

## Effects of the methanolic extracts of *Zizyphus spina christi*, *Olea europaea* and *Morus alba* leaves in Streptozotocin- induced diabetic rats.

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### Abstract

**Background:** The present study aims to investigate the hypoglycemic, hypolipidemic and antioxidant effect of the methanolic crude extracts of *Zizyphus spina christi*, *Morus alba* and *Olea europaea* leaves, individually or in combination against diabetes induced rats by Streptozotocin (STZ).

**Results:** Hyperglycemia and hyperlipidaemia except in high density lipoproteins (HDL) were observed in serum after 5 weeks of STZ administration. This was associated with a depression in hepatic glutathione (GSH) concentration as well as hepatic catalase (CAT), glutathione-S-transferase (GST) and superoxide dismutase (SOD) activities. In addition hepatic thiobarbituric acid-reactive substance (TBARS) and protein carbonyl (PC) were significantly elevated, indicating increased lipid and protein oxidation and oxidative stress. Depression in blood hemoglobin (Hb) content, serum insulin levels, total antioxidant capacity (TAOC) and nitric oxide (NO) levels as well as body weight gain were also observed in diabetic rats. Administration of 100mg/kg alcoholic extracts of *Zizyphus spina christi*, *Morus alba* and *Olea europaea* leaves 3 days before and after STZ injection daily for 5 weeks significantly ameliorated the oxidative stress evidenced by lowering TBARS & PC as well as increasing hepatic GSH concentration and CAT, GST and SOD activities as compared with STZ treated rats. These effects were paralleled with marked protection against STZ induced hyperglycemia and disturbance of lipid profile. They also caused a great improvement in insulin levels, TAOC, NO, Hb content and body weight gain. **Conclusion:** Thus, these results showed that the administration of the crude extracts of either *Zizyphus spina christi*, *Morus alba* or *Olea europaea* leaves individually or in combination might improve the clinical manifestation of diabetes and decrease the oxidative stress, this study supports the beneficial effects of these extracts especially *Zizyphus spina christi*, which showed marked amelioration and this may be attributed to the presence of saponin glycosides which have an inhibitory effect of serum glucose level in addition to enhance the cellular antioxidant defense. This activity contributes to the protection against oxidative damage in STZ induced diabetes.

**Key words:** diabetes; *Zizyphus spina-christi*; *Olea europaea*; *Morus alba*, antioxidants; lipids; oxidative stress markers; nitric oxide.

### Introduction:

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels and disturbances in carbohydrate, fat, and protein metabolism. These metabolic abnormalities result, in part, from a deficiency of the blood sugar lowering hormone insulin; this deficiency in insulin results in type 1 diabetes (IDDM).

Type 2 diabetes mellitus or non-insulin-dependent diabetes mellitus (NIDDM) results from hyperglycemia caused by overproduction of glucose at the hepatic level or because of abnormal  $\beta$  cell function or insulin resistance at target cells (Fajans *et al.*, 1997).

The field of herbal medicines research has been gaining significant importance in the last few decades and the demand to use natural products in the treatment of diabetes is increasing worldwide. The available literatures show that there are more than 400 plant species showing antidiabetic activity (Rai, 1995).

Since numerous studies demonstrated that oxidative stress, mediated mainly by hyperglycemia-induced generation of free radicals, contributes to the development and progression of diabetes and related contributions, it became clear that ameliorating oxidative stress through treatment with antioxidants might be an effective strategy for reducing diabetic complications. To this end, several clinical trials investigated the effect of antioxidants on the prevention of diabetic complications (Ceriello and Motz, 2004)

Since *Zizyphus spina christi*, *Olea europaea* and *Morus alba* are wild trees commonly available in Egypt and their leaves are used in folk medicine for the treatment of diabetes mellitus, therefore deemed interesting to reexamine the potential antidiabetic activity of these leaves to determine their biological activity against the deleterious effects of diabetes mellitus.

## Material and Methods:

Adult male albino rats weighing 160-180 g were used. They were kept under good ventilation; adequate stable diet and water.

### Animals groups and experiments:

Rats were divided into the following groups each group contains 8 rats.

### Normoglycemic groups

Normal control rats only received a single dose of citrate buffer, normal control rats received *Zizyphus spina-christi* methanolic extract at dose 100mg/kg, normal control rats received *Olea europaea* methanolic extract at dose 100mg/kg, normal control rats received *Morus alba* methanolic extract at dose 100mg/kg, normal control rats

received a mixture of the previous extracts at dose 100mg/kg.

