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Research Article

ANTIDIABETIC ACTIVITY OF *CLERODENDRUM SERRATUM (L.)* MOON LEAVES IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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ABSTRACT

Objective: The present study has been undertaken to evaluate the antidiabetic activity of Clerodendrum serratum leaves.

Methods: The fresh leaves were collected from Khandagiri hills of Khurda district in the state of Odisha, India and extracted successively with n-hexane, methanol, and water. The effect of extracts at the dose level of 400 mg/kg body weight was studied in normal, glucose-loaded, and streptozotocin (STZ)-induced diabetic rats along with glucose utilization potential in rat hemi-diaphragm.

Results: The test extracts showed a significant reduction of blood glucose level in normal, glucose-loaded, and STZ-induced diabetic rats and also exhibited better glucose utilization by isolated rat hemi-diaphragm. Methanol extract demonstrated maximum blood glucose lowering potential as compared to other extracts.

Conclusion: The leaf of C. serratum (L.) Moon is endowed with blood sugar lowering potential in both normal and diabetic rats.

Keywords: Clerodendrum serratum (L.) moon, Antidiabetic activity, Streptozotocin, Glucose-uptake.

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by hyperglycemia with derangement of carbohydrate, lipid and protein metabolisms resulting from defective insulin secretion, insulin action, or both. Insulin deficiency and/or insulin resistance is associated with the pathogenesis of diabetic dyslipidemia and micro/macrovascular complications [1]. DM is a common health problem worldwide, and the prevalence of this disease is rapidly increasing, the number of people with diagnosed diabetes is projected to increase by 165% from the year 2000 to 2050. The vast majority of these cases will be of Type 2 DM (non-insulin-dependent DM) [2]. In spite of the availability of various anti-hyperglycemic agents, diabetes and its secondary complications continue to be a major problem in the world population. Medicinal plants and their bioactive constituents are used for the treatment of diabetes throughout the world and popular as nutraceutical. Many indigenous medicinal plants have been found to be useful to successfully manage diabetes [3,4]. The synthetic drugs are either too expensive or have undesirable side effects or contraindications [5]. Therefore, the search for more effective and safer hypoglycemic agents has continued to be an area of active research [6].

Clerodendrum serratum Linn. belongs to family Verbenaceae is a shrub widely distributed in tropical and subtropical regions of the world. It is commonly known as Blue Glory (English), Bharangi (Sanskrit) and Chinds in the state of Odisha, India. Ethno-medicinal importance of the plant has been reported in various indigenous systems of medicines such as Ayurveda, Siddha, and Unani for the treatment of various life-threatening diseases [7]. Leaves of C. serratum have been used as traditional medicine for treatment of cancer [8], malaria, stomach upset, labor pain [9], high fever, cough [10], etc. The root is used for treatment of rheumatism [11], dropsy [12], typhoid [13], asthma [14]. The methanol extract of C. serratum leaves exhibited antioxidant, antiangiogenic, and vasorelaxant activities [15]. The ethanol extract of C. serratum roots showed hepatoprotective [16], antibacterial [17] and antiasthmatic activity [18]. Different species of Clerodendrum like C. viscosum, C. phlomoides, C. capitatum, C. inerme, C. multiforum, and C. philippinum are reported to have antidiabetic property [19-24]. The present study has been undertaken to evaluate the antidiabetic activity of C. serratum leaves.

METHODS

Chemicals

Streptozotocin (STZ) and glibenclamide were procured from SIGMA-Aldrich, Mumbai. All other chemicals and reagents used were of analytical grade.

Plant material and extraction

The fresh plant parts (leaves) were collected during the month of September, 2010 from Kuruan village of Jajpur district in the state of Odisha, India. The taxonomic identity of the plant was confirmed by Dr. K. B. Satapathy, P.G. Department of Botany, Utkal University and the voucher specimen (SVN-535) was deposited at the departmental herbarium. The collected leaves were washed under running tap water to remove the surface pollutants. The plant material was air dried under shade. The dried sample was powdered and extracted successively with n-hexane, methanol, and water using Soxhlet apparatus. Finally, the extracts were concentrated by evaporating the solvent using rotary evaporator and kept inside the desiccator for further studies. The yield of n-hexane, methanol, and aqueous extracts were 4.16%, 14.82%, and 21.67% w/w, respectively.

