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

[1] Abdullah Mohammed Al-Adhreai, [2] Fahmi S Moqbel, [3] Alqadasi AAA, [*4] Fahd M Abd Algalil
[1, 2, 4] Department of Zoology, Faculty of Applied Science, Thamar University, Yemen
[3] Agriculture Department, College of Agriculture and Veterinary Medicine, Thamar University, Yemen

Abstract
Caralluma quadrangula extract is widely used by different ethnic group of the world for a long time for the treatment of diseases like diabetes, wounds, cuts, hepatoprotective, etc. white albino rats were rendered diabetic by intraperitoneal administration of alloxan (150 mg/kg body weight). The male albino rats were grouped into eight groups of six animals per group. Daily orally treatment with the extract for 15 days significantly reduced blood glucose, glycosylated haemoglobin (HbA1C), triglycerides, total cholesterol, low density lipoprotein and very low density lipoproteinalso insulin, blood urea and high density lipoprotein (HDL) found to be improved ($p \lessdot 0.05$) as compared to diabetic control group. It is concluded that *Caralluma quadrangular* extract has significant anti-diabetic and hypolipidemic effect.

Keywords: antihyperglycemic, *Caralluma quadrangular*, diabetes and hypolipidemic

Introduction
Diabetes mellitus is a metabolic disease characterized by a chronic hyperglycemia, resulting from a deficiency in insulin production by β-cell or insulin cellular resistance [1].
As common endocrine disease, diabetes mellitus is defined as a group of metabolic diseases characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action or both, causing impaired carbohydrate, lipid and protein metabolism and increased risk of cardiovascular disease [2].
Diabetes is categorized into two types; Type 1 diabetes is also called insulin dependent diabetes mellitus. In this type, the body does not produce insulin; therefore, patients with this type of diabetes must receive daily insulin injections to remain alive. Type 1 diabetes also accounts for 5%–10% of diabetes cases. Type 2 diabetes is known as non-insulin-dependent diabetes mellitus. In this case, the body does not produce enough amounts of insulin or does not properly use this substance. Type 2 diabetes is the most common among patient nowadays. In adults, this type of diabetic accounts for about 90%–95% of all diagnosed cases. However, 9 out of 10 people of this group do not know that they have pre-diabetes [3-4].
Though there is a considerable progress in the treatment of diabetes through oral hypoglycemic agents, searching for more developed drugs is in full swing because the existing synthetic drugs have several limitations. The herbal drugs with anti-diabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine [5].
The use of traditional medicine at the primary health care level is widespread in Yemen [6-8]. Under developing countries like Yemen depend mainly on plant resources for herbal medicines. The use of medicinal plants as a traditional medicine is well known in rural areas of many under developing countries [9-10].
The medical significant genus *Caralluma* is deeply studied for its stem and fruits. It belongs to the family Asclepiadaceae, which comprises 200 genera and 2500 species [11-12].
Caralluma species (Family: Asclepiadaceae) have been used in semi-arid areas of Africa, South-Asian, Middle East and UAE as emergency foods where they are harvested from the wild [13-14].
The most common *Caralluma* species in Yemen is *C. penicillata* that widely is used in folk medicine having an antiulcer effect. *C. penicillata* has been used in Yemeni traditional medicine for the treatment of peptic ulcer and as anti-inflammatory [15].
A range of medicinal uses of *Caralluma* species have been documented in both Arabic and Indian traditional medicine including treatment of diabetes, cancer, tuberculosis, snake and scorpion bites, skin rashes, scabies, fever, and inflammation [16-19]. *Caralluma* species have shown anti-diabetic [20-21].
Herbal drugs are of low cost and free from adverse effects [22-23] studied the effect of 10% ethanolic extract of *Caralluma Arabica* for the anti-nociceptive activity *Caralluma Arabica* showed significant anti-nociceptive properties in all the models studied. The blood glucose level reduced in normal rat and diabetic rats were also significantly lowered. The anti-diabetic effect of extracts of *Caralluma adscendens* on fasting blood glucose level after two weeks of daily treatment of various extract of *Caralluma adscendens* led to reduce blood glucose level by 30-70% Butanol, methanol, aqueous and petroleum ether extract significantly decreased the elevated blood glucose level in comparison to untreated diabetic rats-treated with glibenclamide and *Caralluma adscendens* extract of alloxan induced diabetic rats produced significant reduction in total cholesterol, triglyceride and LDL levels. HDL levels were significantly increased by Glibenclamide, n-butanol and

methanol extract while aqueous and pet ether extract have little effect on lipid profile [21].

