Research article

Coconut (*Cocos nucifera* L.) inflorescence sap-derived sugar restores the glucose and lipid homeostasis in streptozotocin-induced diabetic Wistar rat model

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ABSTRACT

Introduction and Aim: Coconut palm sugar (CPS) is a functional food comprising unique phytonutrients such as polyphenolics, minerals, inulin, etc., and has a low glycemic index (GI). Based on its distinctive biochemical composition, it was hypothesized that CPS would provide a glucose homeostatic effect. We investigated the effects of CPS oral administration in Wistar rats with streptozotocin-induced diabetes.

Materials and Methods: Diabetic Wistar rats were administered with different doses of CPS (200,400 and 800 mg/Kg body weight) and standard gliclazide (5 mg/Kg b.w.) for 28 days. Biochemical estimations for fasting blood glucose, lipid profile and antioxidant status were performed.

Results: Treatment with CPS significantly ($P \leq 0.001$) decreased the plasma glucose levels at 120 min after glucose load. Serum blood glucose, hepatic enzymes (alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP)), total cholesterol (TC), total triglycerides (TG), and low-density lipoprotein (LDL) levels were also decreased. However, levels of total serum protein and high-density lipoprotein (HDL) increased in a significant manner. Pancreatic enzymatic antioxidant levels were restored, and lipid peroxidation was decreased by CPS.

Conclusion: CPS showed quite a few health benefits in diabetic rats by bringing back the glucose and lipid homeostasis to normal and yielded favorable outcomes in case of oxidative stress.

Keywords: Coconut sugar; diabetes; lipid; antioxidant; oxidative stress.

INTRODUCTION

The metabolic disease Diabetes Mellitus (DM) is characterized by impaired carbohydrates, lipids, and protein metabolisms causing chronic hyperglycemia with defective insulin secretion and insulin action or both (1). Traditionally, two types of DM are identified. Type-I is the deficiency of endogenous insulin caused due to the autoimmune induced destruction of pancreatic β-cells which secrete insulin, and type-II, by the inadequate response of the cellular receptors to the insulin, insulin resistance, and/or irregular insulin secretion attributed to factors such as obesity, genetic inheritance, sedentary lifestyle, and dietary features (2). In 2019, a total of 463 million people (9.3% of the global population) were estimated to have DM, which is stipulated to rise to 578 million by 2030. India, which ranks second next only to China in population, is home to 77 million diabetics, which is expected to increase to 134.2 million by 2045. Thus, in the absence of well-coordinated prevention or treatment programs, the world will witness a 25% increase in diabetic people by 2030. Consequently, there has been extensive research for anti-diabetic drugs worldwide, including the search for plant-derived products with hypoglycemic effects because plant products are readily available, exert few side effects, and are cost effective (3).

The coconut (*Cocos nucifera* L.) is an essential crop of the tropics, which is eulogized as the 'tree of life' because of its multitude of uses, including the products with medicinal properties. The products of coconut are used in many treatments, such as childhood diarrhea, gastroenteritis, and oral rehydration etc., (4). The coconut-derived oil possesses antimicrobial, antiviral, anti-inflammatory, and anti-ulcerogenic activities and improve the lipid profile by increasing the HDL-C fraction and reducing LDL-C fraction, promoting weight loss, and improving thyroid function.

The immature inflorescence of coconut possesses antidiabetic properties as it improves glucose homeostasis and antioxidant status in rats. Pharmacologically active constituents and volatiles have been extracted from the coconut inflorescence to treat polycystic ovarian disease in rat models. Similarly, coconut inflorescence sap (*neera* or *Kalparasa*®)-derived natural sugar or coconut palm sugar (CPS) is a product with untapped nutraceutical potential. The sap is rich in nutrients like vitamins, amino acids, and minerals such as iron, zinc, etc., It is also rich in polyphenols and antioxidants and may

provide health benefits (5). CPS was reported to have low Glycemic Index (GI) values of 35±4 and 42±4 (6). With the enormous nutrition potential already reported, we hypothesized that CPS would exert favorable glucose and lipid homeostasis and provide antioxidant protection in diabetic rat models. With this the study aimed to determine the effect of coconut inflorescence sap (*neera*)-derived sugar or CPS in treating or alleviating the imbalance of glucose and lipid homeostasis linked with experimentally induced DM in Wistar rat models.

