

## **Anti – diabetic and anti-obesity effects of plant extract from *Cleome droserifolia* (SAMWA)**

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### **Abstract**

In this work the mechanism of the hypoglycemic effect of an aqueous extract from *Cleome droserifolia* (SAMWA) was studied in a group of glucose intolerant senile rats and compared with normal senile control rats. The plant extract significantly suppressed the rise in blood glucose concentration. The hypoglycemic effect of the plant extract without increasing insulin secretion was explained by: 1) potentiation of peripheral and hepatic insulin sensitivity, 2) by diminishing intestinal glucose absorption, which was evident by blunting plasma glucose levels throughout the oral glucose challenge. This was accompanied by a significant decrease of liver glycogen content and a highly significant increase in leptin concentration which may suggest an anti-obesity role for the plant extracts. Plant extracts also decreased serum urea nitrogen. No changes on liver or heart function were observed. In histological sections of liver and kidney minor changes were noticed. These extracts might prove to have a promising therapeutic value in the treatment of diabetes mellitus. Besides its suppression to hepatic glucose output, SAMWA beneficial therapeutic finding in favor of the plant as a replacement for insulin which is the most important drug that brings about this effect.

### **Introduction**

Although diabetes mellitus is a multifunctional disease with several causes and with complex consequences any consideration of the disease must deal with the importance of B- cell function and the production of adequate amount of active insulin.

Insulin secretion is primarily stimulated by glucose and a variety of non-glucose secretagogues including arginine, isoproterenol, glucagon and secretin. However, studies in vitro (Levin et al., 1972 and Gerich et al., 1974) and in vivo (Efendic et al., 1971) confirmed that the amount of insulin secreted in response to these non-glucose stimuli depends basically on the underlying glucose concentration.

In the non-insulin dependent diabetes mellitus (NIDDM), the total B-

cell mass has been reported as normal (Rahier et al., 1983), or only partially reduced (Gepts, 1972) and the pancreatic insulin reserve appears, in itself, sufficient for a normal glucose homeostasis. In NIDDM, a defect seems located in the insulin secretory capability of the pancreatic B-cell but it is unknown whether this deficiency is of a primary or secondary origin (Reaven, 1984).

Secretion appears to result from an autoimmune process involving the pancreatic insulin producing cells leading to their destruction with development of diabetic syndrome (O'Brien et al., 1996) The autoimmune process is probably triggered by some environmental factors (viral or toxic) in genetically susceptible individuals (Grunfield et al.,

1995; Yoon, 1990). Thus, these factors appear to interact to produce insulin deficiency, genetic factors, immunological factors and environment factors.(Yoon, 1990).

Non insulin dependent diabetes mellitus (NIDD) is usually associated with old age (Baird,1984). Senile rats are considered a good model for NIDD since they normally show high blood glucose level and glucose intolerance (Mattar and Moustafa, 1994; Moustafa et al., 1995). In this type of diabetes, the total p-cell mass has been reported as normally (Rahier et al.,1983) or only partially reduced(Gepts,1972) and the pancreatic insulin reserve appears, in itself, sufficient for a normal glucose homeostasis. In this case, any conditioning effect of a drug or herb can be attributed to activation of insulin receptors and/ or post glucose transport metabolic activity (Mattar and Moustafa, 1994; Moustafa et al., 1995) The history of spices and herbs was closely related to the old civilization in Egypt, India, Irak, Iran and China. The ancient Egyptians used plants in some medical treatments.

Plants were widely used in folk remedy such as sage which was used as stimulant, astringent, antifungal tonic and carminative where as peppermint was used as tonic, stomachic and as an insectifuge (Crisan and Hodis, 1972; Roberto, 1984). Thyme was used as antiseptic, antispasmodic, antibacterial and for relieve of pain in head (Farrage et al., 1986; Kaur S. and Shinna, 1982). Funnel can be employed as substitute for cod-liver oil in scrofula, rickets and anemia and the oil of dill was used in the flatulence of infants and was useful as a vehicle for children's medicine generally (Grieve, 1959).*Cleome droserifolia* is used as a decoction in Sinai by Bedouins and other inhabitants of the

area for the treatment of diabetes mellitus.

(El-Seifi et al ., 1993) provided the evidence which substantiated the traditional claim for oral hypoglycemic effect of *cidroserifolia* in diabetic rats.

The present study was planned to achieve the following goals. The first was to study the effect of both water and ethanolic extracts on the senile rats with glucose intolerance. The second was to follow up its effect on some vital organs as liver and kidney . The last was to elucidate its mode of action and which extract is more effective.

## **Material And Methods**

### **Animals:**

Male adult (3-4 month) and senile (15-18 month) albino rats (Sprague Dawley strain) were used in this study. Their body weight ranged from 120-150 gm for adult and 250-300gm for senile. They were acclimatized in the laboratory for one week.

### **Glucose tolerance:**

Rats were fasted overnight (10-12hr) and then drenched glucose solution (3g/kg.b.w) by gastric intubation. Blood was collected from the caudal vein by cutting the tip of tail. Glucose level was then measured for both adult and senile rats over 3 hour period. Senile rats with serum glucose level ranging from 180-300mg% were considered as intolerant in the experiment.