Preliminary phytochemical analysis of extracts

Qualitative chemical tests were carried out in order to identify the phytoconstituents present in various extracts [25].

Animals

Healthy adult Wistar albino rats of either sex (150-200 g body weight) from animal house of School of Pharmaceutical Sciences (SPS), S'O'A University, Bhubaneswar were used for the study. Rats were housed in polypropylene cages with standard environmental condition (temperature 25±2°C, relative humidity 55±10% and 12:12 light: Dark cycle). They were fed on a standard pellet diet and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics

Committee vide proposal No. 23/11, dated 24/01/2012 of SPS, S'O'A University, Bhubaneswar bearing Registration No. 1171/c/08/CPCSEA.

Acute oral toxicity study

Healthy adult female Wistar albino rats starved overnight were divided into eight groups, each consisting four rats and were orally fed with the test extracts in increasing dose levels of 500, 1000, 2000, and 4000 mg/kg body weight. The acute toxicity study was carried out according to OECD guidelines 425. The rats were observed continuously for 2 hr under the following profiles [26]:

I. Behavioral profile: Alertness, restlessness, irritability, and fearfulness
II. Neurological profile: Spontaneous activities, reactivity, touch response, pain response, and gait
III. Autonomic profile: Defecation and urination.

After a period of 24 hr, 72 hr and 14 days, the rats were observed for any lethality or death.

Induction of diabetes

Experimental diabetes was induced by single intra-peritoneal injection of 55 mg/kg of STZ, freshly dissolved in cold citrate buffer, pH 4.5. After 5 days of STZ injection, rats with fasting blood glucose above 250 mg/dl were considered as diabetic and included in the study [27].

Effect of extracts on normoglycemic rats

The effect of extracts on blood glucose level was studied in normal rats [28]. The rats were divided into five groups of six rats each and fasted for 12 hr with free access of water. The treatments were made orally as: Group I: Solvent control (Tween 40 + distilled water); Group II: Glibenclamide (2.5 mg/kg); Group III: n-hexane extract (400 mg/kg); Group IV: Methanol extract (400 mg/kg); Group V: Aqueous extract (400 mg/kg). The blood glucose level was estimated using gluco-monitor (Contour TS, Bayer HealthCare Limited) by puncturing the tail vein at 0, 1, 2, 4, 6, 8, and 10 hr following the treatment.

Effect of extracts on glucose loaded hyperglycemic rats

The rats were ingested with glucose (2 g/kg) in distilled water, 30 minutes following the administration of the test substances by gastric intubation. The treatments were made orally as: Group I: Solvent control (Tween 40 + distilled water); Group II: Glibenclamide (2.5 mg/kg); Group III: n-hexane extract (400 mg/kg); Group IV: Methanol extract (400 mg/kg); Group V: Aqueous extract (400 mg/kg). The blood glucose level was measured at 1, 2, and 4 hr following the administration of test substances.

Effect of extracts on STZ induced diabetic rats

The effect of extracts on blood glucose level was studied in STZ-induced diabetic rats. The diabetic rats were divided into seven groups of six rats each and fasted for 12 hr with free access of water. The treatment for the studies was made orally as: The treatments were made orally as: Group I: Solvent control (Tween 40 + distilled water); Group II: Glibenclamide (2.5 mg/kg); Group III: n-hexane extract (400 mg/kg); Group IV: Methanol extract (400 mg/kg); Group V: Aqueous extract (400 mg/kg). The blood glucose level was estimated at 0, 1, 2, 4, 6, 8, and 10 hr following the treatment.

