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LIFESTYLE MANAGEMENT TO REDUCE DIABETES/CARDIOVASCULAR RISK (B CONWAY AND H KEENAN, SECTION EDITORS)

Natural Alternative Sweeteners and Diabetes Management

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Abstract

Purpose of Review The goal of this review is to discuss the data on natural alternative sweeteners and their effects on glucose homeostasis and other metabolic parameters within the past five years. We sought to answer whether common natural alternative sweeteners have a positive or negative effect on glucose control in both human and animal models, and whether the data supports their widespread use as a tool to help reduce the prevalence of diabetes and associated comorbid conditions.

Recent Findings Recent studies suggest that natural alternative sweeteners may reduce hyperglycemia, improve lipid metabolism, and have antioxidant effects particularly in those that have baseline diabetes.

Summary Diabetes and metabolic syndrome have become a global healthcare crisis and the sugar overconsumption plays a major role. The use of artificial sweeteners has become more prevalent to improve insulin resistance in those with diabetes, obesity, and metabolic syndrome, although the evidence does not support this result. There are however some promising data to suggest that natural alternative sweeteners may be a better alternative to sugar and artificial sweeteners.

Keywords Natural alternative sweeteners · Diabetes · Stevia · Sugar alcohols · Rare sugars

Introduction

Diabetes mellitus (DM) is a metabolic disorder that results from glucose dysregulation. Insulin resistance and/or decreased production of insulin from pancreatic β cells results in chronic hyperglycemia and is considered a pro-inflammatory state [1]. Sedentary lifestyles and an overabundance of sugar-laden processed food and beverage consumption are some of the main culprits associated with this trend. Long-term complications of this disease result from biochemical changes from increased oxidative stress. Complications include, but are not limited to retinopathy, nephropathy, cerebrovascular disease, peripheral vascular disease, and cardiovascular disease [2–4]. Type 2 DM (T2DM) often coexists with other metabolic disorders including hypertension and dyslipidemia, a phenomenon also known as metabolic syndrome which is associated with visceral adiposity and obesity. Nutrition therapy designed to lower serum glucose, triglycerides, blood pressure, and plaque-forming cholesterol is essential in the management of T2DM and improve morbidity and mortality [4].

Epidemiology

The prevalence of T2DM has dramatically increased. According to the Center for Disease Control (CDC), the prevalence of obesity in the USA was 39.8% which is a significant risk factor for the development of T2DM, (93.3 million obese Americans) between 2015 and 2016 [5]. According to the World Health Organization's (WHO) Global Report on Diabetes, it is estimated that 422 million adults were living with diabetes worldwide in 2014, and the global prevalence has nearly doubled since 1980, from 4.7 to 8.5% [6].

This article is part of the Topical Collection on *Lifestyle Management to Reduce Diabetes/Cardiovascular Risk*

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Nutrition Therapy

The American Diabetes Association (ADA) recommends reducing total daily caloric, limiting carbohydrate consumption, and incorporating non-nutritive sweeteners to help maintain a healthful eating pattern and promote weight loss [4]. Interestingly, despite the widespread use of sugar substitutes, the prevalence of T2DM continued to increase while the prevalence of obesity has remained stable. This article discusses natural alternative sweeteners (NAS) and their effects on body weight, glucose homeostasis, lipid metabolism, and antioxidant properties in human and animal models.

Types of Natural Alternative Sweeteners

Non-nutritive sweeteners (NNS) are commonly used as sugar substitutes and are either not metabolized by the host or provide a negligible amount of energy. Although sugar substitutes are marketed as healthier alternatives to sugar, some data suggest that they may have similar effects on metabolic derangements and glucose homeostasis when compared with their sugar counterparts. This review will focus on NAS that include stevia, rare sugars, sugar alcohols, and monk fruit and will not discuss other sugar substitutes like artificial sweeteners (Table 1).

