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Antidiabetic and anti-hypercholesterolemic effects of aerial parts of *Sida cordifolia* Linn. on Streptozotocin-induced diabetic rats

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The present study was under taken to establish the potential of *Sida cordifolia* Linn. (Family—Malvaceae) as anti-hyperglycemic and anti-hypercholesterolemic agent. The effects of the methanol and aqueous extracts on oral glucose tolerance test (OGTT) as well as effect of the aqueous extract (AE) on Streptozotocin (STZ)-induced diabetic model were studied. Anti-diabetic activity was compared with clinically available drug Metformin. In OGTT, administration of methanol (ME) and AE at 500, 750 and 1000 mg/kg, respectively to normal rats showed a dose depended check on the rise of serum glucose level in comparison to control group. Maximum reduction was observed with AE at dose level 1000 mg/kg. In STZ model, the degree of protection was evaluated by fasting serum glucose level at 0, 7th, 14th and 21st day of study. The body weight, lipid profile and liver glycogen level were also evaluated at 21st day. Administration of AE (1000 mg/kg, b.w.) to diabetic rats showed a significant (P<0.05) glucose lowering effect on 7th, 14th and 21st day. Further, a significant improvement (P<0.05) in lipid profile, glycogen content and check on the loss of body weight was also observed. These results could explain the basis for the use of this plant extract to manage serum glucose level and cholesterolemia associated with diabetes mellitus.

Keywords: Anti-cholesterolemia, Antidiabetic, Anti-hyperlipidemia, *Bala*, Diabetes mellitus, Oral glucose tolerance test, *Sida cordifolia,* Streptozotocin.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration which is due to insulin deficiency and/or insulin resistance. Hyperglycemia occurs because the liver and skeletal muscle cannot store glycogen and the tissues are unable to take up and utilize glucose[1]. The chronic hyperglycemia is associated with damage, dysfunction and failure of various organs over the long term and causes complications, including retinopathy, nephropathy, neuropathy, angiopathy, hypertension, atherosclerosis, microcirculatory disorders and several others[2,3]. The oxidative stress caused by chronic elevation of glucose levels in diabetes causes oxidative stress and together they lead to protein oxidation, glycation and dyslipidemia[4]. Hyperlipidemia associated lipid disorders plays a significant role in the manifestation and development of premature atherosclerotic cardiovascular disease (CV)[5]. CV diseases are most common cause of mortality and morbidity worldwide[6]. Despite appreciable progress made in the management of diabetes mellitus its complications using conventional treatments, the search for new plant-based anti-diabetic drugs still continues.

Sida cordifolia Linn. (Family—Malvaceae) is native species of the Brazilian North-east, popularly known as *Bala*. Plant is distributed along with other species of this genus throughout the tropical and sub-tropical plains of India[7,8]. The roots, leaves, stem and seeds are used in the folk medicine as antirheumatic, antipyretic[9], laxative, diuretic, anti-inflammatory, analgesic and hypoglycemic[10,11]. It is also used against chronic dysentery, stomatitis and gonorrhoea[12-14]. In Ayurvedic system of medicine, plant is used for the treatment of Parkinson's disease[15] and as an anti-rheumatic agent[16]. The aqueous extract of the whole plant is specifically used in the treatment of rheumatism[13]. Various parts of plant have been previously reported as antiviral, antimicrobial, antifungal and in the treatment of nasal congestion, as aphrodisiac and anti-asthmatic[17], anti-inflammatory, analgesic, antioxidant, hepatoprotective and CNS depressant[18].

Earlier phytochemical studies have demonstrated the presence of different classes of compounds, viz.

