



Original article

Coconut products alleviate hyperglycaemic, hyperlipidemic and nephropathy indices in streptozotocin-induced diabetic wistar rats

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ARTICLE INFO

Article history:

Received 18 May 2021

Revised 21 June 2021

Accepted 21 June 2021

Available online 25 June 2021

Keywords:

Coconut products
Virgin coconut oil
Filtered coconut oil
Coconut milk
Inflammation
Diabetes
Kidney

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic and one of the most common metabolic diseases affecting large proportion of world population. Diabetes-induced changes in lipid and renal parameters are major risk factors contributing to diabetic complications such as diabetic nephropathy and cardiovascular diseases. Due to adverse effects associated with pharmacological intervention in the T2DM treatment, there is an increased interest in the research focussing on identifying novel plant based therapeutic agents. Here we report the effects of various coconut products on diabetic, lipid and renal parameters in streptozotocin (STZ)-induced diabetic rat model. Diabetic rats demonstrated a significant increase in serum glucose, and glycated haemoglobin levels (HbA1c). Lipid parameters including triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-cholesterol) and very low density lipoprotein cholesterol (VLDL-cholesterol) were found to be significantly increased, while high density lipoprotein cholesterol (HDL-cholesterol) was significantly declined in diabetic rats. Diabetic rats also displayed increased serum and kidney creatinine, urea, and total protein levels and increased urine glucose, urea, albumin and creatinine levels. Contrastingly, treatment with virgin and filtered coconut oils, coconut water and coconut milk resulted in a significant reversal in the levels of above studied parameters in diabetic rats. Further, these coconut products markedly prevented diabetes induced histopathological changes in kidney tissue. Collectively, the data demonstrate the antidiabetic, hypolipidemic and renal protective properties of various coconut products and underscore the importance of regular consumption of plant based medicinal products in the treatment of T2DM and its complications.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is among the most common disorders affecting about 9% of world population (Hosseini et al., 2017). T2DM is characterised by chronically increased glucose levels. Under normal physiological conditions, glucose levels are regulated by insulin levels, however this regulation is derailed in T2DM resulting from reduced insulin secretion or resistance to insulin (Vazquez-Jimenez et al 2021). Besides, dysregulated glucose and insulin levels, there are increased glycated haemoglobin levels in red blood cells (RBCs) of persons with T2DM due to

increased circulating glucose levels (González-Ortiz et al., 2012). Lipoprotein abnormalities are also commonly found in T2DM subjects where there is a predominance of LDL-VLDL, total-cholesterol and triglyceride levels and reduced HDL-cholesterol (Krauss, 2004). Due to the association of T2DM with abnormal lipid profile, the diabetic subjects are prone to develop cardiovascular disease (Athinarayanan et al., 2021). Impaired hepatic clearance of VLDL and increased hepatic triglyceride-rich VLDL levels appears to play crucial role in pathophysiology of dyslipidemia (Krauss, 2004). Intravascular processing of larger VLDL precursors generate small dense LDL, thereby further increasing the risk of dyslipidemia. Typically, in T2DM, depleted plasma HDL levels results in reduction in the HDL(2b) subspecies and concomitant increase in the absolute or relative increases in smaller denser HDL(3b) and HDL(3c) (Smit et al., 2020). Diabetic nephropathy is a major T2DM complication and is secondary to T2DM. A number of studies have described the negative effects of T2DM on kidney function and structure. Urea, creatinine and total protein levels have been reported to be increased in T2DM (Guo et al 2021). Diabetic status has also been shown to affect electrolytes including sodium,

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Peer review under responsibility of King Saud University.



potassium and bicarbonates (Meena et al., 2020). To reflect the effect of T2DM on kidney function, there are changes in urine levels of kidney functional parameters such urea, albumin and creatinine. These parameters have been shown to be increased subjects with T2DM (Nakhoul et al 2020). Histological studies have reported the T2DM not only derail the kidney function but also damage kidney tissue (Demircan et al 2020).

There is an increased interest in the research related to therapeutic application of medicinal plants such as coconut in the treatment of T2DM and its complications (Pascual Fuster et al 2021). Coconut milk have been shown to contain many beneficial components including phenolic and fatty acid compounds, antioxidants, sugars, proteins, and carbohydrates (Karunasiri et al 2020). Similar to coconut milk, coconut oil contains phenolic and fatty acid compounds, phospholipids, tocopherols, sterols and volatile compounds (Deen et al 2021). Accordingly, coconut products are shown to possess anti-inflammatory, anti-oxidant, antidiabetes, bactericidal, antifungal, and antiviral activities (Rinaldi et al., 2009, Jose et al., 2014, Silva et al., 2013). Coconut and its various products are well-studied for their therapeutic applications in various disease conditions including in T2DM. These products are shown to improve insulin sensitivity and lower insulin levels thereby lowering the risk of developing T2DM (Korrapati et al 2019, Tham et al 2020, Bhagya et al 2012). However, comprehensive analysis on the effects of various coconut products on diabetic parameters and the parameters related to diabetic complications has not been carried out in an animal model. Accordingly, here we examined the effects of virgin and filtered coconut oils, coconut water and coconut milk on diabetic parameters, lipid profile, electrolytes, renal and urinary parameters in STZ-induced diabetic rat model. We also evaluated the histopathological changes in diabetic rat kidney tissue.

