Journal of Ayurvedic and Herbal Medicine

Research Article

J. Ayu. Herb. Med.
2016; 2(1): 6-10
January- February

www. ayurvedjournal.com

Role of *Toona ciliate* extract in diabetes against streptozotocin – nicotinamide induced diabetic rats

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ABSTRACT

The present study was carried out to investigate the antihyperglycemic activity of the leaves of *Toona ciliata* hydroalcoholic extract in streptozotocin-induced diabetic rats. In the present study, effect of oral administration of T. ciliata leaves extract (0.2, 0.4g/kg body wt.) for 15 days on the level of blood glucose, serum cholesterol, triglycerides, urea, creatinine, aspartate amino transferase (AST) and alanine amino transferase (ALT) in normal and streptozotocin-induced diabetic rats were evaluated. Histology of liver, kidney and pancreas were also studied. A significant decrease in blood glucose, serum cholesterol and triglycerides levels while total protein and HDL-C level was found to be increased as compared with the diabetic control group. The histology study of the diabetic rats treated with *T. ciliata* extract showed the significant results by showing recovery almost near to normal rats. The extract of the plant leaves at both the doses (0.2, 0.4g/kg body wt.) showed prominent effect and the finding suggest that *Toona ciliata* has significant antihyperglycemic activity in streptozotocin induced diabetes in rats.

Keywords: Antihyperglycemic activity, *Toona ciliata*, Streptozotocin, Blood glucose.

INTRODUCTION

Diabetes mellitus consists of a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, and proteins, and an increased risk of complications from vascular disease arising as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action or both [1]. It is a common health problem worldwide, and prevalence of this disease is rapidly increasing [2]. Globally, the estimated incident of diabetes and projection for year 2030, as given by International Diabetes Federation (IDF) is 350 million [3]. Elevated blood glucose level causes oxidative stress as a result of increased production of the mitochondrial oxidative species (ROS), non-enzymatic glycation of proteins and glucose auto oxidation [4]. Currently available therapies for diabetes include insulin and various oral antidiabetic such as sulfonylureas, biguanides, α- glucosidase inhibitors and glinides, which are used as monotherapy or in a combination to achieve better glycemic regulation. Many of these oral antidiabetic drugs have a number of serious adverse effects. Thus, the management of diabetes without any side effects is still a challenge [5]. This leads to increasing demand for herbal product with antidiabetic factor but little side effects [6]. A variety of ingredients presents in the plants are thought to act on a variety of targets by various mode and mechanism. Hence the present study was carried out to elevate the antidiabetic activity and antioxidant activity of *Toona ciliata*.

Toona ciliata M.Roem. syn. *Cedrela toona* (Family: Meliaceae) is commonly known as Toonee, Tuni in Hindi; Red ceder in English and Nandi in Sanskrit. It is mainly distributed in Sub Himalayan tract. Traditionally, it is useful in chronic dysentery, leprosy, cures fever, headache, blood complaints, cardiotonic, aphrodisiac, and ulcer. The leaves of the plant traditionally used as hypoglycemic agent [7]. The Phytoconstituents present in the plants including triterpenoids, cedrelone, polyynes, limonoids, siderin etc [8-11]. Pharmacologically the plant has been investigated for its Anti-ulcer activity, Analgesic activity, Antifungal activity, Antimicrobial activity, Anti feedant activity and Antitumor activity [12-17]. To our knowledge, there are no available reports on the antidiabetic effects of the leaves of this plant. Hence the present study was carried out to determine the effect of hydro alcoholic extract of leaves of the plant.

MATERIALS AND METHODS

Plant material

Leaves of the plant material *Toona ciliata* were collected from the Himachal Pradesh in the month of October 2012. The plant was authentified by Dr. H.B. Singh; Director, Department of Raw Material

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Herbarium & Museum, National Institute of Sciences Communication and Information Resources (NISCAIR), New Delhi, India, where the voucher specimen (NISCAIR/RHMD/Consult/-2011-12/1849/149) has been deposited.

Preliminary phytochemical screening

Preliminary phytochemical screening [18] revealed the presence of carbohydrates, flavonoids, tannins and steroids.

