ORIGINAL ARTICLE

Evaluation of antihyperglycemic and antihyperlipidemic activities of *Acacia catechu* (l.f) *willd* leaf extract in Wistar albino rats

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Abstract

Aim: The aim of the present study was to evaluate the antihyperglycemic and antihyperlipidemic activities of hydroethanolic extract of *Acacia catechu* (L.f) Willd leaf in streptozotocin (STZ)-induced diabetic rats. **Materials and Methods:** Diabetic rats were treated with oral administration of hydroethanolic leaf extract of *A. catechu* (L.f) Willd (200 mg/kg and 400 mg/kg) for 30 days. Various biochemical parameters such as serum glucose, protein, urea, creatinine, lipid profile, and activities of liver and kidney marker enzymes were measured to assess the antihyperglycemic and antihyperlipidemic activities of the extract. **Results and Discussion:** Administration of the hydroethanolic leaf extract of *A. catechu* (L.f) Willd (200 mg/kg and 400 mg/kg) significantly decreased ($P < 0.05$; $P < 0.01$) blood glucose levels in diabetic rats and has the capacity to correct the metabolic disturbances associated with diabetes. Further, the extract decreased total cholesterol, triglycerides, low-density lipoprotein (LDL), very LDL (VLDL) levels, and increased high-density lipoprotein levels. **Conclusion:** The present investigation suggested that the administration of *A. catechu* (L.f) Willd exhibited antidiabetic activity in STZ-induced diabetic rats and could be considered for further evaluation in drug development.

Key words: *Acacia catechu* (L.f) Willd, antihyperglycemic, antihyperlipidemic activity, glibenclamide, streptozotocin

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by a high blood glucose level that results from defects in insulin secretion. In general, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas.[1] According to the World Health Organization, in November 2014, about 347 million people had diabetes in the worldwide.[2] The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.[3] India has about 45,000 plant species, and several thousand have been claimed to possess medicinal properties.[4] Medicinal plants contain some organic compounds which provide definite physiological action on the human body, and these bioactive substances include flavonoids, tannins, alkaloids, carbohydrates, terpenoids, and steroids.[5] Medicinal plants used to treat diabetic conditions are of considerable interest, and a number of plants have shown varying degrees of hypoglycemic activity.[6] The present study was designed to evaluate the antihyperglycemic, and antihyperlipidemic activity of hydroethanolic leaf extract of *Acacia catechu* (L,f) Willd in streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Chemicals

STZ was purchased from Sigma-Aldrich Co., USA. Glibenclamide manufactured by Aventis Pharma Ltd. Goa,

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Received: 13-05-2018
Revised: 06-08-2018
Accepted: 15-08-2018

India. The chemicals and solvents used in the present study were of analytical grade.

Collection of Plant Material and Extraction

The leaves of *A. catechu* (L.f) Willd were collected from Kanchikode, Kerala, and authenticated by Botanical Survey of India, Tamil Nadu Agricultural University, Coimbatore, (Plant identification No. BSI/SRC/5/23/2014-2015/Tech/699). The leaves were shade dried, coarsely powdered and subjected to extraction with hydroethanol by Soxhlet apparatus, concentrated to dryness in a vacuum evaporator.

Experimental Animals

Male albino rats of Wistar strain with a mean weight of 150 ± 5.35 g were obtained from the animal house of the PSGIMS and R, Coimbatore. The rats were housed in clean cages placed in a well-ventilated house with optimum conditions (temperature: 23 ± 1°C; photoperiod: 12 h light/dark cycle; and humidity: 45–50%). The cleaning of cages was done on a daily basis. This study was carried out following the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, and an ethical clearance number (328/2016/IAEC) was assigned to the project.

Acute Oral Toxicity Study

An acute toxicity study was performed for the extract according to the acute toxic class method.[7] The result of the acute toxicity study of hydroethanolic leaf extract of *A. catechu* (L.f) Willd on laboratory rats showed no lethality up to the dose of 2000 mg/kg body weight. Hence, the rats were safe up to a maximum dose of 2000 mg/kg body weight.

