L-Rhamnose increases serum propionate in humans\textsuperscript{1–3}

Janet A Vogt, Paul B Pencharz, and Thomas MS Wolever

ABSTRACT

Background: Acetic and propionic acids are produced by colonic bacterial fermentation of unabsorbed carbohydrates and are absorbed into the portal circulation. From there, they travel to the liver, where acetate is a lipogenic substrate and propionate can inhibit lipogenesis. The extent to which peripheral blood short-chain fatty acid concentrations reflect differences in colonic fermentation is uncertain. The unabsorbed sugar lactulose produces mainly acetate when fermented in vitro, whereas L-rhamnose yields propionate.

Objective: The objective of the study was to ascertain whether ingestion of L-rhamnose and lactulose would have different acute effects on peripheral acetate and propionate concentrations and on breath hydrogen and methane concentrations.

Design: Twenty-two subjects were fed 25 g L-rhamnose, lactulose, or glucose on 3 separate occasions in a randomized crossover design. Blood and breath samples were collected hourly for 12 h.

Results: Serum propionate was significantly higher with ingestion of L-rhamnose than with that of lactulose or glucose ($P < 0.001$). The area under the curve for serum acetate was significantly higher with ingestion of L-rhamnose than with that of lactulose or glucose ($P < 0.03$). The ratio of serum acetate to propionate was significantly higher with ingestion of lactulose than with that of glucose or L-rhamnose ($P < 0.01$). Breath hydrogen was significantly higher with ingestion of lactulose than with that of L-rhamnose or glucose ($P < 0.0001$).

Conclusions: The selective increases in serum acetate and propionate concentrations in humans were obtained by feeding specific fermentable substrates. Presumably, these changes in serum concentrations reflect changes in colonic production. Selective alteration of colonic fermentation products could yield a new mechanism for modifying blood lipids.


KEY WORDS Propionate, short-chain fatty acids, colon, fermentation, L-rhamnose

INTRODUCTION

The short-chain fatty acids (SCFAs)—acetic, propionic, and butyric acids—are the primary products of bacterial fermentation of carbohydrates and dietary fiber in the human colon. Acetate and propionate, which are absorbed from the colon and which travel to the liver, can have different and opposing effects on lipid metabolism. Whereas the liver can use acetate as a substrate for the synthesis of cholesterol and fatty acids, data from both human and animal studies suggest that propionate may inhibit these processes (1–5).

Not all fermentation substrates produce the same pattern of SCFAs (6–9). For instance, the unabsorbable sugars L-rhamnose and lactulose, when fermented in vitro with human feces for 24 h, produced very different ratios of acetate to propionate (10). L-Rhamnose produced $\approx$two-thirds the amount of acetate and 4 times the amount of propionate that lactulose produced. When subjects’ diets were supplemented with $\approx$20 g lactulose/d for 2 wk, fasting serum total cholesterol, LDL-cholesterol, and apolipoprotein B concentrations were higher than when subjects consumed the control diet for 2 wk, and serum acetate concentrations over day 13 of the study were $\approx23\%$ higher with ingestion of lactulose than with consumption of the control diet, although the difference was not significant (11). There are no published reports of studies evaluating the effects of feeding this amount of L-rhamnose to humans or of studies showing a fermentable dietary substrate to be capable of selectively increasing serum propionate concentrations.

The main aims of this study were to ascertain whether in vitro fermentation results would be reflected in vivo and, specifically, to ascertain whether ingestion of L-rhamnose and lactulose would result in significantly different changes in serum acetate and propionate and in breath hydrogen and methane. A secondary objective was to see if these results differed in methane producers and nonproducers. We hypothesized that ingestion of L-rhamnose would result in significantly higher serum propionate concentrations, whereas ingestion of lactulose would result in significantly higher serum acetate concentrations. In addition, we hypothesized that ingestion of either unabsorbable sugar would produce higher breath hydrogen concentrations than would ingestion of D-glucose as the control sugar.

SUBJECTS AND METHODS

Subjects and test protocol

Twenty-two healthy subjects (12 women, 10 men) with a mean ($\pm$ SEM) age of 30.9 $\pm$ 1.9 y were recruited from the University of Toronto campus. The average body mass index (in kg/m$^2$) was 23.8 $\pm$ 0.7. No subjects had used antibiotics within the previous 3 mo, nor did they have any history of gastrointestinal problems, diabetes, or blood lipid disorders.