2. Materials and methods

2.1. Materials

The STZ was bought from AdooQ BioScience (AdooQ BioScience, LLC, Barranca Parkway, Suite 250, Irvine, CA, USA). Kits for measuring glucose, insulin, HbA1c, cholesterol, triglycerides, HDL, LDL, VLDL, urea, creatinine were obtained from MyBioSource (MyBioSource, Inc., San Diego, CA 92195-3308, USA). Total protein estimation kit was obtained from Abnova (Abnova, Jhouzih St. Neihu District, Taipei City, Taiwan) and albumin estimation kit was purchased from Abcam (Abcam, Cambridge, CB2 0AX, UK). Sodium and potassium were measured using the kits from (BioVision, Inc., Milpitas, California, USA) and Elabscience (Elabscience, Inc., Houston, Texas, USA) respectively. Bicarbonate (Collaborative laboratory services, L.L.C, 1005 Pennsylvania suit102, Ottumwa, IA 52501). Metformin was procured from Merc (Santé, France). Virgin coconut oil was procured from Nutiva (Nutiva Inc., Richmond, CA 94804, USA), Double filtered pure white coconut oil was obtained from Khong Guan oil refinery (Khong Guan Vegetable Oil Refinery Sdn. Bhd., Butterworth, Penang, Malaysia). Coconut water was purchased from Pulau Sambu (Pulau Sambu Singapore Pte Ltd., Singapore) and coconut milk was purchased from Bjorg (Bjorg, Italy). Other chemicals and reagents used were of standard laboratory grade.

2.2. Animals

Forty-two male Wister rats weighing 170–250 g were obtained from Animal house at King Abdulaziz University, in Jeddah, Saudi Arabia and housed in animal care facility. Rats were left to acclimatize to conditions for a week under 12 h light–dark cycle and had

free access to standard diet and water. Rats were divided into 7 groups namely, G1, G2, G3, G4, G5, G6, and G7. Rats from all the groups were fed a high fat diet for two weeks. Following this rats from G2 to G7 groups were rendered diabetic with a single STZ dose (45 mg/kg body weight) injected intraperitoneally, while rats in G1 group served as control. Rats from all the groups were reverted back to normal chow diet. Development of diabetes in the rats was confirmed one week after STZ injection. Rats belonging to G3–G7 groups were treated with virgin coconut oil (10 mg/kg body weight), refined coconut oil (10 mg/kg body weight), coconut water (4 ml/100 g body weight), coconut milk (4 ml/100 g body weight) or metformin (200 mg/kg body weight) respectively, while G2 group rats served as diabetic control. The above mentioned treatment doses were selected based on previous studies (Iranloye, 2013, Ajeigbe et al., 2017). All the treatments were carried out for 28 days. Rats were fasted for 8 h preceding the end of 28-day treatment, anaesthetized using diethyl ether and sacrificed by cervical dislocation. Blood samples were collected and serum was separated by centrifugation. Kidneys were excised and part of tissue was homogenized and used for biochemical analysis while part of the tissue was fixed in formalin solution and used for histological examination. Study was approved by the ethical committee at the King Abdulaziz University, Jeddah, Saudi Arabia (HA-02-J-008, Ref. No. 447-19, Dt. 25th June 2019). All the animal work was carried out following the guidelines set by Animal Care and Use Committee.

2.3. Body weight measurement

Body weight of rats were measured every week beginning from the end of acclimatization period and continuing till the end of treatment duration.

2.4. Urine sample collection

Urine samples from all the rats were collected over 24 h period preceding the end of 28-day treatment duration by placing individual rats in separate cages.

2.5. Tissue homogenization

Tissue homogenates were prepared using TissueLyser in cell lysis buffer. Homogenates were centrifuged at 12,000g for 10 min at 4 °C. The clear supernatant was separated and used for biochemical analysis.

2.6. Serum biochemical parameters

Serum glucose, insulin, HbA1c, total cholesterol, HDL-and LDL-VLDL-cholesterols, triglycerides, creatinine, urea, total protein, Na⁺, K⁺ and HCO₃⁻ were measured following the instructions provided by the manufacturer.

2.7. Kidney biochemical analysis

Creatinine, urea, total protein, Na⁺, K⁺, HCO₃⁻ levels in tissues were measured using the commercial kits as described by the respective manufacturers.

2.8. Urinary analysis

Urine pH was determined by using pH strips. Urine glucose, urea, albumin, and creatinine levels were measured using the kits following the instructions provided by supplier.

