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Antidiabetic Activity Evaluation of Glimepiride and *Nerium oleander* Extract on Insulin, Glucose Levels and Some Liver Enzymes Activities in Experimental Diabetic Rat Model

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Abstract: The present study is aimed to assess the therapeutic potential of sulfonylurea drug glimepiride in comparison with *Nerium oleander* plant extract on insulin, glucose levels and some liver enzymes activities in streptozotocin-induced diabetic rats. Rats were rendered diabetic by intraperitoneal injection of a single dose of 50 mg kg^{-1} body weight streptozotocin. Rats with serum glucose levels >200 mg dL^{-1} were subdivided into three sub-groups: the first sub-group were remained without treatment and considered as diabetics. The second and third subgroups were orally administered 0.1 mg kg^{-1} body weight/day glimepiride and 250 mg kg^{-1} body weight/day *Nerium oleander*, respectively for 4 weeks. Streptozotocin-induced diabetic rats showed hypoinsulinemia and hyperglycemia compared to controls. Strong negative correlation (r = -0.8) was found between serum insulin and glucose levels in diabetic rats. This correlation was +0.4 and -0.3 in glimepiride and *Nerium olender*-treated rats, respectively implying that glimepiride and plant extract improved insulin and glucose levels with the former was more efficient. The activities of serum aspatate aminotransferase, alamine aminotransferase and alkaline phosphatase were significantly increased in streptozotocin-induced diabetic rats compared to controls. Treatment of diabetic rats with glimepiride or *Nerium oleander* extract also improved liver enzymes activities.

Key words: Diabetic rats, streptozotocin, glimepiride, *Nerium oleander*, therapy

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (World Health Organization, 1999). The most common types of diabetes are type I and type II. Type I diabetes is characterized by destruction of the pancreatic β islet cells resulting in an absolute deficiency of insulin. This is usually due to autoimmune damage to the pancreas (George *et al*., 2002). Type II diabetes typically involves abnormal β cell function that results in relative insulin deficiency, insulin resistance accompanied by decreased glucose transport into muscle and fat cells and increased hepatic glucose output, all of which contribute to hyperglycemia (Setter *et al*., 2003).

Experimental diabetes can be produced in laboratory animals by different means including administration of streptozotocin in appropriate doses which cause selective destruction of the β cells of the pancreatic islets (Szkudelski, 2001; Yassin *et al*., 2004). Hypoinsulinemia and hyperglycemia were documented in streptozotocin-induced diabetic rats (Krauss *et al*., 2003; West *et al*., 1996).

Liver is an insulin dependant tissue, which plays a provital role in glucose and lipid homeostasis and severely affected during diabetes (Seifrer and England, 1982). Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes of glucose metabolism in the diabetic liver (Baquer, 1998). In addition, elevation in the activity of liver enzymes including aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase was reported in streptozotocin-induced diabetic rats (El-Agouza *et al*., 2000; Gawronska-Szklarz *et al*., 2003).

Glimepiride is a sulfonylurea drug used in the treatment of type II diabetes. It has the ability to enhance insulin release and action and then to lower blood glucose level (Bando and Yamada, 2001; Sato *et al*., 1993). Herbal medicine is another therapeutic strategy in the treatment

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of diabetes mellitus. The hypoglycemic activity of some medical plants was reported (Ali *et al*., 1995; Grover *et al*., 2002). Although, some studies have been investigated its toxicity and its cure action in diluted preparations (ACS, 2002; Haeba *et al*., 2002), to our knowledge very few research has been conducted on *Nerium oleander* as anti-diabetic plant. Therefore, the present work will be a novel research in the field of traditional medicine.

The current work was undertaken to assess the therapeutic efficacy of the synthetic sulfonylurea drug glimepiride in comparison with *Nerium oleander* plant extract on insulin, glucose levels and some liver enzymes activities in streptozotocin-induced diabetic rats. The findings could open a new avenue of research in the herbal treatment of diabetes.

MATERIALS AND METHODS

Experimental rats: Male Sprague-Dawley rats weighting 170±30 g were used throughout the study. Rats were left for one week before experimentation to adapt the laboratory conditions under normal humidity and room temperature 25°C in the animal house in the Department of Biology, The Islamic University of Gaza. They were fed on commercial balanced diet and water was provided *ad libitum* with fresh supply daily all over the experimental period.