### Hyperglycemic groups

Diabetic control rats received single dose of STZ at dose 50mg/kg dissolved in citrate buffer (PH 4.5) diabetic group with single dose of STZ at dose 50mg/kg received *Zizyphus* methanolic extract at dose 100mg/kg, diabetic group with single dose of STZ at dose 50mg/kg received *Olea europaea* methanolic extract at dose 100mg/kg, diabetic group with single dose of STZ at dose 50mg/kg received *Morus alba* methanolic extract at dose 100mg/kg, diabetic group with single dose of STZ at dose 50mg/kg received a mixture of the previous extracts at dose 100mg/kg.

### **Plant materials and preparation of the methanolic extracts:**

Leaves of *Zizyphus spina christi* and *Morus alba* were collected from trees growing at Mansoura University, Egypt, leaves of *Olea europaea* were purchased from local markets. Fresh leaves (1 kg from each plant) were washed, air dried, powdered and then extracted by 2 liters of methanol by refluxing for 48 hr. The extract obtained was vacuum evaporated to give the crude extract which was redissolved with distilled water just before oral administration. Each extract was given in a dose equal 100 mg/kg (Abdel-Zaher *et al.*, 2005)

### **Sampling and tissue extraction:**

At the end of the experimentation period, over night fasted rats were sacrificed using a sharp razor blade. Blood samples were collected in clean non-heparinized centrifuge tubes and only few droplets were placed in clean heparinized tubes for measuring hemoglobin, then the tubes were let to stand for 15 min at 30°C after which the non heparinized tubes were centrifuged at 3000 rpm for 15 min. Blood sera were carefully separated and each sample were labeled and kept at -20°C for subsequent analysis. Thereafter, liver and pancreas specimens were quickly removed,

weighed and then liver homogenized in cold distilled water to form 10% (w/v) homogenate. Then they were kept at -20°C for later different biochemical determination.

### Experiments

The concentration of glucose in serum was estimated by the method **Trinder** (1969). Insulin was measured by the method of **Flier et al.** (1976). The concentration of hemoglobin in serum was estimated by the method of **Van and Zijlstra** (1961). The concentration of total lipids in serum was estimated by the method of **Zollner and Kirsch** (1962). The concentration of cholesterol in serum was estimated by the method of **Meiattini** (1978). The concentration of triglyceride in serum was estimated by the method of **Buccolo** (1973). The concentration of HDL and LDL in serum was estimated by the method of **Grove** (1979). The amount of Malondialdehyde (MDA) was measured by the method of **Ohkawa et al.** (1982). Protein carbonyl content was measured by method of **Smith et al.** (1961). SOD was assayed by the procedure of **Nishikimi et al.** (1972). The method was adopted by **Prins and Loose** (1969). Catalase activity was determined by the method of **Bock et al.** (1980). Glutathione-S-transferase (GST) activity was measured by the method of **Habig et al.** (1974). The concentration of total antioxidant capacity in serum was estimated by the method of **Koracevic** (2001). The concentration of total nitric oxide in serum was estimated by the method of **Montgomery and Dymock** (1961).

### Statistical analysis

Statistical analysis was performed using MINITAB for Windows statistical package (Version 13) 2001. All results were calculated as the percentage of mean

control values. Group results were then expressed as mean percentages  $\pm$  the standard error of the mean (S.E.M.). Statistical differences from control were determined using one way analysis of variance with a Dunnett correction for multiple comparisons.

### Results

Streptozotocin caused disturbances in all the measured parameters represented as a significant increase in serum glucose levels (hyperglycemia), significant body weight loss, significant decreased ( $p \leq 0.05$ ) insulin levels and significant increase in the lipid profile except HDL cholesterol which showed significant decrease. STZ also showed significant increased content of free radicals represented in significant increase in MDA and Protein carbonyl contents and this disturbance is accompanied with decreased antioxidants which were SOD, GSH, CAT, GST and serum TAOC with significant decrease in NO levels. Treatment with the crude extracts of *Zizyphus spina-christi*, *Olea europaea* or *Morus alba* alone or as a mixture treatment were ameliorated the previous parameters specially blood glucose levels. *Zizyphus spina-christi* was more effective for serum glucose level. The present data also showed that the administration of the crude extracts of each plant was much better than administrating them in combination. The 3 extracts decreased serum glucose levels, increased body weight, increased insulin and hemoglobin levels. They also ameliorated lipid profile and antioxidants contents in the liver and total antioxidant capacity in serum in addition; the extracts used in this experiment worked as free radical scavengers and this was confirmed by the reduction of MDA, PC contents. Unexpected result of NO levels in serum was obtained that the 3 plant extractions increased NO levels.

Table (1) Serum Glucose level, serum insulin level, blood hemoglobin level and % of body wt gain in control and different treated animal groups.

