

Prebiotin Structure/Function Claim: Reduction in Dysbiosis and Endotoxins

Doc No.: VR005

Revision: 1

AUTHOR: Dr. Frank Jackson, MD

1. PURPOSE/SCOPE

The purpose of this document is to explain how Prebiotin plays an active role in strengthening normobiosis which is where micro-organisms with potential health benefits predominate in number over potentially harmful ones. In turn, dysbiosis is eliminated or reduced which also results in decreased endotoxin translocation through the colon wall. This document provides a summary of the clinical literature published in support of this structure/function claim.

This includes studies performed and an evaluation of the relevant scientific literature related to how prebiotin acts in strengthening normobiosis. This results in a reduction of dysbiosis and endotoxins in the colon by nourishing beneficial bacteria.

2. GENERAL DETAILS

2.1 Dietary Supplement Name

Proprietary Product Name:
Prebiotin

2.2 Manufacturer

Jackson GI Medical
1714 N. 2nd Street
Harrisburg, PA 17102
USA

2.3 Dietary Supplement Description

Oligofructose Enriched Inulin

3. BACKGROUND

Prebiotin, a Prebiotic Fiber Supplement offers a full-spectrum prebiotic (Oligofructose-Enriched-Inulin, or OEI). OEI is obtained by combining chicory long-chain inulin and oligofructose. Inulin and oligofructose belong to a class of carbohydrates known as fructans. Because of the beta-configuration of the anomeric C2 in their fructose monomers, inulin -type fructans resist hydrolysis by intestinal digestive enzymes, they classify as 'non-digestible' carbohydrates, and they are dietary fibers.

The main sources of inulin and oligofructose that are used in the food industry are chicory and Jerusalem artichoke. Inulin and oligofructose are considered as functional food ingredients since they affect the physiological and biochemical processes in rats and human beings, resulting in better health.

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Unlike ordinary prebiotics such as Inulin or FOS, OEI ensures that Prebiotin nourishes beneficial bacteria throughout the colon. OEI is also the most-researched prebiotic, used in many university and clinical studies.

A prebiotic has been defined as *'a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health.* Inulin and oligofructose are the best-studied prebiotics so far. They are selectively fermented by the microflora in the human colon leading to a bacterial composition that is dominated by bifidobacteria, a perceived health-promoting genus.

The National Cancer Institute defines OEI as:

A substance that is used to improve the health of the digestive system and bones and is being studied in the prevention of colon cancer. Oligofructose-enriched inulin is made by combining two substances that occur naturally in many plants, including chicory root, wheat, bananas, onion, and garlic. Oligofructose-enriched inulin helps healthy bacteria grow in the intestines and helps the body absorb calcium and magnesium. OEI is also called Raftilose Synergy.

Source: (<http://www.cancer.gov/dictionary>)

The gut microbiome, meaning the vast collection of bacteria within the colon, is an intimate player in many of the metabolic disorders that occur in the body. They speak specifically to cardiovascular disease. What we eat makes a huge difference in the makeup of the gut bacteria factory. Likewise, prebiotics dramatically push this makeup in the correct way, encouraging the growth of bacterial groups that dramatically enhance cardiovascular welfare.

The major actors in the gut microbiome are called **short chain fatty acids (SCFA)**. The substances are made in large quantities in the colon when the right bacteria, the Bifidos and Lactos, are growing prodigously. One of these SCFAs is called propionate. This substance has been shown to reduce cholesterol. However, by far the star SCFA is butyrate. This is the substance that does many good things in the colon and beyond.

Dysbiosis: The word dysbiosis within medicine refers to the abnormal make up of colonic bacteria. Newer methods of identifying bacteria within the gut has outlined the fact that there are good and bad mixes of bacteria within the gut. Dysbiosis occurs when one or a few potentially harmful micro-organisms are dominant, thus creating a disease-prone situation. When bad bacteria mixes are present in the gut, the condition is called dysbiosis. It is not a disease in and of itself. Dysbiosis results in the following known changes within the colon and body:

- Barrier dysfunction of the colon wall (leaky gut)
- Endotoxemia with bacterial products and their metabolites translocating into the portal and systemic blood.
- Mild inflammation within the colon wall and systemically

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- Increased calories produced within the colon by the different bacteria that make up the dysbiotic complex
- Increased insulin resistance

Dysbiosis, changes in microbiome structure, has been linked to inflammatory, functional and metabolic disorders such as IBD, IBS and obesity.

4. PUBLISHED LITERATURE

4.1 Literature Search

A literature search was conducted using PubMed and Medline to identify articles that contained studies on the use of prebiotin (oligofructose enriched inulin) supporting significant changes in the composition of the gut microbiota resulting in strengthening of normobiosis, thereby eliminating a dybiosis state.