Induction of diabetes and treatment

Rats were divided into two major groups: Control and experimental groups. The experimental group of rats was fasted for 24 h and then intraperitoneally injected with a single dose of 50 mg kg^{-1} body weight of freshly prepared streptozotocin dissolved in citrate buffer pH 4.5. Streptozotocin was purchased from Himedia Laboratory Limited, Mumbai, India. The dose of streptozotocin was based on previous work (Szkudelski, 2001; Mythili *et al*., 2004). Rats with glucose levels >200 mg dL^{-1} were subdivided into three subgroups: rats of the first subgroup were remained without treatment and considered as diabetics. Rats of the second subgroup were given glimepiride and considered as glimepiride-treated subgroup. Glimepiride was purchased from local pharmacies as tablets and then grinded using a mortar. The powder was dissolved in distilled water and orally administered at a dose of 0.1 mg kg^{-1} body weight/day for the experimental period of 4 weeks. The dose of glimepiride was based on other studies (Sato *et al*., 1993; Nieszner *et al*., 2002). The third subgroup of rats was received *Nerium oleander* plant extract and considered as *Nerium oleander* extract-treated subgroup.

Plant extraction and dosing: The plant belongs to the family apocynaceae. Leaves were collected from the plant grown in the Gaza strip from different localities on road sides and gardens during the months of May and June, 2005. The leaves were washed with water and dried under shade, then smashed by hand in a small pore sieve and stored in dark dry place at room temperature. Leaf extract was obtained using aqueous decoction method (Hosseinzadeh *et al*., 1998).

The extract was orally administered at a dose level of 250 mg kg^{-1} body weight/day for 4 weeks. The dose of *Nerium oleander* extract was based on previous toxicological studies (Haeba *et al*., 2002; Adam *et al*., 2001). Oral administration of glimepiride and *Nerium oleander* extract was done by using special stomach tube with a smooth tip to protect the interior lining of the oral and buccal cavity of the animal from injury.

Blood sampling and processing: At each sampling date, 8 rats were taken from control groups and 6 rats from each subgroup/week. Rats were decapitated and blood samples were then collected into centrifuge tubes. The collected blood was allowed to clot. Clear serum samples were obtained by centrifugation at 3000 rpm for 20 min and then kept in the refrigerator for bioassay.

Determination of serum insulin and glucose levels: Serum insulin was measured by microparticle enzyme immunoassay, using Abbott IMx Insulin assay, following the instruction manual (NCCLS, 2001; Travis, 1980). Serum glucose was determined by glucose-oxidase procedure (Trinder, 1969) using Dialab reagent kits.

Determination of enzyme activity: Serum aspartate aminotransferase and alanine aminotransferase activities were measured by using optimized ultraviolet-test according to international federation of clinical chemistry and laboratory medicine (Thomas, 1998) using DiaSys reagent kits. Serum alkaline phosphatase activity was determined by kinetic photometric test, according to the international federation of clinical chemistry and laboratory medicine (Bessey *et al*., 1946) using DiaSys reagent kits.

Data analysis: Data were computer analyzed using SPSS version 11.0 for windows (Statistical Package for the Social Sciences Inc, Chicago, Illinois). Means were compared by independent-samples t-test. A probability level less than 0.05 were taken as significant. Percentage change was also calculated. Graphs and correlations between different parameters were plotted using Microsoft excel program.

RESULTS

Serum insulin and glucose levels: Streptozotocin-induced diabetic rats showed significant decrease in insulin levels along the whole experimental intervals examined recording a maximum percentage decrease of 33.3% at the end of the third week of the experiment compared to control levels. Treatment of diabetic rats with glimepiride or *Nerium oleander* extract improved insulin levels showing percentage decreases of 15.2 and 21.7%, respectively compared to controls (Table 1). In contrast, serum glucose levels were markedly increased in diabetic rats allover the experimental periods studied recording a maximum percentage increase of 231.1%. The maximum change in glucose level was concurrent with that of insulin level at the end of the third week of the experiment. Glucose levels were potentially improved upon treatment of diabetic rats with glimepiride or *Nerium oleander* extract registering percentage increases of 83.9 and 142.7%, respectively compared to controls (Table 2). Relationships between serum insulin and glucose levels in STZ-induced diabetic, glimepiride or *Nerium oleander* extract-treated rats were illustrated in Fig. 1. Strong negative correlation (r = -0.8) was found between glucose and insulin levels in streptozotocin-induced diabetic rats allover the experimental periods studied (Fig. 1a). This correlation was changed to positive trend (r = 0.4) in glimepiride-treated rats (Fig. 1b). However, negative correlation (r = -0.3) was recorded for diabetic rats treated with *Nerium oleander* extract (Fig. 1c). This indicated that *Nerium oleander* extract do have antidiabetic activity but to a lower extent than glimepiride did.

