Antidiabetic, Antihyperlipidemic, Antioxidant Property of *Cordia obliqua* on Streptozotocin Induced Diabetic Rats

Prakash Ramakrishnan*, Dhivya Ramadoss, Priyadarshini Muthulingam, Ramya Nedunchezhian, Karthick Krishnamoorthy

Department of Pharmacology, KK College of Pharmacy, Gerugambakkam, Chennai 600128, Tamil Nadu, INDIA.

ABSTRACT

Objective: The main objective is to investigate the antidiabetic, antihyperlipidemic and antioxidant activity of methanolic extract of *Cordia obliqua* (MECO) in streptozotocin- induced diabetic rats. **Methods**: Acute toxicity study of MECO was carried out in rat to determine its dose for further study. Oral glucose tolerance test was performed to evaluate MECO on elevated blood glucose levels. Diabetes was induced in rats by administration of streptozotocin (STZ) (45 mg/kg) and it was confirmed 3 days after induction. The methanolic extract of *Cordia obliqua* (MECO) was orally given to the diabetic rats up to 21 days and the blood glucose levels were estimated at the end of each week. On 21st day of the experiment, rats were sacrificed after the blood collection for the biochemical, antioxidants in kidney and pancreas was isolated for histopathological observation. **Results**: Acute toxicity MECO did not show toxicity and death up to a dose of 2000mg/kg in rats. MECO 200mg/kg and 400 mg/kg doses significantly (P<0.005) reduced blood glucose levels in OGTT. Both the doses MECO treatment significantly (P<0.005) increased the body weight, HDL by dose dependently when compared with STZ treated rats. Also, MECO treated rats significantly (P<0.005) decreased the blood glucose, SGOT, SGPT and ALP when compared with STZ treated rats. Normalized the lipid, antioxidant levels were reversed to near normal in diabetic rats treated with MECO. **Conclusion:** From the above results it was concluded that the plant extract having the ability of managing hyperglycemic and complication of diabetes in STZ induced diabetic rats. Hence this plant may be considered as one of the source for the isolation of new oral anti hypoglycemic agent.

Key words: *Cordia obliqua,* Diabetes mellitus, Streptozotocin, Oral glucose tolerance, Hyperglycemic.

Correspondence :

Dr. Prakash Ramakrishnan, M.Pharm., Ph.D., Professor& Head, Department of Pharmacology, KK College of Pharmacy, Gerugambakkam, Chennai, Tamil Nadu, INDIA.

Phone: 9940634459

Email: prakasheeba@rediffmail.com

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder due to absolute or relative lack of insulin and characterized by hyperglycemia in the postprandial and or fasting state, mainly associated with ketosis and protein wasting in severe condition.[1] DM affects approximately 4% of the population worldwide and is expected to increase by 4.5% in 2025. Diabetes is a chronic disease caused by inherited and or/ acquired deficiency in production insulin by the pancreas or by the ineffectiveness of the insulin produced. Hyperlipidemia and hyperglycemia are two important characters of diabetes mellitus.[2] Free radicals derived from oxygen have been implicated in the pathophysiology of various diseases including diabetes mellitus. Moreover, also, evidence suggested that diabetes induced changes in the activities of antioxidant in various tissues.[3] Oxidative stress is involved in the development and progression of various complications such as atherosclerosis, diabetic nephropathy and neuropathy. Currently, the available therapy for diabetic includes insulin and various oral anti-diabetic agents include sulfonyl ureas, biguanide, thiazolidinedione, and α glucosidase inhibitors.[4] These agents, however, have restricted usage due to several undesirable side effects and fail to significantly alter the course of diabetic complications. In Ayurvedic and Siddha medicines, there are a number of Indian medicinal plants which have found to be useful to successfully manage diabetes. Advantage of traditional medicinal plants is no or lesser adverse effects with multiple therapeutic actions due to the presence of different bioactive compounds.[5]

Cordia obliqua Wild is an important medicinal plant belonging to the family Boraginaceae.[6] It is useful as an expectorant and effective in treating the diseases of the lungs. In the raw condition, they contain a gum which can be used beneficially in gonorrhea.[7] Seeds are utilized as an anti-inflammatory agent.[8] The fruits are also useful in treating coughs, the diseases of the chest, and chronic fever. They lessen thirst and the scalding of the urine, remove pain from the joints and the burning of throat and are also effective in treating the diseases of the spleen. Fruits are used as a demulcent in southern Iran.[9] The preliminary phytochemical analysis of MECO revealed presence of tannins, flavonoids, saponins and phenolic compounds.[10] It is well known phytochemical constituents from this group were reported for many pharmacological actions including antidiabetes activity.

