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Antidiabetic and Antihyperlipidemic Activities of Methanolic Extract of Leaves of *Coccinia grandis* in Diabetic Rats

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ABSTRACT

Coccinia grandis is a one of the edible plant and its antidiabetic and antihyperlipidemic activities are not well explored. Hence, the present is planned to study the antidiabetic and antihyperlipidemic activities of methanolic extract of *Coccinia grandis* leaves in streptozotocin-induced diabetic rats. *Coccinia grandis* leaves was dried under the shade and extracted with methanol. Preliminary phytochemical and pharmacological analysis were conducted using methanolic extract of *Coccinia grandis* (MECG) leaves. Female *Sprague dawley* (SD) was used for acute toxicity studies. Female SD was induced with diabetes by administering streptozotocin (55 mg/kg, i.p.). Glibenclamide (20 mg/kg, p.o.) or MECG leaves (125, 250 and 500 mg/kg, p.o.) used to treat diabetic rats for 28 days. Blood samples were collected at regular intervals to check the antidiabetic effect of MECG. On 28^{th} day, blood sample was collected from the rats to analyse biochemical and lipid profile. MECG did not show any toxic symptoms up to the dose 2000 mg/kg/ BW. MECG at 125, 250 and 500 mg/kg marked significant antidiabetic and antihyperlipidemic activities. *Coccinia grandis* reduced streptozotocin-induced weight loss and significantly recovered lipid levels. At the end of the study, MECG exhibited significant antidiabetic and antihyperlipidemic activities in streptozotocin-induced diabetes in rats.

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INTRODUCTION

Diabetes is known as a type of heterogeneous disease linked with glucose metabolism due to abnormalities in insulin secretion and action. In 2019, approx. 463 million peoples living with diabetes and this will rise to 700 million in 2045. It was classified as one of the top 10 causes of death in adults, and approximately 4.2 million deaths were recorded globally in 2019. Besides this, global health expenditure on diabetes was reported to be USD 760 billion (IDF Diabetes Atlas ninth edition, 2019). It is described as hyperglycemia, various microvas-

cular and macrovascular diseases, including glucosuria (Gong *et al.*, 2017). Illness in diabetes is due to hyperglycemia-induced oxidative stress which reduces anti-oxidant activity by scavenging free radicals (Ayepola *et al.*, 2014). Impairment in lipid metabolisms such as hyperlipidemia and hypercholesterolemia found in late stages and as risk factors in the development of atherosclerosis (Krishnakumar *et al.*, 1999). Chances of liver damage caused by diabetes are high due to excess ketogenesis and gluconeogenesis (Agius *et al.*, 1986). No effective treatment available for diabetes and some of the drugs and insulin preparations which currently being used in controlling the disease are causing various unexpected side effect (Chaudhury *et al.*, 2017). Expensive and unexpected side effects of anti-diabetic drugs tiggers finding of plants with hypoglycemic properties and their role in the management of diabetes (Ajiboye *et al.*, 2014; Calixto, 2000).

Medicinal plants have a significant role with more significant support for alternative medicine and new drug development. Since the suggestions made by World Health Organisation (WHO) on diabetes mellitus, the application of medicinal plant to treat diabetes mellitus gained demand in the past few years. This encourages the finding for effective and safer anti-diabetic compounds obtained from medicinal plants (El-Abhar and Schaalan, 2014). Because of the increasing prevalence of diabetes, investigation on the benefits from traditional medicines might help the findings of possible therapeutic methods to manage and prevent diabetes mellitus and its illness (Patel *et al.*, 2012). Plants showed hypoglycemic properties in managing diabetes due to its contents such as plant polysaccharides, glycosides, alkaloids terpenoids, flavonoids and other bioactive compounds.