2.9. Histological analysis

The Formalin preserved kidney specimens were processed in an automated tissue processor. Briefly, tissue slides were immersed in 10% buffered formalin for 48 h, followed by washing in distilled water for 30 min. Dehydration was carried out by serial immersion of slides in 70%, and 90% alcohol solutions for 2 h, and 90 min respectively and in absolute alcohol twice for one hour each. Thereafter, slides were immersed in a 50% alcohol and 50% xylene solution for 1 h and in pure xylene for one and a half hour. Samples were embedded and paraffin sections of 4–5 μm thick were cut and stained with hematoxylin and eosin (H&E).

2.10. Statistical analysis

The data were analyzed using the IBM SPSS Statistics for Windows, version 23 (IBM SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro – Wilk test was used to determine normal distribution of the data. Statistical comparisons between groups were performed by one-way analysis of variance (ANOVA) followed by least significant test (LSD). Data were expressed as mean \pm standard deviation (SD) and considered statistically significant at $p < 0.05$.

3. Results

3.1. Body weight

Body weights of rats are presented in Table 1. Body weights of rats were comparable among all the groups when tested one week after acclimatization and two weeks after high fat diet feeding. Whereas, one week after the STZ injection for the development of diabetes, the body weights of rats in G2, G3, G6 and G7 groups were significantly decreased while they were unchanged in G4 and G5 groups compared to control. Body weights of rats in diabetic control group remained significantly decreased over four-week period compared to control. On the other hand, body weights of rats in G4 and G5 groups that were treated respectively with filtered coconut oil and coconut water, significantly increased over four-week treatment duration compared to G2 diabetic group. Interestingly, a significant increase in body weights of rats in G3 group was noticed only after two weeks but not after 1st, 3rd and 4th week of virgin coconut oil treatment compared to diabetic group. The treatment with metformin and coconut milk had no significant effect on body weights in G6 and G7 group of rats compared to those in diabetic group. Body weights of G2 to G7 group

of rats remained significantly low compared to control group till the end of four-week treatment duration.

3.2. Serum glucose, insulin and HbA1c

Data on serum glucose, insulin and HbA1c levels are presented in Table 2. Compared to control G1 group, glucose and HbA1c levels significantly increased and insulin levels significantly decreased in G2 diabetic control group. Levels of these diabetes parameters significantly reversed in G3 to G7 groups of rats which were treated with virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin respectively compared to those in diabetic rats.

3.3. Serum lipid profile

Serum lipid profiles of different groups are provided in Table 3. Lipid profile parameters including, triglycerides, total-, LDL- and VLDL-cholesterols were significantly increased and HDL-cholesterol levels were significantly decreased in diabetic rats as compared to control. On the other hand, treatments with virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin resulted in a significant restoration of altered lipid profiles in G3 to G7 group of rats respectively as compared to G2 diabetic group.

3.4. Renal parameters

Serum levels of renal parameters including creatinine, urea, and total protein are presented in Table 4. Compared to control, all the studied renal parameters were significantly elevated in diabetic rats. Diabetic rats treated with virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin demonstrated a significant reduction in serum creatinine, urea and total protein as compared to those in diabetic rats. However, diabetic rats treated with filtered coconut oil showed no significant difference in urea levels compared to that in diabetic rats. The data on renal parameters in kidney tissue are shown in Table 5. Consistent with their serum levels, creatinine, urea and total protein levels in kidney tissue were significantly augmented in diabetic rats as compared to control. Similarly, treatment with virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin led to a significant reduction in all the renal parameters, while rats treated with filtered coconut oil had no significant change in kidney urea and total protein levels.

Table 1

Body weights of control and different treatment groups.

	Weeks	Body weights (g)						
		G1	G2	G3	G4	G5	G6	G7
Pretreatment duration	1st week	180.00 \pm 12.65	188.33 \pm 14.71	185.00 \pm 13.78	191.67 \pm 30.61	198.33 \pm 4.09	180.00 \pm 15.49	183.33 \pm 15.06
	2nd week	220.00 \pm 20.98	230.00 \pm 30.33	222.50 \pm 22.97	229.17 \pm 38.00	247.50 \pm 8.80	218.33 \pm 16.00	230.83 \pm 22.00
	3rd week	242.50 \pm 20.43	250.00 \pm 35.78	245.00 \pm 28.81	243.33 \pm 35.59	263.33 \pm 10.33	240.00 \pm 28.28	241.67 \pm 31.89
	4th week	274.17 \pm 23.33	240.00 \pm 31.78*	245.00 \pm 17.32*	251.67 \pm 24.63	265.83 \pm 13.93	236.67 \pm 24.01**	244.17 \pm 22.98*
Treatment duration	1st week	287.33 \pm 24.05	223.50 \pm 28.86***	242.33 \pm 12.53***	258.50 \pm 20.55*, ##	272.33 \pm 23.42###	228.17 \pm 15.07***	239.17 \pm 27.27***
	2nd week	304.50 \pm 33.88	216.50 \pm 30.67***	247.33 \pm 11.36**, #	264.50 \pm 18.9**, ###	264.50 \pm 21.19**, ###	237.7 \pm 14.73***	234.17 \pm 28.90***
	3rd week	323.67 \pm 24.94	222.67 \pm 29.32***	243.67 \pm 14.81***	265.00 \pm 28.42***, #	259.67 \pm 18.98***, #	204.17 \pm 17.57***	229.33 \pm 31.17***
	4th week	329.00 \pm 30.37	218.33 \pm 29.63***	236.83 \pm 24.11***	257.17 \pm 46.08***, #	261.33 \pm 22.02***, #	231.50 \pm 18.29***	235.00 \pm 39.67***