Materials and Methods

Plant Materials

The Plant materials of *C. quadrangula* were collected from different villages and mountains in Thamar Governorate, Yemen. The Plant materials under study were shade-dried and then ground to powder. The ground powder was extracted by soxhlet apparatus using ethanol until the extract became colorless. The extract was dried using evaporator.

Experimental Animal

Male wistar rats (130-170 g) were used. They were procured from houses animal belong to the faculty of applied sciences Thamar University, Yemen, under the conditions of 12-12 h L- D cycle. Rats were fed with standard diet and water ad libitum. All the selected animals showed the fasting blood glucose values ranging from 250 to 350 mg/100ml indicating hyperglycemia, the diabetic status.

Alloxan Induced Hyperglycemia

Diabetic condition was induced in rats by intraperitoneal injection of alloxan monohydrate (150 mg/kg bw) 72 hours before starting the experiment. Before administration of the different treatments, the animals were bled and level of the blood glucose in the animals was measured. This was the initial measurement at time zero. The animals were again bled hourly until the fourth hour [24].

Experimental Design

Animals were distributed into eight groups, as follows at 15 days. Each group consisted of six animals. Normal control group (1), Normal control group with 20% of *C. quadrangula* extract treatment (2), Normal Control group with 25% *C. quadrangula* extract treatment (3), Normal control group with 30% *C. quadrangula* extract treatment (4), ALX-Diabetic control group (5), ALX-Diabetic+ *C. quadrangula* 20% (6), ALX-Diabetic + *C. quadrangula* 25% (7), ALX-Diabetic + *C. quadrangula* 30% (8).

Every five days, the blood glucose was monitored and after 15 days of treatment, the rats were sacrificed by cervical dislocation. The serum glucose levels were estimated by Tinder's method using GOD POD enzymatic Kit, glycosylated hemoglobin [25], triglycerides [26], HDL-cholesterol [27], LDL-cholesterol and VLDL-cholesterol [28] were estimated. Blood urea was estimated by urea-glutamate dehydrogenase (GLDH) method. Plasma insulin levels were determined in duplicate using insulin RIA Kit (Linco, St. CharlesMO) with rat insulin as a standard [29].

Statistical Analysis

Data were statically evaluated by using one way ANOVA. Wherever the ANOVA values were found to be significant Duncan's new multiple range test (DMRT) was applied (SPSS computer software). The values were considered significant when $p < 0.05$.

Results

The body weight in experimental animals. Group 1 (control group), group 2-4 animals (control + *C. quadrangula* extract with different concentration, 20%, 25%, 30%) showed a significant increase in the final body weight compared to initial body weight (Table 1). There was a significant decrease in the final body weight compared to the initial body weight in group 5 (diabetic group). There was a significant increase in body weight in groups 6-8 (diabetes treated with *C. quadrangula* extract with different concentration, 20%, 25%, 30%) compared to the diabetic group.

Table (2) shows the details of fasting blood glucose level in experimental animals. Group 1 animals did not differ significantly in the blood glucose through out the experimental period. In group 2-4 (control + *C. quadrangula* extract with different concentration, 20%, 25%, 30%) animals showed a significant decrease in the blood glucose level. In animals of group 5, there was a significant increase in the blood glucose level after the induction of diabetes and the hyperglycaemic condition was maintained throughly. Groups 6-8 diabetes treated with *C. quadrangula* extract with different concentration, 20%, 25%, 30%) animals also showed hyperglycemic candition after the induction of diabetes but the blood glucose level was brought down to non-diabetic state after treatment with *C. quadrangula* extract with different concentration, 20%, 25%, 30%).

