Hypoglycemic and Antioxidant Effects of *Cleome Droserifolia* (Samwah) in Alloxan-Induced Diabetic Rats

Eman G.E. Helal*, Nouran Abou Aouf, Inas Z.A. Abdallah***, ALsayeda Mohammed Khattab***

*****Department of Zoology, Faculty of Science (girls), **Department of Physiology, Faculty of Medicine (boys), Al-Azhar University, Cairo, Egypt, ***Department of Nutrition and Food Science, Faculty of Home Economics, Helwan University, Cairo, Egypt.

ABSTRACT

Background: Diabetes mellitus (DM) is a chronic disease caused by inherited or acquired deficiency in insulin secretion and by decreased responsiveness of the organs to the secreted insulin. Recently, some medicinal plants have been reported to be useful in diabetes treatment. *Cleome droserifolia* (Samwah) having a long history in Egyptian folk medicine for treatment of diabetes mellitus.

Aim of the work: The aim of the present study was to evaluate the possible antihyperglycemic property of *Cleome droserifolia* extract (CDE) and its antioxidant mechanism in alloxan induced diabetic rats.

Material and Methods: This study was performed on thirty male albino rats of Sprague Dawely strain with an average body weight of 100-110g. Animals were divided into three groups (ten/cage), control untreated group, diabetic group and diabetic group treated with plant extract that was given orally (28.5 mg/kg body wt. twice/ day).

Results: Results showed marked decline in levels of serum insulin, body weight, total proteins, albumin, globulin and high density lipoprotein cholesterol (HDL). These are accompanied with marked elevation in levels of fasting blood glucose, HOMA-IR, AST, ALT, GGT, urea, creatinine, uric acid, serum total lipids (TL), total cholesterol (TC), triacylglycerols (TG), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL) and ratios of TC/HDL and LDL/HDL (risk factors) in diabetic rats as compared to the corresponding controls. While the daily administration of diabetic rats with CDE showed significant amelioration in most of these parameters.

Conclusion: It could be concluded that CDE treatment exerts a therapeutic protective nature in diabetes by decreasing oxidative stress and pancreatic β-cells' damage which may be attributed to its antioxidative potential and antidiabetic property.

Keywords: *Cleome droserifolia*, Diabetes mellitus, Antidiabetic medicinal plants, Antioxidant.

INTRODUCTION

Diabetes mellitus is represented by hyperglycemia, lipidaemia, and oxidative stress; it predisposes affected individuals to long term complications affecting the eyes, skin, kidneys, nerves, and blood vessels[1]. Diabetes is prevalent in all parts of the world and rapidly increasing worldwide. The estimated number of adults living with diabetes has soared to more than 371 million, having a prevalence of 8.3%[2]. Many herbs and plants have been described as possessing hypoglycemic activity when taken orally[3].

Cleome droserifolia (Forssk.) Del. belongs to Family Cleomaceae (Genus: Cleome), grows in different regions of Egypt, especially in Sinai[4]. It is known in Egypt as Samwah, Afein or Reeh-El-Bard and Cleome herb[5]. *Cleome droserifolia* is used by herbalists in Egypt as a hypoglycemic agent, and its decoction is widely used by the Bedouins of the southern Sinai for the treatment of diabetes[6]. It is also used in various disorders such as diarrhea, fever, inflammation, liver diseases, bronchitis, skin diseases, malaria fever and in the treatment of scabies and rheumatic fever[7].

Previous reports on the biological activity of the plant extract described its hypoglycemic effects on rats[8]. A variety of phytochemicals have been reported for *C. droserifolia*, including; alkaloids, tannins, saponins, coumarins,ocosaniocacid,catechins, amino acids, cardenolides, hydrocarbons, sterols such as (β-sitosterol and stigmasterol),

DOI: 10.12816/0009359

glucosinolates with sulfur aglycones such as glucocapparin, sesquiterpenes like (carotol and dihydrodihydroxy carotol), methoxylated flavones, four flavone aglycones (5-hydroxy-3,6,7,3´,4´,5´- hexamethoxyflavone, chrysosplenetin, 5, 3´-dihydroxy-3,6,7,4´,5´-pentamethoxyflavone and penduletin) and four flavone glycosides [kaempferitin, kaempferol-7-*O*-rhamnoside, kaempferol-3-*O*-glucoside-7-*O*-rhamnoside, and isorhamnetin-3- *O*-glucoside-7-*O*-rhamnoside)[9,10,11].