Induction of Diabetes in Rats

The rats were overnight fasted, and diabetes mellitus was induced by a single intraperitoneal injection of STZ (50 mg/kg body weight) which was dissolved in ice cold 0.1M citrate buffer, pH 4.5.[8] Development of diabetes was confirmed by measuring blood glucose levels 3 days after the administration of STZ. The blood glucose level ≥300 mg/dL was considered to be diabetic and used for the studies.[9]

Experimental Design

The rats were divided into seven groups, each comprising a minimum of six rats as detailed below.

- Group I - Normal control rats received a standard pellet and sterilized water for 30 days.
- Group II - The rats were made hyperglycemic by an intraperitoneal injection of freshly prepared solution of STZ (50 mg/kg body weight).
- Group III - STZ-induced diabetic rats were treated with 200 mg/kg body weight of hydroethanolic leaf extract of *A. catechu* (L.f) Willd orally for 30 days.
- Group IV - STZ-induced diabetic rats were treated with 400 mg/kg body weight of hydroethanolic leaf extract of *A. catechu* (L.f) Willd orally for 30 days.
- Group V - STZ-induced diabetic rats were treated with a standard drug glibenclamide 600 µg/kg body weight orally for 30 days.[10]
- Group VI - Normal rats administrated with *A. catechu* (L.f) Willd leaf extract (200 mg/kg body weight) alone.
- Group VII - Normal rats administrated with *A. catechu* (L.f) Willd leaf extract (400 mg/kg body weight) alone.

Preparation of Serum and Tissue Homogenate

After the experimental regimen, whole blood was collected by cardiac puncture under mild diethyl ether anesthesia. The

Table 1: Effect of *A. catechu* (L.f) Willd on serum protein and glucose lev el in STZ-induced diabetic rats

Groups	Serum protein (g/dL)	Serum glucose (mg/dL)
I	6.06±0.19	92.16±10.92
II	4.83±0.21**[a]	329.16±47.42**[a]
III	5.66±0.24**[b]	275.66±14.94**[b]
IV	5.83±0.16**[b]	242.66±17.65**[b]
V	5.95±0.18**[c]	188.16±16.38**[c]
VI	5.96±0.17	90.5±8.06
VII	6.06±0.12	91.33±7.22

Values are mean±SD for six rats in each group. Values are statistically significant at *P<0.05, **P<0.01; statistical significance was compared within the groups as follows. [a]Diabetic rats were compared with normal rats. [b]*A. catechu* (L.f) Willd and [c]glibenclamide treated diabetic rats were compared with diabetic rats, *A. catechu: Acacia catechu*

Table 2: Effect of *A. catechu* (l.f) Willd on kidney markers in STZ-induced diabetic rats

Groups	Serum urea (mg/dL)	Serum creatinine (mg/dL)
I	38.66±2.16	0.50±0.02
II	42.33±7.84**[a]	0.82±0.03**[a]
III	38.5±6.22*[b]	0.58±0.03**[b]
IV	36.83±5.77**[b]	0.62±0.02**[b]
V	32±4.85**[c]	0.66±0.04**[c]
VI	36.5±4.59	0.47±0.02
VII	37.16±5.41	0.51±0.02

