



Prebiotics in the Treatment and Management of Irritable Bowel Disease

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Article info

Received: 01 June 2022

Revised: 24 July 2022

Available Online: 31 July 2022

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Abstract

Inflammatory bowel disease is an inflammation or swelling in the gastrointestinal tract which can be of two types namely Crohn's disease and ulcerative colitis. IBD causes inflammation of the stomach, small intestine, and colon. More than three million Americans have IBD. Although children are often diagnosed with IBD during adolescence, IBD can be diagnosed at any age. Boys and girls are both as likely to be diagnosed. The prevalence and incidence of IBD in the world is increasing, especially in developed countries. Treatment with medications like anti-inflammatory drugs, immune suppressors, biologics etc are the first therapeutic option. The main goals of medical treatment are to achieve remission (the absence of symptoms), maintain remission (prevent flare-ups of symptoms) and improve quality of life. Prebiotics are a selectively fermented ingredient that results in specific changes in the composition and activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health. Prebiotics are generally found in different food sources, such as chicory, chia seeds, dandelion greens, flaxseeds, onion, garlic, almonds, artichoke, oats, barley, and many other plants, although they can also be synthesized via enzymatic digestion of complex polysaccharides. Indeed, there is a growing interest in the hypothesis that the gut dysbiosis can be related to the immune alteration associated with IBD, and most of the literature regarding the use of prebiotics in GI disorders explore their efficacy in IBD patients. It has been demonstrated that commensal microbiota is able to protect mucosa from inflammation by decreasing intestinal permeability and increasing epithelial defence mechanisms. This review articles summarises the current understanding of inflammatory bowel disease and role of prebiotics in the treatment and management of the disease.

Keywords: Irritable bowel disease; Prebiotics; Gastrointestinal tract; Microbiota; Crohn's disease; Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is an inflammation or swelling in the gastrointestinal tract. There are two main types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These diseases are not contagious. Sometimes it is hard to distinguish between CD and UC. IBD causes inflammation of the

stomach, small intestine, and colon. IBD is not to be confused with irritable bowel syndrome (IBS) which may have some similar symptoms but does not cause damage to the digestive tract. IBD is a progressive disease that can become worse over time and cause other damage if not properly diagnosed. IBD can lead

to disability and can have a significant impact on quality of life, with significant mental health problems, including depression. Moreover, patients develop professional and social constraints that interfere with work and recreational activities and result in decreased sexual satisfaction compared to the general population. Patients are given a diagnosis of IBD-unclassified (IBD-U) until the exact diagnosis is clear. These are life-long conditions that need treatment to prevent future complications. These diseases are not contagious. While these conditions produce similar symptoms and use similar therapies, they are not the same. Inflammation in the GI tract occurs in both Crohn's disease and ulcerative colitis, there are important differences between the two diseases.

More than three million Americans have IBD. Although children are often diagnosed with IBD during adolescence, IBD can be diagnosed at any age. Boys and girls are both as likely to be diagnosed. The prevalence and incidence of IBD in the world is increasing, especially in developed countries. Over 1 million residents in the United States, 200,000 Canadians, and 2.5 million in Europe are estimated to have IBD, with substantial costs for health care: around US\$6 billion, CDN\$1.2 billion, and €4.6–5.6 billion, to year, respectively [1]. The incidence of IBD, as well as prevalence, is highest in the Western world, ranging from 10 to 30 per 100,000. Overall, Europe has a higher prevalence of UC than CD, whereas the opposite is true in Australia, in the United States, the distribution is equal. The risk of developing IBD is between five percent to 30 percent if you have a first-degree relative (parent, sibling or child) with the disease. IBD affects people of all ethnic backgrounds. IBD can first present at any age, but the most common age is between 15-30 years. There is a second smaller peak age for symptoms to start between 50-70 years. There are several factors that have been postulated to have an effect on the development of this group of diseases, which include but are not limited to bacterial contamination, a change in the immune system, and genetic variations. The majority of cases of IBD in women first present before age 30, the years of peak fertility. Some authors report women to have an approximately 30% greater risk than men of developing UC or Crohn disease.

Types of Inflammatory Bowel Disease

Crohn's Disease

Crohn's disease can affect any part of the gastrointestinal tract from the mouth to the anus. Crohn's disease is a chronic, or long-term, condition

that causes inflammation in the digestive tract. Crohn's disease can be painful, debilitating, and sometimes life threatening [2]. It most commonly affects the end of the small intestine (the ileum) where it joins the beginning of the colon. In Crohn's disease, the inflammation may extend through the entire thickness of the bowel wall. According to recent estimates, up to 50% of patients with CD have mildly to moderately active disease at any given time. They can cause problems throughout the body such as anemia, arthritis, abdominal pain, liver inflammation, eye inflammation, and osteoporosis. Lesions are a granulomatous inflammatory reaction throughout entire thickness of bowel wall. In 40% of cases, granulomas are either poorly developed or totally absent. May involve buccal mucosa, oesophagus, stomach, duodenum, jejunum, ileum, and colon. Rectal biopsies during flexible sigmoidoscopy or colonoscopy often reveal granulomas at this site. CD of small intestine is called regional enteritis; colon involvement is called Crohn's disease of the colon or granulomatous colitis (only a portion of patients develop granulomatous lesions). The disease primarily involves the intestinal system, but it also has a variety of other manifestations and can affect the skin, joints, bones, eyes, kidney, and liver.