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Subjects were studied on 3 occasions separated by ≥3 d. To standardize the subjects’ basal state as much as possible from one test day to another, subjects were instructed not to consume any alcohol and to maintain the same physical activity pattern on the day before each test day and to use the same mode of transportation to the clinic on each test day. On the first test day, each subject chose 3 meals and 2 snacks from a fixed menu (Table 1). The exact amounts and types of foods chosen by each subject on the first test day were replicated on the other 2 test days. Food portions were weighed in the metabolic diet kitchen adjoining the test room. Fluid intake, in the form of beverages, was limited to 500 mL with meals and 250 mL with snacks. The mean test-day food intake for all 22 subjects (not including the contribution of the test sugars) was 2350 kcal: 64% of energy was from carbohydrates, 15% was from protein, and 24% was from fat. The mean total dietary fiber was 26 g; 4 g was soluble fiber. A meal of pasta, tomato sauce, parmesan cheese, and mixed vegetables was supplied for dinner the evening before each test day, and subjects were told to eat that meal at 8000 and then to fast until the test the next morning. Test day meals and snacks were eaten in the metabolic kitchen: breakfast at 0800, snack 1 at 1030, lunch at 1300, snack 2 at 1530, and dinner at 1800. Subjects consumed all meals and snacks within 15 min. On each of the 3 test days, 25 g of a test sugar—either L-rhamnose (BDH Inc, Toronto, Canada), lactulose (Inalco Pharmaceuticals, San Luis Obispo, CA), or d-glucose (Sigma-Aldrich Canada Ltd, Oakville, Canada)—was consumed. The sugar dose was divided and dissolved in the hot beverages taken with the main meals: 9 g of sugar at breakfast and 8 g at both lunch and dinner. The 3 sugars were given in random order.

Ethical approval for the work was obtained from the Human Subjects Review Committee, Office of Research Services, University of Toronto. Subjects gave written informed consent to participate in the study.

### Breath samples for hydrogen and methane

Samples of end-expiratory alveolar breath were collected in the fasted state and every hour for 12 h after the breakfast meal with the use of a modified Haldane-Priestley tube (12). Smokers (n = 7) refrained from smoking from 30 min before collection of the fasting breath sample until collection of the 12-h sample was complete (13). Breath hydrogen and methane in expired air were measured by using gas chromatography (model 12i Microlyzer; Quintron Instruments Co Inc, Milwaukee). Methane producers were defined as those subjects whose fasting breath methane concentration was ≥0.045 μmol/L above the concentration in room air (14).

### Blood samples for glucose analysis

Blood from a forearm vein was collected into tubes containing potassium oxalate at the same times that breath was sampled. These samples were centrifuged at 600 × g for 10 min at 4 °C, and the plasma was removed and stored at −70 °C until blood glucose analysis was performed with the use of an automatic analyzer (YSI model 2300 STAT glucose/l-lactate analyzer; Yellow Springs Instruments, Yellow Springs, OH).

### Blood samples for serum short-chain fatty acids

Blood from a forearm vein was collected into glass tubes containing no substrates, allowed to clot at room temperature, and then centrifuged at 600 × g for 10 min at 4 °C. The serum was removed and stored at −70 °C before sample preparation and analysis.

