MEETING THE **DIVERSE** REQUIREMENTS OF GUT **MICROBES** THROUGH DIVERSE PREBIOTIC **COMPOUNDS**

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ABSTRACT

A growing body of research has demonstrated that many of the long-understood health benefits of dietary fiber and other relatively indigestible complex carbohydrates are supported by the effect of these compounds on the microbial communities throughout the human digestive tract, especially the gut. Prebio- tics constitute a growing array of food and supplement ingredients that promote human health by enhancing the function of gut microbiomes. Prebiotics support health through their microbiome-mediated effects on bowel function, metabolic disorders, cholesterol levels, pathogens, nutrient absorption, inflammation disorders, and even mental health. Moreover, many of these findings have been substantiated by randomized, double-blind studies. As such, the most effective and consistent prebiotics are reviewed here, including isomalto-oligosaccharides, fructooligosaccharides, xylooligosaccharides, galactooligosaccharides, polyphenols, pectin, resistant starch, guar fiber, acacia gum, and aloe. In general, the most common prebiotic benefits derive from their indigestibility by mammalian digestive tracts and their eventual breakdown by beneficial bacteria found throughout the lower gastrointestinal tract. When compounds like oligosaccharides reach the small intestines and colon, communities of bacteria that include Bifidobacterium and Lactobacillus break them down into metabolites like the short-chain fatty acid butyrate. By consuming prebiotics that are digested by the bacteria at each stage of the gut, all gut microbial communities can be kept healthy.

Accordingly, it is important to consume prebiotic substances with a diversity of digestibility characteristics.

Making diet changes or selecting a supplement that provides beneficial bacteria at every point along the gastrointestinal tract with the proper nutrients can provide individuals with the full range of benefits associated with prebiotics.

INTRODUCTION

The genomic era of biological research has yielded deep insight into many medically relevant subjects, including the human microbiome, which consists of the extensive diversity of microorganisms that inhabit every portion of the human body, including every portion of the human gut (Turnbaugh et al., 2007). This research has also begun to provide support for the long-understood benefits of a diet rich in prebiotic compounds (Everard et al., 2014), nutrients such as indigestible complex carbohydrates and oligosaccharides that promote the growth of beneficial intestinal microbes (Gibson and Roberfroid, 1995). Each portion of the human gastrointestinal tract, from the oral cavity to the colon, is filled with different species of microbes that occupy the niches provided by human anatomy (reviewed by Walter and Ley, 2011).

The diversity of the bacteria among each of the segments of the human gastrointestinal tract are strongly influenced by diet and nutrition (Turnbaugh et al., 2009a,b; Wu et al., 2011; David et al., 2014).

Moreover, interventions and treatments with prebiotic compounds can alter the composition of gut microbiomes (Langlands et al., 2004; Benjamin et al., 2011). Indeed, the influence of diet on the gut microbiome is so great that even highly unrelated species of mammals with similar diets have similar gut microbiomes (Muegge et al., 2011).

Moreover, the precise overall diversity and vigor of the gut microbiome is linked to human health outcomes

(Robles Alonso and Guarner, 2013), with beneficial impacts on many conditions, including metabolic disorders such as obesity (Turnbaugh et al., 2009a), type 1 and 2 diabetes (Cani et al., 2008; Wen et al., 2008), and related disorders like sleep apnea (Shen et al., 2015; Durgan et al., 2017) as well as autoimmune inflammatory disorders such as Crohn's disease (Fujimori et al., 2006; Benjamin et al., 2011) and arthritis (Rogier et al., 2015; Zhang et al., 2015). The potential benefits of proper prebiotic nutrition indicate that health-conscious individuals should seek out diets and supplements that meet the complete needs of all beneficial gut microbes distributed throughout the human gastrointestinal tract. Additionally, beneficial gut microbes can competitively exclude or prevent pathogenic microbes including Clostridium difficile (Hasegawa et al., 2012) and Toxoplasma gondii (Benson et al., 2009).

In a healthy individual, the gut microbiome is comprised of largely beneficial, or commensal, bacteria that are adapted to extreme environmental conditions. With a steady temperature of 37°C throughout and both rather low and high pH environments (of the stomach and pancreatic juices, respectively), the human digestive tract presents microbes with some of the most inhospitable conditions of the human body. Yet, the microbes that inhabit human guts are far from exotic. Not only are they an essential part of human biology, but the most studied microbiological research organism is Escherichia coli, a bacteria that is ubiquitous in the large intestines of all mammals.

