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Are There Healthy Sweeteners: The Effects of Sugar Substitutes on the Gut Microbiome
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Keywords: Sugar Substitute, Gut Microbiome, artificial sugar, sweetener

Abstract

Objective: This study was designed to examine the effects of sugar substitutes on the gut microbiome.

Methods: PUBMED was used to find articles that studied the gut microbiome after consumption of a sugar substitute in humans. Both observational and interventional studies were selected for this review.

Results: Starting with 31 articles found on PUBMED, 5 articles were included to be reviewed after 26 articles were excluded. Three natural sugar substitutes and four categories of artificial sweeteners were studied. Maltitol, lactitol, and isomalt were the natural sugar substitutes, and aspartame, acesulfame-K, non-caloric artificial sweeteners, and saccharin were the artificial sweeteners. The outcomes for Bifidobacteria, Bacteroides, Clostridium, Lactobacilli, Fusobacterium prausnitzii, and Enterobacteriaceae were addressed. Natural sugar substitutes were seen to increase bacterial populations that are believed to be beneficial to humans while artificial sweeteners established bacterial populations that are considered harmful to health.

Conclusions: The studies examined suggest cautious use of artificial sweeteners due to its effects on the gut microbiome while natural sugar substitutes could have potential health benefits.

Introduction

Sugar substitutes could allow for a lower calorie diet which is important considering the current obesity epidemic. Therefore, sugar substitutes both natural and artificial have been used in foods and beverages such as diet soda, coffee, and cereals. But Suez et al. has shown how certain sweeteners could stimulate glucose intolerance by affecting the gut microbiome¹. The gut microbiome consists of microorganisms that differ between individuals. Depending on one's microbiome, different patterns of microorganisms are associated with medical conditions such as Crohn's disease^{2,3}, ulcerative colitis^{2,3}, cancer⁴, and obesity⁵. Although we are just beginning to understand, generally, Bifidobacteria^{6,7}, Lactobacilli^{6,7}, Firmicutes^{8,9}, and Fusobacterium prausnitzii¹⁰ are seen as beneficial and Bacteroidetes^{8,9} and Enterobacteriaceae¹¹ as harmful. The gut microbiome has the ability to fluctuate depending on one's diet. Thus, this review will inspect six human studies to observe what can be concluded about the effects of sugar substitutes on the gut microbiome.

Methods

Information source

PUBMED was used to find articles relating the effects of sugar substitutes and the gut microbiome. The term “sweetener” or “sweeteners” were used in combination with the search terms “microflora,” “gut microbiota,” or “gut microbiome.”

Eligibility criteria

Once the sources from PUBMED were compiled, the articles were checked to exclude review articles, commentaries, non-English articles, animal studies, and articles that were not related to the effects of sugar substitutes on the gut microbiome. The sources that were left and used for this article were interventional or observational studies that looked at the effects of various sugar substitutes on the gut microbiome in humans.