Pretreatment duration-1st week; acclimatization duration, 2nd & 3rd weeks; high fat diet feeding duration, 4th week; diabetes development period. **Treatment duration**-1st to 4th week, respective treatment durations, G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; # - significance versus G2 for the same week, * $P < 0.05$ when compared to normal control group, ** $P < 0.01$ when compared to normal control group, *** $P < 0.0001$ when compared to normal control group. # $P < 0.05$ when compared to diabetic group; ## $P < 0.01$ when compared to Diabetic group, ### $P < 0.001$ when compared to Diabetic group. Data are expressed as mean \pm SD (N = 8).

Table 2
Serum glucose, insulin and HbA1c in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Serum glucose (mg/dl)	87.17 ± 9.09	238.33 ± 40.15***	129.83 ± 27.45*, ##	174.83 ± 43.90**, #	103.33 ± 10.97*, ###	110.50 ± 14.57**, ###	105.17 ± 12.19*, ###
Serum insulin (IU/L)	18.20 ± 2.64	2.31 ± 0.33***	9.25 ± 5.62**, ###	4.82 ± 1.84***, ###	16.57 ± 2.61###	16.80 ± 3.70###	16.70 ± 3.87###
HbA1c (%)	4.75 ± 0.36	9.80 ± 1.8***	5.73 ± 1.41##	6.53 ± 1.22**, ##	4.65 ± 0.37###	4.74 ± 0.38###	4.85 ± 0.45###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean±/ SD (N = 8).

Table 3
Serum lipid profile in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Triglyceride (mg/dl)	75.83 ± 7.78	140.33 ± 48.34***	75.00 ± 4.56###	76.50 ± 7.34###	73.83 ± 4.45###	75.33 ± 3.83###	87.00 ± 10.24###
Total cholesterol (mg/dl)	125.50 ± 13.59	270.00 ± 19.82***	121.50 ± 10.10###	176.17 ± 12.75***, ###	129.67 ± 9.99###	127.33 ± 7.94###	125.33 ± 6.38###
HDL-C (mg/dl)	43.83 ± 3.49	30.50 ± 9.01**	45.67 ± 4.68###	41.33 ± 8.52##	45.00 ± 4.34###	48.33 ± 6.41###	42.67 ± 9.40##
LDL-C (mg/dl)	33.00 ± 14.39	123.17 ± 29.23***	29.67 ± 11.74###	29.17 ± 12.04###	30.00 ± 16.16###	30.33 ± 8.62###	23.00 ± 3.80 ###
VLDL-C (mg/dl)	15.17 ± 1.56	28.07 ± 9.67***	15.00 ± 0.91###	15.30 ± 1.47###	14.77 ± 0.89###	15.07 ± 0.77###	17.40 ± 2.05###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean±/ SD (N = 8).

Table 4
Serum renal parameters in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Creatinine (mg/dl)	0.68 ± 0.16	1.80 ± 0.25***	0.52 ± 0.15###	0.96 ± 0.74#	0.67 ± 0.18###	0.67 ± 0.13###	0.69 ± 0.17###
Urea (mg/dl)	11.83 ± 1.67	31.33 ± 5.47***	14.13 ± 1.82###	27.17 ± 3.67***	11.98 ± 2.45###	14.97 ± 1.90*, ###	14.63 ± 1.66*, ###
Total protein (g/dl)	7.01 ± 0.67	9.46 ± 0.40***	6.76 ± 0.55 ###	8.12 ± 1.01#	6.60 ± 1.81##	7.45 ± 0.44###	7.33 ± 0.80###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean±/ SD (N = 8).

Table 5
Kidney renal parameters in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Creatinine (mg/dl)	0.65 ± 0.15	1.68 ± 0.24***	0.48 ± 0.10###	0.76 ± 0.24##	0.65 ± 0.19###	0.61 ± 0.12###	0.65 ± 0.17###
Urea (mg/dl)	12.15 ± 1.72	31.63 ± 5.50***	14.48 ± 1.61###	26.30 ± 3.61***	11.98 ± 2.43###	14.75 ± 2.08*, ###	14.42 ± 1.54*, ###
Total protein (g/dl)	6.68 ± 0.63	9.12 ± 0.23***	6.49 ± 0.39###	7.98 ± 1.42	7.48 ± 0.73##	7.23 ± 0.44###	7.14 ± 0.55###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean±/ SD (N = 8).