The human gut harbors a staggering diversity of bacteria far beyond E. coli. Indeed, a healthy human gut is home to between 1012 and 1014 bacterial cells, which roughly outnumbers the total count of human cells in the body of an adult man by about 30% (Sender et al., 2016). Furthermore, there are 1000–1150 different bacterial species found among the guts of all humans, with an average of 160 bacterial species per person (Qin et al., 2010). Collectively, these bacteria encode over 500,000 different proteins (Human Microbiome Jumpstart Reference Strains Consortium, 2010), many of which play important roles in assisting digestion. Accordingly, these different strains of bacteria and the proteins they produce can be highly specific to individual regions of the gut. Moreover, the abundance and diversity of these gut flora bacteria are correlated with metabolic markers for health in nonhuman (Vulevic et al., 2013) and human subjects (Le Chatelier et al., 2013). Beneficial gut bacteria promote overall health and wellbeing by regulating a broad range of human health indicators. These bacteria accomplish this by metabolizing or breaking down oligosaccharides that the human body is otherwise unable to digest into harmless or even beneficial compounds such as short-chain fatty acids (Gibson and Roberfroid, 1995; Collins and Gibson, 1999). While all the bases for these health benefits are not fully understood, the positive relationship of prebiotic consumption with gut microbiome vigor and thus health outcomes is well established (Sheu et al., 2008; Bruzzese et al., 2009; Hughes et al., 2011; Tzounis et al., 2011; Whisner et al., 2013). Similarly, the determinants of gut microbiome diversity are not fully understood, but a considerable body of evidence indicates that the proper diet and nutrition can promote gut microbiome functioning (Wu et al., 2011) and overall human health (Xu and Knight, 2015). Specifically, a diet rich in prebiotic compounds whose digestion requires beneficial microbes promotes the vigorous ecological functioning of gut microbiomes in every portion of the digestive system and the consequent benefits to human hosts (Bindels et al., 2015).

The gut microbiomes of healthy individuals with appropriately prebiotic diets strongly contrast with the gut microbiomes of those who do not consume sufficient levels of prebiotic compounds

(Wen et al., 2008; Turnbaugh et al., 2009a). When individuals consume insufficient amounts of indigestible fiber, the most beneficial bacteria are unable to thrive and propagate, with negative consequences. Without these beneficial bacteria, the lower gastrointestinal tract gradually harbors bacteria that have negative health impacts (Gibson and Roberfroid, 1995). However, a healthy microbial composition can be promoted even without radical dietary changes; therapeutic consumption of supplements and other dietary adjustments to include more functional foods can promote and maintain a productive community of gut microbes (Collins and Gibson, 1999).

Clinical trials have revealed the gut microbiome benefits of prebiotic supplements that are added to otherwise suboptimal or even poor diets (Langlands et al., 2004). Because gut bacteria occur throughout the digestive tract, dietary changes and supplements should be selected that meet the needs of gut bacteria throughout the digestive tract. For example, while pectin is not fully digested until it reaches the colon (Holloway et al., 1983), the fruit carbohydrate pectin promotes beneficial microbial activity within the cecum, a region of the small intestines; moreover, these effects are so specific that they differ with the source of pectin (Tian et al., 2016). In contrast, xylooligosaccharides are largely undigested in the small intestines by mammalian digestive enzymes or microbes (Okazaki et al., 1990); however, xylooligosaccharides promote the growth and fermentation of Bifidobacterium in the colon (Campbell et al., 1997). In short, gut health can be maintained through complementary combinations of various prebiotic substances that meet the specific needs of each bacteria habitat within a healthy gut.

To roughly outline an effective prebiotic supplement, this document lists some of the nutritional compounds that have therapeutic prebiotic effects that promote a productive, vibrant microbiome of the gastrointestinal tract. These compounds include oligosaccharides, such as isomalto-oligosaccharide, fructooligosaccharide, xylooligosaccharide, and galactooligosaccharide, as well as other prebiotic foodstuffs, such as polyphenols, pectin, resistant starch, guar fiber, acacia gum, and aloe. Individually, these compounds, which are mostly carbohydrates, provide clinically documented benefits to intestinal microbiomes and even overall health outcomes. Collectively, these compounds can provide a diversity of intestinal microbes across a diversity of niches within the gastrointestinal tract with the diversity of nutrients they require to fully support positive human health outcomes.

