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ORIGINAL ARTICLE

Hypoglycemic, Hypolipidemic and Antioxidant Activities of Cleome droserifolia in Streptozotocin-Diabetic Rats

OmAli Y. El-Khawaga[1] ; Abou-Seif M.A[1].; El-Waseef A. [1] and Negm A.A[1].*

[1]*Biochemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt.*

**Corresponding Author*: *dr_elkhawaga@yahoo.com*

**Current address: Faculty of Community, King Khalid University, Rejal Almaa 61956, P. Box. 76, Kingdom of Saudi Arabia,*

Fax: 0096672580857

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Background: Diabetes mellitus (DM) is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hypoglycemia clinical research has confirmed the efficacy of several plant extracts in the amelioration of diabetic disorders. Aim of the work hypolipidemic and antioxidant activities of the aqueous extract of *Cleome droseriloia* was investigated in streptozotocin (STZ)-induced diabetic rats.

Methods and Results: A single dose of STZ (60mg/Kg body weight) produced a decrease in hepatic glycogen and GSH contents, hepatic glucose-6-phosphate dehydrogenase, superoxide dismutase, activities and HDL- cholesterol, whereas, hepatic glucose-6-phosphatase activity and level of MDA, cholesterol, triglyceride, LDL-cholesterol and VLDL-cholesterol were increased. An aqueous extract of *Cleome droseriloia* (500, 750 and 1000mg/Kg or Gliclazide (100mg/Kg) was administered orally once daily for two weeks to STZ-induced diabetic rats ameliorated hyperglycemia, improved lipid profile, amelioration of antioxidants and restored the metabolic enzymes of glucose to the normal value in the liver of STZ-treated rats. In addition, the administration of *Cleome droserifolia* induced the secretion of insulin from pancreatic rats. Furthermore, the hypoglycemic efficacy of one dose of aqueous extract *Cleome droserifolia* has extended to 12 hours. The effects produced by *Cleome droserifolia* extract were found to be comparable with that of gliclazide.

Conclusion: The present results suggested that *Cleome droserifolia* could be used as antidiabetic complement of diabetes mellitus. This may be related to its insulin-induction action.

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Diabetes mellitus is probably the fastest growing metabolic disorder in the world and it is a major source of morbidity in developing countries. Once regarded as a single disease entity, diabetes mellitus is now regarded as a heterogeneous group of diseases characterized by a state of chronic hyperglycemia, which causes a number of secondary complications like cardiovascular, renal, neurological and ocular disorders (Miller, 1991). Diabetes mellitus is characterized by hyperglycemia together with biochemical alterations of glucose and lipid metabolism (Mann, 1998). Liver tissues are insulin dependent tissues, which play a pivotal role in glucose and lipid homeostasis and are severally affected during diabetes mellitus (Seifter, 1982). Liver tissues participate in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol and triglycerides . During diabetes mellitus, a profound alteration in the concentration and composition of lipid occurs (Sochor et al.,1985). Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes of glucose metabolism in the diabetic liver (luzi,1998).

There is increasing evidence that complications related to diabetes mellitus are associated with oxidative stress induced by the generation of free radicals[6]Garg et al.1996. Free radicals result in the consumption of antioxidant defenses which may lead to disruption of cellular functions and oxidative damage to membranes and enhance susceptibility to lipid peroxidation. Increased generation of reactive oxygen species (ROS) and lipid peroxidation have been found to be involved in the pathogenesis of many diseases of known and unknown etiology and in the toxic actions of many compounds (Andallu and Varadacharyulu, 2003). In consequence, antioxidants play an important role to protect the human body against damage caused by reactive oxygen species (Giugliano et al. 1996). In diabetes mellitus, oxidative stress has been found to be mainly due to an increased production of oxygen free radicals and a sharp reduction of antioxidant defences (Laaksonen and Sen 2000).