Cleome droserifolia extract is also rich in bioactive compounds as flavonoids such as kaempferol-3,7-dirhamnoside, isorharmnetin-3-gluco-7-rhamnoside, kaempferol-3-gluco-7-rhamnoside, quercetin-3-gluco-7-rhamnoside, kaempferol, artemitin, quercetin-3`-methoxy-3-*O*-(4``-acetyl rhamnoside)-7-*O*-*α*-rhamnoside kaem- pferol-4`-methoxy-3,7-*O*-dirhamnoside[12].

In addition, phytochemical screening of *Cleome droserifolia* indicated the presence of volatile oil, which consist of 3-butenylisothiocyanate, 2-methyl butenylisothiocyanate, benzylisothio-cyanate, α, *β*,andγ-caryophyllene and 2-naphthyl-n-propyl ether[13,14].

Moreover, three terpenoidal compounds such as (buchariol, new diacetyl triterpene lactone, drosericarpone and stigmasterol glucoside) and dolabellane diterpenes like isorhamnetin-3-*O*-*β*-D-glucosidewere isolated from *Cleome droserifolia* [11,15].

Thus, the present investigation is carried out in order to study the possible antihyperglycemic and antioxidant effects of *Cleome droserifolia* (CDE) in diabetic rats.

MATERIALS AND METHODS

Plant material

The aerial parts of *Cleome droserifolia* (Samwah) were collected from Wadi Gonay, Dahab, South Sinai, Egypt.

Preparation of extract

The dried aerial parts of *Cleome droserifolia* were grinded. The aqueous extract of *Cleome droserifolia* (CDE) was prepared by boiling 2g of the dry powdered plant material with 200 ml of tap water for 15 min, left to cool at room temperature then filtered through filter paper. Then, the resultant extract was stored in a glass container in refrigerator. The extract was freshly prepared each two days.

Animals

Thirty adult male albino rats of Sprague Dawely strain, weighing around 100–110 g, at the age of 8-10 weeks were purchased from Theodore Bilharz Research Institute, Giza, Egypt. They were kept under observation for about 15 days before the onset of the experiment for adaptation.

Induction of diabetes

Diabetes mellitus was induced in animals by a single intraperitoneal injection of alloxan (120 mg/kg body weight dissolved in saline solution). Rats were deprived of food for 16 h before alloxan injection. After three days of alloxan injection, rats were deprived of food overnight and they were then given glucose (3g/kg body weight) by gastric intubation. After 2 h of oral glucose administration, blood samples were taken from tail vein and the fasting blood glucose (FBG) concentration was determined by means of one touch ultra glucometer (Johnson & Johnson Company, USA) and compatible blood glucose strips. Animals with fasting blood glucose levels ≥300 mg/dl were selected as diabetic rats for the current experiment.

Experimental design

Experimental animals were divided into three groups ten for each, were used as follows:

- Group I (Control group): Non-diabetic rats.
- Group II (Diabetic group): Rats were injected intraperitoneally with a single dose of alloxan (120 mg/kg dissolved in saline solution).
- Group III: (Treated group): Diabetic rats treated orally with CDE (28.5 mg/kg, twice /day) for 30 days.

Blood sample collection

At the end of the tested periods, the overnight fasted animals (12-16 h) were sacrificed under diethyl ether anesthesia. Blood samples were taken from orbital vein and centrifuged at 3000 rpm for 10 min. The clear non-haemolysed supernatant sera were quickly removed and immediately stored at -20°C till used for further analysis of biochemical parameters.

Biochemical analysis:

Serum glucose, Creatinine, Urea and uric acid were determined by colorimetric method[16]. Serum insulin level was measured according to Reeves[17]. While values of

HOMA-IR were calculated using the following equation[18]:
HOMA-IR= fasting serum glucose (mg/dl) x fasting serum insulin (μU/L)/450.
Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (γGT), albumin and total protein concentrations were determined colorimetrically[19,20,21].Serum globulin was calculated by subtracting albumin from total protein[22].