The following articles support the function claim that a healthy microbiota provided by prebiotics in the diet supports a significant change in the gut microbiota resulting in normobiosis which in turn plays a significant role in preventing endotoxins from translocating from the colon into the portal and systemic blood system. The articles and/or studies listed in Table 1 are summarized individually.

Table 1 Clinical Literature

	Author	Source/Published	Title of Publication	Year of Publication
1	Roberfroid M ¹ , Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A.	British Journal of Nutrition 2010 Aug;104 Suppl 2:S1-63.	Prebiotic effects: metabolic and health benefits.	2010
2	Robles Alonso V ¹ , Guarner F.	Br J Nutr. 2013 Jan;109 Suppl 2:S21-6.	Linking the gut microbiota to human health.	2013

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	Author	Source/Published	Title of Publication	Year of Publication
3	Pendyala S ¹ , Walker JM, Holt PR.	Gastroenterology. 2012 May;142(5):1100-1101.e2	A high-fat diet is associated with endotoxemia that originates from the gut	2012
4	Macfarlane S ¹ , Macfarlane GT, Cummings JH.	Aliment Pharmacol Ther. 2006 Sep 1;24(5):701-14	Review article: prebiotics in the gastrointestinal tract	2006

Article #1

Prebiotic effects: metabolic and health benefits.

Authors

Roberfroid M¹, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A.

Author Information:

Université Catholique de Louvain, Brussels, Belgium.

ABSTRACT

The different compartments of the gastrointestinal tract are inhabited by populations of micro-organisms. By far the most important predominant populations are in the colon where a true symbiosis with the host exists that is a key for well-being and health. For such a microbiota, 'normobiosis' characterises a composition of the gut 'ecosystem' in which micro-organisms with potential health benefits predominate in number over potentially harmful ones, in contrast to 'dysbiosis', in which one or a few potentially harmful micro-organisms are dominant, thus creating a disease-prone situation. The present document has been written by a group of both academic and industry experts (in the ILSI Europe Prebiotic Expert Group and Prebiotic Task Force, respectively). It does not aim to propose a new definition of a prebiotic nor to identify which food products are classified as prebiotic but rather to validate and expand the original idea of the prebiotic concept (that can be translated in 'prebiotic effects'), defined as: 'The selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host.' Thanks to the methodological and fundamental research of microbiologists, immense progress has very recently been made in our understanding of the gut microbiota. A large number of human intervention studies have been performed that have demonstrated that dietary consumption of certain food products can result in statistically significant changes in the composition of the gut microbiota in line with the prebiotic concept. Thus the prebiotic effect is now a well-established scientific fact. The more data are accumulating, the more it will be recognised that such changes in the microbiota's composition, especially increase in bifidobacteria, can be regarded as a marker of intestinal health. The review is divided in chapters that cover the major areas of nutrition research where a prebiotic effect has tentatively been

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investigated for potential health benefits. The prebiotic effect has been shown to associate with modulation of biomarkers and activity(ies) of the immune system. Confirming the studies in adults, it has been demonstrated that, in infant nutrition, the prebiotic effect includes a significant change of gut microbiota composition, especially an increase of faecal concentrations of bifidobacteria. This concomitantly improves stool quality (pH, SCFA, frequency and consistency), reduces the risk of gastroenteritis and infections, improves general well-being and reduces the incidence of allergic symptoms such as atopic eczema. Changes in the gut microbiota composition are classically considered as one of the many factors involved in the pathogenesis of either inflammatory bowel disease or irritable bowel syndrome. The use of particular food products with a prebiotic effect has thus been tested in clinical trials with the objective to improve the clinical activity and well-being of patients with such disorders. Promising beneficial effects have been demonstrated in some preliminary studies, including changes in gut microbiota composition (especially increase in bifidobacteria concentration). Often associated with toxic load and/or miscellaneous risk factors, colon cancer is another pathology for which a possible role of gut microbiota composition has been hypothesised. Numerous experimental studies have reported reduction in incidence of tumours and cancers after feeding specific food products with a prebiotic effect. Some of these studies (including one human trial) have also reported that, in such conditions, gut microbiota composition was modified (especially due to increased concentration of bifidobacteria). Dietary intake of particular food products with a prebiotic effect has been shown, especially in adolescents, but also tentatively in postmenopausal women, to increase Ca absorption as well as bone Ca accretion and bone mineral density. Recent data, both from experimental models and from human studies, support the beneficial effects of particular food products with prebiotic properties on energy homeostasis, satiety regulation and body weight gain. Together, with data in obese animals and patients, these studies support the hypothesis that gut microbiota composition (especially the number of bifidobacteria) may contribute to modulate metabolic processes associated with syndrome X, especially obesity and diabetes type 2. It is plausible, even though not exclusive, that these effects are linked to the microbiota-induced changes and it is feasible to conclude that their mechanisms fit into the prebiotic effect. However, the role of such changes in these health benefits remains to be definitively proven. As a result of the research activity that followed the publication of the prebiotic concept 15 years ago, it has become clear that products that cause a selective modification in the gut microbiota's composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies.