Serum insulin level was decreased in alloxan induced diabetic rats (group 5) as compared to control (group 1) and normal animals treated with *C. quadrangula* plant extract (group 2-4). While diabetic white rats treatment was resulted and fertilized in different concentration (20% .25% .30%) to obtain significant increase ($p>0.05$) in insulin concentration rate in the sub-group (6-8) compared to a rate of concentration in the blood serum of diabetic group. (Table 3, Fig.3).

There was a significant elevation in the blood glycosylated hemoglobin and a decrease in blood urea levels in alloxan diabetic rats as compared to normal rats. Oral administration of *C. quadrangula* extract significantly ($p<0.01$) decreased glycosylated hemoglobin and increased in blood urea levels in alloxan-diabetic rats as comparable to diabetic groups.

The level of plasma lipid such as total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL) are shown in (Table 4). Plasma TC, TG and LDL level were significantly elevated and HDL level was decreased in diabetic rats when compared to control. After the treatment with *Caralluma quadrangula* plant extract, a significant reduction of TG, TC LDL, VLDL and increase in HDL level was observed.

Table 1: Effect of *Caralluma quadrangula* on body weight (g) of experimental groups

Groups	Initial body weight (g)	Final body weight(g)	T. test value
1-Normal Control	148±4.6[a]	151±4.7[b]	-3.200
2-Normal Control+C.q 20%	140±2.7[a]	155.4±2.8[b]	-62.87
3-Normal Control+C.q 25%	137.6±1.3[a]	148.6±1.9[b]	-17.39
4-Normal Control +C.q30%	131.6±0.58[a]	144.6±0.37[b]	-18.38
5-ALX-diabetic V	169.8±2.9[a]	154.4±4[b]	12.74
6-ALX-diabetic+C.q20%	136.6±1.9[a]	147±1.3[b]	-12.8
7-ALX-diabetic+C.q25%	141.6±2.4[a]	151.2±1.8[b]	-11.01
8-ALX-diabetic+C.q30%	140±3.1[a]	147.4±3.02[b]	-7.5

The values are given as means + SE; df, degrees of freedom in each group. The means with different superscripts (a and b) within a column are significantly different from each other at $p<0.05$ determined by T. Test.

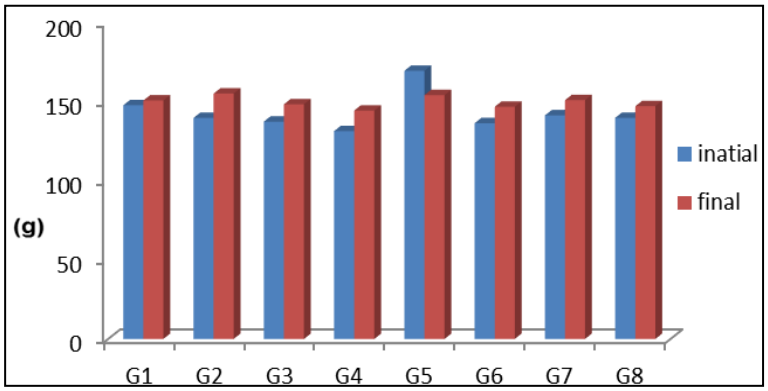

Fig 1: Effect of *Caralluma quadrangula* on body weight level (mg/dl). The vertical bars show the initial as well as the final of mean body weight. The mean values were compared using Student's t. Test. The lines above the bars indicate standard error (SE).