Stevia

Stevia rebaudiana (SR) is a native plant found in South America that has long been used for medicinal purposes. Steviol glycosides, which include stevioside and rebaudioside A, are metabolites responsible for its sweet taste and are mainly found in the plant's leaves [7]. Stevia is 200–300 times sweeter than sucrose and is used in popular foods and beverages and has been used for therapeutic purposes such as an antacid, antimicrobial, antioxidant, and diuretic [3, 8].

The Effects of Stevia in Humans

There have been several studies that evaluated the effects of stevia in humans although many are quite small. Tey et al. compared the effects of AS, NAS, and sucrose on 24-h glucose control in 10 healthy men. Each participant was given a beverage containing aspartame, monk fruit, stevia, or a sucrose. Twenty-four-hour glucose measurements were obtained to calculate the mean 24-h glucose, incremental area under the curve (iAUC), total area under the curve (AUC) for glucose, and 24-h glycemic variability. Overall, the study showed that there were no significant differences in 24-h glucose measurements after ingestion of sucrose compared with those who were given AS or NAS [9].

In a subsequent study, Tey et al. studied the effects of aspartame, monk fruit, stevia, and sucrose on energy intake, blood glucose, and insulin in 30 healthy men. Beverages were administered 1 h prior to lunch. Individuals were asked to rate their desire to eat, hunger, and prospective food consumption using a visual analog scale. The study showed no significant difference in total energy intake between those that consumed NNS versus sucrose. The energy saved by consuming a NNS compared with a sucrose-containing beverage was fully compensated for by the end of the day. Additionally, desire to eat, hunger, and prospective consumption ratings were higher after consumption of the NNS beverage compared with sucrose. Blood glucose and insulin levels spiked within the first hour post-sucrose consumption; however, glucose and insulin levels post-lunch were higher in those that consumed the NNS. As a result, the AUC for glucose was similar amongst all four groups [10].

Ritu et al. investigated the effects of stevia on daily caloric intake using dietary recall, blood glucose, and lipids in 20 individuals with T2DM for 60 days. Individuals either received 1 g of stevia leaf powder per day or no intervention. Though not statistically significant, the mean daily caloric consumption was higher in males who received stevia compared with the control group despite the control group having a greater carbohydrate intake. The stevia group had a statistically significant reduction in fasting and post-prandial blood

Table 1 Examples of non-nutritive sweeteners

Non-Nutritive Sweeteners			
Intense Sweeteners		Bulk Sweeteners	
Artificial	Natural	Carbohydrates	Sugar Alcohols
-Aspartame	-Stevia	-Fructose	-Sorbitol
-Sucralose	-Monk fruit	-Sucrose	-Erythritol
-Saccharin	-Rare sugars	-Hydrogenated fructose corn syrup	-Xylitol
		-Dextrose	-Mannitol

glucose, total cholesterol (TC), triglyceride (TG), and very-low-density lipoprotein (VLDL) compared with the control group [11].

Onakpoya et al. performed a systematic review and meta-analysis (nine studies, $n = 756$ non-diabetic and diabetic individuals) on the effects of steviol glycosides (stevioside and rebaudioside A) on cardiovascular risk factors. The analysis showed that steviol glycosides were associated with non-significant reductions in systolic blood pressure (SBP) and significant reductions in diastolic blood pressure (DBP) and fasting blood glucose. However, studies using only pure rebaudioside A showed non-significant changes in DBP and SBP. A sub-analysis of six studies ($n = 521$) including diabetics and non-diabetics revealed a non-significant difference in TC between steviol glycosides and placebo, whereas another sub-analysis of five studies ($n = 399$) including diabetics and non-diabetics demonstrated a significant increase in triglycerides (TG) with placebo compared with steviol glycosides which was not dose dependent [12].

The Effects of Stevia in Animals

Ahmad et al. studied the effects of varying concentrations of stevia in 60 albino rats versus distilled water. The study showed that diabetic rats given SR aqueous extract had a statistically significant reduction in body weight which was dose dependent, as well as reduction in random, fasting blood glucose levels and hemoglobin A1c (HbA1c) [13].

