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Gastrointestinal Microbiome Modulator Improves Glucose Tolerance in Overweight and Obese Subjects: A Randomized Controlled Pilot Trial

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Abstract

Objective—The objective of this study was to examine the effects of a gastrointestinal microbiome modulator (GIMM) containing inulin, β -glucan, blueberry anthocyanins, and blueberry polyphenols on metabolic parameters, fecal markers of gut microbiota, and satiety.

Design and Methods—Thirty overweight or obese individuals aged 18 to 70 years, were enrolled in a randomized controlled trial. Participants consumed the test product or placebo daily for four weeks. Stool samples were collected and blood was drawn at baseline and week four for assessments of gut microbiota, satiety hormones, glucose control, and lipid measures. Subjective satiety was assessed weekly. Linear models were used to compare differences from baseline to week four.

Results—GIMM consumption improved blood glucose tolerance ($p = 0.008$), and increased satiety ($p = 0.03$). There were no statistically significant differences in insulin sensitivity, fecal markers of gut microbiota, plasma satiety hormones, or serum lipid concentrations between the groups. However, plasma satiety hormones and fecal short chain fatty acid concentrations increased in the test group compared to the placebo.

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Author Contributions

MH and FLG designed the study. CJR and FG conducted the research, JB performed the statistical analyses, CJR wrote the manuscript. FLG, MH, and RB reviewed and edited the manuscript. All authors had final approval of the submitted version. FLG is the guarantor for this manuscript.

Conflicts of Interest

MH is the Chief Scientific Officer and Vice-President of Research at Microbiome Therapeutics LLC. FLG is an advisor and has stock options in Microbiome Therapeutics LLC. CJR and JB have no conflict of interest.

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Conclusions—GIMM consumption for four weeks, increases satiety, and improves glucose tolerance possibly through insulin-independent pathways.

Keywords

Microbiota; β -glucan; Inulin; Blueberry; Glucose Tolerance; Satiety

1. Introduction

The global prevalence of overweight and obesity as estimated in the 2013 Global Burden of Disease, study rose by 27.5% among adults from 1980 to 2013. Despite the evidence for a levelling off in the rise in obesity in developed countries, the rates continue to be high (Ng, et al. 2014). Obesity substantially increases the risk for type 2 diabetes (Whitlock, et al. 2009) and the rise in obesity is followed by an increase in the prevalence of type 2 diabetes. (Bray 1998; Frankish 2001). The potential contributors to obesity include energy intake in excess of physiologic needs, physical inactivity, biological and environmental determinants, and changes in gut microbiome (Ng, et al. 2014).

Evidence suggests that gut microbiota may have an important role in regulating metabolic pathways in health as well as disease (Human Microbiome Project 2012; Tilg and Moschen 2014; Tremaroli and Backhed 2012). Although the composition of core gut microbiota is relatively stable in adulthood, there are components that are metabolically flexible (Clemente, et al. 2012; Nicholson, et al. 2012). For instance, in response to changes in the diet, there are dramatic and rapid alterations in the composition as well as the gene transcription network of the gut microbiota (Backhed and Crawford 2010; Turnbaugh, et al. 2009). In humans, a switch from a high-fat/low-fiber diet to a low-fat/high-fiber diet caused changes in microbiome composition within 24 hours (Wu, et al. 2011).

Prebiotics are non-digestible food components that promote the growth of intestinal bacteria conferring beneficial health effects on the host (Nicholson, et al. 2012). β -glucans and inulin-type fructans are prebiotics that are not only preferentially fermented by specific types of bacteria, but also promote proliferation of the bacterial species such as Bifidobacteria (Delzenne, et al. 2013). These bacteria are associated with a beneficial impact on the host through their potential involvement in diabetes-related inflammation and the development of obesity (Druart, et al. 2014).