OLIGOSACCHARIDES

The simplest forms of carbohydrates are monosaccharides, the simple sugar molecules that follow the generic CnH2nOn formula of sugars and include familiar monosaccharides like glucose, fructose, and galactose. While many monosaccharides are completely digestible to mammals like humans, as more monomers are linked together to form progressively larger carbohydrates like oligosaccharides, they take on new chemical and physical properties and become more difficult to digest. Even the disaccharide lactose, which is found in milk and formed by the combination of one galactose monomer and one glucose monomer, is difficult for many lactose-intolerant adult humans to digest. However, the indigestibility of larger carbohydrates is precisely why they are available for gut microbes to break down and utilize throughout digestion, with various health benefits, many of which stem from promoting the production of short-chain fatty acids.

Isomalto-oligosaccharides

While isomalto-oligosaccharides are not produced by plant or animal cells, they are a natural byproduct of microbial fermentation. Indeed, isomalto-oligosaccharides are produced by the fermentation of starch and other large complex carbohydrates and are consequently found in traditional fermented foods such as soy sauce (Nishino et al., 1981). As isomalto-oligosaccharides contain oligosaccharides ranging from three to six monomers in length, they are relatively easy for bacteria to digest. Accordingly,

gut microbiota begin breaking down isomalto-oligosaccharide in the small intestines

(Oku and Nakamura, 2003), which is relatively early in the digestive process. The consumption of isomalto-oligosaccharides has a wide range of effects including decreased constipation and enhanced blood lipid levels (Wang et al., 2001; Yen et al., 2011).

However, these effects are specific to the composition of the isomalto-oligosaccharide that has been consumed. As isomalto-oligosaccharide is comprised of progressively longer chains of monomers, its promotion of Bifidobacterium increases in turn (Kaneko et al., 1994). Moreover, while Bifidobacterium and the Bacteroides fragilis are quite able to break down isomalto-oligosaccharide—thereby promoting the propagation of these bacteria—less beneficial bacteria such as E. coli are unable to make use of this oligosaccharide (Kohmoto et al., 1988). Accordingly, isomalto-oligosaccharide is not only metabolized into beneficial compounds such as small-chain fatty acids, but also promotes commensal bacteria that may exclude gut pathogens from colonizing the small intestine.

Fructooligosaccharides

Of all the oligosaccharides used in nutritional supplements, fructooligosaccharides may be the one with the most consistent demonstrable effect, including promotion of commensal gut bacteria growth (Gibson et al., 1995; Roberfroid et al., 1997), allergy suppression (Fujitani et al., 2007), and even tumor growth suppression (Pierre et al., 1997) among other benefits (reviewed in Hidaka et al., 1991; Bornet et al., 2002). Fructooligosaccharides belong to the family of naturally occurring carbohydrates called fructans, which are produced by plants such as Jerusalem artichoke, blue agave, garlic, and many others (Muir et al., 2007). Fructans polymers that consist of 20 or fewer d-fructose monomers are considered to be fructooligosaccharides, while longer polymers are considered to be inulin, a related carbohydrate with similar benefits. For this reason, fructooligosaccharides can be prepared from inulin-rich sources like yacón root (Pedreschi et al., 2003) or chicory root (Crittenden, 1999) that use inulin as an energy storage molecule for later conversion to smaller carbohydrates.

Fructooligosaccharides have a strong effect on the growth of Bifidobacterium and Lactobacillus across in vitro experiments (Wang and Gibson, 1993) as well as in human subjects (Gibson et al., 1995; Roberfroid et al., 1997). Though fructooligosaccharides can be relatively short carbohydrates,

- *they are not digested until the large intestine, where they promote the proliferation of Bifidobacterium and other microbes that produce short-chain fatty acids.*

They also promote the production of Immunoglobulin A, which has been implicated as a crucial mediator of the mutualistic relationship between gut microbiota and human hosts (Kato et al., 2014). Accordingly, many of the key benefits of prebiotics may be unlocked through increased consumption of fructooligosaccharides.