Serum total lipids (TL), cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) content were analyzed by the enzymatic colorimetric method[23,16,24]. While, low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were calculated according to the equation of **Friedewald *et al***. [25].
Friedewald's equation: LDL (mg/dl) = TC-[HDL + TG/5].
VLDL = TG/5
Risk 1 = TC / HDL
Risk 2 = LDL / HDL

Statistical analysis:

The results were expressed as Mean ± SE of ten rats per group. Data were subjected to one way analysis of variance (ANOVA) followed by Duncan post Hoc to determine the statistical significance of the difference. An IBM computer with a software system SPSS version 17 was used for these calculations.

RESULTS

The percentage of body weight change was significantly decreased (P<0.01) in diabetic rats when compared to the control. After treatment of diabetic rats with CDE, the percentage of body weight change returned near to the normal (Table 1).

Table (2) showed a significant decrease (p<0.01) in serum insulin levels accompanied with marked elevation (p<0.01) in blood glucose levels in diabetic rats in comparison with control rats. While diabetic group treated with CDE showed significant increase (p<0.01) in insulin accompanied with significant decrease in glucose levels in comparison with diabetic group. HOMA-IR values were significantly high (p<0.01) in diabetic rats when compared to the corresponding controls, while treatment of diabetic rats with CDE returned HOMA-IR values to the normal level**.**

The present results in Table (3) showed a significant increase (p<0.01) in serum ALT, AST and γGT activities in diabetic group when compared to control group. While treatment of diabetic rats with CDE significantly decreased these activities as compared with diabetic group and returned them back to the normal value.

Diabetic animals showed marked decline (p<0.01) in serum total proteins and albumin relative to the corresponding controls. While treatment of diabetic rats with CDE resulted in modulation of the measured serum protein profile parameters. The values of globulin and A/G ratio showed non-significant changes in the control and the experimental groups (Table 4).

Diabetic animals showed marked significant elevation in TL, TC, TG, LDL-C, VLDL-C and ratios of TC/HDL (risk ratio 1) and LDL/HDL (risk ratio 2) accompanied with marked decline in HDL-C relative to the corresponding controls. Treatment of diabetic rats with CDE improved lipid profiles as showed significant reduction in the values of TL, TC ,TG, LDL-C, VLDL-C and ratios of TC/HDL and LDL/HDL with marked elevation in HDL-C (Table 5).

On the other hand, diabetic group showed significant increase (p<0.01) in serum creatinine, urea and uric acid levels in comparison with control group. Treatment of diabetic rats with CDE recorded significant decrease (p<0.01) in serum creatinine, urea and uric acid levels in comparison with diabetic group (Table 6).

DISCUSSION

Diabetes is a heterogeneous metabolic disorder associated with markedly increased morbidity and mortality rate. Consequently, diabetes places a severe economic burden on governments and individuals. There is currently fast-growing diabetes pandemic[26].
The purpose of the present work was to evaluate the hypoglycemic, antioxidant and hypolipidemic activities of *Cleome droserifolia* extract (CDE) in alloxan-induced diabetic male albino rats.

In the present study, alloxan–induced diabetic rats exhibited severe hyperglycemia due to a progressive oxidative insult

interrelated with a decrease inendogenous insulin secretion and release[27]. Our results, showed a significant decrease in levels of serum insulin accompanied with marked significant elevation in levels of blood glucose in diabetic rats when compared to the control rats. These results may be due to the diabetogenic dose of alloxan causes selective destruction of β-cells of the islets of Langerhans resulting in a marked decrease of insulin levels led to elevated blood glucose and impaired glucose tolerance[28].

The Homeostasis Model Assessment of IR (HOMA-IR) has been used as a robust tool for the surrogate assessment of insulin resistance[29]. The present results showed a significant increase in HOMA-IR in diabetic rats. β cells normally compensate insulin resistance by secreting more amounts of insulin to maintain the glucose homeostasis. However, beta cells function gets impaired leading to deterioration in glucose homeostasis because high glucose concentrations lead to the development of insulin resistance in peripheral tissues due to impairment of both insulin secretion and insulin sensitivity[30,31].