### **Preparation of plant extract:**

*Cleome droserifolia* (SAMWA) was obtained from a local market. The infusions(aqueous and ethnolic extracts) were prepared by using Sockslet apparatus.

### **Experimental design:**

Five young male albino rats and fifteen senile diabetic ones were allotted among four groups each of 5 rats. Two groups served as control (one young and

one senile diabetic group). Every animal in the other two groups of 5 senile rats each was drenched 6mg/kgm/day of aqueous or ethanolic extracts of SAMWA for 30 days.

### **Blood sampling**

Blood samples were collected at the end of the experiment from the orbital plexus by means of heparinized capillary glass tubes according to the method of Schermer(1967). Blood was collected, either on EDTA for hematological studies, or in glass centrifuge tubes to separate the serum. After 10 minutes of centrifugation of the blood at 5000 rpm, supernatant sera were immediately separated for biochemical analysis.

### **Hematological study**

Hemoglobin concentration was determined according to Van-kampen & Zalstra(1961).

Red and white blood cell count and hematocrit values (Hct) were estimated using the technique of Rodak(1995).

### **Biochemical study:**

The biochemical analysis was carried out on the blood sera. Glucose determination was based on the enzymatic method described by Siest & Schief(1981). Liver glycogen content was determined according to the technique described by Cara *et al.* (1956). Serum insulin and testosterone concentrations were measured by direct immunoenzymatic determination described by Maruyama, (1987). Serum glucagon and leptin concentrations were measured by radioimmunoassay techniques described by Heding,1971 and Zhongmin *et al.*, 1996 respectively. Serum Aspartate amine transferase (AST) and alanine amino transferase (ALT) activities were accomplished using the method of Reitman and Frankel(1975). $\gamma$ -glutamyltranspeptidase was estimated by the method of Meister

*et al.*(1981). Alkaline phosphatase (AP) and lactic dehydrogenase (LDH) activities were determined according to Belifield and Goldberg (1971) and Raabo (1963) respectively and the activity of Creatine Kinase (CK) Was determined according to the method described by Rosalki(1967) using Pointe Scientific, Inc kits, USA. Activity of acid phosphatase was determined by the method of King and Armstrong (1934). Total proteins were estimated using the Biuret method as described Doumas (1975). Albumin was determined according to the method of Webester, (1977) and urea nitrogen was determined using the method of Knight *et al* (1972), while serum cholesterol was determined as reported by Fossati and Medici (1987) and triglycerides were determined by the method of Rojkin *et al.*(1974).

### **Histological Study:**

At the end of the experimental period, animals were dissected and liver and kidneys were excised immediately. Small pieces were fixed in neutral formol for 48 hours, dehydrated, cleared and embedded in paraffin wax. Thin 6 $\mu$ m sections were cut, mounted on clean slides and stained by hematoxylin and eosin(Drury and Wallington, 1980). The specimens were microscopically examined and nuclear diameter was measured by computerized image analyzer.

### **Statistical manipulation:**

Student, t-test was the statistical analysis used to compare between the means obtained for the different parameters obtained from the different experimental animal groups. Significant differences between the means of control and treated groups were considered only at  $p \leq 0.05$ (Sokal & Rahif, 1981). Statistical analysis and graphic illustration was performed using MS Excell XP software.

**Results**

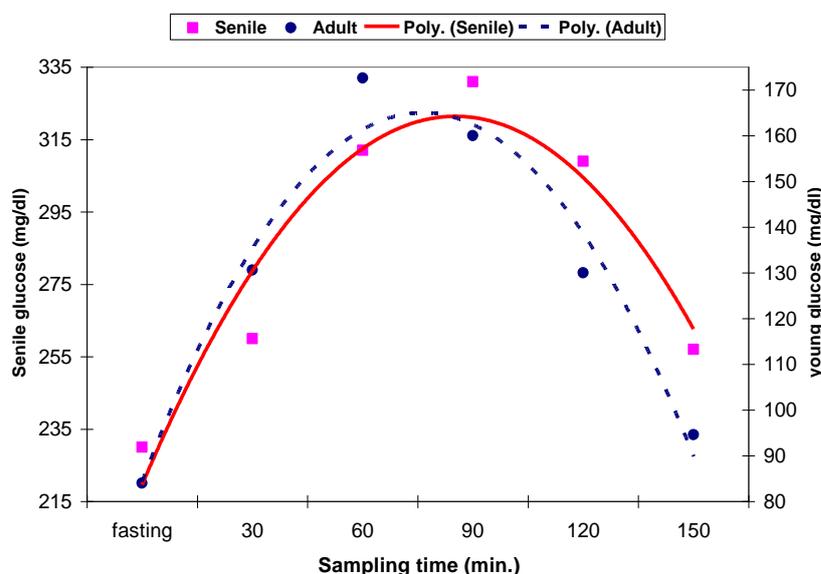
**Glucose tolerance**

The data of the present study showed significant high value in the level of fasting serum glucose of senile rats when compared to that of adults.

Senile rats showed glucose intolerance or even frank diabetes mellitus when compared with adults (Table 1, figure 1), so they were a good model to the present study.

