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ANTIHYPERLIPIDEMIC EFFECT OF *TINOSPORA CORDIFOLIA* EXTRACT IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT

The present study was aimed to evaluate the antihyperlipidemic effect of aqueous extract of stem of *Tinospora cordifolia* in streptozotocin induced diabetic and diet induced hyperlipidemic rats. Diabetes mellitus was induced in male albino Wistar rats by intraperitoneal injection of streptozotocin (45 mg/kg b.w.). Hyperlipidemia was induced in diabetic rats by feeding 0.5% cholesterol and 0.1% cholic acid on diet basis in arachis oil (10 ml/kg b.wt) orally throughout the experimental period and simultaneously, the treatment groups received *T. cordifolia* (100 and 200 mg/kg b.w.) orally for 14 days. Glibenclamide (600 µg/kg b.w) was used as a standard antidiabetic drug and atorvastatin (1.2 mg/kg b.w.) was used as a standard antihyperlipidemic drug. Serum glucose levels were determined at weekly intervals and serum cholesterol, triglycerides, HDL-C, creatine kinase and free fatty acids were analyzed at the end of the experiment. Aqueous extract of *T. cordifolia* at 200 mg/kg b.w. dose decreased serum glucose, cholesterol, triglycerides, creatine kinase, and free fatty acids to normal level when compared to that of standard drug. Thus the study revealed that the aqueous extract of *T. cordifolia* was found to have potential effective in controlling the diabetes associated hyperlipidemic conditions effectively.

INTRODUCTION: The relationship between diabetes and hyperlipidemia is a well-recognized phenomenon. Diabetes mellitus is a syndrome that is characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism.

Accumulation of lipids in diabetes is mediated through a variety of derailment in metabolic and regulatory processes, especially insulin deficiency, thereby rendering the diabetic patient more prone for hypercholesterolemia and hypertriglyceridemia. The major pathogenesis of derailed lipid metabolism in diabetes is increased mobilization of fatty acids from adipose tissue and secondary elevation of free fatty acid level in the blood [1].

Hyperlipidemia is characterized by elevated serum total cholesterol and low-density and very low-density lipoprotein levels. Hyperlipidemia associated lipid disorders are considered to be the cause for atherosclerotic cardiovascular disease [2]. Hyperlipidemia represents a determinant for the development of atherosclerosis and an important risk factor for cardiovascular disease. When hyperlipidemia is present in the context of the insulin resistance syndrome or metabolic syndrome, it predisposes a particular high risk condition.

This constellation, often referred to as the 'lipid triad', is particularly inducing atherogenic changes in the arterial wall and to promote plague instability, thus predisposing acute cardiovascular events [3].

Liver, an insulin-dependent tissue, that plays a pivotal role in glucose and lipid homeostasis, is severely affected during diabetes. Liver participates in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids and triglycerides. Pharmacological treatment of hyper-lipidemia in particular with statin drugs, was shown to greatly influence cardiovascular morbidity and mortality. A body of evidence also underlines the need for a multidisciplinary approach, integrating non-pharmacological life style and diet interventions, as well as treatment of concomitant diseases like diabetes and hyperlipidemia.

Since the currently available hypolipidemic agents lack desired properties of an ideal drug, research is aimed to find out an effective, safe and less expensive drug [4]. Medicinal plants have been reported to be useful in diabetes worldwide and used empirically as antidiabetic and antihyperlipidemic remedies [5]. Herbal therapy for hypercholesterolemia has no side effects and will be economically effective in reducing the lipid levels. *Tinospora cordifolia* (Guduchi) has been used extensively in the Indian system of medicine since ancient times. It is a glabrous climbing succulent shrub, commonly found in hedges. It is native to India and thrives easily on tropical region [6] and possess a variety of pharmacological activities.

In view of the pathogenic mechanisms involved in the progression of hyperlipidemia and plieotropic effects of *T. cordifolia*, the present study was carried out to evaluate the antihyperlipidemic effect of *T. cordifolia* aqueous extract in STZ induced diabetic rats.