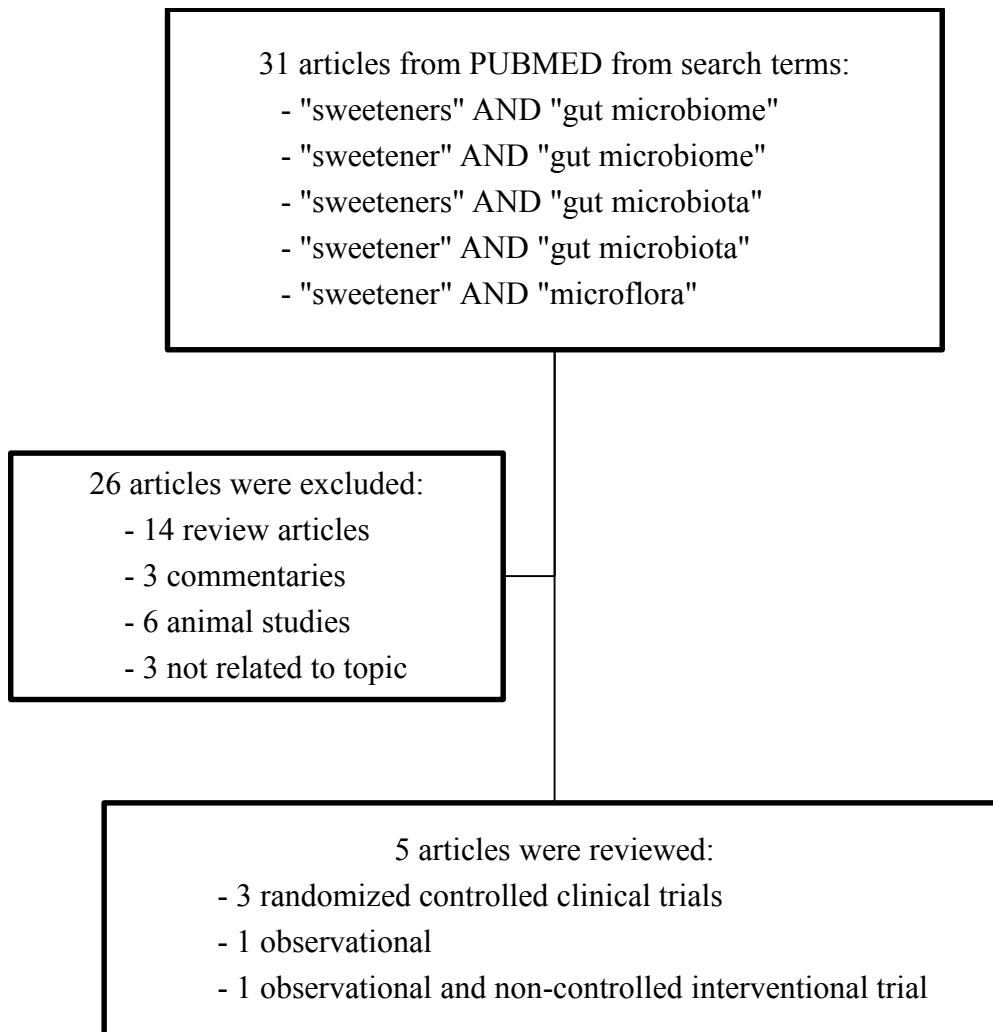


Figure 1

Results

Search results

A total of 31 publications were found when the search terms were inputted into PUBMED. 26 articles were review articles, commentaries, non-English articles, animal studies, or not relevant.

These articles did not meet the criteria and were excluded. There were five^{1,12,13,14,15} relatively recent (2007-2015) remaining publications. The selection process is shown in Figure 1 above.

One article¹ included two different human studies with one observational study and one non-controlled interventional clinical trial. Therefore, it can be said that six studies were used for this review since four of the articles had only one study while the fifth contained two studies. Four studies^{1,12,13,15} were interventional studies and two were observational^{1,14}. Of the four studies that were interventional, three were randomized controlled trials and one had the treatment given to all participants so there was no control. All the studies looked at different sugar substitutes. Three^{12,13,15} of the studies used natural sugar substitutes (maltitol, lactitol, isomalt) while three^{1,14} used artificial sugar substitutes (aspartame or acesulfame-K, saccharin, and non-specified artificial sweeteners). All participants of the six studies were over 18, and the participants of the randomized controlled trials did not have diagnosed gastrointestinal disorders. Table 1 summarizes the sources with the treatment, dose, and duration used.

Outcomes

Each study gathered data on different categories of bacteria. This review will only look at the results on bacterial populations that were covered by more than one study so that comparisons can be made.