Effect of extracts on glucose utilization

Effect of extracts on glucose utilization by rat hemi-diaphragm was estimated using insulin (Biocon Ltd.) as a positive control group. Glucose uptake per gram of tissue was calculated as the difference between the initial and final glucose content in the incubated medium. The healthy rats were killed by decapitation and diaphragm was taken out quickly avoiding trauma and divided into two halves. The hemi-diaphragms were then placed in culture tubes containing 2 ml tyrode solution with 2 g% glucose and incubated for 30 minutes at 37°C in an atmosphere of 95% O_2-5% CO_2 with shaking. Eight sets of experiments were performed. The diaphragms were exposed to tyrode solution with 2 g% glucose, which served as control (Group I), tyrode solution with 2 g% glucose + insulin (0.25 IU/ml) as Group II, tyrode solution with 2 g% glucose + n-hexane extract (400 mg/ml) as Group III, tyrode solution with 2 g% glucose + methanol extract (400 mg/ml) as Group IV, tyrode solution with 2 g% glucose + aqueous extract (400 mg/ml) as Group V, tyrode solution with glucose (2 g%) + insulin (0.25 IU/ml) + n-hexane extract (400 mg/ml) as Group VI, tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml) + methanol extract (400 mg/ml) as Group VII, tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml) + aqueous extract (400 mg/ml) as Group VIII.

Statistical analysis

The results are expressed as mean ± standard error of the mean. The statistical analysis is carried out using one-way ANOVA followed by Dunett's t-test. Statistical $p<0.05$ is considered as significant.

RESULTS

Preliminary phytochemical screening

The study indicates the presence of alkaloids, steroids, triterpenoids in n-hexane extract; alkaloids, flavonoids, glycosides, phenolic compounds, steroids, triterpenoids in methanol extract and flavonoids, glycosides, phenolic compounds, saponins in aqueous extract.

Acute oral toxicity study

The gross observational results revealed that the extracts of *C. seratum* leaves did not show any sign of toxicity and mortality up to 14 days of the study in the dose level of 4000 mg/kg and hence the dose of the extracts for animal study is fixed with 400 mg/kg.

Effect of extracts on normoglycemic rats

The effect of extracts on blood glucose level of normal rats is presented in Table 1. The test extracts at 400 mg/kg body weight showed a significant fall of blood glucose level when compared with solvent control group at the end of 10 hr. Among them, methanol extract exhibited the highest reduction of blood glucose level with the percentage reduction of 33.16 ($p<0.001$) followed by aqueous extract of 24.96 ($p<0.01$) and n-hexane extract 16.07 ($p<0.05$).

Effect of extracts on glucose loaded hyperglycemic rats.

As per the result depicted in Table 2, methanol and aqueous extracts showed 41.10% and 32.91% ($p<0.001$) fall of blood glucose level, respectively, at 4 hr following the administration of test substances. Methanol extract exhibited maximum reduction of blood glucose and better glucose tolerability among all the extracts.

Effect of extracts on STZ induced diabetic rats

The result of extracts on STZ-induced diabetic rats revealed that methanol extract exhibited highest reduction of blood glucose level with the percentage reduction of 56.01 followed by aqueous extract of 42.89 and n-hexane extract 32.52 at 10 hr after administration of test substances when compared with 0 hr (Table 3).

Effect of extracts on glucose utilization by isolated rat hemi-diaphragm

The *in vitro* study of the extracts on glucose utilization by isolated rat hemi-diaphragm suggested that glucose uptake was maximum with methanol extract ($p<0.001$) followed by aqueous extract ($p<0.01$). Test substances also exhibited significant results when exposed in addition with Insulin (Table 4).

