics increase fecal bulk and optimize stool consistency primarily by increasing fecal microbial mass**.** This increase in fecal bulk stimulates passage through the colon, shortening transit time. Colonic water resorption is reduced, stool becomes softer and heavier, and stool frequency increases. Together these factors alleviate constipation and improve colon evacuation. In a study of constipated elderly adults, 20 grams per day of inulin-type fructans had a significantly better laxative effect than lactose [31].

A mixture of inulin-type fructans and galactooligosaccharides has been repeatedly shown to improve the stool frequency and consistency of bottle-fed infants similar to that of breast-fed infants [32]**.** Administration of isomaltooligosaccharides has been shown to increase stool frequency and wet stool output in constipated elderly men [33]**.** Xylooligosaccharides have been shown to reduce severe constipation in pregnant woman [34] and lactulose administration has a long clinical history of alleviating constipation [26]**.**

Production of Short-Chain Fatty Acids: Prebiotics are primarily energy sources for healthful intestinal bacteria that ferment them into short-chain fatty acids**.** Many of the benefits of prebiotics derive from increased bacterial production of short chain fatty acids. Much of the increase in short-chain fatty acids comes about through metabolic cross-feeding in which prebiotics are fermented by certain species, such as *Bifidobacterium*, into end products that are in turn metabolized by other microorganisms resulting in an increased quantity and diversity of short-chain fatty acids [35, 36]**.** Acetate is usually the dominant short-chain fatty acid in the colon followed by approximately equal concentrations of propionate and butyrate [37, 38]**.** Short-chain fatty acids play essential roles in the growth and physiology of intestinal tissue as well as in systemic metabolism [39, 40]**.**

Acetate is an important energy source for the body and is metabolized by skeletal muscle, [41] the heart, [42] and the brain [43]**.** Gut microflora fermentation is the primary source of blood acetate. Propionate stimulates proliferation of normal crypt cells in human cecal biopsy specimens, while having an anti-proliferative effect on HT-29 adenocarcinoma cell lines [44]. Propionate has been shown to reduce hepatic glucose output and cholesterol biosynthesis [45, 46]**.** Butyrate is accepted as the most important short-chain fatty acid produced by the intestinal microflora. It is the preferred energy source for colonocytes and its metabolism accounts for 70% of colonic oxygen consumption**.**

Butyrate modulates colonocyte differentiation and proliferation, and regulates gene expression and transcriptional proteins. Of great importance to human health, butyrate upregulates glutathione S-transferase and catalase expression in colon cells, thereby enhancing cellular detoxification and antioxidant defenses [47] while reducing cell cycle progression and possibly suppressing DNA repair mechanisms in cancer cells [48, 49].

Additionally, receptors for butyrate, as well as for acetate and propionate, have recently been identified on leucocytes, suggesting a role of short-chain fatty acids in enhancing immune function. Enhanced butyrate production may explain why dietary fiber intake is associated with a reduced risk of colon cancer. Although one *in vitro* study has suggested that under conditions of prolonged inflammation, as in ulcerative colitis, accumulation of intestinal butyrate may overload DNA repair and apoptotic mechanisms and facilitate mutations that may contribute to tumorigenesis, [50].

Enhancement of Mineral Absorption: Several animal studies have demonstrated that inulin-type fructans [51], galactooligosaccharides [52]**,** isomaltooligosaccharides [53]**,** lactitol, [54] and lactulose [55] substantially enhance mineral absorption, especially calcium and magnesium. The combination of inulin and oligofructose has been shown to increase calcium and magnesium absorption more effectively than either oligosaccharide alone. In addition to augmenting calcium and magnesium absorption, inulin type fructans have been shown to protect animals from developing symptoms associated

with magnesium deficiency and to correct osteopenia. A number of clinical trials involving adolescents, postmenopausal women, and adult men have confirmed an enhancement of mineral absorption mediated by inulin-type fructans [56]. Increased colonic mineral absorption results from fermentation of inulin-type fructans which leads to higher concentrations of short-chain fatty acids, a lower colon pH, and enhanced mineral solubility and bioavailability.

Studies show that only modest consumption (8 to 10 grams/day) of prebiotics such as inulin-type fructans and lactulose can significantly increase calcium absorption in adolescent girls and boys as well as in postmenopausal women [57]. Improved magnesium absorption has also been observed in postmenopausal women following supplementation with 8 grams/day of fructooligosaccharides. In addition to increasing mineral absorption, research suggests inulin-type fructans enhance calcium accretion and improve bone mineralization and density in young adults [58].

