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Study of Short-term Effects of Stevia Compared to Sucrose on Blood Glucose and Pressure Response in Healthy Medical Undergraduates – A RCT

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Abstract

Stevia is a generic term for the plant Stevia rebaudiana *Bertoni*. Stevia is a natural source of sweetener which acts as an alternative to artificial sweeteners that are available because Stevia replaces cane sugar as it is 20-30 times sweeter. The objective of this study is to compare the short-term effect of Stevia versus sucrose on blood glucose and blood pressure response in healthy medical undergraduates. A randomized controlled trial was conducted from September to October 2019 in Melaka Manipal Medical College, Malaysia. The trial comprised of the intervention group receiving 1g of Stevia powder mixed in 100ml of water and the active control group receiving 20g of sucrose mixed in 100ml of water for 3 consecutive days. Blood pressure was measured on the first and last day using digital blood pressure monitor; whereas blood glucose was measured thrice on third day using a glucometer. Socio-demographic data and side effects were collected using questionnaires. Mean, mean difference, standard deviation, various t-test (paired and unpaired) were calculated in the statistical analysis of the data. From a population of 156 students, a sample size of 20 students per group was obtained. The results of our study were non-significant but we observed a reduction in mean systolic (-1.80 mmHg) and diastolic (-2.85 mmHg) blood pressures in the Stevia group. As for blood glucose response, the Stevia group showed a mean increase at 60 and 90 minute intervals. However, there is mean decrease of 0.15 mmol in blood glucose from 60 to 90 minutes. In conclusion, Stevia has no significant short-term effect on blood pressure and blood glucose response. Stevia could be potentially hypoglycemic provided the study is conducted on a large sample size for long-term consumption.

Keywords

Stevia, Sucrose, Blood Glucose, Blood Pressure, Medical Undergraduates, RCT

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1. Introduction

Stevia is a generic term for different forms of the sweetener, including the whole plant Stevia (Stevia rebaudiana *Bertoni)* as shown in figure 1 below and the leaves which is composed of the sweet compounds. The sweet compounds from the leaf material of Stevia is extracted by steeping the leaves of the Stevia plant. [1] There are 154 members of the genus Stevia and Stevia rebaudiana *Bertoni* (Family-Asteraceae) is one of the only two species that produce steviol glycosides. Among the members of the genus, only Stevia rebaudiana *Bertoni* gave the sweetest essence. Stevia is also known as Sweet

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herb of Paraguay, Candy Leaf, Sweet Leaf and Honey Leaf. [2] In the early 1970s a Japanese consortium was the first one to seriously consider steviol glycosides which is the major sweetener present in leaf and stem tissues of stevia as a sugar substitute for the purpose of commercializing steviol glycosides and stevia extracts. The first chemist to study the chemical compounds of the substance extracted is Rebaudi. Hence, initially the plant was first called *Eupatorium rebaudianum Bertoni* in honour of Rebaudi. Later after some time, its name was changed to Stevia rebaudiana *Bertoni* which remains till today. [3]

Figure 1. Stevia rebaudiana [1].

Production of Stevia begins with the process of drying the Stevia (Stevia rebaudiana *Bertoni*) leaves. The sweet tasting components of Stevia which is the Steviol glycosides are extracted by steeping its dried leaves in hot water, like a tea. The liquid is then filtered and separated from plant material by removing all small leafy particles. Then, activated carbon treatment is done to remove organic residues. This is followed by the ion exchange treatment to remove minerals. Adsorption or desorption of the Resin is done to concentrate the glycosides. Finally, spray drying is done before completing the Stevia extraction [2] Figure 2 below illustrates the process used to extract steviol glycosides from the stevia leaf in brief.

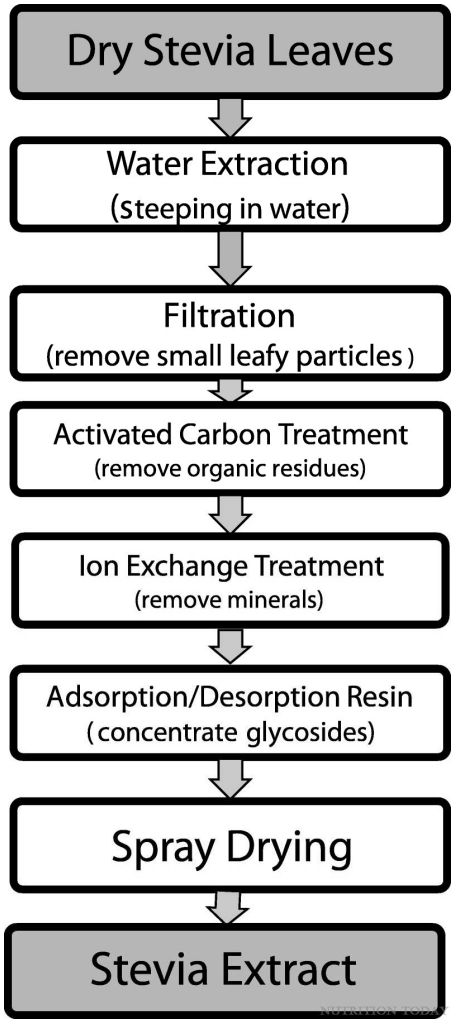

Figure 2. Preparation of Stevia [2].