**Table 1: mean ± standard error of blood glucose level (g/dl) at different periods after drenching 3g/kg body weight of glucose to adult and senile animals.**

time(min.)		fasting	30	60	90	120	150
young	Mean	84	130.6	172.6	160	130	94.6
	S.E.	3.4	4.4	3.8	4.8	7	4.2
Senile	Mean	230	260	312	331	309	257
	S.E.	15.5	14.2	16.8	23.15	25.3	21.7



**Figure 1:** Glucose tolerance curve for young and senile animals.

**Hematological parameters**

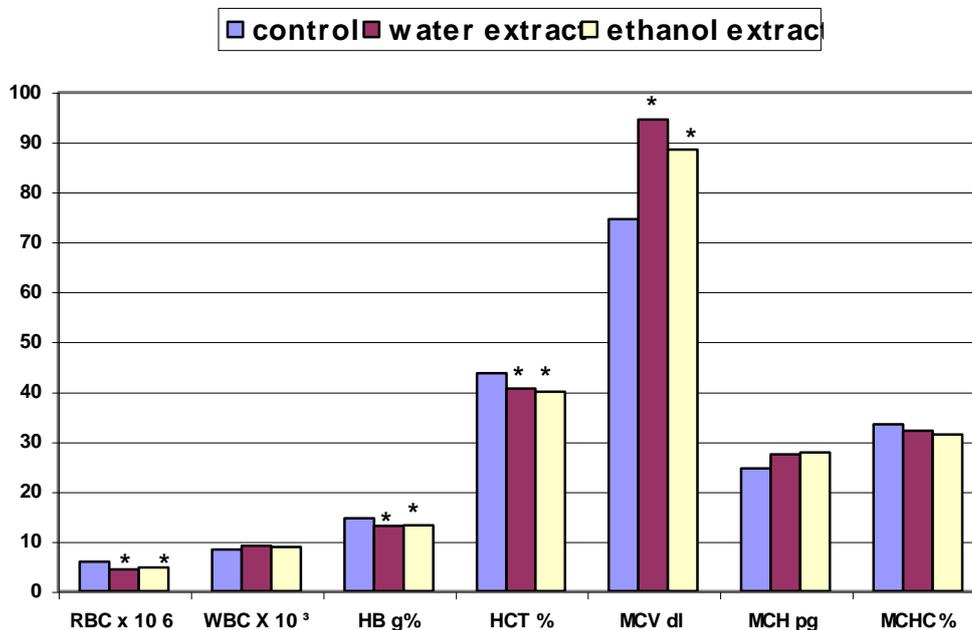
The data of the hematological parameters of senile rats treated with water or ethanol extracts of SAMWA are shown in table (2), figures (2,3). Generally, red blood cell (RBC) counts were significantly decreased in animals treated with either water or ethanolic extract through the treatment period.

Relevant to the decrement in RBC count, Hb%, Hct%, MCV were significantly reduced in association with both extract treatments.

On the other hand, no significant change was recorded in WBC count, MCH or MCHC (table 2).

**Table (2)** some haemtological parameters in senile control and senile rats treated with water or ethonolic extract of *Cleome dreserifolia* .

Parameter		control	water extract	Ethanol. extract	Parameter		control	water extract	Ethanol. extract
RBC x 10 <sup>6</sup>	– X S.E P	5.94 .14	4.3 .08 ≤0.01	4.78 .216 ≤0.01	MCV Dl	– X S.E P	74.48 1.08	94.5 1.45 ≤0.01	88.42 .57 ≤0.01
WBC X 10 <sup>3</sup>	– X S.E P	8.3 .3	9.1 .16	8.8 .26	MCH Pg	– X S.E P	24.6 .9	27.34 .52	27.8 .89
HB 8%	– X S.E P	14.6 .29	13.04 .17 ≤0.01	13.16 .19 ≤0.01	MCHC %	– X S.E P	33.48 .87	32.1 .63	31.32 .3
HCT %	– X S.E P	43.6 .54	40.6 .46 ≤0.05	40 .43 ≤0.05					



**Figure (2)** Some haemtological parameters in senile control and senile rats treated with water or ethonolic extract of *Cleome dreserifolia* . Asterisks indicate significant difference from control.

