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Safety and influence of a novel powder form of coconut inflorescence sap on glycemic index and lipid profile

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ABSTRACT

Carbohydrates are the primary source of energy for human body. Carbohydrates increase resting muscle glycogen levels and help in delaying muscle fatigue. But, higher intake of high glycemic carbohydrates may lead to complications, if not balanced by physical activities. Our earlier studies have indicated that a proprietary powder preparation of coconut inflorescence sap (COCOZEN™, abbreviated as 'CSP' meaning 'coconut sap powder') contains relatively higher levels of micronutrients and possess antioxidant, anti-inflammatory, nephroprotective, hepatoprotective, gastroprotective and ergogenic activities. Thus, the present study was aimed to investigate the safety and efficacy of CSP (15 g/day for 90 days) on healthy and nonathletic subjects (n = 20). The study was performed in two phases. In the first phase, glycemic index (GI) was measured using glucose as a reference standard. In the second phase, CSP was supplemented at (15g × 1)/day dosage for 90 days and monitored the anthropometric parameters, adverse events, blood sugar levels (fasting and postprandial), blood pressure, and other routine hematological and biochemical parameters. It was observed that CSP possess a GI of 52.47 and is safe with an acceptable sensory attribute. It did not contribute any side effects or deviations in blood sugar or other hematological and biochemical parameters, except in Hb and lipid profile which showed significant ($p < 0.05$) enhancement.

1. Introduction

Numerous studies over the past four decades have demonstrated that carbohydrates are the primary macronutrients responsible for enhancing physical performance (Kanter, 2018). Athletes consume a high-carbohydrate diet to increase muscle glycogen which is important for sarcoplasmic Ca^{2+} release thereby affecting muscle contractility and fatigability (Hawley & Leckey, 2015; Helge, 2017; Ørtenblad, Westerblad, & Nielsen, 2013). The contribution of carbohydrates in the diet usually depends on the intensity, duration and type of physical activity (Gollnick & Matoba, 1984). However, high carbohydrate intake, especially with a higher GI (Glycemic index), has been shown to be associated with higher risk of blood sugar spikes which over time may lead to cardiovascular diseases, diabetes, and obesity (Morris & Zemel, 1999), if not balanced by physical activity.

The most popular form of carbohydrate delivery is energy drinks, often in combination with caffeine and ergogenic herbal extracts rich in caffeine, theobromine, and ephedrine (Alsunni, 2015; Sellami et al., 2018; Williams, 2006). Caffeine and these herbal extracts help to release adrenaline into the blood leading to the stimulation of lipolysis of fat tissues and skeletal muscle (Juliana & Rafaella-Maria, 2017). They also act on the central nervous system for neurotransmission, arousal and pain perception (Davis & Green, 2009; Juliana & Rafaella-Maria, 2017). But at high levels, such substances have shown to cause impairments in the fine motor activities and induce head ache, hypertension, heart palpitations, sleep disturbances, dehydration and gastrointestinal distress (Rosenbloom, Coleman, & Academy of Nutrition andDietetics, 2012). Unpleasant organoleptic properties and poor solubility constitute yet another set of issues of these substances when formulating food/-beverages to enhance physical performance (Bahrke, Morgan, & Stegner, 2009).

Coconut sugar, a brownish crystalline powder obtained by the evaporation of the unopened coconut inflorescence sap (*Cocos nucifera L*), is a traditional sweetener in Asian countries and is considered

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globally as a 'nutritious' and 'low glycemic' natural sweetener (Alexandru Grumezescu, 2019, pp. 339–360). Coconut sugar has been characterized to contain almost 80% of sucrose and 3–7% of glucose and fructose. To date, two independent reports states the GI of coconut sugar as 35 and 54, as compared with table sugar with a GI of 70 (Beck, 2018; Kulkarni, 2015). Though fresh inflorescence sap of coconut was reported to contain vitamins (B1, B3, B5, B7, B9, C) and minerals (Na, K, Ca, Mg, P, Fe, Zn), most of them were found to be eliminated during the process of evaporation to make coconut sugar (Jose et al., 2017). However, coconut sugar has been given the status of 'most sustainable sweetener in the world' by the United Nations' Food and Agriculture Organization, since coconut trees use minimal amounts of water as compared to sugarcane and can yield for more than 25 years (Sass, 2017).