In many parts of the world especially Japan, America and Asia, Stevia is known as a natural source of non-caloric sweetener and dietary supplement. Stevia was explored not only for production of food, but also for the role in medicine that were attributed to it. It acts as an alternative to the artificial sweeteners that are currently available to the consumers. Stevia produces stevioside which acts as a non-caloric sweetener that does not get metabolized in the human body. This compound passes through the digestive process without being broken down chemically resulting in stevia being safe for those whom are in need to control their blood glucose level. (Strauss 1995). [3] Steviol glycosides act directly on B-cell islets by enhancing insulin secretion without altering Kt-ATP channel activity and CAMP levels which results in significant increase in glucose tolerance and suppression of plasma glucose level in adult human. [7]

The biosynthesis is initiated from Mevalonic acid through kaurene (I) and kaur-16-en-19-oic acid (III). Four glycosylation reactions that is initiated with steviol and ends with Rebaudioside is needed to form glycosides. The final step of GA biosynthesis, before the branch point to steviol

production, is the formation of kaurenoic acid from kaurene, catalyzed by kaurene oxidase (KO). Downstream of this, the first committed step in steviol glycoside synthesis is the hydroxylation of kaurenoic acid to form steviol, which is then sequentially glycosylated by a series of UDP-glucosyltransferases (UGTs) to produce the variety of steviol glycosides. [2] Figure 3 below illustrates the biosynthesis of Stevia glycosides in Stevia rebaudiana *Bertoni*.

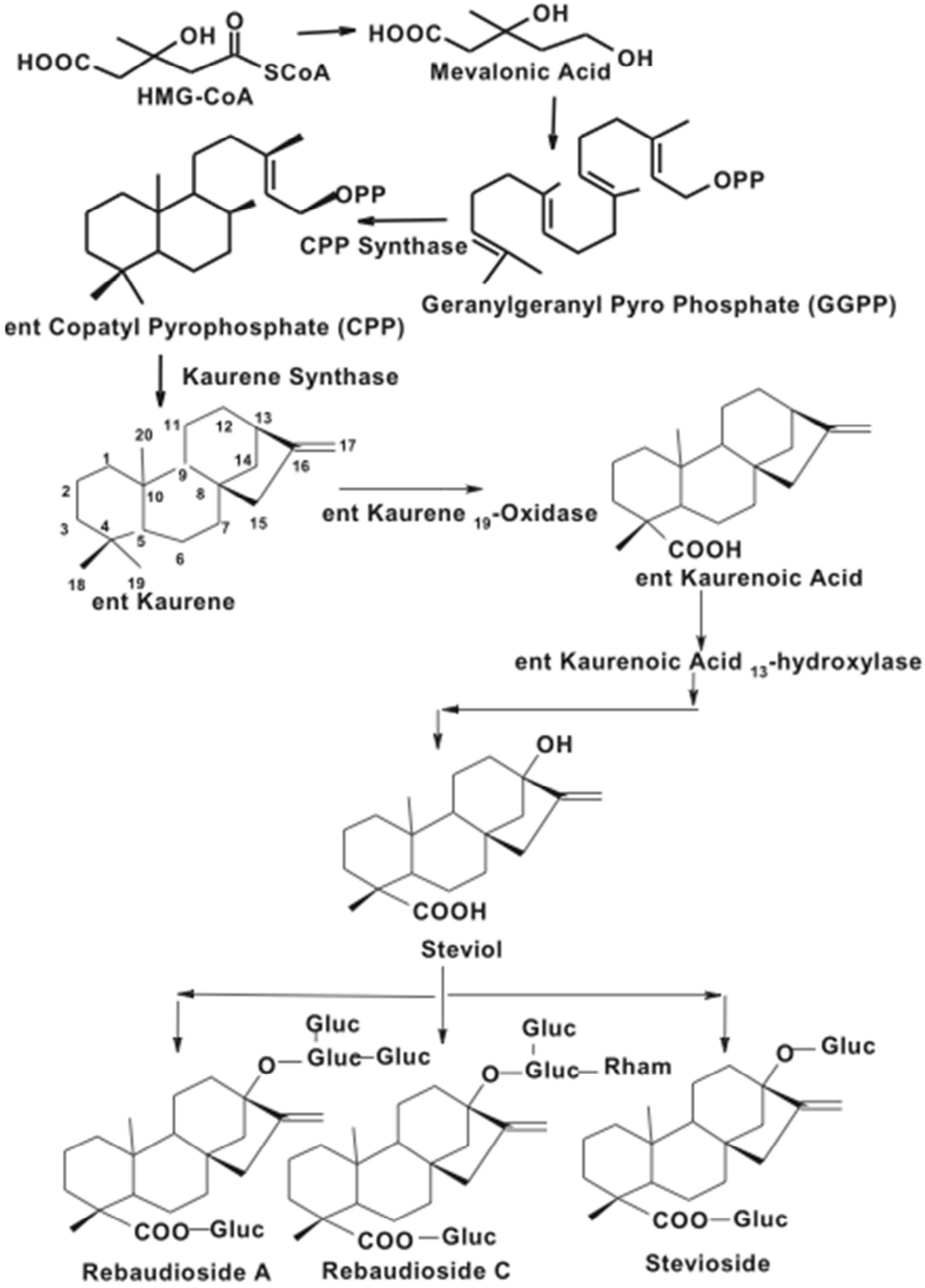

Figure 3. Biosynthesis of Stevia glycosides [2].