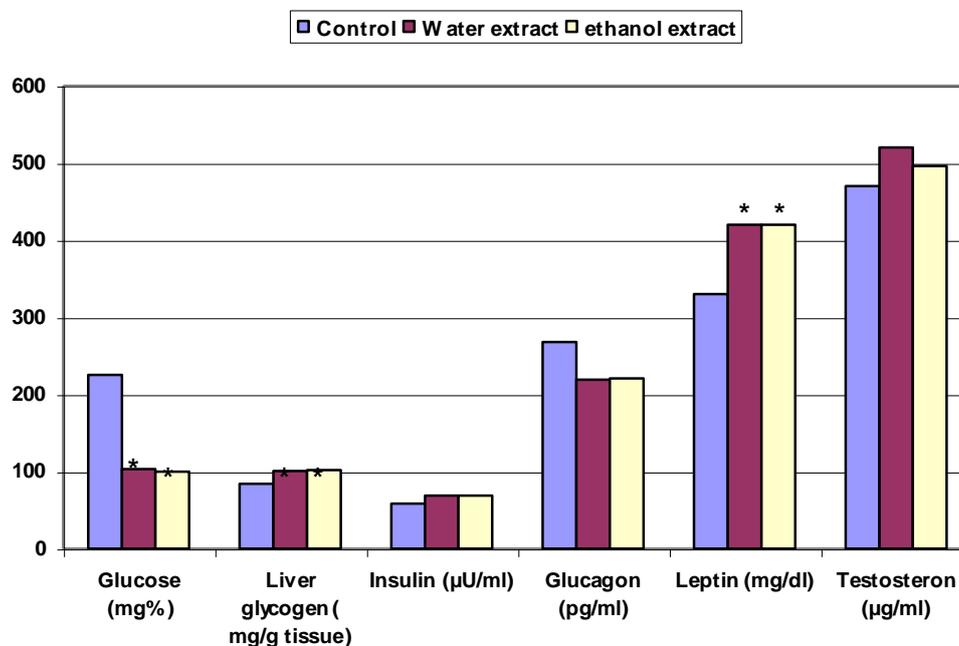
**Table (3) Serum glucose, hormonal activity and liver glycogen**

Parameter		control	water extract	Ethanol. extract	Parameter		control	water extract	Ethanol. extract
Glucose mg%	– X S.E P	225.2 .15	103* 6.25 ≤ 0.01	100* 6.7 ≤ 0.01	Glucagon (pg/ml)	– X S.E P	268 7.69	219 1.67	220.6 6.92
Liver glycogen mg/g tissue	– X S.E P	8.42 .24	10.08* .84 ≤ 0.01	10.18* .63 ≤ 0.01	Leptin (mg/dl)	– X S.E P	330 0.18	420* 0.26 ≤ 0.05	420 * 0.26 ≤ 0.05
Insulin μU/ml	– X S.E P	58.4 2.37	68.8 .17	68.8 .33	Testosterone (μg/ml)	– X S.E P	470 .038	520 .027	496 0.05

**Biochemical parameters**

The biochemical parameters are represented in tables (3,4) and figure (4,5,6). There was a statistically significant reduction in serum glucose level and significant increase in liver glycogen content as compared to control. There was an increase in the

level of insulin and a decrease in the level of glucagons but the changes were not statistically significant. The level of leptin was significantly higher than control, but the increase in the level of testosterone was not statistically significant.



**Figure (3)** Serum glucose, hormonal activity, and liver glycogen levels. The asterisk represents a statistically significant difference between treated and control ( $p \leq 0.05$ )

The activity of the enzymes reflecting liver and kidney function (figure 4) was not significantly different from control. The level of total lipids (figure 5) was significantly lower than control. However, the change in the level of

cholesterol, and triglycerides was not statistically significant. The level of total protein, albumin and globulin (figure 6) was also not significant. However, urea nitrogen was significantly lower than control.

**Table (4): Liver function, kidney function, protein and lipid profile**

Parameter		control	water extract	Ethanol. extract	Parameter		control	water extract	Ethanol. extract
AST U/ml	– X S.E P	27.8 0.59	28.4 1.08	26.2 1.45	Total Lipids g%	– X S.E P	452.2 1.2	402.6* 2.77 ≤ 0.01	402.6* 2.3 ≤ 0.01
ALT U/ml	– X S.E P	24.8 1.3	23 0.8	23.5 0.9	Choleste-rol mg/dL	– X S.E P	131.4 2.44	128.8 2.17	128 5
γ GT U/L	– X S.E P	12.68 0.2	14 1.22	12.72 1.22	Tri- glyceride mg/dL	– X S.E P	90 3.16	91 3.14	94 1.6
LDH U/L	– X S.E P	244 4.56	236.8 3.32	232 3.34	Total Protein g%	– X S.E P	7.56 0.38	6.7 0.22	6.5 0.2
CPK U/ml	– X S.E P	1182 3.62	170 3.16	168 2.28	Albumin g%	– X S.E P	4.38 0.31	3.92 0.22	3.98 0.16
Alkaline Phosph. U/L	– X S.E P	3.2.8 1.8	31.6 1.5	32.8 1.03	Globulin g%	– X S.E P	2.7 0.08	2.58 0.03	2.72 0.03
Acid Phosph. U/ml	– X S.E P	34.66 .44	35.2 2	32.6 0.92	Urea Nitrogen mg%	– X S.E P	34.98 0.4	28.6* 1.16 ≤ 0.01	25.1* 0.28 ≤ 0.01