Streptozotocin is one of the most commonly used substances to induce diabetes in the rat. This toxin causes the death of pancreatic β-cells by alkylation of DNA resulting in reduced synthesis and release of insulin. Furthermore, it has been shown to be involved in the fragmentation of DNA by means of production of reactive oxygen species (). The diabetes induced by streptozotocin is associated with polydipsia and loss in body weight. The sulfonylurea, glibenclamide (GLB) and the semi-essential amino acid taurine (TR), shown to have hypoglycemic and hypocholesterolemic effects in animal models of diabetes (Pari and Venkateswaran, 2004), were used as reference compounds. Hence, compounds with both hypoglycemic and antioxidant properties would be useful as antidiabetic agents (Opara, 2002). Many herbal plants are considered useful means to prevent and/or ameliorate certain disorders, such as diabetes mellitus atherosclerosis and other complications (Scartezzini and Speroni, 2000). Among these herbal resources, *Cleome droseriloia* are selected for the present study. The aqueous and chloroformic extracts has been used as hepatoprotective, hypoglycemic and antimicrobial agents. Moreover the ethanolic extract has antihistaminic, relaxant and tranguilizing effects (El-Askary, 2005).

Therefore, this context was aimed to investigate the activity of an aqueous extract of the *Cleome droseriloia* as hypoglycemia, hpolipidemic and

antioxidant substance in streptozotocin-induced diabetic rats as a model for type II diabetes .

MATERIALS AND METHODS

- **Preparation of plant extracts:**

Cleome droseriloia was purchased from herbalists at local commercial sources in Mansoura, Egypt. The *Cleome droseriloia* herb was spread over the bench and left for drying in the shade, then reduced to a powder. Decoction of the plant material was prepared by boiling 100 g of the dry plant material in 1.5 liters of tap water for 2 minutes and then filtered after 10 minutes. To minimize the volume of the decoction, it was left to dry in a wide container over a boiling water bath (Kamal et al., 1991).

- **Chemicals:**

Streptozotocin, thiobarbituric (TBA), phenazin methosulphate (PMS), nitrobluetetrazolium (NBT), NADH, NADPH and glucose-6-phosphate were purchased from Sigma chemical Company (St.Louis, MO, USA). Gliclazide (Servier Laboratories, France) was purchased from local pharmacies in Mansoura, Egypt. All other chemicals were of analytical grade.

1. Experimental animals:

All experimentals were performed using adult male albino rats, with an average body weight of 100 to 120 g purchased from Theodore Bilharz Research Institute, Giza, Egypt. The rats were housed in steel mech cage and provided with commercial standard diet and tap water *ad libitum*.

Induction of Experimental Diabetes.

The rats were fasted for 12 hours before the induction of diabetes with STZ. The rats were injected intraperitoneally with freshly prepared solution of STZ (60 mg STZ/kg body weight) (Montilla et al., 2004). Seventy two hours after diabetes induction, blood samples were collected from the tail vein for measuring blood glucose levels by One-Touch blood glucose meter from Lifescan (Johnson& Johnson Company, USA).

2. Experimental Procedure

I.Toxicity test of an aqueous extract of the *Cleome droseriloia*

Fifty male rats were divided into five groups of 10 each and were administered orally with aliquot doses of the aqueous extracts of *Cleome droseriloia* (250-1500 mg/Kg). Mortality was observed after 72 hours Litchfield and Wilcoxon, 1949.

II. Hypoglycemic action of *Cleome droseriloia*

A total of 50 rats were divided into 10 groups of 5 rats each as follows: group 1, normal control rats; group 2-4, normal rats treated with *Cleome droseriloia* extract (500, 750, 1000 mg/kg consequently) daily by an intragastric tube for two weeks. group 5, normal control Gliclazide (100mg/ kg body weight); group 6, STZ-diabetic control rats; group 7-9, STZ-diabetic rats treated with *Cleome droseriloia* extract (500 , 750, 1000 mg/kg consequently) daily by an intragastric tube for two weeks ,group 10, STZ-diabetic rats treated with gliclazide (100mg/ kg body weight) daily by an intragastric tube for two weeks. At the end of two weeks, the rats were deprived of food overnight and sacrificed by decapitation. Blood samples were collected and the livers were immediately dissected out, washed in ice-cold saline, blotted dry and weight for measuring various biochemical parameters.