Ulcerative Colitis

Ulcerative colitis (UC) causes irritation and ulcers (open sores) in the large intestine. It belongs to a group of conditions called inflammatory bowel disease (IBD). It often causes diarrhoea with blood, cramping and urgency. Sometimes these symptoms can wake a person up at night to go to the bathroom as well.

The inflammation in ulcerative colitis usually starts in the rectum, which is close to the anus). The inflammation can spread and affect a portion of, or the entire colon. When the inflammation occurs in the rectum and lower part of the colon it is called ulcerative proctitis. If the entire large intestine is affected, it is called pancolitis. If only the left side of the colon is affected, it is called limited or distal colitis. The severity of UC depends on the amount of inflammation and the location. Everyone is a little different. It could have severe inflammation in the rectum (small area) or very mild inflammation in the entire colon (large area).

About half of the people diagnosed with ulcerative colitis have mild symptoms. Others suffer frequent fevers, bloody diarrhoea, nausea and severe abdominal cramps. Ulcerative colitis may also cause problems such as arthritis, inflammation of the eye, liver disease

and osteoporosis. It is not known why these problems occur outside the colon. Scientists think these complications may be the result of inflammation triggered by the immune system. Some of these problems go away when the colitis is treated. Colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age. It affects men and women equally and appears to run in families, with reports of up to 20% of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. In addition, about 20% of patients are diagnosed before they are 20 years old, and it can occur in children as young as two years of age [3].

Epidemiology and Risk Factor of IBD

The epidemiology (incidence, prevalence and morality) and risk factors of inflammatory bowel disease (IBD). IBD is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract and includes Crohn's Disease (CD) and ulcerative colitis (UC). IBD has increasing incidence and prevalence in most of countries and becomes a global emerging disease. A westernized lifestyle or habits and some environmental factors have been found to contribute to the pathogenesis of IBD. The relevant risk factors include Smoking, hygiene hypothesis, microorganisms, appendectomy, medication, nutrition, and stress have all been found to be associated with the modality of IBD, but results are inconsistent on this issue in available studies. Therefore, more studies are required to identify and understand the environmental determinants of IBD. Around 25 percent of patients with IBD are diagnosed in the first 2 decades of their life. Of them, most are diagnosed in childhood (about 13-18 years) and its incidence is increasing in the early second decade of life. Moreover, studies from a variety of countries demonstrate that the incidence of IBD is increasing, especially in adolescence [4]. IBD, comprising Crohn's disease and ulcerative colitis, is a chronic immunologically mediated disease at the intersection of complex interactions between genetics, environment and gut microbiota. Established high-prevalence populations of IBD in North America and Europe experienced the steepest increase in incidence towards the second half of the twentieth century [5].

There are two population-based studies which have looked into the burden of UC in India. The first such study was conducted by Khosla et al. in 1984 in Haryana in North India. The study included 21,971 participants and noted a prevalence of 42.8 UC

patients per 100,000 people. The second study, conducted 15 years later by Sood et al. from Punjab (this state neighbors Haryana), employed a cluster sampling method and calculated age-standardized prevalence rates after screening a population of 51,910 people of which two thirds lived in rural parts of Punjab and the rest in urban parts. Overall, 23 patients were diagnosed with UC leading to a prevalence rate of 44.3/100,000. The incidence was calculated again during a second visit to the same area 1 year later and was reported to be 6.02/100,000. These data again indicate that UC is not rare in India [6]. However, these findings go against the general belief that the burden of IBD is on the rise in Asian countries, especially when data from other regions suggest so. A comparison of incidence and prevalence rates with other countries suggests that among Asian countries the disease burden is highest in India. A recent epidemiological study, entitled "The Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS)" by Ng et al who studied incident IBD cases diagnosed between April 2011 and March 2012, reported the incidence and prevalence of IBD from 8 Asian regions and Australia. The crude overall incidence of IBD, UC, and CD from Asia was 1.37, 0.76, and 0.54 per 100,000, respectively, whereas in Australia it was 23.67, 7.33, and 14.00, respectively. Among the Asian countries, it was highest in mainland China (Guangzhou: 3.4/ 100,000) followed by Hong Kong (3.06/100,000), and Macau (2.2/100,000). Data from Western Asia including studies from Kuwait, Turkey, and Israel revealed an incidence rate of 2.8/100,000 and 5.04/100,000 in Kuwait and Israel, respectively, and a prevalence of 4.9/100,000 and 167/100,000 in Turkey and Israel, respectively [6].

Treatment of Inflammatory Bowel Disease

Treatment with medication is the first therapeutic option. The main goals of medical treatment are to achieve remission (the absence of symptoms), maintain remission (prevent flare-ups of symptoms) and improve quality of life.

Anti-Inflammatory Drugs

Anti-inflammatory drugs are often the first step in the treatment of inflammatory bowel disease. They include:

Corticosteroids: Corticosteroids such as prednisone and budesonide (Entocort EC) can help reduce inflammation in the body, but they don't work for everyone with Crohn's disease. Corticosteroids may be used for short-term (three to four months) symptom

improvement and to induce remission. Corticosteroids may also be used in combination with an immune system suppressor.

Oral 5-aminosalicylates. These drugs include sulfasalazine (Azulfidine), which contains sulfa, and mesalamine (Asacol HD, Delzicol, others). Oral 5-aminosalicylates have been widely used in the past but now are generally considered of very limited benefit.

Immune System Suppressors

These drugs also reduce inflammation, but they target your immune system, which produces the substances that cause inflammation. For some people, a combination of these drugs works better than one drug alone.