MATERIALS AND METHODS

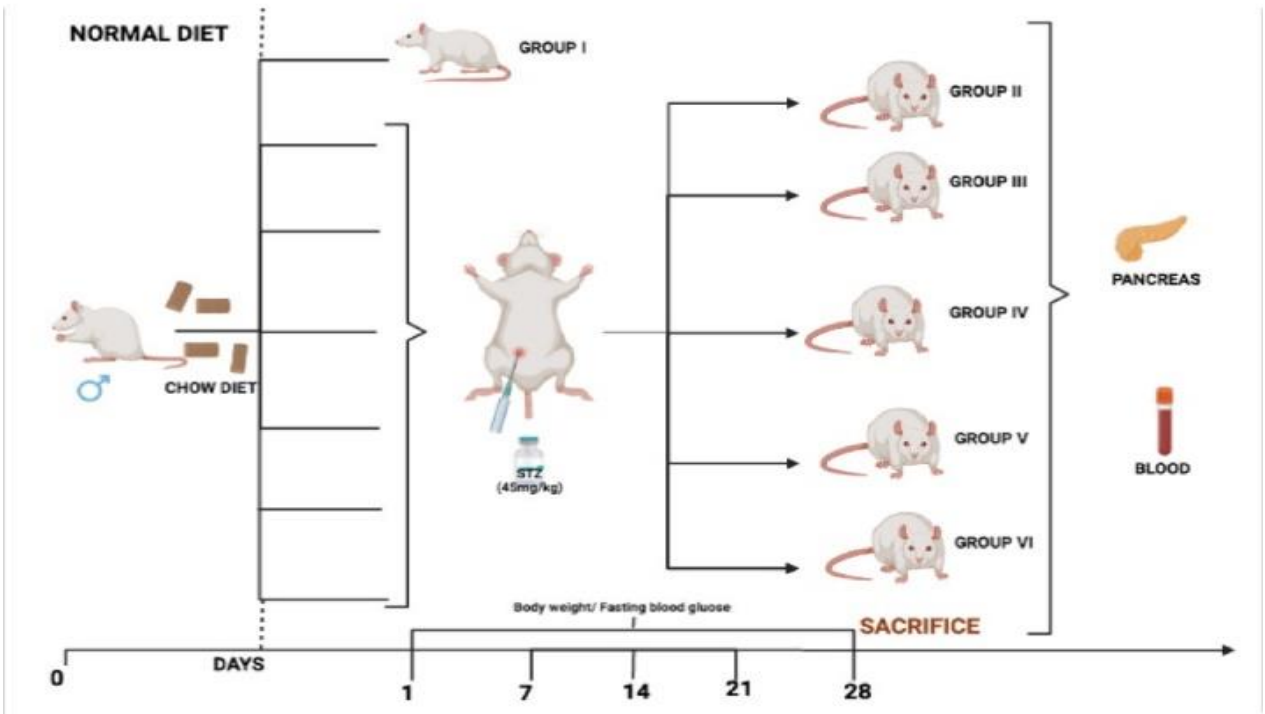
Test animals

The studies were conducted after the approval from the Institutional Animal Ethical Committee (Ref. KSHEMA/IAEC/09/2017). Thirty-six female Wistar rats (each weighing about 150–200g) were used in this study. The animals were maintained under standard conditions (temperature 22±2°C; humidity 55 ± 5%) with 12 hours of light and dark cycle and with standard laboratory pellet diets and water *ad libitum*.

Preparation of coconut palm sugar

Sugar from the coconut inflorescence sap was prepared following the protocol enumerated by Hebbar *et al.*, (7). Briefly, the freshly collected, unfermented coconut inflorescence sap (*neera* or *Kalparasa*®) was heated in an in-house developed double-walled cooker at 115ºC to evaporate the water content. The viscous sap is continuously heated and stirred until it formed crystals, followed by a sudden cooling to obtain sugary granules. Continuous stirring while cooling to avoid clump formation, followed by the sieving, ensured the formation of uniform-sized coconut palm sugar granules (Fig.1; 7).

Fig. 1: Process of preparation of coconut palm sugar (CPS) from the freshly collected coconut inflorescence sap (*Kalparasa*®) using an in-house developed double-jacketed cooker



Group I: Non-diabetic control (NDC); orally received distilled water.
Group II: Diabetic control (DC); Streptozotocin-induced diabetic group, which orally received distilled water.
Group III: DC+Standard; Streptozotocin-induced diabetic group, which orally received Gliclazide -5mg/Kg body weight (b.w) in an aqueous solution.
Group IV: Diabetic-CPS200; Streptozotocin-induced diabetic group, which orally received CPS-200mg/Kg b.w for 28 days.
Group V: Diabetic-CPS400; Streptozotocin-induced diabetic group, which orally received CPS-400mg/Kg b.w for 28 days.
Group VI: Diabetic-CPS800; Streptozotocin-induced diabetic group, which orally received CPS-800mg/Kg b.w for 28 days

Fig. 2: Diagrammatic representation of the experimental grouping

Induction of diabetes

Streptozotocin (45 mg/kg in 0.1 M citrate buffer, pH 4.5) was injected intraperitoneal to induce diabetes in Wistar rats. Fasting blood glucose (FBG) levels of the animals were measured. The rats with FBG levels of 250 mg/dL or above alone were further used in this study.