Bifidobacteria

Bifidobacteria is a genus in the order Bifidobacteriales which is part of the class Actinobacteria. Three studies^{12,13,15} looked specifically at the genus Bifidobacteria, one¹⁴ looked at order Bifidobacteriales, two^{14,15} looked at class Actinobacteria, and one¹ looked at phylum Actinobacteria. Beards et al. found that consumption of maltitol significantly increased Bifidobacteria from 8.9 to 9.4 log₁₀ cells/g (P=0.0006) while the control sucrose did not significantly increase Bifidobacteria¹². Lactitol also significantly increased Bifidobacteria from 9.37 to 10.06 log₁₀ CFU/g wet weight feces (P=0.017) when sucrose did not¹³. Gostner et al. found that people who consumed isomalt compared to those who consumed sucrose had more Bifidobacteria (P<0.01)¹⁵. In terms of order Bifidobacteriales, there was no significant difference found between non-consumers and consumers of aspartame as well as between non-consumers and consumers of acesulfame-K. For class Actinobacteria, one study showed that whether one consumed aspartame or acesulfame-K did not seem to be significant¹⁴ while Gost et al. found that consuming isomalt instead of sucrose increased Actinobacteria (P<0.01)¹⁵. Suez et al. looked at phylum Actinobacteria and saw that non-caloric artificial sweeteners (NAS) were positively associated with increased levels (P<0.0003)¹.

Bacteroides

The genus Bacteroides is part of the order Bacteroidales. Genus Prevotella is also part of the Bacteroidales. One study¹⁵ looked at the combination of genus Bacteroides and genus Prevotella, one¹² at the genus Bacteroides on its own, and two^{1,14} at order Bacteroidales. Gostner et al. found isomalt increased Bacteroides and Prevotella (P<0.05)¹⁵ and Beards et al. saw that maltitol increased Bacteroides¹². For Bacteroidales, aspartame and acesulfame-K did not seem to affect it¹⁴. It appears from the data, in participants who had a glycemic response to saccharin, Bacteroidales increased when saccharin was consumed while those with no glycemic response had little change but began with more Bacteroidales¹.

Clostridium

Clostridium is a genus in the order Clostridiales, class Clostridia, and phylum Firmicutes. *Eubacteria* is also a genus in the class Clostridia. Two studies^{12,15} looked at genus *Clostridium*, two^{1,14} at order Clostridiales, and one⁶ at genus *Eubacteria*. Maltitol increased *Clostridium* ($P < 0.05$)¹² while isomalt consumption did not have a significant difference compared to that of sucrose¹⁵. Aspartame and Acesulfame-K did not affect order Clostridiales¹⁴. Maltitol increased *Eubacteria*¹².

Lactobacilli

Genus *Lactobacilli* is in the order Lactobacillales, class Bacilli, and phylum Firmicutes. Three studies^{12,13,15} looked at genus *Lactobacilli* and two^{1,14} at order Lactobacillales. Maltitol increased *Lactobacilli* ($P = 0.001$)¹² while lactitol and isomalt did not significantly affect *Lactobacilli*^{13,15}. Aspartame and acesulfame-K did not affect Lactobacillales¹⁴ while responders to saccharin had more Lactobacillales and increased it as well¹.

Fusobacterium prausnitzii

There were two studies^{12,15} that looked at *Fusobacterium prausnitzii*. Beards et al. found that maltitol significantly increased¹² while Gostner et al. reported that isomalt did not significantly affect *Fusobacterium prausnitzii*¹⁵.

Enterobacteriaceae

Enterobacteriaceae is a family in the order Enterobacteriales. There were two studies^{1,13} that looked at family Enterobacteriaceae and one¹⁴ that looked at order Enterobacteriales. Lactitol did not significantly affect Enterobacteriaceae¹³ while NAS consumption was positively associated¹. Aspartame and Acesulfame-K did not seem to affect Enterobacteriales¹⁴.

Table 2 displays the findings of the six studies.