Immune system suppressors include Azathioprine (Azasan, Imuran) and mercaptopurine (Purinethol, Purixan). These are the most widely used immunosuppressants for treatment of inflammatory bowel disease. Taking them requires that follows up closely with the doctor and have blood checked regularly to look for the side effects, such as a lowered resistance to infection and inflammation of the liver. They may also cause nausea and vomiting.

Methotrexate (Trexall): This drug is sometimes used for people with Crohn's disease who don't respond well to other medications.

Biologics

This class of therapies targets proteins made by the immune system. Types of biologics used to treat Crohn's disease include

Natalizumab (Tysabri) and vedolizumab (Entyvio). These drugs work by stopping certain immune cell molecules integrins from binding to other cells in intestinal lining. Because natalizumab is associated with a rare but serious risk of progressive multifocal leukoencephalopathy—a brain disease that usually leads to death or severe disability— it must be enrolled in a special restricted distribution program to use it.

Vedolizumab recently was approved for Crohn's disease. It works like natalizumab but appears not to carry a risk of brain disease.

Infliximab (Remicade), adalimumab (Humira) and certolizumab pegol (Cimzia). Also known as TNF inhibitors, these drugs work by neutralizing an immune system protein known as tumor necrosis factor (TNF).

Ustekinumab (Stelara). This was recently approved to treat Crohn's disease by interfering with the action of an interleukin, which is a protein involved in inflammation.

Antibiotics

Antibiotics can reduce the amount of drainage from fistulas and abscesses and sometimes heal them in people with Crohn's disease. Some researchers also think that antibiotics help reduce harmful intestinal bacteria that may play a role in activating the intestinal immune system, leading to inflammation. Frequently prescribed antibiotics include ciprofloxacin (Cipro) and metronidazole (Flagyl).

Other Medication

In addition to controlling inflammation, some medications may help relieve signs and symptoms, but always talk to the doctor before taking any over-the-counter medications. Depending on the severity of Crohn's disease, doctor may recommend one or more of the following:

Anti-diarrheal: A fiber supplement, such as psyllium powder (Metamucil) or methylcellulose (Citrucel), can help relieve mild to moderate diarrhoea by adding bulk to stool. For more severe diarrhoea, loperamide (Imodium A-D) may be effective.

Pain relievers: For mild pain, doctor may recommend acetaminophen (Tylenol, others) — but not other common pain relievers, such as ibuprofen (Advil, Motrin IB, others) or naproxen sodium (Aleve). These drugs are likely to make your symptoms worse and can make your disease worse as well.

Vitamins and supplements: If you're not absorbing enough nutrients doctor may recommend vitamins and nutritional supplements.

Nutrition Therapy

Doctor may recommend a special diet given by mouth or a feeding tube (enteral nutrition) or nutrients infused into a vein (parenteral nutrition) to treat Crohn's disease. This can improve your overall nutrition and allow the bowel to rest. Bowel rest can reduce inflammation in the short term.

Doctor may use nutrition therapy short term and combine it with medications, such as immune system suppressors. Enteral and parenteral nutrition are typically used to get people healthier prior to surgery or when other medications fail to control symptoms.

Doctor may also recommend a low residue or low-fiber diet to reduce the risk of intestinal blockage if a narrowed bowel (structure) is present. A low residue diet is designed to reduce the size and number of stools.

Surgery

If diet and lifestyle changes, drug therapy, or other treatments don't relieve signs and symptoms, doctor may recommend surgery. Nearly half of those with Crohn's disease will require at least one surgery. However, surgery does not cure Crohn's disease.

During surgery, surgeon removes a damaged portion of digestive tract and then reconnects the healthy sections. Surgery may also be used to close fistulas and drain abscesses.

The benefits of surgery for Crohn's disease are usually temporary. The disease often recurs, frequently near the reconnected tissue. The best approach is to follow surgery with medication to minimize the risk of recurrence [7].

Role of Prebiotics in Inflammatory Bowel Disease

Prebiotics

The prebiotics concept was introduced for the first time in 1995 by Glenn Gibson and Marcel Roberfroid [8]. However, in 2004, the definition was updated to “selectively fermented ingredients that specifically improve the activity and composition of gastrointestinal microflora and provide benefits to host health and well-being”, thus describing the conditions that exhibit beneficial effects on the host. Some years later, in 2010, with the development in molecular approaches and cumulative evidence about the density and diversity of bacterial communities, the International Scientific Association for Probiotics and Prebiotics (ISAPP) released a solidarity statement revising the definition of dietary prebiotic as “a selectively fermented ingredient that results in specific changes in the composition and activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health”. This revised definition involves the non-specific bacterial species, which expands the location of bacterial species from only the colon to the entire gut length. However, Bindels et al. (2015) proposed the definition of prebiotics as “non-digestible compounds that, through their metabolization by microorganisms in the gut, modulate the composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host. More

recently, with the progressive clinical development and latest scientific development, ISAPP in 2017 again updated the prebiotic concept, and defined it as “a substrate, i.e., selectively used by host microorganisms and conferring a health benefit(s) to the host while retaining the microflora-mediated health benefits” [9]. According to this updated definition, prebiotics are not limited to carbohydrates and foods and are no longer restrained to the gut [10]. Prebiotics are a group of nutrients that are degraded by gut microbiota. Their relationship with human overall health has been an area of increasing interest in recent years. They can feed the intestinal microbiota, and their degradation products are short-chain fatty acids that are released into blood circulation, consequently, affecting not only the gastrointestinal tracts but also other distant organs. Fructo-oligosaccharides and galacto-oligosaccharides are the two important groups of prebiotics with beneficial effects on human health.