Parameter	Non diabetic groups					Diabetic groups				
	Control	ZSC	Olea	Morus	Mix	Diabetic	ZSC	Olea	Morus	Mix
<b>Glucose (mg/dl)</b>	82.0 ± 0.52	81.3 ± 0.26	83.3 ± 0.46	80.9 ± 0.29	83.6 ± 0.90	384.8 <sup>a</sup> ± 1.6	152 <sup>ab</sup> ± 1.38	174.4 <sup>ab</sup> ± 1.02	175.6 <sup>ab</sup> ± 1.00	193.6 <sup>ab</sup> ± 1.16
<b>Insulin (mg/dl)</b>	3.8 ± 0.16	3.9 ± 0.04	3.8 ± 0.13	3.9 ± 0.07	3.8 ± 0.28	2.2 <sup>a</sup> ± 0.14	3.4 <sup>b</sup> ± 0.1	3.3 <sup>b</sup> ± 0.2	3.1 <sup>b</sup> ± 0.17	2.8 ± 0.13
<b>Hemoglobin (g/dl)</b>	13.7 ± 0.081	13.8 ± 0.125	13.7 ± 0.128	14.2 <sup>a</sup> ± 0.1	13.7 ± 0.068	11.22 <sup>a</sup> ± 0.198	13.5 <sup>b</sup> ± 0.157	13.2 <sup>b</sup> ± 0.066	13.3 <sup>b</sup> ± 0.089	13.2 <sup>b</sup> ± 0.169
<b>% of Body wt gain.</b>	11.7 ± 0.3	11.4 ± 0.04	15.6 <sup>a</sup> ± 0.02	11 ± 0.1	6.3 <sup>a</sup> ± 0.06	-2 <sup>a</sup> ± 0.07	3.9 <sup>ab</sup> ± 0.01	4.9 <sup>ab</sup> ± 0.06	2.6 <sup>ab</sup> ± 0.03	2.4 <sup>ab</sup> ± 0.02

<sup>a</sup> = significance  $\leq 0.05$  as compared with untreated control.

<sup>b</sup> = significance  $\leq 0.05$  as compared with diabetic control.

Table 2 lipid profile in control and different treated animal groups

Parameter	Non diabetic groups					Diabetic groups				
	Control	ZSC	Olea	Morus	Mix	Diabetic	ZSC	Olea	Morus	Mix
<b>Total lipids (mg/dl)</b>	220.2 ± 0.9	226 ± 1.5	219 ± 1.8	224.4 ± 1.4	228 <sup>a</sup> ± 1.3	997.5 <sup>a</sup> ± 1.7	454 <sup>ab</sup> ± 1.8	461 <sup>ab</sup> ± 0.9	495.5 <sup>ab</sup> ± 1.9	496 <sup>ab</sup> ± 2
<b>Cholesterol (mg/dl)</b>	121.7 ± 0.9	124.2 ± 1	123.2 ± 1	123.3 ± 0.8	119.3 ± 0.9	299.1 <sup>a</sup> ± 1	144.9 <sup>ab</sup> ± 1.4	148.9 <sup>ab</sup> ± 0.7	157.3 <sup>ab</sup> ± 1.5	157.9 <sup>ab</sup> ± 1
<b>TG (mg/dl)</b>	86.6 ± 0.8	89.1 ± 0.7	72 <sup>a</sup> ± 0.9	91.7 ± 1	94 ± 1.5	484.7 <sup>a</sup> ± 2	125.4 <sup>ab</sup> ± 0.9	173.9 <sup>ab</sup> ± 0.5	189.2 <sup>ab</sup> ± 1.4	329 <sup>ab</sup> ± 0.7
<b>HDL (mg/dl)</b>	56 ± 0.8	60 <sup>a</sup> ± 0.8	67.2 <sup>a</sup> ± 0.7	59.1 <sup>a</sup> ± 0.3	54.7 ± 0.9	35.5 <sup>a</sup> ± 0.8	42.5 <sup>ab</sup> ± 0.8	39.6 <sup>ab</sup> ± 0.5	42.3 <sup>ab</sup> ± 1	36.1 <sup>ab</sup> ± 0.6
<b>LDL (mg/dl)</b>	48.5 ± 0.8	46.8 ± 0.8	41.5 <sup>a</sup> ± 0.5	45.8 ± 0.4	45.8 ± 0.9	166.6 <sup>a</sup> ± 1.6	77.3 <sup>ab</sup> ± 0.9	74.5 <sup>ab</sup> ± 0.8	77 <sup>ab</sup> ± 1	56 <sup>b</sup> ± 1

<sup>a</sup> = significance  $\leq 0.05$  as compared with untreated control.