Favorable Modulation of Lipid Levels: Most of the results on the effects of prebiotics and lipid metabolism are derived from research with inulin-type fructans. Inulin-type fructans modulate the digestion, absorption, and metabolism of lipids resulting in reductions of serum lipid levels as well as favorable redistributions of lipids among the various lipoproteins. Animal studies show inulin-type fructans decrease both fasting and postprandial plasma triglyceride levels mostly due to a decrease in the concentration of plasma VLDL-triglyceride in the postabsorptive state [59].

Oligofructose has also been shown to prevent hypertriglyceridemia induced by both fructose [60] and high-fat [61] feeding in rats. The principal hypotriglyceridemic mechanism of action appears to be a decrease in liver lipogenesis through increased production of short-chain fatty acids in the large bowel. Short-chain fatty acid production leads to increased portal concentrations of propionate relative to acetate which inhibits lipogenesis in hepatocytes [62]. Reduced lipogenic enzyme activity may also result from a prebiotic-mediated decrease in postprandial glucose and insulin concentrations that has been observed in some studies.

The effect of prebiotics on cholesterol levels is less consistent in animals and reductions are usually mild [59, 63]. In human studies, inulin is more effective than oligofructose in reducing triglyceride and cholesterol levels and the effects are more pronounced in diabetic and hyperlipidemic subjects. Administration of 7 to 20 grams/day of inulin-type fructans has been shown to reduce blood triglyceride and cholesterol levels by as much as 27% and 20%, respectively, in studies involving normal, diabetic, and hyperlipidemic human subjects [64, 65].

While the exact mechanism underlying inulin's hypocholesterolemic effect is not clear, evidence suggests it may result from propionate-induced inhibition of hepatic cholesterol synthesis. Galactooligo saccharides and xylooligosaccharides have also been shown to decrease serum cholesterol and triglycerides, respectively, in animal models [52].

Improved Gut Mucosal Barrier & Immune Function: The gastrointestinal tract is one of the most important components of the body's defensive system. In addition to providing non-specific protection in the form of a physical barrier against toxins and pathogenic organisms, the intestinal tract also provides specific protection in the form of gut-associated lymphoid tissue, or GALT. GALT represents the largest immune organ in the body and consists of a highly complex network of aggregated and non-aggregated immune cells [66]. Research indicates prebiotics modulate both intestinal and systemic immunity largely through their association with gut microflora.

Prebiotic support of health-promoting intestinal microorganisms leads to increased competition with pathogens for colonization sites, up regulated GALT expression of secretory IgA and immune-stimulating cytokines, and enhanced production of short chain fatty acids and other antimicrobial substances that create an inhospitable environment for pathogen growth [67, 68]. Prebiotics have been shown to further enhance the integrity of the intestinal mucosa by increasing villous height, augmenting mucin release, and enhancing healthy mucosal biofilm composition [69]. The morphological and functional enhancements prebiotics bring to the gut all improve colonization resistance and reduce the risk of pathogen translocation.

Prebiotics such as inulin, inulin-type fructans, galactooligosaccharides, and lactulose have been shown to enhance colonization resistance against a variety of enteropathogenic organisms, including *Clostridium difficile*, *Clostridium perfringens, E. Coli* [70, 71] and other coliforms [72]. Research indicates some prebiotic-like substances may also be able to directly stimulate immune cells. Yeast beta-glucans have been shown to activate receptors on phagocytes, NK cells, and certain classes of T- and B-lymphocytes and a novel class of oligosaccharides known as nigeroligosaccharides has been found to augment splenocyte proliferation and production of immune-potentiating cytokines such as interleukin-12 and interferon-γ [73].

Leukocytic receptors for short chain fatty acids have been identified suggesting that immune cells located within the GALT may be stimulated by enhanced production of these fatty acids following prebiotic supplementation. Prebiotic augmentation of both gastrointestinal and systemic immunity helps to reduce the risk of cancers and infections throughout the body. In animal models, the administration of inulin-type fructans has been shown to lower the incidence of chemically-induced aberrant crypt foci in the distal colon, diminish levels of *Candida albicans* in the small intestine and reduce mortality from systemic infection with *Listeria monocytogenes* and *Salmonella typhimurium* [74].