Experimental design

The rats were divided into six groups of six animals each, and their respective treatments as shown in Fig 2. Body weight was measured on day 1, 7, 14, 21, and 28. Weekly glycemia measurement and oral glucose tolerance test (OGTT) were performed using fresh tail capillary blood samples, One Touch Ultra blood glucose test strips, and a glucometer system (Lifescan Inc. Europe). The results were expressed as a time course of blood glucose measurements. Weekly glycemia was measured after overnight fasting of animals at appropriate Zeitgeber time (ZT) points considering the rats' circadian rhythm (8).

In the last week of the experiment, OGTT was performed under the same fasting conditions as the weekly glycemia assessment. Glucose was administered by oral gavage (2g/kg b.w./10 ml water) 60 mins after the last dose of distilled water, Gliclazide and CPS. Blood samples were collected at regular intervals of 0, 30, 60, 90, and 120 min after glucose loading and blood glucose levels were measured using One-Touch Ultra Easy Glucose Meter (Lifescan Inc. Europe).

On day 28, the rats were on overnight food privation and then euthanized. Blood collected in separate tubes for serum and plasma separation and stored at -80^{o}C until further analysis. The pancreas is dissected, washed and stored in phosphate buffer saline in 80^{o}C until further analysis.

Estimation of biochemical parameters

The levels of plasma glucose, AST, ALT, AP, urea, uric acid, creatinine, total cholesterol, TG, HDL-C, LDL-C were analyzed using a commercially available kit (Agappe diagnostics Ltd.). The Friedewald *et al.*, (9) formula was used to calculate serum LDL-C [LDL-C= TG-(HDL-C+TG/5)].

Biochemical estimation

The tissues were homogenized with a Teflon pestle at 600 rpm for 3min in an ice-cold 0.1 M phosphate buffer saline (pH 7.4) and then centrifuged at 3000 rpm for 10 min at 4^{o} C. The supernatant was used to estimate total protein (Agappe diagnostics Ltd.). Lipid peroxidation malondialdehyde (MDA) (10, 11), superoxide dismutase (SOD) (12), and glutathione reductase (13), were analyzed in the tissue homogenate.

Statistical analysis

Statistical data analysis was performed with GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). The data was presented as mean ± SD. p-value<0.05 was considered as statistically significant.

RESULTS

Coconut palm sugar (CPS) protects against body weight changes in streptozotocin-induced diabetic Wistar rats

Table 1 shows the body weight changes of Wistar rats treated with streptozotocin compared with the control rats. Streptozotocin treatment in rats caused a significant (P<0.001) decrease in body weight compared to the control animals. The decrease in body mass was severe after 14 days of the treatment, and the percentage change in the b.w. of diabetic rats (-44.83±4.21) after 28 days indicated the intense progression of diabetes. Nevertheless, administering CPS and the anti-diabetic drug gliclazide to the streptozotocin-treated rats reversed body mass decline compared to the diabetic control group (Table 1). After 28 days, 200 and 400 mg/kg b.w. of CPS was found to be more effective in restoring the test animals' body weight (b.w.) when administered. The percentage change in b.w. of animals following CPS 200 (-18.82 ± 4.77) and CPS400 (-20.53± 4.16) treatments of diabetic rats was comparable to that of standard care treatment (-17.24 ± 4.64). However, non-diabetic control animals showed high body mass and less percentage change in the b.w. compared to that of all the other treatments.

Table 1: Effect of coconut palm sugar on body weight in streptozotocin-induced diabetic Wistar rats

Treatments	Mean body weight of rats (g)					Percentage change
	Week 0	Week 1	Week 2	Week 3	Week 4	
Non-diabetic control (NDC)	206.07 ± 4.75	199.62±11.59	203.76±13.73	194.65±9.94	201.35±9.83	-2.29 ± 0.74
Diabetic control (DC)	200.08±14.36	175.63 ±8.93	152.85 ±7.35	120.43±16.02	110.38±7.36	-44.83±4.21*
DC+ Standard	205.7 ± 9.55	197.98 ± 8.19	184.26±3.27	178.66±13.08	170.23±15.31	-17.24 ± 4.64^{*,a}
DC+CPS200	199.13 ± 6.65	182.72 ±10.73	171.53 ±5.02	164.27±9.14	161.65±27.36	-18.82 ± 4.77^{*,a}
DC+CPS400	197.12±18.22	190.85 ± 6.99	178.12±9.25	162.35±13.33	156.63±7.74	-20.53± 4.16^{*,a}
DC+CPS800	216.9 ±8.98	191.45 ± 8.86	181.38±10.52	175.83±15.43	163.62±21.29	-24.56 ± 4.43^{*,a}