Moreover up to date literature research revealed that there is no scientific report on *C. obliqua* plant to supports its use in the treatment of diabetes. Hence, objective of the present study is to investigate Antidiabetic, Antihyperlipidemic and antioxidant potential of methanolic extract of *Cordia obliqua* in STZ induced diabetic rats.

MATERIALS AND METHOD

Plant material and extract

Cordia obliqua plants were collected from Chennai, Tamilnadu during 2016. The plant material were shade dried, powdered and extracted with water and methanol using soxhlet apparatus. The extracts was concentrated in rotary evaporator at 35-40°c under reduced pressure. The MECO was stored at 2-8°C until the completion of pharmacological studies and the yield of the extract was 15% (w/w).

Preliminary Phytochemical screening[11, 12]

Several phytochemical tests were performed for testing various different chemical groups present in methanolic extracts.

Experimental animals

Wistar albino rats (180-220 gm) were used to assess anti-diabetic activity. The rats were kept and maintained under standard laboratory conditions. The animal were fed with standard laboratory diet and allowed to drink water *ad libitium*. The studies were carried out in accordance with the institutional ethical guidelines for the care of laboratory animals.

Chemicals

STZ and all other chemicals used in this study were analytically grade and procured from sigma Aldrich laboratory, Mumbai.

Acute toxicity study

Acute toxicity studies were performed according to the organization for economic co-operation and development (OCED 423). The MECO was administered orally to the rats at a dose of 2000 mg/kg. After the rats were orally administered, they were observed individually during first hour and then every 6 h, then up to 24 h, for toxicity determination with special attention and for any physical signs of toxicity such as writhing, gasping, palpitation and mortality [13].

Oral glucose tolerance test

The oral glucose tolerance test (OGTT) was performed in overnight fasted normal rats. Rats were divided into three groups (n = 6). Group I served as normal control and received orally distilled water (5 ml/kg) and groups II and III, received MECO orally at the doses of 200 and 400 mg/kg respectively. After these treatments all groups received glucose (5 g/kg) orally. Blood was withdrawn from the tail vein just prior to and 30, 60, 120 and 240 min after the oral glucose administration.[14] Blood glucose levels were measured using single touch glucometer (Accu-check, Roche Diagnostics, USA).

Induction of experimental diabetes

Diabetes was induced in overnight fasted rats by STZ (45mg/kg, i.p) after dissolving in freshly prepared cold citrate buffer.[15] STZ induce fatal hypoglycemia as a result of massive pancreatic insulin release, the rats were provided with 5% dextrose solution after 6 hours of STZ administration for next 24 hours to prevent hypoglycemia.[16] Diabetes was confirmed 72 h after induction by measurement of tail vein blood glucose levels with the glucose meter. Diabetic rats were kept for 14 days under standard laboratory condition for the stabilization of blood glucose level.[17] After 14 days induction of diabetes, blood glucose was again determined and only animals with a blood glucose level greater than 300 mg/dL were selected for the study.

Experimental design

Rats were divided into five groups each consists of minimum of six animals.

Groupings	Treatment
1	Normal rats received CMC (5 ml/kg., p.o.)
2	STZ-induced diabetic rats (45 mg/kg., i.p)
3	STZ-induced diabetic rats with glibenclamide (5 mg/kg., p.o.)
4	STZ-induced diabetic rats with MECO (200 mg/kg., p.o.)
5	STZ-induced diabetic rats with MECO (400 mg/kg., p.o.)