MATERIALS AND METHODS:

Chemicals: Streptozotocin (STZ) was purchased from Sigma Chemicals Co. (USA). Atorvastatin and glibenclamide were provided by Blue Cross Laboratories Limited and Aventis Pharma Limited, India *as gratis*, respectively. Cholesterol and cholic acid were purchased from Himedia Laboratories Private Limited (India). All other chemicals used were of analytical grade.

Plant material collection and preparation of extract: Fresh, mature *Tinospora cordifolia* stem portions were obtained as gratis from M/s SKM Siddha & Ayurveda Nature's Wealth, Erode District, Tamilnadu, India. The plant was identified and authenticated by the Botanist in the Department of Botany, Pachaiyappa's College, University of Madras, Chennai, India. The specimen sample was assessed and validated for its quality by the M/s Natural Remedies Private Limited, Bangalore, India.

The stem portions of the plant were shade-dried at room temperature for 10 days and powdered. The aqueous extract was prepared by soaking the powder in distilled water at the ratio of 1:2 (w/v) with constant stirring for 12-18 hrs and then filtered. The aqueous portion of the filtrate was evaporated by using rotary evaporator (Heidolph, Laborota 4000 efficient) at 40–50°C under reduced pressure, to yield dark brown coloured pasty product. The yield from this process was 4 per cent (w/w).

Experimental animals: Male albino Wistar rats, weighing about 150 - 200 grams were used for the present study. The animals were maintained in cages under controlled animal house conditions with 12/12 hours light/dark cycle. The animals were fed with standard rat feed (M/s Tetragon Chemie Private Limited, Bangalore, India) and provided water *ad libitum* throughout the experimental period. The animals were acclimatized under experimental conditions for one week prior to the start of experiment. All the animal procedures were carried out as per CPCSEA norms and the study was approved by Institutional Animal Ethics Committee (IAEC) of Madras Veterinary College, Chennai (India).

Induction of Diabetes mellitus: Mature normoglycemic rats (blood glucose level of 50-70 mg/dl) [7] were used for the present study. Diabetes was induced in overnight fasted rats by single intraperitoneal injection of STZ (45 mg/kg b.wt.) in 0.1 M cold citrate buffer (pH 4.5). Diabetes was confirmed 3 days (72 hours) after STZ injection by determining blood glucose concentration.

Only animals with blood glucose levels above 250 mg/dl were considered as diabetic.

Experimental design and induction of Hyperlipidemia: Rats were divided into nine groups with 6 animals in each. Hyperlipidemia was induced in STZ induced diabetic animals by oral administration of 0.5 % cholesterol and 0.1 % cholic acid on diet basis in arachis oil (10 ml/kg body weight) along with standard rat feed for 14 days. The composition of the feed fed to animals is as follows:

Carbohydrate – 70.72%; Fat (EE) – 13.77%; Crude protein – 26.29%; Total energy – 2800 Kcal/kg

Groups	Treatments
Group I	Normal control (Citrate Buffer)
Group II	STZ (45 mg/kg B.W *i/p*) (Diabetic control)
Group III	STZ + Cholesterol + Glibenclamide (600 µg/kg B.W *p/o*)
Group IV	STZ + Cholesterol + Atorvastatin (1.2 mg/kg B.W *p/o*)
Group V	STZ + Cholesterol + Glibenclamide + Atorvastatin
Group VI	STZ + Cholesterol + *T. cordifolia* extract I (100 mg/kg B.W *p/o*)
Group VII	STZ + Cholesterol + *T. cordifolia* extract (200 mg/kg B.W *p/o*)
Group VIII	STZ + Cholesterol + Glibenclamide + *T. cordifolia* extract I

All the treatments were started on the fourth day after STZ injection and continued for 14 days. Blood glucose levels and body weight were measured at weekly intervals during the treatment period. At the end of the experimental period, animals were anaesthetized and blood samples were collected from the heart. Serum was separated and stored at -20ºC until assay. After blood collection, the animals were sacrificed and the different tissues (heart, liver, pancreas, and kidney) were excised and stored in 10% formalin for histopathological studies.