Table 2: Effect of *Caralluma quadrangula* on serum glucose (mg/dl) of experimental groups:

Group	0 day	5th day	10th day	15th day
1-Normal Control	96.4±1.8 [a]	102.4±1.4 [a]	102.4±1.4 [a]	101±1.1 [a]
2-Normal Control+C.q 20%	94.6±0.3 [a]	84.2±1.3 [b]	84.2±1.4 [b]	80.2±0.8 [b]
3-Normal Control+C.q 25%	97.6±1.3 [a]	85.4±2.4 [b]	86.8±1.9 [b]	84.4±2.08 [b]
4-Normal Control +C.q30%	95.4±0.6 [a]	84.6±1.7 [b]	85.2±1.2 [b]	82±1.5 [b]
5-ALX-diabetic V	241.4±10.5[b]	255.2±4.7 [c]	311±3.4 [c]	325.4±2.9 [c]
6-ALX-diabetic+C.q20%	288±7.8 [c]	106±4.1 [a]	101±2.5 [a]	100.8±0.9 [a]
7-ALX-diabetic+C.q25%	298±3.7 [c]	108.4±6.3 [a]	111.8±7.8 [a]	97.2±0.7 [a]
8-ALX-diabetic+C.q30%	284±4.8 [c]	98±0.5 [a]	105±4.03 [a]	98.4±0.9 [a]

The values are given as means ± SE; df, degrees of freedom in each group. The means with different superscripts (a, b and c) within a column are significantly different from each other at $p<0.05$ determined by Duncan's Multiple Range Test.

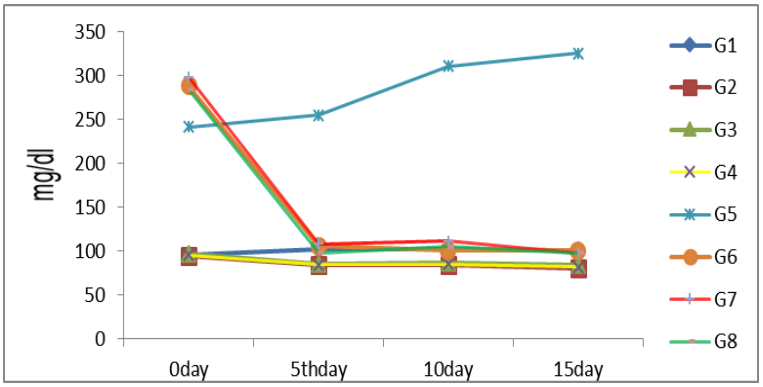

Fig 2: Effect of *Caralluma quadrangula* serum glucose level (mg/dl). The curve show mean serum glucose levels (mg/dl) during the experiment.

Table 3: Effect *Caralluma quadrangula* on serum insulin, glycosylated hemoglobin, blood urea level of experimental groups:

Group	Insulin (µU / ml)	Glycosylated haemoglobin (HbA1C)	Blood urea (mg/dl)
1-Normal Control	16.02±0.3[a]	9.26±0.06 [a]	22±0.15 [a]
2-Normal Control+C.q 20%	18.24±0.23[b]	9.26±0.25 [a]	22±0.17 [a]
3-Normal Control+C.q 25%	18.44±0.19[b]	8.52±0.20 [b]	21.1±0.39 [a]
4-Normal Control +C.q30%	17.52±0.13[c]	9.28±0.08 [a]	22.1±0.20 [a]
5-ALX-diabetic V	6.56±0.13[d]	10.46±0.20 [d]	14.02±1.7 [d]
6-ALX-diabetic+C.q20%	10.2±0.13[e]	9.8±0.25 [a]	19.28±0.25 [b,c]
7-ALX-diabetic+C.q25%	11.48±0.14[f]	10.24±0.20 [c, d]	18.56±0.28 [c]
8-ALX-diabetic+C.q30%	13.04±0.10[g]	10.2±0.23 [c,d]	19.12±0.27 [b,c]

The values are given as means ± SE; df, degrees of freedom in each group. The means with different superscripts (A, B and C) within a column are significantly different from each other at $p<0.05$ determined by Duncan's Multiple Range Test.

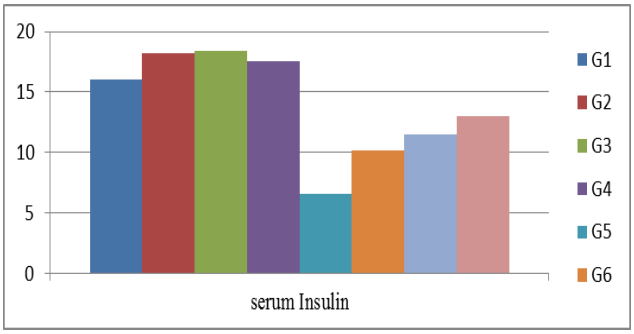

Fig 3: Effect of *Caralluma quadrangula* on treatment on serum insulin level (µU / ml). The vertical bars show serum insulin level. The values were compared using one way ANOVA (df = 3.16) and DMRT. The lines above the bars indicate standard error (SE).