Human appetite is controlled by central and peripheral mechanisms that interact with the environment. Foods varying in their nutrient composition engage differently with the mediating processes to exert diverse physiologic effects. Some of these effects are satiety signals that inhibit hunger after a meal is eaten (Blundell, et al. 1996). There is substantial evidence to suggest that oat β -glucan increases satiety (Beck, et al. 2009; Geliebter, et al. 2015; Geliebter, et al. 2014; Juvonen, et al. 2009; Lyly, et al. 2010; Pentikainen, et al. 2014; Rebello, et al. 2014; Rebello, et al. 2013) and that oat products reduce the human glycemic response, compared to similar wheat foods or a glucose control (Tosh 2013). Further, certain polyphenols such as the anthocyanins found in berries exhibit an insulin-like effect to influence starch degradation and thereby the post meal blood glucose response (McDougall and Stewart 2005).

In order to counteract the subtle influences on food intake that act on individual vulnerabilities, there is a need for development of nutraceuticals that promote satiety and address the adverse health consequences of obesity. In the present study, the effects of a gastrointestinal microbiome modulator (GIMM) containing inulin, oat β -glucan, blueberry anthocyanins, and blueberry polyphenols shown to augment glucose control (Greenway, et al. 2014), on metabolic parameters, fecal markers of gut microbiota, and subjective satiety were evaluated. It was hypothesized that supplementation of the diet with the GIMM would improve glucose tolerance, induce changes in fecal markers, increase plasma PYY concentrations, decrease ghrelin concentrations, and increase satiety.

2. Subjects, Materials, and Methods

This study was approved by the Institutional Review Board of the Pennington Biomedical Research Center, Baton Rouge, where the full protocol may be accessed. Participants provided written informed consent. The trial was registered on ClinicaTrials.gov (NCT01724736).

2.1. Participants

Thirty individuals, 18 to 70 years, having body mass index between 25 and 45 kg/m², and fasting blood glucose concentrations between 100 mg/dl and 200 mg/dl, were enrolled in a randomized double blind placebo-controlled pilot trial. Subjects were excluded if they had existing medical conditions or were taking medications for diabetes, or medications that could alter body weight, intestinal bacterial flora, and blood concentrations of glucose, insulin, or lipids. Baseline characteristics of subjects are presented in Table 1. Screening involved measurement of body weight, height, vital signs (blood pressure, pulse rate), and blood chemistry-15 panel (glucose, creatinine, potassium, uric acid, albumin, calcium, magnesium, creatine phosphokinase, alanine aminotransferase, alkaline phosphatase, iron, cholesterol [total, high density lipoprotein, low density lipoprotein], and triglycerides). Subjects were randomized to two groups of 15 each. Block randomization was used to construct the randomization schedule. The randomization was done by the study statistician and participants were enrolled by the study coordinator. The study pharmacist who had no interaction with study subjects prepared the study products for dispensation to the participants, and had sole access to the random assignment until data analysis.

2.2. Study Design

Subjects reported for the baseline visit with their fresh stool specimen, fasting except for water, from 9 p.m. the prior night. Visual analog scale (VAS) assessment of satiety (hunger, fullness, desire to eat, prospective intake, and satisfaction) (Flint, et al. 2000) and a gastrointestinal symptoms questionnaire were administered. After subjects completed the VAS ratings they were weighed, and blood was drawn for: i) fasting chemistry-15 panel, homeostasis model assessment as an index of insulin resistance (HOMA-IR), glycosylated hemoglobin (HbA_{1C}), and highly sensitive C-reactive protein (hsCRP) (ii) Three hour oral glucose tolerance test (OGTT) with serum insulin and glucose (baseline and hours one, two, and three), plasma peptide YY (PYY), and plasma active ghrelin, (before the start and at hour one of the OGTT). PYY and ghrelin were measured by radioimmunoassay

(PYYT-66HK, and GHRA-88HK, Millipore, Billerica, MA). Baseline metabolic parameters of subjects are presented in Table 2.

