

Anti-dyslipidemic activity of acacia tortilis seed extract in alloxan-induced diabetic rats

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ABSTRACT

Background: The present study was carried out to evaluate the anti-dyslipidemic activities of seed extract of acacia tortilis (ATE) in alloxan induced diabetic rats.

Methods: The Rats were divided into five groups of six animals each. Groups I and II received normal saline, group III received ATE in dose of 100 mg/kg body weight, group IV received ATE in dose of 200 mg/kg b.w.; and group V received standard drug pioglitazone dose 3 mg/kg b.w. Drugs were administered orally once a day for 30 days. At the end of 0th, 10th, 20th and 30th day, blood was collected to analyse serum glucose, serum insulin, total cholesterol (TC), serum phospholipid (PL), serum triglyceride (TG), Free fatty acids (FFA) and High density lipoprotein (HDL).

Results: The results has been showed that ATE in above doses significantly increase the serum insulin and HDL level but significantly decreased the elevated level of TC, PL, TG, FFA, LDL and VLDL. It also decreased the atherogenic index and coronary risk index level significantly which was comparable with the pioglitazone.

Conclusions: It is concluded that the seed extract of acacia tortilis at the dose of 100 and 200 mg/kg body weight produced significant anti-dyslipidemic activity in alloxan-induced diabetic rats.

Keywords: Anti-dyslipidemic activity, Acacia tortilis, Alloxan-induced diabetic rats

INTRODUCTION

Diabetes mellitus (DM) is defined as a syndrome of metabolic disorder characterized by hyperglycemia due to absolute or relative deficiency of insulin hormone which is secreted by β cells of pancreas.¹ Hyperglycemia, if not controlled, can lead to serious health complications and even death. The risk of death for a person with DM is two times in contrast to a person of similar age who does not have diabetes. It is also a major cause of heart disease and stroke which increase the death rates about two to four times.² If diabetes is associated with hypertension, high cholesterol levels, and smoking, there may be increased risk of heart disease and stroke.³ DM may be responsible for other complications, such as retinopathy, nephropathy, and vasculopathy of legs or feet.

In experimental diabetic rats, acceleration of lipolysis occurs due to impairment of glucose utilization which leads to hyperlipidemia.⁴⁻⁵ In diabetes, dyslipoproteinemia often occurs through the various metabolic derangements due to insulin deficiency.⁶ Despite the availability of known anti-diabetic and hypolipidemic medicines in the pharmaceutical market, diabetes and the related complications continued to be a major health burden worldwide. Moreover, patients have to face the adverse drug reactions of these medicines in frequent manner. Recently, some medicinal plants have been reported to be beneficial in DM worldwide and used empirically as anti-diabetic and anti-hyperlipidemic remedies.⁷⁻⁹ As per literature, More than 400 plant species having hypoglycemic activity, however, searching for new anti-diabetic activities from natural plants is still attractive because they contain substances which may be alternative or complementary to well-known anti-diabetic medications.¹⁰ Most of these plants contain alkaloids, glycosides, flavonoids, carotenoids terpenoids, etc. that are frequently implicated as having anti-diabetic effect and some also showed significant impact on lipid profile.¹¹

Acacia is a genus of shrubs and trees related to the subfamily; mimosoideae, family; fabaceae and it was first found in Africa by Linnaeus in 1773. The acacia tortilis known as in English (umbrella thorn); Hindi (Israeli babool) is distributed mainly in Africa and Arab countries as native place. It's dried; powdered bark has been used as a disinfectant in healing wounds. It also serves as an anti-helminthic in Senegal. In Somalia, the stem and seeds are used to treat asthma and diarrhoea respectively.¹² Moreover another species of Acacia (Acacia catechu) has also been reported for hypoglycemic antipyretic, hepato-protective and digestive properties.¹³⁻¹⁵ In our previous studies, we have shown the hypoglycemic and anti-hyperglycemic activity of Acacia tortilis seed extract (ATE) in experimental animal.^{16,17} Now, the present study is an attempt to evaluate the anti-dyslipidemic effect of ATE in diabetic rats.

