



In vivo antidiabetic activity of *Capparis erythrocarpos* (Capparaceae) root extract

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ABSTRACT

Background: *Capparis erythrocarpos* Isert has been reported to have antidiabetic effect on normoglycemic animals. However, there are no reports on its effect on the control of blood sugar levels in diabetic animals.

Objective: This study aimed to investigate the *in vivo* antidiabetic activity of *C. erythrocarpos* in streptozotocin (STZ)-induced diabetic mice.

Methods: Plants materials were collected in April 2018, and the study was conducted from April to July 2019. Antidiabetic activity of the hydroethanolic extract of *C. erythrocarpos* was determined at different doses of 250, 500, and 1,000 mg/kg bwt and compared to positive and negative controls. Acute antihyperglycemic activity in normal mice was investigated by oral glucose tolerance test (OGTT) method. Safety of the extract was evaluated by the use of “up and down” oral acute toxicity testing method. Statistical differences between the groups were assessed by Student’s t-test and one-way analysis of variance with Tukey’s multiple comparisons.

Results: *C. erythrocarpos* produced a significant reduction in fasting blood glucose level compared to the negative control in STZ-induced diabetic mice after 14 days of daily oral doses of the extract at 250 mg/kg bwt ($p = 0.0267$), 500 mg/kg bwt ($p = 0.0002$), and 1,000 mg/kg bwt ($p = 0.0011$). OGTT showed that the extract significantly lowered the blood glucose levels at 2 hours after oral glucose load at all doses provided 100 mg/kg bwt ($p = 0.0322$), 200 mg/kg bwt ($p = 0.0118$), and 500 mg/kg bwt ($p = 0.0222$). There were no statistically significant difference in clinical signs and symptoms of acute oral toxicity observed between control and treatment groups.

Conclusion: Oral administration of the hydroethanolic root extract of *C. erythrocarpos* is nonacutely toxic and exhibited a significant hypoglycemic activity in STZ-induced diabetic mice.

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Introduction

Diabetes mellitus is a chronic endocrine and metabolic syndrome which results when pancreatic beta-cells are unable to maintain adequate insulin secretion or insulin resistance when the cells of the body fail to respond adequately to the

insulin produced [1]. It is characterized by persistent hyperglycemia and alterations in protein and lipid metabolism (dyslipidemia) which leads to other metabolic complications such as retinopathy, neuropathy, nephropathy, accelerated atherosclerosis, and other cardiovascular diseases [2].

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The global prevalence of diabetes was estimated to be 2.8% in 2000, but this is expected to rise to 4.4% by 2030 with the number of affected people increasing from 171 million to 366 million [1]. In the African region, the WHO reported the prevalence to be 3.1% in 1980 and 7.1% in 2014 [3]. In 2016, the WHO reported the prevalence of diabetes in Tanzania to be 4.3%, and it causes more deaths in the age group of 30–69 years with the overall contribution of 2% of total mortality in the country [2].

The critical intervention in the management of diabetic complications and improving quality of life is the control of blood glucose levels [4,5]. This can be achieved by the use of insulin and other oral hypoglycemic agents such as metformin and insulin secretagogues as indicated in the WHO essential medicine list [5].

The modern treatment options for diabetes mellitus have several limitations which include serious adverse effects of each class of drugs [6] and high cost for some drugs [3]. There is a great dependence on traditional medicine for the management of chronic diseases including diabetes mellitus in the resource-limited to the middle-income world. This is partly attributed by the difficulty to access and afford the conventional medicines [7,8].