Use of Stevia in confectionary, cooked/baked food, acidified beverages and household products is highly recommended as it is non fermentable, heat stable up to 200 and acid stable. This is mainly because Stevia can replace cane sugar easily as it is 20-30 times sweeter than cane sugar. It was found that 10% sucrose solution between pH 3.0-7.0 had the similar potency of sweetness in Stevia. [5] With the increased in incidence of Type 2 diabetes mellitus in Malaysia and abroad, there is definitely a vital need for a natural non-caloric sweetener with an acceptable taste and health properties to be explored. In addition to that, Malaysia is 1 out of the 22 countries and territories of the International Diabetes Federation Western Pacific Region (IDFWP). Based on IDF WP region in 2017, from 20,722,000 of total adult population, 3,492,600 of total cases of diabetes were reported in adults. This showed diabetes prevalence of 16.9% in adults [4] A study on the effect of Stevia Rebaudiana on Glucose Tolerance in Normal Adult Humans whereby 16 healthy volunteers were given boiled extracts of the Stevia leaves, a total of 65g in 13 doses of 5g at 6 hour intervals; whereas the control group was administered with 250mg of arabinose instead of the extract. The study proved that plasma glucose levels measured after administration of Stevia was significantly lower than the control at each time tested (30, 60, 90, 120, and 180 minutes after ingestion. [12]

On the other hand, adding on to its non-caloric sweetening role, it also has many other therapeutic values which includes its role in prevention of caries and promotion of oral health. For example, studies indicate that growth suppression is experienced and less acid is secreted by the Streptococcus mutans when grown on media containing steviosides compared to when grown on sucrose, glucose or fructose media. [5] Stevia also helps in prevention of obesity which is now one of the most common nutritional disorder in Malaysia.[1] This is achieved by subtituting sugar with Stevia, assisting with weight control and weight loss by restricting calorie intake in diet. This is also contributed by zero calorie substances like steroside and rebaudiosides found in Stevia which are not metabolized in the body to produce energy.[7] In addition to that, Stevia when consumed has an antioxidant property by availability of phenol compound which would inhibit the free radicle formation by a continuous oxidation process due to lack of electrons.[8]

Next, studies on Stevia extracts and its isolated glycosides show its hypotensive and diuretic effects where Stevia is used to regulate the heartbeat and normalised blood pressure level. Stevia has similar mechanism of action as the calcium channel agent as Stevia also acts at the cell membrane level. [7] Regular consumption of glycosides present in Stevia decreases cholesterol content in the blood, improve blood coagulation and cell regeneration, strengthen blood vessel and suppress neoplastic growth. [2] For instance, the study conducted in 20 selected hypercholesterolemic women shows that's consumption of 20ml Stevia extract in a glass of water of 200ml helps in significant increase in good cholesterol, high-density lipoprotein (HDL) and reduction of triglycerides and low-density lipoprotein (LDL).[7]

Stevia also exerts an anti-inflammatory effect on colonic epithelial cells which is for the antidiarrheal efficacy, the effect of stevioside and its analogs, steviol, dihydroisosteviol, isosteviol and isosteviol 16-oxime, on cAMP- regulated CL-secretion were studied in human T84 colonic epithelial cells and in vivo whereas in animal studies stevioside causes smooth muscle contraction to reduce hypermotility-associated diarrhea. [7]

As for the cons in consumption of Stevia, there is no major side effects of Stevia found on human experiments. However, they've found out that human body doesn't metabolize the raw form of sweet glycosides. Prolong use of stevia may have potential of causing dental caries. [10] Moreover, in an experiment, patients from the active treatment group experienced abdominal fullness, muscle tenderness, nausea and asthenia, but all of the symptoms disappeared after 1 week. [11] To conclude, till today there's no major side effects experienced in human body. However, further studies need to be conducted to explore its long term adverse effects in human body.

Previously, a study was conducted among healthy young Malay adults from International Islamic University Malaysia (IIUM) Kuantan and Centre of Foundation in Studies (CFS IIUM) Petaling Jaya, Selangor entitled effect of acute stevia consumption on blood glucose response in healthy Malay young adults which proved that sucrose has higher glycemic response followed by stevia 1000mg and 500mg. [13] Another study was done among 106 Chinese hypertensive subjects for a year to determine the long-term anti-hypertensive effect of stevia which showed a decrease in both systolic and diastolic blood pressure of hypertensive patients after a year. This study also proved that there are no significant adverse effects in consumption of stevia. [14] We conducted this study to compare the short-term effect of Stevia versus sucrose on blood glucose response and blood pressure response in healthy medical undergraduates.

Research Objectives:

To compare the short term effect of Stevia versus sucrose on blood glucose response in healthy medical undergraduates.

To compare the short term effect of Stevia versus sucrose on blood pressure response in healthy medical undergraduates.

Research Hypothesis:

Stevia when given in equal amount as Sucrose will result in lower post prandial blood glucose levels in healthy medical undergraduates.

Stevia when given in equal amount as Sucrose will result in lower blood pressure levels in healthy medical undergraduates.

2. Methodology

Study Design

A double blinded randomized controlled trial was conducted to study the short-term effects of Stevia (natural sweetener) versus sucrose (table sugar) on blood glucose response and blood pressure response in healthy medical undergraduates.

Study setting, population, and time

The study was conducted in Melaka Manipal Medical College, Muar campus, Johor, Malaysia. The population selected for this study is of semester 7 students of the Bachelor of Medicine & Bachelor of Surgery program which approximately consists of 150 students within the time period of September to October 2019.

Sample size

The sample size for this study was estimated using results from a previous randomized controlled trial done to compare the effects of Stevia versus sucrose on healthy Malay young adults [14]. The mobile application SampleCalc was used to calculate an estimated for this study.