III. Preparation of homogenates.

An accurately weight piece of liver tissue homogenized in ice-cold 0.9 % saline using a

Teflon pestle connected to a homogenizer motor. The liver homogenate was diluted to yield 5%(w/v) liver homogenate. The homogenate was centrifuged at 5000 rpm for 30 minutes at 4 ^{0}C to remove cell debris and nuclei. The resulting supernatant was used for biochemical analysis.

IV. Biochemical Analysis.

Serum glucose concentrations were estimated by the method of Trinder (1969) using a commercial available diagnostic kit (Diamond Diagnostics, Egypt). Glycogen content in tissue homogenates was determined as described by the method of Damsbo et al.(1991). Hepatic glucose-6-phosphate dehydrogenase activity was measured by applying the method of Chan et al. (1965). Hepatic glucose-6-phosphatase was assayed according to the method of Rossetti et al. (1993). Superoxide dismutase (SOD) activity was determined using the method of Nishikimi et al. (1972). Reduced glutathione (GSH) content in the liver homogenate was estimated by the method of Beutler et al. (1963). Lipid peroxidation in the liver tissues was estimated by measuring the formation of thiobarbituric acid reactive substance (TBARS) as an index of malondialdehyde (MDA) production according to the method of Draper and Hadley (1996). Cholesterol content was quantified in the liver homogenate by the method of Ellefson and Caraway (1976) using a commercial available diagnostic kit (Spectrum Diagnostics, Egypt), triglycerides content was determined by the method of Bucolo and David (1973) using a commercial available assay kit (Spectrum Diagnostics, Egypt) and HDL-cholesterol content was determined by applying the method of Gordon et al(1977).

Statistical analysis: The results are expressed as means ± SD. Statistical analysis was performed according to the method of Murray (1982). Data were analyzed using unpaired Student's t-test. P values of < 0.05 were considered to be statistically significant.

RESULTS

The acute oral toxicity of *Cleome droseriloia* extract showed neither toxicity nor mortality up to 1500 mg/kg. Thus, the maximum tolerated dose of the extract was found to be 1500 mg/kg body weight. Also no toxic signs observed over 72 hours of administering the extract. Table 1 demonstrates serum blood glucose levels in normal-control, normal STZ-treated and normal- *Cleome droseriloia* treated rat groups after two weeks of treatment. A highly significant increase in blood glucose level is observed in STZ-control untreated rats compared with that of normal rats. In contrast, a highly significant decrease in the mean value of blood glucose level is observed in either STZ-treated with gliclazide or *Cleome droseriloia* extract (500, 750, 1000mg/kg body weight) respectively as compared to STZ-control rats without treatment. Also, table 1, shows serum insulin levels in the STZ-treated groups with gliclazide or *Cleome droseriloia* extract. It has shown that, the insulin level of STZ-diabetic rats is 1.1 µU/ml while the insulin levels of STZ-diabetic rats treated with (500, 750, 1000 mg/kg body weight) *Cleome droseriloia* and gliclazide are 1.3, 1.5, 1.8 and 1.9 µU/ml respectively. Table 2, illustrates hepatic glycogen content, glucose-6-phosphate dehydrogenase and glucose-6-phosphatase activities of different experimental rat groups. There are no significant change in glycogen content and glucose-6-phosphate dehydrogenase and glucose-6-phosphatase activities in normal treated with 500 mg/kg as compared to normal-control group . A highly significant increase in the hepatic glycogen content and glucose-6-phosphate

