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Original Article

ANTIDIABETIC ACTIVITY OF *CLERODENDRUM PHILIPPINUM* SCHAUER 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 philippinum* Schauer leaves.

Methods: The fresh leaves were collected from Kuruan village of Jajpur 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-induced diabetic rats.

Results: The test extracts showed significant reduction of blood glucose level in normal, glucose loaded and streptozotocin-induced diabetic rats. Methanol extract demonstrated maximum blood glucose lowering potential as compared to other extracts.

Conclusion: The leaf of *Clerodendrum philippinum* Schauer is endowed with blood sugar lowering potential in both normal and diabetic rats.

Keywords: *Clerodendrum philippinum* Schauer, Antidiabetic activity, Streptozotocin.

INTRODUCTION

Clerodendrum philippinum Schauer (Synonym: *Clerodendrum fragrans* Willd.) belongs to family Verbenaceae, is a semi woody shrub distributed in southern Asia. It is commonly known as Chinese glory tree, Scent malli and Brajamalli in the state of Odisha, India. It grows wild, spreads vegetative and is also grown as ornamental [1, 2]. Various species of *Clerodendrum* are used as folk and traditional medicines in various parts of the world like India, China, Korea, Japan, Thailand, Africa etc. and are reported to be used for the remedial purpose in inflammatory disorders, diabetes, cancers, malaria, fever, etc [3].

Leaves of *C. Philistinism has* been used as traditional medicine for treatment of colic pain and exhibited anti-fungal activity [4]. The dried root is used as an anti-inflammatory [5] and for myalgia, tinea and rheumatoid arthritis [6]. The seed is used in constipation [7]. The water and ethanol extracts of leaf show anti-fungal [8] and ethanol extract possesses antibacterial activity [1]. The ethanol extracts of flower exhibits anti-anxiety and CNS depressant properties [9]. The leaf juice is used externally for scabies, cuts and burns [10]. The leaf juice mixed with the equal amount of 'tulsi' (*Ocimum sanctum*) juice is used to reduce sugar content in blood by tribal and rural people in the state of Odisha, India [2].

The major chemical constituents reported from *Clerodendrum philippinum* are phenolics, flavonoids, terpenoids, steroids, etc. Flavones such as Cirsimaritin and Sorbifolin were isolated from the leaf and stem [11]. Flavone, 5-7-8-Trihydroxy-4-Methoxy [12] and Kaempferol [13] were isolated from the dried leaf. Phenolic compounds, Acteoside, Leucosceptoside A, Isoacteoside, Methyl and Ethyl esters of Caffeic acid, Jinoside, etc. were reported from the whole plant [13].

Toubi *et al.* [14] isolated Bascoside, Derhamnosyl, Verbascoside, Iso-Verbascoside, and Calceolarioside A from the leaves and also reported the presence of *O*-Iridoids and *O*-flavonoids. Triterpenes (α-Amyrin and Clerodolone) and N-Triacontane were isolated from different parts of *C. philippinum* [15]. Steroids (Clerosterol, Daucosterol, β-Sitosterol, Poriferasterol, Stigmasterol, etc.) were also reported from leaves of *C. philippinum* [15-18]. The present investigation deals with the evaluation of antidiabetic activity of various extracts of *C. philippinum.*

MATERIALS AND 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 plants were collected 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-534) was deposited at the departmental herbarium. The collected fresh leaves were washed, shade dried, powdered and extracted successively with *n*-hexane and methanol by using soxhlet apparatus. Then the marc was extracted with distilled water by the method of continuous hot extraction at 60 °C for 6 h [19]. Finally, the extracts were concentrated by evaporating the solvent using rotary evaporator. The yield of *n*-hexane, methanol and aqueous extracts were found to be 3.81%, 11.75% and 11.82% w/w respectively.

Qualitative phytochemical screening

The presence of phyto constituents in the extracts was determined by standard & prescribed chemical procedure [20-23].

Animals

Healthy adult Wistar albino rats of either sex (150-200 g body weight) procured from the animal house of School of Pharmaceutical Sciences (SPS), S'O'A University, Bhubaneswar were used for the study, and 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 of 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. The rats were observed continuously for 2 h under the following profiles [24].

(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 h, 72 h 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 Streptozotocin (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 for the study [25].

The blood glucose level (BGL) was estimated using gluco-monitor (Contour TS, Bayer HealthCare Limited) by puncturing the tail vein.

Effect of extracts on normoglycemic rats

The effect of extracts on BGL was studied in normal rats [26], were divided into five groups of six rats each and fasted for 12 h with free access of water, and the treatments were made orally as: Group I: solvent control (Tween 40+distilled water); Group II: Glibenclamide (10 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 BGL was measured at 0, 1, 2, 4, 8 and 10 h following the treatment.

