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Protective Potential of Glimepiride and *Nerium oleander* Extract on Lipid Profile, Body Growth Rate, and Renal Function in Streptozotocin-Induced Diabetic Rats

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Abstract: This study aimed to assess the protective potential of glimepiride and *Nerium oleander* extract on lipid profile, body growth rate, and renal function in streptozotocin-induced diabetic rats. The animals were divided into control and experimental groups. The experimental group was rendered diabetic by intraperitoneal injection of a single dose of 50 mg/kg body weight streptozotocin. Rats with glucose levels >200 mg/dl were subdivided into 3 sub-groups. Rats in the first sub-group remained without treatment and were considered diabetic. Those in the second and third subgroups were orally administered 0.1 mg/kg body weight daily glimepiride and 250 mg/kg body weight daily *Nerium oleander* extract, respectively, for 4 weeks. In the streptozotocin-induced diabetic rats, serum triglycerides and cholesterol were significantly increased whereas body growth rate was markedly decreased compared to the controls. In contrast to uric acid and creatinine, urea concentrations were markedly elevated. Treatment of diabetic rats with glimepiride or plant extract improved all of these parameters, indicating their antidiabetic efficacy.

Key Words: Diabetes rats, lipids, growth rate, kidney, glimepiride, *Nerium oleander*, protection

Introduction

Diabetes is a major threat to global public health that is rapidly getting worse, and the biggest impact is on adults of working age in developing countries. At least 171 million people worldwide have diabetes. This figure is likely to be more than double by 2030 to reach 366 million (1). Insufficient production of insulin (either absolutely or relative to the body's needs), or the inability of cells to use insulin properly and efficiently leads to hyperglycemia and diabetes (2). The effect of diabetes is not limited to carbohydrate metabolism. Lipid and protein metabolism play an important role in the progression of the disease (3).

Induction of diabetes in laboratory animals is a convenient and useful strategy in the understanding and treatment of the disease. An appropriate dose of streptozotocin was used to induce experimental diabetes. Streptozotocin selectively destroyed pancreatic β cells, resulting in hypoinsulinemia (4).

In diabetes there is inability to store fat and protein along with breakdown of existing fat and protein stores. Streptozotocin-induced diabetic rats showed significant increases in the levels of cholesterol, phospholipids, triglycerides, and free fatty acids (5,6). These changes remain important in terms of explaining the accelerated atherosclerosis. In addition, there is a loss of body weight (7).

Impairment of kidney function is a prominent feature of diabetes. Elevated levels of urea and decreased concentrations of uric acid and creatinine were shown in diabetes (8,9). Over time diabetic nephropathy will develop, characterized by proteinuria, a loss of renal function, and a rapid progression to end-stage renal failure (10).

Glimepiride is a novel sulfonylurea used as the drug of choice in the treatment of type II diabetes in the Gaza Strip. The hypoglycemic activity of glimepiride relied on its ability to enhance insulin release and action (11,12). Although some studies have assessed *Nerium oleander* toxicity and its cure action in diluted preparations (13,14), to the best of our knowledge no research has been conducted on it as an anti-diabetic plant.

The present research was carried out to assess the protective potential of the synthetic sulfonylurea drug glimepiride and *Nerium oleander* plant extract on lipid profile, body growth rate, and renal function in streptozotocin-induced diabetic rats. The findings could translate into better protection against human diabetes.

Materials and Methods

Experimental animals

Male Sprague-Dawley rats weighing 170 ± 30 g were used throughout the study. The animals were maintained under ambient conditions in the animal house in the Department of Biology, The Islamic University of Gaza. They were fed a commercial balanced diet and water was provided with fresh supply daily throughout the experimental period.