C. erythrocarpos is a plant belonging to the Capparidaceae (Capparaceae) family. The genus *Capparis* contains small trees and perennial shrubs which are found in tropical and warm temperate regions, and its fruits are edible [9,10]. The plant has been reported to have antidyslipidemic activity and decrease body weight, serum cholesterol, low-density lipoprotein, triglycerides, and serum leptin. It also lowers systolic blood pressure and increases the levels of high-density lipoprotein [11]. In addition, *C. erythrocarpos* has been scientifically proved to have anti-inflammatory and aphrodisiac activities [12,13]. Diabetes mellitus has been associated with metabolic dysregulation which itself induces inflammation; therefore, the use of agents with anti-inflammatory effects may affect both the insulin resistance and cardiovascular risk [14]. Many of available medicines for diabetes mellitus exert anti-inflammatory effects, which is likely to be mediated through their metabolic effects on hyperglycemia and hyperlipidemia or by directly modulating the immune system [14]. The disease is also among other chronic diseases, which is highly associated with sexual dysfunction. Erectile dysfunction among men with diabetes has strongly been associated with premature ejaculation and reduced libido [15]. Therefore, the use of product which can work on both diabetes

mellitus and sexual dysfunction will be of added advantage. Despite these exciting pharmacological reports on *C. erythrocarpos*, the antidiabetic activity of this plant has not been evaluated *in vivo*. This study was aimed to assess the antidiabetic activity and the safety profiles of *C. erythrocarpos* root extract using streptozotocin (STZ)-induced diabetic mice model and acute oral toxicity test, respectively.

Materials and Methods

Materials

Streptozotocin (Sigma-Aldrich, Germany), glibenclamide, chlorpropamide, ethanol, Glucometer (Medisign®, Tianjin, Empecs Medical Device Co., Ltd., Tianjin, China), pH meter, and carboxymethyl cellulose (CMC) were used. All materials were purchased through local suppliers in Dar es Salaam, Tanzania.

Study design and area

This was an *in vivo* study, in which acute oral toxicity and antidiabetic activity of *C. erythrocarpos* root extract were evaluated in white albino mice. The study was conducted in the laboratories at the School of Pharmacy and at the Institute of Traditional Medicine of Muhimbili University of Health and Allied Sciences (MUHAS) from April to July 2019.

Collection and identification of plant material

The plant materials were collected in April 2018 at Byamtemba village, Missenyi District in Kagera Region, Tanzania, and were taxonomically identified by Mr. Haji. O. Selemani, Botanist from the Department of Botany, University of Dar es salaam. Voucher specimen (Voucher number: AIM 07) was deposited at the Institute of Traditional Medicine Herbarium, MUHAS.

Extraction of plant material

The extraction was carried out by cold maceration method using 80% ethanol in water. Coarse-powdered root materials were mixed with 80% ethanol and kept at room temperature for 48 hours with occasional agitation. The mixture was strained, the marc was pressed, and the obtained mixture was filtered after standing. The filtrate was then concentrated at low temperature (50°C) using rotary evaporator (Rotavapor R-205, BÜCHI Labortechnik, Flawil, Switzerland), and complete drying was achieved by freeze-drying (BenchTop Pro®, SP Scientific, Suffolk, England).

Experimental animals

Male white albino mice (*Mus musculus*) weighing 20–30 g were obtained from the animal house at the Institute of Traditional Medicine, MUHAS. The mice were kept in good and clean environments in aluminum cages and had unrestricted access to standard pellet laboratory food and water under a 12-hours light/12-hours dark cycle. They were acclimatized to the laboratory environmental conditions for 5 days before carrying out the experiments. Streptozotocin was injected through intraperitoneal route, and *C. erythrocarpos* extract was given orally to minimize discomfort. The experimental protocol was approved by MUHAS Institutional Review Board (IRB).

Preparation of drug solution

The dried hydroethanolic root extract of *C. erythrocarpos* was suspended in 1% (w/v) CMC solvent. Appropriate dilutions were made to obtain the desired doses according to the bodyweight of mice.

Oral acute toxicity study

Oral acute toxicity of the plant extract was done by “up and down procedure” as per the Organisation for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals number 425 [16]. The study was aimed to develop first ideas about safe dose levels to be tested in studies with repeated administration and levels of acute tolerance. A limit dose of 2,000 mg/kg of the root extract was used, followed by 100, 300, and 700 mg/kg. Animals were observed for the clinical signs of toxicity for 14 days. Bodyweight was recorded at Days 0, 7, and 14.

