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Original Article

Antihyperglycemic activity of *Caralluma quadrangula* in streptozotocin-induced diabetic rats

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ABSTRACT

Diabetes of type 2 is a worldwide epidemic disease of global prevalence. *Caralluma quadrangula* is wild Saudi plant used by traditional healers as antidiabetic, in case of hunger, and many other diseases. Nothing was reported to justify the use of the plant in case of diabetes. The plant material was extracted with water and with methanol, the methanol fraction was further fractionated into chloroform, *n*-butanol, in addition to the remaining mother liquor. The water and methanolic extracts as well as different methanolic fractions were evaluated in STZ-induced diabetic rats for their antihyperglycaemic activity. The results showed a significant decrease in fasting blood glucose levels in diabetic treated rats after the administration of most of the extracts and fractions of *C. quadrangula* and glibenclamide. The most potent activity was shown by administration of the methanolic extract (200 mg/kg), chloroform, *n*-butanol fraction at dose of 100 mg/kg, as well as the major pregnane glycoside russelioside B isolated from *C. quadrangula*. In conclusion, this study proved the traditional use of *C. quadrangula* in diabetes mellitus.

1. Introduction

Diabetes of type 2 is a worldwide epidemic disease of global prevalence. The high incidence of this disease stimulated the researchers to look for antidiabetic agents in the traditional wealth of the humanity. Herbal drugs or their extracts are prescribed widely, even when their biological active compounds are unknown, because of their relatively low costs. Wide array of plant-derived active principles were shown to have antidiabetic activity [1].

Several *Caralluma* species showed antihyperglycemic activity of their crude extracts or their corresponding fractions [2–5].

In a continuation of our interest in the chemical and biological investigation of the members of genus *Caralluma* [2,3], the antihyperglycemic activity of the extracts, fractions and the major pregnane glycoside of the aerial parts of *C. quadrangula* indigenous to the Kingdom of Saudi Arabia was investigated. *C. quadrangula* extract has been used in Saudi traditional medicine in cases of thirst and hunger and for the treatment of diabetes, vitiligo, melasma and freckles [6].

2. Materials and methods

2.1. Chemicals

Streptozotocin (STZ) and α-D-glucose, glibenclamide, N-acetylcysteine and glucose-6-phosphatase (G-6-Pase) were purchased from Sigma–Aldrich (St Louis, MO, USA). Insulin kit (Coat-A-Count Insulin) was purchased from Siemens, Medical Solutions Diagnostics (Los Angeles, USA). All other biodiagnostic kits were purchased from Diagnostic and Research Reagents (Giza, Egypt).

2.2. Plant material

The whole plant of *C. quadrangula* (Forssk.) N.E.Br. (syn. *Stapelia quadrangula* Forssk.) was collected from Abha-Al-Taif road, Saudi Arabia, in May 2010 and were dried in shade. A specimen was deposited in the herbarium of College of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia (#CQ 1027).

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2.3. Extraction and isolation

The air dried powdered aerial parts of *C. quadrangula* (100 g) were extracted with boiling water (300 ml) for 15 min and the marc was extracted twice by washing boiling water (2 × 100 ml) to give on evaporation under reduce pressure 11 g water extract (WE). The air dried powdered aerial parts of *C. quadrangula* (480 g) were extracted with MeOH (3 × 2 L) on cold using Ultra-turrax T50 homogenizer. The solvent was evaporated under reduced pressure to give 82 g of brown residue (ME). Part of the residue (65 g) was suspended in distilled water (300 ml) and partitioned successively with chloroform (4 × 500 ml), and *n*-butanol (4 × 500 ml) to yield 8.8 (CE) and 35.8 g (BE), respectively. The remaining water fraction (WRF) was evaporated to give 20.1 g. Russelioside B [(calogenin 20-*O*-*β*-D-glucopyranosyl-3-*O*-[*β*-D-glucopyranosyl-(1 → 4)-*β*-D-(3-*O*-methyl-6-deoxy)galactoside, RB] was isolated from *n*-butanol fraction by chromatography on a Si gel column following procedure reported by Al-Yahya et al. [7]. The purity of compound RB was checked by measuring its mp, superimposed IR and comparing its spectral data (^{1}H- and ^{13}CNMR) with those reported in literature [7]. RB was first isolated from *Caralluma russeliana* in a high yield (~3% of dry powder) and further isolated from *Caralluma tuberculata* (unpublished data) and quantified by LC-MS [3].

2.4. Animal study

2.4.1. Animals

Adult male albino Wistar rats (180–200 g) were purchased from laboratory animals' house of National Institute of Cancer, Cairo-Egypt. All animals were housed in plastic cages with free access to drinking water and a pellet diet, under controlled conditions of humidity (50 ± 10%), light (12/12 h light/dark cycle) and temperature (25 ± 2 °C). The investigation complies with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). All experimental experiments are conducted according to the guidelines of the ethical committee for animals experimentation at faculty of Pharmacy Cairo University.