Mean 1 (sucrose): 4.9

Mean 2 (Stevia): 5.2

Standard Deviation: 0.44

Size of difference: 0.3

Significance level (alpha): 0.05

Power: 80%

Sample size calculated: 34 in each group

However, due to the time limitations of this study, a sample size of 20 students per group (intervention and control) was obtained.

Sampling and Randomization

Purposive sampling, a non-probability type of sampling was done for this study. A total of 40 volunteers satisfying the inclusion and exclusion criteria (as shown in Table 1 below) were chosen to participate in this study. They were divided equally into 2 groups (intervention and control). The students were randomized into the groups using a Research Randomizer software (www.randomizer.org). Block randomization was done with 20 sets of 2 numbers per set with the range of numbers being 1-2 as shown in Table 2. Therefore, participants assigned with 1 were given the active control ingredient (sucrose) and participants assigned with 2 received intervention ingredient (Stevia) for the 3-day period. Initially, all participants filled out a written informed consent form with a brief explanation of the procedures involved in the trial.

Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Males and females	Smoking during the period of trial
Any age	Consuming alcohol during the period of trial
BMI within 18.5-24.9 kg/m^2	Pre-existing medical conditions (Diabetes/Hypertension/Obesity)
Any nationality	Not willing to provide consent
Any ethnicity	Intolerance towards Stevia/sucrose

Table 2. Research Randomizer results.

Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11	Set 12	Set 13	Set 14	Set 15	Set 16	Set 17	Set 18	Set 19	Set 20
1	2	1	1	1	1	1	2	2	2	2	2	2	1	1	1	2	1	2	2
2	1	2	2	2	2	2	1	1	1	1	1	1	2	2	2	1	2	1	1

Intervention Procedure

At the beginning of the study, the resting blood pressure of all participants were recorded to establish a baseline before consumption of Stevia or sucrose. Participants in the intervention group received 1g of EqualStevia powder mixed in 100ml of water for 3 consecutive days, whereas participants in the active control group received 20g of CSR sucrose powder dissolved in 100ml of water for 3 consecutive days. The weightages of Stevia and sucrose are based on a previous trial [13] as it was concluded that 1g of Stevia powder in 100ml of water is equivalent to 20g of sucrose mixed in 100ml of water. The respective powders were weighed using an electronic weighing scale and mixed with 100ml of water measured with a measuring cup. The participants then consumed the colourless mixtures orally. As this is a double blinded trial, the participants were unaware of which group they have been assigned to and therefore have no knowledge of which substance they have consumed for the period of the trial. On the final day, a random blood

glucose test was done before participants consumed their respective mixtures, followed by post-prandial blood glucose tests taken at 60 minutes and 90 minutes after consumption. Blood pressure was also taken at 90 minutes after consumption of the mixtures on the final day.

Data Collection

The independent variable in this study was the consumption of Stevia (natural sweetener) versus sucrose (table sugar) while the dependent variables were the blood glucose response and the blood pressure response. 40 participants were divided into 2 groups of 20 participants each and labelled as group 1 (control) and group 2 (intervention). Capillary blood glucose levels were measured using OneTouch UltraEasy blood glucose monitoring system. Alcohol swabs were used to sterilize the finger prick region before samples were taken. Blood pressure measurements were taken using a digital blood pressure monitor on participants' right arms while they were sitting upright after allowing a rest period of 5 minutes. Both systolic and diastolic pressures were recorded for the purpose of this study. Participants were also asked to fill out a questionnaire at the end of the trial regarding any experience of side effects after consumption of the mixtures.