Values are mean±SD for six rats in each group. Values are statistically significant at *P<0.05, **P<0.01; statistical significance was compared within the groups as follows. [a]Diabetic rats were compared with normal rats. [b]*A. catechu* (L.f) Willd and [c]glibenclamide treated diabetic rats were compared with diabetic rats, *A. catechu: Acacia catechu*

rats were sacrificed by cervical dislocation, liver, kidney, and pancreas were excised immediately and thoroughly washed with ice-cold physiological saline. The blood was centrifuged at 2500 rpm for 10 min to separate the serum which was used for various biochemical experiments. 1 g of liver and kidney were homogenized with 0.1M cold citrate buffer, (P^H 7.4) in a potter homogenizer filled with Teflon plunger at 600 rpm for 3 minutes. The homogenate was used for spectrophotometric analysis of various biochemical parameters such as glucose,[11] protein,[12] urea,[13] creatinine,[14] aspartate aminotransferase (AST), alanine aminotransferase (ALT),[15] alkaline phosphatase (ALP),[16] triglyceride,[17] total cholesterol,[18] high-density lipoprotein (HDL),[19] very low-density lipoprotein (VLDL), and LDL cholesterol.[20]

LDL = TC-(HDL+VLDL); VLDL=TG/5

Statistical Analysis

Data were expressed as the mean ± standard deviation of six replicates and subjected to one-way ANOVA followed by Tukey HSD test to determine significant differences in all the parameters.

RESULTS AND DISCUSSION

Effect of *A. catechu* (L.f) Willd on Serum Biochemical Parameters

Total protein

Proteins are essential to maintain the structure and functions of all life forms as well as vital for growth and development.[21] The level of serum protein was found to be significantly ($P < 0.01$) decreased in diabetic rats when compared to the normal rats [Table 1]. This may be due to gluconeogenesis or enhanced protein catabolism/reduced protein synthesis in the diabetic condition. The serum protein levels were found to be significantly ($P < 0.01$) increased in plant extract (Groups III and IV), and glibenclamide (Group V) treated rats when compared with diabetic rats [Table 1]. This may be due to inhibition of proteolysis or enhancement of protein synthesis.[22] Similar observations were reported using *Acacia melanoxylon* linen seed extract in diabetic rats.[23]

Glucose

Glucose is a main source of energy in the human body. The blood glucose levels are maintained under the influence of

Table 3: Effect of *A. catechu* (l.f) Willd on liver function in STZ-induced diabetic rats

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)
I	114.9±14.12	47.78±5.45	253.76±9.08
II	265.21±13.74**[a]	67.55±7.93**[a]	370.4±17.81**[a]
III	229.1±33.16*[b]	57.5±5.36**[b]	293.85±25.72*[b]
IV	211.23±16.36**[b]	54.21±4.83**[b]	282.31±41.52**[b]
V	204.43±12.89**[c]	50.15±3.51**[c]	263.35±20.62**[c]
VI	107.88±5.14	46.81±5.18	250.43±10.00
VII	111.66±9.12	43.86±5.18	253.18±13.39

Values are mean±SD for six rats in each group. Values are statistically significant at *P<0.05, **P<0.01; statistical significance was compared within the groups as follows. [a]Diabetic rats were compared with normal rats. [b]*A. catechu* (L.f) Willd and [c]glibenclamide-treated diabetic rats were compared with diabetic rats. *A. catechu: Acacia catechu*, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase

Table 4: Effect of *A. catechu* (l.f) Willd on lipid profile in STZ-induced diabetic rats

Groups	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	VLDL- cholesterol (mg/dL)
I	112±7.61	96.21±7.85	34.28±3.85	58.51±8.29	19.25±1.57
II	143.16±8.18**	202.7±34.62**	17.6±1.71**	85.03±11.27**	40.53±6.93**
III	124.66±7.33*	157.03±24.92*	25.48±2.05*	67.78±8.02*	31.4±4.97*
IV	114.16±11.56**	152±30.75*	27.21±4.16**	56.55±5.24**	30.4±6.15*
V	102.16±10.10**	142.33±14.76**	29.1±6.28**	44.6±9.20**	28.46±2.95**
VI	105.16±10.02	95±10.44	30.83±7.57	58.5±9.20	19.28±2.08
VII	107.66±5.08	96.83±6.08	31.83±7.02	59.03±8.52	19.36±1.21