Subjects were randomly assigned to the GIMM (4 g of inulin, the amount of blueberry extract equivalent to two cups of whole blueberries without the sugar, and 2.5 g of oat β -glucan [8.8 g total fiber] in a powder form [NM504TM, Microbiome Therapeutics LLC, New Orleans, LA]) or placebo (0 g β -glucan, 8.8 g total fiber) groups. They were instructed to mix each product with six ounces of water and consume it twice daily, within one hour of consuming breakfast or lunch and within an hour of dinner. The composition of the study products is provided in Table 3.

Subjects returned to the center weekly. At each visit subjects turned in the used and unused study product packages by which compliance was assessed. Subjects were given weekly supplies of the study products. At week four, assessments conducted at baseline were repeated. Gastrointestinal symptoms questionnaire and VAS were administered at all study visits. Participants were also asked about adverse events at each study visit. The Gastrointestinal Effects Comprehensive Stool Profile test was performed on all stool samples (Genova Diagnostics, Asheville, North Carolina (formerly 2100 Gastrointestinal Function Profile, Metamatrix, Duluth, Georgia).

The stool profile test assesses obligate anaerobes (*Bacteroides*, *Clostridia*, *Prevotella*, *Fusobacteria*, *Streptomyces*, and *Mycoplasma* sp.), facultative anaerobes (*Lactobacillus* and *Bifidobacter* sp.), obligate aerobes (*E. coli*), opportunistic bacteria, pathogenic bacteria (*H. pylori*, *E.H.E. coli*, *Clostridium difficile*, and *Campylobacter* sp.), yeast/fungi (*Candida* sp.), and parasites (*Blastocystis hominis*). Organisms are detected by DNA analysis. One colony forming unit (CFU) is equivalent to one bacterium. Each genome detected represents one cell or one CFU and the results are provided as CFU/g. Additionally, the test assesses the adiposity index derived by using DNA probes to detect multiple genera of the phyla Firmicutes and Bacteroidetes, drug resistant genes (presence), short chain fatty acids (SCFA) (total [mM/g], n-butyrate [mM/g], acetate, butyrate, propionate and valerate [%]), inflammation markers (lactoferrin [μ g/ml], white blood cells and mucus [presence]), immune system markers (fecal and anti-gliadin sIgA [mg/dl]), pH, red blood cells [presence], digestion markers (Elastase 1 [μ g/g], triglycerides [mg/dL], putrefactive SCFA [mM/g], vegetable fibers [presence]), and absorption markers (long chain fatty acids and total fat [mmol/L], cholesterol [mg/dL]).

2.3. Statistical Analysis

The primary outcome was a change in glucose excursion, assessed by the OGTT. Secondary outcomes included changes in: 1) fecal *Bacteroidetes:Firmicutes* ratio, pH, and short-chain fatty acids; 2) serum concentrations of lipids, and hsCRP; 3) plasma PYY, ghrelin, and Hb_{A1c}; 4) Homa-IR. Changes in glucose and insulin concentrations from baseline to week four as assessed by the OGTT were analyzed using a linear mixed model for repeated measures. The response variable in the model was change from week 0 to week four at time points 0, 60, 120, and 180 minutes. Using this model, the difference in the glucose response at the OGTT was assessed by testing that mean changes from baseline to week four at each time point were simultaneously equal between placebo and GIMM groups. Satiety

hormones, metabolic parameters, and fecal markers were calculated as mean change from baseline to week four. For each question of the VAS and gastrointestinal symptoms, the ratings were summed across weeks for every subject and the means calculated for each group. All differences were compared using t-tests. Analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

3. Results

Subjects were recruited from Baton Rouge and the surrounding areas. Two subjects did not complete the study due to schedule conflicts. Data relating to 14 participants in each group were analyzed. Fecal pH decreased in the GIMM group ($p = 0.04$). Flatulence increased ($p < 0.01$) compared to the placebo group, but no adverse events were reported. Analyses of the stool profile test results showed no other significant differences between the groups from baseline to week four. The overall rise in serum glucose over the three hour period of the OGTT ($p = 0.008$) was lower in the GIMM group compared to placebo (Figure 1), with no difference in serum insulin concentrations. The change from baseline to week four in all the other metabolic parameters including serum lipids and hsCRP, HOMA-IR, and plasma Hb_{A1C} were not significantly different between the groups. Desire to eat ($p = 0.03$) and prospective intake ($p = 0.03$) were reduced in the GIMM group compared to placebo. There was an increase in the fasting plasma concentrations of PYY, a decrease in plasma ghrelin concentrations, and an increase in the fecal SCFA in the GIMM group compared to the placebo; however, large variability in the data precluded a statistically significant result (Table 4).

