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Potential Effects of Samwa (*Cleome Droserifolia*) Ethanol Extract on Hyperglycemia, Oxidative Stress and Inflammation in Diabetic Rats Induced by Alloxan

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Abstract Diabetes is a pathological condition that affects the organism and leads to a high level of glucose in the blood which is called hyperglycemia. Besides hyperglycemia, many other factors play a great role in the pathogenesis of diabetes including oxidative stress and inflammation which leading to serious complications. The present study was carried out to investigate the effectiveness of Samwa (*Cleome droserifolia*) ethanol extract (CDE) intervention on hyperglycemia, oxidative stress and inflammation in diabetic rats induced by alloxan. Normal control rats recorded 94.41 mg/dL for blood glucose which significantly ($p \leq 0.01$) increased to 312.22 mg/dL in alloxan-treated rats. Intervention with CDE (200 to 800 mg/kg bw) in feeding protocol rats for 28 days led to significant ($p \leq 0.05$) decrease the levels of blood glucose by the rates of -21.16, -35.40, -43.48 and -49.51% compared to the diabetic rats, respectively. The opposite direction was recorded for free insulin level in serum. The rate of decreasing in blood glucose and increasing in free serum insulin were exhibited a dose-dependent manner. The same behavior was recorded for the biomarkers of oxidative stress (malondialdehyde, MDA) and inflammation (nitric oxide, NO) levels in plasma. On contrary, significant ($P \leq 0.05$) improvement in different antioxidant defense systems in both serum including bioactive molecules (glutathione fractions, GSH and GSSG) and RBC's including antioxidant enzymes (glutathione peroxidase, GSH-Px, glutathione reductase, GSH-Rd, superoxide dismutase, SOD and catalases, CAT) were recorded. In conclusion, these findings provide a basis for the use of Samwa extracts for the prevention and/or treatment of type-2 Diabetic Mellitus and its complications.

Keywords: *hyperglycemia, insulin, glutathione fractions, antioxidant enzymes, malondialdehyde, nitric oxide*

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1. Introduction

Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus [1,2]. Diabetes affects approximately 537 million people globally, the majority of whom live in low- and middle-income countries. It is one of the leading causes of death in the world. In 2021, diabetes will be five seconds. In Egypt, people with DM estimates 10.93 responsible for 6.7 million fatalities or one every million in 2020 which is foretold to rise to 13.74 million by 2030 [3]. There are two main categories of this disease. Type 1 diabetes mellitus (T1DM) also called insulin-dependent diabetes mellitus (IDDM) and Type 2 (T2DM), the noninsulin- dependent diabetes mellitus (NIDDM). T1DM accounts for only 5–10% of those with diabetes while T2DM which accounts for 90–95% of diabetic patient, previously referred to as non–insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and insulin deficiency but these individuals do not need insulin treatment to survive. Also, T2DM is one of the world's most common chronic diseases as changing lifestyles lead to reduced physical activity and increased obesity [4]. Early phenomenon of T2DM is insulin insensitivity, which not only has negative metabolic consequences but also contributes subsequent pancreas β-cell exhaustion, resulting in the onset of clinical hyperglycemia [5].

Oxidative stress was defined by Lushchak and Storey [6] as a serious imbalance between oxidation and antioxidants, "a disturbance in the pro-oxidant/antioxidant balance in favor of the former, leading to potential damage". Different reactive species including oxygen (ROS),

nitrogen (RNS) and chlorine (RCS) represent the basic radicals/oxidants produced by living organisms as a result of normal cellular metabolism [7,8,9,10]. High concentrations of such radicals produce adverse modifications to cell components, such as lipids, proteins, and DNA [11,12]. Therefore, oxidative stress is thought to be involved in the development of several diseases including diabetes [9,13,14,15,16,17,18,19]. Associations between diabetes and markers of oxidative stress including lipid oxidative modification have been observed in humans [20]. For example, lipid peroxidation contributes to the development of atherosclerosis [21], a process known to be accelerated in diabetic patients. Lipid peroxidation process end products such as peroxides, malondialdehyde (MDA), etc may be toxic to vascular endothelium in diabetics [14,18,22,23]. Also, free radicals including such end products of lipid peroxidation attack can generate protein peroxides in diabetes, which may decompose to generate other free radicals [24]. Furthermore, glycol-oxidation seems to play an important role in the vascular endothelial dysfunction detected in diabetic patients and perhaps in nephropathy. Elevated glucose may cause increased generation of ROS such $O^{\cdot-}$ by endothelium, antagonizing the action of NO and perhaps forming peroxynitrite, $ONOO^-$ [9,17,25,26]. On the other side, the metabolic disorders could lead to oxidative stress, which harmfully affects the insulin activity through several interacting potential pathways and generates ROS such as hydrogen peroxide (H_2O_2) and superoxide anions ($O_2^{\cdot-}$) [9,26]. These ROS could deteriorate the pancreatic islets β-cells which lead to reduce the release of insulin [26,27,28]. Also, ROS could be activated several signaling pathways in cells such as NF-κB (nuclear factor-κB) and PKC (protein kinase C). Such interference of ROS with the insulin signaling pathways leads to develop the insulin resistance [29].

Several strategies to improve diabetic complications including oxidative stress have been proposed, because early treatment and/or prevention play a vital role in reducing the population burden of diabetes. Benefits of drugs/pharmaceutical formulae to treat the disease aggressively early have been recommended, but medical formulae may have not required side effects. Also, the treatment cost of modern antidiabetic drugs is beyond the reach of most people in the low income/poor group and those living in the rural areas [30]. Thus, the therapeutic approach of several traditional medicinal systems is more holistic. With this context, there has been a growing interest in herbal remedies that can be but have been difficult to maintain over a long term introduced into the general population with the least side effects and the maximal preventive outcome [9,31]. Many phytochemicals naturally occurring in such plant parts would be desirable options. Amongst all of these phytochemicals, carotenoids, polysaccharides, flavonoids, phenolic compounds, alkaloids, volatile compounds, anthocyanins terpenoids, coumarins and organosulfur compounds are represent the central position. Such compounds has been reported to improve diabetic status by decreasing the hyperglycemia, oxidative stress and other complications [18,19,20,28] [32,33,34,35] [36,37,38,39,40]. Among these plant parts resources, samwa aerial part is selected for the present study.