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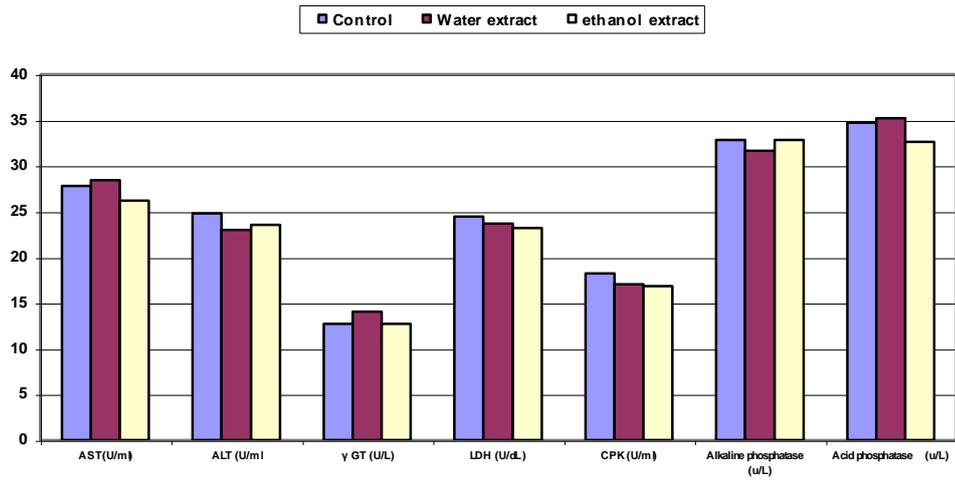


Figure (4): Liver and kidney function enzymes.

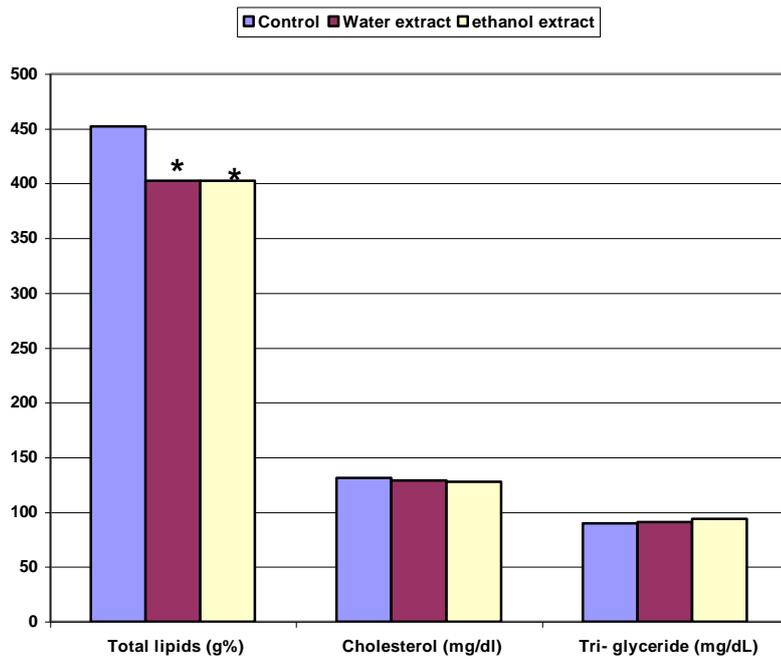
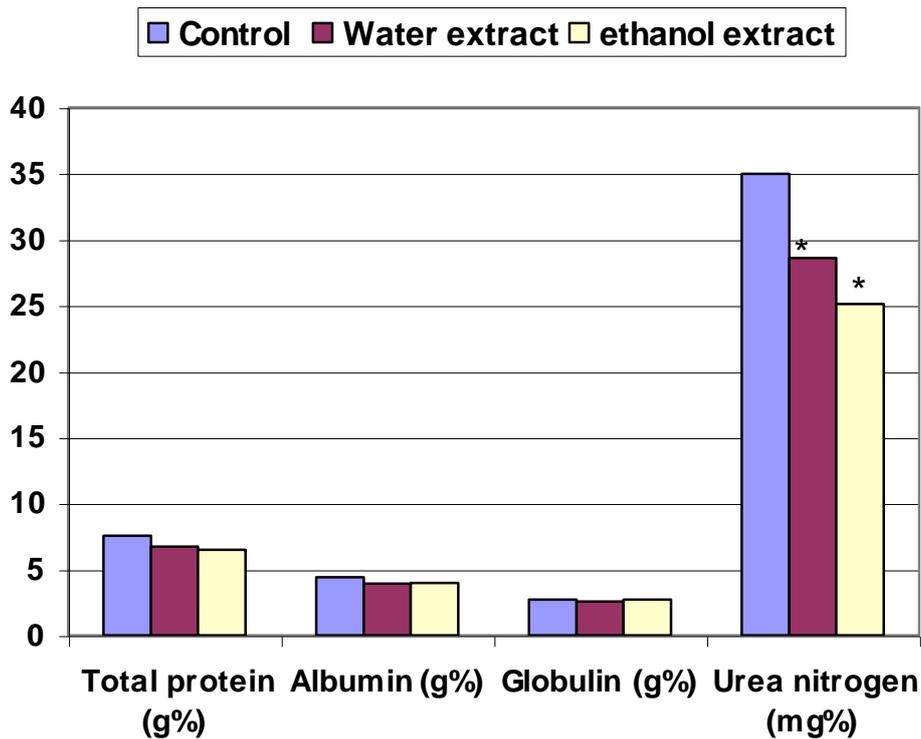


Figure (5): Lipid profile. Asterisks indicate a mean value significant ( $p \leq 0.05$ ) from the mean of control.