Induction of diabetes and treatment

The animals were divided into 2 major groups: control and experimental groups. The experimental group of animals was fasted for 24 h and then intraperitoneally injected with a single dose of 50 mg/kg 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 (4,15). Rats with glucose levels >200 mg/dl were subdivided into 3 subgroups. Those in the first subgroup remained without treatment and were considered diabetic. Those in the second subgroup were given glimepiride and considered the glimepiride-treated subgroup. Glimepiride was purchased from local pharmacies in tablet form and ground using a mortar. The powder was dissolved in distilled water and orally administered at a dose of 0.1 mg/kg body weight per day for the experimental period of 4 weeks. The dose of glimepiride was based on previous studies (12,16). The third subgroup received *Nerium oleander* plant extract and was considered the *Nerium oleander* extract-treated subgroup. This plant belongs to the family apocynaceae. Leaves were collected from plants growing in the Gaza strip from different localities on road sides and gardens during 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 a dark dry place at room temperature. Leaf extract was obtained using aqueous decoction (17). The extract was orally administered at a dose level of 250 mg/kg body weight per day for 4 weeks. The dose of *Nerium oleander* extract was based on previous toxicological studies (14,18). Oral administration of glimepiride and *Nerium oleander* extract was done using a special stomach tube with a smooth tip to protect the interior lining of the oral and buccal cavity of the animal from injury.

Monitoring of body growth rate

Animals were individually weighed daily in order to record the changes in their body growth rates. A sensitive balance was used.

Blood sampling and processing

At each sampling date, 8 rats were taken from the control group and 6 rats from each subgroup per week. The animals 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 triglyceride and cholesterol

Serum triglyceride levels were measured by colorimetric enzymatic test using glycerol-3-phosphate-oxidase (19) with DiaSys reagent kits. Serum cholesterol was determined with a "CHOD-PAP" enzymatic photometric test (20) using DiaSys reagent kits.

Determination of urea, uric acid, and creatinine

Serum urea was determined by colorimetric test (21) using DiaSys reagent kits. Serum uric acid was measured by direct enzymatic assay (22) using DiaSys reagent kits. Serum creatinine was determined by kinetic test without deproteinization (23) using DiaSys reagent kits.

Data analysis

The data were analyzed using SPSS version 11.0 for Windows (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). Means were compared by independent-samples t-test. A probability level less than 0.05 was regarded as significant. Percentage changes were also calculated.

Results

Serum triglyceride and cholesterol

Streptozotocin-induced diabetic rats showed significant increases in the levels of serum triglyceride and cholesterol, registering increases of 27.3% and 25.6%, respectively, at the end of the experiment compared to the controls. Glimepiride and *Nerium oleander* extract treatment lowered serum triglyceride in diabetic rats to increases of 10.1% and 14.5%, respectively. This protective effect was also observed for cholesterol, where increases in diabetic rats treated with glimepiride and *Nerium oleander* extract were 9.3% and 15.9%, respectively (Tables 1 and 2).

Body growth rate

Table 3 shows a marked decrease in the body growth rate of diabetic rats throughout the experimental period, with a decrease of 64.7% at the end of the experiment compared to the controls. Treatment of diabetic animals with glimepiride and *Nerium oleander* extract improved the growth rate, recording decreases of 28.4% and 37.5%, respectively, compared to the controls.

Serum urea, uric acid and creatinine

Streptozotocin-induced diabetic animals showed a significant elevation in serum urea concentrations, with an increase of 33.0% at the end of the experiment compared to the controls. Glimepiride therapy returned urea concentrations to near control values, showing an increase of 10.5%. On the other hand, urea concentrations still showed a significant increase, with *Nerium oleander* extract treatment recording an increase of 17.1% compared to the controls (Table 4). In contrast, serum uric acid and creatinine exhibited significant decreases in streptozotocin-induced diabetic rats, with percentages of 17.5% and 23.7%, respectively, at the end of the experiment compared to the controls. Both glimepiride and *Nerium oleander* extract treatment reversed such changes to approach control levels (Tables 5 and 6).