Prebiotics are generally found in different food sources, such as chicory, chia seeds, dandelion greens, flaxseeds, onion, garlic, almonds, artichoke, oats, barley, and many other plants, although they can also be synthesized via enzymatic digestion of complex polysaccharides. Some common prebiotics, such as fructooligosaccharides (FOS), guar gum, galactooligosaccharides (GOS), and inulin, are available on the market, whereas hydrolysed xylan prebiotic products, such as xylooligosaccharides (XOS) are still in the development stage. Because of the health benefits of prebiotics, many pharmaceutical industries have gained interest in using prebiotics and have started manufacturing them at a cost-effective ratio [11]. Nowadays, a synthetic approach involving enzymatic digestion is predominantly used for the synthesis of high-quality prebiotics [11].

Prebiotic was described 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”. This definition was almost unchanged for more than 15 years. According to this definition, only a few compounds of the carbohydrate group, such as short and long chain β -fructans [FOS and inulin], lactulose, and GOS, can be classified as prebiotics. In 2008, the 6th Meeting of the International Scientific Association of Probiotics and Prebiotics (ISAPP) defined “dietary prebiotics” as “a selectively fermented ingredient that results in specific changes in the composition and/or activity of the

gastrointestinal microbiota, thus conferring benefit(s) upon host health” [12].

The following criteria are used to classify a compound as a prebiotic: (i) it should be resistant to acidic pH of stomach, cannot be hydrolyzed by mammalian enzymes, and also should not be absorbed in the gastrointestinal tract, (ii) it can be fermented by intestinal microbiota, and (iii) the growth and/or activity of the intestinal bacteria can be selectively stimulated by this compound and this process improves host's health.

Although not all the prebiotics are carbohydrates, the following two criteria can be exploited to distinguish fiber from carbohydrate-derived prebiotics: (i) fibers are carbohydrates with a degree of polymerization (DP) equal or higher than 3 and (ii) endogenous enzymes in the small intestine cannot hydrolyze them. It should be taken into account that the fiber solubility or fermentability is not crucial.

There are also some revised definitions for prebiotics published in the scientific literature. However, the above-mentioned definition, which was given in 2008, has been accepted in recent years. Despite the absence of a consensus definition, the important part of the original and other definitions is that the consumption of prebiotics is associated with human well-being [13]. Since low quantities of fructo-oligosaccharides and galacto-oligosaccharides naturally exist in foods, scientists are attempting to produce prebiotics on an industrial scale [13].

Prebiotics is a non-active food constituent that shifts to the colon and is then selectively fermented. The benefit to the host is mediated during selective stimulation of the growth and/or activity of one or a limited number of bacteria. Prebiotics pass by the small intestine to the lower gut and become accessible for probiotic bacteria without being utilized by other intestinal bacteria.

Lactulose, galacto-oligosaccharides, fructo-oligosaccharides, inulin and its hydrolysates, Maltooligosaccharides, and resistant starch are prebiotics Normally used in the human diet. The essential end components of carbohydrate metabolism are short-chain fatty acids, particularly acetic acid, propionic acid and butyric acid, which are used by the host organism as an energy source. They can also be found in different sources such as chicory, onion, garlic, asparagus, artichoke, leek, bananas, tomatoes and many other plants [14].

They are nutraceuticals which promotes the flourishing of probiotics before reaching to chronic region, the probiotics microorganisms have to survive the digestive enzyme and acids in the upper gut. To overcome this problem, nutraceuticals in the form of prebiotics are available. Prebiotics are the reach food substance which reach to colon in intact form, without getting depleted by bacteria. Hence, prebiotics act as fertilizer for these symbiotic bacteria [15].

Types of Prebiotics

There are many types of prebiotics. The majority of them are a subset of carbohydrate groups and are mostly oligosaccharide carbohydrates (OSCs).

Fructans

This category consists of inulin and fructo-oligosaccharide or oligofructose. Their structure is a linear chain of fructose with $\beta(2\rightarrow1)$ linkage. They usually have terminal glucose units with $\beta(2\rightarrow1)$ linkage. Inulin has DP of up to 60, while the DP of FOS is less than 10 [16].

However, over recent years, there are some investigations showing that the chain length of fructans is an important criterion to determine which bacteria can ferment them. Therefore, other bacterial species can also be promoted directly or indirectly by fructans.

Galacto-Oligosaccharides

GOSs were first chemically synthesized by nucleophilic and electrophilic displacement, but this method is currently deemed to be uneconomical at the industrial scale. The key enzymes for GOS formation are galactosyl-transferase and galactosidase. Galactosyl-transferase is a stereoselective enzyme that can produce GOS in high quantities [24]. Nevertheless, the bio-catalysis of GOS via galactosyl-transferase is so costly, because this reaction needs nucleotide sugars as a donor. There are some approaches to decrease the cost of this reaction, such as globotriose production or using human milk oligosaccharides. GOSs can greatly stimulate Bifidobacteria and Lactobacilli. Bifidobacteria in infants have shown high incorporation with GOS. Enterobacteria, Bacteroidetes, and Firmicutes are also stimulated by GOS, but to a lesser extent than Bifidobacteria.