METHODS

Animals

The study was conducted on male and female healthy albino wistar rats weighing 150-250 gm. The animals were obtained from Central animal house, GSVM Medical College, Kanpur. The rats were housed in polypropylene cages and maintained under standard conditions (12 hours light/dark cycle, at room temperature $25\pm 3^\circ\text{C}$ and 35-60% humidity), standard pellet as a basal diet and purified drinking water ad libitum. The study was approved by the Institutional Animal Ethics Committee, Kanpur. The albino rats were maintained and followed under the good laboratory practices and the guidelines of committee for the purpose of control and supervision on experiments on animals.¹⁸

Induction of experimental diabetes

Diabetes was chemically induced in overnight fasted wistar rats by a single intraperitoneal injection of aqueous alloxan monohydrate (135 mg/kg body weight) (sigma chemical Co. USA).¹⁹ The fasting blood glucose was measured after 72 hours.²⁰ Twenty four rats showing a blood glucose level of >200 mg/dl were selected for the experiment.

Preparation of plant extract

The seeds of acacia tortilis were arranged for the study. Dried seeds of the plant were properly grinded and sieved with mesh size 40-60. Extraction of powdered seed was done with distilled water to separate volatile and non-volatile fraction with the help of klevenger apparatus and heating mental at 100°C . Non-volatile fraction was cooled and further precipitated with the help of ethyl alcohol for isolation of gum and other solutes. Isolated gum was purified with the help of filtration technique followed by ion exchange and freeze-drying process. Finally, the acacia tortilis seed extract (ATE) was stored in refrigerator until use.

Acute oral toxicity test in rats

After an overnight fasting of rats, ATE was given orally in doses of 50,100,200,500 and maximum dose of 1000 mg/kg body weight and observed carefully for the first 2-3 hours for signs of toxicity. The behavioural changes and % mortality were documented beginning with 24 hours up to a period of 14 days.²¹

Experimental design

The rats were divided in five groups having six animals in each. The group I were normal and group II-V were diabetic. The Animals in group I (NC) were administered with 1 ml normal saline and served as normal control. Rats of diabetic group II (DC) were administered with 1 ml normal saline and served as diabetic control. Rats of

diabetic group III (DATE-100) were treated with ATE at a dose of 100 mg/kg and group IV (DATE- 200) with ATE at a dose of 200 mg/kg, group V (DP) with pioglitazone at a dose of 3 mg/kg. The pioglitazone treated groups served as positive control. The animals of all groups were received the doses daily orally for 30 days by intra-gastric tube. At the end of 0th, 10th, 20th and 30th day, blood was collected in appropriate tubes for the estimation of biochemical parameters.

Biochemical parameters

Blood samples were collected from orbital sinus of rats and centrifuged. The serum was taken for estimation of all biochemical parameters. The plasma blood glucose levels were analysed by using GOD-POD method.²² The appropriate methods were used for estimation of serum TC23, PL24, TG25, FFA26 and HDL27. The serum insulin was estimated by radioimmunoassay (RIA) method.²⁸ Very low density lipoprotein: VLDL and low

density lipoprotein: LDL were calculated by using the formula as for VLDL (VLDL = TG/5) and for LDL (LDL = total cholesterol - (HDL + VLDL)).²⁹ The atherogenic index (AI) 30 and coronary risk index (CRI) 31 were also calculated as AI is the ratio of LDL-cholesterol and HDL-cholesterol whereas CRI is the ratio of total cholesterol and HDL-cholesterol.

Statistical analysis

Data were calculated as mean±standard error of mean (SEM). Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 20.0). The values were analysed using one way analysis of variance (ANOVA), followed by post hoc Dunnett's multiple comparison test applied for comparing with the diabetic control group. The results were considered to be significant when p values were less than 0.05 (p<0.05).

RESULTS

Table 1: Effect of acacia tortilis seed extract on serum glucose of alloxan induced diabetic rats.