Figure 1. Samwa (*Cleome droserifolia*) plant in Sinai desert, Egypt and there were collected samples for the study by the author

Samwa (*Cleome droserifolia*; Family: *Cleomaceae*) (Figure 1) that are geographically distributed in the Middle East countries including Egypt, Libya, Palestine, Syria, and other arid and semi-arid regions [41]. It is one of the most popular medicinal herbs common in South Sinai, Egypt. Bedouin of South Sinai use samwa medicinally for treating stomachache, skin allergies, and open wounds, as well as for exhibiting anticancer and hepatoprotective properties [42,43]. The aqueous and chloroformic extracts has been used as hepatoprotective, antidiabetic and antimicrobial agents. Moreover the ethanolic extract has antihistaminic, relaxant and tranquilizing effects [44]. Several authors have recorded the biological roles for Samwa including antioxidant, antiparasitic, anticarcinogenic and antimicrobial activities [43,45]. These biological effects are related to the vast array of bioactive compounds that occur naturally in Samwa including terpenes, flavonoids, glucosinolates, anthocyanin alkaloids, and polyphenols [41,42].

According to the best of our knowledge, studies related to explaining the relationship between samwa aerial parts extracts intervention and diabetes treatments, as well as the mechanics involved, are so limited. Therefore, the present study was carried out to investigate the effectiveness of samwa (*Cleome droserifolia)* aerial part ethanol extract (CDE) intervention against hyperglycemia and oxidative stress in living cells with special emphasis on its mechanistic aspects in the treatment of T2DM.

2. Materials and Methods

2.1. Materials

2.1.1. Date Seeds

Samwa (*Cleome droserifolia*) was collected in March, 2023, from Sinai desert, Egypt by special arrangement with colleges in Faculty of Home Economics, El-Arish University, El-Arish, North Sinai Governorate, Egypt. The samwa samples were verified by the Bedouin herbal

experts, El-Arish City, North Sinai Governorate, Egypt

2.1.2. Chemicals

Alloxan and thiobarbituric acid (TBA were purchased from Sigma Chemical Co., St. Louis, MO. Casein was purchased from Morgan Company for Chemicals, Cairo, Egypt. All other chemicals (Except as otherwise stated), vitamins and salts mixtures, reagents and solvents were of analytical grade were purchased from El-Ghomhorya Company for Trading Drug, Chemicals and Medical Instruments, El-Amiryia, Cairo, Egypt.

2.1.3. Kits

Kit's assays for glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), malondialdehyde (MDA) were purchased from BIODIAGNOSTIC, Dokki, Giza, Egypt. Reduced glutathione (GSH) and oxidized glutathione (GSSG) were assayed by the kit provided by MyBioSource, Inc., San Diego, CA, USA. Superoxide dismutase (SOD) activity was assayed the kit assayed by Creative BioLab, NY.

2.1.4. Equipment's

Absorbance (Abs) and fluorescence (FL) for different assays were measured using Labo-med. Inc., spectrophotometer, CA and Schematzu fluorescence apparatus, Japan, respectively.

2.2. Methods

2.2.1. Preparation of Samwa Aerial Part Powder

Samwa (*Cleome droserifolia*) aerial part samples were cleaning and sorting manually and washing by water to remove the all strange bodies attached and then dried in a hot air oven (Horizontal Forced Air Drier, Proctor and Schwartz Inc., Philadelphia, PA) at 70°C for six hours. The dried samwa samples were milled into a fine powder in high mixer speed (ElAraby Co., Benha, Egypt). The powder that passed through 40 mesh sieve was retained, kept in polyethylene bottles and stored in refrigerator at 4^0C until used for chemical and biological experiments.

2.2.2. Preparation of Samwa (*Cleome droserifolia*) Aerial Part Ethanol Extract (CDE)

Samwa (*Cleome droserifolia*) aerial part ethanol extract (CDE) was prepared according to the method mentioned by Gharib et al., [46]. A 20g of samwa aerial part dried powder were extracted with 80% aqueous ethanol and water (180 ml) on an orbital shaker (Unimax 1010, Heidolph Instruments GmbH & Co. KG, Germany) for three hours at 60°C. The mixtures were subsequently filtered (Whatman No. 5) on a Buchner funnel. The ethanol residues were removed under reduced pressure at 50°C using a rotary evaporator (Laborata 4000; Heidolph Instruments GmbH & Co. KG, Germany). The resulted extract were stored at 4 ^{0}C for future use.

2.2.3. Biological Experiments

2.2.3.1. Animals

Animals used in this study, adult male albino (Sprague Dawley) rats, (160± 8.5g per each) were purchased from Helwan Station, Ministry of Health and Population, Helwan, Cairo, Egypt.

2.2.3.2. Basal/Standard Diet

Basal diet (BD) was prepared according to Reeves et al., [47]. The compositions of salt and vitamin mixtures were prepared for the BD according to the same reference.

2.2.3.3. Induction of Diabetic Mellitus (DM)

DM was induced in normal healthy rats by subcutaneous injection with freshly prepared alloxan monohydrate in saline at a dose level of 160 mg/ kg body weight [48]. After one week of injection, fast blood glucose (FBG) was assayed using a specific by a drop of blood was obtained from tail vein and subjected to a strip of haemogluco test. All injected rats with FBG >200 mg/dl were considered to be diabetics and included in the experiments [9]

2.2.3.4. Experimental Design

All biological experiments were carried out in accordance with the National Research Council's Institute of Laboratory Animal Resources, Commission on Life Sciences Rules (NRC) [49]. Rats (n=36) were housed individually in wire cages in a room maintained at 25 ± 4.5 ^{0}C and kept under normal healthy conditions. All rats were fed a BD for two week before starting the experiment for accommodation. Then, the rats were divided into two main groups, the first main group, normal control, (Group 1, 6 rats) still fed on BD and the other main group (30 rats) was used for diabetes induction and classified into five sub groups as follow: group (2), model control, fed on BD only as a positive control (rats with diabetes) and groups (3-6) fed on BD containing 200, 400 , 600 and 800 mg/kg body weight of samwa aerial part ethanol extract, respectively. The tested concentration of samwa aerial part concentrations were suggested for present experiments based on many of the results of previous studies [9,50,51]. For 28 days, each of the above groups was housed in a single cage. For biological evaluation [body weight gain (BWG, %), food intake (FI) and food efficiency ratio (FER)], the diet consumed was recorded every day and body weight was recorded every week during the experimental period (28 days). The BWG (%),FI and FER were determined according to Chapman et al., [52] using the following equations: BWG (%) = (Final weight – Initial weight)/ Initial weight×100, FER= Grams gain in body weight (g/28 day)/ Grams feed intake (g/28 day).