Human studies examining the effects of prebiotics on systemic immunity involving elderly residents of a nursing facility, shows that supplementation with 8 grams/day of fructooligosaccharides for 3 weeks resulted in a significantly increased percentage of peripheral T lymphocytes and CD4 and CD8 lymphocyte subsets [75]. Paradoxically, a decrease in phagocytic activity of granulocytes and monocytes was also observed, along with a diminution of pro-inflammatory IL-6 mRNA expression.

The authors speculate these effects may have resulted from a reduced intestinal pathogen load leading to an attenuated inflammatory response. This is a plausible explanation as anti-inflammatory effects of prebiotics have been noted in both animals and humans.

Administration of short-chain fructooligosaccharides was shown to reduce multiple chemical mediators of inflammation such as myeloperoxidase, inducible nitric oxide synthase, and leukotriene B4 in rats with experimentally-induced colitis [76]. In an open trial examining the effects of prebiotics on a small group of patients with Crohn's disease, supplementation with fructooligosaccharides for 3 weeks brought about a significant reduction in disease activity concomitant with a marked increase in mucosal bifidobacteria and a shift in dendritic cell function away from pro-inflammatory and towards immunoregulatory activity [77] and in a study involving infants, a formula containing a mixture of galactooligosaccharides and fructooligo saccharides was shown to significantly reduce the incidence of atopic dermatitis compared to the same formula without the prebiotics [78].

Influences on Glucose & Insulin Levels: Evidence suggests prebiotics can favorably influence serum glucose and insulin levels in a variety of ways. DGOs and other prebiotics can reduce the amount of glucose available for absorption into the bloodstream. Prebiotics also prevent excessive blood glucose elevations after a meal by delaying gastric emptying and/or shortening small intestine transit time. Bacterial fermentation yielding short-chain fatty acids is another mechanism whereby prebiotics can modulate glycemia and insulinemia.

Propionate has been shown to reduce hepatic gluconeogenesis and enhance hepatic glycolysis, [79] and fermentation end products, mainly butyrate, are believed to be responsible for increases in the glucose-regulating and satiety-inducing hormone glucagon-like peptide-1 (GLP-1) observed in prebiotic-fed animals [80]. Consumption of 20 grams/day of inulin-type fructans by healthy volunteers did not modify fasting plasma glucose and insulin concentrations, but decreased basal hepatic glucose production after 4 weeks.65

Another study examining the effects of 10 grams/day of inulin in healthy middle-aged men and women reported significantly decreased insulin concentrations after 4 weeks [81]. A study of non-insulin-dependent diabetic subjects administered 8 grams/day of inulin-type fructans reported significantly lower blood glucose levels after 4 weeks [65].

Carcinogenesis & Reduction in Colon Cancer Risk: Carcinogenic substances introduced into the intestinal tract from exogenous dietary sources, or produced endogenously by the gut microflora, represent an environmental insult thought to play a role in the initial stages of cancer. *In vitro* and animal studies have revealed the potential of prebiotics to enhance detoxification processes in colon cells, reduce toxic metabolite production in the gut, and protect against colonic tumor development. In animal models, inulin-type fructans, galactooligosaccharides, and xylooligosaccharides have been shown to suppress chemically induced colon cancer and precancerous colon lesions [82, 83, 84].

This effect is potentiated by the presence of lactic acid bacteria and associated with microflora fermentation and production of butyrate. Health-promoting bacteria inhibit the growth of pathogenic bacteria and thus decrease the production of carcinogenic substances such as ammonia, and tumor-promoting bacterial enzymes such as beta-glucuronidase. At the same time, bacterial growth increases biomass and thus stool bulk and accelerates colonic transit time decreasing exposure of the colon to potential carcinogens. Prebiotics reduce both the incidence and multiplicity [85, 86] of aberrant crypt foci and colon tumors in animal models and research indicates synbiotics have an even more pronounced preventive effect [87].