There are some GOSs derived from lactulose, the isomer of lactose. This lactulose derived GOSs are also considered as prebiotics. GOSs can greatly stimulate Bifidobacteria and Lactobacilli. Bifidobacteria in

infants have shown high incorporation with GOS. Enterobacteria, Bacteroidetes, and Firmicutes are also stimulated by GOS, but to a lesser extent than Bifidobacteria [13].

Formation of GOS by means of galactosidase is much cheaper than galactosyl-transferases. However, galactosidase produces GOS in lower quantities, and this enzyme is less stereospecific than galactosyl-transferase. The amount of GOS produced by galactosidase can be improved in different ways: (i) increasing the concentration of donors and acceptors in the reaction, (ii) lowering water activity of the reaction, (iii) shifting the reaction equilibrium to the end product direction by the product elimination in the medium, and (iv) altering the synthesis conditions [17].

β -Galactosidases come from different sources, such as *Aspergillus Oryzae*, *Sterigmatomyces Elviae*, Bifidobacteria, and Lactobacilli. Different sources of β -galactosidases cause various types of GOS that differ in the amount, DP, and glycosidic linkages. Various sources of β -galactosidases need different conditions for optimizing GOS production. For example, fungal and bacterial, as well as yeast sources, require acidic and neutral pH, respectively. There are some by-products, such as glucose and galactose, which do not have prebiotic effects and may decrease GOS synthesis yield. When the whole cell is used, these by-products can be removed by other metabolic processes.

Starch And Glucose-Derived Oligosaccharides

There is a kind of starch that is resistant to the upper gut digestion known as resistant starch (RS). RS can promote health by producing a high level of butyrate; so, it has been suggested to be classified as a prebiotic. Various groups of Firmicutes show the highest incorporation with a high amount of RS. An in vitro study demonstrated that RS could also be degraded by *Ruminococcus bromii*, and *Bifidobacterium adolescentis*, and also to a lesser extent by *Eubacterium rectale* and *Bacteroides thetaiotaomicron*. However, in the mixed bacterial and fecal incubations, RS degradation is impossible in the absence of *R. Bromii* [18].

Polydextrose is a glucose-derived oligosaccharide. It consists of glucan with a lot of branches and glycosidic linkages. There is some evidence that it can stimulate Bifidobacteria, but it has not been confirmed yet.

Other Oligosaccharides

Some oligosaccharides are originated from a polysaccharide known as pectin. This type of oligosaccharide is called pectic oligosaccharide (POS). They are based on the extension of galacturonic acid (homogalacturonan) or rhamnose (rhamnogalacturonan I). The carboxyl groups may be substituted with methyl esterification, and the structure can be acetylated at C2 or C3. Various types of sugars (e.g., arabinose, galactose, and xylose) or ferulic acid are linked to the side chains. Their structures vary significantly depending on the sources of POSs [19].

Non-Carbohydrate Oligosaccharides

Although carbohydrates are more likely to meet the criteria of prebiotics definition, there are some compounds that are not classified as carbohydrates but are recommended to be classified as prebiotics, such as cocoa-derived flavanols. In vivo and in vitro experiments demonstrate that flavanols can stimulate lactic acid bacteria [20].

Production of Prebiotics

Prebiotics play an important role in human health. They naturally exist in different dietary food products, including asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato, rye, soybean, human's and cow's milk, peas, beans, etc., and recently, seaweeds and microalgae. Because of their low concentration in foods, they are manufactured on industrial large scales. Some of the prebiotics are produced by using lactose, sucrose, and starch as raw material. Since most prebiotics are classified as GOS and FOS regarding industrial scale, there are many relevant studies on their production [21].

Fructooligosaccharide [FOS]

FOS exists in about 36,000 plants; however, the concentration of FOS in these sources is not enough to have prebiotics effects. Therefore, FOS should be synthesized. FOS can be synthesized chemically by using glycosidase and glycosyl-transferase. The compounds that are used in these reactions are hazardous and costly, and the concentration of the end product (FOS) is very low. Thus, it cannot be produced on an industrial scale. Fructosyl-transferase (FTase) is a key enzyme in producing FOS. FTase produces FOS from sucrose by transferring one to three molecules of fructose. Several microorganisms have FTase, such as *Fusarium sp.*, *Aspergillus sp.*, *Aureobasidium sp.*, *Penicillium sp* [22].

For FOS production, the whole cell of a microorganism or free enzyme can be used. There are different factors that can affect the concentration of produced FOS. The maximum number of FOS produced by FTases depends on the initial concentration of sucrose (theoretically around 55–60%). Glucose, which is a co-product of fermentation, inhibits trans-glycosylation. Therefore, removing glucose and sucrose residues is a critical step to achieving higher yields of FOS fermentation. Some scientists claimed to utilize glucose oxidase and β -fructofuranosidase to enhance the yield of FOS production. β -fructofuranosidase is capable of converting sucrose to FOS. The glucose produced during FOS fermentation is converted to gluconic acid by glucose oxidase [23].

Lactulose

Lactulose is a colonic acidifier that works by decreasing the amount of ammonia in the blood. It is a man-made sugar solution. Lactulose has been used in clinical practice since 1957, and it is considered as “bifidus factor”, because it is able to increase the Bifidobacteria count. Lactulose administration is patient- and dose-dependent; not all subjects have the same beneficial response to lactulose administration and the microbiota composition, before the beginning of the consumption could influence the bifidogenic effect of the lactulose. A recent in vitro study showed the dose–response relationship in administering from 2 to 5 g/day of lactulose on a computer-controlled model of the human bowel. At a low dosage (2–3 g), they observed an increase in Bifidobacteria, but not in Lactobacilli, and a low production of SCFs. Nutrients 2020,12, 1037 7 of 24 while the administration of the maximal experimental dose (5 g/day) determined the correct balance among the microbial population (Bifidobacteria, Lactobacilli and Anaerostipes) and SCFAs production [24].