Considering the thermal degradation of micronutrients during the traditional process of evaporation of the sap to produce coconut sugar, we had reported a low-temperature process to produce a micronutrient preserved coconut sugar (Jose et al., 2017; Ratheesh et al., 2017). The novel coconut sugar thus prepared (herein after referred to as 'CSP' meaning Coconut Sap Powder; patent pending and registered as COCOZEN™), has been shown to possess significant bioactivities including nephroprotective, hepatoprotective, antioxidant and anti-inflammatory effects (Jose et al., 2017, Jose, Mohanan, Sandhya, Asha, & Krishnakumar, 2018; Ratheesh et al., 2017). It has also been found to possess significant ergogenic activity upon both aerobic and anaerobic exercises (unpublished data), indicating the potential to be a natural agent to boost physical performance. However, no human studies are available on the safety of CSP. Thus, the present study was aimed at the investigation of safety of CSP following the supplementation at 15 g/day for 90 days in healthy human volunteers. The study was also designed to measure the GI of CSP following a standard protocol by WHO/FAO using glucose as the standard reference.

2. Materials and methods

2.1. Study material

A standardized form of micronutrients preserved coconut sugar (CSP) prepared from the unopened coconut inflorescence sap was provided by M/s Akay Flavours & Aromatics Pvt. Ltd, Cochin, India. It was kept in amber colored airtight containers made of high density polypropylene and stored under ambient conditions. A detailed analytical test report of CSP indicating the nutritional profile and safety parameters (heavy metals, microbial status, and pesticides), was received from the manufacturer.

2.2. Study population

Healthy male and female volunteers (n = 20) with age ranging from 18 to 55 years and BMI 18.5 to 27 (in kg/m^2) were recruited from the database of the contract research organization, Leads Clinical Research and Bio-services, Bangalore, India. The volunteers were not allowed to use any medication, supplements or vitamins during the study period. The detailed inclusion and exclusion criteria were listed in Table 1. All volunteers were informed about the nature and risks of the experimental procedures and their written informed consent was obtained prior to the study.

2.3. Study design

An open label design was adopted for the study and was conducted in two phases as shown in Fig. 1a. The study was conducted at M/s Sri Rama Hospital, Bangalore, India, under the supervision of a qualified medical doctor, in accordance with the clinical research guidelines of the Government of India following the protocol approved by the registered ethical committee (Reg. No. ECR/184/Indt/KA/2014) and was retrospectively registered in the clinical trial registry of India at http://ctri.nic.in (CTRI/2018/03/012389).

Table 1
Inclusion and exclusion criteria.

Criteria
Inclusion
1) Males and females in the age 18–55 years
2) Subject with body mass index 18.5–27 kg/m2 (both inclusive)
3) Must be willing to comply with all study requirements
4) Subject should agree to avoid any kind of herbal formulations in the study period
5) Must be able and willing to provide a written informed consent
Exclusion
1) Subject with history of cardiovascular, Type 2 Diabetes mellitus, pulmonary, hepatic and renal problems.
2) Subjects who are currently under any kind of long term medication.
3) Subjects with a known allergy to herbal products.
4) Chronic drinkers
5) Subject with a habit of smoking.
6) Pregnant or Lactating Women
7) Any condition that in opinion of the Investigator, does not justify the Subjects' participation in the study.

During screening (visit 1), the demographic characteristics of the subjects were recorded and anthropometric measurements including body weight, recumbent length and head circumference were measured (Table 2). All measurements were performed in duplicates and documented with an accuracy of 10 g for weight and 0.1 cm for length. Blood samples were collected for hematological and biochemical assessment and the values obtained from enrolled subjects were considered as the baseline values for the study.

In phase I (visit 2 to visit 5), the GI of CSP was measured and during phase II of the study (visit 6 and 7), safety and tolerance were estimated. A detailed protocol of the study is depicted in Fig. 1.