Biochemical Analysis: Serum glucose and total cholesterol, triglycerides, HDL-C and creatine kinase were estimated using commercial standard kits (Merck diagnostics, India) using semi auto analyzer.

Acute oral Toxicity Study: Acute oral toxicity of *T. cordifolia* extract in Wistar Female rats was performed as per OECD Guideline 425. Two groups of three rats each were used for the study. Group I served as control and received distilled water. Group II received single oral dose of *T. cordifolia* extract (2000 mg/kg). The animals were observed for gross behavioral, neurological, autonomic and toxic effects at short intervals for 24 h and then daily for 14 days. Feed intake was recorded daily and body weight was recorded weekly. On 14th day, animals were sacrificed and gross pathological examination performed.

Statistical Analysis: The results were expressed as mean ± S.E. All the data were analyzed by one way analysis of variance followed by Duncan's test multiple comparison test [8]. A value of $p<0.05$ was considered statistically significant.

RESULTS:

Effect of *Tinospora cordifolia* extract on Serum Glucose Level: A significant reduction ($P < 0.05$) in blood glucose levels was observed at the end of first week (day 7) of treatment with *T. cordifolia* extract in diabetic rats; this was further reduced after 14 days of treatment. Maximum reduction in blood glucose was observed in group VII with *T. cordifolia* extract at 200 mg/kg compared to glibenclamide and the other treatment **(Table 1).**

TABLE 1. EFFECT OF *TINOSPORA CORDIFOLIA* EXTRACT ON SERUM GLUCOSE LEVEL

Groups	1st Day (mg/dl)	7th Day (mg/dl)	14th Day (mg/dl)
Group I	77.61^{a1}±1.51	77.39^{a1}±1.22	81.26^{a1}±3.00
Group II	363.77^{b2}±12.08	380.81^{c2}±14.58	388.16^{e2}±13.52
Group III	378.94^{b4}±15.28	262.11^{b3}±15.76	158.86^{d2}±10.79
Group IV	379.61^{b2}±11.16	384.82^{c2}±11.46	386.34^{e2}±11.66
Group V	380.05^{b4}±15.50	272.78^{b3}±14.50	154.00^{d2}±12.09
Group VI	385.74^{b4}±14.49	272.27^{b3}±13.24	162.30^{d2}±11.36
Group VII	378.44^{b4}±8.19	247.14^{b3}±17.47	116.90^{bc2}±10.33
Group VIII	389.88^{b4}±7.51	275.74^{b3}±8.51	140.41^{cd2}±5.07
Group IX	375.16^{b3}±17.81	235.61^{b2}±9.25	102.37^{ab1}±4.77

Means bearing different superscripts (a,b,c,d,e) differ significantly between groups ($P<0.05$); Means bearing different superscripts (1,2,3,4) differ significantly between periods ($P<0.05$)

Effect of *Tinospora cordifolia* extract on Serum Triglycerides and Serum Total Cholesterol: The rats in groups II and III showed a marked increased in serum total cholesterol, triglycerides, LDL-C and a fall in HDL-C levels when compared to normal control rats indicating the induction of hyperlipidemia. Treatment with atorvostatin, *T. cordifolia* extract alone or in combination with atorvostatin significantly decreased serum total cholesterol, triglycerides when compared to group II and III. Maximum decrease in serum total cholesterol and triglycerides was observed in group treated with *T. cordifolia* extract at 200 mg/kg and atorvostatin. There was no significant difference between group IX and normal control group.

There was a significant increase in serum HDL-C level in groups IV, V, VI, VII, VIII and IX when compared to rats in group II and III. Treatment with *T. cordifolia* extract at 200 mg/kg alone or in combination with atorvastatin caused significant decrease in serum LDL-C level when compared to diabetic rats and levels of LDL-C were comparable to normal control rats. *T. cordifolia* extract at 200 mg/kg was found to be more effective in reducing LDL-C when compared to atorvastatin alone (**Table 2**).