Elnaga et al. compared the effects of sucrose and varying doses of stevia to distilled water in 60 Wistar female rats over 12 weeks and showed that stevia was associated with a reduction in food consumption compared with those that received distilled water with sucrose. The stevia rats also had less weight gain in a dose-dependent fashion while those that received sucrose had an increase in body weight. Feed efficiency ratios (FER) and blood glucose concentrations were lower in stevia groups with a dose-dependent relationship (highest stevia dose associated with the lowest FER). The stevia groups showed a significant reduction in TC, TG, and LDL and a significant increase in HDL when compared with the control groups [14].

Assaei et al. studied the effects of stevia in 40 streptozotocin (STZ)-induced diabetic Sprague-Dawley (SD) rats for 28 days. Treatment groups received pioglitazone or SR aqueous extract versus water. Rats that received stevia showed a significant reduction in body weight compared with the pioglitazone group, whereas pioglitazone significantly increased body weight compared with those that received water. Stevia was shown to be more effective at lowering blood glucose and serum TG compared with pioglitazone, although no differences were seen in serum cholesterol. Pancreatic β cells were found to be degenerated and vacuolated, with a significant decrease in the number of islets in diabetic rats. However, both stevia and pioglitazone groups demonstrated significant regeneration of islets [15].

Antihyperglycemic effects of minor steviol glycosides were also studied in non-diabetic and STZ-induced diabetic Wistar rats. Rats were given metformin; rebaudioside B, C, or D; dulcoside A, or steviolbioside which were incorporated in food pellets. Intraperitoneal glucose tolerance test (IPGTT) was administered before and after 28 days of treatment. The study showed that acute intraperitoneal or chronic oral administration of minor steviol glycosides at 20 mg/kg had no antihyperglycemic effects in normoglycemic or diabetic rats. These results are in accordance with previous research and suggest that minor glycosides may be similar to rebaudioside A [16].

Akbarzadeh et al. studied the effects of SR aqueous extract on serum omentin and visfatin levels, liver cell morphology, lipid, and glycemic parameters in rats. Rats were given distilled water or varying doses of SR aqueous extract for 30 days. Visfatin and omentin are two adipocytokines that are involved in insulin signal transduction, glucose homeostasis, and exhibit insulin-mimetic effects. The study showed a significant reduction in fasting homeostasis model assessment insulin resistance (HOMA-IR), TG, and omentin levels in those that received SR compared with the diabetic control group. There was no significant difference in fasting insulin concentrations, homeostasis model assessment insulin B cells (HOMA-B), visfatin, cholesterol, HDL, or number of pancreatic β cells between the control and treatment groups. The authors propose that stevia works through a negative control feedback mechanism to reduce omentin levels via insulin-mimetic properties [17•].

Rare Sugars

D-Allulose (D-psicose), D-tagatose, D-sorbose, and D-allose are four naturally occurring monosaccharides that are either not metabolized or only partly metabolized by humans and are used because of their palatability, absence of unpleasant aftertaste, and lack of significant calories compared with sugar [18].

The Effects of Rare Sugars in Humans

Noronha et al. evaluated the effects of allulose on postprandial plasma glucose incremental AUC in a double-blind RCT in 24 individuals with T2DM. Each individual was randomly assigned six treatments with a one-week washout period. Treatment doses consisted of 0 g, 5 g, or 10 g of fructose or allulose plus 75 g glucose solution. An oral glucose tolerance test (OGTT) was performed at 30-min intervals starting

30 min pre-treatment and ending 120 min post-treatment. Treatment with 10 g of allulose resulted in a significant reduction in plasma glucose iAUC by 8% while fructose had no effect [19].

Han et al. evaluated the effect of D-allulose on fat mass in a double-blind, RCT in 121 Korean adults with a BMI ≥ 23.The placebo group received 0.012 g of sucralose twice per day, and the treatment groups received either low-dose D-allulose (4 g twice per day) or high-dose D-allulose (7 g twice per day) for 12 weeks. Follow-up body composition analysis revealed that BMI, body fat mass, body fat percentage, and body weight were significantly reduced in those who received D-allulose versus sucralose. High-dose D-allulose resulted in a significant decrease in total fat area and subcutaneous fat when compared with the placebo group using abdominal CT scan fat analysis. There was no significant change from baseline in plasma lipid levels or blood glucose-related parameters across all groups [20].