### Gas chromatography of short-chain fatty acids

An 800-μL aliquot of serum was filtered through a micropartition system with a 30 000-dalton molecular weight cutoff (Cen trifree; Millipore, Billerica, MA) by centrifugation at 1500 × g at 4 °C for 70 min. Before use, the filters were washed by centrifugation 4 times, at 1500 × g for 15 min each time, with doubly distilled deionized water to remove glycerine that interfered with the propionate and butyrate peaks. The protein-free filtrate was stored at −20 °C before vacuum distillation with the use of the procedure described by Tollinger et al (15). Distillation was performed by using a 225-μL sample of protein-free serum to which we added a 25-μL internal standard solution consisting of 1.1 mmol methyl butyric acid/L and 1 mol [3H]-formic acid/L (Cambridge Isotopes, Andover, MA) to prevent ghosting in the injector sleeve and to reduce the pH in the sample to 3, thus ensuring complete SCFA acid recovery. An automatic sampler (HP 7673; Hewlett-Packard, Mississauga, Canada) was used to inject 1-μL aliquots of sample into a gas chromatograph (HP 5890 Series II; Hewlett-Packard) equipped with a direct-cool, on-column inlet, a polyethylene glycol column (30 m × 0.53 mm × 1.0 μm film; Agilent 19095F-123, Agilent, Mississauga, Canada), and a flame ionization detector. The oven temperature was 80 °C until 0.1 min after injection, at which time it was increased by 10 °C/min to 125 °C, then increased by 5 °C/min to 135 °C, held for 0.1 min at 135 °C, and then increased by 15 °C/min to 165 °C and held for 1 min. The carrier gas was pure helium at a flow rate of 15 mL/min, and the detector was supplied with helium at a flow rate of 30 mL/min, hydrogen at a flow rate of 30 mL/min, and air at a flow rate of 410 mL/min.

Each protein-free serum sample was distilled in duplicate, and each distilled sample was injected in triplicate. SCFA concentrations were determined from the ratio of each SCFA’s peak

### TABLE 1

<table>
<thead>
<tr>
<th>Test day menu</th>
<th>Food choices</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meal and time</strong></td>
<td><strong>Cold cereal (choice of 2 cereals, matched for fiber content)</strong></td>
</tr>
<tr>
<td>Breakfast, 0800</td>
<td>2% Milk, orange or apple juice, or water†</td>
</tr>
<tr>
<td></td>
<td>9 g Test sugar, dissolved in coffee, tea, or herbal tea</td>
</tr>
<tr>
<td>Snack 1, 1030</td>
<td>≥1 Apple or banana or both</td>
</tr>
<tr>
<td></td>
<td>2% Milk, orange or apple juice, or water</td>
</tr>
<tr>
<td>Lunch, 1300</td>
<td>Multigrain or rye bread (matched for fiber content)</td>
</tr>
<tr>
<td></td>
<td>Dijon or yellow mustard, mayonnaise (if desired)</td>
</tr>
<tr>
<td></td>
<td>Tomato slices</td>
</tr>
<tr>
<td></td>
<td>Baby carrots</td>
</tr>
<tr>
<td></td>
<td>2% Milk, orange or apple juice, or water</td>
</tr>
<tr>
<td></td>
<td>8 g Test sugar, dissolved in coffee, tea, or herbal tea</td>
</tr>
<tr>
<td>Snack 2, 1530</td>
<td>Chocolate chip cookies or digestive biscuits</td>
</tr>
<tr>
<td></td>
<td>2% Milk, orange or apple juice, or water</td>
</tr>
<tr>
<td>Dinner, 1800</td>
<td>Chicken primavera or fettuccine with creamy pesto sauce</td>
</tr>
<tr>
<td></td>
<td>Dinner roll or rolls with margarine (optional)</td>
</tr>
<tr>
<td></td>
<td>2% Milk, orange or apple juice, or water</td>
</tr>
<tr>
<td></td>
<td>8 g Test sugar, dissolved in coffee, tea, or herbal tea</td>
</tr>
</tbody>
</table>

† Fluid consumption was restricted to 500 mL at a meal and to 250 mL at a snack.
TABLE 2
Area under the curve for breath hydrogen and serum acetate and propionate in all subjects and for breath methane in methane producers.

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Hydrogen (n = 22)</th>
<th>Methane (n = 7)</th>
<th>Acetate (n = 22)</th>
<th>Propionate (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L -rhamsone</td>
<td>40.9 ± 32.8b</td>
<td>46.3 ± 24.8</td>
<td>−130.6 ± 53.5cd</td>
<td>16.3 ± 1.8a</td>
</tr>
<tr>
<td>Lactulose</td>
<td>263.6 ± 37.4a</td>
<td>−3.0 ± 21.0</td>
<td>−74.1 ± 46.4c</td>
<td>2.4 ± 0.9b</td>
</tr>
<tr>
<td>Glucose</td>
<td>40.0 ± 35.7b</td>
<td>−19.6 ± 27.0</td>
<td>−255.5 ± 65.5a</td>
<td>3.0 ± 1.6b</td>
</tr>
</tbody>
</table>

All values are x ± SEM. Values in the same column with different superscript letters are significantly different: hydrogen and propionate columns, P < 0.0001; acetate column, P < 0.03.