Mechanisms of Action of Prebiotics

In recent decades, several studies have underlined the health benefits of prebiotics, including effects on the gastrointestinal (GI) tract (i.e., the prevention of pathogen damage or immune system Modulation, the improvement of gut barrier function, a reduction in the pathogenic bacteria population, the production of short-chain fatty acids), on the cardiovascular system (i.e., a reduction in Blood lipid levels or effects on insulin resistance), on mental health (i.e., metabolites that influence Brain function, energy and cognition) and on bone (i.e., mineral bioavailability), etc [25].

The mechanism of action of prebiotics is postulated to be largely due to indirect effects. This includes acting as a fuel source for selective fermentation by resident health-promoting microorganisms of the GI tract, which are required for protecting against pathogens, or to improve intestinal barrier function, orchestrate immune pathways and influence brain function. Short chain fatty acids (SCFAs) are the main end products of selective fermentation.

They mediate the direct effects of the prebiotics by providing an energy source to the gut epithelium. They also play a role in local gene expression by improving accessibility to transcription factors, enhancing intestinal barrier by regulating the assembly of tight junction proteins, improving gut motility, metabolite absorption, sugar and lipid homeostasis and immune function. Acetate, propionate, and butyrate are the major SCFAs formed out of the fermentation process. Along with lactic acid, they participate in lowering the pH of the gut to levels that inhibit the growth of pathogens. SCFAs are also thought to increase mucin production that can contribute to a lower incidence of bacterial translocation across the gut barrier. Prebiotics, such as GOS, can exert a direct antimicrobial effect by adhering to the binding sites of bacteria on the enterocyte surface and thus, block the adhesion of pathogenic bacteria to intestinal epithelial cells [26].

Actually, a specific advantage of prebiotics is the growth of target microorganisms that, in turn, compete with species that are injurious to energy sources and exclude them by protecting or promoting the production of beneficial fermentation substances, such as SCFAs, which have immunomodulatory properties, influencing toll-like receptor-4 signaling and the production of pro-inflammatory cytokines. Among many potential prebiotics assessed, only a few substrates, i.e., inulin, FOS and GOS, have been validated by means of human studies. Nevertheless, fructans are known to be the main substrate of healthy microbes, GOS and lactulose, which seems to determine a major growth of Lactobacilli and Bifidobacteria, compared to inulin [27].

Role of Prebiotic in Inflammatory Bowels Disease

There are a few studies about the effects of prebiotics Inflammatory bowel Disease [IBD]. Inflammatory bowel disease (IBD) is an inflammation or swelling in the gastrointestinal tract. The pathogenesis of IBD has not been fully understood, but both genetic and

environmental factors, including gut microbiota, seem to be involved.

Indeed, there is a growing interest in the hypothesis that the gut dysbiosis can be related to the immune alteration associated with IBD, and most of the literature regarding the use of prebiotics in GI disorders explore their efficacy in IBD patients. It has been demonstrated that commensal microbiota is able to protect mucosa from inflammation by decreasing intestinal permeability and increasing epithelial defense mechanisms. Antibiotic-mediated microbial manipulation has some efficacy, particularly in active CD and pouchitis, but cannot be chosen in the maintenance of remission because of the lack of long-term efficacy and side effects. A novel treatment approach is represented by prebiotics that selectively manipulate gastrointestinal microbiota. In fact, in patients with chronic pouchitis, treated with 24 g per day of inulin, a significant reduction in the number of Bacteroidetes was reported. In another randomized study, involving 103 Crohn's Disease [28]. Patients, who received FOS 15 g/day, no clinical improvement was reported, but a reduction of the IL-6 of lamina propria dendritic cells (DC) and an increase of IL-10 DC staining were observed. In a single-arm study intervention, fructan administration determined an improvement of disease symptoms in 10 CD

patients, correlated with an increase of the Bifidobacteria concentration and of the percentage of interleukin-10, positive dendritic cells those that express toll-like receptor-2 and toll-like receptor-4. This condition highlights a beneficial modification of mucosal dendritic cell function. On CD patients, another study was also conducted, in which fructans administration showed a reduction in dyspeptic symptoms and in the levels of calprotectin, a bowel inflammatory biomarker, 7 days after the beginning of the intervention. Joossens et al. conducted two studies to evaluate the effects of fructans supplementation: in the first one, the authors administered 20 g of fructans for 4 weeks to 17 healthy subjects, and they observed an increment of *Bifidobacterium longum* and *B. adolescentis*. The second study of the same research group evaluated a 10 g administration of fructans to 67 subjects affected by mild IBD for 4 weeks, and they had no effects on *F. prausnitzii* and *B. adolescentis*, while *Rhannococcus gnavus* and *B. longum* increased, with a significant improvement of disease symptoms. Furthermore, two studies included in a recent metanalysis—one focused on prebiotics in an adult population and the other in children and young individuals—reported that the response to mesalazine is positively influenced by prebiotics through a mitigation of intestinal inflammation [29] (Figure 1).

