



Evaluation of Antihyperglycemic Effect of *Gynocardia odorata* Roxb in Streptozotocin Induced Diabetic Rats

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ABSTRACT

The hypoglycemic effect of methanol extract of *Gynocardia odorata* roxb (MEGO) in streptozotocin (STZ)-induced diabetic Wistar rats was studied in this present study. Hyperglycemia was induced in rats by single intraperitoneal injection of STZ (55 mg/kg body weight). Three days after STZ induction, the hyperglycemic rats were treated with MEGO orally at the doses of 200 and 400 mg/kg body weight daily for 21 days. Glibenclamide (1 mg/kg, orally) was used as reference drug. The fasting blood glucose levels were measured on each 7th day during the 21 days of treatment. Serum biochemical parameters including lipid content were estimated. MEGO at the doses of 200 and 400 mg/kg orally significantly ($P < 0.01$) and dose dependently reduced and normalized blood glucose levels as compared to that of STZ control group; the dose 400 mg/kg being the most potent showing complete normalization of blood glucose levels. Serum biochemical parameters including lipid profile were significantly ($P < 0.01$) restored toward normal levels in MEGO-treated rats as compared to STZ control animals. This study concludes that *Gynocardia odorata* roxb demonstrated promising hypoglycemic action in STZ-induced diabetic rats substantiating its ethno medicinal use. Although this study establishes the traditional role of *Gynocardia odorata* roxb in the diabetes but still further exhaustive studies are required to find out and establish the main compound responsible for this activity as drug.

Keywords: Diabetes, glibenclamide, streptozotocin, biochemical parameters

INTRODUCTION

Diabetes mellitus is metabolic disorder characterized by chronic hyperglycaemia and glucosuria produced by an absolute or relative insufficiency of insulin. The ailment may result into the development of further metabolic and anatomic disturbances among which is lipemia, hypercholesterolemia, loss of weight, ketosis, arteriosclerosis, gangrene, pathologic changes in the eye, neuropathy, renal disease and coma.¹ There are a unit Associate in Nursing calculable 143 million folks within the world with diabetes and this variety will most likely double by the year 2030.² Many synthetic drugs are used in treatment of diabetes, but plant drugs are frequently considered to be less toxic, and are free from side effects. In recent times, there has been a revived interest within the plant remedies.

Gynocardia odorata roxb is also known as Chaulmoogra plant, belongs to the family of Flacourtiaceae, which is indigenous to parts of India, Malaysia and tropical countries of the world, contain fatty acids chaulmoogric acid, hydnocarpic acid. Chaulmoogra oil is an important therapeutic agent in certain medical traditions.³ The seeds of *Gynocardia odorata* roxb are most commonly used. The fruits are hot anthelmintic and used in bronchitis, skin diseases, small tumor's leprosy, and as an analgesic. *Gynocardia odorata* roxb is reported to contain antioxidant properties.⁴ *Gynocardia odorata* roxb may have its antiulcer activity because of its active

constituents like flavonoids and especially quercetin.⁵⁻⁶ It was reported that *G. odorata* roxb could be a natural medication alternative of thrombolytic agents as well as source of potent bioactive compounds.⁷ These activities have been already reported but anti-diabetic activity is not established yet. In the present study we made an attempt to establish the anti-diabetic potential of methanol leaf extracts of *Gynocardia odorata* roxb.

MATERIALS AND METHODS

Drugs and chemicals

STZ was from Sigma Chemical Co., USA. Glibenclamide was from Hoechst, India. All other reagents used were of analytical grade obtained commercially.

Collection and extraction

The fresh leaves of *Gynocardia odorata* roxb were collected from the Authenticated crude drug supplier in Delhi and authentication of the plant was carried in Botanical Survey of India, Coimbatore, India. A voucher specimen has been deposited in the laboratory for future reference (BSI/SC/7/46/13-14/TECH.785).