Xylooligosaccharides

The carbohydrates classified as xylooligosaccharides are chains of xylose sugar molecules and related monomers. Remarkably, food-grade xylooligosaccharides are typically produced from lignin- and cellulose-rich materials, which tend to be woody, and include corn cobs, straw, and even some hardwoods (reviewed in Vazquez et al., 2000). Perhaps expectedly, xylooligosaccharides are more difficult for microbes to break down relative to other oligosaccharides (Hopkins et al., 1998).

- *Accordingly, the limited fermentation of these oligosaccharides by gut bacteria occurs very late in the digestive process, largely within the colon by Bifidobacterium (Amaretti et al., 2013);*

however, pathogenic bacteria like E. coli or Clostridium are unable to use xylooligosaccharides as an energy source (Okazaki et al., 1990). Supplementation of diets with xylooligosaccharides has confirmed benefits in human subjects that include the promotion of beneficial gut microbes such as Lactobacillus and Bifidobacterium (Lin et al., 2016), improved cholesterol and blood lipid levels (Sheu et al., 2008), and enhanced production of butyrate (May et al., 1994), a short-chain fatty acid that is essential for the health and longevity of epithelial cells of the colon (Donohoe et al., 2011).

Galactooligosaccharides

Just like xylooligosaccharides, galactooligosaccharides are largely undigested until reaching the colon (Bouhnik et al., 1997);

in contrast, they are most often found in milk and dairy products as opposed to plants. Again, like xylooligosaccharides, once within the colon, Lactobacillus and Bifidobacterium begin to break down the long chains of galactose molecules known as galactooligosaccharides and produce beneficial compounds like short-chain fatty acids. However, the body of evidence for beneficial effects of galactooligosaccharides is even better established than that of xylooligosaccharides (Tuohy et al., 2005). Galactooligosaccharide consumption in human subjects is associated with a consistent increase in Bifidobacterium, which is demonstrated both in the total quantity of the bacteria (Ito et al., 1993; Gopal et al., 2003) as well as gut microbiome diversity (Davis et al., 2011). The reliable effects of galactooligosaccharides on gut bacteria are also reflected in benefits to human health. This group of prebiotic compounds has been demonstrated to increase calcium absorption (Whisner et al., 2013), reduce infant intestinal and respiratory infections (Bruzzese et al., 2009), and decrease both duration of flu as well as gastrointestinal distress (Hughes et al., 2011). Notably, each of these findings resulted from a randomized double-blind study, the most rigorous means for determining the efficacy of a specific treatment on human subjects.

OTHER PREBIOTIC COMPOUNDS

There are many other prebiotic compounds, but most of the common compounds with proven prebiotic benefits tend to be complex carbohydrates with digestibility characteristics similar to those of oligosaccharides.

Polyphenols

Many attributes make polyphenols unique among prebiotic compounds. Most obviously, the large family of molecules known as polyphenols are not carbohydrates. Additionally, while many prebiotic compounds do not have an impact on digestion until reaching the small intestines, antioxidant polyphenols take effect quite early in the process of digestion. Polyphenols are, as the name suggests, formed by many repeated phenols, which are aromatic six-carbon rings with a hydroxyl group. Many different polyphenols have been linked to positive health outcomes, including flavonoids like flavanones (Tomás-Barberán and Clifford, 2000), isoflavones (Ren et al., 2001), and quercetin (Formica and Regelson, 1995).

One of the richest sources of polyphenols are the pods from the cocoa plant Theobroma cacao (Wu et al., 2004), with beneficial phenolic compounds found in essentially all chocolate products (Miller et al., 2006). These polyphenols are typically the procyanidin monomers epicatechin and catechin (Kim and Keeney, 1984), which have been associated with beneficial effects ranging from decreased susceptibility to blood clot formation (Murphy et al., 2003) and anti-infection activity (Petti and Scully, 2009) to decreased inflammation and improved circulation (Sies et al., 2005). Cocoa polyphenols inhibit key digestive enzymes such as the lipases and amylases responsible for breaking down fats and carbohydrates as early in digestion as the oral cavity and stomach (Gu et al., 2011), thereby having a potential weight loss benefit.

Remarkably, cocoa polyphenols can withstand the high acid stomach environment and continue to show activity in the small intestines (Rios et al., 2002).