2.4. Determination of glycemic index (GI)

The measurement of GI was in accordance with WHO/FAO recommendations (Carbohydrates in human nu, 1998). In the typical protocol, the blood samples were collected during visit 2 for hematological and biochemical assessment and were considered as the baseline values for the study. The baseline blood glucose level was assessed as the average of two fasting blood sugar readings 11 ± 0.5 h apart in fasted subjects. After baseline blood collection on visit 2, the subjects were requested to consume the reference substance (50 g, anhydrous glucose dissolved in 250 mL of water). During visit 3, the subjects were requested to consume the test substance (62.5 g of CSP dissolved in 250 mL of water). In the subsequent visits (visit 4 and visit 5) the subjects were requested to consume reference (50 g, anhydrous glucose) in the same manner. The amount of CSP was equivalent to 50 g of digestible sugar. Following the consumption, the capillary blood samples were withdrawn at 15, 30, 45, 60, 90, and 120 min respectively and assayed for blood glucose levels as per Fig. 1b. Capillary blood was obtained by finger-prick and blood glucose levels were checked using ACCU-CHEK Active glucose strips and an ACCU-CHEK Active glucose meter (Roche Diagnostic GmbH, Mannheim, Germany). A graph was plotted with blood glucose concentration versus time and the area under the curve (AUC) was calculated. From the AUC, the post-prandial blood glucose (PPG) was also determined. The incremental AUC (iAUC) was calculated by ignoring the area under fasting blood glucose.

The GI was calculated as follows:

$$GI\ \ of\ \ the\ \ test\ \ food,\ \ GI = \frac{AUC\ \ of\ \ the\ \ test\ \ food}{Average\ \ AUC\ \ of\ \ the\ \ reference\ \ food} \times 100$$

2.5. Safety evaluation

The safety of CSP at the dosage of 15 g/day was evaluated by monitoring the hematological and biochemical parameters. Briefly, 15 g