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flavones, flavonoids, flavonol glycosides, alkaloids, steroids, amino acids in the genus *Sida*, and the species *S. cordifolia* showed the presence of ephedrine, quinazoline alkaloids e.g. vasicine, vasicinol, vasicinone, along with N-methyl tryptophan[19]. Studies also showed the presence of fatty oils, steroids, resin, resin acids, mucin and potassium nitrate in the plant. Toxicity studies and antidiabetic activity of methanol extract on roots are reported previously[10,20]. Moreover, the aerial parts of the plant are the active ingredient of an Ayurvedic oral antidiabetic formulation, INSOL-N[21]. However, still there is no scientific report on the aerial parts of this plant. Hence, the present study was undertaken to evaluate the antidiabetic potential of the aerial parts of *S. cordifolia* in oral glucose-tolerance test (OGTT) and Streptozotocin (STZ) induced diabetes in rats and compared with clinically available drug Metformin.

Materials and Methods

Plant material

Aerial parts of *S. cordifolia* were procured from Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, Sri Venkateswara University, Tirupati, Andhra Pradesh, India, in October-2008. Botanical identification and authentication were performed at National Institute of Science Communication & Information Resources (NISCAIR), New Delhi. The voucher specimen number NISCAIR/RHMD/ Consult/-2009-10/1280/84 has been preserved in our research laboratory for future reference.

Preparation of extract

The plant material was dried under shade at room temperature and powdered to coarse particles. The powdered plant material (2 kg) was defatted with petroleum ether (60-80°C) in a Soxhlet extraction apparatus and marc was extracted with methanol. Whereas, the aqueous extract was prepared by macerating 1.5 kg of coarsely powdered plant material. The solvents in both the cases were removed using rotatory vacuum evaporator to get methanol and aqueous extracts. The methanol (ME) and aqueous extracts (AE) were dried to constant weight under vacuum and stored in desiccator till further use.

Identification of phytochemical constituents

Preliminary phytochemical screening was carried out on various extracts for the qualitative determination of phytochemical constituents like alkaloids, glycosides, carbohydrates, saponins, proteins and phenols[22].

Test animals

Wistar albino rats of either sex, weighing 180-250 g, were procured from CPCSEA (Reg. No. 816/04/C) approved animal house of I.S.F. College of Pharmacy, Moga. Ethical clearance for performing the experiments on animals was obtained from Institutional Animal Ethics Committee (IAEC). Animals were maintained in the animal house at an ambient temperature of 25-30°C at 12 h dark and light cycle and humidity of 45-60%. The animals were fed with pellet diet (Ashirwad Industries, Ropar, India) and water *ad libitum*.

Chemicals and reagents

Streptozotocin was procured from Sigma Chemical Co. (St Louis, MO, USA); glucose oxidase/peroxidase (GOD/POD) kits were purchased from Coral Company, Goa, India. Metformin was procured from Zen labs, Chandigarh, India. All other chemicals and reagents were of highest commercial grade available.

Extract and drug administration

The quantities of the individual extracts to be administered were calculated and suspended in vehicle (1% w/v suspension of CMC in water). The extract was administered using an infant feeding tube.

Studies in normal rats

Oral Glucose Tolerance Test (OGTT) in normal rats

The oral glucose tolerance test (OGTT) was performed for different extracts of aerial parts of *S. cordifolia* at different dose levels, viz. ME (500, 750 and 1000 mg/kg b.w.) and AE (500, 750 and 1000 mg/kg b.w.) orally. The serum glucose level for all the groups were estimated prior to the administration of test materials and reference drug (Metformin, 500 mg/kg)[23] and were considered as basal readings. Immediately after blood withdrawal, all the experimental groups were administered with respective test materials and reference drug. The serum glucose level was estimated after 1 h of drug administration to evaluate the hypoglycaemic effect of test materials and reference drug in normal rats and these readings were considered as the readings of 0 min. Glucose (1.5 g/kg) was loaded in all the groups at 0 min. Further, the glucose level was measured at the intervals of 30, 60, and 120 minutes.