Cucurbitaceae belongs to a plant family and contains around 125 genera and 960 species. The number of species such as *Citrullus colocynthis* (L), Schrad, *Coccinia indica* Wight et Arn., *sativus L., Cucumis Bryonia alba* L., *Momordica cymbalaria* Hook.,*Momordica charantia* L., *Tricosanthes dioica* Roxb., *Momordica foetida* Schumach. *Coccinia indica* Wright and Arn., and *Coccinia cordifolia* (L.) Cogn., *Cephalandra indica*, Naud., and *Bryonia cordifolia* (L.) Voigt. are the other names of *Coccinia grandis (Nagare et al., 2015)* . Scientific investigations have supported the potency of *Coccinia grandis* leaves extracts in curing skin diseases, urinary tract infections, bronchitis, itchy skin eruptions and ulcers (Krishnakumari *et al.*, 2011). Furthermore, the leaves also act as antioxidative, anti-inflammatory agent and showed ability to treat antimicrobial infections (Yadav *et al.*, 2010). However, limited scientific information available on efficiency of glucose tolerance and biochemical assessment. Therefore, aim of current study is to analyse the antidiabetic and antihyperlipidemic activities of methanolic extract of *Coccinia grandis* leaves in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Plant material

Coccinia grandis leaves were collected from Semeling, Sungai. Petani, Kedah and botanist recognized it at the herbarium section, voucher code (USM 11768/09/2018). The leaves were cleaned in running water; dried under the shade and powdered using a grinding machine. The powder was stored in an airtight container for further use.

Chemicals

Streptozotocin (STZ) and all other chemicals used in this experiment were purchased from Sigma, Malaysia and Merck or SD fine Chemicals respectively and were of analytical grade.

Extraction

Coccinia grandis powder were weighed and subjected to maceration with methanol solvent in a conical flask and kept aside for 7 days at the room temperature with frequent agitation. After the completion of maceration process, the extract was then filtered through muslin cloth and the extract was concentrated to a solid mass by evaporation under reduced pressure using rotary evaporator (Rotavapor® R-210, BUCHI Corporation). The MECG was stored at room temperature until use.

Phytochemical screening

The methanolic extract of *Coccinia grandis* (MECG) leaves tested for the presence of secondary metabolites like phenolic compounds, alkaloids, flavonoids, carbohydrate, steroids, saponins, tannins by using standard procedures. Total phenolic content of methanol was quantified by spectrophotometric method. Sample (0.5ml) was mixed with 0.75% sodium carbonate solution (2.5 ml) followed by 1% Folin-Ciocalteu reagent (2.5 ml). The mixture was incubated for 15 minutes at a temperature of 45°C and absorbance was measured at 765 nm. The standard calibration curve was plotted using gallic acid concentration. The total phenolic content was calculated from the calibration curve, and the results were expressed as gallic acid equivalent in mg/g (Kumari *et al.*, 2016).

Total flavonoid content of methanol was quantified using aluminium chloride colorimetric assay. The

sample (1ml) mixed with standard quercetin solution (1ml), distilled water (4ml) and 5 % sodium nitrite solution (0.3ml) followed by 1M sodium hydroxide (2 ml). The absorbance was measured at 510 nm. The standard calibration curve was plotted using standard quercetin. The total flavonoid content was calculated from the calibration curve, and the results were expressed as quercetin equivalent in mg/g (Kumari *et al.*, 2016).

Experimental animals

Adult female *Sprague Dawley (SD) rats* rats free from diseases weighing 180-200 g were purchased from (Universiti Sains Malaysia, Penang, Malaysia). The rats were kept at 23 $\pm$ 2°C in 50 $\pm$ 5% humidity and 12 hours of light-dark cycles. Standard rat pellet diet and tap water was given and acclimatized for seven days before the rats are used in the experiment. All the protocols are approved by the Committee on the Care of Laboratory Animal Resources, AIMST University (AUHAEC/FAS/2017/01) and conducted regarding Guide for the Care and Use of Laboratory Animals.

Acute toxicity

Adult female *Sprague Dawley (SD) rats* free from diseases were selected for this study. The fixed-dose procedure was performed to test acute toxicity. *Coccinia grandis* with dose levels of 250, 500, 1000 and 2000 mg/kg body weight (n = 6 per dose) were given orally to the rats after overnight fasting. Behavioural, neurological and autonomic profiles of the rats were observed continuously for 24 hours followed by 14 days observation for mortality accordance with the current guidelines of Organization for Economic Co-operation and Development (OECD), revised draft guidelines 423 (Organization for Economic Cooperation and Development (OECD), 2001).