Values are given as Mean ±SD, n = 6**.** $^{***}P$<0.001 is considered statistically significant; non–diabetic control (NDC); diabetic control (DC) group

Table 2: Effect of coconut palm sugar on fasting blood glucose (FBG) levels in streptozotocin-induced diabetic Wistar rats

Treatments	Average fasting blood glucose levels (mg/dL)					Percentage change
	Week 0	Week1	Week2	Week3	Week4	
Non-diabetic control (NDC)	72.67 ± 4.18	70.67 ± 4.45	72.66 ± 6.18	71.82 ± 5.93	73.83 ± 4.40	-1.1.7 ± 0.25
Diabetic control (DC)	267.66 ±35.22	275.50 ± 9.07	286.54 ± 8.64	312.32 ± 9.59	318.34 ±11.65	+19.15± 5.90*
DC+Std. care	213.5 ± 10.67	203.16 ±8.72	178.66± 8.93	162.83± 19.76	151.83± 21.87	-28.88± 6.32^{*,a}
DC+CPS200	234.50 ± 14.26	230.83 ± 19.38	221.73 ±14.54	205.51± 4.97	170.83 ±14.23	-27.14± 5.24^{*,a}
DC+CPS400	228.83 ± 20.63	225.24 ± 15.81	212.16 ±17.45	185.76± 13.54	162.16 ± 8.79	-28.98± 4.43^{*,a}
DC+CPS800	221.17 ± 17.25	219.33 ± 12.12	208.82 ±21.13	173.57 ±12.67	157.12 ±11.37	-29.10± 4.16^{*,a}

Values are given as Mean ±SD, n = 6**.** $^{***}P$<0.001 is considered statistically significant.; non–diabetic control (NDC); diabetic control (DC) group.

CPS lowers fasting blood glucose levels (FBG) in diabetic rats

From the day 7 of the oral intervention with CPS the mean FBG levels showed a significant (P<0.001) decrease when compared to the diabetic control group (table 2). CPS was found to be more effective in reducing the FBG (-27.14± 5.24; -28.98± 4.43; and -29.10± 4.16) at respective doses of CPS200, CPS400 and CPS800, which is statistically comparable to the effect of standard drug gliclazide (-28.88± 6.32).

Oral glucose tolerance test

At 60 minutes following an oral glucose load, the blood glucose level in the non-diabetic control group peaked at 163.50 19.41 mg/dL, and then it steadily decreased to values that were close to normal (90.53 5.39 mg/dL). In the diabetic control group, the blood glucose level increased from the basal level (285.66 ± 27. 52 mg/dL to 376.66 ± 15.21 mg/dL) after 60 min and the hyperglycaemic condition prevailed over until 120 min (327.00 ± 19.12 mg/dL). On the other hand, CPS-fed animals showed basal glucose levels which were raised to (227.66 ± 14.56 to 259.16 ± 11.35 mg/dL) in 60 minutes following the administration of glucose (Fig. 3). It was followed by a significant decrease in blood glucose level at 120 min when compared to the diabetic rats (Fig. 3). CPS was found to be significantly (P<0.001) effective in reducing the OGTT at the dose of 400 mg/Kg b.w. (143.66 ± 12.69 mg/dL) and 800 mg/kg b.w (139.83 ± 21.82 mg/dL) at 120 min, but when compared to the glucose levels (129.83 ± 7.75) mg/dL of Gliclazide treated animals it was found to be less effective.

CPS improves serum lipid profile and reduces the blood glucose

The total cholesterol (94.17±7.38 mg/dL) and triglycerides (70.26±11.88 mg/dL) levels of the diabetic control rats significantly increased (P<0.001) compared to the non-diabetic control group. The rats under standard treatment of Gliclazide were able to restore to the normal cholesterol level; however the level of triglycerides showed a spike (59.36±11.12 mg/dL). Similarly, the animal groups administered with CPS showed a significant (P<0.001) decrease in total cholesterol and triglycerides levels, improved the HDLc levels (35.46± 8.55 mg/dL to 40.07±4.46 mg/dL) compared to control and standard treatment groups. (Table 3). Interestingly, CPS was more effective in reducing the mean blood glucose (^{a}P<0.05) levels in the animals when administered at all three doses (CPS 200, CPS 400, and CPS 800 representing 200, 400 and 800 mg/kg b.w., respectively) compared to the standard treatment of Gliclazide (5 mg/kg b.w.).