Hayashi et al. conducted a double-blind, RCT on 34 individuals with average BMI of 25.6 kg/m^2. Individuals received 30 g of rare sugar syrup (RSS) or the control drink containing 28 g of high fructose corn syrup, 30 min prior to breakfast daily for 12 weeks. The RSS contained 6% allulose, 7.5% sorbose, glucose, and other sugars. The study showed a significant reduction in body weight, waist circumference, and body fat percentage in those that received the RSS compared with high-fructose corn syrup (HFCS) [21].

Ensor et al. evaluated the safety and efficacy of D-tagatose on glycemic control in 112 subjects with diet- and exercise-controlled T2DM in a prospective, RCT, to determine the lowest dose of D-tagatose required to reduce HbA1c. Each group received beverages containing 2.5 g, 5.0 g, or 7.5 g of D-tagatose three times per day prior to each meal for 6 months. Although not statistically significant, the study showed a reduction in HbA1c from baseline in those that received 5.0 g and 7.5 g of D-tagatose and all dosages resulted in a reduction of TC, LDL, and HDL from baseline. Interestingly, 5.0 g D-tagatose resulted in a marked increase in TG levels after 3 months of treatment. Individuals treated with 7.5 g of D-tagatose were the only treatment group which had a statistically significant reduction in fasting blood glucose at the end of the 6-month treatment period. Mean body weight reduction was statistically significant in a dose-dependent fashion, with 5.0 g and 7.5 g of D-Tagatose having the greatest effects [22•].

Ensor et al. investigated the effects of D-tagatose on 480 individuals with T2DM (90% of which were diet and exercise controlled). The treatment group received 15 g D-Tagatose and the control group received 1.5 g of Splenda in water three times per day with meals for 10 months. Measurements were taken at 2, 6, and 10 months. D-tagatose significantly decreased HbA1c, fasting blood glucose (after 6 months only), LDL, TC, HDL at 2, 6, and 10 months compared with the control but had no effect on TGs [23••].

The Effects of Rare Sugars in Animals

Nagata et al. studied the effects of rare sugars on lipid metabolism in 30 rats. The rats were divided into five groups and received a commercial rat chow with D-allulose, D-tagatose, D-sorbose, or the control rat chow with corn starch or fructose. At the end of 4 weeks, there were no differences in body weight, food efficiency, liver weight, food intake, TG, or cholesterol amongst each group. There was, however, a significant increase in serum-free fatty acids (FFA) in rats who received D-tagatose compared with those that received the fructose-containing chow. D-sorbose containing chow resulted in a significant decrease in adiponectin levels compared with the control groups. D-Allulose and D-sorbose decreased hepatic lipogenic enzyme activity whereas D-tagatose increased hepatic lipogenic enzyme activity. Rare sugar–containing chow tended to cause a decrease in adipose tissue weight compared with the fructose-containing chow [24].

Shintani et al. evaluated the effects of RSS on glucose tolerance and insulin sensitivity via the glucokinase (GK) pathway which is involved in glycogen production in the liver and post-prandial glucose suppression. Rats received water, HFCS, or RSS for 10 weeks with otherwise identical diets. Rats in the RSS group had less weight gain and although rats given HFCS actually consumed less calories, they had significantly more total abdominal fat compared with the water and RSS groups. The RSS group had significantly lower insulin levels 30 min post-glucose loading compared with the water group and a significantly lower insulin AUC compared with the other groups. Researchers observed more GK in hepatocyte cytoplasm of RSS-fed rats, thus implying that RSS in part modulated glucose homeostasis via translocation of GK resulting in improved glucose tolerance and insulin sensitivity [25•].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the small intestine which increases satiety, in part, because of its effects on delayed gastric emptying. Iwasaki et al. investigated the effects of D-allulose on feeding behaviors and glucose metabolism using the glucose tolerance test (GTT), insulin tolerance test (ITT), and pyruvate tolerance test (PTT) in mice. D-Allulose was given to mice at varying concentrations and showed that after a single oral administration of D-allulose, GLP-1 was released and resulted in decreased food intake and promoted glucose tolerance in normal and obese/hyperglycemic mice. Sub-chronic oral administration of D-allulose once daily at diurnal onset decreased LP hyperphagia, obesity, adiposity, and IGT in obese mice. The LP was from 7:30–19:30 and was not manipulated. The effects of decreased feeding and glucose tolerance were diminished by