TABLE 2. EFFECT OF *TINOSPORA CORDIFOLIA* EXTRACT ON SERUM TRIGLYCERIDES, SERUM TOTAL CHOLESTEROL, SERUM HDL-C AND SERUM LDL-C

Groups	Serum Total Cholesterol (mg/dl)		Serum Triglycerides (mg/dl)		HDL-C (mg/dl)	LDL-C (mg/dl)
	1st Day	14th Day	1st Day	14th Day	14th Day	14th Day
Group I	80.00^{a}±1.14	79.90^{a}±1.57	79.86^{a}±1.04	81.99^{a}±1.52	34.46^{e}±1.85	29.05^{a}±2.17
Group II	119.21^{b}±0.88	147.40^{d}±1.75	120.93^{b}±0.59	142.04^{d}±2.37	19.91^{b}±0.49	99.07^{c}±1.69
Group III	119.49^{b}±0.92	164.42^{e}±2.40	121.06^{b}±0.48	158.88^{e}±2.33	14.86^{a}±0.57	117.78^{d}±2.83
Group IV	120.48^{b}±0.54	90.32^{bc}±3.43	119.72^{b}±0.66	99.47^{c}±7.80	27.38^{c}±1.67	43.05^{b}±4.04
Group V	120.14^{b}±0.46	85.44^{ab}±1.47	121.07^{b}±0.67	87.22^{ab}±2.19	29.63^{cd}±1.67	38.36^{b}±1.79
Group VI	118.80^{b}±0.54	93.29^{c}±1.85	120.70^{b}±0.77	102.21^{c}±4.23	28.55^{c}±1.22	44.29^{b}±2.60
Group VII	119.49^{b}±0.51	81.10^{a}±3.71	119.84^{b}±0.50	95.67^{bc}±3.78	31.18^{cde}±0.99	30.79^{a}±3.21
Group VIII	120.21^{b}±0.54	90.58^{bc}±2.17	118.99^{b}±0.69	92.58^{abc}±1.27	30.27^{cd}±0.87	41.79^{b}±2.18
Group IX	121.03^{b}±0.37	79.38^{a}±0.56	119.76^{b}±0.60	82.05^{a}±1.23	33.47^{de}±1.26	29.50^{a}±1.58

Means bearing different superscripts differ significantly between groups ($p<0.05$)

Effect of *Tinospora cordifolia* extract on serum creatine kinase - MB and Serum Free Fatty Acids: Serum creatine kinase - MB level was significantly increased ($P<0.05$) diabetic rats when compared to normal control and these levels were further increased in hyperlipidemic rats (Group III). The serum creatine kinase - MB level was significantly decreased in groups VI, VII, VIII and IX when compared to that of diabetic control group and hyperlipidemic rats. The levels of serum creatine kinase-MB in plant extract treated groups did not differ significantly when compared to that of normal control. **Table 3** shows the alterations in the free fatty acid levels in serum of control and experimental groups of rats. There is a significant elevation in serum free fatty acids levels observed in diabetic and group III rats and these altered free fatty acid levels were restored by treatment with standard drugs and plant extract **(Table 3)**.

Effect of *Tinospora cordifolia* on Atherogenic Index: The atherogenic index values were showed a significant increase in diabetic group and group III when compared to normal control group. The atherogenic index values were nearly similar in groups V and VI. There is no significant difference between high doses of plant extract administered groups (groups VII and IX) and normal control group **(Table 3)**.

TABLE: 3 EFFECT OF *TINOSPORA CORDIFOLIA* EXTRACT ON SERUM CREATINE KINASE-MB, SERUM FREE FATTY ACID LEVELS AND ATHEROGENIC INDEX