2.2.3.5. Blood Sampling

After twelve hours of fasting at the end of the experiment (28 days), rats were anesthetized by diethyl ether and blood samples were collected using the abdominal aorta at specific centrifuge tubes. Blood samples were left to clot in water bath (35°C) for 28 minutes, then centrifuged for 10 minutes at 4000 rpm to separate the serum, which were carefully aspirated and transferred into clean cuvette tube and stored frozen at -18°C for future analysis according to the method described by Schermer [53]. The erythrocyte residue was washed with

three successive portions of NaCl solution (0.9 %) and then haemolysed with deionized water for 30 min. Haemolysate was then centrifuged at 30,000 rpm for 30 min and the supernatant fractions were transferred to a clean test tube and analyzed of antioxidant enzymes [glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd), superoxide dismutase (SOD) and catalase (CAT)].

2.2.3.6. Hematological Analysis

Serum glucose and insulin

Serum glucose was determined by the colorimetric method explained by Xianchang, [54]. Insulin was determined using the colorimetric detection method mentioned by Mirsalari and Elhami, [55].

Liver functions

Alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) activities were measured in serum using the modified kinetic method of Tietz, [56] while alkaline Phosphatase (ALP) activity was determined using modified kinetic method of Vassault et al., [57].

Glutathione fractions (GSH and GSSG)

Reduced glutathione (GSH) and oxidized glutathione (GSSG) were measured by calorimetrically methods in serum samples such as described by Davies et al., [58].

Antioxidant enzymes

Glutathione peroxidase (GSH-Px) and catalase (CAT) activities were measured as mentioned by Splittgerber and Tappel, [59] and Aebi, [60]. Superoxide dismutase (SOD) activity was measured by a colorimetric assay kit (Creative BioLab, NY) according to the method of Mett and Müller [61]. The International Committee for Standardization in Haematology recommended a method for determining GSH-Rd activity [62].

Malonaldehyde (MDA) content

MDA content was measured using the colorimetric method described by Buege and Aust, [63] based on the reaction of thiobarbituric acid (TBA) with MDA, one of the main final aldehyde products of lipid peroxidation. In brief, a 0.5 mL of serum was added to 1.0 ml of thiobarbituric acid (TBA) reagent [15% TCA, 0.375% TBA, and 0.01% butylated hydroxytoluene (BHT) in 0.25 N HCl]. A 25µl of 0.1 M $FeSO_4.7H_2O$ were added and the mixture was heated for 20 min in boiling water. The samples were centrifuged at 1000 xg for 10 min and the absorbance (Abs) was measured at 535 nm against a reagent blank. The Abs of the samples were compared to a standard curve of known MDA concentrations.

Nitric oxide determination

Nitric oxide (NO) determination was done as the sum of NO_2 and NO_3 as mentioned by Miranda et al., [64]. The levels of NO were estimated by using Classical Griess Reaction (1% sulphanilamide, 1% naphthylethylene diamine dihydrochloride, and 2.5% phosphoric acid). Serum samples were added to the Griess reagent, and their Abs were recorded spectrophotometrically. The standard curve was plotted and the Abs of the rat sample were taken and correlated over the standard curve.

2.3. Statistical Analysis

All experiments were carried out in triplicate. Data were subjected to the analysis of variance (ANOVA) and mean comparisons were performed using Duncan's multiple range test [65]. Statistical analysis was carried out using the statistical Package for Social Sciences (SPSS for windows: SPSS Inc., Chicago, IL, USA).

3. Results and Discussion

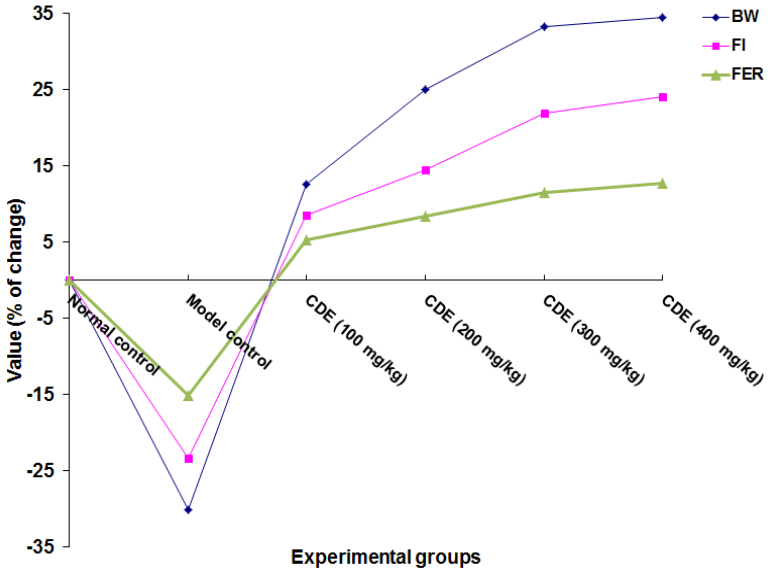
3.1. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Body Weight Gain (BWG), Feed Intake (FI) and Feed Efficiency Ratio (FER) of Diabetic Rats

Data in Table 1 and Figure 2 indicated the effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats. Such data declared that alloxan-injection rats induced significantly ($p \leq 0.05$) decreasing in BWG (-30.09%), FI – (23.30%) and FER (-15.16%) compared to the normal animals. However, intervention with CDE (200 to 800 mg/kg bw) in feeding rats for 28 days led to significantly ($p \leq 0.05$) increase the values of all these parameters by the rates of 12.54, 24.94, 33.27 and 34.39% (BWG), 8.55, 14.41, 21.84 and 24.06% (FI), and 5.33, 8.38, 11.43 and 12.73% (FER) compared to the model/diabetic controls. The rate of increasing in BWG, FI and FER exhibited a dose-dependent manner. Several studies found that the percentage of body weight change was significantly ($P \leq 0.01$) decreased in diabetic rats when compared to the control [16,18,23,35,66,67,68]. Intervention the diabetic rats with CDE, the percentage of changes in BWG, FI and FER were returned near to the normal group values. Also, such data are in partially agreement with that observed by several authors in different plant parts other than *Cleome droserifolia* but have the same content of bioactive constituents [16,26,28,40,69,70,71,72]. All of these studies indicated that the decreasing in BWG, FI and FER as the result of intervention with plant parts could be attributed to their bioactive compounds content and the consequences their different biological effects. With the same context, Tahoon, [73] and Elhassaneen et al., [74] reported that injection of rats by CCl_4 induced hepatotoxic and diabetic effects led to decrease in BWG, FI and FER. Such disorders were improved by consumption of plant parts contains bioactive compounds such as found in CDE. Also, Hamzawy *et al.*, [75] and Abd El-Rahman [72] found that liver rat's disorders probably due to diabetes reveal significant decreasing of the BW and FI. Additionally, several studies reported that diabetes and liver disorders can lead to malnutrition which the major causes of malnutrition in patients with diabetes and liver diseases are poor dietary/feed intake, maldigestion, malabsorption and abnormalities in the metabolism and storage of macro and micro nutrients [9,35,72] [76,77,78].