Discussion

Gut microbiome populations increase or decrease rapidly in response to one's diet. The major groups in the gut microbiome explored in the studies were Bifidobacteria, Bacteroides, *Clostridium*, *Lactobacilli*, *Fusobacterium prausnitzii*, and Enterobacteriaceae. Bifidobacteria and *Lactobacilli* are agreed to have an impact on the gut microbiome that results in positive health outcomes. Lower levels of Bifidobacteria and *Lactobacilli* are seen in irritable bowel syndrome⁶ and Crohn's disease⁷. A higher Bacteroidetes-to-Firmicutes ratio has been related to obesity⁸. Phylum Firmicutes has been shown to result in beneficial health, but the negative effects of phylum Bacteroidetes are not as clear⁹. *Fusobacterium prausnitzii* is considered a probiotic and is also reduced in intestinal inflammatory disease¹⁰. Family Enterobacteriaceae is associated with inflammation in the gut¹¹.

Generally, the three natural sugar substitutes that were studied in this review increased the bacterial species that are believed to be beneficial to the host. Consumption of maltitol saw an increase in Bifidobacteria, Bacteroides, *Clostridium*, *Lactobacilli*, and *Fusobacterium prausnitzii*¹². All with the exception of Bacteroides are usually associated with a healthy gut. Lactitol increased Bifidobacteria without increasing Enterobacteriaceae¹³ which is also seen as being beneficial. Isomalt was also associated with an increase in Bifidobacteria¹⁵.

On the other hand, the studies that used artificial sugar substitutes reflected more negative effects to the gut microbiome. NAS were seen to increase Enterobacteriaceae and Actinobacteria¹. Like mentioned before, Enterobacteriaceae is increased with inflammation, but the increased Actinobacteria is difficult to interpret. Although Bifidobacteria which is seen as being beneficial is part of the phylum Actinobacteria, because the phylum Actinobacteria is so large, it does not suggest NAS increases Bifidobacteria. Saccharin which is another artificial sugar substitute increased Bacteroidetes and decreased Firmicutes¹ which are associated with obesity. The reason why aspartame and acesulfame-K did not seem to affect the gut microbiome may be because the Frankenfeld et al. study which looked at aspartame and acesulfame-K measured the relative abundance of bacteria by class and order instead of counting CFU or cells. However, Frankenfeld et al. found overall diversity were different for aspartame or acesulfame-K non-consumers and consumers ($P < 0.01$; $P = 0.03$)¹⁴. This suggests that aspartame and acesulfame-K does affect the gut microbiome, but the lower abundance bacteria may be more disturbed¹⁴.

Although this review is limited to five articles and is not able to observe the effects of every natural and artificial sugar substitute (or even focus on one sweetener since there was only one study per sweetener), from the studies considered, natural sugar substitutes could have the potential to contribute to a beneficial gut microbiome. Furthermore, artificial sugar substitutes should be used more cautiously. Otherwise, in an attempt to lower caloric intake, a microbiome that is associated with obesity could be formed. The natural sugar substitutes could possibly be used as a healthy replacement of sucrose in terms of lower calories and changing the gut microbiome for the better.

There were limitations to the studies that were chosen for this review. Each paper only looked at one or two different sweeteners which were all given in different doses which makes it difficult to make conclusions. To further complicate the analysis, the articles measured gut microbiome populations differently and examined different bacteria. Certain studies did not control for outside food. The observational studies relied upon food diaries which can be inaccurate, and the interventional studies lacked number of participants or did not have a control group. In gut microbiome studies, a large number of samples need to be taken because of the wide varieties of microbiota.

It is now known that sugar substitutes affect the human microbiome and can potentially be harmful or beneficial depending on the specific sweetener. Therefore, more human studies with more participants that focus on specific substitutes need to be performed in the future. These studies also need to consider what the effects of the sweetener are in the short term and long term as well as at different doses.