Groups	Creatine kinase - MB (IU/L) 14th day	Serum free fatty acids (mg/dl) 14th day	Atherogenic index (Units)
Group I	105.47^{a}±3.42	74.67^{a}±1.22	1.35^{a}±0.13
Group II	131.00^{cd}±2.59	105.28^{d}±1.81	6.43^{c}±0.23
Group III	140.37^{d}±4.19	120.94^{e}±2.96	10.14^{d}±0.46
Group IV	122.69^{bc}±3.92	80.24^{b}±1.24	2.37^{b}±0.27
Group V	114.09^{ab}±2.26	77.42^{ab}±0.36	1.92^{ab}±0.14
Group VI	113.35^{ab}±3.30	90.46^{c}±0.99	2.29^{b}±0.15
Group VII	107.48^{a}±2.01	81.35^{b}±0.62	1.60^{a}±0.11
Group VIII	106.68^{a}±4.06	78.84^{ab}±0.39	2.00^{ab}±0.10
Group IX	104.72^{a}±5.29	75.41^{a}±0.55	1.39^{a}±0.10

Means bearing different superscripts differ significantly between groups ($p<0.05$)

Effect of *Tinospora cordifolia* on Vital Organs: STZ induced diabetic control rats showed marked microscopical changes like degeneration of islet cell in pancreas **(Fig. 1B)** and tubular epithelial cell degeneration with interstitial nephritis in kidney **(Fig. 2B)** when compared to that of normal control rats.

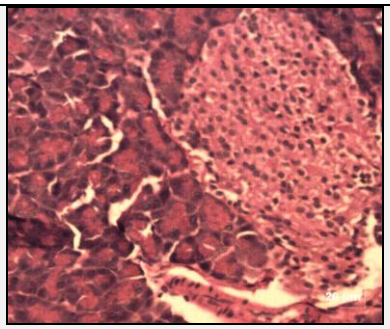

FIG. 1A: PANCREAS - NORMAL CONTROL

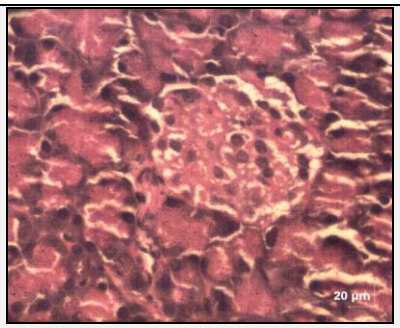

FIG. 1B: PANCREAS - DIABETIC CONTROL

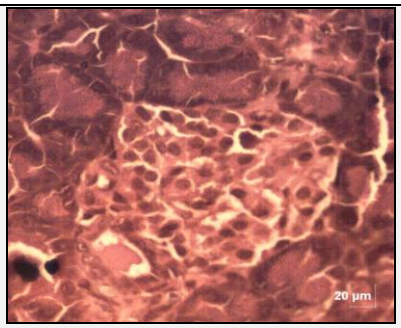

FIG. 1C. PANCREAS – TREATED WITH *TINOSPORA CORDIFOLIA* EXTRACT 200mg/kg

But this degenerative changes in pancreas and kidney were restored back to near normal in 200 mg/kg b.wt. of *Tinospora cordifolia* extract treated group when compared to diabetic control group **(Fig.1C & Fig. 2C)**.

Histopathological examination of liver and heart showed no remarkable changes.