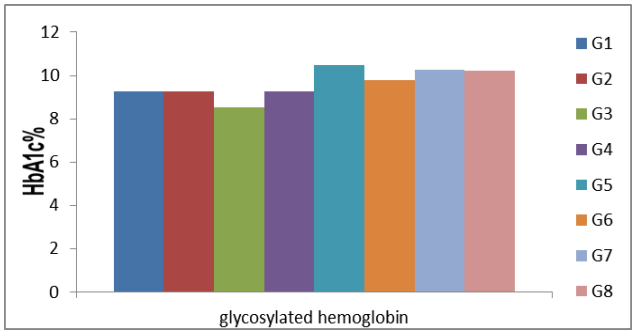

Fig 4: Effect of *Caralluma quadrangula* on glycosylated hemoglobin percentage (HbA1c%). The vertical bars show glycosylated hemoglobin percentage (HbA1c %). The mean values were compared using one way ANOVA (df = 3.16) and DMRT. Lines above the bars indicate standard error (SE).

Table 4: Effect *Caralluma quadrangula* on triglycerides, cholesterol, LDL,VLDL, HDL,(mg/dl) level of experimental groups

Group	Triglycerides (mg/dl)	Cholesterol (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	HDL (mg/dl)
1-Normal Control	135±1.7 [a]	115±1 [a]	80±0.7 [a]	25±1.5 [a]	35±1.1 [a]
2-Normal Control + C.q 20%	114.2±1.3 [b]	94±0.7 [b]	60±0.7 [b]	20.6±0.5 [b]	43.6±1.02 [b]
3-Normal Control + C.q 25%	110.2±2.1 [b]	96±1.2 [b]	59.6±0.5 [b]	21±0.7 [b]	46±0.8 [b]
4-Normal Control + C.q30%	108±1.9 [b]	94.6±0.5 [b]	60±0.5 [b]	21±0.4 [b]	45±0.5 [b]
5-ALX-diabetic V	181.8±1.1 [c]	160±2.8 [d]	115.6±1.4 [e]	35±1.1 [c]	25±1.4 [c]
6-ALX-diabetic + C.q20%	133.4±55. [a]	124.2±1.3 [c]	91.8±1.3 [d]	25.6±.6 a	32.6±0.5 [a]
7-ALX-diabetic + C.q25%	126.8±1.5 [a]	126.8±1.5 [c]	90±0.7 [c]	27.6±0.4 [a]	33±0.7 [a]
8-ALX-diabetic + C.q30%	132.4±4.7 [a]	124.2±0.5[c]	88.6±0.5[c]	27.6±0.5 [a]	33.4±0.4 [a]

The values are given as means ± SE; df, degrees of freedom in each group. The means with different superscripts (a, b and c) within a column are significantly different from each other at $p<0.05$ determined by Duncan's Multiple Range Test.

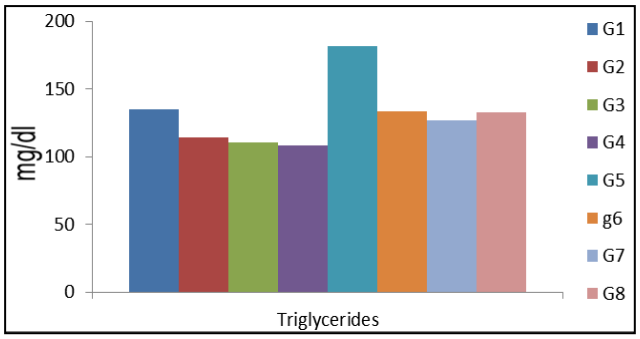

Fig 5: Effect of *Caralluma quadrangula* on triglyceride (mg/dl). The vertical bars show triglyceride. The mean values were compared using one way ANOVA (df = 3.16) and DMRT. The lines above the bars indicate standard error (SE).