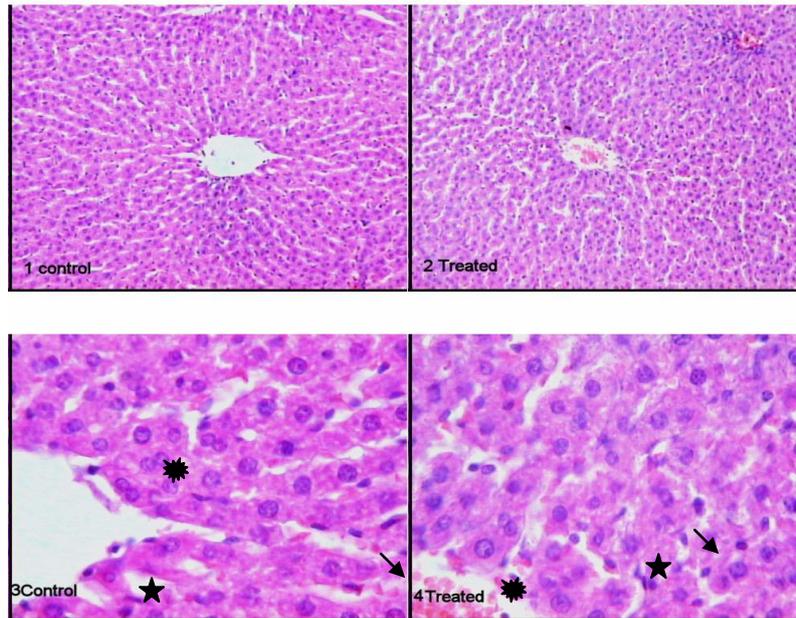
**Figure (6):** Protein and urea nitrogen. Asterisks indicate a mean value significant ( $p \leq 0.05$ ) from the mean of control.

**Histological results:**

Plate (1) illustrates the histological features of control and treated rat liver. At low power, the liver cords are less regularly arranged in treated animals than control. The central vein is slightly congested. At high power, most of the control nuclei are vesicular; this is less noticed in sections from treated animals. More kupffer cells are noticed in sections of treated animals. The mean nuclear diameter of hepatocytes of treated animals is significantly smaller than control (Table 5, figure 7). Frequency distribution analysis of liver

nuclear diameter (Figure 8) indicates three population of nuclei in control sections: a small size population representing Kupffer and endothelial cells, a population with larger size nuclei representing newly formed nuclei and/or less active hepatocyte nuclei, and a population of large nuclei representing the active vesicular nuclei. In sections from treated animals, the population of Kupffer and endothelial cells is very high, the population of cells with small nuclei is slightly higher than control, and the population of vesicular nuclei is much smaller than control.

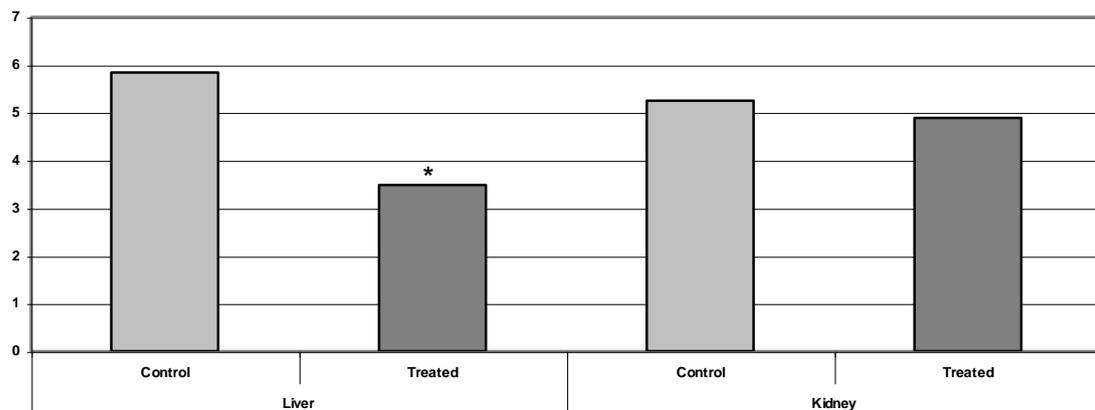
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**Plate (1):** Section in liver of control and treated animals. (★) endothelial nucleus ( \* ) vesicular hepatocyte nucleus ( ↘) Kupffer cell nucleus. (Hx,E.X400)