Groups	Serum glucose level (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	81.66±1.99	81.00±1.78	82.66±1.62	81.33±1.25
DC	277.00±7.75	281.15±7.99	285.16±7.05	288.16±5.06
DATE-100	278.83±7.18	262.50±5.07 (6.63%)	234.16±3.45*** (17.88%)	232.00±3.96*** (19.48%)
DATE-200	283.33±7.28	239.66±5.76*** (14.75%)	219.83±4.83*** (22.90%)	205.16±4.19*** (28.80%)
DP	281.50±4.82	206.50±3.25*** (26.55%)	164.83±4.53*** (42.19%)	146.00±2.30*** (49.33%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Table 2: Effect of acacia tortilis seed extract on serum insulin of alloxan induced diabetic rats.

Groups	Serum insulin level (µu/ml)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	2.12±0.03	2.13±0.03	2.12±0.02	2.11±0.02
DC	0.37±0.02	0.38±0.01	0.38±0.02	0.36±0.01
DATE-100	0.38±0.01	0.66±0.03*** (73.68%)	0.88±0.01*** (131.57%)	0.98±0.02*** (172.22%)
DATE-200	0.36±0.02	1.05±0.02*** (176.31%)	01.27±0.01*** (234.21%)	1.54±0.02*** (327.77%)
DP	0.37±0.01	0.41±0.02 (7.89%)	0.41±0.01 (7.89%)	0.38±0.02 (5.55%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Acute toxicity study

The results showed that no signs of toxicity, behavioural changes and mortality were there up to a dose of 1000 mg/kg body weight of the ATE.

Effect on diabetic rats

Effects of acacia tortilis seed extract on different parameters of blood of diabetic rats are being presented in

tabulated form. Tables are also showing the percentage changes in parameters and significance level with respect to control group.

Mean blood glucose concentration

The mean blood glucose concentration of controlled and ATE treated rats are presented in Table 1. The progressive reduction of blood glucose was observed at the end of 10th, 20th and 30th days respectively in ATE treated

animals at both doses and it was highly significant ($p < 0.001$) at all points except 10th day for ATE 100 mg/kg dose. The anti-hyperglycemic activity of the ATE treated

animals is comparable to positive control group but it was not as effective as pioglitazone (Table 1).

Table 3: Effect of acacia tortilis seed extract on total cholesterol in alloxan induced diabetic rats.

Groups	Serum total cholesterol (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	75.83±2.02	77.50±0.80	78.16±0.79	79.83±0.65
DC	132.33±2.56	135.50±3.12	132.16±3.78	131.38±2.65
DATE-100	133.66±2.15	123.50±1.94** (8.85%)	112.50±1.23*** (14.87%)	108.33±0.98*** (17.54%)
DATE-200	135.50±2.06	120.50±1.70*** (11.07%)	108.66±2.02*** (17.78%)	99.50±1.56*** (24.26%)
DP	131.33±2.47	111.50±1.47*** (17.71%)	104.66±1.96*** (20.80%)	90.50±1.80*** (31.11%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Table 4: Effect of acacia tortilis seed extract on serum triglyceride in alloxan induced diabetic rats.

Groups	Serum triglyceride level (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	69.66±1.80	69.00±1.89	70.50±2.12	71.16±2.19
DC	164.00±2.92	163.33±2.85	166.66±2.01	163.83±2.30
DATE-100	165.00±3.35	141.33±3.52*** (13.46%)	122.66±3.24*** (26.40%)	114.16±2.72*** (30.31%)
DATE-200	164.00±2.92	136.50±2.71*** (16.42%)	119.16±2.49*** (28.50%)	107.66±1.89*** (34.28%)
DP	169.83±2.62	122.00±2.35*** (25.30%)	109.16±2.31*** (34.50%)	92.66±2.07*** (43.44%)

The values are expressed as Mean ±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Table 5: Effect of acacia tortilis seed extract on serum phospholipid in alloxan induced diabetic rats.