Discussion and Conclusion

The current study is the second part of our work on diabetes. In the first part most of the rats in our

Table 1. Serum triglyceride level (mg/dl) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	65.4 ± 3.1	59.8 ± 3.2	66.7 ± 2.7	68.2 ± 3.0
Diabetic	73.1 ± 3.7	70.3 ± 2.8	83.4 ± 3.3	86.8 ± 3.6
% Change	11.8	17.6	25.0	27.3
P	>0.05	<0.05	<0.01	<0.01
Glimepiride-treated diabetics	68.6 ± 3.8	63.4 ± 3.0	69.8 ± 2.6	75.1 ± 3.1
% Change	4.9	6.0	4.6	10.1
P	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	70.8 ± 2.9	66.0 ± 3.4	75.5 ± 2.9	78.1 ± 3.1
% Change	8.3	10.4	13.2	14.5
P	>0.05	>0.05	<0.05	<0.05

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

Table 2. Serum cholesterol level (mg/dl) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	80.3 ± 3.2	82.1 ± 2.8	83.8 ± 2.9	78.6 ± 3.1
Diabetic	88.4 ± 2.9	93.8 ± 3.1	101.5 ± 3.2	98.7 ± 3.0
% Change	10.1	14.3	21.1	25.6
P	>0.05	<0.05	<0.01	<0.01
Glimepiride-treated diabetics	84.9 ± 29	86.4 ± 3.4	89.5 ± 3.5	85.9 ± 3.2
% Change	5.7	5.2	6.8	9.3
P	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	86.3 ± 3.1	89.6 ± 3.5	94.5 ± 3.5	91.1 ± 3.3
% Change	7.5	9.1	12.8	15.9
P	>0.05	>0.05	<0.05	<0.05

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

Table 3. Body growth rate (g/day) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	4.37 ± 0.26	4.77 ± 0.21	4.28 ± 0.21	3.63 ± 0.20
Diabetic	2.10 ± 0.22	1.33 ± 0.25	1.27 ± 0.30	1.28 ± 0.21
% Change	-51.9	-72.1	-70.3	-64.7
P	<0.001	<0.001	<0.001	<0.001
Glimepiride-treated diabetics	3.92 ± 0.29	3.08 ± 0.29	2.95 ± 0.28	2.60 ± 0.17
% Change	-10.3	-35.4	-31.1	-28.4
P	>0.05	<0.01	<0.01	<0.01
Nerium oleander- treated diabetics	3.55 ± 0.25	2.35 ± 0.19	2.38 ± 0.31	2.27 ± 0.16
% Change	-18.8	-50.7	-44.4	-37.5
P	<0.05	<0.001	<0.001	<0.001

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

Table 4. Serum urea concentrations (mg/dl) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	33.6 ± 1.6	37.4 ± 1.9	34.8 ± 1.8	35.1 ± 1.7
Diabetic	41.5 ± 2.2	51.8 ± 2.7	47.1 ± 2.5	46.7 ± 2.1
% Change	23.5	38.5	35.3	33.0
P	<0.05	<0.01	<0.01	<0.01
Glimepiride-treated diabetics	36.7 ± 2.0	42.5 ± 2.0	39.2 ± 2.3	38.8 ± 2.1
% Change	9.2	13.6	12.6	10.5
P	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	37.8 ± 2.3	45.6 ± 2.1	42.3 ± 2.0	41.1 ± 1.9
% Change	12.5	21.9	21.6	17.1
P	>0.05	<0.05	<0.05	<0.05

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

Table 5. Serum uric acid concentrations (mg/dl) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	1.72 ± 0.08	1.76 ± 0.07	1.69 ± 0.06	1.77 ± 0.08
Diabetic	1.65 ± 0.10	1.57 ± 0.09	1.44 ± 0.08	1.46 ± 010
% Change	-4.1	-10.8	-14.8	-17.5
P	>0.05	>0.05	<0.05	<0.05
Glimepiride-treated diabetics	1.69 ± 0.09	1.78 ± 0.11	1.61 ± 0.09	1.66 ± 0.10
% Change	-1.7	-1.1	-4.7	-6.2
P	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	1.64 ± 0.08	1.68 ± 0.1	1.57 ± 0.1	1.59 ± 0.11
% Change	-4.7	-4.5	-7.1	-10.2
P	>0.05	>0.05	>0.05	>0.05

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

Table 6. Serum creatinine concentrations of (mg/dl) in control, streptozotocin-diabetic, glimepiride and *Nerium oleander* extract-treated albino rats at different time intervals.

