



Original article

Phytotherapeutic efficacy of the medicinal plant *Terminalia catappa* L.

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ABSTRACT

Diabetes is a chronic, lifelong condition due to inadequate production of insulin or the cells does not properly respond it. Recently, the significance and effectiveness of herbal drugs associated with diabetes has emerged. The aim of the present study was to determine the anti-diabetic effects of *Terminalia catappa* L. leaves on streptozotocin (STZ)-treated rats. Two different concentrations of ethanolic leaf extract (300 and 500 mg/kg) of *T. catappa* were used to treat diabetic rats, and biochemical parameters were analyzed in blood samples. The results of herbal treatments were compared with the standard drug, glibenclamide. The ethanolic extract (500 mg/kg) had significant anti-diabetic activity by altering blood glucose, glycosylated hemoglobin, liver glycogen, glucose 6-phosphatase, fructose 1,6-bisphosphatase, glucokinase, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea, uric acid and creatinine levels while increasing insulin levels. Thus, the present study suggests that the supplementation of the diabetic patients with *T. catappa* leaves can lead to recovery from diabetic effects.

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1. Introduction

Diabetes mellitus is a metabolic ailment resulting from a failure of insulin production, insulin action, or both. Insulin insufficiency in turn leads to long-lasting hyperglycemia with impairments of carbohydrate, fat and protein metabolism. As the disease progresses, it causes damage to the vascular tissues, leading to severe diabetic complications such as neuropathy, nephropathy, retinopathy, cardiovascular complications and ulceration (Arkkila et al., 2001). Thus, diabetes leads to a wide range of ailments.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; STZ, Streptozotocin.

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In patients suffering from type 2 diabetes mellitus, the management of hyperglycemia starts with modifications to the diet and physical activity (Nathan et al., 2009). Glycemic maintenance in diabetic patients is not possible through diet and physical exercise alone, but requires the intake of oral hypoglycemic agents to prevent diabetic effects. Various blood glucose lowering drugs such as sulfonylureas, biguanides and intestinal α -glucosidase inhibitors are available in the marketplace, but these drugs have some side effects and are also expensive. Glibenclamide is commonly used by diabetic patients and reduces blood glucose levels in animal models of diabetes (Holmes et al., 1984). Drugs from medicinal plants are prescribed universally because of their efficiency, lower side effects and relatively low cost (Venkatesh et al., 2003). *Terminalia catappa* L. is growing in warmer parts of Asia and is called the Indian almond, Malabar almond and tropical almond. It is a medium size tree, and the leaves are clustered towards the ends of the branches. Various extracts of the leaves of this plant have been reported to have anti-cancer, anti-HIV reverse transcriptase, hepatoprotective, anti-inflammatory, anti-hepatitis and aphrodisiac effects (Lin et al., 1997). Although the fruits of *T. catappa* and the

leaves of *T. glaucescens* and *T. arjuna* have been reported to have anti-diabetic activity in some studies (Nagappa et al., 2003; Njomen et al., 2008; Biswas et al., 2011), there have been no reports of anti-diabetic activities of *T. catappa* leaves. Previously, we found that the *T. catappa* leaf extract contains phytochemicals such as phenol, flavonoids, and steroidal glycosides (Divya and Vijaya Anand, 2014), which are responsible for its therapeutic activity. Toshiya et al. (1999) examined the anti-oxidant activity of methanolic extract of the leaves of 39 plant species. Two extracts from *Excoecaria agallocha* and *T. catappa* showed remarkably potent activity in all assay systems. Hence, the present study was aimed to determine the anti-diabetic potential of *T. catappa* leaves in an STZ-induced animal model.