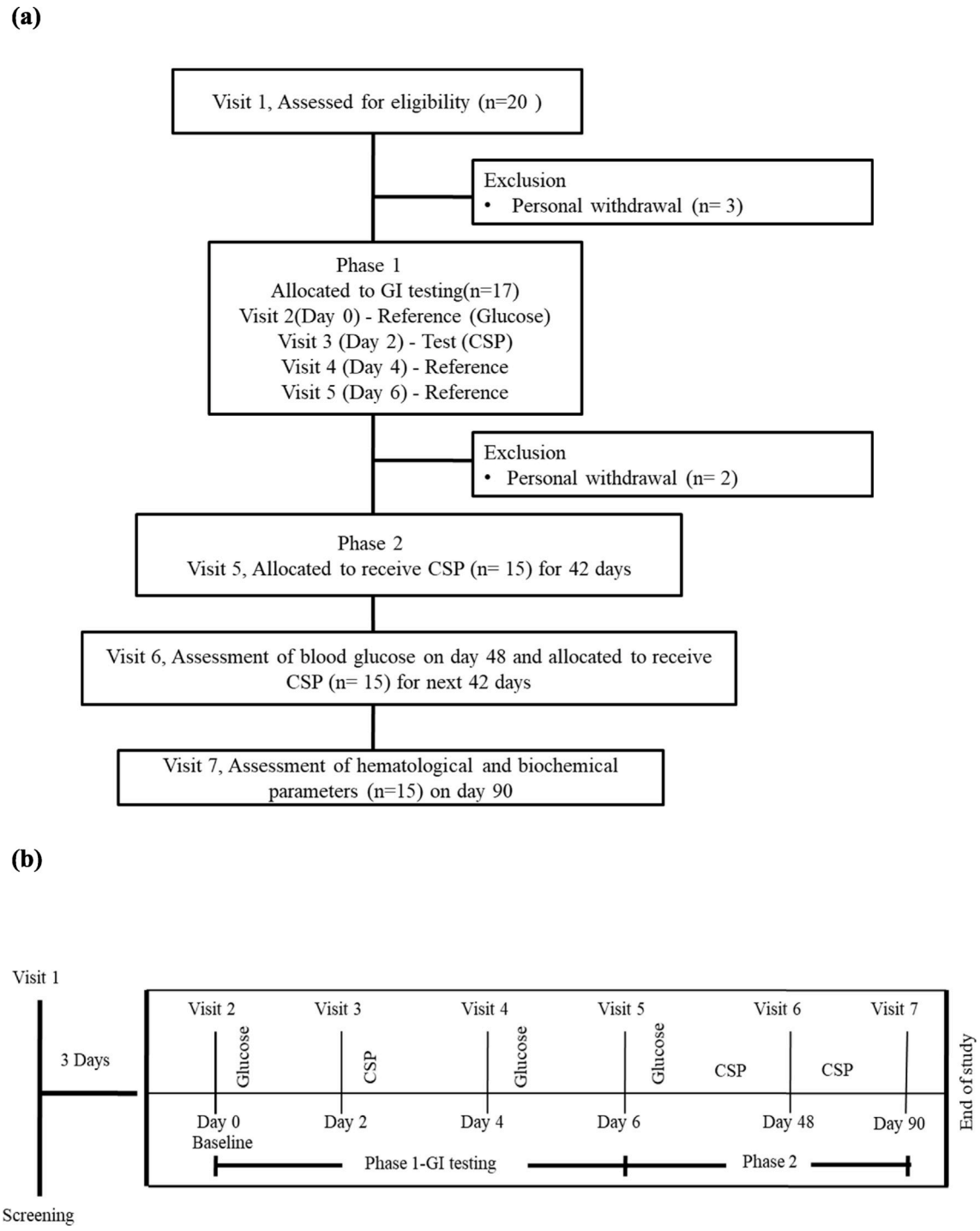

Fig. 1. (a). Consort diagram showing the study design, **(b)** Study plan with number of visits and allocation details of Glucose or CSP.

of CSP was dissolved in 250 mL water and the subjects were requested to drink the whole volume within 2 min on every day after breakfast for 90 days. On visit 6, the fasting and postprandial blood glucose levels were measured and on visit 7 (final visit), all the measurements (hematological, biochemical, and anthropometric) were performed. Data regarding any adverse reactions, clinical changes or discomfort were collected individually. The hematological parameters were assessed using an autoanalyzer (Meril Biochemistry analyzer, Eris diagnostics and Instruments, India). The biochemical parameters [serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum creatinine, fasting blood sugar (FBS), lipid profiling (total cholesterol, HDL cholesterol, LDL cholesterol, VLDL and triglycerides) and renal function markers] were analyzed with respective assay kits provided by M/s Agappe Diagnostics Pvt. Ltd Bangalore, India.

2.6. Statistical analysis

The sample size was designed to detect a difference in the postprandial glucose response with 95% confidence interval and 80% power. Statistical analyses were carried out using the statistical package SPSS (SPSS Inc. Chicago, IL, USA) version 25.0. The efficacy end points included the comparison of data at the baseline and at the end of the study. A within-group comparison was carried out using paired sample t-

Table 2
Demographic characteristics and anthropometric measures at initial screening.

Characteristics	Visit 1	Visit 2	Visit 3	Visit 4
Weight	79.23 ± 5.4	79.23 ± 5.4	78.94 ± 5.4	79.17 ± 5.3
BMI	23.88 ± 1.11	23.76 ± 1.09	23.52 ± 0.87	23.88 ± 1.11
Radical pulse (beats/min)	73.17 ± 7.55	73 ± 2.1	73 ± 1.6	74.35 ± 2.78
Systolic BP (mmHg)	122 ± 9.8	124 ± 5.8	123 ± 8.7	124.7 ± 6.16
Diastolic BP (mmHg)	79 ± 6.0	77 ± 4.8	78 ± 4.1	80 ± 4.06
Temperature (°F)	98.10 ± 0.33	98 ± 0.1	98 ± 0.3	98.20 ± 0.08

Data expressed as mean ± SD from 15 subjects. $p < 0.05$ is considered significant.

test and intergroup comparison was perfomed by independent sample t-test. The iAUC was calculated by comparing glucose levels measured at each time point with the initial value using a two-tailed t-test employing GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA). $p < 0.05$ was considered to be significant and the results were presented as mean ± SD.