Traditional antidiabetic plants might provide a useful source of new oral hypoglycemic compounds for development as pharmaceutical entities. There are a large variety of compounds obtained from several plants was found to be responsible for the hypoglycemic action. Of these are flavonoids, glycosides, glycans, sulfide molecules, polysaccharides, oils, vitamins, alkaloids, saponins, glycoproteins, peptides and amino acids from different plant families[32].

Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from intestine and glucose production from liver[33]. Therefore, treatment of diabetic rats with CDE showed decrease in blood glucose levels with increasing in insulin levels and returned HOMA-IR near to the normal values.These results indicated that CDE exhibited hypoglycemic and anti-hypoinsulinemic activities as it significantly suppressed the rise in peripheral blood glucose concentrations and increased serum insulin level in albino rats[34].

The hypoglycemic effect of the studied plant extract may be attributed to the presence of certain constituents such as flavonoids, glycosides, glycans, alkaloids, saponins and glycoproteins, these compounds were shown to have insulin mimetic effects and reduce blood glucose levels[35]. Also, flavonoid-enriched extract inhibited a-glucosidase activity and may inhibit the non-Na+dependentfacilated diffusion of monosaccharides in intestinal epithelial cells[36].

On the other hand, induction of diabetes by alloxan caused a significant decrease in the percent change of body weight in diabetic animals when compared to the control one. This in accordance with previous study that may due to catabolic effect on protein metabolism by retarding protein synthesis and stimulating protein degradation[37]. However, treatment with CDE causes significant enhancement of body weight in accordance with previous literature[38]. This reflects an improved health of CDE treated animals, may be attributed to enhance glucose uptake by adipose tissues or muscle and glucose production from liver and diminishing intestinal glucose absorption[39].

Earlier it has been explored that diabetes exhibits high oxidative stress due to persistent and chronic hyperglycemia, which thereby depletes the activity of antioxidative defense system and thus promotes de novo free radicals generation[40].

The present study showed a significant elevation in serum levels of AST, ALT and GGT enzymes in diabetic rats when compared with the control group. This may be as a result of metabolic changes in the liver due to leaking out of enzymes from the tissues and migrating into the circulation by the adverse effect of alloxan[41]. The elevation in the activities of ALT, AST and GGT enzymes in diabetic rats reflects a state of hepatocyte injury. This is may be attributed to the insulin deficiency in the diabetic state results in the impairment of glucose utilization leading to an increased generation of oxygen free radicals which induced liver injury[42].

On the other hand, daily treatment of diabetic rats with CDE significantly reduced the disturbances occurred in the activities of these enzymes. *Cleome droserifolia* was known to be rich in phenolic compounds, such as flavonoids (kaempferol-3,7-dirhamnoside, isorharmnetin-3-gluco-7-

rhamnoside, kaempferol-3-gluco-7-rhamnoside)[12]. Several researchers have demonstrated that flavonoids act as reducers of hyperglycaemia[43].

Flavonoids have long been recognized to possess anti-inflammatory, antioxidant, and hepatoprotective activities. They can exert their antioxidant activity by various mechanisms, e.g., by scavenging or quenching free radicals, by chelating metal ions, or by inhibiting enzymatic systems responsible for free radical generation[44]. So, they can ameliorate the functions of the liver and the reduction of body weight by inhibition the proinflammatory mediators and protection of hepatocytes. The amelioration of body weight reduction and liver functions may be due to betatrophin hormone which primarily produced in the liver and adipose tissues, was recently described as a key stimulator of beta-cell mass expansion in response to obesity and insulin-resistant states[45]. This hormone stimulates beta cells in the pancreas to multiply and produce more insulin[45]. In addition, essential oils (3-butenylisothiocyanate, 2-methyl-butenylisothiocyanate, benzylisothiocyanate) among components of CDE, have antioxidant and anti-inflammation activities[46]. The components of essential oils might be stimulating normal beta cells for insulin production and reduced hepatic and pancreas injury by their antioxidant activity probably by oxygen and nitrogen radical scavenging[47].