<sup>b</sup> = significance  $\leq 0.05$  as compared with diabetic control.

Table 3 hepatic MDA, PC and antioxidants in control and different treated animal groups

Parameter	Non diabetic groups					Diabetic groups				
	control	ZSC	Olea	Morus	Mix	Diabetic	ZSC	Olea	Morus	Mix
<b>MDA</b> nM/mg wt tissue	96.9 ± 0.8	96.2 ± 0.8	96.6 ± 0.7	95.6 ± 0.9	96.8 ± 0.6	202.6 <sup>a</sup> ± 0.9	195.4 <sup>ab</sup> ± 0.7	194 <sup>ab</sup> ± 1.1	199.1 <sup>ab</sup> ± 0.5	197 <sup>ab</sup> ± 0.9
<b>PC</b> nM/mg wt tissue	43.2 ± 1.24	36.1 <sup>a</sup> ± 1.06	39.4 <sup>a</sup> ± 0.39	37 <sup>a</sup> ± 1.73	40.5 <sup>a</sup> ± 0.6	304.5 <sup>a</sup> ± 4.94	86.5 <sup>ab</sup> ± 1.23	90.6 <sup>ab</sup> ± 0.48	88.9 <sup>ab</sup> ± 0.997	105.5 <sup>ab</sup> ± 1.19
<b>SOD</b> U/g wt tissue	86.8 ± 1.7	89.4 <sup>a</sup> ± 0.5	88.5 ± 1.5	88.4 ± 0.9	86.9 ± 1.1	69.4 <sup>a</sup> ± 1.2	74.0 <sup>a</sup> ± 1.3	73.9 <sup>a</sup> ± 1	77.6 <sup>ab</sup> ± 1.3	70.6 <sup>a</sup> ± 0.7
<b>GSH</b> mg/g wt tissue	4.1 ± 0.1	4.6 ± 0.1	4.2 ± 0.1	4.8 ± 0.1	4.2 ± 0.1	2.7 ± 0.1	3.5 ± 0.1	3.3 ± 0.1	3.6 ± 0.1	3.3 ± 0.1
<b>CAT</b> µM H2O2/Sec/g wt tissue	1.6 ± 0.02	2 ± 0.04	2.1 ± 0.1	2.9 ± 0.1	2 ± 0.02	0.7 <sup>a</sup> ± 0.03	1.6 <sup>b</sup> ± 0.02	1.6 <sup>b</sup> ± 0.1	1.7 <sup>b</sup> ± 0.1	1.3 ± 0.03
<b>GST</b> µM/g wt tissue	6.6 ± 0.126	7.8 <sup>a</sup> ± 0.08	6.8 ± 0.12	7.9 <sup>a</sup> ± 0.2	7.2 <sup>a</sup> ± 0.1	4.8 <sup>a</sup> ± 0.3	6.3 <sup>b</sup> ± 0.2	5.3 <sup>a</sup> ± 0.4	6.2 <sup>b</sup> ± 0.06	5.9 ± 0.4
<b>TAOC</b> mM/L	1.9 ± 0.04	2.4 <sup>a</sup> ± 0.06	2.4 <sup>a</sup> ± 0.05	2.4 <sup>a</sup> ± 0.06	1.8 ± 0.05	0.9 <sup>a</sup> ± 0.06	2.1 <sup>b</sup> ± 0.04	2 <sup>b</sup> ± 0.03	2.1 <sup>b</sup> ± 0.1	1.6 <sup>b</sup> ± 0.05
<b>NO</b> µmol/L	50.4 ± 1.9	53.5 ± 1.3	50.4 ± 1.9	52.4 ± 2	53.5 ± 2.3	21.5 <sup>a</sup> ± 1.3	49.9 <sup>b</sup> ± 1.5	45.7 <sup>b</sup> ± 1.4	48.7 <sup>b</sup> ± 2.2	46.7 <sup>b</sup> ± 1.8

<sup>a</sup> = significance ≤.05 as compared with untreated control.

<sup>b</sup> = significance ≤.05 as compared with diabetic control.

## Discussion

In the present study the alcoholic crude extracts of *Zizyphus spina-christi*, *Morus alba* and *Olea europaea* leaves alone or as a mixture were used to identify their hypoglycemic and antioxidative effect as well as their effect on body weight, insulin, hemoglobin, lipid profile and oxidative stress markers. The oral administration of these extracts daily at a dose of 100 mg/kg for 5 weeks showed a significant amelioration in glucose levels

and most of the measured parameters in normal and diabetic rats.