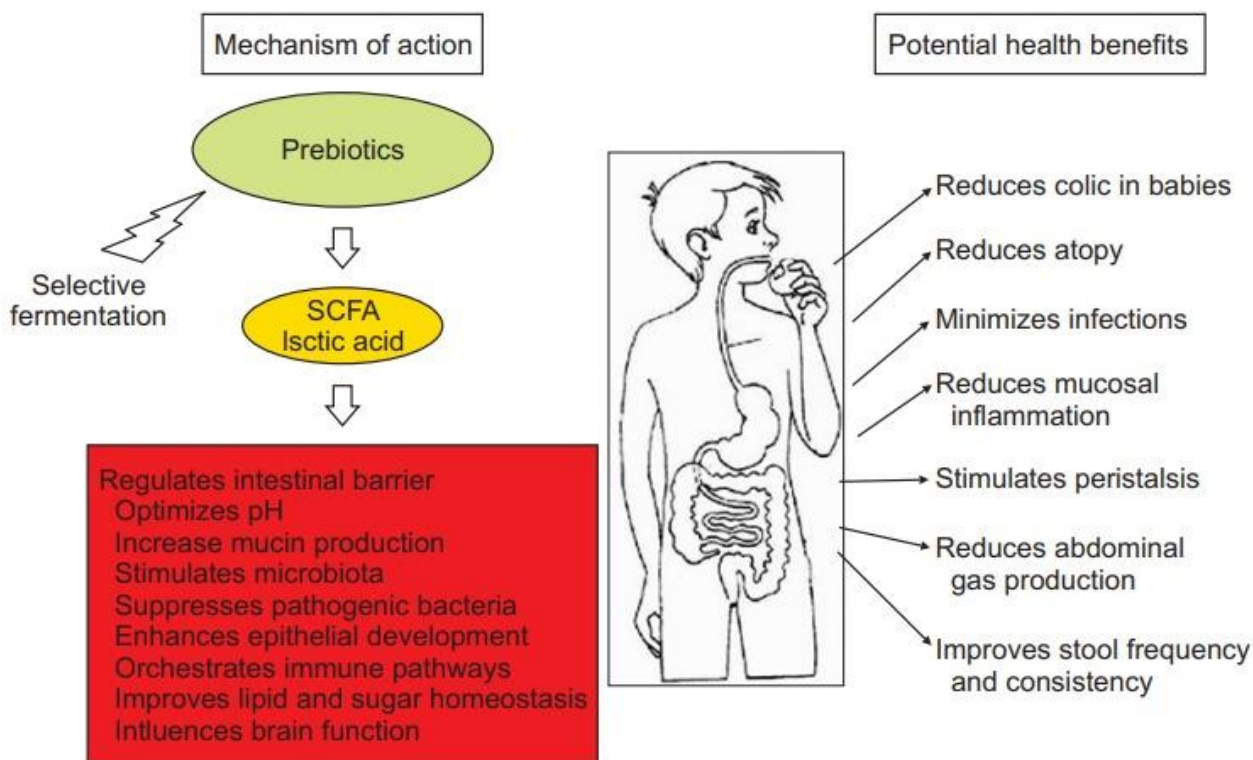


Figure 1: Schematic demonstrating the mechanism of action and potential health benefits of prebiotics.

Hafer et al. conducted a pilot study on 31 subjects suffering from IBD (both UC and CD) and found that a 10 g lactulose administration did not show any beneficial effect, except for an improvement of the clinical symptoms and the quality of life of patients with CU, without significant modifications at the endoscopic level. As Fellerman et al. reported, this discrepancy could be related to a defensin deficiency in IBD, which is reversible only in UC and not in CD patients, following lactulose administration.

Arabinooligosaccharides (AOS) seem to reduce inflammatory conditions in UC subjects, even if there are only preliminary results. Interestingly, an in vitro study showed that AOS, as well as FOS, are able to stimulate an increase of Lactobacilli and Bifidobacterium in fecal microbiota derived from UC patients. The FOS effects were clearly positive in increasing the content of both Bifidobacterium and Lactobacilli, while for AOS there was a positive trend, but the evidence was not so strong. However, AOS determined a significant reduction, especially in Firmicutes, but also in Bacteroidetes and Desulfovibrio. The increase of Lactobacilli and Bifidobacterium in the UC patients' fecal microbiota was associated with a higher production of acetate, which determines a decrease in pH, probably contributing to the amelioration of inflammation and prevention of flare-ups nutrients.

It has been demonstrated, in a 4-month RCT, that psyllium husk has beneficial effects in patients with inactive UC, improving symptoms, such as bloating, diarrhea, abdominal pain, urgency, incomplete evacuation and constipation, compared to the baseline. A one-year RCT tested the prebiotic effect versus the drug effect in UC patients, divided into a psyllium treatment group, a mesalazine group and a psyllium and mesalazine group. They observed that the synergic effect determined better but not significant results, compared to the other two groups. However, the psyllium group increased the fecal levels of butyrate

Moreover, starch seems to have other gastrointestinal beneficial effects, such as the increase of the stool bulk, promoting regular intestinal movement, a decrease of the cecal pH and a prevention of the mucous layer degradation in the colon.