3.5. Electrolyte levels

Serum levels of sodium, potassium and bicarbonate in control and different treatment groups are provided in Table 6. Diabetic rats demonstrated a significant decrease in the studied electrolyte levels compared to those in control. In contrast diabetic rats treated with virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin have all displayed a significant elevation in sodium, potassium and bicarbonate levels compared to diabetic rats. Sodium levels in filtered coconut oil treated diabetic rats remained insignificant compared to diabetic rats. Sodium, potassium and bicarbonate levels in kidney tissue in different groups are shown in Table 7. All the studied electrolytes were found to be significantly down regulated in diabetic rats as compared to those in control. Consistent with their effects on serum electrolyte

levels, virgin coconut oil, filtered coconut oil, coconut water, coconut milk and metformin have all upregulated sodium, potassium and bicarbonate levels matched to those in diabetic rats.

3.6. Urinary parameters

The levels of urinary parameters including urine pH, glucose, urea, albumin and creatinine are provided in Table 8. Compared to control, there was a significant decrease in urine pH in diabetic rats compared to control. On the other hand, urine glucose, urea, albumin and creatinine levels were found to be significantly elevated in diabetic rats in relation to those in control. Treatment with virgin coconut oil, filtered coconut oil, coconut water, and metformin led to a significant increase in urine pH. No change in pH value was observed in diabetic rats treated with coconut milk. Glu-

Table 6
Serum electrolyte levels in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Sodium (mmol/L)	138.22 ± 3.48	126.22 ± 9.26***	138.62 ± 4.13###	131.50 ± 6.35*	139.86 ± 2.57###	139.72 ± 4.17###	139.87 ± 3.61###
Potassium (mmol/L)	4.40 ± 0.62	2.29 ± 0.69***	4.47 ± 0.67###	3.68 ± 1.07##	4.21 ± 0.83###	4.32 ± 0.39###	4.42 ± 0.69###
Bicarbonate (mEq/L)	23.69 ± 1.17	16.70 ± 1.64***	23.97 ± 1.09###	21.96 ± 1.93*,###	24.40 ± 1.19###	23.77 ± 1.69###	23.15 ± 0.59###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean± SD (N = 8).

Table 7
Kidney electrolyte levels in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Sodium (mmol/L)	132.76 ± 7.23	125.73 ± 8.28*	139.77 ± 6.92*,###	131.51 ± 5.96#	139.71 ± 4.08*,###	136.91 ± 6.96###	136.58 ± 6.91###
Potassium (mmol/L)	4.46 ± 0.77	2.25 ± 0.81***	4.36 ± 0.71###	3.42 ± 0.97**,###	3.98 ± 1.04###	4.47 ± 0.50###	4.24 ± 0.72###
bicarbonate (mEq/L)	23.92 ± 1.27	16.04 ± 1.83***	24.22 ± 1.32###	21.13 ± 2.20***,###	24.44 ± 1.20###	23.89 ± 0.98###	23.27 ± 1.01###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean± SD (N = 8).

Table 8
Urinary parameters in control and different treatment groups.

Parameters	G1	G2	G3	G4	G5	G6	G7
Urine pH	7.70 ± 0.30	7.07 ± 0.06*	7.87 ± 0.40##	7.80 ± 0.35##	7.66 ± 0.30#	7.53 ± 0.15	7.60 ± 0.26#
glucose (mg/dl)	86.67 ± 11.06	206.67 ± 21.78***	101.00 ± 15.72##	123.67 ± 9.61*,###	117.67 ± 25.42###	105.67 ± 22.05###	113.67 ± 17.47###
urea (mg/dl)	14.83 ± 3.12	31.67 ± 11.50**	16.37 ± 3.21##	31.33 ± 8.50**	18.57 ± 1.40#	15.87 ± 2.01##	14.20 ± 2.86##
albumin (g/dl)	3.68 ± 0.36	5.73 ± 0.25***	4.23 ± 0.67##	5.09 ± 0.28**	4.33 ± 0.51##	4.20 ± 0.72##	3.70 ± 0.46###
creatinine (mg/dl)	0.54 ± 0.10	1.89 ± 0.17***	0.59 ± 0.22###	1.20 ± 0.68*,#	0.77 ± 0.29###	0.70 ± 0.27###	0.57 ± 0.19###

G1; normal control, G2; diabetic control, G3; virgin coconut oil treated diabetic group, G4; filtered coconut oil treated diabetic group, G5; coconut water treated diabetic group, G6; coconut milk treated diabetic group, G7; metformin treated diabetic group. *significance versus G1; #significance versus G2 for the same week, *P < 0.05 when compared to normal control group, **P < 0.01 when compared to normal control group, ***P < 0.0001 when compared to normal control group. #P < 0.05 when compared to diabetic group; ##P < 0.01 when compared to Diabetic group, ###P < 0.001 when compared to Diabetic group. Data are expressed as mean± SD (N = 8).

case and creatinine levels were significantly decreased in diabetic rats treated with all the coconut products, while urea and albumin levels were significantly decreased in diabetic rats treated with virgin oil, coconut water, coconut milk and metformin as matched to diabetic rats. On the other hand, filtered coconut oil had no significant effect on urea and albumin levels as compared to those in diabetic rats.