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Table 1 Studies on Sweeteners and Gut Microbiome

	Author/Year	Population	Treatments	Dose	Duration	
1	Beards et al. (2010)	Human (40)	1. Sucrose 2. Maltitol 3. Maltitol and Polydextrose 4. Maltitol and Resistant Starch	3 dosing periods Treatment 1 -Dose 1: 50 g chocolate -Dose 2: 75 g -Dose 3: 100 g Treatments 2-4 -Dose 1: 22.8 g -Dose 2: 34.2 g -Dose 3: 45.6 g	Dose period 1: days 1-14 Dose period 2: days 15-29 Dose period 3: days 30-44 Consumed daily	
2	Finney et al. (2007)	Human (75)	1. Sucrose 2. Sucrose and lactitol 3. Lactitol	T1: 10 g sucrose T2: 5 g sucrose and 5 g lactitol T3: 10 g lactitol	7 days -Consumed daily	
3	Frankenfeld et al. (2015)	Humans (31) - observational	1. Nonconsumers of aspartame (24) 2. Consumers of aspartame (7) 3. Nonconsumers of acesulfame-K (24) 4. Consumers of acesulfame-K (7)	Aspartame: 5.3 mg/day to 112 mg/day Acesulfame-K: 1.7 mg/day to 33.2 mg/day	4 days	
4	Gostner et al. (2006)	Human (19)	1. Sucrose 2. Isomalt	T1: 30 g T2: 30 g	Two 4 week cross-over design	
5a	Suez et al. (2014)	Human (381) - observational	1. Not long-term non-caloric artificial sweeteners (NAS)consumption 2. Long-term NAS consumption			
5b	Suez et al. (2014)	Human (7) - controlled	Saccharin	5 mg per kg (body weight)	7 days	Responders: increased glycemic response (4) Non-responders: unchanged glycemic response (3)

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Table 2 Summary of Gut Microbiome Results

Study	1 (Beards et al.)	2 (Finney et al.)	3 (Frankenfeld et al.)	4 (Gostner et al.)	5a (Suez et al.)	5b (Suez et al.)
Actinobacteria (phylum)					Pearson r=0.27, FDR corrected P<0.0003 Positively associated with sweetener	
Actinobacteria (class)			Aspartame P=0.16 Non-consumers: <0.1% Consumers: <0.1% Acesulfame-K P=0.13 Non-consumers: <0.1% Consumers: <0.1%	Sucrose: 5.1% Isomalt: 11.0% P<0.01		
Bifidobacteriales (order; class Actinobacteria)			Aspartame P=0.44 Non-consumers: <0.1% Consumers: <0.1% Acesulfame-K P=0.34 Non-consumers: <0.1% Consumers: <0.1%			
Bifidobacteria (genus; order: Bifidobacteriales; class: Actinobacteria)	Sucrose: 8.9 to 9.1 log ₁₀ cells/g (not significant) Maltitol: 8.9 to 9.4 log ₁₀ cells/g (P=0.0006) Maltitol and Polydextrose: 8.9 to 9.3 log ₁₀ cells/g (P=0.0009) Maltitol and Resistant Starch: 8.8 to 9.2 log ₁₀ cells/g (P=0.001)	Sucrose: not significant (P>0.05) Sucrose/Lactitol: not significant (P>0.05) Lactitol: 9.37 to 10.06 log ₁₀ CFU/g wet weight faeces (P=0.017)		Sucrose: 21.2 cfu x 10 ⁸ /g faeces wet weight Isomalt: 50.2 cfu x 10 ⁸ /g faeces wet weight P<0.01		
Bacteroidales (order)			Aspartame P=0.67 Non-consumers: 47.2% Consumers: 51.0% Acesulfame-K P=0.74 Non-consumers: 49.5%			Non-responders: little change Responders: increased Bacteroidales