2. Materials and methods

2.1. Plant material

The leaves of *T. catappa* were collected from Tiruchirappalli and authenticated at St. Joseph's College, Tiruchirappalli, Tamil Nadu (ND 006). The collected plant leaves (5.0 Kg of leaves) after plugging from the tree were air dried under shade and ground into a powder using a mortar and then sieved. The plant material was subjected to extraction with solvents of ascending order of polarity. In this process the substance, which is soluble in a solvent with a particular range of polarity was extracted in the solvent and remaining material further extracted with next solvent. The present finding indicates that useful bioactive substances exist in the *T. catappa* extracts. Hence, further studies were carried out by using ethanol extract only. The powdered plant material was subjected to successive with a solvent of 95% ethanol (100 g of leaf powder/ 600 mL) by hot continuous percolation method. The residues extract was concentrated by rota-evaporator. Finally, the extract was concentrated by drying process at the temperature of 40–50 °C. The ethanol was evaporated and the extract made into a powder, which was used for later in vivo studies.

2.2. Animal material

Six to seven-week-old Wistar albino rats (150–200 g) totally 36 were used for the experiments, of which six animals were used for each group. The rats were kept at the Periyar College of Pharmaceutical Sciences, Tiruchirappalli. The animals were fed and watered *ad libitum*. The animal experiments were approved by the Institutional Animal Ethical Committee by No: CPCSEA/265.

2.3. Experimental design

Wistar albino rats were used as the experimental animals and were randomly divided into six groups with six animals in each group.

Group I – Control; Group II - Diabetic control (60 mg/kg of STZ); Group III – 500 mg/kg of *T. catappa* leaf extract; Group IV - STZ and 300 mg/kg *T. catappa* leaf extract; Group V - STZ and 500 mg/kg *T. catappa* leaf extract; Group VI - STZ and 3 mg/kg glibenclamide. Preliminary oral LD⁵⁰ dose of ethanol extract of *T. catappa* in rats was found to be 5000 mg/kg. One-tenth of their LD⁵⁰ dose of ethanol extract (500 mg/kg per day) was selected for treatment as the maximum dose.

2.4. Induction of diabetes

STZ was purchased from Himedia Laboratories Pvt Ltd, Mumbai. Hyperglycemia was induced by a single injection of STZ dissolved in 2 mL of 0.1 M citrate buffer pH 4.5. The Wistar albino rats were

fasted overnight and STZ (60 mg/kg) was administered intraperitoneally. Rats with a blood glucose level above 200 mg/dl were considered diabetic. After the confirmation of the disease, the animals were treated with a dose of various concentrations of ethanolic leaf extract (300 mg/kg b.w, or 500 mg/kg b.w) of *T. catappa* for 45 days.

2.5. Analysis of biochemical parameters

Blood samples were collected by the retro-orbital plexus puncture method. The levels of glucose (Folin and Wu, 1919), insulin (Morgan and Lazarow, 1963), glucose-6-phosphatase (King, 1965), fructose-1,6-bis-phosphatase (Fiske and Subbaro, 1957), glycogen (Morales et al., 1973), HbA1c (Nayak and Pattabiraman, 1981), glucokinase (Brandstrup et al., 1957), alanine aminotransferase (ALT; King, 1965), alkaline phosphatase (ALP; King, 1965), aspartate aminotransferase (AST; King 1965), urea (Fawcett and Scott, 1960) and creatinine (Bonsnes and Tausky, 1945) were analyzed standard procedures at the end of the experimental period.

2.6. Statistical analysis

The experiment was repeated three times with six animals for each group. Statistical analysis was carried out by one way ANOVA using the standard statistical software package of social science (SPSS) version 12.0. $P \leq 0.05$ was considered as the level of significance.

3. Results and discussion

In the present study, the elevation of blood glucose was found in the toxin treated group (Table 1). Glucose is derived from the diet and utilized by cells with the help of insulin. Insulin insufficiency elevates the blood glucose and causes hyperglycemia, which leads to diabetes. The ethanolic leaf extracts (300 mg/kg and 500 mg/kg) decreased blood glucose levels in diabetic rats. A similar effect has been found in treatment with different extracts of *T. catappa* fruits (Nagappa et al., 2003), which confirm the anti-diabetic effects of *T. catappa* (Malviya et al., 2010). The secretion of insulin by beta cells of the pancreas was affected by diabetic agents. On the other hand, the lower concentration of insulin in the toxin treated rat group was due to damage to the pancreatic cells, which were not able to produce insulin due to DNA alkylation arising from the production of carbonium ions (Wright et al., 1999). STZ-induced diabetes not only affects the pancreas, but also causes damage to the liver, the kidneys and cardiac cells (Biswas et al., 2011). Related studies have reported that the induction of diabetes in animals by beta cell destruction, through the production of free radicals, leads to the alkylation of DNA and a consequent increase in the blood glucose concentration (Takasu et al., 1991). In the present study, there was a substantial increase in serum insulin levels of diabetic animals after *T. catappa* (300 mg/kg and 500 mg/kg) treatment. Hence, it might be recognized that secondary metabolites of this plant extract stimulate the beta cells.