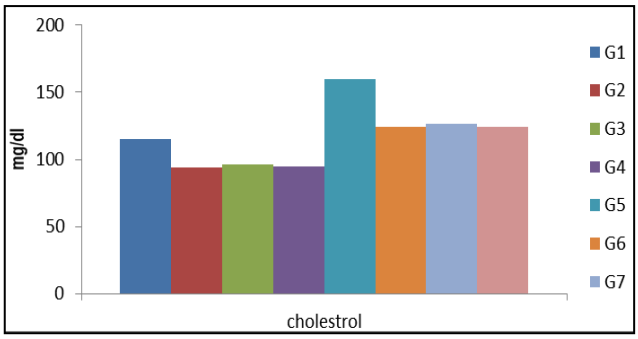

Fig 6: Effect of *Caralluma quadrangula* on total cholesterol (mg/dl). The vertical bars show total cholesterol. The mean values were compared using one way ANOVA (df = 3.16) and DMRT. The lines above the bars indicate standard error (SE).

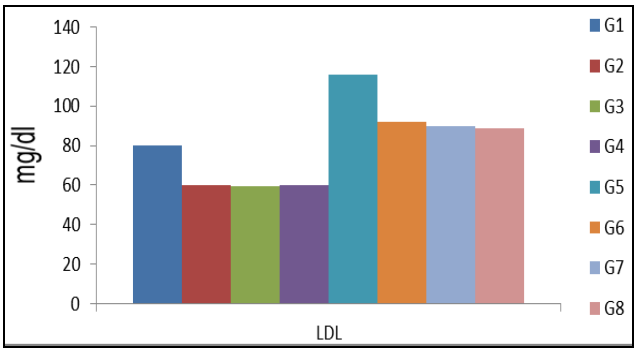

Fig 7: Effect of *Caralluma quadrangula* on LDL (mg/dl). The vertical bars show LDL. The mean values were compared using one way ANOVA (df = 3.16) and DMRT. Lines above the bars indicate standard error (SE).

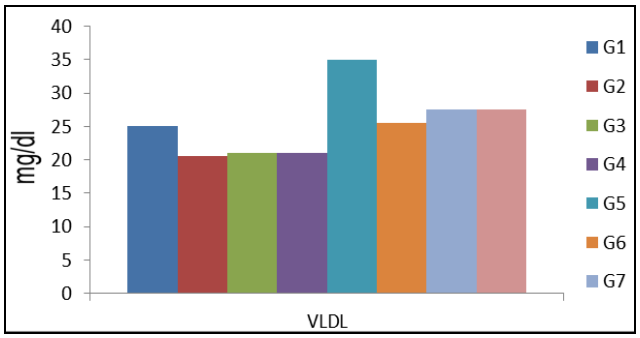

Fig 8: Effect of *Caralluma quadrangula* on VLDL (mg/dl). The vertical bars show VLDL. The mean values were compared by using one way ANOVA (df = 3.16) and DMRT. The lines above the bars indicate standard error (SE).

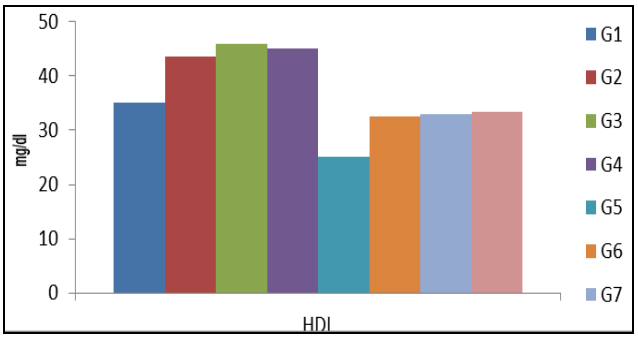

Fig 9: Effect of *Caralluma quadrangula* on HDL (mg/dl). The vertical bars show HDL. The mean values were compared using one way ANOVA (df = 3.16) and DMRT. The lines above the bars indicate standard error (SE).