			Consumers: 46.9%			Non-responders had more Bacteroidales
Bacteroides (genus; order: Bacteroidales)	Sucrose: 9.2 to 9.2 log ₁₀ cells/g (not significant) Maltitol: 8.7 to 9.4 log ₁₀ cells/g (P=0.001) Maltitol and Polydextrose: 9.0 to 9.3 log ₁₀ cells/g (P=0.003) Maltitol and Resistant Starch: 9.1 to 9.6 log ₁₀ cells/g (P=0.002)					
Bacteroides, Prevotella (genus; order: Bacteroidales)				Sucrose: 26.8 counts x 10 ⁹ /g faeces wet weight Isomalt: 18.3 counts x 10 ⁹ /g wet weight faeces P<0.05		
Clostridiales (order; class: Clostridia; phylum: Firmicutes)			Aspartame Non-consumers: 43.1% Consumers: 37.1% P=0.64 Acesulfame-K Non-consumers: 41.3% Consumers: 37.6% P=0.74			Non-responders: little change Responders: unclear change in Clostridiales Unclear which group had more Clostridiales
Clostridium (genus; order: Clostridiales; class: Clostridia; phylum: Firmicutes)	Sucrose: 8.2 to 8.8 log ₁₀ cells/g (P<0.05) Maltitol: 8.2 to 8.7 log ₁₀ cells/g (P<0.05) Maltitol and Polydextrose: 8.3 to 8.5 log ₁₀ cells/g (P=0.007) Maltitol and Resistant Starch: 8.2 to 8.9 log ₁₀ cells/g (P=0.002)			Sucrose: 0.004% Isomalt: 0.003% P>0.05		

Eubacteria (genus; class: Clostridia; phylum: Firmicutes)	Sucrose: 9.2 to 9.2 log ₁₀ cells/g (not significant) Maltitol: 8.9 to 9.5 log ₁₀ cells/g (P<0.05) Maltitol and Polydextrose: 9.0 to 9.4 log ₁₀ cells/g (P<0.05) Maltitol and Resistant Starch: 9.2 to 9.6 log ₁₀ cells/g (P<0.05)					
Lactobacillales (order; class: Bacilli; phylum: Firmicutes)			Aspartame Non-consumers: <0.1% Consumers: <0.1% P=0.88 Acesulfame-K Non-consumers: <0.1% Consumers: <0.1% P=0.33			Non-responders: little change Responders: increased Lactobacillales Responders had more Lactobacillales
Lactobacilli (genus; order: Lactobacillales; class: Bacilli; phylum: Firmicutes)	Sucrose: 8.1 to 8.2 log ₁₀ cells/g (not significant) Maltitol: 8.3 to 9.1 log ₁₀ cells/g (P=0.001) Maltitol and Polydextrose: 8.1 to 9.2 log ₁₀ cells/g (P=0.00001) Maltitol and Resistant Starch: 8.2 to 8.8 log ₁₀ cells/g (P=0.004)	Sucrose: not significant (P>0.05) Sucrose/Lactitol: not significant (P>0.05) Lactitol: not significant (P>0.05)		Sucrose: 0.002 cfu x 10 ⁸ /g faeces wet weight Isomalt: 0.002 cfu x 10 ⁸ /g faeces wet weight P>0.05		
Fusobacterium prausnitzii	Sucrose: 8.6 to 9.3 log ₁₀ cells/g (P<0.05) Maltitol: 8.4 to 9.4 log ₁₀ cells/g (P=0.0001) Maltitol and Polydextrose: 8.9 to 9.4 log ₁₀ cells/g (P<0.05) Maltitol and Resistant Starch: 9.1 to 9.4 log ₁₀ cells/g (not significant)			Sucrose: 0.3% Isomalt: 0.4% P>0.05		

Enterobacteriales (order; phylum: Proteobacteria)			Aspartame Non-consumers: <0.1% Consumers: <0.1% P=0.44 Acesulfame-K Non-consumers: <0.1% Consumers: <0.1% P=0.43			
Enterobacteriaceae (family; order: Enterobacteriales; phylum: Proteobacteria)		Sucrose: not significant (P>0.05) Sucrose/Lactitol: not significant (P>0.05) Lactitol: not significant (P>0.05)			Pearson r=0.36, FDR corrected P<10 ⁻⁶ Positively associated with high-intensity sweetener	

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