HbA1c is an important diabetic parameter and was elevated in rats injected with STZ. In severe diabetes, blood glucose levels are elevated, and the excess glucose combines with hemoglobin, which is converted to HbA1c (Edelman et al., 2004). *T. catappa* extract (300 mg/kg and 500 mg/kg) decreased the HbA1c level, which might be due to regulation of glucose synthesis. In addition, the liver glycogen levels were elevated in the STZ-treated group. Glycogen storage is promoted by insulin, but the capacity for storage within tissues is physically limited because it is a large molecule. Glycogen in the liver can be abnormally accumulated or depleted. Carbohydrate regulation by the liver is completed by

Table 1

Effect of *T. catappa* leaf extract on various anti-diabetic parameters in diabetic rats. Group I - Control, Group II - Diabetic rat, Group III - 500 mg/kg of *T. catappa* leaf extract, Group IV - STZ and 300 mg/kg of *T. catappa* leaf extract, Group V - STZ and 500 mg/kg of *T. catappa* leaf extract and Group VI - STZ and 3 mg/kg of glibenclamide.

Parameters	Group I	Group II	Group III	Group IV	Group V	Group VI
Glucose (mg/dL)	91.01 ± 5.56	199.95 ± 11.02**	91.03 ± 1.08#	128.99 ± 4.35**	100.00 ± 4.44**	95.05 ± 3.02**
Insulin (mU/mL)	17.06 ± 0.62	11.99 ± 0.20**	17.08 ± 0.61#	22.15 ± 1.26**	18.57 ± 1.12**	17.92 ± 1.06**
Glycosylated Haemoglobin (mg/g of Hb)	0.34 ± 0.01	0.82 ± 0.05**	0.36 ± 0.01#	0.54 ± 0.024**	0.40 ± 0.02**	0.35 ± 0.01**
Liver Glycogen (mg/100 g tissue)	26.12 ± 1.41	59.02 ± 2.21**	26.14 ± 1.01#	41.14 ± 2.14**	30.00 ± 1.21**	27.96 ± 1.59**
Glucose 6-phosphate dehydrogenase (U/mg protein)	27.98 ± 1.21	40.00 ± 2.31**	26.98 ± 1.20#	35.97 ± 1.47**	32.93 ± 1.40**	28.00 ± 1.14**
Fructose 1,6 bis-phosphatase (U/mg protein)	37.98 ± 0.61**	86.50 ± 1.81**	36.98 ± 1.57#	65.93 ± 1.00**	44.27 ± 1.39**	39.10 ± 1.17**
Glucokinase (U/h/mg protein)	8.99 ± 0.26	6.30 ± 0.13**	9.01 ± 0.15#	7.59 ± 0.11**	8.41 ± 0.12**	8.59 ± 0.16**

Values are means ± SD of six rats in each group;

** Highly significant different at $p < 0.01$ and

non-significant different at $p > 0.05$.

Table 2

Effect of *T. catappa* leaf extract on hepatic markers in serum of diabetic rats. Group I - Control, Group II - Diabetic rat, Group III - 500 mg/kg of *T. catappa* leaf extract, Group IV - STZ and 300 mg/kg of *T. catappa* leaf extract, Group V - STZ and 500 mg/kg of *T. catappa* leaf extract and Group VI - STZ and 3 mg/kg of glibenclamide.