DISCUSSION

This study was undertaken to evaluate the hypoglycemic activity of *C. serratum* in normal, glucose-loaded hyperglycemic and STZ-induced diabetic rats. Sulfonylureas like glibenclamide are commonly used as a standard antidiabetic drug in STZ-induced diabetes to compare the efficacy of a variety of anti-hyperglycemic compounds [29]. In normoglycemic rats, the test extracts showed significant and progressive fall of blood glucose level till the end of 10 hr. From the result of the study, it is concluded that methanolic extract showed maximum fall of blood sugar level compared to other test extract. When test extracts

Table 1: Effect of *C. serratum* leaves on normoglycemic rats

Groups and treatments	Blood glucose levels (mg/dl)							
	0 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	% age decrease at the end of 10 hrs
Solvent control (Tween+Water)	102.5±5.01	101.16±5.95	101.83±4.50	99.83±4.16	98.16±4.63	96.33±4.28	95.83±3.95	-
Glibencamide (10 mg/kg)	99.83±4.96	89.83±4.11	78.16±3.56[b]	65.33±3.40[c]	61.66±2.90[c]	58.16±2.72[c]	54.16±3.95[c]	45.74
n-hexane extract (400 mg/kg)	97.66±4.21	98.16±5.44	99.5±4.25	94.33±5.03	88.33±4.81	81.66±5.48[a]	81.83±4.96[a]	16.07
Methanol extract (400 mg/kg)	98.5±4.19	93.5±3.93	84.16±3.85[a]	74.83±3.64[b]	69.66±3.78[c]	65.5±3.31[c]	65.83±4.04[c]	33.16
Aqueous extract (400 mg/kg)	96.83±4.62	97.33±5.40	91.33±4.76	83.16±4.62[a]	77.83±4.72[b]	75.16±4.97[b]	72.66±4.77[b]	24.96
$F_{(4,25)}$	-	0.76	5.65**	11.09**	11.74**	11.90**	14.63**	

Values are expressed in mean±SEM of six animals. One-Way ANOVA followed by Dunnet's t-test, (F-value denotes statistical significance at *p<0.05, **p<0.01), (t-value denotes statistical significance at [a]p<0.05, [b]p<0.01 and [c]p<0.001, respectively, in comparison to Group-I, SEM: Standard error of the mean, C. serratum: Clerodendrum serratum

Table 2: Effect of *C. serratum* leaves on glucose-loaded hyperglycemic rats

Groups and treatments	Blood glucose levels (mg/dl)				
	Pre-treatment	Post-treatment			
		1 hr	2 hrs	4 hrs	% age decrease at the end of 4 hrs
Solvent control (Tween+Water)	68.5±2.99	155.33±4.69	139.16±4.80	132.16±5.98	
Glibencamide (10 mg/kg)	72.66±3.59	136.16±4.56[a]	98.66±3.43[c]	66.83±2.79[c]	50.91
n-hexane extract (400 mg/kg)	73.83±3.81	149.16±4.26	126.5±5.29	120.66±6.18	19.10
Methanol extract (400 mg/kg)	71.16±3.95	139.5±4.29[a]	109.83±4.46[b]	82.16±4.60[c]	41.10
Aqueous extract (400 mg/kg)	74.66±4.18	145.83±4.28	117.33±5.34[b]	97.83±5.17[c]	32.91
$F_{(4,25)}$		2.94*	10.78**	27.81**	-

Values are expressed in mean±SEM of six animals. One-way ANOVA followed by Dunnet's t-test, (F-value denotes statistical significance at *p<0.05, **p<0.01), (t-value denotes statistical significance at [a]p<0.05, [b]p<0.01 and [c]p<0.001, respectively, in comparison to Group I, SEM: Standard error of the mean, C. serratum: Clerodendrum serratum