The vehicle, MECO and glibenclamide were administered orally to the respective groups for 21 days. The fasting blood glucose level and weight were estimated on 0,7,14, 21 days periodically. At the end of the experimental period the blood was collected from all the animals through retro-orbital plexus and rats were sacrificed and pancreas was isolated after the blood collection for the estimation of biochemical parameters.

Estimation of blood glucose and body weight

The body weight and fasting blood glucose level was determined after 21 days of treatment with extracts and drug control. The blood was collected from the tip of the tail vein from the overnight fasted rats and the blood glucose was measured (using Gluco Chek glucose estimation kit) [Aspen diagnostic (P) Ltd. Delhi, India]. The results were expressed in terms of milligrams per deciliter (mg/dL) of blood. Body weight of all experimental animals was recorded using a digital weighing scale.

Measurement of Biochemical parameters

Estimation of serum cholesterol was carried out by Zlatkis method.[18] Serum triglycerides were estimated by Foster and Dunn method[19] and HDL-cholesterol was estimated by Burstein method.[20] The VLDL cholesterol was calculated using the formula, TG/5 mg/dl. The serum LDL cholesterol was calculated by Friedwald formula.[21] Plasma SGOT and SGPT activities were determined by Reitman and Frankel method.[22] Activity of serum alkaline phosphatase (ALP) was determined by p-nitro phenyl phosphate method.[23]

Estimation of antioxidant levels

Kidneys was dissected out and washed immediately with ice cold saline to remove blood. The antioxidants such as TBARS, SOD, GPx, GSH and CAT were estimated.[24]

Histopathological investigation

The animals were sacrificed and pancreas was dissected out, washed in normal saline, for Histopathological studies. Pancreatic tissues were fixed in 10% formalin, dehydrated with 50%-100% ethanol solution, and embedded in paraffin. The sections of 5μm thick were cut and stained with hematoxyllin-eosin, then examined under light microscope.

Statistical analysis

All the data expressed as mean ± SEM were analyzed by one-way analysis of variance (ANOVA), followed by Dunnett's test using Prism Graph Pad and values of $P<0.05$ were considered as statistically significant.

RESULTS

Phytochemical analysis

Phytochemical analysis showed presence of flavonoids, phenolics, alkaloids, tannins and saponins.

Acute toxicity study

The oral administration of MECO treated rats upto the dose of 2000 mg/kg did not exhibit any signs of toxicity for 14 days. It indicates that MECO was nontoxic in rats up to an oral dose of 2000 mg/kg of body weight. Therefore, the biological evaluation was carried out using 1/10 and 1/20 dose of MECO *i.e.* 200 mg/kg and 400 mg/kg dose levels.
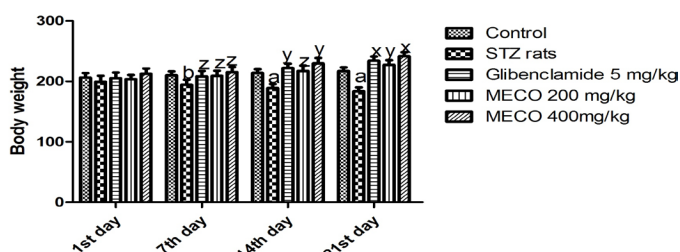
Effect of MECO on OGTT

Glucose challenge to normal rats increased blood glucose levels with maximum level at 60 minutes and returned to normal level at 240 min. The MECO administration improved glucose tolerance significantly ($P<0.001$ and $P <0.001$) at 30 min to 120 min compared to diabetic control animals. Glucose loading to normal rats (OGTT) increased serum glucose levels from 61.26 ± 1.7 to 174. 66 ± 5.8 at 60 min and reduced to normal at 240 min. In MECO treated rats improved glucose tolerance significantly ($P<0.001$) in a dose dependent manner (Figure 1).