The leaves of the plant were shade dried and pulverized. The powder was defatted with petroleum ether. Later, it had been subjected to continuous hot extraction with 95% aqueous methanol in a Soxhlet apparatus. The extract (MEGO) was concentrated under vacuum and dried in desiccators (yield 69gm, 6.9% w/w). The dry extract was kept in vacuum desiccators until use.



Preliminary phytochemical analysis⁸ revealed the presence of flavonoids, alkaloids, and steroids in MEGO Plant material.

Animals

Adult male Wistar albino rats weighing 150–200 g were procured from Venkateshwara Enterprises, Bangalore, Karnataka, India and used throughout the study. All the animals were under the age of 8–12 weeks. They were housed in a very clean polypropylene cage and maintained under standard laboratory conditions (temperature $25 \pm 2^\circ\text{C}$ with dark/light cycle 12/12 h). They were fed with standard pellet diet and water *ad libitum*. The animals were acclimatized to laboratory conditions for one week before experiment. Experiments were performed complied with the rulings of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) New Delhi, India under the registration No: 1135/a/07/CPCSEA.

Acute toxicity

Acute toxicity studies were performed as per OECD-423 guidelines.⁹ Male Wistar albino rats selected by random sampling technique were utilized during this study. The animals were fasted for 4h with free access to water only. The plant extract was administered orally at a dose of 5mg/kg initially and mortality if any was observed for 3 days. If mortality was ascertained in two out of three animals, then the dose administered was considered as toxic dose. However, if the mortality was ascertained in only one animal out of three animals then the identical dose was repeated again to confirm the toxic effect. If no mortality was ascertained, then higher (50,300 and 2000mg/kg) doses of extract were utilized for further toxicity studies.

Oral glucose tolerance test (OGTT)

The OGTT was performed in overnight fasted normal rats. Rats were divided into four groups ($n = 6$). Group I served as normal control (NC) and received distilled water (5 ml/kg b.w., p.o.) and groups II and III received MEGO at the doses of 200 and 400 mg/kg b.w., p.o., respectively. Group IV received glibenclamide 1 mg/kg b.w. p.o. 30 min after these treatments, all groups received glucose (4 g/kg b.w.) orally. Blood was withdrawn from the tail vein just prior to and 30, 60, and 120 min after the oral glucose administration.^{10,11} Blood glucose levels were measured using glucoseoxidase-peroxidase reactive strips and a portable glucometer (Accu Sure blood glucose monitoring system).

Induction of experimental diabetes mellitus

The rats were rendered diabetic by a single intraperitoneal dose of 55 mg/kg b.w. STZ freshly dissolved in ice cold 0.1 M citrate buffer (pH 4.5). After 72 h, fasting blood glucose (FBG) levels were measured and only those animals showing blood glucose level ≥ 225 mg/dl were used for the subsequent investigation. The

day on which hyperglycemia had been confirmed was designated as day 0.^{12,13}

Treatment schedule and estimation of FBG level

Normal and hyperglycemic rats were divided into six groups ($n = 6$) receiving the following treatments:¹⁴

Group I: Non-diabetic or normal control, received the vehicle (distilled water) 5 ml/kg b.w., p.o. (NC).

Group II: Non-diabetic control, received MEGO 400 mg/kg b.w., p.o.

Group III: Diabetic control, received the vehicle (distilled water) 5 ml/kg b.w., p.o. (DC).

Group IV: Diabetic treatment, received MEGO 200 mg/kg b.w., p.o.

Group V: Diabetic treatment, received MEGO 400 mg/kg b.w., p.o.

Group VI: Diabetic treatment, received glibenclamide 1 mg/kg b.w., p.o.

The above treatment was continued daily for 21 days. Fasting blood glucose concentrations were measured with a portable glucometer (Accu Sure blood glucose monitoring system) at days 0, 7, 14, and 21.