The present results showed that a single injection of STZ to rats of a dose 50mg/kg body weight caused a significant increase in serum glucose levels and significant decrease in body weight, serum insulin and blood hemoglobin levels as compared to the control group. These results agreed with **Ruzaidi et al.** (2005) who reported that intraperitoneal administration of STZ led to five-fold elevation of serum

fasting glucose levels. In addition in the present work STZ injected rats showed a significant increase in total lipids, cholesterols, triglycerides and low density lipoprotein (LDL) levels and a significant decrease in high density lipoprotein (HDL) levels. These findings are consistent with **Hye et al.** (2009) who stated that the levels of serum lipids are usually elevated in diabetes mellitus, and this represents the risk of coronary heart disease. The hyperglycemic effect of STZ showed significant increase in oxidative stress markers (lipid peroxidation and protein oxidation) and significant decrease in antioxidants status. Similar changes were already observed in different experimental situations reported by **Rajani et al.** (2008). These effects may take place due to STZ injection, which destroys the islet beta cells which associated with generation of free radicals and rise in the oxidative stress markers (**Bhor et al.**, 2004). In the present work *Zizyphus spina-christi* extract showed the highest improvement of serum glucose levels in diabetic rats as compared to the control. The hypoglycemic effect of *Zizyphus spina-christi* was also observed by **Glombitza et al.** (1994) and **Abdel-Zaher et al.** (2005) who revealed that the alcoholic extract of *Zizyphus spina-christi* leaves improved glucose utilization in diabetic rats after 4 weeks of treatment because of the presence of major saponin glycoside (christinin-A).

In addition the present results showed the hypoglycemic effect of *Olea europaea* on diabetic rats. **Gonzalez et al.** (1992) indicated that *Olea europaea* possessed a hypoglycemic effect by two mechanisms the first is by potentiation of glucose induced insulin release and the second is by increasing peripheral uptake of glucose. Administration of *Morus alba* alcoholic crude extract also showed significant decrease in serum glucose levels as compared to diabetic control rats. **Andallu and Varadacharyulu** (2003) reported that mulberry administration remarkably decreased blood glucose concentrations in diabetic rats. This effect may be due to the presence of the N-containing sugars which inhibit the

functions of  $\alpha$ -glucosidase,  $\alpha$ -mannosidase and  $\beta$ -galactosidase (**Asano et al.**, 1994) and fagomine which potentiates the glucose induced insulin release similar to the action of glibenclamide (**Kimura et al.**, 1995) as well as increasing the tissue uptake of glucose (**Chen et al.**, 1995). As the best of our knowledge there is not enough data supporting the effect of the administration of the mixture of the three extracts on serum glucose levels or other measured parameters. It is believed that the hypoglycemic effect of this mixture may be due to the presence of hypoglycemic constituents which are found in each of those plants.

STZ treated group showed a significant decrease in serum insulin levels. This result is in harmony with **Subash-Babu et al.** (2009) who reported that STZ showed a significant decrease in serum insulin levels as compared with control rats. **Jong-Dae et al.** (2007) cleared that in STZ treated rats the numbers of immunoreactive insulin-producing cells were reduced and they were distributed in restricted pancreatic islets.

Treatment of diabetic rats with *Zizyphus spina-christi*, *Olea europaea* and *Morus alba* leaves crude extracts showed significant increase in serum insulin levels. **Abdel-Zaher et al.** (2005) reported that the saponin glycoside which is the active constituent in *Zizyphus spina-christi* leaves stimulate insulin secretion. In addition **Gonzalez et al.** (1992) stated that the hypoglycemic effect of olive leaves may be due to improved glucose stimulated insulin release. **Singab et al.** (2005) cleared that this effect may be attributed to the high flavonoids content of *Morus alba* leaves which increased antioxidant mechanisms and may be preserves the capability of insulin secretion.

In the present study the data showed significant body weight loss in diabetic rats when compared to the control group. **Jagannath and Surendra** (2004) indicated that administration of STZ resulted in body weight loss. This may be due to protein sparing action i.e. gluconeogenesis from muscle protein (ketogenic amino acid) and

this would result in decrease in total protein (Ene *et al.*, 2007).

Goldstein *et al.* (2004) also referred that the metabolism of glucose, proteins and lipids is abnormal in diabetes due to insulin secretion defect, leading to various metabolic disorders and hence decrease body weight.

Treatment of diabetic rats with *Zizyphus spina-christi*, *Olea europaea* and *Morus alba* leaves crude extracts resulted in body weight gain as compared to the diabetic group. This may be due to the improvement of serum glucose levels. These results are compatible with Al-Azzawie and Alhamdani (2006) for *Olea europaea* Jamshid and Prakash (2008) for *Morus alba* leaves. They indicated that the increase in body weight may be attributed to the improvement in serum glucose levels and metabolism.