Table 3: Effects of *C. serratum* leaves on STZ-induced diabetic rats

Groups and treatments	Blood glucose levels (mg/dl)							
	0 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	% age decrease at the end of 10 hrs
Solvent control (Tween+Water)	302.83±9.29	298.16±8.43	293.66±8.42	301.83±9.56	293.33±10.99	296.83±10.31	298.5±12.62	-
Glibencamide (10 mg/kg)	299.66±6.61	241.33±7.72[b]	174.66±8.46[c]	146.33±9.81[c]	122.5±8.24[c]	111.83±6.58[c]	104.66±6.16[c]	65.07
n-hexane extract (400 mg/kg)	293.66±9.87	291.16±0.79	269.83±9.47	251.66±10.37[b]	228.66±8.65[c]	212.5±8.46[c]	198.16±8.55[c]	32.52
Methanol extract (400 mg/kg)	296.33±9.58	249.83±10.68[b]	213.33±9.67[c]	183.5±9.37[c]	159.83±8.97[c]	141.33±8.01[c]	130.33±7.78[c]	56.01
Aqueous extract (400 mg/kg)	289.5±9.84	266.5±10.53[a]	248.33±11.26[b]	227.16±11.24[c]	196.66±10.21[c]	179.66±11.68[c]	165.33±10.48[c]	42.89
$F_{(4,25)}$	-	6.56**	24.36**	35.50**	47.82**	64.05**	64.37**	-

Values are expressed in mean±SEM of six animals. One Way ANOVA followed by Dunnet's t-test, (F-value denotes statistical significance at *p<0.05, **p<0.01), (t-value denotes statistical significance at [a]p<0.05, [b]p<0.01 and [c]p<0.001, respectively, in comparison to Group II, SEM: Standard error of the mean, C. serratum: Clerodendrum serratum, STZ: Streptozotocin

were administered to glucose loaded normal rats (OGTT), reduction in blood glucose levels was observed after 60 minutes in case of methanol extract and standard. The decline reached its maximum at 4 hr where both methanol and aqueous extract showed a significant reduction in blood glucose level, out of which methanol extract exhibited maximum improvement in glucose tolerance.

The hypoglycemic activity of the methanol extract was compared with glibenclamide, a standard hypoglycemic drug. The perusals of Tables 1-3 reveal that the extract produced significant decrease in the blood glucose level when compared with the controls in normoglycemic, STZ-induced hyperglycemic and glucose-loaded rats in the single dose treatment study at tested dose levels. This might suggest that the said effect is due to extraintestinal action of the test extract [30]. The blood glucose lowering ability of the test extracts showed encouraging result among which methanol extract showed maximum potency. In vitro study showed an increased utilization of the glucose by hemi-diaphragm in presence of different extracts which suggest that test extracts had some extra pancreatic mechanism like glucose uptake by peripheral tissues. Moreover, methanolic extract also showed more pronounced effect in the presence of insulin compared to the positive control group which signifies the interaction between extract and insulin suggesting secretagogue action of the test substances. The possible mechanism might be the potentiation of pancreatic secretion of insulin from existing β-cells of islets, as was evident by the significant increase in glucose utilization by skeletal muscle of the hemi-diaphragm.

CONCLUSION

The experimental results of the present investigation conclude that the extracts of C. serratum are endowed with antidiabetic potential.

Table 4: Effect of *C. serratum* leaves on glucose-uptake by isolated rat hemi-diaphragm

Groups, treatments and incubation medium	Glucose uptake (mg/g/30 minutes)
Tyrode solution with glucose (2 g%)– Solvent control	2.48±0.35
Tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml)	7.06±0.29[c]
Tyrode solution with glucose (2 g%) + n-hexane extract (400 mg/ml)	3.11±0.34
Tyrode solution with glucose (2 g%) + Methanol extract (400 mg/ml)	5.21±0.29[c]
Tyrode solution with glucose (2 g%) + Aqueous extract (400 mg/ml)	4.21±0.30[b]
Tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml)+n-hexane extract (400 mg/ml)	7.34±±0.26[c]
Tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml)+Methanol extract (400 mg/ml)	8.76±0.28[c]
Tyrode solution with glucose (2 g%) + Insulin (0.25 IU/ml)+Aqueous extract (400 mg/ml)	7.91±0.30[c]
F (7,40)	13.47**

Values are expressed in mean±SEM of six observations. One-way ANOVA followed by Dunnet's t-test. F-value denotes statistical significance at *p<0.05, **p<0.01 and t-value denotes statistical significance at [a]p<0.05, [b]p<0.01 and [c]p<0.001, respectively, in comparison to solvent control, SEM: Standard error of the mean, C. serratum: Clerodendrum serratum

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