Groups	Serum phospholipid level (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	69.33±1.78	68.66±2.15	70.00±2.06	70.50±1.56
DC	96.33±2.90	97.00±2.60	98.83±2.40	99.83±2.00
DATE-100	96.50±2.98	85.50±2.68** (11.85%)	82.83±2.03*** (16.18%)	81.16±1.77*** (18.70%)
DATE-200	95.50±2.43	84.33±2.15** (13.06%)	80.00±1.80*** (19.05%)	71.16±2.19*** (28.71%)
DP	97.50±2.61	82.66±1.62** (14.78%)	79.83±0.65*** (19.22%)	77.16±1.47*** (22.70%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Table 6: Effect of acacia tortilis seed extract on serum free fatty acid in alloxan induced diabetic rats.

Groups	Serum FFA level (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	1.64±0.02	1.64±0.03	1.66±0.01	1.63±0.02
DC	2.60±0.06	2.63±0.04	2.63±0.05	2.61±0.05 ^a
DATE-100	2.63±0.06	2.48±0.05 (5.70%)	2.40±0.04** (8.74%)	2.27±0.02*** (13.02%)
DATE-200	2.58±0.04	2.33±0.02*** (11.40%)	2.16±0.01*** (17.87%)	2.03±0.03*** (22.22%)
DP	2.63±0.05	2.34±0.03*** (11.02%)	2.10±0.01*** (20.15%)	1.85±0.02*** (29.11%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett's multiple comparison test).

Serum insulin level

Serum insulin level increased significantly ($p < 0.001$) after oral administration of acacia tortilis in dose of 100 and 200 mg/kg body weight in diabetic rat at all-time points.

As far as the positive control group is concerned, Pioglitazone did not show any significant effect on insulin in diabetic rats (Table 2).

Lipid profile parameter

Table 3 to 6 are showing the serum TC, TG, PL and FFA levels of control and alloxan induced diabetic rats. Serum TC, TG, PL and FFA were significantly increased after alloxan but restored in significant manner after treatment with 100 and 200 mg dose of ATE. Acacia has the

restoring capability like that of pioglitazone (Table 3, 4, 5 and 6).

Table 7 presents that HDL level was decreased in diabetic rats which was moved progressively in direction of normal limit in ATE treated and positive control groups (Table 7).

Table 7: Effect of acacia tortilis seed extract on serum HDL in alloxan induced diabetic rats.

Groups	Serum HDL level (mg/dl)			
	0 Day	After 10 days	After 20 days	After 30 days
NC	41.66±1.64	43.10±2.4	41.66±2.01	43.50±2.43
DC	29.66±1.33	30.66±1.45	29.33±1.30	30.83±1.24
DATE-100	28.50±1.17	33.83±2.41 (10.33%)	36.50±2.43* (24.44%)	39.66±1.78** (28.64%)
DATE-200	29.50±1.82	36.16±2.49 (17.93%)	38.33±2.15** (30.68%)	41.00±1.77*** (32.98%)
DP	30.33±1.45	35.16±1.53 (14.67%)	38.33±1.45** (30.68%)	43.00±1.23*** (39.47%)

The values are expressed as Mean±S.E (% reduction); n=6; Significance levels when compared with diabetic control: * P ≤0.05, ** P≤0.01, *** P≤0.001 (One way ANOVA followed by Dunnett’s multiple comparison test).

Serum LDL and VLDL level

Serum LDL and VLDL level were significantly increased in diabetic rats after ATE administration. The status of VLDL and LDL were restored in significant manner as like that of positive controls after treatment with ATE (Figure 1 and 2).

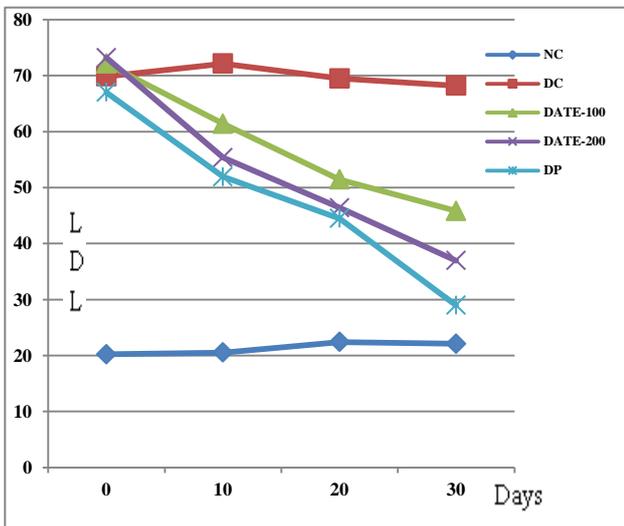


Figure 1: Effect of acacia tortilis seed extract on serum LDL in alloxan induced diabetic rats.