Therefore, our findings are in agreement with previous studies reported that the *Cleome droserifolia* had a hepatoprotective effect by inhibiting the liver damage leading to improvement in the liver functions[48].

Moreover, diabetic animals showed significant marked decline in serum total proteins, albumin relative to the corresponding controls. In this regard, the decrease of serum total protein and albumin in diabetic animals was restored in control rate by insulin treatment, which accelerates amino acid transport through cells and stimulates the protein manufacturing machinery of the cell[49]. While, treatment of diabetic rats with CDE maintained these parameters near the normal values. This may be attributed to the increasing serum insulin level due to the presence of different classes of phytochemicals such as alkaloids, flavonoids and saponins which have hepatoprotective activity due to their antioxidant properties.

The current study revealed significant elevation in serum levels of TL, TC, TG, LDL-C, VLDL-C and TC/HDL and LDL/HDL ratios along with significant reduction in HDL-C in diabetic rats as compared to control rats. These results indicated marked hyperlipidemia that characterized the diabetic state which are known as the risk factor for cardiovascular diseases[50]. This may be attributed to hypoinsulinemia and hyperglycemia, which may be a result of the uninhibited actions of lipolytic hormones on the fat depots due to injection of alloxan caused an increase of sera lipid profiles and due to the absence of insulin[51].

While administration of CDE to diabetic rats caused reduction in the levels of TL, TC, TG, LDL, VLDL and ratios of TC/HDL and LDL/HDL with marked elevation of HDL. These results may be due to the presence of flavonoids (quercetin-3-gluco-7-rhamnoside, kaempferol, artemitin) in CDE. Flavonoids inhibit the various stages thought to be involved in the initiation of atherosclerosis and endothelial damage through its antioxidant activity by free radical scavenging assay[52]. These results indicated that the *Cleome droseriforlia* possess significant antihyperglycemic, antihyperlipidemic and pancreatic antioxidative properties, it would also be beneficial in the prevention of the development of atherosclerosis and other coronary artery diseases[53].

The present results showed significant elevation in the levels of serum creatinine, urea and uric acid in diabetic rats as compared to control rats. Creatinine, urea and uric acid are often regarded as reliable markers of renal function. Elevation in levels of these markers in diabetic rats indicates renal dysfunction[54]. Diabetes mellitus is characterized by hyperglycaemia, which has been strongly linked to nephropathy that may lead to renal failure[55].

This may be due to metabolic disturbance in diabetic animals reflected in high activities of xanthine oxidase, lipid peroxidation, and increased triacylglycerol and cholesterol levels[56].

While CDE induced significant improvements in kidney functions including, serum creatinine, urea and uric acid in treated rats. This may be due to the presence of flavonoids, which lowered creatinine, urea and uric acid concentrations as they possess free radical scavenging properties[57].

In conclusion, the results of this study demonstrate that CDE possess antidiabetic and antihyperlipaedemic activities with antioxidative properties. Hence, apart from controlling hyperglycemia it can also protect against the development of diabetic complications. However, further studies are needed to investigate and elucidate the possible mechanism of action of the active ingredients, establish complete safety profiles and evaluate the potential value of CDE for the management of diabetes and hyperlipidemia in the clinic.

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Table 1: Change inbody weight (g) in control, diabetic and treated diabetic rats

Groups	% Change in Body weight
Control	9.92± 7.41
Diabetic	4.98± 3.54**
Diabetic + CDE	8.98± 5.90

Each value represents mean of 10 rats ± SE. ** p<0.01:significant decrease in the parameters levels of diabetic group in comparison to control group.