In addition to reducing the risk of colon cancer, dietary supplementation with inulin and oligofructose reduces the incidence of chemically-induced mammary cancer, slows the growth of implanted tumors, decreases metastases of implanted cancers, and enhances the efficacy of cancer chemotherapy [88]. Two recent human studies demonstrate the potential benefit of prebiotic feeding in chemoprevention. In a 3-month trial, administration of 10 grams/day of short-chain fructooligosaccharides to healthy individuals significantly reduced the level of toxic bile acids in fecal samples [89]. In another trial, a synbiotic combination of 12 grams of oligofructose-enriched inulin, *Bifidobacterium lactis*, and *Lactobacillus rhamnosus* significantly reduced DNA damage to colon cells and the cytotoxicity of fecal water in a group of subjects with a history of adenomatous colon polyps (but not those with extant colon cancer) [90].

Prebiotics & Infant Microflora: Formula-fed infants often have an altered balance of microorganisms in their gastrointestinal tract characterized by lower numbers of bifidobacteria and higher numbers of bacteroides, clostridia, enterobacteria, and staphylococci [91, 92]. Formula-fed infants also have a higher risk of intestinal infections. Human breast-milk contains numerous antibodies and a very high concentration of oligosaccharides that contribute to the natural defense against infection and promote a bifidobacteria-dominant microflora in the infant. Efforts to replicate the immunoprotective and bifidogenic effects of human breast milk on the intestinal tract of bottle-fed infants have led to research examining the effects of incorporating prebiotics into infant formulas.

Formulas containing a mixture of galactooligosaccharides and fructooligo-saccharides in a ratio of 9:1 have been shown to promote a microflora in infants similar to that seen in breast-fed infants [93]. Infants consuming this prebiotic mixture have significantly higher levels of fecal bifidobacteria, lower fecal pH, reduced levels of fecal pathogens, improved stool characteristics such as frequency and consistency, and short-chain fatty acid patterns more characteristic of breast-fed infants compared to infants fed a control formula.

One recent study also shows this type of prebiotic supplementation can reduce the incidence of both intestinal and systemic infections during infancy [94]. These data suggest that supplementing formula-fed infants with prebiotics can have significant beneficial effects on intestinal microbial ecology, immune development, and protection against infection.

CONCLUSIONS: The emerging area of prebiotics points towards the holistic role of nature in the health and nutrition of human being. We seem to be heading for coming a full circle from the times the aboriginal human was using tree bark as apparel and all vegetation along with animal flesh as its food, speedingly delineating health and nutrional effects of prebiotics has begun to underscore the role of non nutritive vegetation in our life. Probiotics have potential applications in many areas of human health. Probiotic products are widely marketed, and consumer interest in probiotics is growing rapidly.

The commercial use of probiotics has proceeded because essentially no risk is associated with consumption of well-defined probiotics in foods and many benefits are possible.

REFERENCES:

1. Roberfroid M: Prebiotics: the concept revisited. J Nutr. 2007; 137(3 Suppl 2): 830S-837S.
2. Crittenden RG and Playne MJ: Production, properties and applications of food-grade oligosaccharides. Trends Food Sci Technol 1996; 7: 353–360.
3. Dimer C and Gibson GR: An overview of probiotics, prebiotics and synbiotics in the functional food concept: perspectives and future strategies. Int Dairy J 1998; 8: 473–479.
4. Zimmer CJ and Gibson GR: An overview of probiotics, prebiotics and synbiotics in the functional food concept: perspectives and future strategies. Int Dairy J 1998; 8: 473–479.
5. Manning TS and Gibson GR: Prebiotics. Best Pract Res Clin Gastroenterol 2004; 18: 287–298.
6. Macfarlane S, Marfarlane GT and Cummings JH: Prebiotics: key issues. Aliment. Pharmacol. Ther. 2006; 24:701-714.
7. Macfarlane, GT, Steed H and Macfarlane S: Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. J. Appl. Microbiol. 2008; 104: 305-344.
8. Gulewicz P, Ciesiołka D, Frias J, Vidal-Valverde C, Frejnagel S, Trojanowska K and Gulewicz K : Simple method of isolation and purification of α-galactosides from legumes. J Agric Food Chem 2003; 48: 3120–3123.
9. Gibson, GR and Roberfroid M: Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J. Nutr. 1995; 125:1401-1412.
10. György P, Mello MI, Torres FE and Barness LA: Growth promotion in rats by crude concentrates of the bifidus factor. Proc Soc Exp Biol Med 1953; 84:464-7.
11. György P, Norris RF and Rose CS: Bifidus factor. I. A variant of *Lactobacillus bifidus* requiring a special growth factor. Arch Biochem Biophys 1954; 48:193-20.
12. Gauhe A, György P, Hoover JR, Kuhn R, Rose CS, Ruelius HW, Zilliken F: Bifidus factor. IV. Preparations obtained from human milk. Arch Biochem Biophys 1954; 48:214-24.
13. Petuely F: Lactobacillus bifidus flora produced in artificially-fed infants by bifidogenic substances (bifidus factor).] Z Kinderheilkd 1957; 79:174-179. (Article in German; Abstract in English)
14. Yazawa K, Imai K and Tamura Z: Oligosaccharides and polysaccharides specifically utilizable by bifidobacteria. Chem Pharm Bull (Tokyo) 1978; 26:3306-11.
15. Minami Y, Yazawa K, Tamura Z, Tanaka T and Yamamoto T: Selectivity of utilization of galactosyl-oligosaccharides by bifidobacteria. Chem Pharm Bull (Tokyo) 1983; 31:1688-91.
16. Louis P, Scott KP, Duncan SH and Flint HJ: Understanding the effects of diet on bacterial metabolism in the large intestine. J Appl Microbiol 2007; 102:1197-208.
17. Warrand J: Healthy polysaccharides. Food Technol Biotechnol 2006; 44:355-70.
18. De Vries JW: On defining dietary fibre. Proc Nutr Soc 2003; 62:37-43.
19. Tuohy KM, Rouzaud GC, Brück WM and Gibson GR: Modulation of the human gut microflora towards improved health using prebiotics – assessment of efficacy. Curr Pharm Des 2005; 11:75-90.
20. Roberfroid MB: Introducing inulin-type fructans. Br J Nutr 2005; 93(Suppl 1):S13-25.
21. Cummings JH, Macfarlane GT and Englyst HN: Prebiotic digestion and fermentation. Am J Clin Nutr 2001; 73(Suppl):415S-420S.
22. Tuohy KM, Ziemer CJ, Klinder A, Knöbel Y, Pool-Zobel BL and Gibson GR: A human volunteer study to determine the prebiotic effects of lactulose powder on human colonic microbiota. Microb Ecol Health Dis 2002; 14:165-73.
23. Gibson GR, Probert HM, Van Loo J, Rastall RA and Roberfroid, M: Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr. Res. Rev. 2004; 17:259-275.
24. Niness KR: Inulin and oligofructose: what are they? J Nutr 1999; 129 (7 Suppl):1402S-1406S.
25. Van Loo J, Coussement P, De Leenheer L, Hoebregs H and Smits G: On the presence of inulin and oligofructose as natural ingredients in the western diet. Crit Rev Food Sci Nutr 1995; 35:525-52.
26. Schumann C: Medical, nutritional and technological properties of lactulose: An update. Eur J Nutr 2002; 41(Suppl 1):1/17-1/25.
27. Petuely F:The bifidus factor. Dt Med Wschr 1958; 82:1957–60. (Article in German; Abstract in English)
28. Terada A, Hara H, Kataoka M and Mitsuoka T: Effect of lactulose on the composition and metabolic activity of the human faecal microbiota. Microb Ecol Health Dis 1992; 5:43-50.
29. Kaur N and Gupta A: Applications of inulin and oligofructose in health and nutrition. J Biosci 2002; 27:703-14.
30. Brandt LA: Prebiotics enhance gut health. Prepared Foods 2001; 179:NS7-10.
31. Kleessen B, Sykura B, Zunft HJ and Blaut M: Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons. Am J Clin Nutr 1997; 65: 1397-1402.
32. Moro G, Minoli I, Mosca M, Fanaro S, Jelinek J, Stahl B and Boehm G: Dosage related bifidogenic effects of galacto- and fructooligosaccharides in formula fed term infants. J Pediatr Gastroenterol Nutr 2002; 34:291–5.
33. Chen HL, Lu YH, Lin JJ and Ko LY: Effects of isomalto-oligosaccharides on bowel functionsand indicators of nutritional status in constipated elderly men. J Am Coll Nutr 2001; 20:4-49.
34. Tateyama I, Hashii K, Johno I, Iino T, Hirai K, Suwa Y, Kiso Y: Effect of xylooligosaccharide intake on severeconstipation in pregnant women. J Nutr Sci Vitaminol (Tokyo) 2005; 51:445-8.
35. Belenguer A, Duncan SH, Calder AG, Holtrop G, Louis P, Lobley GE and Flint HJ: Two routes of metabolic cross-feeding between *Bifidobacterium adolescentis* and butyrate-producing anaerobes from the human gut. Appl Environ Microbiol 2006; 72:3593-9.
36. Flint HJ, Duncan SH, Scott KP and Louis P: Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol 2007; 9:1101-11.
37. Cummings JH, Pomare EW, Branch WJ, Naylor CP and Macfarlane GT: Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 1987; 28:1221-7.
38. Weaver GA, Krauser JA, Miller TL and Wolin MJ: Short chain fatty acid distributions of enema samples from a sigmoidoscopy population: an association of high acetate and low butyrate ratios with adenomatous polyps and colon cancer. Gut 1988; 29:1539-43.