However, those polyphenols that are broken into monomers are then available for uptake in the lower gastrointestinal tract (Spencer et al., 2000). Cocoa polyphenols also have substantial health effects that are consistent with enhanced gut microbiome function (reviewed by Hayek, 2013). Specifically, cocoa polyphenols promote beneficial Bifidobacterium and inhibit harmful Clostridium, which is associated with healthy reductions of both blood plasma triglyceride and C-reactive protein levels (Tzounis et al., 2011).

Pectin

The prebiotic supplement pectin is perhaps better known as the food additive used for gelling jams and jellies. Pectin is a natural compound that holds together the cell walls of plants as a structural heteropolysaccharide formed from a diversity of saccharides, including 1,4-linked α-d-galactosyl uronic acid, d-xylose, d-apiose, and a broad array of other sugars. The low digestibility of large pectin molecules leaves them relatively intact until they reach the colon (Holloway et al., 1983). Once in the colon, pectin significantly promotes the growth of Bifidobacterium—an effect that is increased by hydrolysis of pectin molecules (Olano-Martin et al., 2002)—as well as stimulates apoptosis of colon cancer cells (Hotchkiss et al., 2003). Like the other prebiotic compounds, pectin also promotes beneficial bacteria growth and short-chain fatty acid production (Gullón et al., 2011). The effects of kiwi carbohydrates like pectin can be highly specific and even differ in prebiotic effect among the microbiota of individual subjects (Rosendale et al., 2012).

‣ *Additionally, kiwi pectins increase the adhesiveness of beneficial bacteria to intestinal epithelial cells while decreasing the adhesion of harmful bacteria (Parkar et al., 2010).*

Pectin may even have a role in DNA repair, as has been observed in the seeds of desert-adapted plants (Huang et al., 2007).

Resistant starch

The complex carbohydrate structures of resistant starch, which is mostly composed of α-d-glucose monomers, makes them an ideal source of fiber and a strong-acting prebiotic compound that releases long amylose oligosaccharides (with their own benefits) as they are digested (reviewed by Haralampu, 2000). Consumption of RS3—the resistant starch form found in sources such as potatoes, bananas, and whole grains—is associated with a mild laxative effect as well as increased levels of short-chain fatty acids (Cummings et al., 1996). The vast majority of resistant starch is not digested until it reaches the colon (Englyst, et al., 1996), where it has been well documented to promote the growth of healthy gut microflora (reviewed by Topping et al., 2003; Nugent, 2005; Fuentes-Zaragoza et al., 2011). Consumption of resistant starch has been shown to optimize the quality and frequency of bowel movements (Storey et al., 2007), increase stool butyrate levels while consequently decreasing plasma triglyceride levels (Noakes et al., 1996), and lower cholesterol levels (Behall et al., 1989). Additionally, early-stage research in rats suggests resistant starch consumption may increase gut function in a way that even reduces obesity-related sleep apnea (Shen et al., 2015; Durgan et al., 2017).

‣ *Each of these benefits of resistant starch is consistent with a strong prebiotic effect on colon microflora.*

OTHER PREBIOTIC COMPOUNDS

Guar fiber

Bean-derived prebiotic guar fiber is a strong prebiotic food owing to its long chains of galactose and mannose sugars that slow its digestion and stimulate many positive effects (reviewed by Slavin and Greenberg, 2003). This polysaccharide, which is also known as guar gum, has been used extensively in a wide variety of processed foods because of its remarkable ability as a water-soluble fiber to thicken and stabilize foods.

The combined water solubility and extremely low digestibility of guar fiber makes the substance particularly impactful in the colon, where nearly all of the limited guar fiber digestion occurs.

Indeed, the indigestibility of guar fiber is so high that it is used as a pharmaceutical delivery vehicle for oral medications that target the colon specifically (Prasad et al., 1998; Krishnaiah et al., 2002); when a therapeutic compound is surrounded in guar fiber, the compound is protected from digestion until the guar fiber is eventually broken down in the colon. Consumption of guar fiber by healthy individuals has been shown to both promote Bifidobacterium and Lactobacillus growth (Okubo et al., 1994) as well as increase levels of the beneficial short-chain fatty acid butyrate (Ohashi et al., 2015). In its partially hydrolyzed form, guar fiber has long been known to relieve constipation (Homann et al., 1994; Takahashi et al., 1994), but it also effective in the treatment of irritable bowel syndrome (Parisi et al., 2002; Giannini et al., 2006) and in lowering cholesterol (Miettinen and Tarpila, 1989) by decreasing the bioaccessibility of dietary cholesterol (Minekus et al., 2005).