3. Results

The test substance, CSP was a white crystalline powder obtained by the low-temperature evaporation of unopened coconut inflorescence sap and was found to contain various minerals and vitamins in relatively higher levels as compared to coconut sugar which showed only sodium and potassium (Jose et al., 2017, 2018). It was completely soluble in water and provided a naturally sweet taste with no after taste or difficulty to consume.

The present study recruited twenty healthy volunteers and fifteen subjects completed the study. Three volunteers withdrew during the GI testing and two during phase II studies due to personal reasons. Fifteen subjects received all the study treatment and completed all the seven visits as per the study protocol. The demographic and anthropometric measures showed no abnormal findings during the study (Table 2).

3.1. Glycemic response and postprandial blood glucose

The blood glucose response to both CSP and glucose were measured over the course of 2 h study period as shown in Fig. 2a. The incremental AUC (iAUC) reflected the changes in blood glucose over 2 h post-supplementation of CSP (Fig. 2b). The AUC of CSP was significantly ($p < 0.05$) lower when compared to that of glucose (2548 and 4552, respectively). The postprandial blood glucose levels were lower for CSP when compared to glucose, especially at 30 and 45 min post-consumption time points. Glycemic index of CSP was found to be 52.47. The mean blood glucose concentration at the end of the study was observed to be normal in CSP-subjects (Fig. 3a). The individual analysis also showed no significant difference in blood glucose concentrations during the study period indicating the absence of any hyper or hypoglycemic effects of CSP when supplemented at 15 g/day for 90 days (Fig. 3b).

3.2. Safety studies

The hematological parameters did not show significant deviations during the study period, except for the Hb level ($p = 0.016$). The lipid profile showed a significant difference upon supplementation of CSP. Biochemical analysis indicated a decrease for TG, LDL and VLDL cholesterol levels ($p = 0.011$, $p = 0.035$ and $p = 0.042$ respectively). The HDL cholesterol showed a significant increase ($p = 0.032$) from baseline to end of the study. Moreover, the fasting blood sugar level was also found to remain unchanged. All the other biochemical parameters including the liver function markers (SGOT, SGPT, and bilirubin) and renal function parameter (creatinine) also remained in the normal range during the study period (Table 3). The consumption of CSP at a dose of 15 g/day was also well-tolerated without any difficulties in consumption. It was well accepted and none of the subjects had any adverse effects or side effects such as nausea, vomiting, and dizziness.

4. Discussion

Carbohydrates, the main source of energy for the brain and body, are stored in the liver and skeletal muscle as glycogen which is an important substrate for energy metabolism during physical activity (Ivy, 1999). Carbohydrate supplementation has thus become the best strategy for the improvement of physical performance. However, repetitive spikes in blood sugar concentrations over time, if not balanced by physical activities, may predispose individuals to risk for metabolic disease (Morris & Zemel, 1999).