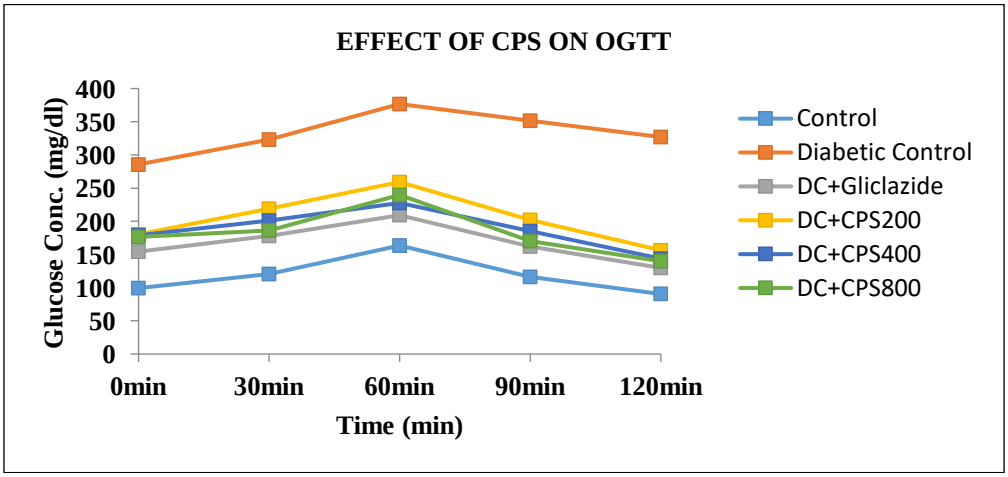


Fig. 3: Effect of coconut palm sugar on oral glucose tolerance test (OGTT) in streptozotocin - induced diabetic Wistar rats

Table 3: Effect of coconut palm sugar on serum lipid profile and mean blood glucose content in streptozotocin-induced diabetic Wistar rats

Parameters	Non-diabetic control (NDC)	Diabetic control (DC)	DC+ Standard care	DC+CPS-200	DC+CPS-400	DC+CPS-800
Total cholesterol (TC) (mg/dL)	60.10±10.02	94.17±7.38*	68.65±8.01*	64.52±10.50*	60.38±5.43*	67.03±12.66*
Triglycerides (TG) (mg/dL)	24.83±4.06	70.26±11.88*	39.36±11.12[a]	32.51±6.10[a]	35.55±16.73[a]	54.28±25.57
HDLc (mg/dL)	46.58±2.24	22.53±1.70*	43.96±2.50*	36.72±8.28*	40.07±4.46*	35.46±8.55[a]
LDLc (mg/dL)	12.02±7.56	57.59±9.55*	12.88±9.11*	21.23±6.52*	13.19±6.74*	14.04±8.34*
Mean blood glucose (mg/dL)	96.54±11.10	289.38±92.20*	162.49±26.81[a]	155.35±39.78[a]	153.36±72.85[a]	158.60±33.06[a]

Values are given as Mean ±SD, n = 6. ***P<0.001 is considered statistically significant; non–diabetic control (NDC); diabetic control (DC) group

Table 4: Effect of coconut palm sugar on hepatic marker enzymes in streptozotocin-induced diabetic Wistar rats. Activities of serum AST, alanine aminotransferase ALT, and alkaline phosphatase AP are presented

Enzymes (U/L)	Non-diabetic control (NDC)	Diabetic control (DC)	DC+ Standard care	DC+CPS-200	DC+CPS-400	DC+CPS-800
Aspartate amino-transferase (AST)	61.79±17.35	127.26±26.54*	86.56±12.13[a]	79.85±14.87[a]	74.96±9.94[a]	82.12±12.20[a]
Alanine amino-transferase (ALT)	25.54±12.97	98.29±23.02*	58.02±12.55[a]	57.14±11.76[a]	53.4±32.47[a]	60.45±19.06[a]
Alkaline phosphatase (AP)	93.36±7.06	172.41±17.18*	117.95±18.38[a]	123.68±23.01[a]	120.33±15.42[a]	127.90±21.09[a]

Values are given as Mean ±SD, n = 6. ***P<0.001 is considered statistically significant; non–diabetic control (NDC); diabetic control (DC) group

Table 5: Effect of coconut palm sugar on plasma metabolites, MDA, and activity of enzymatic antioxidants (SOD and GR) in streptozotocin-induced diabetic Wistar rats