Body weight

The body weights of rats of each group were recorded on 1st, 7th, and 15th day of MEGO treatment.

Estimation of serum biochemical parameters

After twenty one days treatment, blood samples were drawn from overnight fasted rats by retro orbital vein puncture technique from light-ether anesthetized animals. The non-heparinized blood was allowed to coagulate before being centrifuged (4000 rpm for 20 min) and the blood serum separated. Blood serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), glycosylated hemoglobin (HbA1C), aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were estimated enzymatically using commercially available reagent kits (Erba Diagnostics and Span diagnostics Ltd.)

Statistical analysis

The data were expressed as mean \pm standard error of mean (SEM). Statistical significance was analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's *posthoc* test of significance using Graph Pad (Instat) software version 4.0. *P* values of < 0.05 were considered as statistically significant.

RESULTS

Acute toxicity

The MEGO did not show any toxic effect or death up to the dose of 2000 mg/kg, b.w., p.o. in mice.



Oral glucose tolerance (OGTT)

Effects of the MEGO on glucose-loaded rats are shown in Table 1. Results of the OGTT strongly supported the improved ability of glucose tolerance with treatment of MEGO and glibenclamide. Among the groups, the concentrations of blood glucose baseline (0 min) were not

considerably different. Though plasma glucose levels were increased after loading with glucose, animals treated with MEGO at 200 and 400 mg/kg showed slight increase when compared with the NC group at 30, 60, and 120 min during OGTT. Glibenclamide significantly blocked ($P < 0.01$) the rise in blood glucose levels after glucose administration at 120 min.

Table 1: Effect of methanol extract of *Gynocardia odorata* (MEGO) on oral glucose tolerance in normal rats.

Time (min)	Control glucose (4 g/kg)	MEGO 200 mg/kg + glucose (4 g/kg)	MEGO 400 mg/kg + glucose (4 g/kg)	Glibenclamide (1 mg/kg) + glucose (4 g/kg)
0	86.83±2.60	78.52±3.25	84.33±1.17	74.16±4.01
30	138.65±2.94	126.16±2.30	114.16±2.18 ^b	72.05±2.31 ^b
60	122.79±3.22	108.50±3.38 ^a	98.13±3.44 ^b	64.50±2.18 ^b
120	113.66±2.26	92.31±3.86 ^b	90.27±1.10 ^b	62.29±3.05 ^b

Values are mean ± SEM ($n = 6$). ^a $P < 0.05$, ^b $P < 0.01$ when compared with control group at corresponding time.

Table 2: Effect of methanol extract of *Gynocardia odorata* (MEGO) on fasting blood glucose levels in normal and streptozotocin (STZ) - induced diabetic rats.

Treatment	Fasting blood glucose level (mg/dl)			
	0 day	7th day	14th day	21st day
Normal control	84.23±4.30 ^a	88.16±4.37 ^a	80.28±5.28 ^a	84.32±6.69 ^a
NC+MEGO (400 mg/kg)	98.22±5.12 ^a	86.58±5.10 ^a	74.20±5.62 ^a	72.8±5.00 ^a
STZ control (55 mg/kg)	342.40±8.3 ^b	512.20±21.26 ^b	398.54±25.29 ^b	302.92±22.94 ^b
STZ+MEGO (200 mg/kg)	322.84±22.8 ^b	292.28±19.69 ^{ab}	196.10±16.66 ^{ab}	130.22±9.38 ^a
STZ+MEGO (400 mg/kg)	406.06±22.3 ^b	214.22±20.29 ^{ab}	132.84±15.63 ^{ab}	92.16±9.60 ^a
STZ+Glibenclamide (1 mg/kg)	344.28±16.1 ^b	126.4±11.36 ^{ab}	66.40±4.94 ^a	56.12±3.73 ^a

Values are mean ± SEM ($n = 6$). ^a $P < 0.01$ when compared with STZ control group; ^b $P < 0.01$ when compared with normal control group.