<http://www.ncbi.nlm.nih.gov/pubmed/20920376>

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Article #2

Linking the Gut Microbiota to Human Health

Robles Alonso V¹, Guarner F.

Author Information :

Digestive System Research Unit, University Hospital Vall d'Hebron, Ciberehd, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain. vrobles@vhebron.net

ABSTRACT

The human gut is the natural environment for a diverse and dynamic microbial ecosystem, whose structure and functions are presently a major target of research in biomedicine. Experimental studies in germ-free animals performed some decades ago revealed the importance of these microbial communities for normal growth and development and for the maintenance of health in adult life. The host provides habitat and nutrition to the microbial communities and derives many benefits from its symbionts that contribute to metabolic, defensive and trophic functions. Development of novel gene sequencing technologies as well as availability of powerful bioinformatic analysis tools provide new insights into the composition and structure of the human gut microbiota. There is no clear definition of the characteristics of a normal 'healthy' gut microbiota in human subjects, but several disease states have been associated with changes in the composition of faecal and intestinal mucosal communities, including inflammatory bowel diseases, obesity and the metabolic syndrome. Probiotics and prebiotics are used to improve symbiosis between enteric microbiota and the host or restore states of dysbiosis.

<http://www.ncbi.nlm.nih.gov/pubmed/23360877>

Article #3

A high-fat diet is associated with endotoxemia that originates from the gut.

Pendyala S¹, Walker JM, Holt PR.

Author Information:

Laboratory of Biochemical Genetics and Metabolism, The Rockefeller University, New York, New York 10065, USA

ABSTRACT

Endotoxemia, characterized by an excess of circulating bacterial wall lipopolysaccharide, is associated with systemic inflammation and the metabolic syndrome. Placing 8 healthy subjects on a Western-style diet for 1 month induced a 71% increase in plasma levels of endotoxin activity (endotoxemia), whereas a prudent-style diet reduced levels by 31%. The Western-style diet might, therefore, contribute to endotoxemia by causing changes in gastrointestinal barrier function or the composition of the microbiota. Endotoxemia might also develop in individuals with gastrointestinal barrier impairment. Therapeutic reagents

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that reduce endotoxemia might reduce systemic inflammation in patients with gastrointestinal diseases or metabolic syndrome.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=a+high-fat+diet+is+associated+with+endotoxemia+that+originates+from+the+gut>

Article #4

Review article: prebiotics in the gastrointestinal tract

Macfarlane S1, Macfarlane GT, Cummings JH.

Author information:

Dundee University Gut Group, Division of Pathology and Neuroscience, Ninewells Hospital and Medical School, Dundee, UK. s.macfarlane@dundee.ac.uk

ABSTRACT

BACKGROUND:

Prebiotics are short-chain carbohydrates that alter the composition, or metabolism, of the gut microbiota in a beneficial manner. It is therefore expected that prebiotics will improve health in a way similar to probiotics, whilst at the same time being cheaper, and carrying less risk and being easier to incorporate into the diet than probiotics.

AIM:

To review published evidence for prebiotic effects on gut function and human health.

METHODS:

We searched the Science Citation Index with the terms prebiotic, microbiota, gut bacteria, large intestine, mucosa, bowel habit, constipation, diarrhoea, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pouchitis, calcium and cancer, focussing principally on studies in humans and reports in the English language. Search of the Cochrane Library did not identify any clinical study or meta-analysis on this topic.

RESULTS:

Three prebiotics, oligofructose, galacto-oligosaccharides and lactulose, clearly alter the balance of the large bowel microbiota by increasing bifidobacteria and Lactobacillus numbers. These carbohydrates are fermented and give rise to short-chain fatty acid and intestinal gas; however, effects on bowel habit are relatively small. Randomized-controlled trials of their effect in a clinical context are few, although animal studies show anti-inflammatory effects in inflammatory bowel disease, while calcium absorption is increased.

CONCLUSIONS:

It is still early days for prebiotics, but they offer the potential to modify the gut microbial balance in such a way as to bring direct health benefits cheaply and safely.

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<http://www.ncbi.nlm.nih.gov/pubmed/16918875>

5. DATA SUMMARY – CLINICAL LITERATURE

Based on the clinical literature and research presented, prebiotin, oligofructose-enriched inulin, has been shown to have an active role in decreasing or eliminating a dysbiosis state through nourishing beneficial bacteria throughout the colon. Based on studies and literature, prebiotic properties have been shown to also reduce the translocation of endotoxins in the colon.

6. ATTACHMENTS

6.1 Clinical Literature referenced is maintained in the Structure/Function Technical File for Dysbiosis and Endotoxins.

APPROVALS:

CEO: _____ Date _____

COO: _____ Date _____

QUALITY/REGULATORY: _____ Date _____