Studies in diabetic rats

Induction of experimental diabetes

The animals were fasted for 12 h and made diabetic by injecting Streptozotocin (STZ) at the dose of

45 mg/kg of the body weight intravenously. STZ was freshly dissolved in 0.05 M citrate buffer (*p*H 4.5) immediately before administration because of the instability of STZ in aqueous medium. The rats were allowed to drink 5% glucose solution overnight to overcome the drug-induced hypoglycaemia. Diabetic state was confirmed on the seventh day and rats with fasting serum glucose (FSG) levels > 250 mg/dl were considered to be diabetic. The treatment with test drug and standard drug (Metformin 500 mg/kg)[23] were started on the seventh day after STZ injection, which was considered as first day of the treatment[24].

Experimental design

Studies on Streptozotocin-induced diabetic rats

The rats were divided into six groups comprising of six animals each (n=6).

Group 1: Normal control; normal rats received 1% w/v CMC, orally for 21 days,

Group 2: Diabetic control; diabetic rats received 1% w/v CMC, orally for 21 days,

Group 3: Test I; diabetic rats treated with Metformin (500 mg/kg, orally) in aqueous solution for 21 days,

Group 4: Test II; diabetic rats treated with AE (1000 mg/kg, orally) suspended in 1% w/v CMC solution for 21 days.

Collection of blood and tissues samples

Blood samples (1.5 ml) were collected by retro-orbital plexus under mild anaesthesia and allowed to clot and were centrifuged at 3000 rpm for 15 min. The serum was separated and used for the biochemical estimations[25]. The animals were sacrificed by overdose of anaesthetic ether after 21 days of daily treatment of extract and Metformin orally and tissue samples were collected.

Biochemical estimations and body weight

The serum glucose level in OGTT and serum glucose level, lipid profile and liver glycogen in STZ-induced diabetic model were evaluated. Serum glucose level was estimated by GOD/POD method[26]. Serum lipid profile including total cholesterol (CHOD/PAP method), triglycerides (GPO/PAP method), HDL cholesterol (PEG Precipitation method), LDL cholesterol[27] and VLDL cholesterol were estimated[28], liver glycogen level in tissues[29] was also measured. In order to detect any changes in body weight, animals were weighed on 0, 7th, 14th and 21st day[30].

Calculations

Percent variation of blood glucose was calculated for each group in OGTT and STZ-induced diabetic model using following formula:

$$\%\,\text{var}\,iation\,of\ blood\ glu\cos e = \frac{Gt - Gi}{Gi} \times 100$$

Where G_i and G_t were the values of initial glucose concentration (0 min in OGTT and 0 day in STZ-induced diabetes model) and glucose concentration at different intervals (30, 60 and 120 min in OGTT and 7th, 14th and 21th day in STZ induced diabetic model), respectively[31].

Statistical analysis

Data was analyzed using one way analysis of variance test (ANOVA) followed by Tukey's multiple comparison test. $P<0.05$ were considered statistically significant.

Results

Phytochemical screening

The percentage yields of the ME and the AE were 10.79 and 19.91% w/w, respectively. The ME extract revealed the presence of alkaloids, glycosides and steroids and traces of phenolic compounds. Whereas, the AE showed the presence of carbohydrates, alkaloids, glycosides, amino acids and phenolic compounds (flavonoids).

Studies in normal rats

Oral glucose tolerance test

The serum glucose level, after oral administration of glucose in normal control and treated rats are given in Table 1. Neither the reference drug (metformin) nor the test drugs (ME and AE) showed any hypoglycaemic effect in normal rats as evident by basal to 0 min. readings. In the normal control rats, the glucose induced hyperglycemia reached maximum during 60 min and returned back near to the normal levels after 120 minutes. Whereas, all the test drugs at different dose levels and metformin drastically depressed the peak of blood glucose level at 60 min after glucose loading (Table 1). These changes in glucose levels were significant *(P*<0.05*)* versus normal control. There was a significant (*P*<0.05) decrease of glucose level as the dose of ME and AE increased from 750 to 1000 mg/kg. AE at the dose of 1000 mg/kg showed the maximum tolerance for glucose, suggesting secretion of insulin in

Table1—Effect of the ME and AE on serum glucose levels on glucose loaded normal rats (OGGT study)