**Table (5) Mean nuclear diameter of liver and kidney cells**

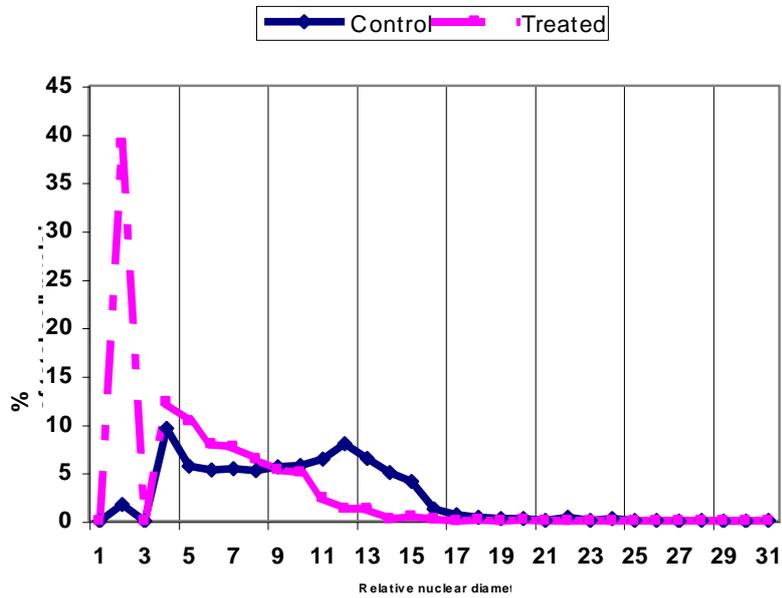
Organ	Group	Mean ± Stdev.	t-test (p≤ )
Liver	Control	5.84± 4.04	
	Treated	3.48± 2.68	3.2 x 10 <sup>-49</sup>
Kidney	Control	5.24± 2.8	
	Treated	4.89± 3.25	0.11



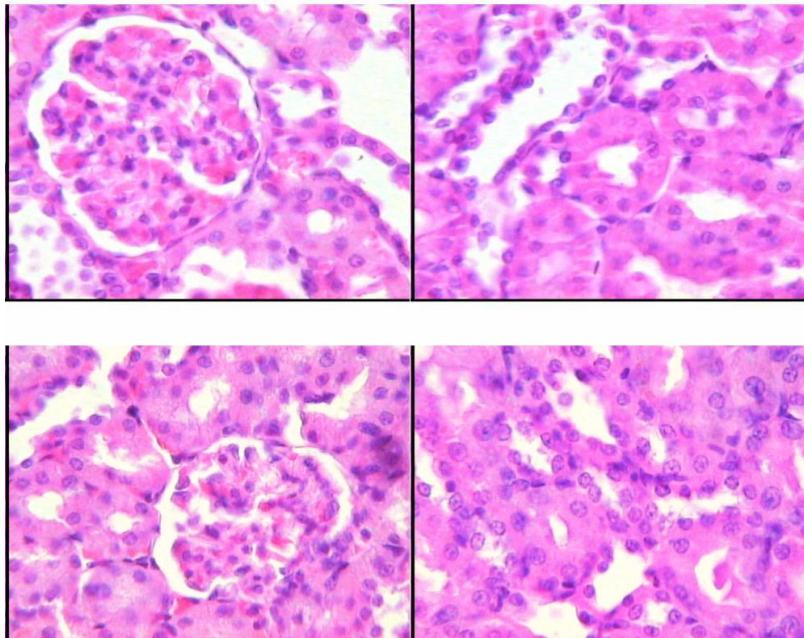
**Figure (7):**Mean nuclear diameter of kidney and liver cells. Asterisks indicate a mean value significant (p≤ 0.05) from the mean of control.

Sections of kidneys from control and treated animals (Plate 2), show minor morphological differences. The mean

nuclear diameter (Table 5, figure 7) has no statistically different values compared with control.



**Figure (8):** Frequency distribution of nuclear diameter of control and treated hepatocyte nucl



**Plate (2):** Section in Kidney of control (upper sections) and treated (lower sections) animals. The difference in the diameter of the capsules is due to the level of sectioning. (H&E, X400)

## Discussion

There is a great need for evaluation, identification of active ingredients, the mode of action and safety of the herbs used in folk medicine. Samwa (*Cleome droserifolia*) is one of the herbs used in Egyptian folk medicine by Sinai Bedouins as a remedy for diabetic patients. In the present study, evaluation of administration of water and ethanol extract of samwa was performed on senile diabetic rats. Such study is expected to be more informative than studies on experimentally induced diabetes (Mattar and Moustafa, 1994; Moustafa *et al.*, 1995). The senile rats proved to be diabetic as revealed from the high basal blood glucose and glucose tolerance curve.

In the present study, drenching of either water or ethanolic extract to senile diabetic rats resulted in a significant drop in serum glucose level and increase in liver glycogen. This may be due to stimulation of the secretion of insulin by  $\beta$  cells, inhibition of  $\alpha$  cells of the pancreatic islets, or production of hyperglycemic factors, or by enhancing insulin activity. (Winkelman, 1989). This increase may be, also, as observed here, due to increased activity of glycogen synthetase induced by the plant extract as reported, also, after administration of garlic oil (Rawi *et al.*, 1996) and *Gymnea sylvestra* extracts (Shanmuga - sundaram *et al.*, 1990). The increased enzyme activity may be due to direct effect of the extracts, or indirect through induced insulin hormone release which activates glycogen synthetase (Gold, 1970). The level of insulin was higher in animals drenched either extract and glucagons was lower than control. However, the change in the level of both hormones was not statistically significant.