2.4.2. Experimental design

Animals made diabetic by a single intraperitoneal (i.p.) injection of STZ (50 mg/kg body weight) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5) after overnight fasting. STZ injected animals were allowed to drink 5% glucose solution overnight to overcome the initial drug-induced hypoglycemic mortality [8,9]. The animals were allowed to recover for two days before their blood glucose levels were tested using Accu check Active glucose strips (Roche Diagnostics Polska Ltd., Warszawa, Poland) from blood samples collected via the tail vein. Rats were considered diabetic if their fasting blood glucose level was at or over 250 mg/dl (**Groups 2–15**). Animals that did not become diabetic were not used in the study.

The rats were equally divided and randomly assigned in the following groups: **Group 1**: healthy rats received both vehicles (0.1 M citrate buffer, pH 4.5 and daily oral dose of 0.5% CMC) and served as normal control group. **Group 2**: diabetic rats received daily oral dose of 0.5% CMC and for 28 days, served as diabetic group. **Groups 3 and 4**: diabetic rats received daily oral dose of 100 and 200 mg/kg (in 0.5% CMC) of methanol extract, respectively. **Groups 5 and 6**: diabetic rats received daily oral dose of 100 and 200 mg/kg (in 0.5% CMC) of water extract, respectively. **Groups 7 and 8**: diabetic rats received daily oral dose of 50 and 100 mg/kg (in 0.5% CMC) of chloroform fraction, respectively. **Groups 9 and 10**: diabetic rats received daily oral dose of 50 and 100 mg/kg (in 0.5% CMC) of *n*-butanol fraction, respectively. **Groups 11 and 12**: diabetic rats received daily oral dose of 50 and 100 mg/kg (in 0.5% CMC) of water remain fraction, respectively. **Groups 13 and 14**: diabetic rats received daily oral dose of 15 and 25 mg/kg (in 0.5% CMC) of russelioside B. **Group 15**: diabetic rats received daily oral dose of 5 mg/kg (in 0.5% CMC) of glibenclamide.

All the treatment started 3 days after induction of diabetes and continued for 28 days. At the end of the treatment period, the rats were fasted overnight, sacrificed by decapitation. The blood was collected for assaying the levels of blood glucose and serum insulin. The liver of each animal was rapidly isolated, washed with ice cold saline and blotted dry. Portion of the liver was accurately weighed and homogenized in ice cold solution containing 0.15 M KCl; 4 mM $MgSO_4$, 4 mM EDTA and 4 mM N-acetylcysteine, pH 7 and centrifuged at 12,000×*g* at 4 °C for 10 min. The resultant supernatant was used in estimation of glucose-6-phosphatase [10]. Body weights of all the animals were recorded prior to the treatment and sacrificed.

2.4.3. Biochemical analysis

Blood samples were allowed to clot, centrifuged at 1000×*g* at 4 °C for 15 min and the separated sera were used for the determination of insulin and glucose levels using Rat Insulin ELISA ki, DRG international Inc., USA and Bicon (Germany) colorimetrically, respectively.

3. Statistical analysis

Results were expressed as mean ± standard error of the mean (SEM) for eight rats in each group. Data were analyzed using one-way analysis variance (ANOVA), and groups means were compared with Tukey-Kramer's test. A value of $P < 0.05$ was considered statistically significant.

4. Results

4.1. Effect on body weight

Table 1 shows that the final body weight of the untreated control group increased significantly compared to the beginning of the experiment, whereas a significant decrease in body weight was observed in the diabetic group in respect to the control. Water and methanolic extracts, as well as fractions chloroform, *n*-butanol and remaining water fractions resulted from

Table 1
Effect of the methanolic extract and its different fractions of the aerial parts of *Caralluma quadrangula* on body weight in STZ diabetic rats.

	Body weight g (day 0)	Body weight g (day 28)
Control, Gr-1	192.45 ± 3	240 ± 5
Diabetic, Gr-2	188.8 ± 2.9	149.2 ± 5.4[a]
MeOH, Gr-3(100 mg/kg)	190.5 ± 3.1	174.2 ± 5.2[a]
MeOH, Gr-4 (200 mg/kg)	192.8 ± 3.1	208.3 ± 3.8[a,b]
Water, Gr-5(100 mg/kg)	188.3 ± 3.3	174.2 ± 7.6[a]
Water, Gr-6(200 mg/kg)	190.2 ± 2.88	183.3 ± 2.47[a,b]
$CHCl_3$, Gr-7(50 mg/kg)	188.8 ± 2.9	182.5 ± 4.9[a,b]
$CHCl_3$, Gr-8(100 mg/kg)	185.8 ± 2.7	189.16 ± 4.36[a,b]
n-Butanol, Gr-9(50 mg/kg)	194.16 ± 2.7	174.16 ± 4.17[a]
n-Butanol, Gr-10 (100 mg/kg)	186.7 ± 3	204.17 ± 3[a,b]
H_2O remain, Gr-11(50 mg/kg)	186.16 ± 3	170 ± 5.9[a]
H_2O remain, Gr-12 (100 mg/kg)	189.16 ± 3.7	173.33 ± 5.4[a]
RB, Gr-13(15 mg/kg)	190.83 ± 3.2	174.16 ± 5.23[a]
RB, Gr-14 (25 mg/kg)	187.5 ± 4	210.83 ± 5.8[a,b]
Glibenclamide, Gr-15(5 mg/kg)	189.16 ± 3.27	217.7 ± 7.5[b]