Groups	Serum glucose level (mg/dl)			
	Basal	0 min	60 min	120 min
Normal Control	94.55 ± 2.57	92.64 ±2.25	143.91 ± 2.96 (↑35.62%)	89.79 ± 6.74
Test I (ME 500 mg/kg)	88.04 ± 5.74	82.80 ± 5.98	113.79 ± 5.73 (↑27.23%)	92.35 ± 6.52
Test II (ME 750 mg/kg)	88.40 ± 4.79	80.78 ± 5.03	105.81 ± 9.22 (↑23.65)[a]	87.62 ± 6.42
Test III (ME 1000 mg/kg)	94.12 ± 6.20	84.57 ± 5.00	107.1 ± 5.89 (↑21.03%)[a]	88.85 ± 7.44
Test IV (AE 500 mg/kg)	93.40 ± 6.10	89.44 ± 6.36	119.46 ±92.35 (↑24.87%)	92.35 ± 5.60
Test V (AE 750 mg/kg)	92.37 ± 6.00	84.02 ± 5.35	104.63 ± 6.59 (↑19.69%)[a]	92.21 ± 6.52
Test VI (AE 1000 mg/kg)	96.25 ± 4.28	87.30 ± 4.48	104.14 ± 7.81 (↑16.17%)[a]	83.84 ± 6.14
Test VII (MF 500 mg/kg)	90.44 ± 6.04	78.01 ± 4.74	95.83 ± 5.52 (↑18.59%)[a]	91.36 ± 4.91

MF = Metformin; All values represent means ±S.D. of the mean (n=6); a = $P< 0.05$ vs normal control group

Table 2—The effects of 3 weeks treatment of AE (1000 mg/kg) and of MF (500 mg/kg) on serum glucose level in STZ induced diabetic rats

Groups	0 day	7th day	14th day	21st day
Normal Control	90.37±5.20	91.35±4.42	90.43±5.23	91.97±8.40
Diabetic Control	277.92±8.45[a]	287.31±6.26[a]	296.43±6.91[a]	312.27±7.57[a]
Test I (AE 1000 mg/kg)	257.67±5.78	220.42±6.58[b] (↓14.45%)	165.75±4.53[b] (↓35.67%)	121.39±8.02[b] (↓52.88%)
Test II (MF 500 mg/kg)	190.71±5.68[b]	109.09±6.17[b] (↓42.79%)	105.76±5.90[b] (↓42.97%)	102.87±6.60[b] (↓46.05%)

MF = Metformin; All values represent means ± S.D. of the mean (n=6); a = $P< 0.05$ vs normal group; b = $P< 0.05$ vs diabetic control group

Table 3—Effect of the AE treated rats at the dose of 1000 mg/kg on body weight in STZ induced diabetic rats

Groups	0 day	7th day	14th day	21st day
Normal Control	210.5±7.12	215±6.34	214.0±4.85	217±5.09
Diabetic Control	196.66±6.53[a]	171.5±9.16[a] (↓12.79%)	148.5±9.85[a] (↓24.48%)	106.33±8.89[a] (↓45.93%)
Test I (AE 1000 mg/kg)	171.83±6.24	164±6.74 (↓4.55%)	159.16±5.11[b] (↓7.37%)	156.5±5.20[b] (↓8.92%)
Test II (MF 500 mg/kg)	189.0±11.15	181.66±11.44 (↓3.9%)	177.83±9.32 (↓5.92%)	175±8.19[b] (↓7.40%)

MF = Metformin; All values represent means ±S.D. of the mean (n=6); a = $P< 0.05$ vs normal group; b = $P< 0.05$ vs diabetic control group

response to hyperglycemia (glucose load) and increased peripheral utilization of glucose and hence selected for further study in STZ-induced diabetic rat model.