GLP1-R antagonists, vagotomy, and in *Glp1r* knockout mice. Unlike current GLP1-R agonists commonly used for the treatment of obesity and diabetes, oral D-allulose does not cross the blood-brain barrier and did not produce any adverse side effects. D-Allulose significantly lowered basal glucose levels in hyperglycemic mice but had no such effect in normoglycemic mice, thus suggesting that D-allulose has the potential to treat hyperglycemia without the risk of hypoglycemia [26].

D-Allulose has been used many times to evaluate rare sugars' effects on body weight and fat accumulation; however, D-allulose is not the only rare sugar in the RSS mixture. Ochiai et al. compared the antiobesity effects of RSS (6% allulose) with modified glucose syrup (MGS, 13% allulose) in male rats. Rats were divided into four groups for 8 weeks and received a high-sucrose control diet, HFCS diet, RSS diet, or MGS diet and showed that abdominal adipose tissue weight and total body fat percentage were significantly lower only in the RSS group compared with the sucrose group. These findings suggest that other rare sugars present in the RSS also contribute to its effects. The MGS group had significantly lower final body weights compared with other groups; however, there was no significant change in food intake or muscle mass. Overall, these results suggest that RSS can be used in place of sucrose or HFCS and may provide beneficial effects compared with the more expensive MGS alternative [27].

Nagata et al. quantified the effects of a 3% D-allulose (psicose) diet on blood glucose, lipids, and 24-h energy expenditure in 48 rats fed ad libitum for 4 weeks. The control group received a diet containing cornstarch and the treatment group received a diet containing 3% allulose as the main carbohydrate source. Body weight, food intake, and serum leptin levels were significantly reduced in the allulose group compared with the control group. No differences in blood glucose levels were found between groups; however, rats were not fasting prior to testing. Additionally, allulose was shown to alter gene expression of intestinal proteins involved in lipid absorption such as CD36, SR-B1, and MTP [28•].

Long-term effects of 5% D-allulose (psicose) on blood glucose, β cell damage, and markers of inflammation were tested in rats for 60 weeks. Otsuka Long-Evans Tokushima Fatty (OLETF) rats and Long-Evans Tokushima Otsuka rats (LETO) were divided into two groups. OLETF rats were given 5% allulose and the control group of OLETF and LETO rats were administered water. Allulose-treated rats maintained normoglycemia throughout the duration of treatment, had less average weight gain, decreased HbA1c, serum LDL, TC, and TG compared with the control group. Pro-inflammatory markers such as TNF-α and IL-6, macrophage infiltration, and serum leptin levels were significantly lower in the treatment group compared with the control group. Short- and long-term allulose treatment resulted in less β cell damage compared with control groups. Glutathione levels were also significantly greater in allulose-treated rats compared with the control [29•].

Yamada et al. studied the effects of D-sorbose on 14 rats. The treatment group was administered a 3% D-sorbose diet and the control group was fed an American Institute of Nutrition–based diet for rat growth consisting of 53% dextrinized cornstarch with all other components being equal. After 28 days, final body weight, degree of weight gain, dietary intake, and feed efficiency did not differ between the D-sorbose group and control group. Markers of lipid metabolism including TC, HDL, TG, and phospholipids were also similar between the two groups. Serum insulin concentrations were significantly lower in the treatment group than in control group, and although not statistically significant, there was a decreasing trend in serum glucose in the D-sorbose group. Dietary intake was lower in the D-sorbose groups, but a paired-feeding study is needed to confirm this observation [30].