Treatments	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Group I	68.95 ± 2.69	28.63 ± 2.11	71.34 ± 3.86
Group II	111.63 ± 3.55**	52.90 ± 4.06**	118.56 ± 4.42**
Group III	68.91 ± 1.36#	28.31 ± 1.70#	72.38 ± 2.46#
Group IV	94.66 ± 3.35**	41.11 ± 3.40**	95.58 ± 3.44**
Group V	73.33 ± 2.08**	29.99 ± 1.98**	76.34 ± 2.75**
Group VI	74.17 ± 2.24**	33.22 ± 1.67**	79.46 ± 3.05**

Values are means ± SD of six rats in each group;

* Significant different at $p < 0.05$,

** Highly significant different at $p < 0.01$ and

Non-significant different at $p > 0.05$.

many biochemical modifications that occur in hepatic cells due to diabetes and must be studied to understand how liver disease may affect glucose metabolism (Mann and Magath, 1922). There was a significant alteration of the glycogen level in plant treated (300 mg/kg and 500 mg/kg) group. STZ induced diabetic rats are affected by irregular activity of enzymes, such as glucose-6-phosphatase and fructose-1,6-bis-phosphatase, which play unique roles in the homeostatic regulation of glucose. Gluconeogenesis and glycogenolysis are processes that are mediated through the action of glucose-6-phosphatase and fructose-1,6-bis-phosphatase, which catalyze the irreversible steps in gluconeogenesis (Arati and Sachdanandam, 2003). Administration of ethanolic extract of *T. catappa* (300 mg/kg and 500 mg/kg) had the ability to increase the amount of insulin by altering those enzyme activities. However, glucokinase activity is decreased in diabetic rats. Glucokinase is an enzyme that has a most important role in the regulation of blood glucose. Hexokinase expressed in the liver controls hepatic glucose disposal (Agius, 2008) and acts as a glucose sensor for insulin (Matschinsky et al., 2006). Glucose is converted to glucose-6-phosphate by the action of glucokinase. The ethanolic extract of *T. catappa* leaves (300 mg/kg and 500 mg/kg) treated groups had higher amounts of glucokinase and higher glucokinase activity, especially in the liver. This elevation of glucokinase increases the utilization of glucose (Goyal et al., 1999). Liver marker enzymes were elevated under diabetic conditions caused by STZ in the present study (Table 2). AST, ALP and ALT are the key enzyme markers for hepatic function in animals. These enzymes are present in various tissues, including liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs, leukocytes and erythrocytes (Breitling et al., 2011). The increased activities of these enzymes in the blood indicate an increased permeability and damage or necrosis of hepatocytes (Adjroud, 2011). After the administration of the plant extract, the activities of those enzymes

Table 3

Effect of *T. catappa* leaf extract on kidney markers in serum of diabetic rats. Group I - Control, Group II - Diabetic rat, Group III - 500 mg/kg of *T. catappa* leaf extract, Group IV - STZ and 300 mg/kg of *T. catappa* leaf extract, Group V - STZ and 500 mg/kg of *T. catappa* leaf extract and Group VI - STZ and 3 mg/kg of glibenclamide.

Treatments	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)
Group I	19.43 ± 0.40	0.95 ± 0.06	1.65 ± 0.09
Group II	73.0 ± 0.68**	2.03 ± 0.014**	5.05 ± 0.18**
Group III	27.83 ± 0.70#	1.02 ± 0.013#	1.70 ± 0.14#
Group IV	46.0 ± 0.78**	1.66 ± 0.009**	2.75 ± 0.19**
Group V	33.15 ± 0.43**	1.05 ± 0.017**	2.00 ± 0.04**
Group VI	29.12 ± 0.78**	0.92 ± 0.014**	1.54 ± 0.07**

Values are means ± SD of six rats in each group;

* Significant different at $p < 0.05$,

** Highly significant different at $p < 0.01$ and

non-significant different at $p > 0.05$.

gradually decreased and ameliorated the STZ-induced diabetic effect in rats. Similarly, urea, uric acid and creatinine levels elevated in the STZ-treated animals (Table 3), which indicated impaired renal function in response to STZ treatment. The urea and creatinine are kidney markers that are raised under diabetic conditions (Muhammad et al., 2008). The levels of urea and creatinine were decreased in the *T. catappa* (300 mg/kg and 500 mg/kg) treated groups. This may indicate that *T. catappa* leaves prevented the STZ-induced biochemical alterations and did not cause renal damage.