Values are expressed as means ± S.E of 8 observations.
[a] Significant difference from normal control group at $p < 0.05$.
[b] Significant difference from diabetic group at $p < 0.05$.

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fractionation of methanolic extract showed a significant increase in body weight compared to the diabetic group. Nearly recovery in body weight was significant with methanolic extract (200 mg/kg), the *n*-butanol fraction (100 mg/kg), RB (25 mg/kg) in comparison to other fractions and this change was comparable to the glibenclamide treated group.

4.2. Effect on fasting blood glucose level

From the results in Table 2, a significant decrease in fasting blood glucose levels in diabetic treated rats was observed after the administration of most of the extracts and fractions of *C. quadrangula* and glibenclamide. The most potent activity was shown by the methanolic extract (200 mg/kg), chloroform, *n*-butanol fraction at dose of 100 mg/kg, as well as RB to diabetic animals, which resulted in decrease FSG from 600.3 ± 33.96 (diabetic control) to 319.5 ± 26.34, 320.16 ± 22.52, 318.5 ± 21.86, and 322.66 ± 20.4, respectively.

4.3. Effect on hepatic glucose-6-phosphatase (G-6-Pase) activity

The activity of gluconeogenic enzyme, G-6-Pase was significantly increased in the diabetic rats compared to those in normal control. The activity of hepatic G-6-Pase (Table 2) was significantly reduced by MeOH extract (200 mg/kg), chloroform, *n*-butanol fractions (100 mg/kg) and RB (25 mg/kg) by about 51.1%, 57.7%, 51.8% and 54.8%, respectively.

4.4. Effect on serum insulin

There was a significant decrease in the plasma insulin levels in diabetic untreated group compared to those in normal rats. The treatment with the various extracts and fractions and RB showed various activities. The methanolic extract (200 mg/kg), chloroform and *n*-butanol fractions (100 mg/kg) showed significant increase in the insulin levels in the diabetic treated rats, which is similar to that of glibenclamide treated rats (Table 2).

5. Discussion

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, abnormal lipid and protein metabolism along with specific long-term complications [11].

Members of genus *Caralluma* have been reported to have antihyperglycemic, viz *C. tuberculata* [2,3], *Caralluma attenuate* [12], *C. fimbriata* [5], *C. umbellata* [13], *C. adscendens* [14]. In the course of screening program for biologically active medicinal plants with antidiabetic activity, *C. quadranguala* was evaluated for its antihyperglycemic activity in diabetic rats.

In this study, different extracts and fractions of *C. quadrangula*, as well as the major pregnane glycoside isolated were investigated for their effects in STZ-diabetic rats. n-Butanol fraction which was identified as the most active fraction, was subjected to chromatographic separation to afford four compounds. All the isolated compounds were previously isolated and identified as russelioside A (**1**), russelioside C (**2**), russelioside B (**3**) and a flavone glycoside (**4**) identified as luteolin 4′-*O*-*β*-D-neohesperidoside. The structural elucidation of the isolated compounds were carried out by comparison to the reported spectral data (^{1}H- and ^{13}NMR) and by chromatographic comparison with reference samples [7].

The obtained changes in physiological parameters in this study included decrease in body weight, increase in serum glucose, increase in G-6-Pase and decrease in insulin level in STZ-diabetic rats, which are consistent with the previously reported findings [15]. STZ selectively destroys pancreatic β-cells, inhibits synthesis and release of insulin and causes the onset of DM [16]. Hyperglycemia results from decrease in glucose utilization by the liver and peripheral tissues and increase in hepatic glucose production [16]. The decrease in body weight in diabetic rats could be attributed to the degradation of structural proteins as a weight [17]. In experimental diabetes, enzymes of glucose metabolism are markedly altered. Insulin decreases glucogenesis by decreasing the activities of key enzymes such as glucose-6-phosphatase, fructose-1, 6-bioposphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxykinase [18]. Glucose-6-phosphatase is an important enzyme in homeostasis of blood glucose as it catalyzes the terminal step both in glucogenesis and glycogenolysis [19].