Discussion

Severe loss in body weight is remarkably observed in Alloxan-induced diabetes which was observed in the present study. Administration of *C. quadrangula* extract significantly improved the body weight loss in diabetic rats in comparison to diabetic control group. The observed decrease in body weight of diabetic control rats could be attributed to insulin deficiency, which causes degradation of structural proteins and lipids that are known to contribute to body weight [30].

In the present study, diabetes was introduced in rats using intraperitoneal administration of alloxan and the hypoglycemic effect *C. quadrangula* was investigated. Blood sugar level increased in alloxan induced diabetic rats. Since alloxan causes a massive reduction in insulin release by the destruction of β-cell of the islets of Langerhans [31]. In our study, the *C. quadrangula* extract decreased blood glucose level significantly ($p<0.05$), when compared to diabetic control. The anti-diabetic effect of *C. quadrangula* may be due to increased release of insulin from the existing β-cell of pancreas or due to enhanced transport of glucose to the peripheral tissue Our finding are in agreement with those reported by Kalaivani [32]. Further, the antihyperglycemic activity of *C. quadrangula* was associated with an increase in plasma insulin level, suggesting an insulinogenic activity of the plant extracts. The observed increase in the level of plasma insulin indicates the *C. quadrangula* stimulates insulin secretion from the remnant beta cells or from regenerated beta cells. In this context, a number of other plants have been also reported to exert hypoglycemic activity through insulin release stimulatory effect [33-34]. During diabetes, the excess glucose presents in the blood reacts with hemoglobin to form HbA1c [35]. In the present study, the diabetic rats had shown higher level of HbA1c compared to those in normal rats, indicating their poor glycemic control. *C. quadrangula* treated diabetic rats significantly decreased the level of HbA1c which might be the result of an improvement in the glucose metabolism. Glycosylated hemoglobin comprises about 3.4-5.8% total hemoglobin in normal red cells, but it is increased inpatients of overt Diabetes [36].

Elevated levels of urea are seen during increased protein breakdown in renal disorders like glomerular nephritis and chronic nephritis. In the present investigation, control group animals exhibited raised levels of blood urea whereas after treatment with *C. quadrangula* there was a significant reduction in blood urea levels compared to the infected group and this refers to the role of the plant extract in reducing sugar which led to the decline of sugar stored in the liver and therefore not inflation liver and its manufacture of urea [37].

The most commonly observed lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [38-39].

It is well known that in uncontrolled diabetes mellitus, there will be an increase in total cholesterol, triglycerides, low density lipoprotein and very low density lipoprotein associated with decrease in HDL cholesterol. In the present study, the total cholesterol, triglycerides, low density lipoprotein and very low density lipoprotein was increased in diabetic control groups and it was reduced in 15 days treatment with *C. quadrangula* as well as the high density lipoprotein level was significantly increased and this could account for its use in traditional medicine for the treatment of diabetes and hypertension.

The results of this study clearly indicate that the administration of *C. quadrangula* extract produces hypoglycemic and hypolipidaemic effect and may prevent cardiovascular diseases. Studies have shown that increased in the risk factor of cardiovascular disease correlate with increase in plasma TC, TG, LDL and VLDL and a decrease in HDL-Cholesterol concentrations. These results suggest that *C. quadrangula* extract has a regulatory role in reducing blood glucose level and lipids parameters. This may be due to blood glucose suppressing effect by improving insulin sensitivity or slowing absorption of carbohydrates in the small intestine.

Conclusion

In conclusion, the present study indicates that *C. quadrangula* extract has a significant anti-diabetic activity in alloxan induced diabetic rats. The anti-diabetic activity in alloxan induced rats is due to decrease in elevated blood glucose level, restored the increased glycosylated haemoglobin, reduction of TG, TC, LDL and VLDL and increase in the insulin, blood urea and HDL level. This confirmation justifies its use in ethno medical medicine for the treatment of diabetes when treated with alcoholic plant extract.

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