dehydrogenase activity are observed in *Cleome droseriloia* extract (750, 1000mg/kg body weight) normal treated rats as compared to normal-control rats. A highly significant increase in hepatic glycogen content, glucose -6-phosphate dehydrogenase activity are observed in either gliclazide or *Cleome droseriloia* extract (500, 750, 1000 mg/kg) STZ-treated rats as compared to STZ-control rats without treatment. No significant change is observed in the activity of glucose-6-phosphatase of normal treated rats with either gliclazide or (500, 750, 1000 mg/kg body weight) of *Cleome droseriloia* extract compared to the corresponding value of normal- control rat group although a highly significant decrease in its activity was observed in either gliclazide or *Cleome droseriloia* extract (500, 750, 1000mg/kg body weight) STZ-treated rats as compared to STZ-control rats without treatment. Table 3 represents superoxide dismutase activity and reduced glutathione and malondialhyde contents in the liver of different experimental groups. The activity of superoxide dismutase is highly significant increase in the liver of normal rats treated with (500, 750, 1000mg/kg body weight) of *Cleome droseriloia* extract compared to normal-control rat group. On the other hand, no significant changes were observed in the contents of hepatic GSH and MDA of rats treated with either (500, 750, 1000mg/kg body weight) of Cleome droseriloia extract or gliclazide but a significant increase in the content of hepatic GSH and a significant decrease in the level of MDA of normal treated rats by 1000mg/kg *Cleome droseriloia* compared to normal-control group. Moreover, there are a highly significant increase in the activity of SOD and GSH content but a highly significant decrease of the level of MDA are observed in the groups treated with either (500, 750, 1000mg/kg body weight) of *Cleome droseriloia* extract or gliclazide STZ-diabetic groups compared to STZ- control groups without treatment. Table 4, shows the lipid profiles as total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol contents in the liver of different experimental rat groups. A highly significant decrease in total cholesterol, triglycerides, LDL-cholesterol contents but a significant increase in HDL-cholesterol content are observed in hepatic homogenates of STZ-diabetic rats treated with either (500, 750, 1000mg/kg body weight) of *Cleome droseriloia* extract or gliclazide as compared to STZ-diabetic control group. No significant changes is observed in total cholesterol, HDL- cholesterol in the liver of normal rats treated with (500, 750, 1000mg/kg body weight) of *Cleome droseriloia* extract or gliclazide as compared to normal-control group. Also, no significant changes is observed in the contents of triglyceride and LDL-cholesterol of normal rats treated with *Cleome droseriloia* extract (500 mg/kg) compared to normal rats. On the other hand, a significant decrease is observed in the level of triglycerides and LDL-cholesterol of treated rats with *Cleome droseriloia* extract (750, 1000 mg/kg) or gliclazide as compared to normal-control group.

Table 1: Effect of two weeks treatment with Cleome droseriloia extract on blood glucose and insulin levels of normal and STZ-diabetic rats.

Groups	Blood glucose (mg/dl)		Insulin level (µU/ml)	
	Normal	Diabetic	Normal	Diabetic
Control	103.48±9.75	408.07±27.9	……	1.1
Treated with Cleome droseriloia (500mg/kg)	85.92±5.64**	232.53±20.33++	……	1.3
Treated with Cleome droseriloia (750mg/kg)	76.07±7.99 **	175.06±23.22++	……	1.5
Treated with Cleome droseriloia (1000mg/kg)	75.75±6.96 **	144.15±5.315++	……	1.8
Treated with Gliclazide	80.17±5.16**	165.06±23.9++	……	1.9

The results are expressed as mean ± SD for five rats in each group.

** highly significant compared to normal-control groups.

++ highly significant compared to diabetic-control groups.

Table 2: Effect of two weeks treatment with Cleome droseriloia extract on hepatic glycogen content, glucose-6-phosphate dehydrogenase(G6PD) and glucose-6-phosphatase(G6Pase) activities in the liver of normal and STZ-diabetic rats.