Table 1. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Body weight gain (BWG, g)						
Mean	0.903 [a]	0.631 [c]	0.710 [b]	0.788 [ab]	0.841 [a]	0.848 [a]
SD	0.112	0.131	0.091	0.081	0.067	0.103
% of Change	0.00	-30.09	12.54	24.94	33.27	34.39
Feed intake (FI, g/28 day)						
Mean	11.76 [a]	9.02 [c]	9.79 [bc]	10.32 [b]	10.99 [ab]	11.19 [a]
SD	0.94	1.04	0.90	0.83	0.72	0.95
% of Change	0.00	-23.30	8.55	14.41	21.84	24.06
Feed efficiency ratio (FER)						
Mean	0.077 [a]	0.066 [b]	0.069 [b]	0.071 [ab]	0.073 [a]	0.074 [a]
SD	0.007	0.021	0.019	0.014	0.012	0.017
% of Change	0.00	-15.16	5.33	8.38	11.43	12.73

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.

Figure 2. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) (as a % of control) of diabetic rats

3.2. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Liver Function of Diabetic Rats

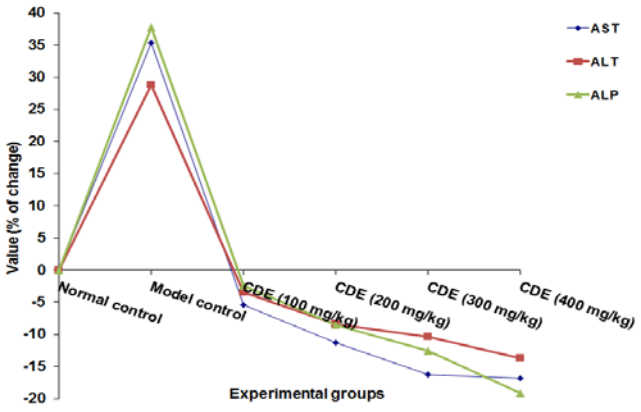
The effect of dietary intervention with *Cleome droserifolia* **ethanol extract (CDE)** on liver function of diabetic rats was shown in Table 2 and Figure 3. From such data it could be noticed that alloxan injection caused a significant ($p \leq 0.05$) increase in enzymatic liver functions including AST, ALT and ALT with the ratio of 35.39, 28.74 and 37.75% compared to the normal animals group, respectively. Intervention with CDE (200 to 800 mg/kg bw) in feeding rats protocol for 28 days led to significant ($p \leq 0.05$) decrease the levels of these enzymes activity by the rates of -5.46, -11.32, -16.21 and -16.84 (for AST), -3.44, -8.43, -10.33 and -13.74% (for ALT) and -2.39, -8.51, -12.58 and -19.06% (for ALP) compared to the diabetic animals group. The rate of decreasing in serum liver function enzymes activity was exhibited a dose- dependent manner. Aminotransferases enzymes (ALT and AST) plus ALP are normally intracellular enzymes. The presence of high levels of AST, ALT and ALP in the serum illustrated damage to cells rich in these enzymes including to the liver cells. Liver and pancreas disease process such as found in diabetes probably cause

cell lysis resulting to release the intracellular enzymes into the blood [68,71,79]. Data of the present study found to be partially agreement with that reported in many studies carried out with different plant parts extract other than

Table 2. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on liver function of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Serum Aspartate aminotransferase (AST) activity (U/L)						
Mean	54.68 ^{c}	74.03 ^{a}	69.98 ^{ab}	65.65 ^{b}	62.03 ^{b}	61.56 ^{b}
SD	4.01	6.01	4.74	5.31	3.21	5.11
% of Change	0.00	35.39	-5.46	-11.32	-16.21	-16.84
Serum alanine aminotransferase (ALT) activity (U/L)						
Mean	31.50 ^{c}	40.56 ^{a}	39.16 ^{a}	37.14 ^{a}	36.37 ^{ab}	34.98 ^{b}
SD	2.29	3.11	3.65	1.99	3.05	2.07
% of Change	0.00	28.74	-3.44	-8.43	-10.33	-13.74
Serum alkaline phosphatase (ALP) activity (U/L)						
Mean	113.61 ^{d}	156.50 ^{a}	152.76 ^{a}	143.18 ^{ab}	136.81 ^{b}	126.68 ^{c}
SD	8.87	10.43	13.74	11.87	8.15	7.77
% of Change	0.00	37.75	-2.39	-8.51	-12.58	-19.06

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.

Figure 3. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) (as a % of control) on liver functions of diabetic rats

Cleome droserifolia but including the same content of bioactive compounds [18,19,23,26,28] [40,68,70,72,80,81]. With the same context, several studies indicated that plant parts contains polysaccharides and terpenoids such as found in CDE exhibited protective activities against liver injury induced by toxic chemicals [42,82,83]. Also, different plant parts extract including CDE are a rich source of different bioactive compounds such phenolics, carotenoids, anthocyanin's, polysaccharides, terpenoids and flavonoids [84,85,86,87,88]. Such bioactive compounds could be lowered liver serum enzymes activity through many proposed effects including block the hepatocellular uptake of bile acids and improved the antioxidant capacity of the liver, diminished the bilirubin concentration reduce the damage of hepatocytes, immunomodulating effects, modulation of hepatic Phase I and II metabolizing enzymes, scavengers of reactive oxygen species, inhibition of the lipid oxidation [8,9,71,83] [89,90,91,92]

3.3. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Blood Glucose and Insulin Levels of Diabetic Rats