Sugar Alcohols (Polyols)

Sugar alcohols (polyols) are hydrogenated monosaccharides and disaccharides which are commonly used as sweeteners and bulking agents. Polyols provide half as many calories as nutritive sweeteners (2 kcals/g). Studies have shown that consumption of polyols result in less post-prandial glucose response than sucrose or glucose in both diabetic and non-diabetic subjects [31]. Sorbitol and mannitol are the only polyols found abundantly in nature in foods like berries of mountain ash, marine algae, and mushrooms. Erythritol is the only non-caloric polyol, is found naturally in many fruits and vegetables, and is also commercially produced by fermentation. Erythritol is not metabolized by the body and does not produce a glycemic or insulinemic response [32].

The Effects of Sugar Alcohols in Humans

Wölnerhanssen et al. conducted a double-blind, RCT on lean and obese individuals to evaluate the effect of sugar alcohols on plasma glucose, insulin, GLP-1, CCK, rate of gastric emptying and satiety. Individuals received 50 g of xylitol, 75 g of erythritol, and 75 g of glucose in tap water, or tap water (as the control) via nasogastric tube. The doses of xylitol and erythritol caused 70% and 60% of patients, respectively, to experience bloating and diarrhea; however, no individuals withdrew from the study. Both xylitol and erythritol led to a significant increase in CCK and GLP-1 secretion when compared with the control. The obese group–receiving polyols showed a statistically significant increase in blood glucose and insulin concentrations compared with the lean group;

however, this glucose response was much less than those that were administered glucose. Additionally, there was no statistically significant difference in satiety amongst the four groups or between lean and obese individuals [33].

Overduin et al. evaluated the effects of erythritol consumption on gut hormone levels, hunger/satiety scores, ad libitum food intake, sucrose preference, and food intake on lean and obese individuals. The three treatments consisted of the following breakfast on separate days: a sucrose control meal, isovolumic (reduced calorie meals containing erythritol), or isocaloric erythritol meal similar to the control meal. Erythritol was found to induce a smaller blood glucose excursion and plasma insulin response compared with sucrose-containing meals. The effects on gut hormones including GLP-1, PYY, acute satiation, post-prandial hunger, fullness 4 h post-meal, subsequent energy intake, and sucrose preference during an ad libitum lunch buffet showed no significant differences between the isovolumic erythritol meals and sucrose meal. Only in lean individuals did hunger decrease significantly after consumption of the isocaloric erythritol meal compared with the control meal; however, there was no difference in hunger and fullness scores across the three treatment groups in obese individuals [34].

Mohsenpour et al. studied the effects of lacritose (mixture of sucrose, fructose, lactose, and erythritol) on post-prandial blood glucose levels in a double-blind, RCT in individuals with and without T2DM. Individuals received 50 g glucose, sucrose, or lacritose on three separate occasions in random sequence. Lacritose consumption in individuals with T2DM resulted in a significantly lower mean serum glucose at all time points compared with the glucose and sucrose treatments. No significant adverse GI reactions were observed in any of the treatment groups [35].

The Effects of Sugar Alcohols in Animals

Wen at al. tested the effects of erythritol on blood glucose in 30 non-diabetic and diabetic mice. Treatments were administered intra-gastric with 0.5 g of starch dissolved in water after 12 h of fasting. Mice received an acarbose or erythritol solution and blood glucose levels were measured every 0, 30, 60, 100, 140, and 180 min. Treatment with acarbose and erythritol had no effect on post-prandial blood glucose in non-diabetic mice; however, in diabetic mice, post-prandial blood glucose was significantly lower and there was a significant decline in AUC in mice who received acarbose and erythritol. Biochemical analysis indicated that erythritol exerts its hypoglycemic effects by competitively inhibiting α-glucosidase [36].