Studies in diabetic rats

Fasting serum glucose level

The administration of streptozotocin increase the serum glucose levels in time-dependent manner; this increase in glucose level was approx. 67.50% ($P<0.05$) in comparison to normal control rats. Effect of oral treatment with the AE on FSG level of experimental rats is shown in Table 2. Three weeks of daily oral treatment of AE (1000 mg/kg) and metformin (500 mg/kg) produced a significant reduction in the FSG level in diabetic rats ($P<0.05$). The reduction in FSG level with AE and metformin was about 14.45, 35.67, 52.88 and 42.79, 42.97, 46.05%, respectively on 7th, 14th and 21st day.

Body weight

Normal control animals were found to be stable in their mean body weight but diabetic rats showed significant ($P<0.05$) reduction in their body weight during the study. STZ mediated body weight reduction was significantly ($P<0.05$) reversed by the three weeks daily oral treatment of AE at the dose level 1000 mg/kg. Results are shown in Table 3.

Lipid profile level

The results obtained reveal significant increased in serum cholesterol, triglycerides, LDL-C and VLDL-C and decreased serum HDL-C in diabetic control group over a period of 21 days. The hypolipidemic profile observed with extract was similar to that seen with reference drug, metformin. The three weeks treatment with AE (1000 mg/kg) showed a significant reduction in cholesterol, triglycerides, LDL-C and VLDL-C in treated rats when compared with the diabetic control ($P<0.05$). HDL-C was significantly improved by

Table 4—Effect of AE (1000 mg/kg) and MF (500 mg/kg) on serum cholesterol, triglycerides, HDL-C, VLDL-C, LDL-C levels and tissue glycogen level after treatment for 21 days in diabetic rats

Groups	Total Cholesterol level (mg/dl)	Triglycerides level (mg/dl)	HDL-C level (mg/dl)	LDL-C level (mg/dl)	VLDL-C level (mg/dl)	Tissue glycogen level (mg/g of tissue)
Normal Control	99.81±5.87	63.57±5.95	38.15±6.71	49.02±8.52	12.71±1.19	48.93±4.78
Diabetic Control	253.09±8.84[a]	145.24±9.33[a]	21.84±4.58[a]	202.20±14.45[a]	29.04±1.86[a]	17.78±1.88[a]
Test I (AE 1000 mg/kg)	139.65±5.17[b]	96.61±6.16[b]	33.50±3.98[b]	86.83±11.19[b]	19.32±1.23[b]	34.41±2.37[b]
Test II (MF 500 mg/kg)	113.80±6.86[b]	81.13±6.28[b]	37.46±4.52[b]	60.27±7.24[b]	16.22±1.24[b]	42.27±2.77[b]

MF = Metformin; All values represent means ±S.D. of the mean (n=6); a = $P< 0.05$ vs normal group; b = $P< 0.05$ vs diabetic control group

treatment of extract. The reference drug, at a dose of 500 mg/kg for three weeks also lowered serum cholesterols and triglycerides significantly but did not bring them to baseline values and HDL-C was effectively increased than the normal group (Table 4).

Glycogen level

The diabetic control group showed significant (P<0.05) decrease in tissue glycogen level. However, after three weeks of treatment with AE (1000 mg/kg), liver glycogen level was significantly (P<0.05) increased with respect to diabetic control group but this was not restored to the normal group glycogen level. Results are shown in Table 4.

Discussion

Pancreas is the primary organ involved in sensing the organism's dietary and energetic states via glucose concentration in the blood and in response to elevated blood glucose; insulin is secreted[2,20]. STZ causes a massive reduction in insulin release by the destruction of β-cells of the islets of Langerhans. An insufficient release of insulin, that leads high blood glucose namely hyperglycemia[32]. Insulin deficiency leads to various metabolic alterations in the animals, viz. increased blood glucose, increased cholesterol and transaminases[33].