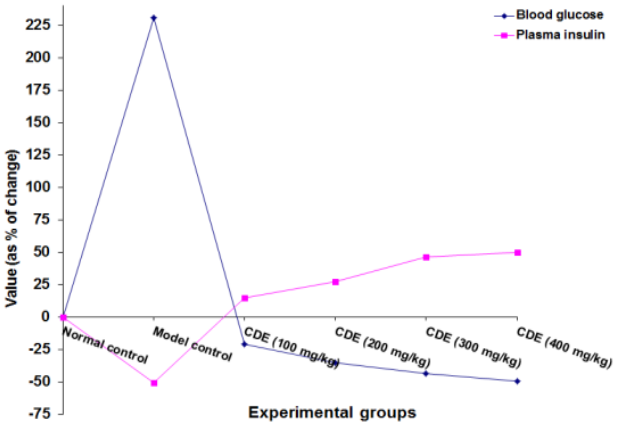
The effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on blood glucose and insulin levels of diabetic rats was shown in Table 3 and Figure 4. From such data it could be noticed that injection of rats with alloxan induced a significant ($p \leq 0.05$) increased in serum glucose concentration by the ratio of 230.72% compared to normal rats. Intervention with CDE (200 to 800 mg/kg bw) in feeding protocol rats for 28 days led to significant ($p \leq 0.05$) decrease the levels of blood glucose by the rates of -21.16, -35.40, -43.48 and -49.51% compared to the diabetic rats, respectively. The opposite direction was recorded for insulin level. Treatment of rats with alloxan caused a significant ($p \leq 0.05$) decrease in free serum insulin concentration by the ratio of -51.13% compared to the normal rats. Intervention with CDE (200 to 800 mg/kg bw) in feeding protocol rats for 28 days led to significant ($p \leq 0.05$) increase in the levels of free serum by the rates of 14.76, 27.05, 46.35 and 50.03% compared to the diabetic rats group, respectively. The rate of decreasing in blood glucose and increasing in free serum insulin were exhibited a dose-dependent manner. Data of the present study are in agreement with several authors [43,44,93,94]. In general, alloxan is widely used as inducer of diabetes in different experimental animals. Alloxan induce pathological effects through inhibits glucose-induced insulin secretion by inhibition of glucokinase, the glucose sensor of the β-cell, and its ability to induce ROS formation, resulting in the selective necrosis of β-cell [18,95,96]. Thus, the hyperglycemia recorded in the present study, rats injected with alloxan, could be attributed to generate some types of reactive oxygen species/radicals (ROS) that attack DNA inducing DNA-strand breaks in β-cells and, cellular functions including insulin synthesis and secretion, and thus the β-cell ultimately dies [20,95,96,97]. All of these factors lead to reduce the uptake of glucose by peripheral tissues such muscles and adipose tissue (glycogenolysis) and increased gluconeogenesis i.e.hepatic glucose production [98,99,100,101]. This theory may be in line with the data of the present study, which are serum glucose levels significantly decreased while serum insulin levels significantly increased in diabetic group treated with. Such hypoglycemic effect of CDE in diabetic rats may be related to the diverse bioactive constituents found in CDE.

With this context, several studies indicated that different bioactive constiuents including phenolics, polysaccharides, terpenoids , flavonoids, and carotenoids are known for their biological properties including antioxidant and free radicals scavenging activities and inhibition of lipid oxidation which lead to improve glucose response, alleviating metabolic dysregulation of free fatty acids and insulin resistance associated with type 2 diabetes [17,35,72,77] [78,102,103,104].

Table 3. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on blood glucose and insulin levels of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Blood glucose (mg/dl)						
Mean	94.41 ^{f}	312.22 ^{a}	246.15 ^{b}	201.70 ^{c}	176.46 ^{d}	157.64 ^{e}
SD	4.11	10.54	7.10	8.10	111.41	9.4
% of Change	0.00	230.72	-21.16	-35.40	-43.48	-49.51
Insulin level (µU/ml)						
Mean	13.71 ^{a}	6.70 ^{c}	7.69 ^{c}	8.51 ^{c}	9.81 ^{b}	10.05 ^{b}
SD	0.99	0.77	0.64	0.83	0.72	0.59
% of Change	0.00	-51.13	14.76	27.05	46.35	50.03

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.

Figure 4. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on blood glucose and insulin levels (as a % of control) of diabetic rats

3.4. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Glutathione Fractions of Diabetic Rats

The effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on glutathione fractions of diabetic rats was shown in Table 4 and Figure 5. Such data indicated that normal rats recorded 9.02 and 0.701 µmol/L for GSH and GSSG, respectively. The alloxan-treated rats exhibited a significant ($p \leq 0.05$) decrease in GSH (-47.78%) and GSSG (-13.98%) compared to the normal animals. Intervention with CDE (200 to 800 mg/kg bw) in feeding rats protocol for 28 days leads to a significant ($p \leq 0.05$) increase in the levels of both GSH and GSSG by different rates. The rate of increase in GSH and GSSG has exhibited a dose-dependent increase with the CDE level intervention. GSH, a tripeptide (L-glutamyl-L-cysteinyl-glycine) present in millimolar concentrations in all cells, is an important biological antioxidant (Lu, 1999). Such antioxidant functions include its role in the activities of the GSH enzymes family including glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd), and peroxiredoxins (PRXs) as well as serve as a nonenzymatic scavenger of oxyradicals [11,16]. Several oxidative injuries have been associated with GSH depletion (Lina *et al.*, 2002). For example, a relationship between hyperglycemia and GSH depletion was reported [18,19,35]. Such a relationship could be interpreted as follow: in hyperglycemia conditions, glucose is preferentially used in the polyol pathway that consumes NADPH necessary for GSH regeneration by the GSH-Rd enzyme [105]. Therefore, hyperglycemia is indirectly the cause of GSH depletion. On the other side, the same data also indicated that the decrease in glutathione fractions (GSH and GSSG) reported in alloxan-diabetic rats was accompanied by a concomitant decrease in the ratio of GSH/GSSG. The GSH/GSSG in normal animals was 12.29 which significantly decreased in alloxan-diabetic rats to 7.81. Intervention with CDE (200, 400, and 800 mg/kg bw) in feeding rats protocol for 28 days leads to a significant ($p \leq 0.05$) increase in such ratio which recorded 8.75, 11.24, 12.42 and 12.49, respectively. Several studies have reported that increasing fluxes of oxy-radicals may be decreased in the case of a high GSH/GSSG ratio, either due to direct radical scavenging or increased peroxidase activity [35] [106,107,108]. This effect could also occur indirectly due to reduced NADPH availability (necessary for GSH-Rd activity) which resulting from the oxidations in the first step of the redox cycle [109]. Various enzymes inside the cells such as nitric oxide synthase can also generate ROS and such an effect could be one of the most important reasons for reducing the GSH/GSSG ratio in diabetic rats [110]. Such data are was reported in several simillar studies [9,35,108]. Therefore, these results were confirmed by treating diabetic rats with SDE extract, which led to a high level of GSH/GSSG due to the fact that it contains many bioactive compounds with important biological activities including antioxidant and scavenging activities.