RESULTS
All subjects completed the 3 treatment phases. Seven subjects were classified as methane producers and 15 as methane nonproducers. Fasting concentrations of serum SCFAs and breath gases did not differ significantly between treatments. The treatment effects on blood and breath measurements are reported in Table 2 and Figures 1–3.

Breath hydrogen concentrations, whether expressed as the mean 0–12 (Figure 1A) or as the AUC (Table 2), were significantly higher with ingestion of lactulose than with that of L-rhamnose or glucose. At 3 and 4 h, lactulose and L-rhamnose concentrations were significantly greater than glucose concentrations, and from 5 h through 11 h, lactulose concentrations were significantly greater than both L-rhamnose and glucose concentrations (time × sugar interaction, P < 0.0001; Figure 1A). For the breath methane data, there was a significant interaction between methane-producing status, sugar, and time (P < 0.02). However, when ANOVA was performed separately on producers and nonproducers, there was no effect on breath methane in either group. Data for methane producers are shown in Table 2 and Figure 1B.

**FIGURE 1.** Mean (± SEM) concentrations of breath hydrogen (A), breath methane (B), serum acetate (C), and serum butyrate (D) in 22 subjects (n = 7 for methane) who took L-rhamnose (●), lactulose (○), or glucose (▲) with meals (larger arrows) at 0, 5, and 10 h. Smaller arrows, snacks. Time × sugar interaction, P < 0.0001 for hydrogen; time × sugar × methane-producing status interaction, P < 0.02 for methane. Values with the letter “a” indicate significantly higher concentrations in the subjects who took lactulose or L-rhamnose than in those who took glucose (P < 0.05, Bonferroni-corrected); values with the letter “b” indicate significantly higher concentrations in the subjects who took lactulose than in those who took L-rhamnose or glucose (P < 0.05, Bonferroni-corrected); values with the letters “c” and “d” are significantly different from one another (P < 0.0001).
higher concentrations in the subjects who took L-rhamnose than in those who are significantly different from one another (interaction, \( P \leq 0.05 \), Bonferroni-corrected); values with the letter “a” indicate significantly higher concentrations in the subjects who took L-rhamnose than in those who took lactulose or glucose (\( P < 0.05 \), Bonferroni-corrected); values with the letter “b” indicate significantly higher concentrations in the subjects who took L-rhamnose than in those who took glucose and significantly higher concentrations in the subjects who took glucose than in those who took lactulose (\( P < 0.05 \), Bonferroni-corrected); values with the letters “c” and “d” are significantly different from one another (\( P < 0.05 \), Bonferroni-corrected).

There was no effect of sugar on serum acetate concentrations, and the mean 0–12 serum acetate did not differ between L-rhamnose, lactulose, and glucose (Figure 1C). However, the AUC for serum acetate was significantly higher with ingestion of lactulose than with that with ingestion of glucose, whereas the AUC for serum acetate with ingestion of L-rhamnose did not differ significantly from the other 2 AUCs (Table 2). The AUC for serum acetate was significantly correlated with that of breath hydrogen (\( r = 0.2707, P < 0.03 \)) in all 22 subjects. The slopes for the 3 treatments did not differ significantly from one another. There was no significant effect of sugar on the mean 0–12 or hourly serum butyrate concentrations (Figure 1D), and the AUC for butyrate did not differ between L-rhamnose (3.3 ± 0.9), lactulose (3.1 ± 1.6), and glucose (0.2 ± 1.4).

The effect of sugar on the mean 0–12 and hourly serum concentrations of propionate differed significantly between methane producers and nonproducers (methane-producing status × sugar × time interaction; \( P < 0.005 \)). Hourly serum propionate concentrations were significantly higher at 6 h with ingestion of L-rhamnose than with that of lactulose or glucose in methane producers, whereas they were significantly higher with ingestion of L-rhamnose than with that of lactulose or glucose from 6 through 11 h in methane nonproducers (time × sugar interaction for each group; \( P < 0.0001 \); Figure 2). The mean 0–12 serum propionate was significantly higher with ingestion of L-rhamnose than with that of lactulose and glucose in nonproducers (Figure 2). The AUC for propionate was significantly higher with ingestion of L-rhamnose than with that of lactulose and glucose in all subjects (Table 2). The mean 0–12 acetate-propionate ratio was significantly higher (\( P < 0.001 \)) with ingestion of lactulose (17.2 ± 1.0) than with that of glucose (14.8 ± 1.0) or L-rhamnose (13.6 ± 0.9).