Preparation of the extract

The plant material was washed under running tap water and dried in shade for 3 weeks. Dried leaves were powdered, sieved and stored in an air tight container at room temperature. The leaves were extracted with hydroalcohol (30:70) in Soxhlet apparatus at a temperature not exceeding 60°C. The hydroalcoholic extract (HAEt) was concentrated under reduced pressure in rotary evaporator to yield a crude semi-solid mass. It was then dried, concentrated and used. Then the extract was stored in a refrigerator at 4 °C until use for the biological testing and phytochemical screening.

Drugs and chemicals

Streptozotocin and Nicotinamide were purchased from Sigma Chemical Company. All others chemicals were obtained either from Hi Media (Mumbai) or SD- Fine Chemicals (Mumbai). All chemicals used were of analytical grade. Standard drugs Glibenclamide and Metformin were received as gift sample from Tirupati, Ponta Sahib, Himachal Pradesh.

Animals

Experiment were performed on the Albino rats at weights ranging from 150-250gm.

Animals were obtained from the Institutional Animal House, Kurukshtera University, India. The animals were kept and maintained under laboratory conditions of temperature (21.5±22 °C), humidity (60±1%) and 12 hour light/dark cycle. They were allowed free access to food (standard pellets) and water. Experimental protocols and procedures used in this study were approved by Institutional Animal Ethics Committee of Kurukshetra University, Kurukshetra, India.

Induction of non - insulin - dependent diabetes mellitus (NIDDM)

NIDDM was induced in the overnight fasted albino rats weighing 150-250 gm by single intraperitoneal injection of 60 mg/kg streptozotocin, 15 min after the i.p. administration of 120 mg/kg of nicotinamide. Streptozotocin (STZ) was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline [19]. Hyperglycemia was confirmed by elevated glucose level in plasma determined at 72 h. Only rats confirmed with permanent NIDDM were used in the antidiabetic study.

Experimental design

Animals were divided in to five groups of five rats each. The extract was administered for 15 days.

Group I: Normal control received distilled water for 15 days. Group II: Diabetic control received vehicle (Tween 80, 5% v/v and distilled water). Group III: Diabetic rats received hydroalcoholic extract (HAEt) (200 mg/kg) for 15 days. Group IV: Diabetic rats received hydroalcoholic extract (HAEt) (400 mg/kg) for 15 days. Group V: Diabetic rats received metformin (10mg/kg) for 15 days. Blood glucose level was estimated on 5, 10 and 15 days of extract administration. The effect of administration of the HAEt was determined by measuring the plasma blood glucose level, serum lipid profiles and initial and final changes in the body weight. All the biochemical parameters were determined on the day 15 after the animal were scarified by cardiac puncture. On the 15 day when all the animals were scarified the pancreas, kidney and liver of one animal from each group were excised and stored in 10 % formalin for the histopathological study.

Statistical analysis

All the results are presented as mean ± standard error of mean (S.E.M.) The statistical analysis involving two groups was evaluated by means of Student's t-test whereas one way analysis of variance (ANOVA) followed by Dunnet's multiple comparison post-test was used for statistical comparison between control and various treated groups. Statistical significance was accepted at the $p< 0.05$ values.

RESULTS

Assessment of hypoglycemic activity in the diabetic rats

Inductions of diabetes in the experimental rats were confirmed by presence of high blood glucose level. Table 1 depicts the hypoglycemic activity of oral administration at dose of 200 mg/kg and 400 mg/kg of hydroalcoholic extract of *Toona ciliata* in the diabetic rats. The difference between the experimental and control rats in lowering the fasting plasma glucose levels was statistically significant ($P < 0.01$) in diabetic rats. The most effective dose was found to be 400 mg/kg as it produces a significant reduction in blood glucose level.