Groups	Glycogen content (mg/g wet tissue)		G6Pase (µmole/min/g wet tissue)		G6PD (U/g wet tissue)	
	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic
Control	12.17±2.53	4.58±0.619	2.38±0.48	5.62±0.51	16.26±1.85	8.3±.091
Treated with Cleome droseriloia(500mg/kg)	18.02±6.36NS	6.07±0.558++	2.29±0.62NS	3.49±0.39++	18.76±3.01NS	11.6±2.54+
Treated with Cleome droseriloia (750mg/kg)	22.43±2.79 **	8. 7±1.047++	2.01±0.431 NS	3.06±0.34++	20.84±1.31**	13.37±3.67+
Treated with Cleome droseriloia1000mg/kg)	22.98±2.57 **	9.73±0.689++	1.78±0.418 NS	2.40±0.39++	22.76±0.50**	15.92±4.09++
Treated with Gliclazide	18.71±2.79**	6.11. ±0.596++	2.09±0.609 NS	3.26±0.67++	18.52±1.73NS	10.90±1.54++

The results are expressed as mean ± SD for five rats in each group.

** highly significant compared to normal-control groups.

++ highly significant c

Table 3: Effect of two weeks treatment with Cleome droseriloia extract on superoxide dismutase(SOD) activity, reduced glutathione (GSH) and malondialdehyde (MDA) contents in the liver of normal and STZ-diabetic rats.

Groups	SOD (U/g wet tissue)		GSH (mmole /g wet tissue)		MDA (nmole/g wet tissue)	
	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic
Control	2631±78.21	973±73.74	1.62±0.299	0.688±0.093	209.31±1.85	305.7±27.02
Treated with Cleome droseriloia(500mg/kg)	3052±167.5**	2016±199.03++	1.73±0.17NS	1.16±0.14++	173.4±33.1NS	230±10.86++
Treated with Cleome droseriloia (750mg/kg)	3084±108.3 **	2345±93.56++	1.9±0.167 NS	1.19±0.16++	171.6±48.7NS	190.6±8.96++
Treated with Cleome droseriloia(1000mg/kg)	3245±119.25 **	2484±135.16++	2.15±0.212*	1.413±0.09++	140.0±40.59*	165.8±16.4++
Treated with Gliclazide	2997±91.69**	2054 ±85.34++	1.77±0.15NS	0.894±0.09++	177.1±29.2NS	189.4±14.5++

The results are expressed as mean ± SD for five rats in each group.

** highly significant compared to normal-control groups.

++ highly significant compared to diabetic-control groups.

NS not significant

Table 4: Effect of two weeks treatment with Cleome droseriloia extract on total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol contents in the serum of normal and STZ-diabetic rats.

Groups	Cholesterol (mg/g dl serum)		Triglycerides (mg/g dl serum)		HDL-Cholesterol (mg/g dl serum)		LDL-Cholesterol (mg/g dl serum)	
	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic
Control	144±15	204±27	228±29. 4	281±14.1	68±8.9	38±6	38±11	109±30.3
Treated with Cleome droseriloia (500mg/kg)	139±15NS	170±8.6+	204±22NS	246±8.5++	70.4±3 NS	43±3 NS	27±14NS	77±10NS
Treated with Cleome droseriloia (750mg/kg)	118±12 NS	154±11++	184±5.7 *	233±14.03++	73±6 NS	49±5+	15±4.1**	58±14++
Treated with Cleome droseriloia (1000mg/kg)	106±4.5 NS	139±17++	138±11**	222±12++	74±4.8 NS	53±4.6++	7.4±3**	41.16±19++
Treated with Gliclazide	131±6.6NS	164.±10 +	192±13 *	244±14.5++	71±6 NS	45±4+	22±8*	69±12+

The results are expressed as mean ± SD for five rats in each group.

** highly significant compared to normal-control groups.

++ highly significant compared to diabetic-control groups.