The AUC for plasma glucose did not differ significantly between treatments. However, the mean 0–12 plasma glucose concentration was significantly higher with ingestion of glucose than with that of L-rhamnose or lactulose (Figure 3). At 9 h, plasma glucose was significantly higher with ingestion of glucose than with that of lactulose, whereas L-rhamnose did not differ significantly from either (time × sugar interaction, \( P < 0.03 \); Figure 3).

Both abdominal distention and flatulence were significantly greater with ingestion of L-rhamnose and lactulose than with that of glucose (\( P < 0.0005 \)). For abdominal distention, the total ratings greater than zero were 16.3% with ingestion of L-rhamnose, 23.1% with that of lactulose, and 8.3% with that of glucose; for flatulence, those same ratings were 27.3% with ingestion of L-rhamnose, 31.8% with that of lactulose, and 17.0% with that of glucose.

**DISCUSSION**

This study has shown that serum concentrations of acetate and propionate and breath hydrogen concentrations in humans can be selectively increased by feeding specific fermentable substrates. Colonic fermentation is the only source of hydrogen in the human body, but serum SCFA can originate from both exogenous (ie, colonic fermentation) and endogenous sources. Acetate is produced by fat oxidation, whereas propionate is produced by branched-chain amino acid metabolism. Thus, increased serum acetate and propionate concentrations have been observed during states of enhanced fat and amino acid oxidation, such as prolonged starvation (18), diabetes (19), and impaired glucose tolerance (20). However, in healthy subjects such as those studied here, colonic fermentation is generally considered the primary source of blood acetate. Insulin secretion after the meals and snacks that were eaten every 2.5 h in this study minimized endogenous SCFA production, and the positive correlation between serum acetate and breath hydrogen also suggests that the increases in blood acetate and propionate that we observed were mainly due to increased colonic fermentation. Furthermore, the AUC for serum acetate on the glucose trial can be interpreted as an indicator of endogenous acetate production. Replacement of glucose with either lactulose or L-rhamnose on test days results in much higher serum acetate concentrations.

Lactulose is a synthetic disaccharide of galactose and fructose. Because humans cannot hydrolyze it in the small intestine, it is fermented in the colon (21), producing organic acids such as acetate and lactate (22, 23) and the gases hydrogen and carbon dioxide (22, 24–26). L-Rhamnose is a monosaccharide found in polysaccharides of gums and mucilages (27), cardiac glycosides (28), and foods such as oranges, French beans, winter cabbage, and carrots (29). It is not absorbed from the human small intestine, and it reaches the colon intact.
The serum SCFA profiles elicited by L-rhamnose and lactulose ingestion in this study are consistent with in vitro fermentation data. Fermentation of lactulose with human fecal inocula yields more acetate, whereas that of L-rhamnose yields more propionate, which results in acetate:propionate ratios of 5.7 for lactulose and 0.8 for L-rhamnose (7, 10). In the present study, lactulose ingestion increased the serum acetate:propionate ratio to 17.3, as compared with 14.4 with ingestion of L-rhamnose and 16.0 with ingestion of glucose. The smaller difference in the acetate:propionate ratio between lactulose and L-rhamnose in serum than in the ratio between lactulose and L-rhamnose obtained from in vitro fermentation could be due to differences in either the rate of appearance (which depends on production and absorption rates) or the rate of removal of acetate and propionate. Propionate is better absorbed from the human colon than is acetate (30, 31), and studies in ruminal mucosa show that propionate is activated to its coenzyme A derivative (a step required for its oxidation) to a greater extent than is acetate (32). The liver extracts 90% of propionate, as opposed to 75% of acetate, during a single pass (33, 34), and colonic infusions of equal amounts of acetate and propionate suggest that the amount of colonic propionate reaching the peripheral blood is only 25% of the amount of colonic acetate doing so (35).