Chukwuma et al. studied the effects of xylitol on in vitro and in vivo antioxidant activity in 24 normal and T2DM rats. In vitro, xylitol increased free radical scavenging and ferric-reducing potentials (hydroxide and nitric oxide) in a dose-dependent relationship. In the in vivo study, non-diabetic and diabetic rats were administered either water or 10% xylitol solution ad libitum for 5 weeks. Lipid peroxidation, a marker for oxidative stressed, is determined by measuring the TBARS (thiobarbituric acid reactive substances) as MDA (malondialdehyde) equivalent. After 5 weeks, MDA concentration increased in the serum, cardiac, and pancreatic tissues of diabetic-induced mice, indicating the onset of oxidative stress. MDA concentrations were significantly reduced in the serum and pancreas after xylitol treatment in the diabetic rats compared with diabetic rats that received water. These findings suggest that xylitol has antioxidative properties in both non-diabetic and diabetic rats [37].

Rahman et al. investigated the dose-response effect of xylitol on organ-specific parameters in diabetic rats to determine the most effective antidiabetic oral dose of xylitol. Diabetic rats were administered varying doses of xylitol for weeks while the control group received water. The study found lower food intake across diabetic rats administered xylitol compared with the diabetic control group. Proposed mechanisms for this observation include delayed gastric emptying and shorter intestinal transit times which are known effects of xylitol. The 10% xylitol solution proved to be the most effective at improving glucose tolerability and serum insulin concentrations along with reducing blood glucose and serum fructosamine levels. Congruent with previous research, xylitol had TC-, LDL-, and HDL-lowering effects, along with increasing TG levels in a dose-dependent fashion. Pancreatic β cell histopathology in diabetic rats post-treatment with 10% xylitol also revealed a higher number of β cells suggesting recovery [38].

Luo Han Guo (*Siraitia grosvenorii)*

Luo han guo (*Siraitia grosvenorii)*, commonly known as monk fruit, is a native fruit of China. The sweet constituents of the plant are triterpene glycosides known as mogrosides. Monk fruit has long been used in Chinese traditional medicine for respiratory, digestive, and cardiovascular diseases [39].

The Effects of Monk Fruit in Humans

Gangoso et al. evaluated the effects of monk fruit on blood glucose in 12 healthy adult individuals. Blood glucose levels were obtained fasting and at 15, 30, 45, 60, 90, and 120 min after consumption of 50 g of sugar or 50 g of monk fruit. The

Table 2 Effects of natural alternative sweeteners in humans

Natural alternative sweetener	Effects on blood glucose	Effects on blood pressure	Effects on weight control or energy intake	Effects on cholesterol	Effects on triglycerides
Stevia	-No significant effect on 24- h blood glucose measurements [9] -No effect on AUC of blood glucose concentrations [10] -↓ FBG and PPBG [11]* -↓ FBG [12]*	-↓ Diastolic BP [12]*	-No caloric over-consumption [11] -↓ caloric intake in males ↓ carbohydrate energy consumption in males and females [11]	-↓TC and VLDL levels [11]* -No effect [12]	-↓TG levels [11]* - ↓ TG levels [12]*
Rare sugars	Allulose: -↓PPBG [19]* -no effect [20] **Tagatose**: −7.5 g ↓FBG [22]* -↓ FBG, HbA1c [23]*		Allulose: -↓ BMI, % body fat, body fat mass, total fat area and subcutaneous fat* - no effect on energy intake [20] Rare Sugar Syrup: -↓BW, waist circumference and % body fat [21]* -↓BW [22]*	Allulose: -no effect on LDL [20] Tagatose: -↓LDL, HDL, TC [22] -↓LDL, TC, HDL [23]*	*Allulose: -no effect [20] Tagatose: −5.0 g dose ↑TG [22]* -No effect [23]
Sugar alcohols	Xylitol and Erythritol: -↑ blood glucose and insulin secretion in obese subjects [33]* Lacritose: -↓ mean serum glucose concentration [35]*		Xylitol and Erythritol: -↓ rate of gastric emptying [33]* -No effect on satiety [33] Xylitol: -No effect on hunger, satiety, fullness, or subsequent energy intake [34]		