The coconut inflorescence sap, commonly known as 'Neera' in India,

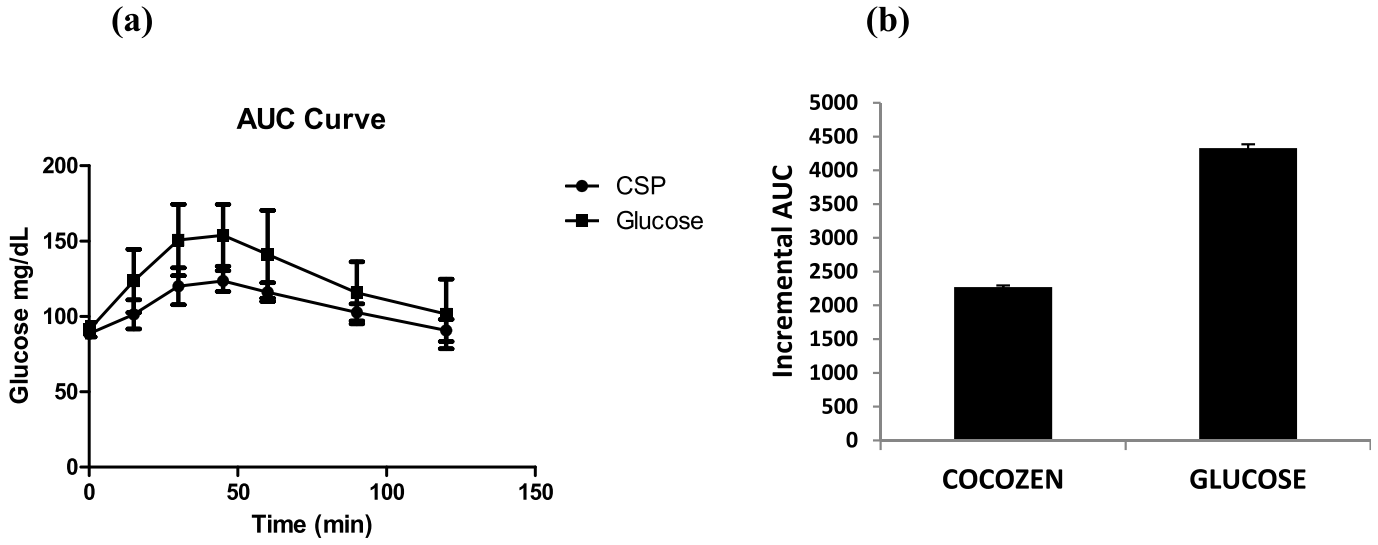

Fig. 2. (a). Postprandial blood glucose level following the oral administration of reference standard glucose and CSP over 2 h of post-administration time period (b) The incremental AUC (iAUC) of CSP and glucose. Data shown are mean ± SD. Statistical significance (*$p \leq 0.05$) was calculated by comparing blood glucose levels at each time point to the initial value using a two-tailed t-test in GraphPad Prism 5.0 software.

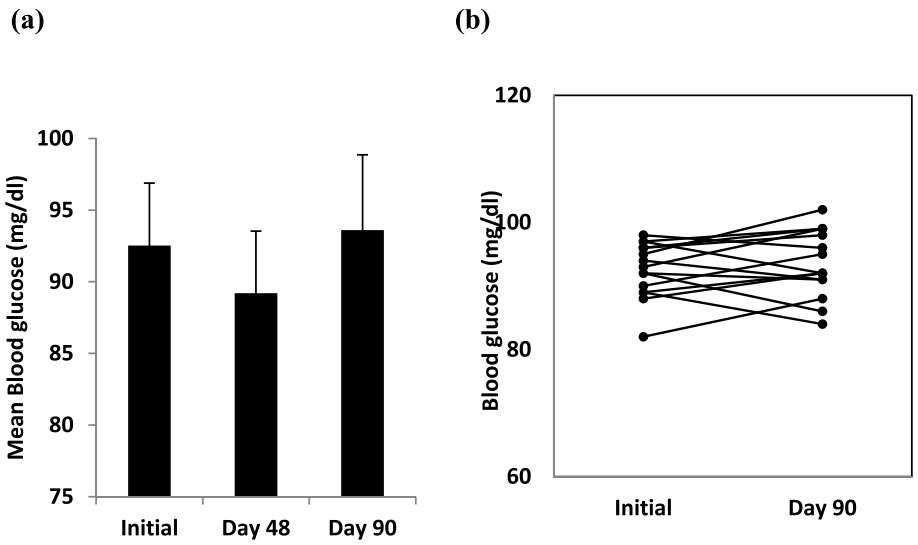

Fig. 3. (a). The mean blood glucose level of subjects on day 1, day 48 and day 90 following the consumption of CSP at 15 g/day (b) Individual fasting blood glucose variation on day 1 and day 90. Data shown are mean ± SD. Statistical significance ($p \leq 0.05$) was calculated by comparing glucose levels measured at each time point to the initial value using a two-tailed t-test in GraphPad Prism 5.0 software.

was found to contain various vitamins and minerals (Jose et al., 2017, 2018), but the rapid fermentation of the sap to ethyl alcohol limited its production, storage, and distribution as a natural nutritious drink. The fermented Neera is widely used in Asian countries as a traditional alcoholic beverage and is popular in India as 'Toddy'. Yet another way of the utilization of coconut inflorescence sap is by converting it to coconut sugar via evaporation. But, the evaporation process was found to cause degradation of valuable micronutrients and observed only sodium and potassium. CSP has been reported to contain about 81% of digestible carbohydrates as sucrose (73%), glucose (3%) and fructose (5%) along with vitamins B6 (336 ppm), B1 (304 ppm), B2 (278 ppm) and C (312 ppm) and minerals K (6600 ppm), Na (1378 ppm), Mg (220 ppm), P (580 ppm), Ca (240 ppm), Fe (40 ppm) and Zn (3 ppm) (Jose et al., 2017, 2018). Thus, CSP is a micronutrient-preserved coconut sugar which could also be considered as a powder form of Neera or Coconut inflorescence sap.