Table 1: The effects of 2 weeks treatment of hydroalcoholic extract of leaves of *Toona ciliata and* of metformin (10 mg/kg) on serum glucose level (mg/dl) in STZ+NIC induced diabetic rats

Groups	0 day	5day	10 day	15 day
I: Normal Control	93.0 ± 5.45	95.8 ± 4.07	85.6 ± 7.01	97.4 ± 5.43
II: Diabetic Control	283.0 ± 5.64	295.8 ± 5.37	311.8 ± 4.00	328.0 ± 5.11
III: STZ+NIC+ Metformin	301.8 ± 4.73	239.2 ± 10.31**	155.2 ± 6.57**	100.2 ± 4.07**
IV: STZ+NIC (HAEt 200 mg/kg)	283.6 ± 6.60	262.8 ± 6.13*	213.4 ± 5.79**	186.8 ± 5.70**
V: STZ+NIC (HAEt 400 mg/kg)	295.4 ± 5.04	242.8 ± 7.79**	200.8 ± 3.54**	179.8 ± 23.18**

All values represent means ± SEM of the mean (n=5), * $p< 0.05$; ** $p< 0.01$, when group III to V compared with group II

Induction of diabetes with STZ had been associated with the loss of body weight, which is due to increased muscle wasting and loss of tissue proteins [20]. Diabetic rats treated with extract also showed a significant increase in total body weight as compared to the diabetic control group (Table 2).

Table 2: Effect of treatment of hydroalcoholic extract of leaves of *Toona ciliata* and metformin on body weight (gm) in STZ+ NIC induced diabetic rats

Groups	0 day	5 day	10 day	15 day
I: Normal Control	225 ± 1.41	226 ± 0.70	227.2 ± 1.39	229 ± 1.61
II: Diabetic Control	233.4 ± 3.28	230 ± 3.30	220.4 ± 1.77	215.4 ± 2.73
III: STZ+NIC+ Metformin	229.8 ± 4.55	232.2 ± 1.59	233.6 ± 1.50**	235.8 ± 1.39**
IV: STZ+NIC (HAEt 200 mg/kg)	234.4 ± 4.41	233.6 ± 3.98	232.8 ± 3.24*	234.8 ± 2.26**
V: STZ+NIC (HAEt 400 mg/kg)	232 ± 4.88	231.6 ± 4.17	232.8 ± 4.05*	235 ± 2.7**

All values represent means ±SEM of the mean (n=5), * $p< 0.05$; ** $p< 0.01$, when group III to V compared with group II

Elevated serum cholesterol and serum triglycerides levels in STZ challenged rats indicated impaired fat metabolism. The test extract decreased in the total cholesterol level, serum triglycerides level and increased in HDL cholesterol level as compared to diabetic control group. (Table 3).

Table 3: Effect of hydroalcoholic extract of leaves of *Toona ciliata* on biochemical parameters

Groups	Total Cholesterol level (mg/dl)	Triglycerides level (mg/dl)	HDL-C level (mg/dl)	LDL-C level (mg/dl)
I: Normal Control	86.0 ± 1.00	86.20 ± 1.85	39.20 ± 1.24	73.8 ± 1.82
II: Diabetic Control	257.20 ± 2.35	152.0 ± 2.82	32.40 ± 1.43	179.4 ± 4.61
III: STZ+NIC+ Metformin	97.2 ± 1.59**	89.0 ± 1.22**	47.4 ± 1.50**	50.60 ± 2.48**
IV: STZ+NIC (HAEt 200 mg/kg)	132.6 ± 1.88**	103.8 ± 3.35**	37.6 ± 1.72*	96.2 ± 3.55**
V: STZ+NIC (HAEt 400 mg/kg)	97.4 ± 1.63**	99 ± 2.86**	41.8 ± 1.96**	83.2 ± 2.80**

All values represent means ±SEM of the mean (n=5), * $p< 0.05$; ** $p< 0.01$, when group III to V compared with group II

A decreased in serum urea, serum Creatinine and increased in the serum protein level was observed (Table 4).