Induction of Diabetes

Adult female SD rats free from diseases were selected for this study. After acclimatized for one week, diabetes mellitus was induced in rats by intraperitoneally injecting STZ (55 mg/kg body weight) dissolved in 0.05M citrate buffer and pH maintained to 4.0 to 4.5 before injecting. Twenty-four hours later upon induction of diabetes mellitus, 5% w/v of glucose solution (2 mL/kg body weight) were given to the rats to avoid hypoglycemic mortality. Citrate buffer alone was intraperitoneally injected to the control rats. Two days after STZ treatment, the blood sample was collected from the tail vein to record glucose level using a glucometer (ACCU-CHEK® Active, Roche Diagnostics, Mannheim, Germany). Non-fasting rats with glucose levels above 11 mmol/L were considered as diabetic rats and introduced in the study.

Experimental Design

The total of 30 diabetic induced rats and six normal control rats were used in this study to analyze the effect of the MECG. The rats were divided into six groups (n = 6) as follows:

Group 1- Normal control

Group 2- STZ control

Group 3- STZ + glibenclamide (20 mg/kg)

Group 4- STZ + MECG (125 mg/kg)

Group 5- STZ + MECG (250 mg/kg)

Group 6- STZ + MECG (500 mg/kg)

The rats in group 1 and 2 were administered with 0.5% w/v carboxymethyl cellulose (CMC). Glibenclamide (20mg/kg body weight) was administered to rats in group 3. *Coccinia grandis* dose levels of 125, 250, 500 mg/kg body weight were administered to the rats in group 4 to group 6. The doses of *Coccinia grandis* were selected from the acute toxicity study findings. The rats were treated with respective assigned treatment for 28 days. During the study, changes in body weight and blood glucose levels were measured at regular intervals. At the end of the study, the blood sample was collected through the tail vein and used for biochemical and lipid analysis.

Blood glucose levels measurement

To evaluate the glucose levels, few drops of blood samples were retrieved from the tail vein, and glucose levels were then measured using a blood glucometer by using test strips to analyze glucose oxidoreductase mediated dye reaction, as per manufacturer's guide. Blood glucose levels were recorded on day 0, 7, 14, 21 and 28^{th} day of the experiment.

Biochemical analysis

At the 28^{th} day, a blood sample (few millilitres (mL)) were collected from the tail vein in EDTA containing tubes. Triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), Low-density lipoprotein (LDL), Very low-density lipoprotein (VLDL), Total protein Total plasma, serum glutamic pyruvic transaminase (ALT), alkaline phosphatase (ALP), serum glutamic oxaloacetic transaminase (AST), Albumin, Globulin, A/G, Total bilirubin, Urea and Creatinine were estimated by "Cobas Integra 400 plus" analyzer, Roche.

Statistical analysis

The mean $\pm$ standard error of the mean (SEM) values was calculated for all the groups. One-way

Table 1: Effect of *Coccinia grandis* on body weight of rats (g).

Day	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
0	175.88 ± 2.26	172.70 ± 1.36	174.04 ± 2.03	175.21 ± 2.35	172.54 ± 2.57	171.21 ± 2.31
14	182.27 ± 1.88	162.19 ± 1.35***	176.72 ± 2.01	178.94 ± 1.92	180.52 ± 2.74	180.77 ± 1.36
28	191.77 ± 1.05	150.94 ± 1.28***	187.44 ± 1.66	186.37 ± 1.72	189.94 ± 2.56	193.94 ± 1.70

Values are Mean ± SEM.,n = 6 per group.
***P<0.001 compare with control.

Table 2: Effect of *Coccinia grandis* on glucose levels in rats (mmol/L).