39. Topping DL and Clifton PM: Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001; 81:1031-64.
40. Säemann MD, Böhmig GA and Zlabinger GJ: Short-chain fatty acids: bacterial mediators of a balanced host-microbial relationship in the human gut. Wien Klin Wochenschr 2002; 114:289-300.
41. Karlsson N, Fellenius E and Kiessling KH: The metabolism of acetate in the perfused hind-quarter of the rat. Acta Physiol Scand 1975; 93:391-400.
42. Kodde IF, Van Der Stok J, Smolenski RT and De Jong JW: Metabolic and genetic regulation of cardiac energy substrate preference. Comp Biochem Physiol A Mol Integr Physiol 2007; 146:26-39.
43. Juhlin-Dannfelt A: Ethanol effects of substrate utilization by the human brain. Scand J Clin Lab Invest 1977; 37:443-9.
44. Scheppach W, Bartram HP and Richter F: Role of short-chain fatty acids in the prevention of colorectal cancer. Eur J Cancer 1995; 31A:1077-80.
45. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, Laffitte A, Guyon F, Bornet FRJ and Slama G: Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. Am J Clin Nutr 1996;63:939-45.
46. Venter CS, Vorster HH and Cummings JH: Effects of dietary propionate on carbohydrate and lipid metabolism in healthy volunteers. Am J Gastrenterol 1990; 85:549-53.
47. Sauer J, Richter KK and Pool-Zobel BL: Physiological concentrations of butyrate favorably modulate genes of oxidative and metabolic stress in primary human colon cells. J Nutr Biochem 2007;18:736-45.
48. Munshi A, Kurland JF, Nishikawa T, Tanaka T, Hobbs ML, Tucker SL, Ismail S, Stevens C, and Meyn RE: Histone deacetylase inhibitors radiosensitize human melanoma cells by suppressing DNA repair activity. Clin Cancer Res 2005;11:4912-
49. Sowa Y and Sakai T: Butyrate as a model for gene-regulating chemoprevention and chemotherapy. Bio-Factors 2000; 12:283-7.
50. Yoshida T, Haga S, Numata Y, Yamashita K, Mikami T, Ogawa T, Ohkusa T and Okayasu I: Disruption of the p53-p53r2 DNA repair system in ulcerative colitis contributes to colon tumorigenesis. Int J Cancer 2006;118:1395-403.
51. Beynen AC, Baas JC, Hoekemeijer PE, Kappert HJ, Bakker MH, Koopman JP and Lemmens AG: Faecal bacterial profile, nitrogen excretion and mineral absorption in healthy dogs fed supplemental oligofructose. J Anim Physiol Anim Nutr 2002; 86:298-305.
52. Chonan O, Matsumoto K and Watanuki M: Effect of galactooligosaccharides on calcium absorption and preventing bone loss in ovariectomized rats. Biosci Biotechnol Biochem 1995; 59:236-9.
53. Kashimura J, Kimura M and Itokawa Y: The effects of isomaltulose, isomalt, and isomaltulosebased oligomers on mineral absorption and retention. Biol Trace Elem Res 1996; 54:239-50.
54. Mineo H, Hara H and Tomita F: Sugar alcohols enhance calcium transport from rat small and large intestine epithelium in vitro. Dig Dis Sci 2002; 47:1326-33.
55. Brommage R, Binacua C, Antille S and Carrié A: Intestinal calcium absorption in rats is stimulated by dietary lactulose and other resistant sugars. J Nutr 1993;123:2186-94.
56. Scholz-Ahrens KE, Ade P, Marten B, Weber P, Timm W, Açil Y, Glüer CC and Schrezenmeir J: Prebiotics, probiotics, and synbiotics affect mineral absorption, bone mineral content, and bone structure. J Nutr 2007; 137(3 Suppl 2):838S-46S.