The total serum lipids in treated animals was statistically lower than control. A similar decrease in serum total lipids was also reported in rats treated with fruit extract of *B. egyptiaca* in alloxan induced diabetes (Helal, 2000, Mattar and Helal, 2001). The level of serum triglycerides and cholesterol, however, was not significantly different from control. The decrease in total lipid, therefore, may be due to a comparable decrease in free fatty acids (Harper *et al.*, 1993). Such a decrease is expected in the case of accumulation of fat in adipocytes, both by synthesis and decreased liberation of fatty acids. Accumulation of fat in adipocytes is possibly the reason behind the high level of the fat cell- produced hormone, leptin (Mattar and Helal, 2001; Bennett *et al.*, 1997) in the serum of treated rats. Increased leptin level may be also due to direct action of some extract components on the adipocytes (Mattar and Helal, 2001).

The high level of serum leptin is expected to induce loss of appetite through repression of the hypothalamic neuropeptide Y (NPY) production (Baranowska *et al.*, 1999). The loss of appetite is expected to result in symptoms of undernourishment (Maffei *et al.*, 1995) such as decreased intake of amino acids and iron. Decreased amino acid uptake may explain the observed low level of serum urea in treated animals due to depression of deamination and ornithine cycle in the liver (Harper *et al.*, 1993).

The observed high testosterone level in treated animals is expected as a result of high leptinemia and low NPY production (Himms-Haagen, 1999). NPY is a regulator of gonadotropin releasing hormone production (Nagatoni *et al.*, 1998) which induces the production of pituitary gonadotropins (Keisler *et al.*, 1999).

The present study revealed that the oral administration of *samwa* extract to senile diabetic rats caused alterations in some haematological and biochemical parameters. Our results showed significant decrease in RBCs, Hb and Hct and these results may be attributed to the synchronous significant decrease in serum iron of treated rats. Iron deficiency, and hence, signs of anemia observed in the results, may be attributed to malabsorption mediated by leptin action (Maffei et al, 1995).

Test for the toxicity of the extracts using the biochemical analysis of liver, kidney and heart functions indicated that they were safe. The parameter used to test these functions in treated animals did not differ significantly from those of control animals.

Histological evaluation of kidney sections of extract drenched animals revealed almost no morphological difference from control. The variation in mean nuclear diameter of kidney cells of treated animals was, also, not significantly different from control. Although the results of biochemical and histological results may indicate that drenching SAMWA extract is safe on rat kidney, more investigations are needed to ensure these results.

The histological investigation of liver section, however, showed disturbed arrangement of liver cords and congestion of central vein in the liver of treated animals as compared to control. The mean nuclear volume was significantly smaller in treated animals than control. Analysis of frequency distribution of nuclear diameter indicated a large population of cells with the diameter of Kupffer and endothelial cells. The population of nuclei in the range of diameter of less active nuclei was higher than control, while the population of nuclei representing active

vesicular nuclei was much lower than control.

The increased Kupffer cell population may indicate active role of these cells in phagocytosis of RBCs which is normally met with in cases of iron deficiency (Nicolas et al., 2002) as observed in this study. The application of the plant extract may, therefore, be harmful and repress the vital activities of the liver.

In conclusion, although the extract of SAMWA results in a decrease in blood glucose level and an increase in leptin which may act as anridiabetic and anti-obesity, more careful investigation is needed to test its safety. The investigation on this plant should also concentrate on the isolation of different gradients rather than whole extract in order to identify the active non-harmful ingredients which can play the role of anti-diabetic anti-obesity effect without harmful side effects.

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## التأثير المضاد لمرض البول السكري والسمنة لمستخلص نبات كليومي دروسيريفوليا (السامواه)

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في هذا البحث تم دراسة تأثير المستخلص المائي لنبات كليومي دروسيريفوليا (السامواه) علي مجموعة من الجرذان المسنة التي ظهر عليها أعراض السكر مقارنة بمجموعة ضابطة من الجرذان المسنة ولقد كان للمستخلص تأثير مثبط علي الزيادة في تركيز الجلوكوز في الدم. ولقد تم تفسير مظاهر قلة تركيز الجلوكوز في الدم مع عدم المساس بمستوى هرمون الأنسولين على انه :

- 1) إحداث زيادة في حساسية الخلايا الكبدية وغيرها لهرمون الأنسولين
- 2) تقليل قدرة الأمعاء علي امتصاص الجلوكوز والذي تمثل في ثبات مستوى الجلوكوز في الدم عند تجريع الفئران بمحلول الجلوكوز والذي صاحبه قلة في مستوى الجلايكوجين في الكبد وزيادة في مستوى هرمون اللبتين في الدم ، وهذه المظاهر تضي علي المستخلص خاصة مضادة السمنة وقد وجد أن التجريع بالمستخلص تزال قد تسبب أيضا في تقليل تركيز نيتروجين اليوريا في الدم ، ولم تظهر أي تغيرات في مستوى الأنزيمات المبينة لوظائف الكبد والكلية ، وفي القطاعات الهستولوجية لكل من الكبد والكلية لم يظهر للمستخلص تأثير في تركيب أي منها.

وعلى ذلك فإن هذا المستخلص قد تكون له أهمية دوائية في علاج البول السكري والسمنة مما يجعله مرشحا لأن يكون بديلاً لهرمون الأنسولين الذي مازال يتمتع بالأولوية في هذا المجال.