Table 4: Effect of treatment of Hydroalcoholic extracts of leaves of *Toona ciliata* and metformin on Urea, Creatinine, Protein after treatment for 15days in diabetic rats

Groups	Urea	Creatinine	Proteins
I:Normal rat	27.8 ± 1.39	0.76 ± 0.03	6.84 ± 0.29
II: Diabetic control	63.4 ± 4.27	1.24 ± 0.08	5.42 ± 0.22
III: STZ+NIC+ Metformin	31.8 ± 2.76**	0.66 ± 0.04**	7.08 ± 0.26**
IV: STZ+NIC (HAEt 200 mg/kg)	38.2 ± 2.22**	0.77 ± 0.03**	6.54 ± 0.26*
V: STZ+NIC (HAEt 400 mg/kg)	35.0 ± 2.34**	0.69 ± 0.02**	6.74 ± 0.30**

All values represent means ±SEM of the mean (n=5), * $p< 0.05$; ** $p< 0.01$, when group III to V compared with group II

Extract showed a significant reduction in the elevated level of serum enzymes (SGOT, SGPT) as compared to diabetic control group (Table 5).

Table 5: Effect of hydroalcoholic extract on liver parameters

Groups/Treatment	SGOT U/ML	SGPT U/ML
I: Normal Control	41.2 ± 2.92	47.8 ± 1.98
II: Diabetic control	106 ± 4.82	112.2 ± 2.03
III: STZ+ NIC+ metformin	42 ± 3.74	49.8 ± 2.95
IV:STZ+ NIC+ HAEt (200 mg/kg)	61.8 ±3.05**	58.6 ± 1.72**
V: STZ + NIC + HAEt (400 mg/kg)	49.4 ± 1.93**	50.8 ± 1.93**

All values represent means ±SEM of the mean (n=5),), * $p< 0.05$; ** $p< 0.01$, when group III to V compared with group II

3.2 *Result of Histopathological studies*

Histopathological examinations supported the biochemical results and progressive glomerulosclerosis and fibrosis associated kidney sections showed progressive damage with decreased kidney function, The effects of diabetes on hepatic ultrastructure include hypertrophy and the necrosis of hepatic cell occurred in STZ treated rats. The present histopathological investigation showed that diabetic pancreas revealed necrotic and fatty infiltration of the islet cells and showed a extensive damage of the pancreatic islet cells. Animals treated with the extract showed a recovery nearest to normal rats (Figure 1-3).

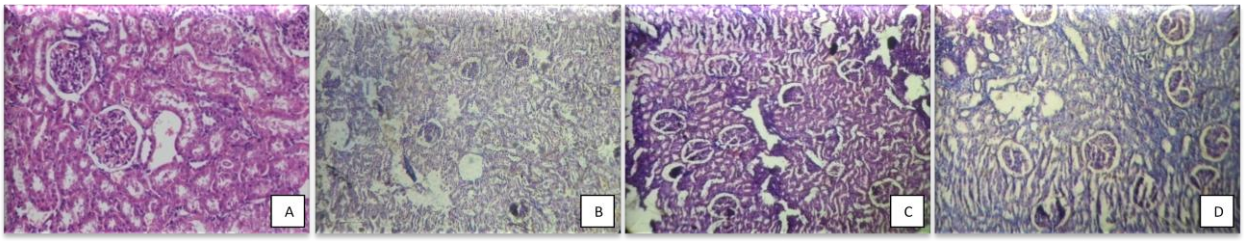

Figure 1: Effect of HAEt on rat kidney (A: Normal, B: Diabetic, C: Diabetic+ HAEt 200 mg/kg, D: Diabetic + HAEt 400mg/kg)

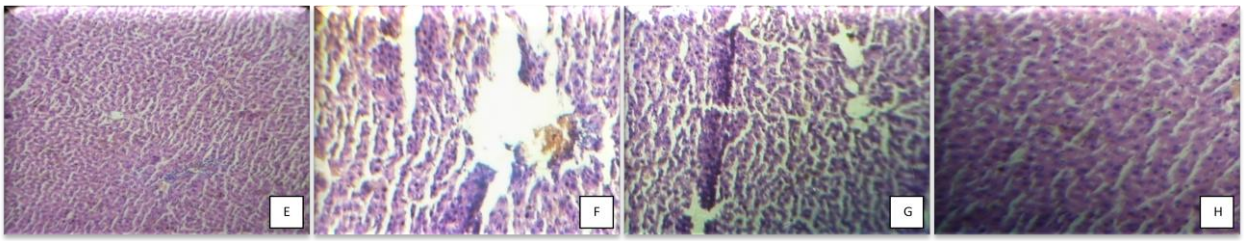

Figure 2: Effect of HAEt on rat liver (400X) (E: Normal, F: Diabetic: severe retention of fat, G: HAEt 200 mg/kg: fatty changes, H: HAEt 400mg/kg): nearest to normal rat liver