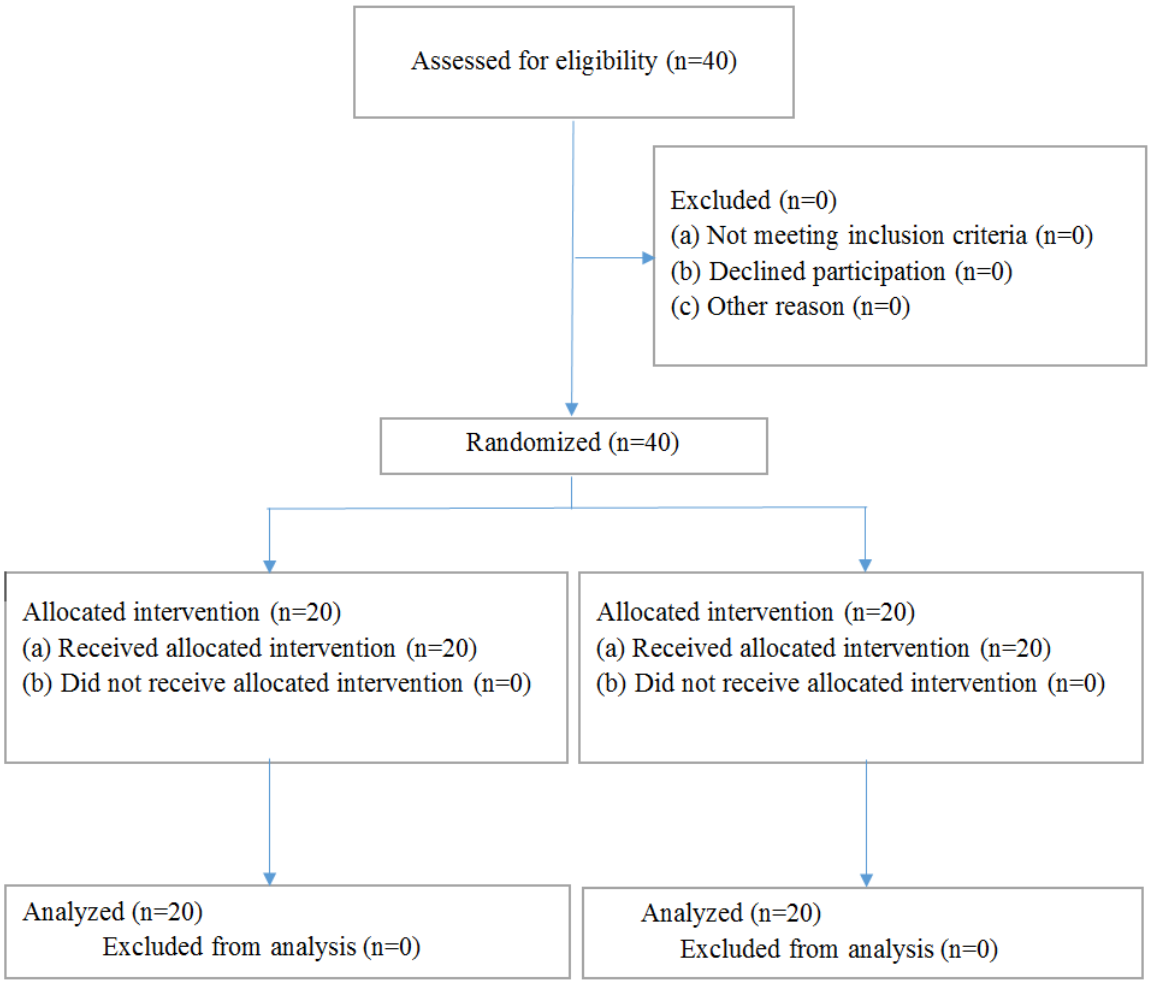

Figure 4. Consort Flow Diagram.

Data Analysis and Processing

Data entry was done using Microsoft Excel to tabulate the demographic data as well as the results of this study. Data analysis was done using the GraphPad software as well as Epi Info version 7.2.3.1 from the Centers for Disease Control and Prevention (CDC) website. The mean and standard deviation of the blood glucose response as well as the systolic and diastolic blood pressure response of participants in both the intervention and active control group were used as comparison values to analyze the data. The measure of association was calculated using Relative Risk (RR). The results were interpreted based on the mean difference, 95% confidence interval and P value (level of significance of 0.05). Table 3 shows the statistical tests chosen for each dependent variable of the study.

Table 3. Statistical Tests.

Independent variable	Dependent variable	Statistical test
Intervention group (Stevia) versus active control group (sucrose)	Difference in blood glucose response at 60 mins	Unpaired T test
	Difference in blood glucose response at 90 mins	Unpaired T test
	Difference in systolic blood pressure	Unpaired T test
	Difference in diastolic blood pressure	Unpaired T test
Intervention group (Stevia) (before versus after)	Blood glucose response at 60 mins	Paired T test
	Blood glucose response at 90 mins	Paired T test
	Systolic blood pressure	Paired T test
	Diastolic blood pressure	Paired T test
Active control group (sucrose) (before versus after)	Blood glucose response at 60 mins	Paired T test
	Blood glucose response at 90 mins	Paired T test
	Systolic blood pressure	Paired T test
	Diastolic blood pressure	Paired T test

Ethical Consideration

A total of 40 participants were chosen to participate in this study voluntarily and were briefed regarding the rights as a participant before the research commenced. Written informed consent with signatures were obtained and the participants were reassured regarding the confidentiality of their private information, to be used only for research purposes. Only the research investigators have access to all their information. The research study was reviewed and approved by Research Ethics Committee, Faculty of Medicine of Melaka Manipal Medical College, Malaysia.

3. Results

Table 4. Baseline characteristics between stevia (n=20) and sucrose (n=20).

Variables		Sucrose n (%)	Stevia n (%)	Total n (%)
Age (years)[a]		21.90 (1.02)	22.45 (1.28)	22.18 (1.17)
Gender	Male	9 (45%)	9 (45%)	18 (45%)
	Female	11 (55%)	11 (55%)	22 (55%)
BMI[a]		21.34 (2.01)	22.37 (1.60)	21.86 (1.87)
Nationality	Malaysian	18 (90%)	15 (75%)	33 (82.5%)
	Non-Malaysian	2 (10%)	5 (25%)	7 (17.5%)
Baseline systolic blood pressure (mmHg)[a]		112.95 (14.66)	116.70 (10.65)	114.83 (12.79)
Baseline diastolic blood pressure (mmHg)[a]		71.15 (8.30)	73.90 (6.71)	72.53 (7.58)
Random blood sugar (mmol)[a]		5.57 (0.69)	5.35 (0.51)	5.46 (0.61)

[a]Mean (SD)

Interpretation:

Table 4 shows the baseline characteristics between stevia and sucrose. The total study group consists of 40 participants and the participants were randomized in to the control and intervention groups each consists of 20 participants. The mean age of the group received sucrose is 21.90 and the standard deviation is 1.02 whereas the mean age of the group received stevia as the intervention is 22.45 and the standard deviation is 1.28. The total study group shows a mean age of 22.18 years with a standard deviation of 1.17. Male participation for both the control and intervention groups are 45% while the female participation for both the control and intervention groups are 55% The group receiving sucrose has a mean BMI of 21.34 with a standard deviation of 2.01 whereas the group receiving stevia as the intervention has a mean BMI of 22.37 with a standard deviation of 1.60. The mean BMI of the total study group is 21.86 with a standard deviation of 1.87. Among the participants in the group who received sucrose, 90% are Malaysians where as 10% are non-Malaysians. 75% of the participants who received stevia as the intervention are Malaysians and 25% of the participants in the same group are non-Malaysians. The total study group has 82.5% Malaysian participants and 17.5% non-Malaysian participants. The mean baseline systolic blood pressure in the control group is 112.95 mmHg with a standard deviation of 14.66 whereas the stevia intervention group has a mean baseline systolic blood pressure of 116.70mmHg with a standard deviation of 10.65. The mean baseline systolic blood pressure of the total study group is 114.83mmHg with a standard deviation of 12.79. The mean baseline diastolic blood pressure of the control group is 71.15 mmHg (SD 8.30) and the mean baseline diastolic blood pressure in the stevia intervention group is 73.90 mmHg (SD 6.17). The total study group shows a mean baseline diastolic blood pressure of 72.53 mmHg (SD 0.61). The mean random blood sugar of the control group is 5.57 mmol (SD 0.69) whereas of the stevia intervention group is 5.35 mmol (SD 0.51). The total study group has a mean random blood sugar level of 5.46

mmol (SD 0.61).

Table 5. Comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), post prandial blood glucose response (PPBG) (mmol) after 60 and 90 mins between sucrose and stevia groups.

Variable	Mean (SD)		Mean difference (95% CI)	t-statistic (df)	P-value
	Sucrose	Stevia			
SBP (mmHg) (change score)	-0.45 (14.20)	-1.80 (16.85)	1.35 (-8.62, 11.32)	0.27 (38)	0.786
DBP (mmHg) (change score)	0.70 (9.22)	-2.85 (6.29)	3.55 (-1.50, 8.60)	1.42 (38)	0.163
PPBG after 60 mins (mmol) (change score)	5.40 (0.56)	5.75 (1.03)	-0.35 (-0.88, 0.18)	-1.34 (38)	0.188
PPBG after 90 mins (mmol) (change score)	5.33 (0.71)	5.60 (0.84)	-0.27 (-0.76, 0.23)	-1.08 (38)	0.287

Interpretation:

Table 5 is the comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), post prandial blood glucose response (PPBG) (mmol) after 60 mins and 90 mins between sucrose and stevia. The control group has a mean SBP of -0.45 with a standard deviation of 14.20 and the stevia intervention group has a mean SBP of -1.80 with a standard deviation of 16.85. The mean difference of SBP between sucrose and stevia intervention groups is 1.35 with a 95% confidence interval range from -8.62 to 11.32. The unpaired T-test value for SBP of stevia when compared to sucrose is 0.27 with the number of degree of freedom is 38 and the P value for the same is 0.786. Thus, it was not significant. The mean DBP of the control group is 0.70 with a standard deviation of 9.22 while the mean DBP of stevia intervention group is -2.84 with a standard deviation of 6.29. The mean difference of DBP between sucrose and stevia intervention groups is 3.55 with a 95% confidence interval ranges from -1.50 to 8.60. The unpaired T-test shows a value of 1.42 for DBP when stevia intervention group compared to sucrose intervention group with a degree of freedom of 38. The P value for the same is 0.163. Thus, it was not significant. The mean PPBG after 60 mins in the control group is 5.40 mmol (SD 0.56) and in the stevia intervention group is 5.75 (SD 1.03). The mean difference of PPBG after 60 mins between the control and stevia intervention group is -0.27 with a 95% confidence interval from -0.88 to 0.18 and the unpaired T-test value is -1.34 (df 38). The P value for the same is 0.188. Thus, it was not significant. The mean PPBG after 90 mins in the control group is 5.33 mmol (SD 0.71) whereas in the stevia intervention group it is 5.60 mmHg (SD 0.84). Mean difference of the PPBG after 90 mins between the control group and stevia intervention group is -0.27 (95% CI -0.76, 0.23). The unpaired T-test value for the PPBG after 90 mins is -1.08 (df 38) and the P value for the same is 0.287. Thus, it was not significant.

Table 6. Comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), blood glucose response (mmol) of RBS vs 60 mins, RBS vs 90 mins and 60 mins vs 90 mins of sucrose.

Variable	Mean (SD)		Mean difference (95% CI)	t-statistic (df)	P-value
	before	after			
SBP (mmHg)	112.95 (14.66)	112.50 (14.02)	0.45 (-6.19, 7.09)	0.14 (19)	0.889
DBP (mmHg)	71.15 (8.30)	71.85 (10.73)	-0.70 (-5.02, 3.62)	0.34 (19)	0.738
Blood Glucose RBS vs 60 mins (mmol)	5.57 (0.69)	5.40 (0.56)	-0.17 (-0.08, 0.42	1.41 (19)	0.175
Blood Glucose RBS vs 90 mins (mmol)	5.57 (0.69)	5.33 (0.71)	0.24 (-0.12, 0.60)	1.41 (19)	0.174
Blood Glucose 60 mins vs 90 mins (mmol)	5.40 (0.56)	5.33 (0.71)	0.07 (-0.22-0.36)	0.51 (19)	0.615

Interpretation:

Table 6 shows the comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), blood glucose response (mmol) of RBS vs 60 mins, RBS vs 90 mins and 60 mins vs 90 mins of sucrose. The mean SBP before administrating sucrose is 112.95 mmHg with a standard deviation of 14.66 and after administrating sucrose the mean SBP is 112.50 mmHg (SD 14.02). The mean difference between before and after administrating sucrose is 0.45 (95% CI -6.19, 7.09). Paired T-test has a value of 0.14 (df 19) and the P value is 0.889. Thus, it was not significant. The mean DBP before administrating sucrose is 71.15 mmHg (SD 8.30) and after administrating sucrose the mean DBP is 71.85 (SD 10.73). The mean difference between before and after administrating sucrose is -0.70 with the 95% confidence interval from -5.02 to 3.62. Paired T-test value is 0.34 (df 19) and the P value for the same is 0.738. Thus, it was not significant. The mean blood glucose level before administrating sucrose is 5.57mmol (SD 0.69) and 60 mins after administrating sucrose is 5.40 mmol (SD 0.56). The mean difference between RBS and blood glucose level 60 mins after administrating sucrose is 0.17 (95% CI -0.08, 0.42). Paired T-test value for the same comparison is 1.41 (df19) and the P value is 0.175. Thus, it was not significant. The mean blood glucose level before administrating sucrose is 5.57mmol (SD 0.69) and 90 mins after administrating sucrose is 5.34 mmol (SD 0.71). The mean difference between RBS and blood glucose level 90 mins after administrating sucrose is 0.23 (95% CI -0.12, 0.60). Paired T-test value for the same comparison is 1.41 (df19) and the P value is 0.174. Thus, it was not significant. The mean blood glucose level 60 mins after administrating sucrose is 5.40 mmol (SD 0.56) and 90

mins after administrating sucrose is 5.34 mmol (SD 0.71). The mean difference between blood glucose level 60 mins after administrating sucrose and blood glucose level 90 mins after administrating sucrose is 0.06 (95% CI -0.22, 0.36). Paired T-test value for the same comparison is 1.51 (df19) and the P value is 0.615. Thus, it was not significant.

Table 7. Comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), blood glucose response (mmol) of RBS vs 60 mins, RBS vs 90 mins and 60 mins vs 90 mins of stevia.

Variable	Mean (SD)		Mean difference (95% CI)	t-statistic (df)	P-value
	before	after			
SBP (mmHg)	116.70 (10.65)	114.90 (14.44)	1.80 (-6.09, 9.69)	0.48 (19)	0.638
DBP (mmHg)	73.90 (6.71)	71.05 (7.66)	2.85 (-0.09, 5.79)	2.03 (19)	0.057
Blood Glucose RBS vs 60 mins (mmol)	5.35 (0.51)	5.75 (1.03)	-0.40 (-0.92, 0.13)	1.56 (19)	0.135
Blood Glucose RBS vs 90 mins (mmol)	5.35 (0.51)	5.60 (0.84)	-0.24 (-0.72, 0.24)	1.05 (19)	0.306
Blood Glucose 60 mins vs 90 mins (mmol)	5.75 (1.03)	5.60 (0.84)	0.15 (-0.09, 0.40)	1.31 (19)	0.206

Interpretation:

Table 7 shows the comparison of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), blood glucose response (mmol) of RBS vs 60 mins, RBS vs 90 mins and 60 mins vs 90 mins of stevia. The mean SBP before consuming Stevia is 116.70 while the standard deviation is 10.65. The mean SBP then dropped to 114.90 while the standard deviation is 14.44. The mean difference of SBP is 1.80 with 95% CI is between -6.09 and 9.69. The t-statistic of SBP is 0.48 while the degree of freedom is 19. The P-value of SBP is 0.638. Thus, it was not significant. Next, the mean DBP before consumption of Stevia is 73.90 which then dropped to 71.05. The standard deviation of SBP before consumption is 6.71 and after consumption is 7.66. The mean difference of DBP is 2.85 while the 95% CI is between -0.09 and 5.79. The t-statistic is 2.03 and the degree of freedom is 19. The P-value of DBP is 0.057. Thus, it was not significant. Next, the mean RBS vs 60 mins (mmol) before is 5.35 while the standard deviation is 0.51. The mean RBS vs 60 mins (mmol) after is 5.75 while the standard deviation is 1.03. The mean difference of RBS vs 60 mins (mmol) is -0.4 and the 95% CI is between -0.92 and 0.13. The t-statistic is 1.56 and the degree of freedom is 19. The P-value of RBS vs 60 mins (mmol) is 0.135. Thus, it was not significant. Next, the mean RBS vs 90 mins (mmol) before is 5.35 while the standard deviation is 0.51. The mean RBS vs 90 mins (mmol) after is 5.60 while the standard deviation is 0.84. The mean difference is -0.24 while the 95% CI is between -0.72 and 0.24. The t-statistic is 1.05 while the degree of freedom is 19. The P-value of RBS vs 90 mins (mmol) is 0.306. Thus, it was not significant. Lastly, the mean 60 mins vs 90 mins (mmol) before is 5.75 while the standard deviation is 1.03. The mean 60 mins vs 90 mins (mmol) after is 5.60 while the standard deviation is 0.84. The mean difference is 0.15 while the 95% CI is between -0.09 and 0.40. The t-statistic is 1.31 while the degree of freedom is 19. The P-value of 60 mins vs 90 mins (mmol) is 0.206. Thus, it was not significance.

Table 8. Side effects of consumption of stevia and sucrose after 90 mins on third day.

Side effects	Sucrose n (%)	Stevia n (%)
Abdominal fullness/bloating	0 (0)	0 (0)
Nausea	2 (10)	1 (5)
Asthenia	0 (0)	0 (0)
Muscle tenderness	0 (0)	0 (0)
Headache	2 (10)	1 (5)
Dizziness	0 (0)	1 (5)

Interpretation:

Table 8 shows the incidence of side effects among participants in the intervention (Stevia) and control (Sucrose) group. There were 2 people who experienced nausea in sucrose group and only 1 person in stevia group experienced nausea. Next, there were 2 participants who experienced headache which was 10% of sucrose group and there was only 1 person from stevia group who experienced headache. Lastly, 1 participant from stevia group experienced dizziness. Other side effects like abdominal fullness/ bloating, muscle tenderness and asthenia were not experienced by the participants.