4. Conclusion

Treatments of the diabetic rats with ethanol extracts of *T. catappa* reduced blood glucose and other diabetes-related parameters and increased insulin levels. The restoration of pancreatic and liver cell populations in the diabetic rats indicated that 500 mg/kg of *T. catappa* leaf extract was more effective than a lower dose. The anti-oxidant activity of *T. catappa* leaves protected the liver and restored the levels of AST, ALT and ALP. The results of various liver and kidney marker enzymes and parameters revealed that *T. catappa* based synthetic or chemical drugs can provide a remedying agent for future medication and protect the liver and kidney from diabetic complications.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

ND and AVA designed the experiment. ND, RLR, RR and RM conducted the experiment. AVA, EFA and AAA performed the statistical

analysis. EFA, and AH wrote and revised the manuscript. EFA, RR and AH and performed the English editing. All authors approved the final version of this manuscript.

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References

- Adjroud, O., 2011. Protective effects of selenium against potassium dichromate-induced hematotoxicity in female and male Wistar albino rats. *Ann. Toxicol. Anal.* 22, 165–172.
- Agius, L., 2008. Glucokinase and molecular aspects of liver glycogen metabolism. *Biochem.*
- Arati, G., Sachdanandam, S., 2003. Therapeutic effect of semecarpus and sardiumlinn, nut milk extract on carbohydrate metabolizing and mitochondrial TCA cycle and respiratory chain enzymes in mammar carcinoma rats. *J. Phar. Pharmacol.* 55, 1283–1290.
- Arkkila, P.E., Koskinen, P.J., Kantola, I.M., Ronnema, T., Seppanen, E., Viikari, J.S., 2001. Diabetic complications are associated with liver enzyme activities in people with type 1 diabetes. *Diabetes Res. Clin. Pract.* 52, 113–118.
- Biswas, M., Kar, B., Bhattacharya, S., Suresh-Kumar, R.B., Ghosh, A.K., Haldar, P.K., 2011. Antihyperglycemic activity and antioxidant role of *Terminalia arjuna* leaf in streptozotocin-induced diabetic rats. *Pharma. Biol.* 49 (4), 335–340.
- Bonsnes, R.W., Tausky, H.H., 1945. A colorimetric determination of creatinine by the Jaffe reaction. *J. Biol. Chem.* 158, 581–600.
- Brandstrup, M., Kruk, J.E., Bruni, C., 1957. Determination of hexokinase in tissues. *J. Gerondol.* 12, 166–171.
- Breitling, L.P., Yang, R., Korn, B., Burwinkel, B., Brenner, H., 2011. Tobacco-smoking-related differential DNA methylation: 27K discovery and replication. *Am. J. Hum. Genet.* 88, 450–457.
- Divya, N., Vijaya-Anand, A., 2014. Phytochemical investigation and in vitro anti-diabetic activity of *Terminalia catappa* leaves. *Int. J. Phyto. Pharm.* 4, 132–134.
- Edelman, D.M.K., Olsen, T.K., Dudley, A.C., Harris, E.Z., Oddone, J., 2004. Utility of hemoglobin A1c in predicting diabetes risk. *J. Gen. Intern. Med.* 12, 1175–1180.
- Fawcett, J.K., Scott, J.E., 1960. A rapid and precise method for the determination of urea. *J.*
- Fiske, S.H., Subbarow, Y., 1957. *Methods in Enzymology*. Colowick and Kaplan (eds.) Academic Press, New York. 3, 843.
- Folin, O., Wu, H., 1919. A system of blood analysis. *J. Bio. Chem.* 38, 81.
- Goyal, R.K., Bhullar, S.S., Singh, R., 1999. Comparative sensitivity to inorganic phosphate of sucrose to starch conversion in sorghum and wheat grains raised through culture. *Plant Physiol. Biochem.* 28, 755.