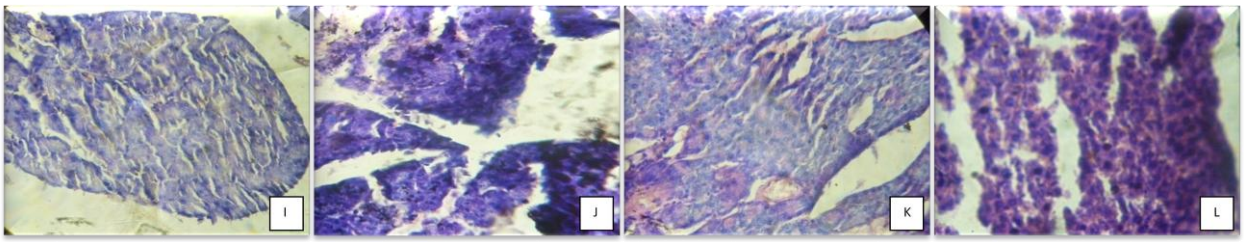

Figure 3: Effect of HAEt on rat pancreas (400 X) (I: Normal, J: Diabetic: destruction of β- cells, K: HAEt 200 mg/kg: improvement in β-cells, L: HAEt 400 mg/kg): nearest to normal rat

DISCUSSION

Streptozotocin is used as an agent to induce diabetes mellitus by selective cytotoxicity effect on pancreatic beta cells. Thus it affects endogenous insulin release and asa result increases blood glucose level [21]. The present paper reports the antidiabetic activity of hydroalcoholic extract of *Toona ciliata*. The results demonstrated that hydroalcoholic extract of *T. ciliata* induced significant decrease of plasma glucose levels in STZ induced diabetic rats was achieved after 2 weeks of oral treatment indicating that the hypoglycaemic effect of plant hydroalcholic extract is cumulative.

The repeated administration of *Toona ciliata* extract for 15 days resulted in a significant decrease in lipid parameter levels of various tissues when compared to the diabetic control. It is not known whether *Toona ciliata* has a direct effect on lipids or hypolipidemia is achieved

due to controlled hyperglycemia. Diabetic rats treated with the HAEt showed an increase in bodyweight as compared to the diabetic control, which may be due to its protective effect in controlling muscle wasting [20]. The extract also showed a significant effect on the liver enzyme levels. Histopathological study (Figure 1-3) also supported our study. STZ was suspected to destroy the kidney, pancreas and liver of the diabetic animals. Animals treated with the extract showed a recovery nearest to normal rats.

It has been previously reported that flavonoids are responsible for the hypoglycemic action of a plant extract [23-26]. So, the antidiabetic action of this extract might be attributed to its flavonoids content which was indicated in the preliminary phytochemical screening.

CONCLUSION

The present study indicate that the *Toona ciliata leaves* extract has beneficial effects on decreasing blood glucose levels and also decrease hyperlipidemia which is produced due to diabetes. Further pharmacological and biochemical investigations are under way to elucidate the mechanism of the antidiabetic effect and hypolipidaemic effect of *Toona ciliata*. The bioactive constituents responsible for this antidiabetic effect need further investigation.

CONFLICTS OF INTEREST

No conflicts of interest.

SOURCE OF FUNDING

Nil.

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HOW TO CITE THIS ARTICLE

Rana M, Kumar S, Rana M, Dhatwalia V. Role of *Toona ciliate* extract in diabetes against streptozotocin – nicotinamide induced diabetic rats. J Ayu Herb Med 2016;2(1):6-10.