3.7. Histology

Histological changes in kidney tissue from control and different treatment groups are shown in Fig. 1. Tissue sections from control rats displayed renal corpuscles with normal glomerular capillary loops having normal population of glomerular epithelial cells. The proximal convoluted tubules had narrow lamina and fewer cells. The distal convoluted tubules showed wider lamina lined with large number of cells with normal vesicular nuclei (Fig. 1A). Contrastingly, tissue sections from diabetic rats had degenerated and sclerosed glomeruli in corpuscles of renal cortex that were surrounded by wide space of the Bowman's capsule. A large number of proximal convoluted tubules (PCT) showed dark nuclei. The cytoplasm of distal tubules showed unstained cytoplasm a feature of hydropic degeneration. Other tubules showed dilated lamina and atrophy of their lining epithelium (Fig. 1B).

Diabetic rats treated with virgin coconut oil demonstrated intact renal corpuscles, glomerular structure and normal Bowman's capsule space. The nuclei and cytoplasm of the lining epithelium of proximal and distal convoluted tubules showed a normal appearance with few hydropic degenerated distal tubules

(Fig. 1C). In rats treated with refined coconut oil, near normal glomeruli, renal tubules with few dilated lamina and degenerated cells (Fig. 1D). Renal cortex showed predominance of normal renal corpuscles with normal glomeruli surrounded by narrow Bowman's capsule space were found in kidney tissue from diabetic rats treated with coconut water. Additionally, proximal convoluted tubules had fewer cells with dark basophilic nuclei and lining epithelium of the distal tubules showed normal appearance. However, still numerous distal tubules showed dilated lumina or hydropic degeneration (Fig. 1E). Diabetic rats treated with coconut milk displayed normal renal corpuscles and glomeruli with narrow Bowman's capsule space. Proximal convoluted tubules showed normal cells with vesicular and basophilic nuclei. The lining epithelium of the distal tubules showed also normal lining epithelium with dark basophilic nuclei. Distal tubules with degenerated epithelium are less frequently seen (Fig. 1F). In metformin treated rats, most renal corpuscles looked normal. Most of the proximal convoluted tubules were with small pyknotic nuclei. Most distal tubules looked normal. However, few tubules still showed lining cells with unstained cytoplasm which is a features of hydropic degeneration (Fig. 1G).

4. Discussion

In this study we assessed the effects of different coconut products including virgin coconut oil, double filtered coconut oil, coconut water, and coconut milk as well as of diabetic drug metformin on STZ induced diabetes in Wister rats. We examined the effects of