Parameters	Non-diabetic control (NDC)	Diabetic control (DC)	DC+ Standard care	DC+CPS-200	DC+CPS-400	DC+CPS-800
Urea (mg/dL)	38.67±9.12	63.80±8.99*	42.05±13.64 [a]	48.41±19.99 [a]	45.54±10.86 [a]	49.76±10.15 [a]
Uric acid (mg/dL)	2.58±0.43	5.11± 0.66*	3.17± 0.86 [a]	3.32±1.48 [a]	3.03± 1.43 [a]	3.20 ±1.44 [a]
Creatinine (mg/dL)	0.65± 0.22	2.23± 0.56*	1.42±0.63 [a]	1.21± 0.62 [a]	1.03 ± 0.60 [a]	1.07 ± 0.67 [a]
Total protein (g/dL)	8.19±0.83	4.15±1.35*	7.65± 1.28[a]	6.05± 1.05 [a]	6.36± 1.04 [a]	6.26± 0.87 [a]
Malondialdehyde MDA (µM/g tissue)	0.24± 0.08	0.46±0.06*	0.29± 0.09[a]	0.31± 0.09[a]	0.32± 0.07[a]	0.38± 0.06[a]
Superoxide dis-mutase (U/ mg of protein)	3.83±0.67	1.43±0.39*	3.06± 0.86[a]	3.78± 0.43[a]	3.35± 0.73[a]	3.34± 0.37[a]
Glutathione reductase (U/mg of protein)	1.74 ±0.22	0.67±0.13*	1.43±0.12 [a]	1.39± 0.35 [a]	1.27± 0.19 [a]	1.22±0.21 [a]

Values are given as Mean ±SD, n = 6. ***P<0.001 is considered statistically significant; non–diabetic control (NDC); diabetic control (DC) group.

CPS modulates serum hepatic enzyme markers

The hepatic marker enzyme analysis revealed a significant (P<0.001) upward change in the activities of AST, ALT, and AP in the diabetic control group of animals. However, animal groups under CPS administration (CPS 200, CPS 400, and CPS 800) showed a marked reduction in these liver marker enzymes comparable to the levels found in standard control (Table 4). Even among the CPS-administered animals, it was found to be effective in reducing the liver enzyme levels at the dose of 400 mg/kg b.w. since further increment of CPS (800 mg/kg BW) resulted in a slight increase in these enzyme activities (Table 4).

CPS and its effect on plasma metabolites and antioxidants

Animal groups treated with CPS showed a decrease in plasma metabolites such as uric acid, urea, and creatinine metabolites (Table 6) compared to the diabetic control group. In particular, CPS treatment of 400 and 800 mg/kg BW ensured a significant decrease in uric acid ($p<0.05$). However, CPS, when administered to diabetic rats at all three doses (200-800 mg/Kg b.w.) showed a significant decrease in creatinine content ($P<0.05$). Interestingly, CPS was more effective in reducing the uric acid and creatinine levels at all three doses investigated compared to the standard treatment of Gliclazide (5 mg/Kg b.w.). On the contrary, total protein content significantly increased ($P<0.05$), albeit less than the levels of animals under standard care of Gliclazide, when compared to the diabetic control group.

There was a significant ($P<0.05$) decrease in the MDA level in Gliclazide (0.29± 0.09 µM/g) and CPS-treated groups (0.31 ± 0.09 µM/g to 0.38 ± 0.06 µM/g) when compared to the diabetic control group (0.46 ± 0.06 µM/g). The coconut palm sugar was found to be more effective in decreasing the MDA level at the dose of 200 and 400 mg/kg BW, but when compared to the Gliclazide, it was found to be less effective in reducing the MDA content (Table 6.). The pancreatic enzymatic antioxidants, both SOD (1.43±0.39) and GR (0.67±0.13) showed a significant diminution in diabetic control rats ($P<0.001$) since the activities of normal control, respectively, were 3.83±0.67 U and 1.74 ±0.22 U. However, treatment of diabetic animals with CPS exhibited a significant ($P<0.05$) restoration of enzyme activities compared with the diabetic control animals (Table 5).

DISCUSSION

Diabetes mellitus (DM) is a metabolic disease affecting around 450 million people worldwide (14). The global drug market for the treatment of DM was valued at USD 48,753 million in 2018, estimated to reach USD 78,262 million by 2026. Hence, there is a need to search for and develop a plant-derived product with anti-diabetic potential. Coconut products such as virgin coconut oil and CPS have promising therapeutic potential (15). Antihyperglycemic activity of coconut inflorescence and dietary coconut kernel protein was established (16). Palm sugar has been used as a traditional sweetener for years in Asia and has gained global attention due to its attributes, such as minimal processing of natural and healthy alternatives for widely consumed cane sugar. Also, CPS has been shown to exhibit low GI values of 35±4 and 42±4 (6). Hence, this study was designed to elucidate the biochemical effects of oral administration of CPS in streptozotocin-induced diabetic rat models.

Diabetic rats orally administered with CPS showed a significant improvement in body mass in a dose-dependent manner. The treatments *viz*., CPS200 and CPS400 effectively reduce weight loss compared to the diabetic control group. The mechanisms by which CPS improves body mass are unclear. CPS contains more fructose (3.7mg/100g) than sucrose and glucose. Dietary fructose is known to activate glucokinase, a key enzyme involved in the intracellular metabolism of glucose, which in turn exerts a positive influence on glucose metabolism and thus improves the BW of diabetic rats (17). Diabetic rats administered with CPS400 and CPS800 treatments showed significantly reduced FBG levels on the 28th day.