Among gastro-intestinal disorders, colorectal cancer would also seem to be a therapeutic target of prebiotics. A systematic review analyzed some clinical

trials to underline the effect of some prebiotics (fructans, lactulose, and resistant starch) on colorectal cancer biomarkers, but they did not find any positive association between prebiotic consumption and a reduction of colorectal cancer biomarkers, except for lactulose administration—researchers found that it decreased the adenoma recurrence. On the other hand, the potential effects of the use of a symbiotic therapy (Lactobacillus Rrhamnosus and Bifidobacterium Lactis plus inulin) would seem to improve the integrity and the function of the epithelial barrier, as well as reduce the rate of cell proliferation in patients with colon cancer. However, as our knowledge of gut microbiota improves, it seems that other microorganisms could benefit from prebiotic administration, such as Clostridium coccoides or the Eubacterium rectale cluster, which includes bacteria-producing butyric acid, a beneficial metabolite for gut functionality that is potentially protective against bowel cancer. Interestingly, some degradation products of prebiotics are able to promote beneficial effects and to have protective effects on colonic epithelial cells during the progression of colorectal cancer, inhibiting the nuclear factor kappa B activation and the histone deacetylation. Butyrate seems to have a protective effect in the prevention of colonic cancer cell proliferation by provoking apoptosis through the induction of autophagy and by blocking the endoplasmic reticulum stress response [30].

Dietary polyphenols have also been studied in relation to colon cancer prevention, even if the data are conflicting. In animal models, it was demonstrated that resveratrol supplementation reduced bacterial enzyme activity, such as the activity of b-glucuronidase, b-glucosidase, b-galactosidase, mucinase and nitroreductase, and this decrease was linked with a major decline in colonic tumor occurrence [31].

The prebiotic impact of inulin on the management of the gastrointestinal disorder. Prebiotics shows a positive effect in the prevention of IBD by modulating the trophic functions of the flora. Inulin enhances the growth of indigenous *lactobacilli* and/or *bifidobacteria* by inducing colonic production of short chain fatty acids (SCFA's) and these properties are related to decreased mucosal lesion scores and diminished mucosal inflammation. Inulin shows a positive approach to retain microbial populations and to support epithelial barrier function by their prebiotic effect which helps in the host defense against invasion and pathogens

translocation (endogenous and/or exogenous) and in the inhibition of gastrointestinal diseases and this impact should be verified in further clinical studies. In the present review, we discussed the positive effect of prebiotics in rat IBD models and in human subjects along with their potential protective mechanisms. Preclinical and clinical data revealed that the gut mucosal barrier would be improved by the use of prebiotics in IBD [32].

Meanwhile, more and more functional oligosaccharides have been reported as prebiotics to alleviate UC, since many of them can be metabolized by gut microbiota to produce short-chain fatty acids (SCFAs). The present review is focused on the structure, sources and specific applications of various functional oligosaccharides related to the prevention and treatment of UC. The available evidence for the usage of functional oligosaccharides in UC treatment are summarized, including fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), chito-oligosaccharides (COS), alginate-oligosaccharides (AOS), xylooligosaccharides (XOS), stachyose and inulin [33].

Prebiotics are often specific carbohydrate structures that may be categorized as a type of dietary fiber. Although several researchers have shown that dietary fiber from whole foods and specific high-fiber dietary patterns can influence IBD outcomes, no studies have been done that examine the impact of specific prebiotic-containing whole foods on IBD. Thus, evaluation of the literature to determine the impact of prebiotics on IBD is limited to prebiotic supplementation (Table 1). Mixed results exist for supplementation of fructan-based prebiotics. A 1-group, open-label study supplemented 15 g of FOS for 3 weeks in 10 patients with CD. Supplementation reduced the HBI score, increased fecal *Bifidobacterium* concentrations, and increased the percentage of IL-10-positive DCs. However, fluorescence in situ hybridization was used to assess changes in microbiota, a method that may not be directly comparable with more common sequencing methods used currently [34].

Although fructan-containing compounds are the most well-known prebiotics, other fibers may have prebiotic capacity and thus may benefit patients with IBD. One such example is germinated barley. Composed of not only fiber (cellulose, hemicellulose, and lignin), but malted barley in the form also used in IBD studies (termed germinated barley foodstuff, GBF) contains protein and lipid as major and minor components,

respectively, of the dietary compound. Several studies by the same researchers reported a benefit of this compound for patients with UC [35].

Conclusion

Inflammatory bowel disease (IBD) is an inflammation or swelling in the gastrointestinal tract. There are two main types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These diseases are not contagious. Sometimes it is hard to distinguish between Crohn's disease (CD) and ulcerative colitis (UC). IBD causes inflammation of the stomach, small intestine, and colon. More than three million Americans have IBD. IBD can be diagnosed at any age. The prevalence and incidence of IBD in the world is increasing, especially in developed countries. Treatment with medication is the first therapeutic option. The main goals of medical treatment are to achieve remission (the absence of symptoms), maintain remission (prevent flare-ups of symptoms) and improve quality of life. Prebiotics are a selectively fermented ingredient that results in specific changes in the composition and activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health. Prebiotics are generally found in different food sources, such as chicory, chia seeds, dandelion greens, flaxseeds, onion, garlic, almonds, artichoke, oats, barley, and many other plants, although they can also be synthesized via enzymatic digestion of complex polysaccharides. Indeed, there is a growing interest in the hypothesis that the gut dysbiosis can be related to the immune alteration associated with IBD, and most of the literature regarding the use of prebiotics in GI disorders explore their efficacy in IBD patients. It has been demonstrated that commensal microbiota is able to protect mucosa from inflammation by decreasing intestinal permeability and increasing epithelial defence mechanisms. Prebiotics can be proved to be an important alternative in the treatment and management of IBD however, more research needs to be done in support of the claim.

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