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EXPLORING NATURAL SUGAR SUBSTITUTES: CAN THEY BE A FRIENDLY DIET FOR TYPE 2 DIABETES MELLITUS? WEIGHING THE PROS AND CONS

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Abstract:
Type 2 Diabetes Mellitus (T2DM) is a metabolic disease when the body did not have insulin in sufficient amounts or lack of sensitivity. This condition impacts an increase in glucose concentration. The treatment is focused on lifestyle changes including a healthy diet. One healthy diet option is to substitute sweeteners sourced from glucose with another sweetener that has a lower impact on blood sugar concentration. Substitution of sugar as a sweetener to claim "healthier" than sucrose can be seen in some parameters such as glycaemic index, structure, and sweetness relative that impact glucose response. National and international journals were used as a literature review for primary data sources. Diabetes mellitus type 2 and natural sweeteners are inclusion criteria to be reviewed. High sweetness ratio and low glycaemic index help to reduce amounts of sugar added into a diet that impacts low glucose response. The complexity of the sugar impacting speed and percent absorption directly impacts blood sugar concentration. But some sugar substitutes should be considered for adverse impacts like cholesterol, gastrointestinal problem, and flora normal growth. The selection of sugar substitutes can be based on the glycaemic index, sweetness ratio, and sugar structure. Some substitute sweeteners have potentially adverse effects that should be considered. Replacement of the sugar doesn't mean patients are free from monitoring of sugar blood concentration and other treatments. But it can be the option to replace sugar as a sweetener in diets that are consumed by the patient.

Keywords: Natural sweetener, sugar substitution, type 2 diabetes mellitus

INTRODUCTION

Diabetes Mellitus is a metabolic disease that responsible in 1 death every 5 seconds in the world in 2021. One in every 10 adults are living with diabetes, and the proportion predicted will be increase by 10 million in a year [1]. Diabetes are classified into 2 main types. Type 1 diabetes is a category when the body cannot produce insulin due to the disruption of immune system that attack cells to produce

insulin. Commonly, type 1 is genetically inherited. While type 2 diabetes (T2DM) is categorised when the body did not have insulin in sufficient amounts or lack of sensitivity. One of the functions of insulin was breaks glucose into glycogen, excess glucose into fatty acid and precursor triglyceride (TAG) [2]. Insufficient of insulin function impact to the increase of glucose concentration (hyperglycaemia). Diabetes is marked by a concentration of fasting blood sugar above 126 mg/dL, a concentration of glucose tolerance is above 200 mg/dL and a concentration of random blood sugar above 200 mg/dL [3].

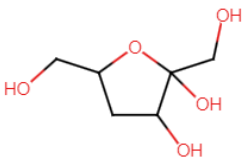
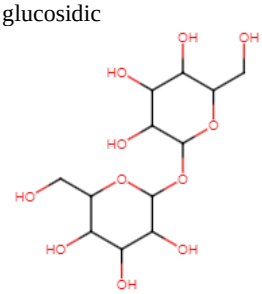
The first intervention for a patient with T2DM is focus on lifestyle changes and control the glycaemic index. Lifestyle means a healthy diet, physical activity, and modest body weight [4]. A lot of food and drinks contain high glucose concentrations that directly impact the glucose concentration in the body. Nowadays, the are some products, that claim as 'diabetic-friendly' that offer the substitution of sugar (sucrose) with others sweeteners that not breaks into glucose or break down in longer time [5]. Sucrose and other dietary sugars induce a stronger postprandial glycaemic response than longer-chained carbohydrates. High sucrose diets or other rapidly absorbable carbohydrates can increase of T2DM risk through obesity, increasing dietary glycaemic load that can lead to resistance of insulin[6]. Some other sweeteners are classified as natural and synthetic. Natural sweetener attracts a lot of attention due to safety claim of the substances. But actually, some sweeteners have adverse effect on the body like flora normal population or laxative impact. Then, pros and cons of sugar substitute using natural sweetener should be discussed.

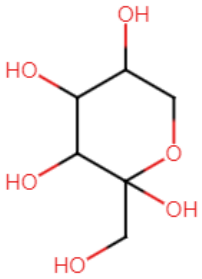
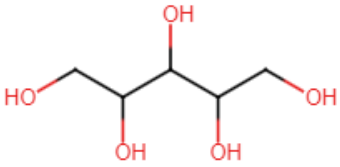
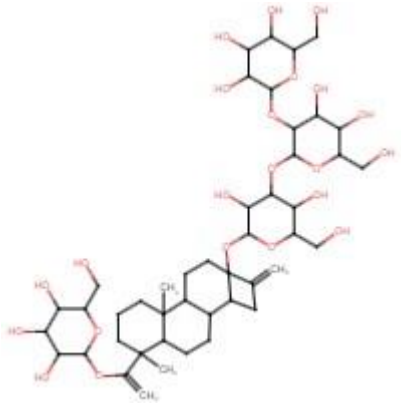
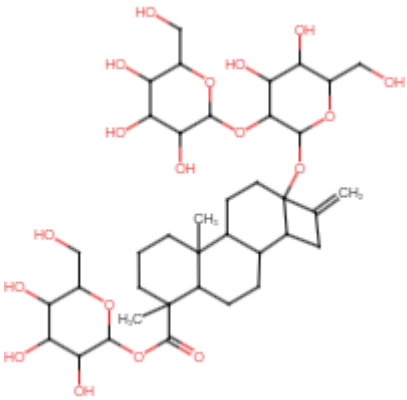
METHODOLOGY