3.5. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Antioxidant Enzymes in Red Blood Cells (Rbcs) of Diabetic Rats

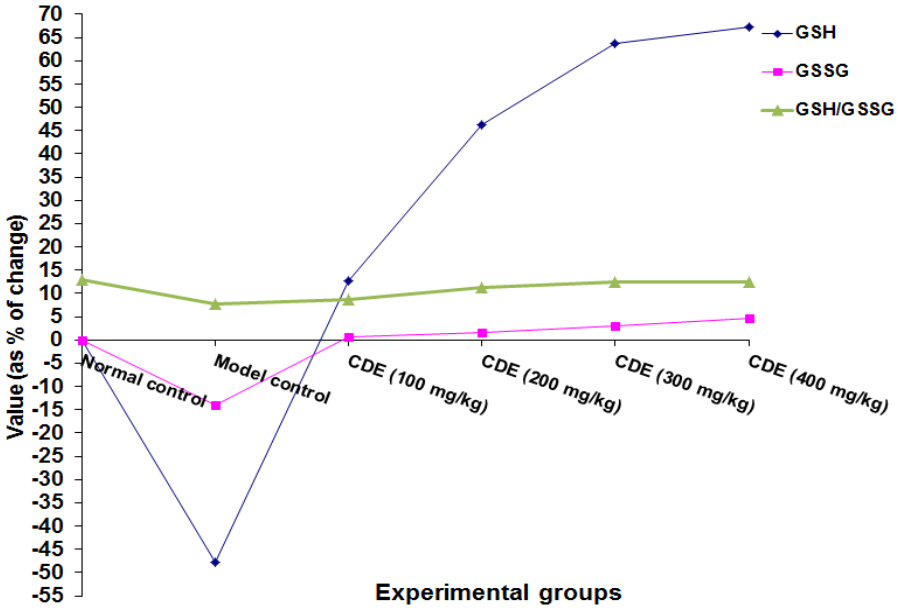
The effect of dietary intervention with *Cleome*

droserifolia ethanol extract (CDE) on antioxidant enzymes in red blood cells (RBCs) of diabetic rats was shown in Table 5 and Figure 6. Such data indicated that normal rats recorded 29.54, 10.56, 153.20 and 6.46 U/g Hb for GSH-Px, GSH-Rd, CAT, and SOD, respectively. The alloxan-treated rats exhibited significantly ($p \leq 0.05$) decreasing in GSH-Px, GSH-Rd, CAT and SOD by the rate of -31.63, -16.45, -28.51 and -36.51compared to the normal group, respectively. Intervention with CDE (200, 400, 600 to 800 mg/kg bw) in feeding rats protocol for 28 days leads to a significant ($p \leq 0.05$) increase in the levels of GSH-Px, GSH-Rd, CAT and SOD by different rats. The rate of increasing in the all of these antioxidant enzymes exhibited a dose-dependent manner. It is well known that different organisms have developed antioxidant defense systems largely based on antioxidant enzymes including GSH-Px, GSH-Rd, CAT, and SOD which able to scavenge the free radicals as well as prevent their damages. SODs are responsible for the reduction of $O_2^{\cdot -}$ to H_2O_2 and multiple enzymes will remove H_2O_2 including GSH-Px and CAT (Mccord et al., 1976). Also, the GSH reduces the Se and the reduced form of the enzyme then reacts with H_2O_2. The ratio of nine *GSH/GSSG* in normal cells is kept high. So, there should be a mechanism for reducing GSSG back to GSH. This is achieved by the GSH-Rd enzyme which catalyzes the reaction: GSSG + NADPH + $H^+ \rightarrow$ 2GSH + $NADP^+$. Mammalian RBCs operate the pentose phosphate pathway to provide NADPH required for GSH reduction. GSH-Rd can also catalyze the reduction of certainly mixed disulfides (-S-S-) such as that between GSH and Co-enzyme A [111]. Decreasing the activity of the antioxidant enzymes in both *in vitro* and *in vivo* studies resulted in elevating the reactive oxygen species production and different cell organelles dysfunction including mitochondria, lysosomes and cell wall membrane [8,112]. CDE used in the present study for interventions experiments is rich in bioactive compounds such phenolics, carotenoids, terpenoids, polysaccharides, flavonoids and carotenoids which exhibited antioxidant and scavenging activities in different biological systems [9,17,35,82,104]. Such antioxidant activities are significant in the manipulation of the diabetes development/complications through reactive oxygen species scavenging processes in RBC's.

Table 4. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on glutathione fractions of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Reduced glutathione (GSH, mmole/L)						
Mean	9.02 [a]	4.71 [d]	5.31 [d]	6.89 [c]	7.71 [bc]	7.88 [b]
SD	0.75	0.59	0.67	0.54	0.88	0.69
% of Change	0.00	-47.78	12.74	46.28	63.69	67.30
Oxidized glutathione (GSSG, mmole/L)						
Mean	0.701 [a]	0.603 [b]	0.607 [b]	0.613 [b]	0.621 [ab]	0.631 [a]
SD	0.062	0.076	0.021	0.062	0.052	0.099
% of Change	0.00	-13.98	0.66	1.66	2.99	4.64
GSH/GSSG ratio						
Mean	12.86 [a]	7.81 [c]	8.75 [c]	11.24 [b]	12.42 [a]	12.49 [a]
SD	0.98	0.88	0.69	0.77	0.65	0.48

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



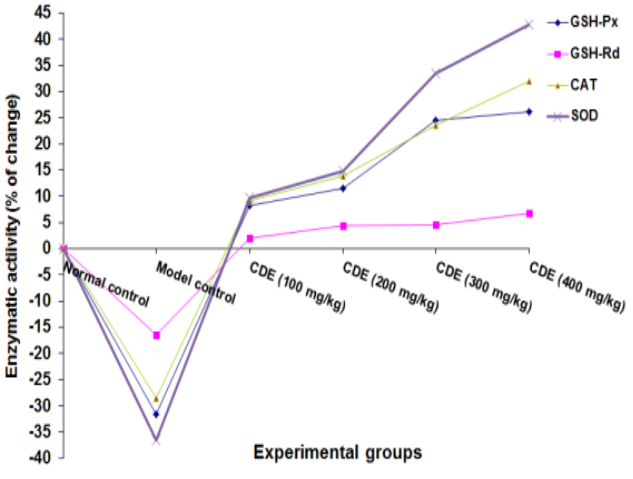
Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, Cleome droserifolia ethanol extract; bw, body weight.