FBG levels

Fasting blood glucose levels measured in normal and STZ-induced diabetic rats after a single day and at the end of 7, 14, and 21 days of treatment are given in Table 2.

Here, diabetic rats had a significant effect on blood sugar response after treat for 21 days. NC rats did not show any significant variation in the blood sugar throughout the experimental period. Administration of STZ (55 mg/kg, i.p.) led to several fold elevation of blood glucose levels relative to that of the NC group, indicating stable hyperglycemia during the experimental period. FBG level of normal animals treated with MEGO at 200 mg/kg (Group II) did not vary significantly from that of the NC group. Although MEGO at 200 mg/kg reduced hyperglycemia significantly ($P < 0.01$) as compared to the diabetic control (DC) group, it failed to restore the level to that of the NC group; while MEGO at 400 mg/kg or glibenclamide (1 mg/kg) significantly ($P < 0.01$) reduced the blood glucose levels close to NC group level.

Effect on body weight

The effect of MEGO on body weight of normal and diabetic animals is presented in Table 3. NC animals were found to be stable in their body weight but diabetic rats showed significant reduction in body weight during 21 days. STZ caused body weight reduction, which was significantly ($P < 0.01$) reversed by MEGO treatment.

Serum biochemical parameters

Results of biochemical parameters are represented in Table 4. MEGO had a significant ($P < 0.01$) effect in lowering HbA1C. After 21 days, the effect of MEGO on groups II, IV, and V was not significant as compared to the NC group. Treatment with MEGO at 400 mg/kg and glibenclamide (1 mg/kg) decreased HbA1C significantly ($P < 0.01$) in the diabetic rats. There was a significant ($P < 0.01$) decrease in the level of serum HDL-cholesterol and significant ($P < 0.01$) increase in the levels of TC, LDLC, and TGs in diabetic rats when compared to NC rats. Administration of MEGO at 400 mg/kg and glibenclamide (1 mg/kg) significantly ($P < 0.01$) brought their levels



toward normal. The activities of serum enzymes AST, ALT, and ALP were found to be significantly ($P < 0.01$) increased in diabetic rats compared to normal rats. Oral

administration of MEGO at 200 and 400 mg/kg and glibenclamide at 1 mg/kg for 21 days significantly ($P < 0.01$) normalized the enzymatic activities in diabetic rats.

Table 3: Effect of methanol extract of *Gynocardia odorata* (MEGO) on body weight in normal and streptozotocin (STZ)-induced diabetic rats.

Treatment	Body weight (g)			
	0 day	7th day	14th day	21st day
Normal control	180.66±1.22	185.17±2.17 ^a	194.20±1.30 ^a	203.27±1.98 ^a
NC + MEGO (400 mg/kg)	172.63±2.89	188.00±2.85 ^a	194.63±2.30 ^a	204.26±2.54 ^a
STZ control (55 mg/kg)	176.33±1.43	169.50±1.46 ^c	159.87±2.12 ^c	142.00±1.24 ^c
STZ + MEGO (200 mg/kg)	178.62±3.25	184.26±1.33 ^b	192.18±2.42 ^{ab}	206.88±1.68 ^{ac}
STZ + MEGO (400 mg/kg)	180.23±2.60	188.66±1.47 ^a	196.26±2.45 ^a	208.41±2.37 ^a
STZ + Glibenclamide (1 mg/kg)	182.30±3.28	196.30± 1.21 ^a	204.82±2.34 ^a	214.92±1.44 ^a

Values are mean ± SEM ($n = 6$). ^a $P < 0.01$ when compared with STZ control group; ^b $P < 0.05$ and ^c $P < 0.01$ when compared with normal control group.

Table 4: Effect of methanol extract of *Gynocardia odorata* (MEGO) on serum biochemical parameters in normal and streptozotocin (STZ)-induced diabetic rats.