Effects of MECO on body weight and blood glucose

Typographical error such as Table 1 is not cited. The STZ treated rats produced marked hyperglycemia as significant ($P<0.001$) elevation
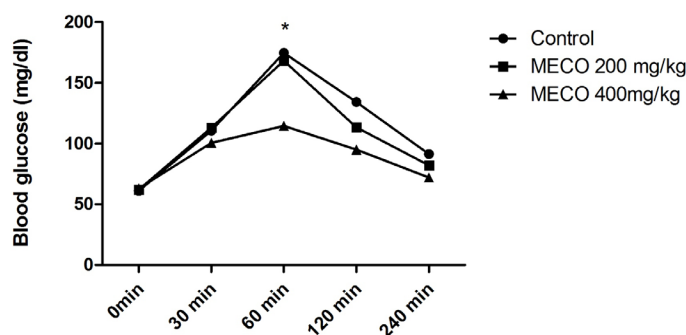
Figure 1: Effect of MECO on oral glucose tolerance test (n=6). *P<0.001 compared to control rats.

Figure 2: Effect of MECO on body weight in STZ induced diabetic rats (n=6). aP<0.001, bP<0.01 and cP<0.05 compared to control rats. xP<0.001, yP<0.01 and zP<0.05 compared to control rats.
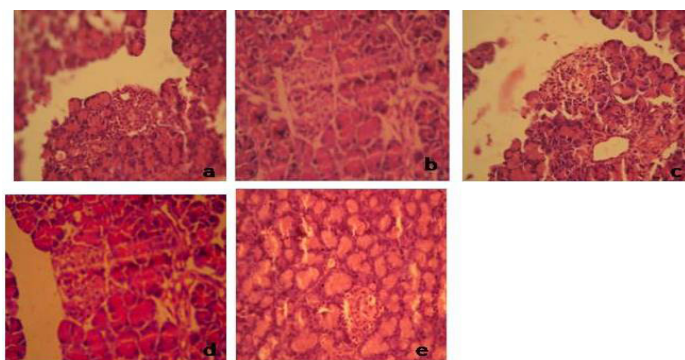
Figure 3: Histopathology of Pancreas a: Control b. Diabetic control indicates necrosis of β cells, karyolysis and nuclear changes. c. Diabetic rats treated with Glibenclamide. (5 mg/kg) showed prevented the destruction of β cells. d. Diabetic rats treated with MECO 200 mg/kg showed minimal damage of β cells e. Diabetic rats treated with MECO 400 mg/kg showed that prevented the β cells almost near to standard glibenclamide treated rats.

in blood glucose level as compared to control rats. Administration of MECO in STZ induced diabetic rats at the dose of 200 and 400 mg/kg produced significant (P<0.001) and dose dependent fall in blood glucose levels when compared with STZ treated rats.

Normal rats were found to be stable in their body weight, but STZ treated rats, the body weight was significantly (P<0.001) decreased when compared to the normal rats. In STZ caused body weight reduction which was significantly reversed by MECO (200 and 400 mg/kg) and gliben-clamide (5 mg/kg) regained the body weight to near normal which is comparable with the normal rats (Figure 2).

Effect of MECO on SGOT, SGPT and ALP levels

The effects of MECO on the levels of SGOT, SGPT and ALP in control and diabetic rats are given in table 2. In STZ induced diabetic rats, all the biochemical parameters are significantly (P<0.001) increased when compared to control rats. The increase levels of SGOT, SGPT and ALP were significantly reduced after the administration of both doses of MECO (200 and 400 mg/kg) by dose dependently and Glibenclamide (5 mg/kg) in compared with STZ induced diabetic rats.

Effect of MECO on lipid profile

In STZ rats, significant (*P*<0.001) elevated level of total cholesterol, triglycerides, LDL and VLDL as well as decreased levels of HDL were observed, compared to normal rats. Both the doses of MECO significantly reduced elevated TC, TG, LDL and VLDL level in STZ induced diabetic rats. In MECO 400 mg/kg shows significant (P<0.05, P<0.01 and P<0.001) higher reduction of TC, TG, LDL and VLDL level in diabetic rats than MECO 200 mg/kg. Moreover, HDL level was significantly (P<0.001) increased in diabetic rats treated with MECO both doses and Glibenclamide than diabetic control rats. The administration of MECO 400 mg/kg increases in HDL levels significantly (P<0.001) than MECO 200 mg/kg (Table 3).