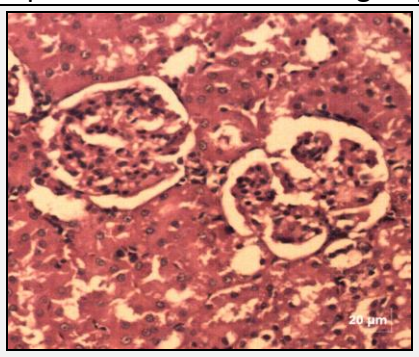

FIG. 2A; KIDNEY - NORMAL CONTROL

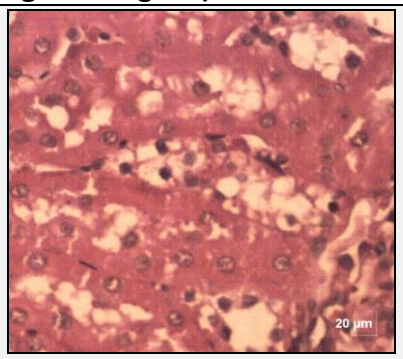

FIG. 2: KIDNEY - DIABETIC CONTROL

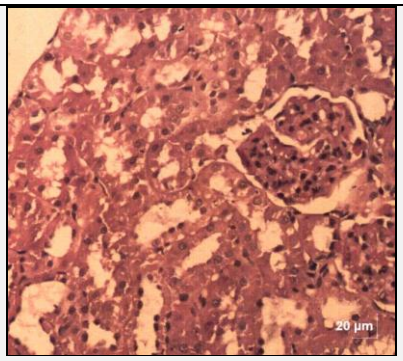

FIG. 2C: KIDNEY – TREATED WITH *TINOSPORA CORDIFOLIA* EXTRACT 200mg/kg

DISCUSSION: STZ was widely used for inducing type I diabetes in a variety of animals [9]. In the present study, STZ (45 mg/kg, i.p.) produced significant hyperglycemia and body weight loss. The hyperglycemia was persistent throughout the experimental period, since STZ caused degeneration of islets of Langerhans of pancreas [10].

TCAE showed significant and consistent reduction in fasting blood glucose levels and also it significantly improved the body weight loss at different intervals throughout the period of experiment as compared to the vehicle treated diabetic controls indicating its potent antidiabetic activity. Since *T. cordifolia* extract could not exert any effect on normoglycemic animals, but reduced the blood glucose level, it may exert its mode of action on extrapancreatic pathways rather than stimulating insulin secretion like glibenclamide. It includes stimulation of peripheral glucose utilization or retarding gluconeogenesis or decreasing the intestinal absorption of glucose [11].

However, histological examination revealed a recovery from degenerative changes in islets brought out by the *T. cordifolia*, indicating its capacity to regenerate the damaged cells. This may augment the release of insulin and reversal of hyperglycemia as that of glibenclamide.

The rise in the level of serum triglycerides and total cholesterol is attributed due to accumulation of lipids and insulin deficiency induced derangements in lipid metabolism. These observations were observed on first and throughout the period of experiment [12, 13, 14]. Hypercholesterolemia in the present study was high on 14th day in STZ induced diabetic group which may be due to inhibited actions of lipolytic hormones on fat depot and phospholipids along with cholesterol and triglycerides were discharged from liver to blood [11].

However, *T. cordifolia* extract at 200 mg/kg b.w. could produce better effect than glibenclamide. According to Randle's glucose-fatty acid cycle, increased triglycerides will elevate free fatty acids availability and oxidation that impair insulin action, via glucose

utilization leading to development of hyperglycemia [14]. Therefore, the reduction of triglyceride following *T. cordifolia* extract treatment might facilitate better utilization of lipid along with reduction in hyperglycemia. The restoration of lipoprotein lipase activity will bring back triglyceride level to normal and *T. cordifolia* extract was able to correct the high triglyceride to normal, there by indicating its possible action on lipase [1].

In the present study, *T. cordifolia* extract at both doses produced a remarkable increase in serum HDL-C and the effect was comparable to that of atorvastatin alone and atorvastatin combined with glibenclamide treated rats. An increase in total lipids in liver and kidney in STZ induced diabetic rats indicate an increased synthesis of lipids and storage capacity which in turn increase the triglyceride and phospholipids. HDL serves as acceptor of lipids for ultimate excretion in bile. The ability of *T. cordifolia* to increase HDL-C is largely attributed to its central function in the reverse cholesterol transport, a process whereby excess cell cholesterol is taken up and processed by HDL particles for further delivery to the liver for metabolism [15, 16].

Therefore it is logical that an increase in HDL-C level can contribute to lower risk of atherosclerosis [17]. It is observed from the present study that *T. cordifolia* extract is capable of increasing the serum level of good cholesterol i.e., Serum HDL-C in the treated rats compared to diabetic rats, thereby indicating its usefulness as a potent therapeutic agent [18].It is widely accepted that elevation of plasma LDL-C levels is the major risk factor for CVD. Direct correlation exists between LDL-C and atherosclerosis and also the reversibility of the related pathological events by lowering the serum LDL-C level [19].