Effect of extracts on glucose loaded hyperglycemic rats

The rats were ingested with glucose (2 g/kg) in distilled water, 30 min following the administration of the test substances by gastric intubation. The treatments were made similarly as above and the BGL was measured at 1, 2 and 4 h following the administration of test substances.

Effect of extracts on STZ-induced diabetic rats

The effect of extracts on BGL was studied in STZ-induced diabetic rats on a similar basis, and BGL was estimated at 0, 1, 2, 4, 8 and 10 h following the treatment.

Statistical analysis

The results are expressed as mean±SEM 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 data represented in table 1 depicted the preliminary phytochemical investigation reports of the various extracts of *C. philippinum* indicates that the *n*-hexane extract was found to contain alkaloids, steroids, triterpenoids; whereas methanol extract shown the presence of alkaloids, flavonoids, glycosides, phenolic compounds, saponins, steroids, triterpenoids; and the aqueous extract showed the presence of flavonoids, glycosides, phenolic compounds, saponins.

Table 1: Preliminary phytochemical screening of *Clerodendrum philippinum* Schaur leaf extracts

Extracts	Alkaloids	Carbohydrates	Flavonoids	Glycosides	Phenolic compounds	Proteins	Saponins	Steroids	Triterpenoids
n-Hexane	+	-	-	-	-	+	-	+	+
Methanol	+	+	+	+	+	+	+	+	+
Aqueous	+	+	+	+	+	-	+	-	-

'+' indicates present, '-'indicates absent.

Acute oral toxicity study

The gross observational results revealed that the extracts of *C. philippinum* leaves did not show any sign of toxicity and mortality up to 14 d of the study in the dose level of 4000 mg/kg. One-tenth of the observed safety dose was taken for experimental purpose considering the fact it may show the therapeutic effect as well as safe in longer duration of use, as per previously published literature [27, 28].

Effect of extracts on normoglycemic rats

The effect of extracts on BGL of normal rats, depicted in table 2, showed a significant fall when compared with the solvent control group at the end of 10 h. Among them, methanol extract exhibited highest reduction of BGL with the percentage reduction of 36.28% (P<0.001) followed by aqueous extract of 26.62% (P<0.01) and *n*-hexane extract 18.58% (P<0.05).

Table 2: Effect of extracts of *C. philippinum* leaves on BGL in normal rats

Treatment	Blood Glucose Levels (mg/dl)						% decrease at 10 h
	0 h	1 h	2 h	4 h	8 h	10	
Solvent Control (Tween+Water)	103.66±5.47	101.5±5.82	102.66±4.21	101.66±4.12	96.16±4.18	96.33 4.28	-
Glibencamide (10 mg/kg)	101.83±5.16	91.5±3.29	77.16±2.38^{c}	68.16±3.02^{c}	58.83±2.78^{c}	53.33±3.77^{c}	47.62
n-Hexane Extract (400 mg/kg)	94.16±4.23	101.16±4.69	101. 83±4.04	98.33±4.60	82.66±4.81^{a}	76.66±3.27^{a}	18.58
Methanol Extract (400 mg/kg)	99.66±4.49	98.66±3.01	84.16±3.85^{b}	79.66±3.36^{b}	68.66±3.13^{c}	63.5±4.86^{c}	36.28
Aqueous Extract (400 mg/kg)	102.66±3.92	97.83±4.98	88.83±4.72^{a}	82.33±4.68^{b}	76.5±4.97^{b}	75.33±5.73^{b}	26.62
F (4, 25)	-	-	8.04**	11.91**	12.02**	13.01**	

Values are expressed in mean±SEM of six rats. 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 the solvent control.

Effect of extracts on glucose loaded hyper glycemic rats

Methanol and aqueous extracts showed 46.51% and 37.28% (P<0.001) fall of BGL respectively at 4 h following the administration of test substances, whereas 52.97% (P<0.001) with the standard. Methanol extract exhibited maximum reduction of blood glucose and better glucose tolerability among all the extracts when compared with the solvent control group at the end of 4 h (table 3).

Table 3: Effect of extracts of *C. philippinum* leaves on BGL in glucose loaded rats

Groups and treatments	Blood glucose levels (mg/dl)				% decrease at 4 h
	Pre-treatment	Post-treatment			
		1 h	2 h	4 h	
Solvent Control (Tween+Water)	62.5±2.34	152.83±3.60	138.33±4.34	125.83±4.78	17.66
Glibencamide (10 mg/kg)	72.33±6.91	137.16±3.86[a]	95.83±4.49[c]	64.5±3.11[c]	52.97
n-Hexane Extract (400 mg/kg)	71.83±3.34	151.33±2.83	125.83±4.11	116.16±6.25	23.24
Methanol Extract (400 mg/kg)	62.16±4.19	138.66±3.69[a]	112.16±4.63[b]	74.16±3.60[c]	46.51
Aqueous Extract (400 mg/kg)	74.66±3.33	147.5±3.73	116.16±3.26[b]	92.5±5.89[c]	37.28
F (4, 25)	-	4.08*	14.24**	28.98**	

Values are expressed in mean±SEM of six rats. 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 the solvent control.