Atherogenic index (AI) and coronary risk index (CRI)

The Figure 3 and 4 is showing the comparison of AI and CRI respectively in control and treated groups. ATE decreased the AI and CRI level significantly which was comparable with the pioglitazone (Figure 3 and 4).

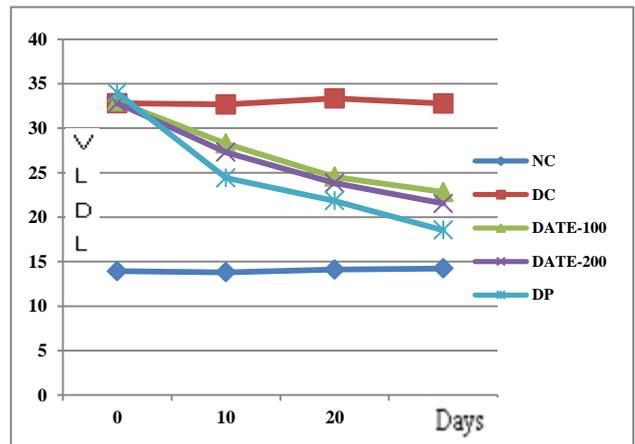


Figure 2: Effect of acacia tortilis seed extract on serum VLDL in alloxan induced diabetic rats.

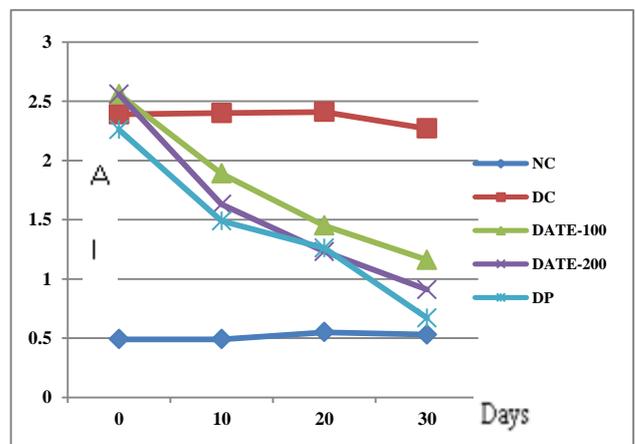


Figure 3-Effect of acacia tortilis seed extract on atherogenic index in alloxan induced diabetic rats.

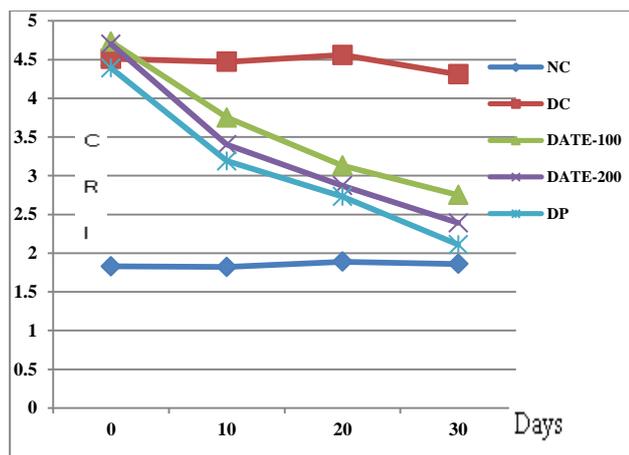


Figure 4: Effect of acacia tortilis seed extract on coronary risk index in alloxan induced diabetic rats.