Diabetic rats showed great disturbance in lipid profile as they had very high levels of total lipids, total cholesterol, triglycerides and low density lipoprotein (LDL) and very low levels of high density lipoprotein (HDL). These results are similar to those obtained by Zargar *et al.* (1995).

Treatment of diabetic rats with *Zizyphus spina-christi*, *Olea europaea* and *Morus alba* greatly normalized measured lipid profile as compared to the diabetic group. These results agreed with those of Hussein *et al.* (2006). This may be attributed to saponins in *Zizyphus* which has a hypolipidemic effects by decreasing total cholesterol, triglycerides, and LDL-C in hyperlipidemic rats (Zhang *et al.*, 2004; Zhao *et al.*, 2005). Khan *et al.* (2007) reported that *Olea europaea* leaf showed hypolipidemic activity when studied in laboratory animals. This effect may be due to the presence of the active constituent oleuropein, with a proposed mechanism of action of potentiation of glucose-induced insulin release, and an increase in peripheral blood glucose uptake. In addition El-Beshbishy *et al.* (2006) reported the same effect of *Morus alba* on cholesterol, T.G, LDL-c and HDL-c. This was due to the presence of flavonoids in *Morus alba* leaves. On the other hand Weggemans and Trautwein (2003) revealed that flavonoids

intake decreased LDL-C and increased HDL-C that may hasten removal of cholesterol from peripheral tissue to liver for catabolism and excretion.

The present results showed the antioxidative effect of *Zizyphus spina christi*, *Olea europaea* and *Morus alba* leaves extract by decreasing the hepatic MDA and protein carbonyl (PC) contents. These results were in accordance with the previous studies of Hussein *et al.* (2006) for *Zizyphus spina christi*. This may be attributed to the presence of tannins (Adzu *et al.*, 2001) and carotenes (Guil-Guerrero *et al.*, 2004) in some *Zizyphus* species.

Al-Azzawie and Alhamdani (2006) reported that oleuropein the active constituent of *Olea europaea* leaves have the ability to scavenge the superoxide anions. Andallu and Varadacharyulu (2003) reported that *Morus alba* leaves extract treatment attenuated MDA levels. This may be due to the antioxidative effect of nine flavonoids (Husain *et al.*, 1984) and moracins (Sharma *et al.*, 2001) present in the leaves which act as strong superoxide radical scavengers and singlet oxygen quenchers.

Present data showed that *Zizyphus spina christi*, *Olea europaea* and *Morus alba* leaves extract ameliorated hepatic SOD activity in different treated diabetic groups as compared to diabetic control group. The administration of *Zizyphus* was able to increase the activities of endogenous antioxidant enzymes such as SOD because it has a maximum conjugation with injurious free radicals and diminishes their toxic properties

(Shen *et al.*, 2009). In addition Somova *et al.* (2003) reported that leaves of *Olea europaea* increased SOD activity and claimed that this effect was due to the presence of oleanolic and ursolic acid which act as antioxidant substances. Also, Andallu and Varadacharyulu (2003) reported that the antioxidant effect of *Morus alba* is due to the presence of antioxidant flavonoids (quercetins) and moracins in leaves. In the present study all treated diabetic groups showed significant increase in hepatic Glutathione content as compared to the diabetic group.

**Dembinska-Kiec et al.** (2008) reported that *Zizyphus* as well as *Trigonella foenum-graceum L.* have antioxidant effect for STZ diabetic rats. This may be attributed to the presence of flavonoids which have an antioxidant activity. **Al-Azzawie** and **Alhamdani** (2006) reported that the glutathione level was ameliorated in diabetic rabbits when treated with oleuropein (the active constituent of *Olea europaea*). The observed enhancement in GSH content could be attributed to the sparing effect of oleuropein in competing with free radicals that burden the antioxidative function of these antioxidants. The experimental control group and diabetic group that received *Morus alba* crude extract showed significant increase in hepatic GSH content as compared with control group and diabetic group. These results are similar to those obtained by **Andallu** and **Varadacharyulu** (2003) who reported that mulberry improved the concentrations of glutathione due to the presence of antioxidant flavonoids and moracins in leaves. Catalase activity was greatly improved in all diabetic rats treated with herbal extracts. **Shen et al.** (2009) cleared that administration of *Zizyphus* improved hepatic catalase levels. They commented that *Zizyphus* provides maximum conjugation with injurious free radicals and diminishes their toxic properties.