Effect of MECO on antioxidant levels

There was a significant elevation in TBARS and reduction in SOD, CAT and GSH level in kidney of diabetic rats compared to control rats. The administration of MECO (200 and 400 mg/kg) and glibenclamide significantly (P<0.001) reversed these changes to near normal levels (Table 4).

Histopathological investigation

The control rats showed normal structure of β-cells in the islet of Langerhans on the endocrine portion and normal structure of acini in exocrine portion. In diabetic control rats nuclear changes, karyolysis and residue of destroyed cells were observed. Treatment of MECO 200 mg/kg to the diabetic rats showed minimal necrosis of β cells when compared to diabetic control rats. At high dose of MECO 400 mg/kg treated diabetic rats prevented destruction of β cells and size of islets of Langerhans towards normal when compared to diabetic control rats. The standard drug glibenclamide also prevented the destruction of β cells and increases its number as well as size than diabetic rats (Figure 3).

DISCUSSION

The treatment of diabetes with medicines of plant origin that proved much safer than synthetic drugs is an integral part of many cultures throughout the world and gained importance in recent years. India has a rich history of using various potent herbs and herbal components for treating various diseases including diabetes.[25]

The present study is to investigate Antidiabetic, antihyperlipidemic and antioxidant potential of methanolic extract of *Cordia obliqua* in diabetic rats. In our study STZ was used to induce diabetes mellitus in rats. In STZ (45 mg/kg) treated rats were showed partially destructs the beta cells resulting in insufficient insulin secretion causing type 2 diabetes.[26] It is widely accepted animal model and reported to resemble human hyperglycemic non ketotic diabetes mellitus[27] is often associated with kidney hypertrophy which may contribute to end stage renal damage, hepatotoxicity, oxidative stress and hypercholesterolemia.[28, 29]

Acute toxicity study of the methanolic extract demonstrated that two different doses of *Cordia obliqua* were non-toxic throughout the experiment. The lethality was found to be zero in the groups of *Cordia obliqua* extract. Phytochemical investigation of MECO reveals the presences of flavanoids, saponins and tannins and phenolic compounds. It is well known that certain flavonoids exhibit hypoglycemic activity and pancreas beta cell regeneration ability.[30] These principles phytoconstituents are known to be bioactive for the management of diabetes. In our present study the MECO produced significant antihyperglycemic activity at a dosage of 400 mg/kg when compared with STZ treated rats.

Table 1: Effect of MECO on blood glucose in STZ induced diabetic rats (n=6).

Treatment	Blood glucose level (mg/dl)			
	Day 1	Day 7	Day 14	Day 21
Control	62.50± 2.83	65.92± 3.15	72.87 ± 1.26	61.12 ± 0.89
Diabetic control	505.12 ± 9.56 [a]	450.16 ± 8.65[a]	403.80 ± 8.20[a]	291.80 ± 2.20[a]
Glibenclamide 5 mg/kg	425.16 ± 8.12	265.67 ± 12.23[x]	199.77 ± 1.70[x]	97.10 ± 2.80 [x]
MECO 200 mg/kg	498.17 ± 10.12	430.18 ± 5.90[1]	306.89 ± 3.50[y,1]	130.99 ± 1.70[x,2]
MECO 400 mg/kg	490.16 ± 9.15	402.16 ± 7.78[1]	229.85 ± 2.20[x,1]	119.12 ± 3.33[x]

[a]$P<0.001$ diabetic control compared with control group. [x]$P<0.001$, [y]$P<0.01$, [z]$P<0.05$ MECO 200, 400 mg/kg and glibenclamide 5 mg/kg compared with diabetic control. [1]$P<0.001$, [2]$P<0.01$, [3]$P<0.05$ MECO 200, 400 mg/kg compared with glibenclamide 5 mg/kg.

Table 2: Effect of MECO on SGOT, SGPT, ALP in STZ induced diabetic rats (n=6).