Day	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
0	5.60 ± 0.30	17.45 ± 0.61***	17.50 ± 0.61***	17.23 ± 0.66***	17.70 ± 0.68***	18.32 ± 0.59***
7	5.57 ± 0.35	17.12 ± 0.68***	11.46 ± $0.57^{\#\#\#}$	15.07 ± 0.15	13.63 ± $1.03^{\#}$	11.61 ± $0.78^{\#\#}$
14	5.28 ± 0.12	15.98 ± 0.54***	10.68 ± $0.38^{\#\#\#}$	14.05 ± 0.48	12.40 ± $0.67^{\#\#\#}$	11.33 ± $0.32^{\#\#\#}$
21	5.13 ± 0.26	16.02 ± 0.43***	6.13 ± $0.11^{\#\#\#}$	6.50 ± $0.20^{\#\#\#}$	5.87 ± $0.10^{\#\#\#}$	5.13 ± $0.10^{\#\#\#}$
28	5.22 ± 0.29	16.52 ± 0.45***	5.10 ± $0.09^{\#\#\#}$	5.23 ± $0.09^{\#\#\#}$	5.22 ± $0.09^{\#\#\#}$	5.10 ± $0.09^{\#\#\#}$

Values are Mean ± SEM.,n = 6 per group.
***P<0.001compare with control. $^{\#\#\#}$P<0.05, $^{\#\#}$P<0.01and$^{\#}$ P<0.001 compare with diabetic control.

ANOVA, followed by Tukey's post-hoc test, was used to calculate statistical differences among the groups. P < 0.05 was considered to be significant.

RESULTS AND DISCUSSION

MECG contains saponins, steroids, tannins, carbohydrate, phenolic compounds and flavonoids. Folin-Ciocalteu method was used to evaluate total phenolic content in MECG. Total phenolic content of MECG is 69.33 mg GAE/g and recorded 91.17 mg QE/g in total flavonoid analysis. MECG showed no mortality up to 2000mg/kg during acute toxicity study.

Effect of glibenclamide and MEGC on STZ-induced diabetes rats body weights were outlined in Table 1. A decrease in body weight was seen in the untreated diabetic group compared with non-diabetic rats. Bodyweight decreased significantly from day 14 (P<0.001) onwards. Administration of glibenclamide and MECG at oral doses of 125 mg/kg, 250 mg/kg and 500 mg/kg to the rats prevented diabetes-induced weight reduction.

Throughout the study, diabetic rats show a significant rise in glucose level when compared with non-diabetic rats. Furthermore, rats treated with glibenclamide and MECG at oral doses of 250 and 500 mg/kg showed a significant decline in glucose level on day seven onwards when compared with diabetic control rats. The rats administered with 125 mg/kg MECG showed a significant decline in glucose level from day 21 compared with diabetic control rats.. (Table 2).

In biochemical parameter analysis, diabetic rats showed a significant increase in AST, ALT, ALP, urea, total bilirubin and creatinine levels (P < 0.001). At the end of the experiment, reduced levels of plasma insulin, albumin, globulin, total protein and A/G (P < 0.001) when compared with normal control. However, the levels of the biochemical parameters are found to be within the normal range in the rats with MECG 500 mg/kg and glibenclamide treatment (Table 3). MECG and glibenclamide altered insulin depletion in diabetic rats and also recovered the plasma insulin level to normal. As exhibited in Table 4, an increase in TC, LDL, VLDL, TG and reduced HDL (P < 0.001) were recorded in diabetic control rats compared with non-diabetic rats. Treatment of MECG to STZ-induced diabetic rats prevented the changes in lipid levels.

In the present study, the anti-diabetic and antihyperlipidemic activity of MECG was studied in STZ-induced diabetic rats.

Table 3: Effect of Coccinia grandis on biochemical parameters in rats.