Current data which representing the ameliorating effect of *Morus alba* leaves on catalase activity disagreed with **Andallu** and **Varadacharyulu** (2003) who demonstrated that *Morus alba* decreased catalase activity while we agree with **Al-Azzawie** and **Alhamdani** (2006) who reported that catalase activity is decreased in diabetic rabbits and increased by the treatment with *Olea europaea* active constituent. Glutathione S-transferase activity was increased in diabetic rats received the methanolic crude extract of *Zizyphus spina christi* leaves and this improvement may be due to the presence of saponins glucosides and flavonoids which act as antioxidants (**Agata et al.**, 2009).

Administration of *Olea europaea* leaves crude extract to diabetic rats did not

affect GST activity as compared with the diabetic group. On the other hand administration of *Morus alba* leaves crude extract showed significant increase in hepatic GST content. On the contrary **El-Beshbishy et al.** (2006) reported that flavonoids showed no significant effect on the activity of plasma and liver GST. **Andallu** and **Varadacharyulu**, (2003) stated that GST activity was partially restored in diabetic group treated with mulberry leaves. This improvement might be due to the presence of antioxidant flavonoids and moracins in leaves. In addition **Cai** and **Wei** (1996) suggested that dietary intake of a flavonoids the active compounds in *Morus alba* leaves, enhanced the increase in GST activity.

Diabetic rats showed significant decrease in serum total antioxidant capacity as compared with the control group. This result in agreement with **Jonathan et al.** (2001) who commented that total antioxidant capacity was significantly lowered in the diabetic subjects than in the control subjects.

There is no available data showing the effect of *Zizyphus spina christi* on serum total antioxidant capacity. However many researches showed that *Zizyphus spina christi* is a strong antioxidant agent. Such researches explained that effect as a result of the presence of saponins glucosides and flavonoids which are strong antioxidants (**Agata et al.**, 2009).

The present data showed increased total antioxidant capacity of *Olea europaea* methanolic extract treated rats (table 16). **Ferreira et al.** (2007) reported that *Olea europaea* leaves extract showed higher phenolic content. **Pennycooke et al.** (2005) reported that the antioxidant capacity was related to the content of phenolic compounds in their samples. Higher content of total phenolics reflected higher total antioxidant capacity values. Also **Skerget et al.** (2005) had reported that the antioxidant activity of plant materials is well correlated with the content of their phenolic compounds. For *Morus alba* extract **Arabshahi-Delouee** and **Urooj** (2007) reported that methanol proved to be the most efficient solvent for extraction of



antioxidants from mulberry leaves as it contained the highest amount of phenolic compounds and also exhibited the strongest antioxidant capacity as shown in table 16.

The current data showed that nitric oxide (NO) levels reduced in diabetic rats as compared with control animals. The administration of various herbal extracts resulted in significant increase in NO levels as compared with diabetic rats. These results agreed with **Awad *et al.*** (2004) who indicated that the renal NO levels decreases in diabetic rats.

On the contrary the present results disagree with those obtained by **Chien *et al.*** (2005) as well as **Vadde and Rama** (2008) who reported that diabetic subjects had higher levels of NO as compared with the control group. They concluded that increased oxidative stress and changes in nitric oxide (NO) formation or activity play a major role in the complications of diabetes with decreased antioxidants. Also, **Choi and Hwang** (2005) revealed that methanolic extract of *Morus alba* leaves inhibited NO production.

#### **In conclusion:**

The present study demonstrates that the usage of the crude extracts of *Zizyphus spina-christi*, *Olea europaea* or *Morus alba* leaves individually as well as in combination daily at a dose of 100 mg/kg greatly ameliorates the diabetic disorders induced by streptozotocin in rats. *Zizyphus spina-christi* produces the highest hypoglycemic effect.

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## تأثير المستخلصات الكحولية لأوراق نباتات السدر, الزيتون الإفريقي والتوت المصري علي ذكور الجرذان المصابة بالسكري بواسطة استريبتوزوتوسين.

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يعتبر مرض السكري من أكثر الأمراض انتشارا بين الناس، وتبلغ نسبة الإصابة به حوالي 10% في كافة أنحاء العالم. السكري مرض سببه فشل البنكرياس جزئيا أو كليا في إفراز هرمون الأنسولين مما يؤدي إلى ارتفاع مستوى السكر في الجسم أكثر من المستوى الطبيعي والذي يتراوح بين 80 – 120 ملي غرام / 100 مللتر دم . وتكمن أهمية هرمون الأنسولين في قدرته على تحويل السكر الزائد عن حاجة الجسم إلى مركب ( جلايكوجيني ) يتم تخزينه في الكبد والعضلات لاستخدامه عند الحاجة .