Treatment	Serum marker enzyme (U/L)		
	SGOT	SGPT	ALP
Control	62.09 ± 0.87	69.10 ± 1.48	122.57 ± 0.60
Diabetic control	153.21 ± 9.80[a]	134.98 ± 11.59[a]	243.68 ± 12.32 [a]
Glibenclamide 5mg/kg	73.21 ± 6.10[x]	72.18 ± 7.68 [x]	128.18 ± 12.89[x]
MECO 200 mg/kg	94.93 ± 8.35[y]	85.10 ± 12.25[x]	145.87 ± 9.67[y]
MECO 400 mg/kg	80.89 ± 7.92[x]	79.10 ± 11.30[x]	130.10 ± 8.87[x]

[a]$P<0.001$ diabetic control compared with control group. [x]$P<0.001$, [y]$P<0.01$, [z]$P<0.05$ MECO 200, 400 mg/kg and glibenclamide 5mg/kg compared with diabetic control.

Table 3: Effect of MECO on Lipid profile in STZ induced diabetic rats (n=6).

Treatment	Serum lipid levels (mg/dL)				
	Total cholesterol	Triglycerides	HDL	LDL	VLDL
Control	148.78 ± 1.79	159.98 ± 2.05	81.25 ± 0.95	52.10 ± 2.10	35.61 ± 0.31
Diabetic control	251.10 ±12.10[a]	281.25 ± 10.95[a]	25.01 ± 11.29[a]	262.10 ± 12.8 [a]	113.10 ± 8.57[a]
Glibenclamide 5mg/kg	160.87 ± 5.57[x]	186.12 ± 6.52[x]	50.90 ± 5.25[x]	85.12 ± 9.35[x]	56.87 ± 9.80[x]
MECO 200 mg/kg	195.86 ± 8.20[y]	238.95 ± 7.90[z]	35.17 ± 6.81[y]	112.89 ± 8.90[x]	77.85 ± 6.93[x]
MECO 400 mg/kg	165.32 ± 11.39[x]	227.87 ± 12.50[z]	42.81 ± 8.95[y]	92.18 ± 11.50 [x]	62.89 ± 5.90[x]

[a]$P<0.001$ diabetic control compared with control group. [x]$P<0.001$, [y]$P<0.01$, [z]$P<0.05$ MECO 200, 400 mg/kg and glibenclamide 5mg/kg compared with diabetic control.

Table 4: Effect of MECO and Glibenclamide on Kidney antioxidant enzymes in STZ induced diabetic rats (n=6).

Treatment	SOD (U/mg protein)	CAT (μ mole/L of H_2O_2/ min/mg protein)	GSH (mg of GSH/mg protein)	TBARS (μ M of MDA/ min/mg protein)
Control	106.64 ± 1.46	25.57 ± 0.61	1.56 ± 0.01	165.58 ± 1.22
Diabetic control	61.50 ± 8.35 [a]	11.86 ± 10.33 [a]	0.467 ± 1.21[a]	328.28 ± 6.04 [a]
Glibenclamide 5mg/kg	91.63 ± 6.93 [y]	18.67 ± 0.41[y]	0.86 ± 0.12 [x]	202.33 ± 5.61[x]
MECO 200 mg/kg	71.43 ± 8.83	13.25 ± 0.25	0.58 ± 0.18	269.07 ± 6.50 [y]
MECO 400 mg/kg	85.44 ± 11.62 [y]	16.03 ± 0.44	0.73 ± 0.26 [y]	250.08 ± 8.85 [y]

[a]$P <0.001$ diabetic control compared with control group. [x]$P <0.001$, [y]$P <0.01$, [z]$P <0.05$ MECO 200, 400 mg/kg and glibenclamide 5mg/kg compared with diabetic control.