4. Discussion

In the present study, consuming the GIMM containing β -glucan, inulin, and blueberry extract for four weeks reduced the rise in serum glucose over the three hour OGTT. Additionally, there was an increase in satiety in the group consuming the GIMM. The changes in fecal markers did not differ between the groups. However, there was a decrease in fecal pH in the GIMM group which suggests greater fermentation. The differences in plasma gut hormones and fecal SCFA did not attain statistical significance between the groups which was perhaps be due to large variability in the small sample of this pilot study; although, fecal SCFA concentrations increased, and fasting plasma concentrations of PYY increased while ghrelin declined in the GIMM group compared to the placebo.

Obesity or high fat diets produce changes in gut microbiota and increase gut permeability. The release of bacteria and bacterial products into systemic circulation, and the production of bioactive metabolic products could result in the low grade inflammation associated with insulin resistance (Burcelin, et al. 2012; Nicholson, et al. 2012). In mice, the administration of prebiotics improves glucose tolerance, modifies gut microbiota and improves gut barrier function by lowering plasma lipopolysaccharide levels, a component of the outer membranes of Gram-negative bacteria that generates metabolic endotoxemia (Everard, et al. 2011). Individuals with the metabolic syndrome and type 2 diabetes exhibit significant endotoxemia (Lassenius, et al. 2011; Pussinen, et al. 2011). In humans, supplementing the diet with inulin type fructans reduces serum lipopolysaccharide levels and HOMA-IR

(Malaguarnera, et al. 2012). However, in the present study there was no difference in the HOMA-IR between the groups; although, post-prandial glycemia improved.

Certain polyphenols such as anthocyanins can directly influence pancreatic secretion of insulin *ex vivo*, but low serum bioavailability of anthocyanins, makes their effect on post-meal blood glucose concentrations more likely to be a result of inhibition of starch digestion (McDougall and Stewart 2005). Polyphenolic extracts from berries are effective inhibitors of α -glucosidase as well as α -amylase activity thereby potentially have therapeutic effects on post-meal blood glucose concentrations (McDougall, et al. 2005). Supplementation with whole blueberry powder has been shown to improve insulin sensitivity (Stull, et al. 2010). However, in the present study, the reduction in serum glucose was not accompanied by changes in insulin secretion or sensitivity suggesting that the effects on serum glucose may be through insulin-independent pathways which is consistent with results from a study evaluating the effects of fermented blueberry juice on glucose uptake and the signaling pathways that regulate glucose transport, in murine muscle cells (Vuong, et al. 2007).

There is growing evidence to suggest that oat β -glucan increases satiety (Beck, et al. 2009; Geliebter, et al. 2015; Geliebter, et al. 2014; Juvonen, et al. 2009; Lyly, et al. 2010; Pentikainen, et al. 2014; Rebello, et al. 2014; Rebello, et al. 2013) and reduces post-prandial glycemia (Tosh 2013). The most likely mechanism is the viscosity generated in the gastrointestinal tract which has physiologic responses such as delayed gastric emptying, increased stomach distension, delayed intestinal transit, and reduced absorption of nutrients. These physiologic events stimulate satiation and satiety signals (Beck, et al. 2009; Geliebter, et al. 2015; Geliebter, et al. 2014; Juvonen, et al. 2009; Lyly, et al. 2010; Pentikainen, et al. 2014; Rebello, et al. 2014; Rebello, et al. 2013).