This review looks for primary data sources from the internet by using online search engines, both national and international journals. The search was done manually on the related bibliography so that other search sources can be obtained through e-books or e-journals. The online search keyword was diabetes mellitus type 2, sweetener, adverse effects of-, and glucose intakes. The inclusion criteria in the article search were impact of natural sweeteners on diabetes mellitus type 2. The exclusion criteria used were articles that review the formulation of synthetic sweeteners.

RESULTS AND DISCUSSION

Table 1. Comparison of Natural Sweetener as A Sugar Substitute

Compound	Relative sweetness (sucrose = 1)	The glycemic index (GI) (glucose = 100)	Structure	Impact on T2DM (Pros)	Adverse Effect (Cons)
Fructose	1.43 [7]	20 [8]	Monosacaharide 	Subject T2DM with fructose diets produce the smallest increment in plasma glucose (before and after meals 240 min) compare to sucrose, glucose and starch (potato and wheat) [8]	Fasting serum LDL-cholesterol on d 28 of the fructose diet was 11% higher than the corresponding value for LDL-cholesterol on d 28 of the starch diet. [8]
Trehalose	0.5 [9]	70 [10,11]	Two glucose unit linked by an -1,1-glucosidic bond 	• Plasma glucose concentration after 2 h meals was significantly higher compared to plasma glucose fasting concentration. While trehalose treatment shows no significant increase in terms of plasma glucose concentration between 2 h after meals to fasting. [12] • Trehalose increases insulin sensitivity through	For those who lack the enzyme trehalose, ingesting trehalose-containing foods causes them to experience nausea, vomiting, and diarrhea. [14]

				glucose signaling pathways (direct) and mitigates pathophysiologic pathways.[13]	
Tagatose	0.92 [15]	3 [16]	Stereoisomer (epimer) of D-fructose 	• In mice, sucrose-enriched diets promoted higher caloric intake, obesity, elevated blood glucose and insulin levels, higher total serum cholesterol concentrations, and significantly accelerated atherosclerosis. In contrast, neither the body weight nor the insulin levels were impacted by a diet containing an equivalent quantity of tagatose.(Police et al., 2009) • D tagatose show a reduction in HbA1c compared to placebo (without treatment) in T2DM-diagnosed patient [18]	Increased collagen was seen in the aortic atherosclerotic lesions of mice fed tagatose, suggesting a more permanent plaque phenotype than mice fed sucrose. [17]
Xylitol	0.63[15]	12 [19]	Alcohol sugar (polyols) 	Due to their inadequate small intestine absorption into the bloodstream, polyols are thought to cause low glycaemic and insulinemic responses. Sucrose has a glycaemic index 48 and 69 while xylitol 12 and 11. [20]	Sugar alcohols are not completely digested, excess consumption can cause gastrointestinal symptoms, such as laxative side effects.[20]
Rebaudioside	250-450 [21]	Non caloric (zero glycemic index) [22]		Blood glucose and insulin incremental AUC of MCJ (Modified Coconut Jelly, means using 50% stevia and 50% sucrose) demonstrated a lower trend than CCJ(Control Coconut Jelly) by 15.7 and 5.4 percent, respectively. After 60 to 120 minutes of MCJ ingestion, blood glucose started to progressively fall. Postprandial blood glucose levels tended to drop with MCJ without increasing insulin secretion.[23]	Have an impact on bacterial population growth • Firmicutes/Bacteroidetes ratio was increased [24,25] • Reduce *Ruminococcaceae* and increase *Porphyromonadaceae*, *Sporobacter*, and *Enterobacteriaceae*. [26,27] • Increased *Bacteroidaceae* and reduced *A. muciniphila Limosilactobacillus reuteri* [28]
Stevioside	250-300 [21]	Non caloric (zero glycemic index)[29]		Blood was taken at 30 minutes before and 240 minutes after the test meal. Stevioside decreased the incremental area under the glucose response curve by 18% as compared to control (miaze starch). Stevioside enhanced the insulinogenic index (AUC(insulin)/AUC(glucose)) by almost 40% when compared to control. Stevioside did not significantly change the area under the insulin, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide curves, it did tend to lower glucagon levels. [30]	