Liver enzymes

Serum transaminases: Serum aspartate aminotransferase and alanine aminotransferase exhibited significant increases in diabetic rats during the experimental periods studied compared to controls (Table 3, 4). However, the increment in alanine aminotransferase activity was more pronounced than that observed for aspartate aminotransferase. Oral administration of glimepiride brought back transaminases activities to near the control values. *Nerium oleander* extract treatment also showed prophylactic action on transaminases particularly on aspartate aminotransferase activity.

Serum alkaline phosphatase: Table 5 shows serum alkaline phosphatase activity in control, streptozotocin-induced diabetic, glimepiride and *Nerium oleander* extract-treated rats during the 4 weeks experimental

Table 1: Serum insulin level (μU/L) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals

	Experimental period (week)			
Treatment	1	2	3	4
Control	1.33±0.05	1.28±0.05	1.38±0.06	1.35 ±0.04
Diabetic	1.0±0.09	0.88±0.07	0.92±0.09	0.95±0.07
% change	-24.8	-31.3	-33.3	-29.6
p-value	<0.01	<0.001	<0.01	<0.01
Glimepiride-treated diabetics	1.18±0.07	1.10±0.08	1.17±0.07	1.17±0.07
% change	-11.3	-14.1	-15.2	-15.2
p-value	>0.05	>0.05	>0.05	>0.05
Nerium oleander-treated diabetics	1.13±0.07	1.03±0.06	1.08±0.08	1.10±0.07
% change	-15.0	-19.5	-21.7	-18.5
p-value	>0.05	<0.01	<0.05	<0.05

The number of rats was 6 in each experimental interval for each treatment except for control it was 8. All values are expressed as Mean±SEM. p>0.05: Non significant, p<0.05: Significant, p<0.01: Highly significant, p<0.001: More highly significant

Table 2: Serum glucose levels (mg dL^{-1}) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals

	Experimental period (week)			
Treatment	1	2	3	4
Control	101.3±6.4	107.8±7.1	103.5±5.7	104.6±5.2
Diabetic	301.2±11.3	331.4±13.1	342.7±12.7	328.2±11.0
% change	197.3	207.4	231.1	213.8
p-value	<0.001	<0.001	<0.001	<0.001
Glimepiride-treated diabetics	181.7±10.0	176.3±8.6	190.3±9.7	173.8±9.0
% change	79.4	63.5	83.9	66.2
p-value	<0.001	<0.001	<0.001	<0.001
Nerium oleander- treated Diabetics	232.3±11.2	236.7±10.4	251.2±11.3	238.5±10.3
% change	129.3	119.6	142.7	128.0
p-value	<0.001	<0.001	<0.001	<0.001

The number of rats was 6 in each experimental interval for each treatment except for control it was 8. All values are expressed as Means±SEM. p>0.05: Non significant, p<0.05: Significant, p<0.01: highly significant, p<0.001: More highly significant