The SCFA produced by microbial fermentation of dietary fiber have been shown to stimulate the release of the anorectic hormone PYY (Cherbut, et al. 1998). Produced in the enteroendocrine cells in the ileum and colon, PYY acts to reduce gastric emptying. In the appetite centers of the brain, PYY acts to induce signals of satiation and satiety (Murphy and Bloom 2006). In humans, peripheral administration of the circulating form (PYY₃₋₃₆) has been shown to increase satiety and reduce energy intake (Batterham, et al. 2003). Similarly, ghrelin activates the orexigenic neurons expressing neuropeptide Y, and decreased levels of ghrelin blunt this effect (Murphy and Bloom 2006). In the colon, dietary fiber may be fermented by gut microbes to SCFA, namely butyrate, propionate, and acetate which activate the enteroendocrine cells of the gut to secrete a host of metabolically active peptides that regulate satiety (Tolhurst, et al. 2012). The mechanisms involving SCFA and gut hormones may offer an explanation for the increase in satiety in the GIMM group.

This study is limited by the small sample size and the use of fecal biomarkers which may not reflect the full *in vivo* dynamics of the gut. Moreover, the methods employed for fecal collection and analysis, while being suitable for clinical purposes may not have been appropriate in a research setting. Participants were required to fill a vial containing a preservative with their stool so as to displace a certain volume. The volumes displaced were variable; hence, the measures which depended on volume may not have been accurate. Analyses of freeze-dried feces may have provided more accurate results.

5. Conclusions

Consumption of the GIMM for four weeks improves post-prandial glycemia in overweight and obese participants with abnormal fasting serum glucose. Although some of the individual GIMM components have been shown to influence the insulin response, the combination may influence insulin-independent pathways and may be used in conjunction with pharmacological approaches for the management of diabetes. However, cellular mechanistic studies are warranted to elucidate the specific pathways by which the GIMM improves glucose control. The added benefit of an increase in satiety provides an integrative approach to addressing obesity and glycemic control.

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References

- Backhed F, Crawford PA. Coordinated regulation of the metabolome and lipidome at the host-microbial interface. *Biochim Biophys Acta*. 2010; 1801(3):240–5. [PubMed: 19782151]
- Batterham RL, et al. Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med*. 2003; 349(10):941–8. [PubMed: 12954742]
- Beck EJ, et al. Oat beta-glucan increases postprandial cholecystokinin levels, decreases insulin response and extends subjective satiety in overweight subjects. *Mol Nutr Food Res*. 2009; 53(10): 1343–51. [PubMed: 19753601]
- Blundell JE, et al. Control of human appetite: implications for the intake of dietary fat. *Annu Rev Nutr*. 1996; 16:285–319. [PubMed: 8839929]
- Bray GA. Obesity: a time bomb to be defused. *Lancet*. 1998; 352(9123):160–1. [PubMed: 9683198]
- Burcelin R, Garidou L, Pomie C. Immuno-microbiota cross and talk: the new paradigm of metabolic diseases. *Semin Immunol*. 2012; 24(1):67–74. [PubMed: 22265028]
- Cherbut C, et al. Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. *Am J Physiol*. 1998; 275(6 Pt 1):G1415–22. [PubMed: 9843779]
- Clemente JC, et al. The impact of the gut microbiota on human health: an integrative view. *Cell*. 2012; 148(6):1258–70. [PubMed: 22424233]
- Delzenne NM, Neyrinck AM, Cani PD. Gut microbiota and metabolic disorders: How prebiotic can work? *Br J Nutr*. 2013; 109(Suppl 2):S81–5. [PubMed: 23360884]
- Druart C, et al. Modulation of the gut microbiota by nutrients with prebiotic and probiotic properties. *Adv Nutr*. 2014; 5(5):624S–33S. [PubMed: 25225347]
- Everard A, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes*. 2011; 60(11):2775–86. [PubMed: 21933985]
- Flint A, et al. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord*. 2000; 24(1):38–48. [PubMed: 10702749]
- Frankish H. Obesity and diabetes epidemics show no sign of abating. *Lancet*. 2001; 358(9285):896. [PubMed: 11567713]