Figure 5. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on glutathione fractions (as a % of control) of diabetic rats

Table 5. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on antioxidant enzymes in red blood cells (RBCs) of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Glutathione peroxidase (GSH-Px, U/g Hb)						
Mean	29.54[a]	20.20[c]	21.87[c]	22.51[bc]	25.16[b]	25.49[b]
SD	1.79	2.35	2.50	3.01	2.10	2.11
% of Change	0.00	-31.63	8.28	11.47	24.57	26.20
Glutathione reductase (GSH-Rd, U/g Hb)						
Mean	10.56[a]	8.82[b]	8.99[b]	9.21[b]	9.22[b]	9.42[b]
SD	1.01	0.93	1.10	1.72	0.99	0.88
% of Change	0.00	-16.45	1.93	4.42	4.54	6.80
Catalase (CAT, U/g Hb)						
Mean	153.20[a]	109.53[e]	119.47[d]	124.78[d]	135.44[c]	144.52[b]
SD	5.78	6.21	3.89	4.09	2.90	5.29
% of Change	0.00	-28.51	9.08	13.92	23.66	31.95
Superoxide dismutase (SOD, U/g Hb)						
Mean	6.46[a]	4.10[c]	4.50[bc]	4.71[b]	5.48[ab]	5.86[a]
SD	0.67	0.55	0.99	0.56	0.72	0.55
% of Change	0.00	-36.51	9.60	14.75	33.55	42.81

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight

Figure 6. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on antioxidant enzymes in red blood cells (RBCs) (as a % of control) of diabetic rats

3.6. Effect of Dietary Intervention with *Cleome Droserifolia* Ethanol Extract (CDE) on Oxidative Stress and Inflammation Parameters of Diabetic Rats

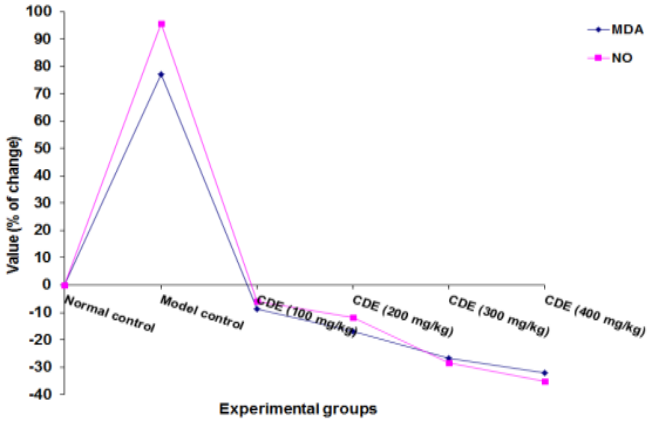
The effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on oxidative stress and inflammation parameters of diabetic rats was shown in Table 6 and Figure 7. From such data it could be noticed that normal rats recorded 5.46 nmol/L and 44.21 µmole/L for malondialdehyde (MDA) and nitric oxide (NO), respectively. The alloxan-injected rats exhibited a significant ($p \leq 0.05$) increasing in MDA (77.07%) and NO (95.69%) compared to the normal animals. Intervention with CDE (200, 400, 600 to 800 mg/kg bw) in rats feeding protocol for 28 days leads to a significant ($p \leq 0.05$) decreasing in the levels of MDA and NO by the rates -8.69, -16.99, -26.58 and -31.95%, and -5.77, -11.80, -28.47 and -35.17% compared to the diabetic animals, respectively. The rate of decreasing in oxidative stress (MDA) and inflammatory (NO) parameters exhibited a dose-dependent increase with the CDE intervention. In similar studies, clinical evidence for diabetes-associated oxidative stress has been established by measurement of either biomarkers or end-products of free radical-mediated oxidative processes [9,18,77,78,107]. For example, lipid peroxidation markers such as malondialdehyde (MDA), the major products of the oxidation of polyunsaturated fatty acids, lipid hydroperoxides, and conjugated dienes (〰) are reported to be increased in serum from diabetic subjects and experimental animals [9,10,113]. Official reports indicated that MDA is a mutagenic and/or carcinogenic [114]. In the present study, it was reported that intervention of the diabetics rats with CDE significantly removed some of the metabolic disorders induced by T2DM in different cells through decreasing the MDA formation. Such data are in partially accordance with that reported by several studies [115,116,117].Thus, the present data proposed that the CDE lead to improve insulin sensitivity, at least in part, through enhancing lipid metabolism and reducing oxidative stress in diabetic rats. For immunological/ inflammation parameter, nitric oxide (NO) is a small molecule that plays significant role in the communication among liver cells and regulates important liver functions [118]. It is generated from catalyzes the conversion of L-arginine to citrulline and highly reactive free radical species, NO by nitric oxide synthase. NO can react with O_2 and H_2O_2 to form nitrite (NO_2) and nitrate (NO_3); with hemoglobin to form iron-nitrosyl adducts and/or nitrate in blood, with superoxide anion ($O_2^{\cdot-}$) to make nitrate, and with the amino and thiol groups of protein to form nitrosylated species [118,119]. The excess production of nitric oxides have been implicated in the pathogenesis and tissue destruction of a growing number of immunological and inflammatory diseases including diabetes [9,35,77,120]. Present data with the others indicated that CDE selected in the present study for intervention experiments is rich in bioactive compounds including phenolics, carotenoids, flavonoids, terpenoids

and alkaloids which exhibited antioxidant and scavenging activities in different biological systems [82,121]. Such antioxidant properties are important in the manipulation of diabetes and the development of its complications through nitric oxides scavenging processes and enhancing the immunological and inflammation parameters in plasma.