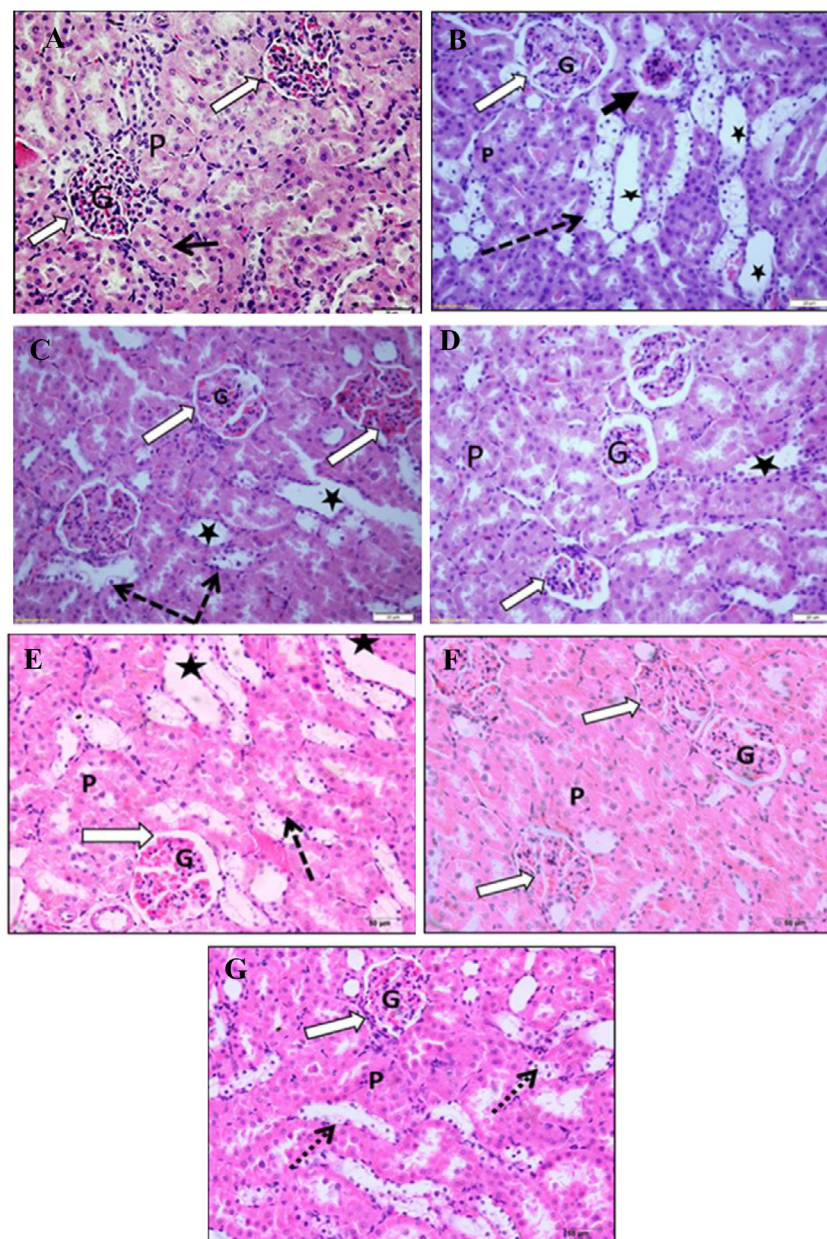


Fig. 1. H&E stained kidney tissue sections from control (A), diabetic (B), virgin coconut oil treated diabetic (C), filtered coconut oil treated diabetic (D), coconut water treated diabetic (E), coconut milk treated diabetic (F) and metformin treated diabetic groups. Tissue section from A group showing normal renal corpuscles (white arrows) with normal cell population of glomerular (G) capillary loops. The proximal convoluted tubules (P) have few cells and the distal are wide and lined by large number of cells with the normal vesicular nuclei (black arrow). In contrast, tissue sections from diabetic group showing renal corpuscles, one with a sclerosed glomerulus (head arrow) and wide Bowman's capsule space compared to normal ones (white arrow). Most of the proximal convoluted tubules (P) have few number of cells with dark basophilic pyknotic nuclei. The lining epithelium of numerous distal tubules showing unstained cytoplasm (hydropic degeneration) and wide lumina (stars) the lining cells showed dark basophilic pyknotic nuclei. Other tubules have wide lumina and degenerated low epithelium (black dotted arrow). The histology of sections from different treatment groups displayed significant recovery with varying degrees as compared to diabetic group.

these products on body weight, diabetes parameters such as glucose, insulin, HbA1c in serum. Further, we studied the effects on lipid profile including triglycerides, total-, HDL-LDL- and VLDL-cholesterols and renal parameters such as creatinine, urea and total protein and electrolytes including sodium, potassium and bicarbonate both in serum and in kidney tissues. Urine pH and levels of renal parameters such as glucose, creatinine, albumin, and urea were also evaluated in response to studied coconut products.

Coconut is one of the globally ubiquitous plants harnessed not only for food but also for medicinal purposes. Various coconut products have been shown previously to possess multiple benefi-

cial health effects. The objective of the present study was to examine whether various coconut products serve as antidiabetic effects and whether are capable to blunt diabetes induced renal complications. Here, we found that compared to control, diabetic status significantly decreased body weight. On the other hand, virgin and filtered coconut oils and coconut water were capable to significantly restore body weights of diabetic rats over the 28-day treatment period. However, coconut milk and metformin had no effects on body weights. The previous findings have shown that diabetes resulted in the loss of body weight, however dietary supplementation of coconut water had no effect on body weight of diabetic rats (Dai et al 2021). Consistent with our study, virgin coconut oil

markedly increased body weight of diabetic rats (Djurasevic et al 2018). Similarly, coconut water has been shown to increase body weight in alloxan-induced diabetic rats (Pinto et al 2015). Glucose and glycated haemoglobin have been shown to be reduced by various coconut products in diabetes. For examples, in a review of literature and in a case report, coconut oil has been shown to lower glucose levels in diabetic patients (Malaeb and Spoke, 2020). In male Sprague diabetic rats, coconut water significantly reduced fasting glucose levels (Dai et al 2021). In THP-1 macrophages, Lauric acid rich coconut oil reduced insulin resistance by improving mitochondrial biogenesis (Tham et al 2020). Virgin coconut oil is reported to improve glucose homeostasis and lipid profile in high fat diet fed Wister rats (Adeyemi et al 2020). In experimental hyperlipidemic rats, coconut oil alleviated blood glucose levels and insulin resistance (Lee et al 2018). Fresh coconut enriched diet is shown to downregulated blood glucose in normal adults (Vijayakumar et al 2018). Diabetic rats treated with coconut water maintained blood glucose as compared to control group besides a decrease in HbA1c levels and an increase in body weight matched to those in diabetic group rats (Pinto et al 2015). All the above reports support the antidiabetic effects of various coconut products and substantiate our finding of decreased glucose and glycated haemoglobin levels in rats treated with coconut products.