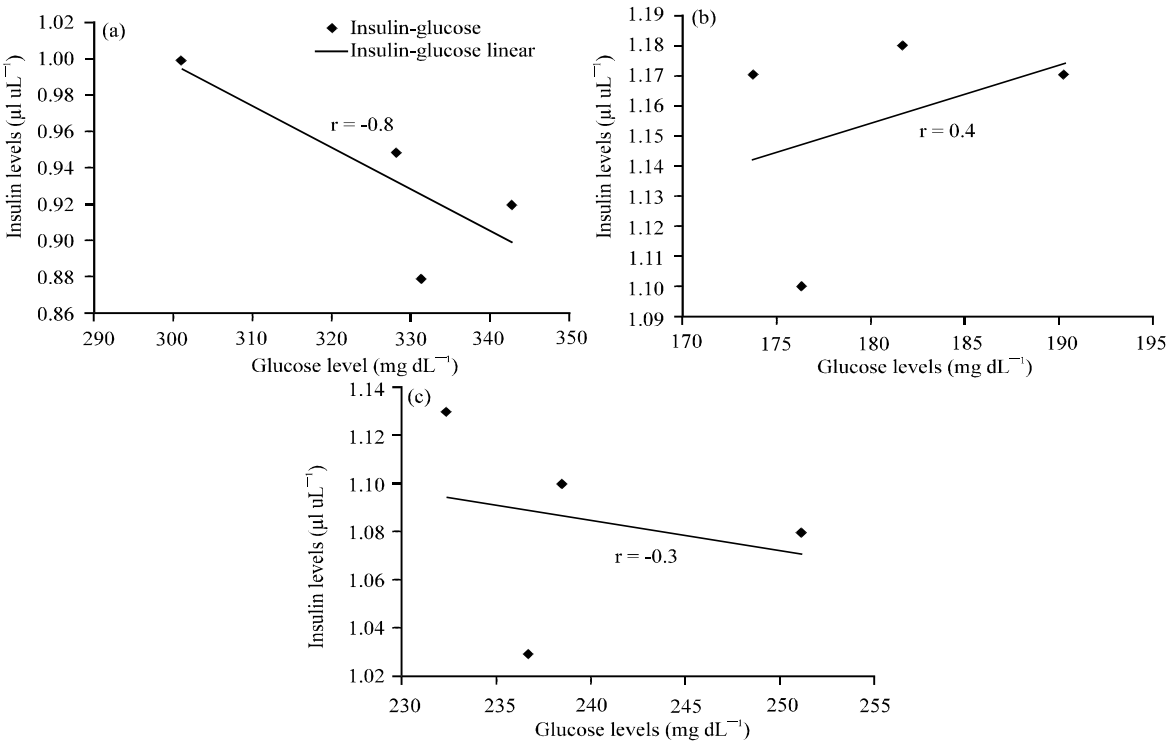

Fig. 1(a-c): (a) Insulin-glucose correlation in streptozotocin-induced diabetic rats (b) in diabetic rats treated with glimepiride and (c) in diabetic rats treated with Nerium oleander extract

Table 3: Serum aspartate aminotransferase activity (U L^{-1}) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals

	Experimental period (week)			
Treatment	1	2	3	4
Control	83.3±3.6	87.9±3.8	86.1±4.2	88.2±2.9
Diabetic	92.6±4.3	104.9±4.6	105.7±5.2	106.2±5.5
% change	11.2	19.3	22.8	20.4
p-value	>0.05	<0.05	<0.05	<0.05
Glimepiride-treated diabetics	85.0±4.5	91.8±5.1	92.4±5.4	94.1±4.9
% Change	2.0	4.4	7.3	6.7
p-value	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	87.3±4.6	96.6±5.4	92.7±4.3	96.3±4.7
% Change	4.8	9.9	7.7	93.2
p-value	>0.05	>0.05	>0.05	>0.05

The number of rats was 6 in each experimental interval for each treatment except for control it was 8. All values are expressed as Means±SEM. p>0.05: Non significant, p<0.05: Significant, p<0.01: Highly significant, p<0.001: More highly significant

Table 4: Serum alanine aminotransferase activity (U L^{-1}), in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals

	Experimental period (week)			
Treatment	1	2	3	4
Control	35.4±1.3	38.5±1.5	36.7±1.4	39.2±1.5
Diabetic	41.8±2.1	49.4±2.3	45.8±1.9	49.6±2.5
% change	18.1	28.3	24.8	26.5
p-value	<0.05	<0.01	<0.01	<0.01
Glimepiride-treated diabetics	37.6±1.7	41.6±2.2	40.2±1.9	43.1±2.0
% Change	6.2	8.1	9.5	9.9
p-value	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	38.7±1.9	44.3±2.0	41.8±1.8	44.4±1.7
% Change	9.3	15.1	13.9	13.3
p-value	>0.05	<0.05	<0.05	<0.05

The number of rats was 6 in each experimental interval for each treatment except for control it was 8. All values are expressed as Means±SEM. p>0.05: Non significant, p<0.05: Significant, p<0.01: Highly significant, p<0.001: More highly significant

Table 5: Serum alkaline phosphatase activity (U L^{-1}), in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals

	Experimental period (week)			
Treatment	1	2	3	4
Control	59.5±2.4	58.0±2.6	59.3±2.1	54.8 ±1.8
Diabetic	66.2±3.2	75.3±3.5	81.3±3.4	69.7±3.0
% change	11.3	29.8	36.8	27.2
p-value	>0.05	<0.01	<0.001	<0.01
Glimepiride- treated diabetics	63.3±2.8	64.8±2.9	68.1±2.7	61.0±2.5
% Change	6.4	11.7	14.8	11.3
p-value	>0.05	>0.05	<0.05	>0.05
Nerium oleander- treated diabetics	65.1±3.1	67.2±2.8	71.0±3.4	63.4±2.9
% Change	9.4	15.9	19.7	15.7
p-value	>0.05	<0.05	<0.05	<0.05

The number of rats was 6 in each experimental interval for each treatment except for control it was 8. All values are expressed as Mean±SEM. p>0.05: Non significant, p<0.05: Significant, p<0.01: Highly significant, p<0.001: More highly significant

period. The enzyme activity was significantly elevated in diabetic rats compared to controls. Glimepiride and *Nerium oleander* extract treatments improved alkaline phosphatase activity with the later was relatively less efficient.