DISCUSSION

In the present study, oral administration of ATE decreased serum glucose and enhanced insulin level in diabetic rats. It might be due to stimulating insulin release from the remnant pancreatic β -cells or by reducing hepatic clearance of the insulin. Another possibility might be that seed extract regenerates the β -cells of islets of langerhans which lead to significant increase in insulin level followed by glucose lowering effect. In our previous study we have shown that The ATE possess glucose lowering effect in normal and diabetic rats and significantly increases glucose tolerance.¹⁶ As far as positive control group is concerned pioglitazone did not show any significant effect on insulin in diabetic animals which is consistence with the theory that thiazolidinediones exerts their effect by lowering insulin resistance by activation of PPAR- γ in adipose tissue reduce the flux of fatty acids into muscle.³²

In the present study, anti-dyslipidemic activity of ATE has been evaluated in normal and alloxan induced diabetic rats. Cholesterol is a neutral lipid which chemically is a sterol serves as integral component of cell membrane and precursor for adrenal and gonadal steroid. The impaired carbohydrate metabolism in DM leads to increased lipolysis and accumulation of acetyl Co A. Increased availability of acetyl Co A is important in cholesterol biosynthesis and causes hyperlipidemia.³³ The hormone Insulin possesses a significant role in lipid metabolism and its deficiency leads to lipolysis, hypercholesterolemia and ketosis.³⁴⁻³⁵ Triglyceride is a neutral fat which serves as major energy reserve in adipose tissue. Diabetic increases the lipolysis and produces more free fatty acids (FFA) which ultimately enhance the synthesis of triglycerides and ketone bodies. In the present investigation, triglycerides are increased in significant manner. Normally, insulin stimulates the enzyme lipoprotein lipase for hydrolysis of triglycerides but in DM, lipoprotein lipase is not stimulated due to insulin deficiency, resulting in hypertriglyceridemia.³⁶ Neutral

lipid such as triglycerides, cholesterol and cholesterol esters are transported into circulation with the help of lipoproteins such as chylomicrons, VLDL, LDL and HDL.³⁷ Lipoproteins play the major role in the occurrence of premature atherosclerosis in DM.³⁸ LDL has the highest potential for atherogenicity among lipoproteins after lipoprotein-(a).³⁷ In the present study VLDL and LDL level were increased and HDL level was decreased in diabetes rats. The liver secretes triglyceride rich VLDL through endogenous transport and hydrolysed by capillary lipoprotein lipase. After hydrolysis of TGs, VLDL particles get converted in to IDL and LDL and they get endocytosed into the liver by LDL receptors. VLDL, IDL and LDL (atherogenic) transports cholesterol from liver to the peripheral tissues and HDL (anti-atherogenic) back to the liver. Extract of acacia reversed the increased level of serum TC, TG, PL, FFA, VLDL and LDL and improved HDL level, exhibiting the anti-atherosclerotic potential. A probable mechanism of ATE might be due to the presence of flavonoids, which significantly increased expression of LDL receptor mRNA levels, which, leads to increase hepatic uptake and degradation of LDL, ultimately to decrease in serum LDL level. Secondly due to insulin-mimetic action, as the effective control of glycemic imbalance will reduce the VLDL and triglyceride levels.³⁹ A decrease in CRI and AI is believed to be beneficial since the raised plasma total cholesterol and LDL concentrations are having negative correlation with plasma HDL and increase in HDL cholesterol is associated with a decrease in coronary risk.^{40,41} Thus, it's both anti-hyperglycemic and ant-dyslipidemic effect may play an important role against the development of atherosclerosis in diabetic animals. An attempt has been made for the first time to describe new properties of acacia tortilis seed as a potent sugar and lipid lowering effects and these beneficial effects may contribute to anti-atherosclerotic activity in diabetic with dyslipidemic patients. Less sample size may be one limitation of the study. To substantiate the present findings, further work is required to assess the biological activity of ATE in vivo and in vitro and isolation and purification of the fractions like flavonoids.

CONCLUSION

It is concluded that the seed extract of acacia tortilis at the dose of 100 and 200 mg/kg body weight produced significant anti-diabetic and anti-dyslipidemic activity in alloxan-induced diabetic rats. Hence it could be very effective in managing the diabetes associated cardiovascular complications which is occurred mainly due to defects in lipid metabolism. However, further studies have to be undertaken to elucidate the exact mechanism by which ATE could be exerting its effects.

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