- Geliebter A, et al. Effects of oatmeal and corn flakes cereal breakfasts on satiety, gastric emptying, glucose, and appetite-related hormones. *Ann Nutr Metab.* 2015; 66(2–3):93–103. [PubMed: 25612907]
- Geliebter A, et al. Skipping breakfast leads to weight loss but also elevated cholesterol compared with consuming daily breakfasts of oat porridge or frosted cornflakes in overweight individuals: a randomised controlled trial. *Journal of Nutritional Science.* 2014; 3:e56–62. [PubMed: 26101624]
- Greenway F, Wang S, Heiman M. A novel probiotic containing a prebiotic and an antioxidant augments the glucose control and gastrointestinal tolerability of metformin: a case report. *Benef Microbes.* 2014; 5(1):29–32. [PubMed: 23685372]
- Human Microbiome Project, Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012; 486(7402):207–14. [PubMed: 22699609]
- Juvonen KR, et al. Viscosity of oat bran-enriched beverages influences gastrointestinal hormonal responses in healthy humans. *J Nutr.* 2009; 139(3):461–6. [PubMed: 19176745]
- Lassenius MI, et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. *Diabetes Care.* 2011; 34(8):1809–15. [PubMed: 21636801]
- Lyly M, et al. The effect of fibre amount, energy level and viscosity of beverages containing oat fibre supplement on perceived satiety. *Food Nutr Res.* 2010:54.
- Malaguarnera M, et al. Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. *Dig Dis Sci.* 2012; 57(2):545–53. [PubMed: 21901256]
- McDougall GJ, et al. Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. *J Agric Food Chem.* 2005; 53(7):2760–6. [PubMed: 15796622]
- McDougall GJ, Stewart D. The inhibitory effects of berry polyphenols on digestive enzymes. *Biofactors.* 2005; 23(4):189–95. [PubMed: 16498205]
- Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. *Nature.* 2006; 444(7121):854–9. [PubMed: 17167473]
- Ng M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014; 384(9945):766–81. [PubMed: 24880830]
- Nicholson JK, et al. Host-gut microbiota metabolic interactions. *Science.* 2012; 336(6086):1262–7. [PubMed: 22674330]
- Pentikainen S, et al. Enrichment of biscuits and juice with oat beta-glucan enhances postprandial satiety. *Appetite.* 2014; 75:150–6. [PubMed: 24434584]
- Pussinen PJ, et al. Endotoxemia is associated with an increased risk of incident diabetes. *Diabetes Care.* 2011; 34(2):392–7. [PubMed: 21270197]
- Rebello CJ, et al. The role of meal viscosity and oat beta-glucan characteristics in human appetite control: a randomized crossover trial. *Nutr J.* 2014; 13(1):49. [PubMed: 24884934]
- Rebello CJ, et al. Acute effect of oatmeal on subjective measures of appetite and satiety compared to a ready-to-eat breakfast cereal: a randomized crossover trial. *J Am Coll Nutr.* 2013; 32(4):272–9. [PubMed: 24024772]
- Stull AJ, et al. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *J Nutr.* 2010; 140(10):1764–8. [PubMed: 20724487]
- Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. *Gut.* 2014; 63(9):1513–21. [PubMed: 24833634]
- Tolhurst G, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes.* 2012; 61(2):364–71. [PubMed: 22190648]
- Tosh SM. Review of human studies investigating the post-prandial blood-glucose lowering ability of oat and barley food products. *Eur J Clin Nutr.* 2013; 67(4):310–7. [PubMed: 23422921]
- Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature.* 2012; 489(7415):242–9. [PubMed: 22972297]
- Turnbaugh PJ, et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med.* 2009; 1(6):6ra14.