In diabetic patients, the main objective of the treatment is to lower blood glucose to near- normal levels.[31] The oral glucose tolerance test confirmed blood glucose lowering activity of MECO. The onset of anti-hyperglycemic action was observed from 60 min of the treatment and a steady state increase in the action continued up to 120 min. The MECO may be involved in enhancement of glucose utilization, so blood glucose levels were significantly decreased in glucose loaded rats. The decrease in body weight, increase in food and water intake was commonly observed in diabetes and it may be due to metabolic changes caused by lack or deficiency of insulin due to destruction of β- cells.[32] In STZ induced diabetic rats, drastic reduction in body weight changes observed might be the result of degradation or catabolism of structural proteins due to

unavailability of carbohydrate for the energy metabolism and increased muscle wasting in diabetes.[33, 34] Previous reports supports for our study reports diabetic rats significantly reduced the body weight when compared to normal rats and body weight was significantly increased in diabetic rats treated with MECO showed the blood glucose stabilization effect which in turn prevents the loss of body weight.

Liver is the vital organ of metabolism, detoxification, storage and excretion of xenobiotics and their metabolites. SGOT, SGPT and ALP are reliable markers of liver function. The liver was necrotized in STZ-induced diabetic rats. Therefore an increase in the activities of SGOT, SGPT and ALP in plasma might be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream which gives an indication of the hepatotoxic effect of STZ.[35] Treatment of the diabetic rats with the MECO caused reduction in the activity of these enzymes in plasma compared to the diabetic control group and consequently alleviated liver damage caused by STZ-induced diabetes.

Lower-extremely arterial disease, coronary heart disease and cerebrovascular disease are frequently vascular complications in diabetes. The atherogenic process occurrences in vascular disease are proceeding at a more rapid rate in diabetic than in non-diabetic subjects.[36] The vascular disease accounts for more than 60% of the morbidity of diabetes that includes both micro and macrovascular disease, and is common in both type of diabetic patients.[37] In this study, administration of MECO significantly reduced elevated total cholesterol, triglycerides, VLDL and LDL levels in diabetic rats. Also, increased level of HDL was observed in diabetic rats treated with 400 mg/kg dose of MECO and glibenclamide compared to diabetic control rats. This action of MECO supports its lipid lowering activity in diabetic condition and therefore it helps to prevents diabetic associated complication.

Increased free radical generation and oxidative stress are hypothesized to play an important role in the pathogenesis of diabetes and it's late to play an important role in the pathogenesis of diabetes and its late complications. Several evidences suggest that STZ induces oxidative stress.[38] The generation of superoxide anion radicals by glucose oxidation and its dismutation to hydrogen peroxide, which if not scavenged by CAT or GPx, leads to the formation of reactive hydroxide radicals.[39,40] Also, superoxide anion radicals react with nitric acid to form reactive peroxynitrite radicals.[41, 42] Free radicals are formed disproportionately in diabetes by glucose auto oxidation, thus result in consumption of antioxidant defenses which lead to disruption of cellular function and oxidative damage to membranes and enhance susceptibility to lipid peroxidation.[43] β-cell is particularly sensitive to damage by free radicals because of their low level of free radical scavenging enzymes that leads to hyper glycaemic condition. Reduced oxidative stress due to reduced hyperglycemic status in diabetic condition had been observed in experimental animals following the administration of certain natural compounds.[44] Administration of MECO significantly reduced TBARS and increased SOD, CAT, GPx and reduced GSH levels in diabetic rats. The action of the MECO to restore the altered antioxidant enzymes in STZ-induced diabetic rats indicates its free radical scavenging potential and hence it has the ability to prevent diabetic associated complications.

The Histopathological investigation clearly supported that MECO has prevent pancreatic β- cell damage, islets of Langerhans size and numbers it may leads to increase production of insulin.

CONCLUSION

The present study clearly concluded that Methanol extract of *Cordia obliqua* possess ability to control blood glucose in diabetes. It's antihyperlipidemic and free radical scavenging property has potential to prevent diabetic associated complications. Our current investigation supports the traditional use of *Cordia obliqua* in the treatment of diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS USED

DM: Diabetes Mellitus; **MECO:** Methanolic extract of Cordia obliqua; **OECD:** Organization for economic co-operation and development; **OGTT:** Oral glucose tolerance test; **STZ:** Streptozotocin; **mg/dL:** Milligrams per deciliter.

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