NS not significant

DISCUSSION

1.Hypoglycemic and hypolipidemic effects of the *Cleome droseriloia* extract:

STZ injection resulted in diabetes mellitus which is probably due to the destruction of β -cells of islets of langerhans as proposed by many authors (Beppu et al., 2006). It is generally accepted that severe diabetes (SD) is of IDDM type and mildly diabetes (MD) is of NIDDM type (Maiti et al., 2005). This effect is being depicted by the high level of blood glucose in animals. The discovery and development of new and more effective diabetic treatments from plants is one of the main goals of the present day and chemical research (Tiwari and Madhusudana, 2002). In the present study, a detailed account has been given to the hypoglycemic and hypolipidemic effects of the *Cleome droseriloia* in STZ- induced diabetic rats. The expanded hypoglycemic effect of *Cleome droseriloia* till two weeks may be attributed to its long efficacy on glucose uptake by the lived cells when compared to the effect of gliclazide. In diabetes mellitus, the disorders of carbohydrates and lipid metabolism play predominant role in diabetic complications (Sridhar et al., 2005). This fact has been observed in the present results in which decreased the levels of hepatic glycogen content, glucose-6-phosphate dehydrogenase activity, HDL-cholesterol content and increased the concentrations of hepatic glucose-6-phosphatase activity, total cholesterol, triglycerides and LDL-cholesterol when compared to normal-control group. The hepatic glycogen contents are significantly lowered in STZ-control group when compared to normal-control group. The decrease in glycogen contents in the liver homogenates of STZ-diabetic group may be attributed to the depression of glycogenesis pathway in the liver of STZ-diabetic group (Ghosh et al., 2004). In the present study, it was observed that the activity of G6PD was significantly decreased in the liver homogenates of STZ-diabetic rats when compared to the corresponding activity of that in the normal control group. The deficiency of the hepatic G6PD in STZ-diabetic rats may be attributed to the decrease in blood insulin levels which enhances the glucose uptake by the liver cells leading to stimulate glucose oxidation by pentose phosphate pathway. These findings are in agreement with the previous studies which reported that, G6PD activity was decreased in STZ-induced diabetic rats (Maiti et al., 2004). Further more, the deficiency of G6PD activity may participate in the building up of glucose and consequently increase the susceptibility of type 2 diabetes mellitus as a result to the reduction in blood insulin levels (Gaskin et al., 2001). Glucose-6-phosphatase(G6Pase), an enzyme located mainly in the liver and catalyzes the terminal step in both gluconeogenesis and glycogenolysis. Thus, an increase in G6Pase activity in the liver homogenates of STZ-diabetic rat cells may cause a marked increase in the rate of glucose formation and also decreases glucose usage (Aistonelal., 1999). Therefore, the elevated G6Pase activity may become a compensatory pathway for building up glucose to compensate the requirements of liver cells for energy from glucose (Ashokkumar and Pari, 2005) . The present results demonstrate that, STZ-induced diabetic rats showed significant increase in the hepatic levels of cholesterol, triglycerides and LD-cholesterol with a significant decrease in hepatic HDL-cholesterol level. These results are in accordance with those of other investigators (Pari and Latha, 2002). The elevation of lipid profiles in STZ-diabetic rats may be attributed to an increase in the rate of lipolysis with a decrease in lipogensis leading to release more fatty acids into the blood circulation (Agardh et al.,

1999). Further more, the increased activity of G6Pase caused formation of excess NADPH which is important for fatty acid biosynthesis and the synthesis of fats from carbohydrates. The elevation of fatty acids concentrations may contribute to triglycerides biosynthesis (Seifter, 1982). In addition, insulin deficiency will lead to a decrease in the activity of lipoprotein lipase and an increase in the metabolism of free fatty acids from peripheral fat depots (Ahmed et al., 2001).The present results demonstrated that, the treatment with *Cleome droseriloia* significantly ameliorated the adverse influence of streptozotocin, such as: a lowered blood glucose levels, an increased hepatic glycogen contents, an improved lipid profiles and a regulation in the metabolic enzymes of glucose utilization as compared to rats administered with streptozotocin alone. These results are in consistent with those of other studies using different other hypoglycemic plants (Prince et al., 2004).