Breath hydrogen is commonly measured to assess the digestibility of dietary carbohydrates (24, 36). Increases in breath hydrogen (11, 25, 26, 37–39) and serum acetate (40, 41) after lactulose ingestion have been reported, and breath hydrogen responses increase linearly with increased doses of lactulose up to 20 g (42). However, our results show that consumption of equal amounts of lactulose and L-rhamnose causes significantly different breath hydrogen responses, which suggests differences in the stoichiometry of the production of hydrogen from these 2 sugars. Ruminant physiology suggests that the lack of increase in breath hydrogen with ingestion of L-rhamnose might be explained by increased propionate production. Fermentation of L-rhamnose in an artificial rumen with bacteria from sheep inhibited methanogenesis and increased propionate production by 61% more than did the control fermentation with no added substrate (43). In the rumen, methane seems to be almost exclusively produced from hydrogen and carbon dioxide. In the absence of methanogenesis, less hydrogen accumulates because of the production of the more reduced fermentation product propionate than accumulates because of the production of acetate (44).

The presence of significant numbers of methanogenic bacteria and their activity in the human colon can affect hydrogen excretion in response to fermentable substrates (45), including lactulose (38). The major methanogenic species in the human colon, Methanobrevibacter smithii, uses 4 mol H₂ to reduce 1 mol CO₂ to 1 mol CH₄, which decreases the total volume of gas produced. However, we found no effect of methane-producing status on breath hydrogen concentration. If we assume similar hydrogen production in methane producers and nonproducers, the microflora of the nonproducers must have used alternative pathways of hydrogen consumption, such as sulfate reduction (46, 47) or acetogenesis (47, 48).

The glucose treatment increased the mean plasma glucose concentration during the test day. This was expected, because the additional 25 g glucose ingested as a test sugar increased the available carbohydrates ingested on the test day from 375 g to 400 g. However, L-rhamnose, which could potentially exert a gluconeogenic effect through increased production of propionate (49), had no significant effect on plasma glucose. Rectal infusion of 180 mmol propionate was shown to increase the plasma glucose concentration by 0.4 mmol/L after 1 h (35), but in vitro fermentation data suggest that the 9-g breakfast dose of L-rhamnose in this study would produce only 2.7 mmol propionate over a 3-h period (10). Assuming a mouth-to-cecum transit time of 90–120 min (40), the amount of propionate reaching the liver at 4.5–5 h in the present study would be <2% of that delivered in the rectal infusion study. Even though that amount of propionate is enough to increase the serum propionate concentration at 5 h, it is not enough to change the plasma glucose concentration.

When incorporated into bread and ingested, sodium propionate can inhibit amylase activity, thereby decreasing the digestibility of the bread and reducing the postprandial glucose response (50) over the span of the test day. However, propionate produced in the colon would not be expected to act through this mechanism.

In this study, subjects were more likely to report abdominal distention and flatulence when taking L-rhamnose and lactulose than when taking glucose. The number of reports with ingestion of lactulose was not significantly different from the number with ingestion of L-rhamnose. However, the breath hydrogen response was higher with ingestion of lactulose, and that with ingestion of L-rhamnose was similar to that with ingestion of glucose. Two previous studies found no significant relation between the volume of gas in the colon and self-reported abdominal symptoms (51, 52). Our results tend to agree with the suggestion that the perception of abdominal distention or bloating might be more strongly related to the irritability of a subject’s colon than to the volume of colonic gas (52).

Dietary fiber, specifically nonstarch polysaccharide, is known to affect colonic function (53). Some fermentation substrates can change the composition and fermentation capacity of the microflora (54, 55). In the present study, the mean intake of dietary fiber on the test days was 26 g, but no information on the subjects’ habitual fiber intake was collected. Therefore, although it is possible that habitual fiber intakes of persons in this study may have affected their responses to the test sugars, we could not assess this possibility on the basis of the present data.

In conclusion, we found that acute consumption of L-rhamnose selectively increases serum propionate in humans, whereas that of lactulose increases serum acetate. This finding may be relevant to our understanding of the effect of dietary soluble fiber on serum cholesterol concentrations and, hence, on cardiovascular disease risk. However, it is important to note that our conclusions apply only to the acute ingestion of these sugars; it is possible that the responses may vary with long-term ingestion because of the adaptation of colonic bacteria.

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REFERENCES