Dyslipidemia is a major pathological complication in diabetic patients (Maliszewska and Kretowski, 2021). In this study we also evaluated the ability of coconut products to improve diabetes induced dyslipidaemia. We found that virgin and filtered coconut oils, coconut water, coconut milk and metformin have all improved lipid profile by decreasing total-, LDL-, VLDL-cholesterols, and triglycerides and by increasing HDL-cholesterol in diabetic rats. In agreement with our findings, treatment of alloxan-Induced Diabetic Rats by virgin coconut oil resulted in a reduction in diabetes induced total-, LDL-, VLDL-cholesterols, and triglycerides (Eleazu et al 2019). In a randomised trial, coconut oil significantly increased HDL-cholesterol and significantly decreased LDL-cholesterol (Khaw et al., 2017). In line diabetic neonatal rats had decreased total and non-HDL cholesterol after 45-day treatment of fat-enriched special diet containing coconut oil (Kochikuzhyil et al 2010). However, in a systematic review and a meta-analysis, coconut oil has found to significantly increase total-, LDL- and HDL-cholesterols and significantly decrease HbA1c and have no effect on triglycerides (Jayawardena et al 2020).

Diabetic nephropathy is a predominant complication of diabetes (Li et al 2021). Previous studies have shown that coconut products were able to mitigate diabetic nephropathy by improving renal parameters including creatinine, urea and total protein. In STZ-induced diabetic rats, serum urea, creatinine, and total protein levels were significantly decreased following treatment with virgin coconut oil (Akinnuga et al 2019). Likewise, urea, creatinine and uric acid were significantly downregulated in virgin oil treated alloxan-induced diabetic rats (Eleazu et al 2019). These data are consistent with our finding of decreased creatinine, urea and total protein levels in diabetic rats treated with coconut products and supports the protective effects of these products against diabetes induced renal complications.

Diabetes is well-known to negatively alter electrolyte levels in the body (Ngozi et al 2018). In this study we found a significant decrease in electrolyte levels including sodium, potassium and bicarbonate in diabetic rats. Treatment of diabetic rats with different coconut products positively modulated the levels of all the studied electrolytes. Recently it is shown that coconut sap contains high content of sodium and potassium (Asghar et al 2019). Coconut haustorium, a spongy tissue formed during coconut germination was found to be rich source of several minerals in including sodium, bicarbonate and potassium (Manivannan et al 2018). Likewise, virgin coconut oil significantly modulated creatinine, sodium

(Na⁺), potassium (K⁺), chloride (Cl⁻) in normal healthy rats (Famurewa et al 2018). These experimental supports our findings and underscores the ability of various products of coconut to blunt diabetes induced changes in electrolyte levels.

Since diabetes negatively affects kidney function, changes in urinary parameters such as urea, albumin and creatinine levels have been reported previously (Wang et al 2021). In this study we found that urine levels of glucose, urea, creatinine and albumin levels were significantly increased in diabetic rats. Moreover, following the treatment with coconut products the levels of these urinary parameters drastically lowered in diabetic rats, emphasizing the potential of these coconut products to reverse the effects of diabetes. In comparison to our data, it is shown that alloxan-Induced diabetic rats had significantly reduced urea, creatinine, uric acid after treatment with virgin coconut oil (Eleazu et al 2019). Likewise, virgin coconut oil attenuated maximum physical activity-induced increase in urea, uric acid and creatinine in rats (Sinaga et al 2019).

The diabetic nephropathy is characterized by hypertrophy, inflammation, and renal fibrosis in kidney tissue. Here we also examined the histological changes in the kidney tissues of diabetic rats and the efficacies of treatments with coconut products in abrogating these pathological changes. We found a significant kidney tissue degeneration in diabetic rats, while a marked protection of coconut products from diabetes induced tissue damage as significantly reduced pathological alterations in kidney tissues from treated rats were noticed. Consistently, pre-supplementation of rats with virgin coconut oil attenuated histological renal damage by restoring antioxidant enzyme activities in rats (Famurewa et al 2020).

In conclusion, we have shown that coconut products including virgin and filtered coconut oils, coconut water and milk were capable to significantly lower serum glucose and glycated haemoglobin levels, improve insulin, lipid profile, renal parameters such as urea, total protein and creatinine and electrolyte levels in diabetic rats. Further, coconut products markedly protected kidney tissues from diabetes induced histopathological changes. Importantly, all the tested coconut products were as efficient as metformin in exerting favourable effects on the studied diabetic parameters highlighting their anti-diabetic utility. To our knowledge this is the first study to comprehensively examine the effect of 4 different coconut products on different parameters of T2DM and diabetic nephropathy. Taken together, dietary consumption of coconut products appears to impart beneficial health effects.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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