2. Antioxidant activity of the *Cleome droseriloia* extract:

Insulin deficiency in the diabetic patients results in the impairment of glucose utilization leading to an increased generation of oxygen free radicals a reduction of antioxidants which may play an important role in both oxidative stress and etiology of diabetic complications (Opara, 2002). In our experimental model of diabetes mellitus it was observed that STZ injection produced a significant decrease in hepatic superoxide dismutase (SOD) activity and glutathione (GSH) content accompanied by a significant increase in MDA content in comparison to the normal control group. These finding are in agreement with the previous studies which have reported on the reduction of hepatic SOD activity and GSH content with the elevation of MDA in STZ-induced diabetic rats (Zhang and Tan, 2000). The elevation of mean concentration of MDA in STZ-injected group may be due to the hypoinulinemia that increases the activity of fatty acyl coenzyme -A -oxidase, which initiates β-oxidation of fatty acids, resulting in lipid peroxidation. Increased lipid peroxidation impairs membrane functions by decreasing membrane fluidity and changing the activity of membrane bound enzymes and receptors (Baynes, 1991). These lipid peroxidation products are more cytotoxic and stable than reactive oxygen species (ROS) that reacts with cellular constituents (Esterbauner et al., 1991). Besides these negative effects, MDA is a modulator of signal transduction pathways that disturb cellular activities (Grune et al., 1997). The increase of ROS and/ or lipid peroxidation products (MDA) could inactivate and reduce the hepatic SOD activity in STZ-diabetic rats. Furthermore, the decrease of SOD activity might be attributed to the following reasons: i) Hyperglycemia activates various biochemical pathways such as glucose auto-oxidation, and activation of protein kinase C which in turn overproduce oxidants like superoxide ($O_2^{\cdot-}$) and hydroxyl (·OH) radicals as well as hydrogen peroxide (H_2O_2) (Abou-Seif and Youssef, 2004). ii) The increase of glycsylated SOD that leads to the inactivation of this enzyme (Aria et al., 1989). Reduced glutathione (GSH) participates in the cellular defense system against oxidative stress by scavenging the free radicals and reactive oxygen intermediates and it is important in the regulation of the cellular redox state. A decline in its cellular level in diabetes has been considered to be indicative of increased oxidative stress (Mclennan et al., 1991). Thus, the decrease in hepatic GSH levels in STZ-diabetic rats might be in part, attributed to the inhibition of glutathione reductase (GSSG-R) activity which is responsible for regeneration of GSH from its oxidized form. Blum and Fridovich (1985) showed that GSSG-R is

inactivated by superoxide anion (O_2^-). Therefore, hepatic containing reduced SOD activity might have enhanced flux of (O_2^-) that potentially could damage GSSG-R and decrease GSH content in the liver tissues. In addition, the decrease in GSH level might reflect a direct reaction between GSH and free radicals generated by STZ (Ananthan et al., 2004). The present results showed that the treatment of STZ-diabetic rats with *Cleome droseriloia* enhanced the activity of G6PDH. G6PDH plays an important role in glutathione synthesis that according to the following reports: G6PDH maintains the levels of the NADPH. In turn, NADPH maintains the level of GSH in liver cells and GSH protects cells against the oxidative damage of ROS (Mehta et al., 2000). Finally, *Cleome droseriloia* induced an increase in hepatic GSH content which might enhance the GSH/GSSG ratio and decrease hepatic lipid peroxidation (MDA) and therefore, improve glucose regulation. It has been illustrated that the GSH/GSSG ratio plays a critical role in glucose homeostasis of diabetes mellitus because thiol groups are important in intracellular and membrane redox state (Soto et al., 1998).

Conclusion: the improvement of SOD activity, GSH content and decreased lipid peroxidation recorded after *Cleome droseriloia* treatment of STZ-diabetic rats might suggest a treating influence of *Cleome droseriloia* against STZ action that might be mediated through neutralization of oxygen free radicals produced by STZ. In addition, the aqueous extract of *Cleome droseril*oia stimulates insulin secretion from β-pancreatic cells of rats. Therefore, the hypoglycemic action of *Cleome droseriloia* may be attributed to its stimulation of β-cells for insulin secretion and its antioxidant properties. Further clinical investigations will be conducted prior utilization as a safe oral hypoglycemic agent.

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