DISCUSSION

Diabetes mellitus is being increased worldwide. Extensive research is employed to cure the disease. For therapeutic strategy it is convenient and simple to induce experimental diabetes in rats. In our laboratory most of rats developed hypoinsulinemia and hyperglycemia following streptozotocin injection and it persisted throughout the whole experimental duration. Strong negative correlation (r = -0.8) was found between insulin and glucose levels. Similar results were reported (Krauss *et al*., 2003; West *et al*., 1996; Bogardus *et al*., 1984).

Streptozotocin is believed to exert its toxicity by entering the β cells of the pancreatic islets via a glucose transporter and causes alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation leading to depletion of cellular NAD+ and ATP. Enhanced ATP dephosphorylation supplies a substrate for xanthine oxidase resulting in the formation of free radicals, hydrogen peroxide and toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage. As result, the β cells undergo the destruction and insulin synthesis diminished (Szkudelski, 2001; Hebden *et al*., 1989). Hyperglycemia is suggested to be due to lack of insulin, increased gluconeogenesis and/or glycogenolysis (Abu-Amra, 2000; Defranzo and Simonson, 1992).

Treatment of diabetic rats with glimepiride increased insulin levels and lowered markedly glucose levels. The antidiabetic action observed for this sulfonylurea drug is in agreement with the findings of other authors (Krauss *et al*., 2003; Cheta *et al*., 1995). Glimepiride is uniquely binds to the 65 kDa protein K (ATP) channel in the β cell membrane. Interaction of glimepiride and K (ATP) channel leads to close up potassium channels and depolarizing the cell membrane. This will activate voltage-gated Ca^{2+} channels and increased Ca^{2+} influx. Arise in cytosolic Ca^{2+} concentrations will enhance insulin releases (Ashcroft and Ashcroft, 1992; Alberti *et al*., 1997). In addition it was shown that glimepiride stimulates insulin action in peripheral tissues, and that glimepiride treatment with insulin improves the insulin resistance observed in streptozotocin-induced diabetic rats (Sato *et al*., 1993).

The current study demonstrated for the first time that treatment of diabetic rats with *Nerium oleander* extract increased insulin levels and lowered glucose levels but to a lower extent than that observed with glimepiride therapy. This implies that *Nerium oleander* could be considered as antidiabetic plant (Yassin and Mwafy, 2007). Extract of *Nerium oleander* leaves may act in one way or another on β cells of the pancreatic islets to induce insulin secretion at least in the experimental diabetes of albino rat model. Herbal therapy is widely accepted in the treatment of diabetes mellitus (Mondal *et al*., 2004; Ravi *et al*., 2004; Yaniv *et al*., 1987).

Serum transaminases and alkaline phosphatase activities were generally increased in streptozotocin-induced diabetic rats during the experimental periods studied. Similar data were recorded (El-Agouza *et al*., 2000; Gawronska-Szklarz *et al*., 2003; Yanardag *et al*., 2005). Increase in the activities of liver enzymes may be due to streptozotocin toxicity, extensive tissue destructions, disturbances in the transphosphorylation and in the general metabolism of the different cells and tissues of diabetic rats (Tanaka *et al*., 1998). It is known that elevation of transaminases could be a common sign of impairment in liver function. Acute cellular necrosis librates alkaline phosphatase in the circulation and serum enzyme level is elevated (Elyazji, 2000).

Oral administration of glimepiride to diabetic rats lowered the elevated liver enzyme activities to near the control levels. Improvement in liver enzyme activities was reported on treatment of diabetic rats with sulfonylurea drugs and was explained by increased insulin secretion, hepatic uptake of glucogenic amino acids and stimulation of amino acid incorporation into protein (Ashour *et al*., 2004). *Nerium oleander* extract also improved liver enzymes activities but to a lower extent than that noted with glimepiride treatment.

CONCLUSION

Administration of streptozotocin to albino rats caused damage to pancreatic β cells resulting in hypoinsulinemia and hyperglycemia. In diabetic rats serum transaminases and alkaline phosphatase were elevated indicating impairment of liver function. Treatment of diabetic rats with glimepiride or *Nerium oleander* extract improved insulin, glucose levels and liver enzymes activities. However, the antidiabetic activity of *Nerium oleander* plant extract was relatively lower than that of glimepiride. Further research is needed to investigate the ability of other herbs to cure diabetes mellitus.

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