Treatment of the animals with different extracts, fractions or major compound RB for four weeks showed significant decrease in BG at the higher doses, except for water remain fraction. Water extract showed less activity relative to other fractions. Serum insulin level was increased in all fractions tested, the best results was obtained by $CHCl_3$ and *n*-butanol fractions (100 mg/kg) which showed increase from 0.15 in diabetic animals into 0.71 and 0.69 (μg/l), respectively, this may indicate that the antihyperglycemic activity of the plant may be due to stimulation of insulin secretion[3]. The increase of G-6-Pase in STZ-diabetic animals

Table 2
Effect of oral administration of *Caralluma quadrangular* extracts and fractions or glibenclamide on blood glucose level, serum insulin and Glucose-6-Phosphatase of STZ-induced diabetic rats after 28 days of treatment.

	Blood glucose (mg/dl)	Serum insulin (μg/l)	Liver G-6-Pase (U/min/mg protein)
Control, Gr-1	97.56 ± 4.5	2.5 ± 0.14	0.27 ± 0.07
Diabetic, Gr-2	600.3 ± 33.96[a]	0.15 ± 0.019[a]	0.675 ± 0.07[a]
MeOH, Gr-3(100 mg/kg)	441.16 ± 34.14[a]	0.35 ± 0.039[a]	0.62 ± 0.05[a]
MeOH, Gr-4(200 mg/kg)	319.5 ± 26.34[b]	0.6 ± 0.038[a,b]	0.33 ± 0.02[b]
Water, Gr-5(100 mg/kg)	427.6 ± 35.16[a]	0.37 ± 0.05[a]	0.075 ± 0.07[a]
Water, Gr-6(200 mg/kg)	362.16 ± 31.5	0.4 ± 0.04[a]	0.5 ± 0.07
$CHCl_3$, Gr-7(50 mg/kg)	413.16 ± 27.85	0.46 ± 0.05[a]	0.42 ± 0.04
$CHCl_3$, Gr-8(100 mg/kg)	320.16 ± 22.52[b]	0.71 ± 0.056[a,b]	0.285 ± 0.03[b]
n-Butanol, Gr-9(50 mg/kg)	424.3 ± 33.86[a]	0.253 ± 0.03[a]	0.405 ± 0.06
n-Butanol, Gr-10(100 mg/kg)	318.5 ± 21.86[b]	0.69 ± 0.05[a,b]	0.325 ± 0.03[b]
H_2O remain, Gr-11(50 mg/kg)	467.83 ± 21.86[a]	0.29 ± 0.03[a]	0.71 ± 0.07[a]
H_2O remain, Gr-12 (100 mg/kg)	422.16 ± 24.38[a]	0.33 ± 0.6[a]	0.54 ± 0.06
RB, Gr-13(15 mg/kg)	434.5 ± 21.07[a]	0.39 ± 0.035[a]	0.59 ± 0.07[a]
RB, Gr-14(25 mg/kg)	322.66 ± 20.4[b]	0.45 ± 0.14[a]	0.305 ± 0.048[b]
Glibenclamide, Gr-15(5 mg/kg)	264.0 ± 14.44[b]	0.88 ± 0.029[a,b]	0.255 ± 0.04[b]

Values are expressed as means ± S.E of 8 observations.
[a] Significant difference from normal control group at p0.05.
[b] Significant difference from diabetic group at p0.05.

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(0.675 U/min/mg protein), was decreased by administration of different extracts and fractions, its level was nearly normalized by $CHCl_3$ (100 mg/kg) to the value of 0.285 U/min/mg protein, followed by RB (25 mg/kg), *n*-butanol fraction (100 mg/kg) and methanol extract, with the values of 0.305, 0.325 and 0.33 U/min/mg protein, respectively. In the present study, the increased activities of glucose-6-phosphatase in the liver of diabetic rats may be due to insulin deficiency, as expression of this enzymes is regulated by insulin. The increased glucose-6-phosphatase activity, in turn, led to a further increase in hepatic glucose production and aggravated the glucose imbalance [20]. The change in body weight was not strong in all tested fractions and RB, this may be due to that the effect of their pregnane gycosidal content which showed appetite depressant activity [21,22].

In conclusion, methanol, $CHCl_3$, *n*-butanol as well as RB are effective in controlling the elevated blood glucose levels in STZ-induced diabetic rats with comparable activity. This antidiabetic activity, at least partly, may be due to stimulation of insulin release, inhibition of G-6-Pase activity, enhancement of glucose utilization and inhibition of glucose absorption. This activity could be attributed to the presence of pregnane glycosides content of the plant in $CHCl_3$ and *n*-butanol fraction and marginal activity for water remain fraction [23–25]. Further investigation of the major compound RB is running to clarify its mechanism and its role as a hypoglycemic agent.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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