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Plasma Insulin (μU/ml)	19.08 ± 0.41	4.11 ± 0.17***	19.26 ± 0.36###	9.96 ± 0.20###	12.20 ± 0.20###	14.65 ± 0.45###
Total Protein (g/dL)	9.81 ± 0.35	4.31 ± 0.38***	8.96 ± 0.41###	6.40 ± 0.20###	7.34 ± 0.16###	8.81 ± 0.26###
AST (IU/L)	46.15 ± 0.66	100.61 ± 1.05***	60.27 ± 0.66###	95.01 ± 0.90###	85.41 ± 0.78###	57.35 ± 0.90###
ALT (IU/L)	60.87 ± 0.37	116.85 ± 0.95***	60.43 ± 0.54###	98.63 ± 0.61###	92.97 ± 0.34###	60.37 ± 0.43###
ALP (IU/L)	121.18 ± 0.53	201.84 ± 0.54***	131.48 ± 0.70###	191.22 ± 0.47	162.15 ± 0.44###	132.15 ± 0.60###
Albumin (g/dL)	4.45 ± 0.17	3.23 ± 0.18***	4.18 ± 0.18###	3.53 ± 0.09	3.81 ± 0.06	4.24 ± 0.27###
Globulin (g/dL)	3.46 ± 0.15	1.99 ± 0.10***	3.32 ± 0.08###	2.75 ± 0.07###	2.94 ± 0.08###	3.33 ± 0.07###
A/G Ratio (g/dL)	1.17 ± 0.02	0.86 ± 0.02***	1.15 ± 0.028###	0.94 ± 0.03	1.00 ± 0.028#	1.12 ± 0.038###
Total Bilirubin (mg/dL)	0.35 ± 0.01	0.97 ± 0.02***	0.38 ± 0.02###	0.90 ± 0.03	0.70 ± 0.02###	0.39 ± 0.01###
Urea (mg/dL)	34.96 ± 0.57	72.96 ± 0.61***	37.50 ± 0.48###	61.15 ± 0.54###	51.19 ± 0.45###	39.08 ± 0.32###
Creatinine (mg/dL)	0.79 ± 0.04	1.48 ± 0.09***	0.75 ± 0.06###	1.13 ± 0.07###	0.98 ± 0.02###	0.87 ± 0.01###

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase: ALP: Alkalinephosphatase.
Values are Mean ± SEM.,n = 6 per group.
***P<0.001compare with control. #P<0.05 and###P<0.001, compare with diabetic control.

Table 4: Effect of *Coccinia grandis* on lipid profile in rats (mg/dL).

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
TC	81.43 ± 0.46	195.83 ±0.65***	94.12 ± 0.76###	172.20 ±0.40###	124.83 ±1.72###	94.38 ± 0.28###
HDL	34.43 ± 0.75	16.08 ± 0.45***	37.95 ± 0.57###	23.28 ± 0.43	27.05 ± 0.52###	34.40 ± 0.66###
LDL	43.72 ± 0.7	101.29 ±2.07***	41.26 ± 0.52###	54.60 ± 1.19###	46.79 ± 0.56###	40.77 ± 0.41###
VLDL	13.94 ± 0.28	42.22 ±0.49***	13.75 ± 0.27###	21.11 ± 0.33###	18.83 ± 0.19###	13.84 ± 0.22###
TG	101.97 ±0.69	168.25 ±0.99***	81.81 ±0.58###	151.24 ±1.51###	120.83 ±0.54###	91.94 ± 0.74###

TC:Total serum cholesterol; TG: Serum triglyceride; HDL: high-density lipoprotein;LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein
Values are Mean ± SEM.,n = 6 per group.
***P<0.001 compare withcontrol.
###P<0.001 compare with diabetic control.

Streptomyces achromogene, a gram-positive bacterium produces STZ, recognized as glucosamine-nitrourea and toxic glucoside can cure pancreatic beta-cell carcinoma (Petchi *et al.*, 2014). STZ treatment caused DNA fragmentation and rapid pancreatic β-cells destruction in rats (Eleazu *et al.*, 2013). It caused irregular glucose-stimulated insulin sensitivity, which reported as a feature of type-1 diabetes (Parasuraman *et al.*, 2015).

Severe body weight loss caused by STZ-induced diabetes mellitus because of a decrease in muscle mass due to lack of carbohydrates (Belayneh *et al.*, 2019). The current study has proven that MECG treatment improved body weights in diabetic rats. Rapid improvement of body weight in glibenclamide treated groups were comparable to non-diabetic rats. This is because of the ability of plant fraction to reduce hyperglycemia and maintain body weight.