Oral glucose tolerance test (OGTT)

Mice of both the sexes weighing 20–30 g were fasted for 18 hours with unrestricted access to water and were divided into five groups of six mice each. Animals were allocated randomly into different treatment groups using computer-generated random numbers. The groups were negative control (1% CMC 5 ml/kg orally) and positive control (chlorpropamide 100 mg/kg orally), and the other groups were orally administered with 100, 200, and 500 mg/kg of the plant extract. All mice were loaded with glucose (1 gm/kgwt orally) 30 minutes after administration of solvent, extract, or chlorpropamide. Blood glucose level of each mouse was measured by partial tail amputation procedure from the tail vein after glucose loading at 0.5, 1, 2, 3, and 4 hours by commercially available glucometer (Medisign®, Tianjin, Empecs Medical Device Co Ltd, Tianjin, China).

Induction of diabetes by STZ

After overnight fasting, diabetes was induced in male mice by intraperitoneal (i.p.) injection of STZ dissolved in 0.1 M citrate buffer (pH = 4.5) at a dose of 100 mg/kg body weight [17]. On the 5th day post injection, the mice with fasting blood glucose level above 8.0 mmol/l were considered diabetic and were used in the study. They were randomized into six groups of six mice each ($n = 6$) as shown in Figure 1.

Group I constituted normal control (un-manipulated mice), group II contained diabetic control (administered with 1% CMC solvent), and group III contained positive control treated with 10 mg/kg/day glibenclamide every day for 14 days. Groups IV, V, and VI contained diabetic mice treated with 250, 500, and 1,000 mg/kg bwt of the extract orally every day for 14 days, respectively. Fasting blood glucose level was measured at days 0 and 14 by partial tail amputation procedure from the tail vein by glucometer. Body weight was recorded at Days 0, 7, and 14.

Statistical analysis

The data for blood glucose level and body weight were analyzed by GraphPad Prism software (Version 8.0.1) and were expressed as mean \pm standard deviation (SD). A comparison between any two groups was done using Student’s paired t-test, whereas a comparison among groups was performed by one-way analysis of variance with Tukey’s multiple comparison tests.

Results

Acute toxicity test

The results of acute oral toxicity test revealed that at higher dose of 2,000 mg/kg bwt, three animals

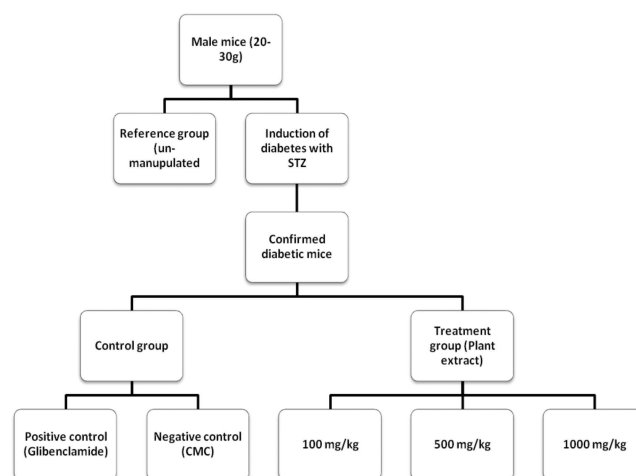


Figure 1. Flowchart for induction of diabetes in mice and assignment of the treatment groups.

showed an increase in respiratory rate compared to the control group which resolved within 3 hours. No other signs of toxicity were observed at 2,000 mg/kg dose and at lower doses of 100, 300, and 700 mg/kg. Changes in body weight of animals within the group at different days were not statistically significant different as shown in Table 1.