Effect of extracts on STZ-induced diabetic rats

Methanol and aqueous extracts at the dose level of 400 mg/kg body weight reduced the BGL significantly, starting from 1 h (P<0.01) to the end of 10 h (P<0.001). The standard drug showed a similar effect during the experiment, and the percentage reductions of the BGL were calculated as 38.99%, 66.76% and 57.17% with respect to *n*-hexane, methanol and aqueous extract at the end of 10 h of the study, while the standard drug showed the reduction of 68.22%. The statistical analysis of variance (one-way ANOVA) of all the experimental results from the test groups found significant (P<0.01) differences among and in between the groups. The potency order of test extracts towards the blood glucose lowering property is found to be methanol>aqueous>*n*-hexane extract (table 4).

Table 4: Effect of extracts of *C. philippinum* leaves on BGL in STZ-induced diabetic rats

Treatments	Blood Glucose Levels (mg/dl)						% decrease at 10 h
	0 h	1 h	2 h	4 h	8 h	10 h	
Solvent Control (Tween+Water)	302.33±7.25	298.5±7.45	291.33±8.13	301.83±10.79	293.33±11.13	299.33±12.78	-
Glibencamide (10 mg/kg)	302.66±6.12	243.33±6.08[b]	164.83±9.08[c]	124.83±7.43[c]	99.83±6.83[c]	96.16±5.68[c]	68.22
n-Hexane Extract (400 mg/kg)	295.33±9.85	287.16±9.26	263.83±10.87	241.83±12.06[b]	192.16±8.26[c]	180.16±13.06[c]	38.99
Methanol Extract (400 mg/kg)	294.33±9.49	247.16±9.58[b]	191.33±8.15[c]	133.33±9.99[c]	103.33±7.13[c]	97.83±7.95[c]	66.76
Aqueous Extract (400 mg/kg)	279.83±10.66	257.33±10.01[b]	227.16±11.38[c]	161.83±8.88[c]	128.66±11.70[c]	119.83±13.33[c]	57.17
F (5, 30)	-	8.24**	28.68**	58.93**	77.76**	60.42**	

Values are expressed in mean±SEM of six rats. 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 the solvent control.

DISCUSSION

The effect of extracts on normoglycemic rats showed a gradual fall of BGL in different tested h by all test extracts, in which methanol and aqueous extract exhibited better effect. It may be suggested that the blood glucose lowering effect of extracts after single dose administration may be due to enhancement of peripheral glucose uptake [29]. Presence of alkaloids, flavonoids, glycosides, phenolic compounds, saponins, steroids and triterpenoids in methanol extract and flavonoids, glycosides, phenolic compounds and saponins in aqueous extract may contribute the hypoglycemic potential of methanol and aqueous extract [30]. After pretreatment with test extracts, BGL reaches to maximum level, 30 min after glucose load and then starts falling at the end to the experiment. Methanol and aqueous extract showed less BGL as compare to solvent control, to the response of glucose load and BGL gradually falls down towards normal. Insulin secretion in response to the oral ingestion of glucose occurs in three phases known as cephalic, gastric and intestinal phase. The cephalic and gastric phases of insulin secretion are part of the initial response to glucose loading, whereas the intestinal response occurs in later stages [31, 32].

The reduction on BGL by the extracts may be due to increased insulin secretion and increased peripheral glucose utilization [33]. Digestive enzymes like α-amylases and α-glucosidases play a major role in absorption of glucose from the digestive system. Inhibition of these enzymes, responsible for hydrolysis of carbohydrates can control post-prandial glucose levels [34]. Natural compounds such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, and phenolics are known to have α-amylases and α-glucosidases inhibitory activity [35-37] and hence α-amylases and/or α-glucosidases inhibitory potential is expected with the tested extracts. STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release, which destroy pancreatic β-cells by necrosis [38]. The possible mechanism by which extracts mediate its antidiabetic effect could be by potentiation of pancreatic secretion of insulin from existing β-cells of islets, as was evident by the significant decrease in BGL in the extracts treated rats at the 10 h of study.

CONCLUSION

The experimental results of the present investigation conclude that the leaf extracts of *C. philippinum* is endowed with antidiabetic potential.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest

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