Acacia

The common food additive known as gum arabic or acacia gum is not only an effective natural thickener and emulsifier, but also a highly water-soluble dietary fiber with strong prebiotic effects. Acacia gum is derived from the sap of one of two tree species, Acacia senegal and A. seyal. It is a complex substance that contains large heteropolysaccharides comprised of galactose, rhamnose, glucuronic acid, and arabinose monomers as well as minerals like potassium, calcium, and magnesium (Williams and Phillips, 2000). The large polysaccharides in gum arabic have been shown to increase populations of healthy gut bacteria like Bifidobacterium in healthy individuals that have consumed the substance as a supplement (Wyatt et al., 1986; Cherbut et al., 2003). Moreover, consumption of as little as 10 g of acacia gum daily has been shown to achieve a maximum effect on Bifidobacterium and Lactobacillus growth as revealed by real-time PCR analyses (Calame et al., 2008). One key advantage of gum arabic as a prebiotic dietary supplement is that its use can actually decrease minor side effects of other prebiotics; for example, a 1:1

blend of fructo-oligosaccharides and acacia gum delivered reduced gastrointestinal discomfort relative to a treatment that used only fructo-oligosaccharides (Goetze et al., 2008).

Aloe

The sap of the traditional medicinal plant Aloe vera, commonly known as aloe, has been used for millennia as a topical treatment for burns and wounds. While there is a lack of compelling clinical evidence demonstrating that aloe is an effective topical treatment (Dat et al., 2014), aloe has considerable promise as a prebiotic dietary supplement. There is a wide range of high-molecular-weight polysaccharides found in the mucilaginous sap of aloe (reviewed in Hamman, 2008), which have been collectively demonstrated to have significant and beneficial immunomodulatory effects (Im et al., 2005).

▸ *Aloe extracts have a well-established effect in promoting the in vitro growth of human gut microbiota (Nagpal et al., 2013; Gullón et al., 2015).*

Similarly, aloe has been shown to have beneficial effects on chickens with both gut infections (Chandrakesan et al., 2009) and healthy guts (Darabighane et al., 2011) including protection against gut infections (Yim et al., 2011; Akhtar et al., 2012). While these prebiotic effects have not yet been demonstrated in human subjects, these preliminary results suggest clinical trials in humans will ultimately reveal similar benefits.

CONCLUSION

The long-appreciated health benefits of high-fiber diets and traditional fermented foods have been gradually revealed to be associated with a wide range of prebiotic substances, particularly oligosaccharides and other relatively indigestible carbohydrates. In general, prebiotic carbohydrates are difficult to digest using the enzymes present in the human digestive tracts and are accordingly available to the specific bacterial communities that reside in portions of the small intestine and colon. These prebiotic compounds chiefly provide benefits through the promotion of commensal bacterial communities that exclude harmful pathogenic bacteria and metabolize the carbohydrates into short-chain fatty acids, which decrease blood lipids such as cholesterol among other benefits. The prebiotic mechanisms differ most substantively between carbohydrates and noncarbohydrates such as polyphenols, which demonstrate most of their beneficial effects earlier in the digestive process. The broad diversity of digestibility characteristics of these compounds indicates their combined consumption can provide appropriate nutrients to all the various microbiota throughout the gastrointestinal tract. Accordingly, supplements and dietary alterations should be selected with the goal of including a broad spectrum of prebiotics.

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BIOGRAPHY

Brad Dennis is a leading pioneer in formulating diverse prebiotic blends that help repair and rebalance the microbiome in the human digestive system. He was an active software engineer and academic when a chance encounter with a gut health research project funded by the National Science Foundation propelled him head-first into the world of gut health and prebiotics.

While working on his doctoral dissertation in Software Engineering, he had the opportunity to provide a stool sample to Rob Knight's American Gut project to assist with their research, and he was absolutely shocked at the results. His gut microbiota was completely out of balance. Was this imbalance the source of his seemingly +relentless series of health problems like anxiety, inflammation, and obesity? This drove Dr. Dennis to pause his software engineering research experiments and to become an expert at gut health, probiotics, and prebiotics. Since then, Dr. Dennis' prebiotic formulas have helped thousands of people conquer their digestive problems and rebalance their biomes.