Oral glucose tolerance test (OGTT)

Administration of glucose (1 g/kg) produced a significant change in blood glucose level of normal mice. Treatment with the extract of *C. erythrocarpos* significantly reduced the blood glucose level at 2 hours at all doses provided such as 100 mg/kg bwt ($p = 0.0322$), 200 mg/kg bwt ($p = 0.0118$), and 500 mg/kg bwt ($p = 0.0222$) compared to normal control. Chlorpropamide (100 mg/kg, p.o) significantly reduced the blood glucose level in normal fasting, at 0.5 hours ($p = 0.0025$), 1 hour ($p = 0.0008$), and 2 hours ($p = 0.0002$) compared to normal control group. The results of mean blood glucose levels at 0, 0.5, 1, 2, 3, and 4 hours are summarized in Table 2.

Hypoglycemic effect of the extract in STZ-induced diabetic mice

Blood glucose levels significantly increased in diabetic control compared to normal control (unmanipulated) after induction of diabetes (Day 0, $p < 0.0001$) which persisted until the end of the study period (Day 14, $p < 0.0001$). A significant decrease in blood glucose levels was observed in CE-250 ($p = 0.0267$), CE-500 ($p = 0.0002$), and CE-1000 ($p = 0.0011$) groups compared to diabetic control at Day 14. A significant reduction in blood glucose level was observed in the positive control (glibenclamide) group compared to diabetic control at Day 14 ($p = 0.0001$). There were no significant differences in blood glucose levels between CE-250, CE-500, CE-1000, and positive control. The results of Days 0 and 14 are shown in Table 3 and Figure 2.

Changes in body weight

There were no statistically significant differences in mean body weight of mice ($p > 0.05$) during the whole treatment period as shown in Table 4.

Table 1. Effect of single-dose hydroethanolic root extract of *C. erythrocarpos* on body weights of normal mice.

Treatment group	Body weight (g)			n	p-value
	Day 0	Day 7	Day 14		
CE-100	23.9 ± 0.71	25.43 ± 1.91	26.33 ± 2.81	5	0.2743
CE-300	25.68 ± 0.50	27.03 ± 0.86	27.00 ± 1.00	5	0.0733
CE-700	28.20 ± 1.32	27.00 ± 1.00	29.33 ± 0.58	5	0.0842
CE-2000	28.20 ± 0.84	27.00 ± 2.58	27.00 ± 2.65	5	0.6149
Control (CMC)	26.60 ± 1.52	27.00 ± 1.72	28.33 ± 2.08	5	0.4103

Values are presented as Mean ± SD. CE-100, CE-300, CE-700, and CE-2000 represent groups administered with *C. erythrocarpos* root extract at doses of 100, 300, 700, and 2000 mg/kgbw, respectively.

Table 2. Effect of hydroethanolic root extract of *C. erythrocarpos* on OGTT.

Treatment group	Fasting blood glucose levels (mmol/l)					
	0 hour	0.5 hour	1 hour	2 hours	3 hours	4 hours
NC	6.43 ± 1.30	9.00 ± 1.52	7.42 ± 0.67	6.16 ± 0.90	4.33 ± 0.38	4.00 ± 0.59
PC	7.02 ± 0.66	5.82 ± 0.90**	4.87 ± 0.52***	3.90 ± 0.19****	3.77 ± 0.39	3.85 ± 0.40
CE-100	6.63 ± 0.51	9.08 ± 1.05	6.72 ± 0.67	4.90 ± 0.53*	4.20 ± 0.48	4.18 ± 0.40
CE-200	6.17 ± 0.80	7.45 ± 1.35	6.17 ± 0.99	4.66 ± 0.61*	4.20 ± 0.50	4.25 ± 0.42
CE-500	6.40 ± 1.40	8.32 ± 1.61	6.68 ± 0.82	4.83 ± 0.86*	4.40 ± 0.97	4.75 ± 1.15

Each value represents Mean ± SD, $n = 6$. NC; Normal control (CMC), PC; Positive control (Chlorpropamide), CE 100; 100 mg/kgbw dose, CE-200; 200 mg/kgbw dose, and CE-500; mg/kgbw dose.