4. Discussion

A double blinded randomized controlled trial parallel design was conducted among healthy medical undergraduates of Melaka Manipal Medical College in Malaysia. The objective of this research is to determine the short-term effect of Stevia versus sucrose on their blood glucose response and blood pressure response.

The procedure of the trial comprised of the intervention group receiving 1g of Stevia powder mixed in 100ml of water for 3 consecutive days and the active control group

receiving 20g of sucrose mixed in 100ml of water for 3 consecutive days. Participants were of healthy BMI range (18.5-24.9 kgm^{-2}) and were requested to not consume alcohol or smoke cigarettes throughout the period of the trial. Baseline blood pressure was measured on the first day and compared with measurements taken on the last day; whereas baseline blood glucose was established before administration of the drinks on the 3rd day and compared with blood glucose tests taken at 60 minutes and 90 minutes respectively.

We found that in both groups, there is a decrease in mean systolic blood pressure after 3 days, with a higher magnitude of decrease in the participants who consumed Stevia (mean difference of 1.35 mmHg). As for diastolic blood pressure, the Stevia group showed a mean decrease of 2.85 mmHg while the sucrose group showed a mean increase of 0.7 mmHg. Despite the results being statistically insignificant, the reduction of systolic and diastolic blood pressures in the participants who consumed Stevia for a period of 3 days can be considered clinically significant. According to previous studies, the systolic and diastolic blood pressure of the stevioside group decreased significantly (systolic: 166.0±9.4–152.6±6.8mmHg; diastolic: 104.7±5.2–90.3±3.6mmHg, $P<0.05$) after three months and the effect remained throughout the whole year. [11]

The participants who consumed Stevia had a mean decrease of 1.8 mmHg in systolic blood pressure as well as a mean decrease of 2.85 mmHg in diastolic blood pressure. This finding suggests that short term consumption of Stevia has a higher effect on diastolic blood pressure compared to systolic blood pressure. As previously mentioned, the mean blood glucose levels increased in both 60 and 90 minute interval measurements when compared to the mean baseline blood glucose levels. However, the mean glucose level at 60 and 90 minute intervals are 5.75 mmol and 5.60 mmol respectively, indicating a 0.15 mmol reduction in glucose levels within those 30 minutes. The control group also showed a decrease from 60 to 90 minutes, albeit only a 0.06 mmol difference. The statistical test results showed no statistical significance in both blood pressure and blood glucose response. According to a previous study, Sucrose significantly increases the post prandial blood glucose while stevia 500 mg reduced the blood glucose after 30 min of consumption. Sucrose also produces higher glycemic response at min 30 when compared to stevia 1000 mg. [13] Another study also showed that the effect of consuming stevia products on blood glucose response varies, but the mean values of urine sodium and serum insulin level increased. The mean values of lipid profile, blood pressure and weight of subjects decreased but the results were found to be non-significant statistically. Thus, it can be concluded that stevia could be a potential hypoglycaemic effect provided the study is conducted on a large sample size for an extended period of time under controlled conditions. [15]

On the final day, participants were requested to answer a questionnaire regarding any side effects experienced throughout the period of the trial. There was only 1 complaint of nausea, dizziness and headache each from the intervention group, whereas there were 2 complaints each of nausea and headache from the active control group. As seen in a previous study, the tolerability of stevioside appeared satisfactory as only a few patients reported minor side-effects, such as dizziness or nausea after taking these stevioside capsules and adverse effects reported from the placebo group were similar. [11]

There were few limitations in this study. The main limitation was time, therefore the long-term effect of Stevia on blood glucose and blood pressure response could not be investigated. An inadequate sample size was also one of the limitations in this study due to the time limitation and exclusion of volunteers who were not within the normal BMI range. Compliance for finger pricking 3 times also contributed to the small sample size. Another limitation is the fact that only healthy medical undergraduates were selected to participate in this study, hence the result obtained cannot be used as a generalized standard for the general population. The final limitation of the study was that we could not control the oral intake of participants in both intervention and control group which would ultimately affect both the blood glucose and blood pressure response.

After conducting this study, we recommend that further studies be done to observe the long-term effects of Stevia consumption on blood glucose and blood pressure response. A larger sample size should be used to obtain a more significant result. We also recommend that the subsequent study be conducted in such a way that the blood glucose response is monitored on a daily basis at 3 separately fixed intervals (random blood glucose before consumption of intervention, 60 minutes and 90 minutes after consumption of intervention). A key addition to the methodology of the study would be regulating the consumption of food and drinks by the participants within the time frame of the study. This is to reduce the effect of external consumption of sugary items that may derange the findings. New researchers can also explore the effect of Stevia on other biochemical parameters such as lipid profile and renal profile. Lastly, a properly designed randomized controlled trial can be conducted to explore the effect of Stevia on blood glucose and blood pressure response in diabetic and hypertensive patients.

5. Conclusion

In conclusion, the research results suggest that short term

consumption of Stevia has a higher effect on diastolic blood pressure compared to systolic blood pressure. Although the statistical test results showed no statistical significance in blood glucose response, there was a reduction in postprandial blood glucose levels between 60 mins and 90 mins after consuming Stevia. Thus, it can be concluded that Stevia could be a potential hypoglycemic provided the study is conducted on a large sample size for an extended period of time under controlled conditions.

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