In our study, *T. cordifolia* extract at 200 mg/kg b.w. dose independently increased HDL-C level to near normal. Our result indicates that, high concentration of LDL-C in diabetic and hyperlipidemic rats was significantly reduced by oral administration of *T. cordifolia* extract. Therefore, *T. cordifolia* might constitute a good candidate for the treatment of CVD and atherosclerosis by lowering serum LDL-C which is responsible for formation of lipid peroxidase that specifically leads to atherogenesis. STZ induced diabetic rats showed an increase in serum creatine kinase - MB. *T. cordifolia* extract in both doses decreased the serum creatine kinase - MB level. Increased serum creatine kinase level in diabetic rats indicates cardiac muscular damage [20]. The quantity of enzyme released from the damaged tissue is a measure of the number of necrotic cells [21]. This indicates possible correlation between this enzyme with cardiomyopathy in diabetes. The extract of *T. cordifolia* extract was able to reverse the level of creatine kinase in treatment groups, there by showing its ability to protect STZ induced cardiomyopathy caused by STZ.

The significant increase of free fatty acid may be due to breakdown of membrane phospholipids by the action of oxygen derived free radicals induced during hyperlipidemia or increased activity of phospholipase [22]. In the present study, *T. cordifolia* extract was able to reduce the free fatty acid level, thereby indicating its antioxidant properties during hyperlipidemic conditions. A decrease in atherogenic index by administering *T. cordifolia* extract in diabetic rats indicates its antihyperlipidemic and antiatherogenic potentials.

The pancreas of diabetic control rats showed islet cell degeneration because of action of STZ on the islet cells. In the present study, *T. cordifolia* extract at 200 mg/kg b.w. caused regeneration of damaged cells. The kidney of diabetic rats showed tubular epithelial degeneration and interstitial nephritis suggestive of diabetic nephropathy because of altered metabolism of lipids and carbohydrates [23].

Treatment of *T. cordifolia* extract at 200 mg/kg b.w. ameliorated the degenerative changes and nephritic conditions, thereby making the kidneys returns to near normalcy. The reversal of serum glucose and lipid profiles and also the normalization of renal nephropathic changes after the administration of *T. cordifolia* extract are suggestive of a beneficial role of *T. cordifolia* in STZ induced nephropathy.

The proposed study revealed that aqueous extract of *T. cordifolia* can be considered as an important addition to the therapeutic armamentarium for the treatment of hyperlipidemia associated with diabetes. Further studies at the cellular and molecular level, may give clues regarding its mechanism in detail.

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REFERENCES:

1. Ravi K, Rajasekaran S, and Subramanian S: Antihyperlipidemic effect of *Eugenia jambolana* seed kernel on STZ-induced diabetes in rats. Food and Chemical Toxicology 2005*;* 43(9): 1433 – 1439.
2. Saravanan R, Rajendra Prasad N and Pugalandi KV: Effect of *Piper beetle* leaf extract on alcoholic toxicity in the rat brain. J. Med. Food 2003; 6(3): 261 – 265.
3. Bertolotti M, Maurantonio M, Gabbi C, Anzivinio C and Carulli N: Review article: Hyperlipidemia and cardiovascular risk. Ailment Pharmacol Ther 2005; 22(2): 28-30.
4. Ramesh B and Pugalendi KV: Antihyperlipidemic and antidiabetic effects of umbelliferone in STZ diabetic rats. Yale J. of Biol and Med. 2005; 78: 187 – 194.
5. Shukla R, Sharma SB, Puri D, Pabhu KM and Murthy PS: Medicinal plants for treatment of diabetes mellitus. Indian J. Clinical. Biochem. (Suppl.) 2000; 15: 169-177.
6. Prince PSM, Menon VP and Gunasekaran G: Hypolipidaemic action of *Tinospora cordifolia* roots in alloxan diabetic rats. J. Ethopharmacol 1999; 64(1): 53-57.
7. Christopher LC, Mathuram LN and Sriram P: Effect of Eicosapentaenoic acid on biochemical parameters in diabetic rat. Ind. Vet. Journal 2003; 80: 81-91.
8. Snedecor GW and Cochran WG: *Statistical methods*. Iowa State University press, USA; 1994.
9. Merzouk H, Madani S and Chabane D: Time course of changes in serum glucose, insulin, lipids and tissue lipase activities in macrosomic offspring of rats with STZ- induced diabetes. Clin. Sci 2000; 98: 21–30.
10. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A, Allah Verdi A, Mofidian SMA and Lame rad B: Induction of diabetes by streptozotocin in rats, Ind J. of Cli. Biochem 2007; 22(2): 60-64.
11. Saha P, Selvan VT, Mondal SK, Mazumder UK and Gupta M: Antidiabetic and antioxidant activity of methanol extract of *Ipomoea reptans* Poir aerial parts in streptozotocin induced diabetic rats. Pharmacologyonline 2008; 1: 409-421.
12. Shukla R, Anandh K, Prabhu KM and Suryanarayana murthy P: Hypolipidemic effect of water extracts of *Ficus bengalensis* in alloxan-induced diabetes mellitus in rabbits. J. Clin. Biochemistry 1995; 10: 119-121.
13. Anandhan R, Latha M, Ramkumar KM, Pari L and Baskar C: Effect of *Gymnema montanum* leaves on serum and tissue lipids in alloxan diabetic rats. Experimental Diab. Res 2003; 4: 183-189.
14. Muruganandan S,Srinivasan K, Gupta S, Gupta PK and Lal J: Effect of mangiferin on hyperglycemia and atherogenicity in STZ diabetic rats. J. of Ethnopharmacol 2005; 97: 497-501.
15. Martinez LO, Jacquet S, Terce F, Collet X, Perret B and Barbaras R : New insight on the molecular mechanism of high-density lipoprotein cellular interactions. Cellular and Molecular life science 2004; 61(81): 2343-60.
16. Yokozawa T, Cho EJ, Sasaki S, Satoh A, Okamoto T and Sei Y: The protective role of Chinese prescription *kangen-karyu* extract on diet-induced hypercholesterolemia in rats. Biol. Pharm. Bull 2006; 29(4): 760-5.
17. Nofer JR, Kehrel B, Fobker M, Levkau B, Assmann G and von Eckardstein A: HDL and atheroscerosis: beyond reverse cholesterol transport. Atherosclerosis 2002; 161(1): 1-16.
18. Nagaraja PK, Kammar KF and Devi S: Efficacy of *Tinospora cordifolia* (Willd.) extracts on blood lipid profile in STZ induced diabetis rats. Biomed Res. 2007; 18: 179–83.
19. Bahramikia S and Yazdanparast R: Effect of hydroalcoholic extracts of *Nasturtium officinale* leaves on lipid profile in high fat diet rats. J. Ethnopharmacol. 2008; 115(1):116-21.
20. Hagar HH: Folic acid and vitamin B_{12} supplementation attenuates isoprenaline-induced myocardial infarction in experimental hyperhomocysteinemic rats. Pharmacol res. 2002; 46(3):213-19.
21. Manjula TS, Geetha A, and Devi CS: Effects of aspirin on isoproterenol induced myocardial infarction-a pilot study. Indian J Biochem Biophys. 1992; 29(4):378-9.
22. Geetha G, Prasanth KG, Samuel Thavamani B, Prudence AR and Hari Bhaskar V: Hypolipidemic effect of *Achyranthes rubrofusca* Linn. Whole plant extracts in high fat diet induced hyperlipidemic rats. *Pharmacologyonline* 2008; **1:** 466-473.
23. Selvan VT, Manikandan L, Senthil Kumar GP, Suresh R, Kakoti BB, Gomathi P, Kumar DA, Saha P, Gupta M, Mazumder UK: Antidiabetic and antioxidant effect of methanol extract of *Artanema sesamoides* in STZ induced diabetic rats. Int. J. of Applied Research in Natural products 2008; 1(1): 25-33.

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