*Represents statistical significance versus negative control ($p \leq 0.05$).

**Represents statistical significance versus negative control ($p \leq 0.01$).

***Represents statistical significance versus negative control ($p \leq 0.001$).

****Represents statistical significance versus negative control ($p \leq 0.0001$).

Discussion

This study indicates that the hydroethanolic root extract of *C. erythrocarpos* exhibited a marked antidiabetic activity in STZ-induced diabetic mice by lowering fasting blood glucose levels. The trend of effect is observed to be dose-dependent despite the insignificant antihyperglycemic effect produced by higher doses of the extract in comparison to a lower dose of the extract. More works need to be done to establish the dose effect relationship.

The previous report indicates that phytochemical screening of *C. erythrocarpos* revealed the presence of alkaloids and flavonoids as predominant constituents in the crude extract [12]. Therefore, the observed hypoglycemic activity could be due to its phytochemical constituents such as alkaloids and flavonoids which are groups of compounds that have

been reported to have antidiabetic potential [12,18]. Alkaloids from a member of the same genus *C. spinosa* have been reported to increase insulin secretion and decrease glucose absorption from the small intestine in animal models. In addition, phenolic compounds from the same plant have been reported to decrease glucose absorption from the small intestine, increase glucose uptake, decrease glucose output, and decrease oxidative stress, thus decreasing diabetic complication [19]. In general, natural products are potential antidiabetic agents because their action involves multiple mechanisms [20].

The results of acute oral toxicity study showed that the extract of *C. erythrocarpos* is safe at dose levels below 2,000 mg/kg bwt which imply that this

Table 3. Effect of hydroethanolic root extract of *C. erythrocarpos* on fasting blood glucose levels in STZ-induced diabetic mice.

Treatment groups	Fasting blood glucose level (mmol/l)	
	Day 0	Day 14
Normal control (Unmanipulated)	6.03 ± 0.41****	6.11 ± 0.66****
Diabetic control	9.42 ± 1.49	11.65 ± 2.91
Positive control	9.15 ± 1.28	6.95 ± 0.92****
CE (250 mg/kg)	9.40 ± 1.12	8.85 ± 0.70*
CE (500 mg/kg)	9.42 ± 0.72	7.08 ± 0.92****
CE (1000 mg/kg)	9.05 ± 0.38	7.72 ± 0.82***

Each value represents Mean ± SD. *n* = 6.

*Represents statistical significance versus diabetic control ($p \leq 0.05$).

**Represents statistical significance versus diabetic control ($p \leq 0.01$).

***Represents statistical significance versus diabetic control ($p \leq 0.001$).

****Represents statistical significance versus diabetic control ($p \leq 0.0001$).

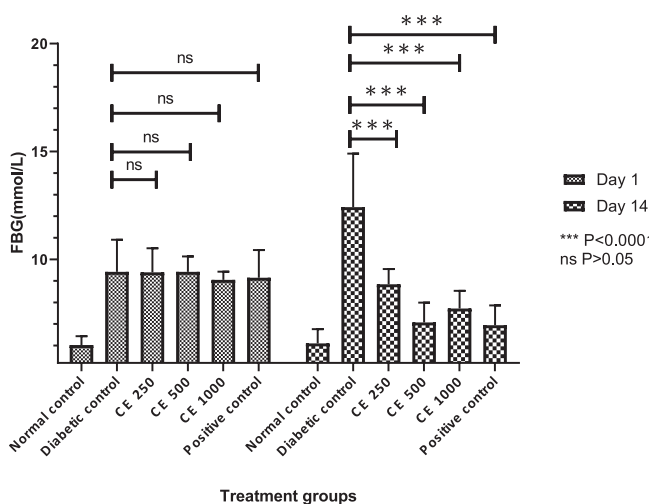


Figure 2. Effect of the plant extracts on fasting blood glucose levels. Positive control (Chlorpropamide), CE 100; 100 mg/kg bwt dose, CE-200; 200 mg/kg bwt dose, and CE-500; mg/kg bwt dose. *Represents statistical significance versus negative control ($p \leq 0.05$), **Represents statistical significance versus negative control ($p \leq 0.01$), ***Represents statistical significance versus negative control ($p \leq 0.001$) and **** Represents statistical significance versus negative control ($p \leq 0.0001$).