Treatment	GH (%)	TG (mg/dl)	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	AST (U/L)	ALT (U/L)	ALP (U/L)
Normal control	6.42±1.29 ^b	62.98±2.23 ^b	82.49±2.46 ^b	32.92±1.08 ^b	44.32±2.20 ^b	60.5± 2.46 ^b	36.7± 1.10 ^b	58.5± 2.66 ^b
NC + MEGO (400 mg/kg)	4.75±0.78 ^b	54.36± 1.80 ^b	79.6± 3.22 ^b	46.98± 1.49 ^b	40.29± 1.44 ^b	53.3± 1.38 ^b	36.5± 1.04 ^b	62.63± 2.06 ^b
STZ control (55 mg/kg)	12.3±0.17 ^d	102.22± 3.20 ^d	182.17± 3.42 ^d	24.85± 1.10 ^d	142.9± 2.48 ^d	92.8± 2.46 ^d	72.2± 2.12 ^d	94.63± 2.32 ^d
STZ + MEGO (200 mg/kg)	10.9±0.88 ^{ad}	96.07± 2.30 ^d	128.06±4.86 ^{bd}	32.21± 2.20	87.79±1.66 ^{bd}	88.4± 1.84 ^d	62.4± 1.64 ^{bd}	82.87± 1.20 ^d
STZ + MEGO (400 mg/kg)	8.66±0.21 ^{bd}	71.15± 3.08 ^{bd}	112.5±3.21 ^{bd}	28.48±2.10 ^a	69.20±2.20 ^{bd}	70.6± 2.16 ^{bd}	48.2± 1.40 ^{bd}	76.07± 1.38 ^{bd}
STZ + Glibenclamide (1 mg/kg)	5.42±0.12 ^b	40.95 ± 1.11 ^{bc}	88.48± 2.30 ^b	36.14± 2.15 ^b	48.82±2.88 ^{bd}	62.1± 2.11 ^b	34.2± 1.83 ^b	64.38± 1.22 ^{bd}

Values are mean ± SEM ($n = 6$). ^a $P < 0.05$ and ^b $P < 0.01$ when compared with STZ control group; ^c $P < 0.05$ and ^d $P < 0.01$ when compared with normal control group.

DISCUSSION

Pharmacological treatment with of diabetes is based on oral hypoglycaemic agents and insulin. However, long term treatment with these drugs is expensive and poses life threatening adverse effects. Management of diabetes without any side effects continues to be a challenge to the medical community.¹⁵ Despite considerable progress made in the conventional anti-diabetic management strategies, the search continues for plant-based products for the management of diabetes, which are deemed safe.¹⁶ Phytotherapy has been extremely accepted worldwide in the health care system for DM. In this study, the hypoglycemic activity of MEGO was evaluated in STZ-induced diabetic rats. Here, STZ at the dose of 55 mg/kg,

i.p., was used to induce hyperglycemia after performing a pilot study for optimized dose to elevate blood glucose >250 mg/dl. The use of lower dose of STZ (55 mg/kg) produced an incomplete destruction of pancreatic β cells although the rats become permanently diabetic.¹⁷

Results of the OGTT powerfully supported the improved ability of glucose tolerance with treatment of MEGO and glibenclamide. MEGO exhibited significant reduction in blood sugar in diabetic rats at the doses of 200, 400 mg/kg. Though MEGO at 200 mg/kg reduced the hyperglycemia significantly as compared to the DC group, it did not restore the FBG level to that of the NC group, while with MEGO at 400 mg/kg the blood sugar levels of diabetic rats were reduced to NC group level. Blood



glucose levels in normal rats treated with MEGO 200 at mg/kg were insignificant from that of the NC group, indicating that MEGO maintained glucose homeostasis. The hypoglycaemic action of MEGO could also be because of promotion of insulin release from existing β cells of the islets of Langerhans. The plasma glucose lowering activity was compared with that of glibenclamide, the reference oral hypoglycemic that has been used for several years to treat diabetes, to stimulate pancreatic β cells.¹⁸