Table 6. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on oxidative stress and inflammation parameters of diabetic rats

Value	Normal control	Model control	CDE intervention (mg/kg bw)			
			200	400	600	800
Malondialdehyde (MDA, nmole/mL)						
Mean	5.46 ^{d}	9.67 ^{a}	8.83 ^{ab}	8.03 ^{b}	7.10 ^{c}	6.58 ^{cd}
SD	0.27	0.98	0.07	0.94	0.54	0.59
% of Change	0.00	77.07	-8.69	-16.99	-26.58	-31.95
Nitric oxide (NO, µmole/L)						
Mean	44.21 ^{e}	86.52 ^{a}	81.53 ^{b}	76.31 ^{b}	61.89 ^{c}	56.0 ^{d}
SD	1.02	2.56	1.67	4.67	4.73	3.17
% of Change	0.00	95.69	-5.77	-11.80	-28.47	-35.17

Means with different superscript letters in the same row are significantly different ($p \leq 0.05$). Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.



Normal control, healthy rats without intervention; Model control, alloxan-induced diabetic rats without intervention; CDE intervention: alloxan induced diabetic rats with CDE intervention; CDE, *Cleome droserifolia* ethanol extract; bw, body weight.

Figure 7. Effect of dietary intervention with *Cleome droserifolia* ethanol extract (CDE) on oxidative stress and inflammation parameters (as a % of control) of diabetic rats

3.7. Correlation Studies

Correlation analysis between oxidative stress (MDA) and inflammation (NO) parameters, and antioxidant defense systems (glutathione fractions and antioxidant enzymes) parameters in diabetes rat intervention with CDE was shown in Table 7. When all treatments were included in the statistical analysis important differences were found between oxidative stress and inflammation, and antioxidant defense systems parameters. There was a strong negative significant ($p \leq 0.05$) relationship between glutathione fractions concentration in plasma [GSH (r^2 = - 0.8976) and GSSG (r^2 = - 0.8393)], and antioxidant enzymes in RBC's [GSH-Px (r^2 = - 0.9102), GSH-Rd (r^2 = - 0.8226), CAT (r^2 = - 0.8392) and SOD (r^2 = - 0.8595)], and MDA concentration in plasma. The same behavior i.e. correlations/relationships were reported between all of those parameters and NO concentrations in plasma. All of these correlations confirm that if there were no change in the antioxidant defense systems parameters of diabetes rats, it would be difficult to observe high concentrations of MDA and NO. In a similar study, Shalaby, [122] reported that high levels of lipid peroxidation i.e. MDA in the plasma of diabetic rats were associated with rather low levels of antioxidant vitamins and enzymes. Also, Elhassaneen et al., [18] reported that some important differences were found between plasma MDA and both GSH fractions and antioxidant enzymes in diabetic rats feeding intervention with *Catharanthus roseus* extracts.. Furthermore, Elhassaneen et al., [9] reported that some important differences were found amongst plasma MDA and NO, and GSH fractions, antioxidant enzymes, and antioxidant vitamins in diabetic rats intervention feeding *Ganoderma lucidum* extract. Such extracts often contain many of the bioactive compounds that are found in the extract understudy, CDE.

Table 7. Correlation between oxidative stress (MDA) and inflammation (NO), and antioxidant defense systems parameters in diabetes rat's feeding intervention with CDE

Parameters	r^{2*}	Parameters	r^2
MDA/GSH	- 0.8976 **	NO/GSH	- 0.8692 **
MDA /GSSG	- 0.8393 **	NO/GSSG	- 0.8109 *
MDA/GSH-Px	- 0.9102 **	NO/GSH-Px	- 0.8834 **
MDA /GSH-Rd	- 0.8226 *	NO/GSH-Rd	- 0.8018 *
MDA /CAT	- 0.8392	NO/CAT	- 0.8404 **
MDA /SOD	- 0.8595 **	NO/SOD	- 0.8341 *

* P ≤ 0.05 ** P ≤ 0.01

4. Conclusion

Diabetes is a pathological condition that affects the organism and leads to a high level of glucose in the blood which is called hyperglycemia. Besides hyperglycemia, many other factors play a great role in the pathogenesis of diabetes including oxidative stress and inflammation which leading to serious complications. Data of the present study has demonstrated the efficiency of CDE to partially attenuate hyperglycemia and diabetes-associated oxidative stress and inflammation in diabetic rats induced by alloxan. All of these amelioration effects could be attributed to the high levels of different bioactive constituents found in CDE. Such compounds exhibited antioxidant and scavenging activities against oxidants/ROS formation and inflammation as the diabetes development through several mechanisms of action including 1) increasing the GSH synthesis, 2) raising redox status (GSH/GSSG ratio), 3) stimulating antioxidant enzymes activity such as GSH-Px, GSH-Rd, CAT and SOD in RBC's, 4) inhibiting the lipid oxidation i.e. decreasing the MDA formation in plasma, and inhibiting

the formation of NO which is considered as a pro-inflammatory mediator that induces inflammation. These findings provide a basis for the use of Samwa (*Cleome droserifolia*) extracts for the prevention and/or treatment of type-2 Diabetic Mellitus and its complications.

Ethical Considerations

The ethical issues of this study was reviewed and approved by the Scientific Research Ethics Committee, Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt (Approval # 22- SREC- 02-2023).

Conflict of interest

The authors declare that they have no conflict of interest in publishing this paper.

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Authors' Contribution

Yousif Elhassaneen participated in preparing and reviewing the study protocol, following up on the application of practical experiments, verifying the validity of the results, preparing a draft of the paper, conducting a critical review to organize the content intellectually, and granting approval to publish the final version of the paper. Ghada ElBasouny participated in following up on the application of practical experiments, participated in conceptual information retrieval, verifying the validity of the results and preparation of the draft paper. Omar Imam followed up the study by providing many advises, participated in conceptual information retrieval and preparation of the draft paper. Shrouk Ismail conducted the practical experiments; collected, analyzed, tabulated the data, and also participated in conceptual information retrieval and preparation of the draft paper.

Abbreviations

AA, antioxidant activity, Abs, absorbance, CDE, *Cleome droserifolia* ethanol extract, CAT, catalase, DM, Diabetes mellitus, DMSO, dimethyl sulfoxide, GSH, reduced glutathione, GSH-PX, glutathione peroxidase, GSH-Rd, glutathione reductase, GSSG, oxidized glutathione, MDA, malondialdehyde, NO, nitric oxide, RBCs, red blood cells, RCS, reactive chlorine species, RNS, reactive nitrogen species, ROS, reactive oxygen species, SD, standard deviation, SOD, superoxide dismutase, T2DM, type 2 diabetes mellitus.

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