The present study was designed to estimate the GI of CSP in healthy subjects and also to investigate its effect on blood sugar, hypertension and other hematological and biochemical parameters of safety when consumed at 15 g/day for about 90 days. Glycemic index is a score to estimate the glycemic response after consuming a portion of food containing carbohydrates. Consumption of high GI foods may result in a rapid increase in blood glucose concentrations which in turn leads to a marked insulin response. Such persistent increase in blood glucose and insulin concentrations may lead to metabolic abnormalities such as diabetes, dyslipidemia, and obesity (Sieri et al., 2013). High GI diet-induced insulin sensitivity may also contribute to cardiovascular risk factors (Sacks et al., 2014). The present study indicated the GI of CSP as 52.4, which would be classified as a low GI food (Wolever, 2013). Table sugar or sucrose, on the other hand, is a high GI sugar which is estimated to have a GI of 70, as compared to the GI of 100 for the reference standard, glucose. It has been shown that low GI food are digested, absorbed and metabolized slowly in the body (Augustin et al., 2015) and maintains lower postprandial blood glucose concentrations which is an important factor in glycemic control (Monnier, Lapinski, & Colette, 2003; Woerle et al., 2007). The postprandial state can stimulate the reactive oxygen species production leading to oxidative stress which can trigger molecular mechanisms of pathogenesis related to hyperglycemia and inflammation which may further lead to endothelial dysfunctions (American Diabetes Association, 2018; Blaak et al., 2012; Ceriello et al., 2002; Node & Inoue, 2009; Zheng et al., 2010). Previously, we had reported the antioxidant effect of CSP to alleviate the oxidative stress associated with liver and kidney damage in animal models (Jose et al., 2017; Ratheesh et al., 2017). The present study demonstrated the better control of CSP over the post-prandial glucose hike as evident from the iAUC. The observed blood-glucose hike after CSP consumption was only 134.05 ± 8.7 mg/dL as compared to 155.80 ± 4.85 mg/dL of glucose. Moreover, the continuous consumption of CSP showed a significant decrease in FBS level, despite its high sugar content which implies the potential of CSP as a safe sugar with low GI.

Liver is the primary metabolic organ and a viable defense against environmental toxicants and metabolic toxins. The endogenous enzymes SGOT and SGPT are widely considered as liver function biomarkers, since they mainly leak into the extracellular space and enter the blood in conditions of hepatocellular injury (Ozer, Ratner, Shaw, Bailey, & Schomaker, 2008). We observed that the consumption of CSP at 15 g/day for 90 days did not show any significant change in liver markers (SGOT, SGPT, bilirubin), suggesting the absence of detrimental effects. The significant decrease observed in TG, LDL and VLDL levels along with the significant increase in HDL indicate a plausible effect of CSP on lipid metabolism. However, more detailed investigations are required in this respect. There was also observed a significant increase in Hb levels, which might, in turn, may increase the oxygen carrying capacity of the blood and hence may relieve conditions of hypoxemia associated with exhaustive exercises (Garvey et al., 2012).

5. Conclusion

In summary, consumption of CSP, a novel form of micronutrient-preserved coconut sugar prepared by a low-temperature evaporation process of unopened coconut inflorescence sap, was found to be well-tolerated at 15 g/day and did not cause any adverse effects or side effects during 90 days of the study period. It is a relatively low GI sugar with a GI of 52.47 and exhibits an attenuated response in postprandial blood glucose compared to glucose. It did not induce any significant changes in hematology and biochemical parameters associated with liver, heart, and kidney functions. However, there was a lipid-lowering effect and also an increase in Hb levels at the end of the study, which demands future investigations. The beneficial effect of CSP despite its high carbohydrate level (~80% w/w) might have attributed to its micronutrient load, which requires further investigations on the nature of existence and bonding of micronutrients in the carbohydrate matrix to better understand the mechanism of action of CSP.