57. Griffin IJ, Davila PM and Abrams SA: Non-digestible oligosaccharides and calcium absorption in girls with adequate calcium intakes. Br J Nutr 2002; 87(Suppl 2):S187-91.
58. Abrams SA, Griffin IJ, Hawthorne KM, Liang L, Gunn SK, Darlington G and Ellis KJ: A combination of prebiotic short- and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. Am J Clin Nutr 2005; 82:471-476.
59. Fiordaliso M, Kok N, Desager JP, Goethals F, Deboyser D, Roberfroid M and Delzenne N: Dietary oligofructose lowers triglycerides, phospholipids and cholesterol in serum and very low density lipoproteins of rats. Lipids 1995; 30:163-7.
60. Busserolles J, Gueux E, Rock E, Demigne C, Mazur A and Rayssiguier Y: Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. J Nutr 2003; 133:1903-8.
61. Kok NN, Taper HS and Delzenne NM: Oligofructose modulates lipid metabolism alterations induced by a fat-rich diet in rats. J Appl Toxicol 1998; 18:47-53.
62. Delzenne NM and Kok N: Effects of fructans-type prebiotics on lipid metabolism. Am J Clin Nutr 2001; 73(2 Suppl):456S-8S.
63. Levrat MA, Favier ML, Moundras C, Remesy C, Demigne C and Morand C: Role of dietary propionic acid and bile acid excretion in the hypocholesterolemic effects of oligosaccharides in rats. J Nutr 1994; 124:531-8.
64. Brighenti F, Casiraghi MC, Canzi E and Ferrari A: Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers. Eur J Clin Nutr 1999; 53:726-33.
65. Yamashita K, Kawai K and Itakura M: Effects of fructo-oligosaccharides on blood glucose and serum lipids in diabetic subjects. Nutr Res 1984; 4:961-6.
66. Watzl B, Girrbach S and Roller M: Inulin, oligofructose and immunomodulation. Br J Nutr 2005; 93(Suppl 1):S49-55.
67. Gibson GR, McCartney AL and Rastall RA: Prebiotics and resistance to gastrointestinal infections. Br J Nutr 2005; 93(Suppl 1):S31-4.
68. Hosono A, Ozawa A, Kato R, Ohnishi Y, Nakanishi Y, Kimura T and Nakamura R: Dietary fructooligosaccharides induce immunoregulation of intestinal IgA secretion by murine Peyer's patch cells. Biosci Biotechnol Biochem 2003; 67:758-64.
69. Kleessen B and Blaut M: Modulation of gut mucosal biofilms. Br J Nutr 2005; 93(Suppl1): S35-40.
70. Wang X and Gibson GR: Effects of the in vitro fermentation of oligofructose and inulin by bacteria growing in the human large intestine. J Appl Bacteriol 1993; 75:373-80.
71. Shoaf K, Mulvey G, Armstrong G and Hutkins R: Prebiotic galactooligosaccharides reduce adherence of enteropathogenic *Escherichia coli* to tissue culture cells. Infect Immun 2006; 74:6920-8.
72. Ballongue J, Schumann C and Quignon P: Effects of lactulose and lactitol on colonic microflora and enzymatic activity. Scand J Gastroenterol Suppl 1997; 222:41-4.
73. Murosaki S, Muroyama K, Yamamoto Y, Kusaka H, Liu T and Yoshikai Y: Immunopotentiating activity of nigerooligo-saccharides for the T helper 1-like immune response in mice. Biosci Biotechnol Biochem 1999; 63:373-8.
74. Tuohy KM, Rouzaud GC, Brück WM and Gibson GR: Modulation of the human gut microflora towards improved health using prebiotics – assessment of efficacy. Curr. Pharm. Des. 2005; 11:75-90.