From the results of this study, it seems that still insulin producing cells are functioning and therefore the stimulation of insulin release could be responsible for most of the metabolic effects. It may be suggested that the mechanism of hypoglycaemic action of MEGO is similar to glibenclamide. Induction of diabetes with STZ is associated with a characteristic loss of body weight, throughout the observation period of 21 days even though the food intake was more in diabetic rats than NC animals. It was because of augmented muscle wasting and loss of tissue proteins.¹⁹ STZ-induced insulin deficiency may lead to protein content decrease in muscular tissue by proteolysis.²⁰

Diabetic rats treated with the MEGO showed significant improvement in body weight as compared to the STZ control animals; thus, MEGO exhibited marked effect in controlling the loss of body weights of diabetic rats. Oral administration of MEGO decreased the level of HbA1C. Lower levels of total haemoglobin observed in diabetic rats may be because of the exaggerated formation of HbA1C. Glycohaemoglobin is made throughout the circulatory life of red blood cells (RBCs) by the addition of glucose to the N-terminal of the haemoglobin β chain. This process, which is nonenzymatic, reflects the average exposure of haemoglobin to glucose over an extended period.

Lipids play a significant role in the pathogenesis of DM. It is documented that in uncontrolled diabetes mellitus, there is a rise in TC in blood, which can contribute to coronary artery diseases.²¹ The foremost common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia. In this study, elevated levels of serum lipids such as TC, LDLC, and TGs were found in diabetic rats. STZ produced various cardinal symptoms of diabetes mellitus including hypoinsulinemia, a condition that is probably responsible for the elevation of serum cholesterol levels because the insulin has an inhibitory action on HMG-CoA reductase, a key enzyme that acts as rate limiting in the metabolism of cholesterol rich LDL particles.²²

In insulin-deficient diabetes, the concentration of serum fatty acids is elevated as a result of free fatty acid out flow from fat depots, wherever the balance of the free fatty acid esterification-TG lipolysis cycle is displaced in favour of lipolysis. High-density lipoprotein (HDL) is an antiatherogenic lipoprotein. It transports cholesterol from peripheral tissues into the liver and thereby acts as a protective factor against coronary cardiovascular disease.

The amount of HDLC, which increased after MEGO administration, may be due to the increase in the activity of lecithin cholesterol acyl transferase (LCAT), which can contribute to the regulation of blood lipids.²³ Oral administration of MEGO reduced the elevated serum lipids such as TC, LDLC, and TGs toward normal in diabetic rats. Elevation of serum biomarker enzymes such as SGOT, SGPT, and SALP was observed in diabetic rats indicating impaired liver function, which was obviously due to hepatocellular necrosis. It has been reported that liver necrosis occurred in STZ-induced diabetic rats. Therefore, increase in the activities of AST, ALT, and ALP gives an indication on the hepatotoxic effect of STZ. Twenty-one days of treatment with MEGO restored all the above-mentioned serum hepatic biochemical parameters toward the normal values in a dose-dependent manner, thereby alleviating liver injury caused by STZ-induced diabetes.

CONCLUSION

In this study, administration of MEGO to STZ-induced hyperglycemic rats incontestable distinguished reduction in blood glucose level, standardization of serum biochemical profiles including lipid contents, comparing to STZ control rats. Therefore, it can be concluded that the MEGO is remarkably effective against STZ-induced diabetes in Wistar rats thereby validating its ethno medicinal usage. From the ascertained oral hypoglycemic activity of MEGO in STZ-induced diabetic rats, it can be further inferred that *G. odorata* will function a motivating candidate in complementary and alternative medicine for the effective management of diabetes. However, the components responsible for the antidiabetic activity are currently unclear. Therefore, further investigation is needed to isolate and identify the constituents present in the leaves extracts.

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