Treatment	Experimental Period (Week)			
	1	2	3	4
Control	0.62 ± 0.02	0.58 ± 0.03	0.61 ± 0.02	0.59 ± 0.02
Diabetic	0.60 ± 0.03	0.50 ± 0.02	0.48 ± 0.02	0.45 ± 0.03
% Change	-3.2	-13.8	-21.3	-23.7
P	>0.05	<0.05	<0.01	<0.01
Glimepiride-treated diabetics	0.63 ± 0.04	0.56 ± 0.03	0.56 ± 0.04	0.55 ± 0.03
% Change	-1.6	-3.4	-8.2	-6.8
P	>0.05	>0.05	>0.05	>0.05
Nerium oleander- treated diabetics	0.61 ± 0.04	0.55 ± 0.03	0.54 ± 0.03	0.52 ± 0.04
% Change	-1.6	-5.2	-11.5	-11.9
P	>0.05	>0.05	>0.05	>0.05

The number of animals was 6 in each experimental interval for each treatment except for the control, in which it was 8.
All values are expressed as means ± S.E.M.
P > 0.05: non-significant, P < 0.05: significant, P < 0.01: highly significant, P < 0.001: more highly significant.

laboratory developed hypoinsulinemia and hyperglycemia following streptozotocin injection. This persisted throughout the whole experimental duration of 4 weeks, where a strong negative correlation (r = -0.8) was obtained between insulin and glucose levels (24).

Increased levels of serum triglycerides and cholesterol observed in streptozotocin-induced diabetic rats were in accord with other studies (25,26). The abnormal high concentrations of serum lipids in diabetic animals are due mainly to an increase in the mobilization of free fatty acids from the peripheral fat depots, since insulin inhibits the hormone-sensitive lipase (27). Excess fatty acids in the serum of diabetic rats are converted into phospholipids and cholesterol in the liver. These 2 substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoproteins (28). The antilipidemic action of glimepiride and *Nerium oleander* extract may reside in their ability to stimulate insulin secretion and action (12,24).

Diabetic rats exhibited decreases in body growth rate. The reduction in body weight may be attributed to insulin depletion provoking a loss of adipose tissues and due to changes in carbohydrates and protein metabolism that occur in rats with streptozotocin-induced diabetes (29). Such a finding is in agreement with previous studies (30,31). However, treatment of diabetic rats with glimepiride or *Nerium oleander* extract did improve body growth rate. This may be explained by enhancement of insulin secretion and action (12,24). It was demonstrated that glimepiride is associated with weight neutrality in diabetics (32).

The data revealed significant elevations in serum urea in streptozotocin-induced diabetic rats. A similar effect was recorded previously (8). Enhanced protein catabolism and accelerated amino acid deamination for gluconeogenesis is probably an acceptable postulate to interpret the elevated levels of urea. In contrast, serum uric acid and creatinine were decreased in diabetic animals. Possible defects in tubular reabsorption and probably increased excretion may explain such decreases in serum uric acid and creatinine. Creatinuria occurs in any condition associated with extensive muscle breakdown as in starvation and poorly controlled diabetes mellitus (33). However, uric acid clearance has been

associated with insulin resistance (34). Previous changes in serum urea, uric acid, and creatinine concentrations strongly suggested impairment of kidney function in diabetes.

Glimepiride and *Nerium oleander* extract therapy returned such changes in urea, uric acid, and creatinine towards normal. The main effect of the sulfonylureas and possibly the plant extract is enhancement of insulin secretion and improvement of metabolism both by pancreatic and extrapancreatic mechanisms (24,35).

In conclusion, streptozotocin-induced diabetic rats had significant increases in serum triglyceride and cholesterol levels. Body growth rate was markedly decreased. Serum urea was significantly elevated whereas uric acid and creatinine were decreased. Treatment of diabetic rats with glimepiride and *Nerium oleander* extract offered protection in terms of lipid profile, growth rate and renal function, indicating their antidiabetic potential.

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