Table 2: Levels of serum insulin, glucose and HOMA-IR in control, diabetic and treated diabetic rats

Groups / Parameter	Control	Diabetic	Diabetic+ CDE
Glucose(mg/dl)	87.44±0.78	350.20±0.85***	92.91±0.62[a]
Insulin (µU/L)	4.13±0.45	2.54 ±0.37**	3.77±0.77[b,c]
HOMA-IR	0.89±0.23	2.20±0.36***	0.86±0.14

Each value represents mean of 10 rats ± SE. *** p<0.01:significant increase in the parameters levels of diabetic group in comparison to control group. ** p<0.01: significant decrease in the parameters levels of diabetic group in comparison to control group. [a] p<0.01: significant decrease in the parameters levels of treated group in comparison to diabetic group. [b] p<0.01: significant decrease in the parameters levels of treated group in comparison to control group. [c] p<0.01: significant increase in the parameters levels of treated group in comparison to diabetic group.

Table 3: ALT, AST and γGT activities in control, diabetic and treated diabetic rats

Groups / Parameters	Control	Diabetic	Diabetic+ CDE
AST(U/L)	22.46±0.56	33.52±0.60***	26.59±0.35[a]
ALT(U/L)	37.02±0.59	53.24±1.08***	33.43±0.42[a]
γGT(U/L)	22.28±0.12	29.66±0.08***	23.41±0.06[a]

Each value represents mean of 10 rats ± SE. *** p<0.01: significant increase in the parameters levels of diabetic group in comparison to control group. [a] p<0.01: significant decrease in the parameters levels of treated group in comparison to diabetic group.

Table 4: Serum protein profiles (g/dl) and A/G ratio in control, diabetic and treated diabetic rats

Groups / Parameters	Control	Diabetic	Diabetic+ CDE
Total protein(g/dl)	7.40±0.08	5.30±0.11**	7.06±0.07^{c}
Albumin(g/dl)	4.68±0.07	3.12±0.06**	4.31±0.03^{c}
Gobulin(g/dl)	2.72±0.05	2.18±0.07	2.75±0.04
A/G ratio	1.72±0.05	1.43±0.04	1.56±0.01

Each value represents mean of 10 rats ± SE. $^{**}p<0.01$: significant decrease in the parameters levels of diabetic group in comparison to control group. $^{c}p<0.01$: significant increase in the parameters levels of treated group in comparison to diabetic group.

Table5: Serum lipid profiles in control, diabetic and treated diabetic rats

Groups / Parameters	Control	Diabetic	Diabetic+ CDE
TL (mg/dl)	474±8.11	1435±11.38***	564±9.26^{a}
TC (mg/dl)	141.08±0.37	231.52±0.53***	173.18±0.57^{a}
TG (mg/dl)	133.10±0.77	283.96±0.86***	142.86±0.54^{a}
HDL-C (mg/dl)	47.88±0.49	38.08±0.39**	42.55±0.41^{b,c}
LDL-C (mg/dl)	66.56±0.48	136.40±0.59***	101.86±0.53^{a}
VLDL-C (mg/dl)	26.62±0.16	56.80±0.17***	28.45±0.12^{a}
TC/HDL	3.00±0.00	6.08±0.04***	4.07±0.04^{a}
LDL/HDL	1.38±0.02	3.58±0.04***	2.39±0.03^{a}

Each value represents mean of 10 rats ± SE. $^{***}p<0.01$: significant increase in the parameters levels of diabetic group in comparison to control group. $^{**}p<0.01$: significant decrease in the parameters levels of diabetic group in comparison to control group. $^{a}p<0.01$: significant decrease in the parameters levels of treated group in comparison to diabetic group. $^{b}p<0.01$: significant decrease in the parameters levels of treated group in comparison to control group. $^{c}p<0.01$: significant increase in the parameters levels of treated group in comparison to diabetic group.

Table 6: Creatinine, urea and uric acid levels in control, diabetic and treated diabetic rats

Groups / Parameters	Control	Diabetic	Diabetic+ CDE
Creatinine (mg/dl)	0.91±0.005	1.66±0.08***	0.90±0.01^{a}
Urea (mg/dl)	32.46±0.55	63.44±0.59***	37.15±0.46^{a}
Uric acid (mg/dl)	3.26±0.04	7.24±0.09***	3.42±0.07^{a}

Each value represents mean of 10 rats ± SE. $^{***}p<0.01$: significant increase in the parameters levels of diabetic group in comparison to control group. $^{a}p<0.01$: significant decrease in the parameters levels of treated diabetic group in comparison to diabetic group.