Table 4. Effect of hydroethanolic root extract of *C. erythrocarpos* on mean body weights in STZ-induced diabetic mice.

Treatment group	Mean Body weight (g)			<i>p</i> value
	Day 0	Day 7	Day 14	
Normal control (Unmanipulated)	25.00 ± 1.79	25.17 ± 1.17	26.00 ± 2.00	0.5598
Diabetic control	26.33 ± 3.08	28.50 ± 3.56	27.00 ± 3.58	0.5441
Positive control	27.33 ± 2.42	30.17 ± 2.23	29.00 ± 2.61	0.1607
CE (250 mg/kg)	27.83 ± 2.32	30.67 ± 2.50	29.50 ± 2.17	0.1414
CE (500 mg/kg)	26.17 ± 3.06	27.83 ± 4.22	27.33 ± 3.01	0.7011
CE (1000 mg/kg)	25.33 ± 1.75	26.67 ± 1.63	26.83 ± 1.17	0.2137

Each value represents Mean ± SD, *n* = 6.

plant could be safe for use. Based on the OECD guideline, the toxicity data have preliminarily shown that the LD₅₀ of the extract is above 2,000 mg/kg, and therefore, the doses used in this study were safe. This concurs with the results reported elsewhere on the chronic toxicity of *C. erythrocarpos* that it produces no organ-specific toxicity at a dose below 2,000 mg/kg bwt [21]. However, the long-term effect of *C. erythrocarpos* on the vital organs should be determined before initiating clinical applications.

OGTT was conducted to evaluate the acute anti-hyperglycemic effect of the extract and this study found that, at doses of 100, 200, and 500 mg/kg, the extract caused a significant improvement in glucose tolerance by inhibiting the elevation of postprandial glycemia at 2 hours as it was observed for the standard antidiabetic agent used, chlorpropamide. These findings may suggest that the hydroethanolic root extract of *C. erythrocarpos* exhibits antihyperglycemic by enhancing glucose utilization since it significantly decreased the blood glucose level in glucose-loaded mice OGTT. Such an effect may be accounted for, in part, by the increase in the pancreatic secretion of insulin from pancreatic beta cells, decrease in the rate of intestinal glucose absorption and stimulation of peripheral glucose utilization, or decrease in glycogenolysis and gluconeogenesis [22]. Impaired glucose tolerance is characterized with persistent hyperglycemia which results from inadequate insulin secretion and actions in the postprandial state and may also be potentiated by overproduction of glucose by the liver [2].

The ethanolic extract of *C. erythrocarpos* has been reported to have a dose-dependent reduction in body weight with time compared to control in Sprague–Dawley rats after receiving a daily oral dose of the plant extract for 12 weeks [11]. However, in this study, we found that there were no significant changes in mean body weight of white albino mice following a daily dose of plant extract for 2 weeks.

The plant has also been reported to have the ability to reduce serum atherogenic lipid levels, and elevation of nonatherogenic lipid levels with subsequent reduction in atherogenic indices may lead to reduction in elevated systolic blood pressure. All these properties together with the observed antidiabetic activity in this study indicate that the plant can find the use in the control of diabetes and other major risk factors associated with cardiovascular disease [11].

Conclusion

Oral administration of hydroethanolic root extract of *Capparis erythrocarpos* is nonacutely toxic and

exhibited hypoglycemic effect in diabetic mice. Further studies should be done to investigate the responsible phytochemicals and their mechanism of actions.

Acknowledgment

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Ethics approval

The study was approved by MUHAS, IRB and given the approval number DA.282/298/01.C.

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