The fundamental mechanism underlying hyperglycemia in diabetes mellitus involves over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues[34]. In the present study the hypoglycemic and anti-hypercholestremic activity of ME and AE was evaluated in normal (OGTT) and AE in STZ-induced diabetic rats, respectively. The activity exhibited was compared with the standard antihyperglycemic drug (metformin). Increasing doses of the hydroalcoholic extract of plant up to 5 g/kg b.w. administered orally to mice were not lethal, which is an indication of the nontoxic nature of the extract[20]. In normal rats, from basal to 0 min (Table 1), the extract did not show significant reduction in the FSG level which evident it as non-hypoglycemic agent in normal rats. Whereas, multiple-dose study in OGTT study with ME and AE demonstrated significant decrease in serum glucose level and the maximum reduction of serum glucose level occurred with AE at the dose of 1000 mg/kg, orally. Daily treatment with the AE for a period of 21 days showed a significant decrease (P<0.05) in the FSG glucose level at 7th, 14th and 21st days and maximum reduction occurred at 14th and 21st days in diabetic rats. It is evident from these investigations that the aqueous extract is effective in maintaining the serum glucose levels in normal glucose loaded and STZ-induced diabetic rats.

The failure of STZ-induced diabetic rat to gain weight has already been reported[35]. During the 21-day experimental period the body weight was reduced in diabetic rats, whereas there was a significant (P<0.05) gain of body weight in treated rats. The administration of AE check the loss in body weight and restored these levels significantly (P<0.05) towards normal. The ability of the AE to restore body weight seems to be a result of its ability to reduce hyperglycemia by increased glucose metabolism[36]. This may also be due to the protective effect of the extract in controlling muscle wasting i.e. reversal of gluconeogenesis.

It is well known that in uncontrolled diabetes mellitus, there will be an increase in total cholesterol, triglycerides and LDL-C associated with decrease in HDL-C and contributes to coronary artery disease[37]. In the present study the total cholesterol, triglycerides and LDL-C were increased significantly (P<0.05) in diabetic control groups and these were significantly (P<0.05) reduced in 21 days treatment with AE as well as the HDL-C level was significantly increased (P<0.05). The hypocholesterolemic effect may be due to inhibition of fatty acid synthesis[38]. In normal metabolism insulin activates the enzyme lipoprotein

lipase and hydrolyses triglycerides and the deficiency in insulin results in inactivation of these enzymes thereby causing hypertriglyceridemia. The significant reduction of serum lipid levels in diabetic rats after AE treatment may be directly attributed to improvements in insulin levels or the extract may inhibit the pathway of cholesterol synthesis and this may be due to the activation of LDL receptors in hepatocyte which is responsible for taken up LDL into the liver and reduce the serum LDL level[39].

Insulin is the main regulator for glycogenesis in liver. The decrease of liver glycogen observed in this study may be due to lack of insulin in diabetic state[32] or oxidative stress by diabetes may inactivate the glycogen synthetase. After 21 days treatment with AE the liver glycogen level was significantly (P<0.05) elevated and this may be due to three possible way of antidiabetogenic action, one possible way may be increased insulin level. Other possible ways may be by preventing the inactivation of the glycogen synthetase and by synthesize the glycogen synthetase[40].

The literature indicates liver regeneration potential of *S. cordifolia* (leaf) aqueous extract[41]. The improvement of liver function and subsequent increase in uptake of blood glucose and its utilization may be another mechanism of action of the extract. Other possible mechanism includes the stimulation of β-cells and subsequent release of insulin and activation of the insulin receptors. Estimation of insulin level and insulin receptor may give more insight into the mechanism of the antidiabetic activity exhibited by the extract. The studies also reveal that alkaloids and flavonoids present in the plant extract known to possess antidiabetic activity[42]. In the present investigation also the observed antidiabetic potential of test extract may be due to presence of similar phytoconstitutes which was evident by preliminary phytochemical screening.

Conclusion

On the basis of the aforementioned results, we concluded that AE has beneficial effects on serum glucose levels as well as improving hypercholesterolemia and other metabolic aberrations as it lowers blood glucose level in normal glucose loaded and diabetic rats and significantly increases glucose tolerance. Therefore, this medicinal plant is considered to be effective and alternative treatment for diabetes. Further pharmacological and biochemical investigations will clearly elucidate the mechanism of action and the molecule(s) responsible for such an effect and will be helpful in projecting this plant as a therapeutic target in diabetes research.

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