ومن المعروف الآن أن استخدام المستخلصات الطبيعية في علاج بعض الأمراض ومنها مرض السكري أصبح أكثر شيوعا وانتشارا لما له من تأثيرات ايجابية في معظم الأحيان مع انخفاض سعره وسهولة الحصول عليه وقلة نسبة سميته ولكن لا بد من إجراء أبحاث مدققة حول بعض المواد التي نستخدم في الطب الشعبي لبيان مدى فاعليتها أو ما لها من أضرار إن وجدت.  
وقد استخدم في هذه الدراسة ذكور الجرذان التي يتراوح وزنها ما بين 160-180 جرام وقسمت إلي مجموعات كل مجموعته تحتوي علي 8 جرذان وهي كما يلي:-

### المجموعات الضابطة وتحتوي على عدة مجموعات وهي :-

**المجموعة ( أ )** حيوانات ضابطة حقنت بجرعة واحدة من المادة المذيبة (Citrate buffer) في التجويف البريتوني.

**المجموعة (ب)** مجموعته ضابطة حقنت بالمستخلص النباتي الخام لأوراق نبات السدر (النبق) بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة (جـ)** مجموعته ضابطة حقنت بالمستخلص النباتي الخام لأوراق نبات الزيتون الإفريقي بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة ( د )** مجموعته ضابطة حقنت بالمستخلص النباتي الخام لأوراق نبات التوت المصري بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة (هـ)** مجموعته ضابطة حقنت بخليط من الثلاث مستخلصات معا بنسب متساوية بجرعة 100مجم/كجم عن طريق الفم.

**مجموعات الجرذان المستحثة كيميائيا بواسطة 50مجم/كجم من وزن الجسم استريبتوزوتوسين لإحداث مرض السكري وتضم عدة مجموعات وهي :-**

**المجموعة ( أ )** حيوانات مصابة بمرض السكري لم يتم معالجتها.

**المجموعة (ب)** حيوانات مصابة بالسكري حقنت بالمستخلص النباتي الخام لأوراق نبات السدر (النبق) بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة (جـ)** حيوانات مصابة بالسكري حقنت بالمستخلص النباتي الخام لأوراق نبات الزيتون الإفريقي بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة ( د )** حيوانات مصابة بالسكري حقنت بالمستخلص النباتي الخام لأوراق نبات التوت المصري بجرعة 100مجم/كجم عن طريق الفم.

**المجموعة ( هـ )** حيوانات مصابة بالسكري حقنت بخليط من الثلاث مستخلصات معا بنسب متساوية بجرعة 100مجم/كجم عن طريق الفم. وبعد انتهاء فترة الحقن (5 أسابيع) تم ذبح الجرذان والحصول علي الدم وبعض الأعضاء الداخلية لتقدير بعض المعايير الفسيولوجية.

### **ويمكن تلخيص النتائج كما يلي:-**

الاستربتوزوتوسين تسبب في حدوث خلل واضح في كل القياسات ويتضح هذا الخلل في زيادة ملحوظة في مستوى سكر الدم مع نقص واضح في وزن الجسم و نسبة الأنسولين في و الهيموجلوبين في الدم.

كما لوحظ زيادة كبيرة في المحتوي الدهني في الدم عدا الدهون عالية الكثافة (HDL) التي أظهرت نقص ملحوظ. في الوقت نفسه أظهرت الدراسة زيادة ملحوظة في الشقوق الحرة التي أدت إلي زيادة الضغط التأكسدي للدهون (MDA) و أكسدة البروتين (PC) وهذه الزيادة في الشقوق الحرة كانت مصحوبة بنقص واضح في مضادات الأكسدة في الكبد (SOD,GSH,CAT,GST) وفي الدم متمثلة في السعة الكلية لمضادات الأكسدة (Total antioxidant capacity) كما لوحظ هبوط في نسبة أكسيد النيتريك في الدم. و من ناحية أخرى حقن المستخلصات كل علي حدة أو عند استخدامهم كخليط بجرعة 100 مجم/كجم من وزن الجسم في حيوانات التجارب الضابطة (غير المعاملة) لم يحدث تغيير ملحوظ في أي من المعايير الكيميائية المعينة في هذه التجربة. عند الحقن بالمستخلص الخام لأوراق نباتات النبق (الصدر), الزيتون والتوت كل علي حدة أو عند استخدامهم كخليط لمعالجة الجرذان المستحثة كيميائيا بواسطة استربتوزوتوسين أوضحت النتائج تحسن كبير في معظم القياسات خاصة مستوى سكر الدم وأوضحت الدراسة أن أوراق نبات النبق أظهرت التأثير الأكبر في تخفيض نسبة السكر في الدم.