- Vuong T, et al. Fermented Canadian lowbush blueberry juice stimulates glucose uptake and AMP-activated protein kinase in insulin-sensitive cultured muscle cells and adipocytes. *Can J Physiol Pharmacol*. 2007; 85(9):956–65. [PubMed: 18066143]
- Whitlock G, et al. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009; 373(9669):1083–96. [PubMed: 19299006]
- Wu GD, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011; 334(6052):105–8. [PubMed: 21885731]

Figure 1. Changes in glucose concentrations from baseline to week four assessed through a 3-hour oral glucose tolerance test ($p=0.008$). Values are mean $\pm$ standard error.

Table 1

Baseline Characteristics of participants including age, body mass index (BMI), weight, and gender

	GIMM	Placebo	Total
Age (years)	54.4 ± 8.0	55.0 ± 6.3	54.7 ± 7.1
BMI (kg/m ²)	34.7 ± 5.8	31.5 ± 5.1	33.1 ± 5.6
Weight (kg)	95.0 ± 16.1	90.9 ± 19.5	93.0 ± 17.6

	n	n	Total
Gender			
Female	10	10	20
Male	4	4	8

Values for Age, BMI, and Weight are mean ± standard deviation

Table 2

Baseline glucose, insulin, glycosylated hemoglobin (HbA1c), Homeostatic Model of Insulin Resistance (HOMA-IR), triglycerides, and total, low density lipoprotein [LDL], and high density lipoprotein [HDL] cholesterol of subjects in the placebo and gastrointestinal microbiome modulator (GIMM) groups

Measure	Units	Placebo	GIMM
Glucose ^{a,b}	min . mg	34515.0 ± 8079.5	30514.3 ± 7225.7
Insulin ^{a,b}	min . mg	12030.4 ± 5951.4	15578.8 ± 6366.3
HbA1c ^c	%	6.0 ± 0.6	5.8 ± 1.0
HOMA-IR ^c	-	3.9 ± 3.7	4.2 ± 3.0
HDL ^b	mg/dl	48.3 ± 11.6	49.2 ± 8.0
LDL ^b	mg/dl	102.8 ± 36.3	103.0 ± 42.0
Total Cholesterol ^b	mg/dl	172.9 ± 48.1	176.4 ± 45.3
Triglycerides ^c	mg/dl	105.0 ± 68.0	104.0 ± 73.0

^a Area under the baseline OGTT (oral glucose tolerance test) curve

^b Normally Distributed: Values are mean ± standard deviation

^c Not normally distributed: Values are mean ± inter-quartile range

Baseline measures were not significantly different between GIMM and placebo conditions, $p > 0.05$

Table 3

Composition of Gastrointestinal Microbiome modulator (GIMM) and Placebo

Ingredient	GIMM	Placebo
Total Anthocyanins (mg)	162.53	0.00
Total Polyphenolics (mg)	723.99	0.00
β-glucan (g)	2.03	0.00
Inulin (g)	3.79	0.00
Other Dietary Fiber ^a (g)	3.03	8.70
Total Dietary Fiber (g)	8.79	8.70

^a GIMM: Xanthan gum; Placebo: Xanthan gum (3.03g) + microcrystalline cellulose with carboxymethyl cellulose (5.67 g)

Table 4

Mean change in short chain fatty acids (SCFA), fasting PYY, and fasting Ghrelin from baseline to week four in the Gastrointestinal Microbiome Modulator (GIMM) and placebo groups

Measure	GIMM	Placebo
Acetate (mM/g)	-0.5 ± 15.1	-1.2 ± 22.9
Butyrate (mM/g)	-0.5 ± 9.2	-0.9 ± 5.6
Propionate (mM/g)	0.5 ± 3.9	-2.6 ± 7.0
Total SCFA (mM/g)	-0.5 ± 21.8	-6.9 ± 30.2
PYY ^a (mg/ml)	6.7 ± 27.9	-10.21 ± 41.5
Ghrelin (mg/ml)	-13.4 ± 72.5	-6.93 ± 23.2

Values are mean $\pm$ standard deviation

^aPeptide YY