Sucrose substitutes already use in food, beverages, supplement, and drugs with a claim for healthy because they have the ability to minimize sugar consumption and, as a result, type 2 diabetes risk [31]. Additionally, sugar is linked to obesity, a chronic condition that is characterized by an increase in body fat storage and has detrimental effects on both metabolic and psychosocial health [32]. For this reason, option for substituting the sugar is coming from synthetic or natural compounds. Unfortunately, some synthetic sweeteners coming up with a 'negative issue'. One of the popular synthetic sweeteners is aspartame. Aspartame dramatically raises plasma Phy, which inhibits Tyr and Trp hydroxylase, the rate-limiting enzymes for the production of dopamine and serotonin, by competitive inhibition. Dopamine and serotonin levels in the brain diminish as a result, which causes severe effects including depression[33,34]. Additional proof of aspartame's carcinogenic consequences was obtained from experiments involving rats from birth to death. Early life exposure to aspartame may boost the substance's ability to cause cancer [35]. This kind of issue was convincing the people who have a strong intrinsic belief that things that are natural are superior, healthier, and safer than synthetic things.

All-natural sweetener that uses as a substitute has lower glycaemic than sucrose. The glycaemic index was the ratio between the incremental area under the blood glucose curve of test food to the incremental area under the blood of glucose curve of reference. The reference usually is glucose solution[36]. The GI was linked to an increased risk of diabetes in persons who were overweight or obese. The risk of type 2 diabetes seems to be more correlated with GL (Glycaemic Load) than GI. Glycaemic load (GL), which accounts for the GI and the amount of available carbohydrate in a portion of the food consumed (GL = GI x available carbohydrate in a given amount of food), was useful in predicting the GR (Glucose Response). GR is defined as the increase in the blood glucose concentration following eating, expressed as the incremental area-under-the-blood-glucose-curve (iAUC) over a period of two hours [37]. Thus, a low glycaemic index doesn't mean lowering the risk of T2DM, the number of total carbohydrate matters. The relative sweetness is one of the parameters that determine the quantity of sweetener to be added. Rebaudioside and stevioside has relative sweetness hundred times more than sucrose. Then it can be used in lower quantity to give the same appealing taste.

Polysaccharides are broken down into monosaccharides by specialized enzymes such as salivary amylase, stomach acid, and specific carbohydrases—glycoside hydrolases, respectively) during digestion in the mouth, stomach, and intestine. The small intestine then absorbs the monosaccharides into the bloodstream. Two distinct types of membrane-associated carrier proteins, sodium-glucose linked transporters (SGLTs) and facilitated diffusion glucose transporters (GLUTs), allow monosaccharides, such as glucose and fructose, to enter mammalian cells[38]. The complexity of the structure of substitute sugar can prolong the sequence of breakdown process. The structure also impacts the binding process of enzymes that cause some sweeteners cannot be fully absorbed like polyols [39]. Prolong process of sugar and not fully absorb of sugar reduce AUC value of glucose concentration in blood compared to sugar.

After all, for reducing glucose concentration can be achieved through two main mechanisms, like increased insulin secretion and increased insulin sensitivity. Ways to promote increased insulin secretion is by choosing low glycaemic index food, as they lead to slower and more gradual increases in blood sugar and also reduce the need for rapid insulin response. To enhance insulin sensitivity, patients should avoid excessive sugar and refined carbohydrates. Limiting the intake of sugary and highly processed foods can maintain the sensitivity of insulin. This mechanism is also conducted by trehalose to maintain glucose homeostasis [13].

However, recent studies have shown that artificial sweeteners affect glucose absorption in the intestinal tract as well as insulin and incretin secretion in humans and animals. Moreover, substitute sweeteners alter the composition of the microbiota and worsen glycaemic control owing to changes in the gut microbiota. Substitution of sugar using another sweetener not immediately reduce all the

risks in T2DM. Besides of adverse effects that may can be experienced by the patient, compatibility with the drug, price, and availability of the product should be considered as sugar substitute option.

CONCLUSION

Substitution of sugar as a sweetener is one option that can patients with T2DM do to help maintain blood sugar concentration. Selection of sugar substitutes can be based on the glycaemic index and sweetness ratio that can impact glucose load then also impact glucose response. Sugar structure also impacts speed and percentage of absorption which impacting sugar blood concentration. Besides that, the safety of the sugar should be considered. Replacement of the sugar doesn't mean patients are free from monitoring of sugar blood concentration and other treatments. But it can be the option to replace sugar as a sweetener in diets that are consumed by the patient.

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