(*) Indicates statistical significance

Patient population:

9- Tey: healthy individuals

10- Tey: healthy individuals

11- Ritu: individuals with T2DM

12- Onakpoya: mild HTN and individuals with T2DM

19- Noronha: individuals with T2DM

20- Han: BMI >23

21- Hayashi: BMI > 25

22- Ensor 2014: individuals with T2DM

23- Ensor 2015: individuals with T2DM

33- Wolnerhansson: BMI > 30

34- Overduin: BMI > 30

35- Mohsenpour: individuals with T2DM

study showed no change in baseline blood glucose levels in monk fruit–treated group compared with those that were treated with sugar; however, those that received sugar had a significant increase in blood glucose from baseline post-consumption. This study suggests that monk fruit does not significantly impact blood glucose and can be consumed by individuals who need to maintain normal blood glucose levels [40].

After a thorough literature search, we were unable to find any recent human studies that evaluated the effects of monk fruit in individuals with diabetes.

The Effects of Monk Fruit in Animals

Liu et al. investigated the antihyperglycemic and antihyperlipidemic effects of mogrosides on non-diabetic and diabetic mice. Control groups consisted of non-diabetic and diabetic mice administered distilled water intragastrically. Treatment groups consisted of diabetic mice who were administered low (150 mg/kg) and high (300 mg/kg) doses of mogrosides-rich extract (MGE), or metformin (200 mg/kg) for 5 weeks. Treatment groups were fed a high-fat diet and the non-diabetic control group received a normal diet. Both low- and high-dose MGE showed a significant reduction in serum HOMA-IR and a significant increase in the insulin sensitivity index (ISI) control diabetic mice. High-dose MGE significantly improved glucose tolerance in IPITT compared with low-dose MGE in diabetic mice. The beneficial effects of high-dose MGE treatment were comparable with metformin for glucose and insulin parameters. Additionally, MGE-treated mice had a statistically significant reduction in LDL levels and increase in HDL compared with control diabetic mice. High-dose MGE treatment showed a restoration of hepatic histopathology with improvement or resolution of the macro-vesicular steatosis, hepatic inflammation, and focal necrosis [41].

Omija (*Schizandra chinensis)* is known to be a functional health food in Korea with antioxidant and antidiabetic properties; however, it is commonly used in beverages that are sweetened with sugar. Lee et al. investigated the effects of sugar-Omija extract tea (SO) and Luo Han Guo-Omija extract tea (LO) on blood glucose, lipid metabolism, and pancreatic cell histopathology in 30 diabetic mice. Groups consisted of water-treated, SO-treated, and LO-treated normoglycemic controls, and water-treated, SO-treated, and LO-treated diabetic mice. LO-treated diabetic mice had a reduction in blood glucose levels compared with control diabetic mice. LO-treated mice also had a reduction in TG, LDL, and TC levels, and increase in HDL levels compared with control diabetic and SO-treated diabetic mice. Damage to β cells and large vacuolation were evident in control diabetic mice and SO-treated diabetic mice; however, blood vessel and β cell structures were preserved, with no vacuolation observed in the LO-treated diabetic mice [39].

Conclusions

Natural alternative sweeteners consist of many compounds, each of which has varying effects on body weight, blood glucose, lipid metabolism, and antioxidant pathways, and at times exhibit dose-dependent effects. Overall, NAS seem to have more beneficial effects on glucose metabolism, lipids, and pro-inflammatory pathways compared with AS and sugar-containing products, although studies thus far show conflicting results in human and animal models (Table 2). There are many limitations in the data thus far including small sample sizes in human studies and study durations often 12 weeks or less. Future research should include individuals with and without diabetes, use larger sample sizes, and evaluate the effects of long-term NAS use on glucose homeostasis, lipid metabolism, inflammation, and the microbiome.

Compliance with Ethical Standards

Conflict of Interest Emily Mejia and Dr. Michelle Pearlman declare that they have no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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