Table 3
Hematological and Biochemical parameters of subjects.

Parameters	Inner group comparison based on paired sample t-test		Mean difference comparison of variables using independent sample t-test	
	Baseline	End of study	Mean difference	p-value
Hemoglobin (g/dL)	14.13 ± 1.49	14.37 ± 1.35	0.36 ± 0.19	0.016*
Platelet Count (thousand/μL)	279.26 ± 62.37	285.66 ± 53.18	10.93 ± 11.21	0.112
Total RBC count (million/μL)	4.88 ± 0.51	5.00 ± 0.42	0.20 ± 0.22	0.057
Total WBC count (thousand/μL)	8.06 ± 1.19	8.04 ± 1.01	0.24 ± 0.20	0.815
PCV (%)	42.06 ± 4.23	43.08 ± 3.74	0.80 ± 0.77	0.095
MCH (pg)	28.98 ± 1.50	28.69 ± 1.59	0.77 ± 0.75	0.302
MCHC (g/dL)	33.14 ± 0.51	33.28 ± 0.44	0.39 ± 0.28	0.245
MCV (fL)	87.33 ± 4.59	86.15 ± 4.79	2.27 ± 2.3	0.158
Neutrophils (%)	61.80 ± 6.13	62.93 ± 5.76	3.7 ± 1.9	0.305
Lymphocytes (%)	30.33 ± 5.60	29.00 ± 4.81	3.06 ± 2.46	0.193
Eosinophils (%)	2.0 ± 1.06	2.33 ± 0.81	1.0 ± 0.75	0.313
Monocytes (%)	5.66 ± 1.58	5.80 ± 1.85	1.06 ± 0.70	0.698
Basophils (%)	0.26 ± 0.45	0.13 ± 0.35	0.13 ± 0.35	0.164
SGOT (U/L)	22.66 ± 4.32	22.93 ± 4.21	3.4 ± 1.45	0.782
SGPT (U/L)	30.40 ± 6.93	30.00 ± 6.01	2.93 ± 1.87	0.668
Creatinine (mg/dL)	0.80 ± 0.15	5.95 ± 19.93	0.039 ± 0.024	0.334
Triglycerides (mg/dL)	114 ± 20.42	111.13 ± 20.88	5.4 ± 2.8	0.011*
Total Cholesterol (mg/dL)	172.02 ± 17.71	169.14 ± 19.40	4.4 ± 3.2	0.039
HDL Cholesterol (mg/dL)	44.13 ± 11.35	46.93 ± 10.15	4.13 ± 3.27	0.032*
LDL Cholesterol (mg/dL)	105.00 ± 15.87	101.13 ± 16.80	6.6 ± 3.7	0.035*
VLDL (mg/dL)	22.86 ± 4.08	22.22 ± 4.00	1.08 ± 0.65	0.042*
FBS (mg/dL)	92.53 ± 4.35	89.20 ± 4.32	4.66 ± 2.71	0.01*

Data expressed as mean ± SD from 15 subjects. RBC-Red blood cell; WBC- White blood cell; PCV-Packed cell volume; MCH-Mean corpuscular hemoglobin; MCHC- Mean corpuscular hemoglobin concentration; MCV-Mean corpuscular volume; SGOT- Serum glutamate oxaloacetate transaminase; SGPT- Serum glutamate pyruvate transaminase; HDL- High density lipoprotein; LDL- Low density lipoprotein; VLDL- Very low density lipoprotein; FBS- Fasting blood sugar.*$p < 0.05$ is considered significant.

Declaration of competing interest

The author(s) declared the following conflicts of interest with respect to the authorship and/or publication of the article. RM, FJ, and KIM are members of Akay Flavours & Aromatics Pvt Ltd, Cochin, India who manufacture COCOZEN™ as a dietary supplement ingredient. RM and BF are Professors in Biochemistry and Physiology and belong to non-profitable educational institutes in India and USA respectively, and have no conflict of interest.

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