- Holmes, B., Heel, R.C., Brogden, R.N., Speight, T.M., Avery, G.S., Gliclazide, A., 1984. A preliminary review of its pharmacodynamic properties and therapeutic efficacy diabetes mellitus. *Drugs.* 27 (4), 301–327.
- King, J., 1965. The dehydrogenases or oxidoreductases-lactate dehydrogenase. In: Van, D. (Ed.), *Practical Clinical Enzymology*. Van Nostrand, London, pp. 93–193.
- Lin, C.C., Chen, Y.L., Lin, J.M., Ujji, T., 1997. Evaluation of the antioxidant and hepatoprotective activity of *Terminalia catappa*. *Am. J. Chinese Med.* 25, 153–161.
- Malviya, N., Jain, S., Malviya, S., 2010. Antidiabetic potential of medicinal plants. *Acta Pol.*
- Mann, F.C., Magath, T.B., 1922. Studies on the physiology of the liver. II. The effect of the removal of the liver on the blood sugar level. *Arch. Intern. Med.* 30, 73–84.
- Matschinsky, F.M., Magnuson, M.A., Zelent, D., Jetton, T.L., Doliba, N., Han, Y., Taub, R., Grimsby, J., 2006. The network of glucokinase expressing cells in glucose homeostasis and the potential of glucokinase activators for diabetes therapy. *Diabetes* 55, 1–12.
- Morales, M.A., Jabbagy, A.J., Terenzi, H.R., 1973. Mutations affecting accumulation of glycogen. *Neurospora News.* 20, 24.
- Morgan, C.R., Lazarow, A., 1963. Immunoassay of insulin: two antibody system, plasma insulin levels of normal, subdiabetic and diabetic rats. *Diabetes* 12, 115–126.
- Muhammad, K., Saeed, Y.D., Rongji, D., 2008. Alteration of Biochemical parameters in streptozotocin induced diabetic rats by oral administration of extracts and fractions of *Cephalatazussinensis*. *J. Clin. Biochem. Nutr.* 42 (1), 21–28.
- Nagappa, A.N., Thakurdesai, P.A., Raob, N.V., Singh, J., 2003. Antidiabetic activity of *Terminalia catappa* Linn fruits. *J. Ethnopharmacol.* 88, 45–50.
- Nathan, D.M., Buse, J.B., Davidson, M.B., Ferrannini, E., Holman, R.R., Sherwin, R., 2009. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the american diabetes association and the european association for the study of diabetes. *Diabetes Care.* 32 (1), 193–203.
- Nayak, S.S., Pattabiraman, T.N., 1981. A new colorimetric method for the estimation of glycosylated hemoglobin. *Clin. Chim. Acta.* 109 (3), 267–274.
- Njomen, G.B.S.N., Kamgang, R., Oyono, J.L.E., Njikam, N., 2008. Antioxidant potential of the methanol–methylene chloride extract of *Terminalia glaucescens* leaves on mice liver in streptozotocin-induced stress. *Indian J. Pharmacol.* 40 (6), 266–270.
- Takasu, N., Asawa, T., Komiya, I., Nagasawa, Y., Yamada, T., 1991. Alloxan induced DNA strand breaks in pancreatic islets. Evidence for H2O2 as an intermediate. *J. Biol. Chem.* 1, 93–99.
- Toshiya, M., Sigetomo, Y., Yosuo, O., Yoshio, T., Tomochika, T., Tadao, A., Ayumi, S., Mami, N.J., 1999. *Agric food chem.* 47: 1749–1754 transcriptional inhibition of Matrix Metalloproteinase-9 by modulating NF-κB and AP-1 activity. *Evid Based Complement Alternat Med.* 595292.
- Venkatesh, S., Reddy, G.D., Reddy, B.M., Ramesh, M., Rao, A.V., 2003. Antihyperglycemic activity of *Carallumaattenuata*. *Fitoterapia* 74, 274–279.
- Wright, J.R., Abraham, C., Dickson, B.C., Yang, H., Morrison, C.M., 1999. Streptozotocin dose–response curve in tilapia, a glucose-responsive teleost fish. *Gen. Comp. Endocrinol.* 114, 431–440.