Similarly, CPS doses of CPS400 and CPS800 were found to be effective in OGTT-a measure of insulin function or the degree of peripheral glucose utilization. Thus, overall, CPS (CPS400 and CPS800) exhibited an increased glucose utilization indicating the improved glucose homeostasis in the treated group. The main sugar constituent of CPS is sucrose, similar to cane sugar. Nevertheless, unlike cane sugar, CPS exhibited a low starch digestion rate and low GI values due to its characteristic phytonutrients like inulin, mineral composition, and natural minimally processed form (6, 18). Although CPS is devoid of dietary fiber, it has a linear fructan fraction called inulin whose fermentation products have a profound role in low glycemic index and protection against coronary heart disease (19). Further, inulin-based modulation of anti-inflammatory biomarkers to treat type-II diabetes in women suggests the importance of linear fructans and dietary fiber in managing DM.

DM is a systemic metabolic disorder that affects glucose metabolism and causes dyslipidemia (20). The observation of high serum cholesterol (TC) and triglycerides (TG) in diabetic rats could be linked to insufficient insulin, defective cholesterol metabolism, or mobilization of fatty acids from adipocytes by lipolysis (21). Administration of CPS restored the levels of TC, TG, LDL, and HDL compared to that of non-diabetic control. The homeotic effect of CPS was dose dependent as CPS of 400 mg/Kg b.w. was effective. Hence, dose-dependent administration of CPS could help reduce or prevent macrovascular complications in diabetes. The beneficial effect of CPS in improving the serum lipid parameters could be due to its impact on lowering the atherogenic index (total cholesterol to HDLc ratio) and may improve the cholesterol metabolism by enhancing the HDL cholesterol ratio as observed in anti-diabetic effects of rice and coconut milk-based herbal porridges (22).

High glucose conditions may inactivate the antioxidant enzymes due to their glycation, causing induced oxidative stress (23). However, CPS

treatment of diabetic rats restored the activity of SOD and GR compared to that of standard drug care, suggesting CPS's efficacy in attenuating oxidative stress in diabetic conditions. Furthermore, phenolic compounds of plant origin have free radical scavenging properties and reduce DM-associated oxidative stress (24). The phenolic fractions of the CPS could have effectively reduced the antioxidant damage in diabetic rats and restored the MDA content significantly. Further, phytophenols can interact with starch, increase the ratio of resistant starch (25), and inhibit the bio-catalysis of starch digestion enzymes (26) with potential implications for reducing the post-prandial glucose levels. Recent evidence based on mechanistic insights has divulged that the starch-polyphenol matrix could be effectively utilized to improve the quality of starch in food (27). Thus, considering the phenolic content of freshly collected coconut inflorescence sap (4.8-5.4 mg/100 g) with an antioxidant capacity of 0.299 to 0.355 mM Trolox equivalent (7), CPS derived from it could be a potential candidate for the development of functional food with nutraceutical value.