75. Guigoz Y, Rochat F, Perruisseau-Carrier G, Rochat I and Schiffrin EJ: Effects of oligosaccharide on the faecal flora and nonspecific immune system in elderly people. Nutr Res 2002; 22:13–25.
76. Lara-Villoslada F, De Haro O, Camuesco D, Comalada M, Zarzuelo A, Xaus J and Galvej J: Short-chain fructooligosaccharides, in spite of being fermented in the upper part of the large intestine, have anti-inflammatory activity in the TNBS model of colitis. Eur J Nutr 2006; 45:418-25.
77. Lindsay JO, Whelan K, Stagg AJ, Gobin P, Al-Hassi HO, Rayment N, Kamm MA, Knight SC and Forbes A: Clinical, microbiological, and immunological effects of fructo-oligosaccharide in patients with Crohn's disease. Gut 2006; 55:348-55.
78. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U and Boehm G: A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 2006; 91:814-9.
79. Roberfroid MB and Delzenne NM: Dietary fructans. Annu Rev Nutr 1998; 18:117-43.
80. Delzenne NM, Cani PD and Neyrinck AM: Modulation of glucagon-like peptide 1 and energy metabolism by inulin and oligofructose: experimental data. J Nutr 2007; 137(11 Suppl):2547S-51S.
81. Jackson K, Taylor G, Clohessy A and Williams C: The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. Br J Nutr 1999; 82:23-30.
82. Wijnands MV, Schoterman HC, Bruijntjes JB, Hollanders VM and Woutersen RA**:** Effect of dietary galactooligosaccharides on azoxymethane-induced aberrant crypt foci and colorectal cancer in fischer 344 rats. Carcinogenesis 2001; 22:127-32.
83. Pool-Zobel BL: Inulin-type fructans and reduction in colon cancer risk: review of experimental and human data. Br J Nutr 2005; 93(Suppl 1):S73-S90.
84. Hsu CK, Liao JW, Chung YC, Hsieh CP and Chan YC: Xylooligosaccharides and fructooligosaccharides affect the intestinal microbiota and precancerous colonic lesion development in rats. J Nutr 2004; 134:1523-8.
85. Reddy BS, Hamid R and Rao CV: Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition. Carcinogenesis 1997; 18:1371-4.
86. Verghese M, Rao DR, Chawan CB,Williams LL and Shackelford L: Dietary inulin suppresses azoxymethane-induced aberrant crypt foci and colon tumors at the promotion stage in young Fisher 344 rats. J Nutr 2002; 132:2809-13.
87. Rowland IR, Rumney CJ, Coutts JT and Lievense LC: Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. Carcinogenesis 1998; 19:281–5.
88. Taper HS and Roberfroid MB: Possible adjuvant cancer therapy by two prebiotics--inulin or oligofructose. In Vivo 2005; 19:201-4.
89. Boutron-Ruault MC, Marteau P, Lavergne-Slove A, Myara A, Gerhardt MF, Franchisseur C and Bornet F: Effects of a 3-mo consumption of short-chain fructo-oligosaccharides on parameters of colorectal carcinogenesis in patients with or without small or large colorectal adenomas. Nutr Cancer 2005;53:160-8.
90. Rafter J, Bennett M, Caderni G, Clune Y, Hughes R, Karlsson PC, Klinder A, O'Riordan M, O' Sullivan G, Pool-Zobel B, Rechkemmer G, Roller M, Rowland I,Salvadori M, Thijs H, Van Loo J, Watzl B and Collins JK **:** Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. Am J Clin Nutr 2007; 85:488-96.
91. Knol J, Scholtens P, Kafka C, Steenbakkers *J*, Gross S, Helm K, Klarczyk M and Schöpfer H: Colon microflora in infants fed formula with galactoand fructo-oligosaccharides: more like breast-fed infants. J Pediatr Gastroenterol Nutr 2005; 40:36-42.
92. Harmsen, Hermie JM, Wildeboer-Veloo, Alida CM, Raangs, Gerwin C, Wagendorp, Arjen A, Klijn, Nicolette, Bindels, Jacques G, Welling and Gjalt W: Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. J Pediatr Gastroenterol Nutr 2000;30:61-7.
93. Knol J, Boehm G, Lidestri M, Lidestri M, Negretti F, Jelinek J, Agosti M, Stahl B, Marini A and Mosca F: Increase of faecal bifidobacteria due to dietary oligosaccharides induces a reduction of clinically relevant pathogen germs in the faeces of formula-fed preterm infants. Acta Paediatr Suppl 2005
94. ; 94(Suppl 449):31-3.
95. Arslanoglu S, Moro GE and Boehm G: Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. J Nutr 2007; 137:2420-4.

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