ALT and AST play a significant role in converting amino acid to ketoacid. Meanwhile, serum ALP can detect both intra-hepatic and extra-hepatic bile obstruction. Furthermore, ALP, ALT and AST are known as enzyme markers for liver function, that released into the serum and increases enzyme activity if liver cells are damaged (Lala *et al.*, 2020). ALP, ALT, AST and total bilirubin levels are increased due to the hepatotoxic effect of STZ. This because, liver cytosol released these enzymes into the bloodstream and caused hepatocellular and posthepatic damages like biliary tract damage and biliary stone formation (Saleem and Naseer, 2014). As an end product of protein catabolism, urea is excreted in the urine. As an end product of creatine metabolism, creatine will be biosynthesized in the liver and enters into the blood circulation (Mohammed, 2019). Increased levels of urea and creatinine may lead to renal dysfunction. However, treatment with the different doses of MECG and glibenclamide significantly decreased ALP, ALT, AST, total bilirubin, urea and creatinine levels in blood indicates ameliorative effect of MECG on renal dysfunction and hepatocytes in the liver after administration of STZ in the diabetic rats (Alshathly, 2019). Restoration of decreased globulin, total protein, albumin/globulin ratio and albumin by plant extract and glibenclamide could be due to inhibition of proteolytic activity due to improved insulin production (Ali *et al.*, 2017).

In diabetic situation, insulin can damage lipid metabolism, and accumulation of lipids in the liver and blood causes abnormal fatty acid metabolism, which occurs after impairment of β-cells function (Erion *et al.*, 2016). Consequently, diabetic dyslipidemia act as significant risk factors for nephrotoxicity, myocardial infarction, atherosclerosis and coronary diseases (Xia *et al.*, 2017). Changes in lipid profile showed the progress of hyperlipidemia in diabetic rats due to increased hormone-sensitive lipase activity. It catalyzes triacylglycerols stored in adipocytes to fatty acids (Bolsoni-Lopes and Alonso-Vale, 2015). The present study reveals that MECG improved the serum lipid levels by reducing (TC, TG, LDL, and VLDL) and increasing HDL, may be due to high level of lecithin cholesterol acyltransferase activity, that resulted in regulation of blood lipids (Hassan *et al.*, 2015). Moreover, MECG showed favourable results on lipid metabolism-related hepatic enzymes. Thus, our study indicates MECG able to control dyslipidemia associated with diabetic complications.

The finding of tannins, alkaloid, cardiac glycosides, saponins, glycosides, terpenoids, and reducing sugars in MECG has proven its anti-oxidant and anti-diabetic effect. Terpenoids caused insulin-like activity to reduce blood glucose and inhibited glycogenolysis and gluconeogenesis (Grover *et al.*, 2002). Saponin can reduce hyperglycemia related oxidative stress in type 2 diabetes by restoring insulin resistance rather than potentially enhance -cell proliferation (Zheng *et al.*, 2018). Similarly, alkaloids (Wätjen *et al.*, 2005) inhibited α-glucosidase, researchers proven that tannins from plant extract contributed inhibitory activities on α- glucosidase and α-amylase (Li *et al.*, 2019), thus reduces intestinal glucose uptake. Flavonoids act as intermediary biosynthetic compound contributed to the inhibition of alpha-amylase, which can restore damaged beta cells in the pancreas. Polyphenolic compounds produced in the plants inhibited glucose transport processes by inhibiting intestinal sodium-glucose co-transporter-1 (S-GLUT-1) (Parasuraman *et al.*, 2019). Referring to the present experimental study, the anti-diabetic effect of the MECG against STZ induced rats might be due to the existence of the polyphenolic compounds, flavonoids, alkaloids, terpenoids, tannins and saponins.

CONCLUSIONS

Methanolic extract of *Coccinia grandis* leaves has significant anti-diabetic activity at the dose levels of 125, 250 and 500 mg/kg body weight in STZ-induced diabetic rats. Furthermore, methanolic extract of *Coccinia grandis* leaves inhibits STZ-induced hyperlipidemia in rats, which may help to prevent hyperlipidemia in diabetes mellitus.

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Conflict Of Interest

The authors declare that they have no conflict of interest for this study.

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