CONCLUSION

In conclusion, our investigation suggests that CPS treatment accords multiple beneficial effects, namely preventing hyperglycemia, restoring serum lipid parameters, and metabolites to near normal, and ameliorating the oxidative stress on diabetic rats. Various compounds, such as polyphenols, inulin, and high mineral content in CPS, may act as antioxidants modulating glycemia and improving lipid homeostasis. Nonetheless, further human clinical studies are warranted to decipher CPS's actual mechanism of action in providing hypoglycemic conditions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Albert, K.G., Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation 13. Diabet Med. 1998;15:539-553.
2. Tripathi, B. K., Srivastava, A.K. Diabetes mellitus: complications and therapeutics. Med Sci Monit. 2006;12:130-147.
3. Venkateswaran, S., Pari, L. Effect of *Coccinia indica* leaves on antioxidant status in streptozotocin-induced diabetic rats. Journal of Ethnopharmacology. 2003;84:163-168.
4. Saat, M., Singh, R., Sirisinghe, R.G.,Nawawi, M. Rehydration after exercise with fresh young coconut water, carbohydrate-electrolyte beverage, and plain water. Journal of Physiological Anthropology and Applied Human Science 2002;21(2):93-104.
5. Van Immerseel, F., De Buck, J., Boyen, F., Bohez, L., Pasmans., Volf, J., *et al.*, Medium-chain fatty acids decrease colonization and invasion through *hil*A suppression shortly after infection of chickens with *Salmonella enterica* serovar Enteritidis. Appl. Environ. Microbiol. 2004;70(6):3582-3587.
6. Trinidad, T.P., Mallillin, A.C., Sagum, R.S., Encabo, R.R. Glycemic index of commonly consumed carbohydrate foods in the Philippines. Journal of Functional Foods. 2010;2:271-274.
7. Hebbar, K.B., Arivalagan, M., Manikantan, M.R., Mathew, A.C., Thamban, C., *et al.*, Coconut inflorescence sap and its value addition as sugar–collection techniques, yield, properties, and market perspective. Current Sci. 2015;109(8):1411-1417.
8. Bowe, J.E., Franklin, Z.J., Hauge-Evans, A.C., King, A.J., Persaud, S.J., Jones P.M. Metabolic phenotyping guidelines: Assessing glucose homeostasis in rodent models. Journal of Endocrinology. 2014; 222(3):G13-25.
9. Friedewald, W.T., Levy, R.I., Fredrickson, D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry. 1972; 18(6):499-502.
10. Buege, J.A., Aust, S.D. Microsomal lipid peroxidation. Methods Enzymol. 1978; 52:302-310.
11. Jose, M., Varghese, V.I., Jayakar, V., Lokapur, V., Srinivasa, K., Shantaram, M. Analysis of oxidative stress induced by different tobacco samples and the protective effect by certain plant extracts. World Journal of Pharmaceutical Research. 2018;7(15):734-769.
12. Beauchamp, C., Fridovich, I. Superoxide dismutase: improved assays and an assay applicable to acrylamide gels. Analytical Biochemistry 1971; 44(1):276-287.
13. Goldberg, D.M., Spooner, R.J. Assay of glutathione reductase. In Methods of Enzymatic Analysis; Bergmeyen, HV, Ed.; Verlag Chemie: Weinheim, Germany, 1983; 258-265.
14. Sumathi, K., Dilliraj, G., Chaganti, S., Lalitha, S. Use of malondialdehyde (MDA) as a screening tool for vestibulopathy in Type 2 diabetes mellitus. Biomedicine. 2021 Oct 29;41(3):576-579.
15. Ramesh, S.V., Krishnan, V., Praveen, S., Hebbar, K.B. Coconut oil–scientific facts. Current Sci. 2019; 117 (4):564-565
16. Salil, G., Nithya, R., Nevin, K.G., Rajamohan, T. Dietary coconut kernel protein beneficially modulates NFκB and RAGE expression in streptozotocin induced diabetes in rats. Journal of Food Science and Technology. 2014; 51(9): 2141-2147.
17. Watford, M. Small amounts of dietary fructose dramatically increase hepatic glucose uptake through a novel mechanism of glucokinase activation. Nutrition reviews. 2002; 60(8): 253.
18. Srikaeo, K., Thongta, R. Effects of sugarcane, palm sugar, coconut sugar and sorbitol on starch digestibility and physicochemical properties of wheat-based foods. International Food Research Journal. 2015; 22(3): 923-929.
19. Trinidad, T.P., Mallillin, A.C., Avena, E.M., Rodriguez, G.R., Borlagdan, M.S., Cid, BBK., *et al.*, Coconut sap sugar and syrup: a promising functional food/ingredient. Acta Manilana. 2015;63: 25-32.
20. Parhofer, K.G. Interaction between glucose and lipid metabolism: More than diabetic dyslipidemia. Diabetes and Metabolism – Journal. 2015;39(5): 353-362.
21. Goldberg, I. J. Diabetic dyslipidemia: causes and consequences. The Journal of Clinical Endocrinology & Metabolism. 2001;86 (3): 965-971.
22. Pari, L., Latha, M. Antihyperlipidemic effect of *Scoparia dulcis* (sweet broomweed) in streptozotocin diabetic rats. J Med Food 2006; 9(1): 102-107.

23. Ling, P.R., Mueller, C., Smith, R.J., Bistrian, B.R. Hyperglycemia induced by glucose infusion causes hepatic oxidative stress and systemic inflammation, but not STAT3 or MAP kinase activation in liver in rats. Metab Clin Exp. 2003; 52:868-874
24. Marina, A.M., Che Man, Y.B., Nazimah, S.A.H., Amin, I. Antioxidant capacity and phenolic acids of virgin coconut oil. Int. Journal of Food Sciences & Nutrition 2009; 60:114-123.
25. Guzar, I., Ragaee, S., Seetharaman, K. Mechanism of hydrolysis of native and cooked starches from different botanical sources in the presence of tea extracts. J Food Sci.2012; 77: C1192-C1196.
26. Coe, S.A., Clegg, M., Armengol, M., Ryan, L. The polyphenol-rich baobab fruit (*Adansonia digitata* L.) reduces starch digestion and glycemic response in humans. Nutrition Res. 2013; 33(11): 888-896.
27. Chen, N., Gao, H. X., He, Q., Yu, Z. L., Zeng, W.C. Interaction, and action mechanism of starch with different phenolic compounds. International Journal of Food Sciences and Nutrition 2020;1-12.