Values are mean±SD for six rats in each group. Values are statistically significant at *P<0.05, **P<0.01; statistical significance was compared within the groups as follows. [a]Diabetic rats were compared with normal rats. [b]*A. catechu* (L.f) Willd and [c]glibenclamide-treated diabetic rats were compared with diabetic rats. *A. catechu: Acacia catechu*, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein

hormones such as insulin and glucagon.[24] The level of serum glucose was found to be significantly ($P < 0.01$) increased in diabetic rats when compared to the normal rats [Table 1]. The administered STZ resulted in the destruction of β- cells of islets, which lead to a reduction in insulin release and thereby to hyperglycemia.[25] The level of serum glucose was found to be significantly ($P < 0.01$) decreased in plant extract (Groups III and IV), and glibenclamide (Group V) treated rats when compared with diabetic rats [Table 1]. This may be due to the presence of secondary metabolites and the hypoglycemic action of glibenclamide, thereby stimulating the insulin release and inhibition of glucagon secretion.[26] In a similar study, Bhuvaneshwari *et al*. had reported that diabetic rats tend to increase the glucose utilization and thereby a decrease in the blood glucose level.[27]

Kidney markers

Urea and creatinine are the prognostic indicators of renal dysfunction.[28] Urea, the end-product of protein metabolism is synthesized in the liver, transported by the blood to the kidney and is excreted.[29] Creatinine is endogenously produced and released into body fluids, and its clearance is measured as an indicator of glomerular filtration rate.[30] The levels of serum urea and creatinine were found to be significantly ($P < 0.01$) increased in diabetic rats when compared to the normal rats [Table 2]. The insulin deficiency caused an inability of glucose to reach the extrahepatic tissues, thereby stimulating gluconeogenesis through proteolysis. The increased level of serum creatinine may be due to renal damage caused by abnormal glucose regulation, excess degradation of amino acids or inefficiency in the clearance of creatinine.[31] An increase in the levels of serum urea and creatinine in diabetic rats were also reported by Gopalakrishnan *et al*.[32]

The levels of serum urea and creatinine were found to be significantly decreased in Group III ([$P < 0.05$]; [$P < 0.01$]) and Group IV ([$P < 0.01$]; [$P < 0.01$]) rats, when compared with diabetic rats. The glibenclamide-treated rats also showed a significant ($P < 0.01$) decrease in the serum urea and creatinine levels [Table 2]. This may be due to decreased disturbances in protein and nucleic acid metabolism.[33] The presence of polyphenols and flavonoids in the plant extract might be responsible for the antioxidant activity, thereby a reduction in serum urea and creatinine levels.[34] In a similar study, Kumar *et al*. had reported that the administration of *A. melanoxylon* extracts significantly decreased serum urea and creatinine levels in diabetic rats.[23]

Liver marker enzymes

AST and ALT found in liver, kidney, heart, brain, and muscle are important markers for diagnostic purpose, play a major role in the conversion of amino acid to ketoacid.[35] ALP is a membrane-bound glycoprotein enzyme, present in the highest concentration in the plasma membrane and endoplasmic reticulum.[36] The activity of AST, ALT, and ALP was found to be significantly ($P < 0.01$) increased in diabetic rats when compared to the normal rats [Table 3]. This may be due to the cellular damage to liver caused by STZ which leads to leakage of enzymes from cytosol into the bloodstream.[37] In a similar study, Sangeetha *et al*. had reported an increase in the activity of serum AST, ALT, and ALP after the administration of STZ to the rats.[38]

The activity of serum AST, ALT and ALP was found to be significantly decreased in Group III ([$P < 0.05$]; [$P < 0.01$]; [$P < 0.05$]) and Group IV ([$P < 0.01$]; [$P < 0.01$]; [$P < 0.01$]) rats when compared with diabetic rats. The glibenclamide-treated rats also showed a significant ($P < 0.01$) decrease in the activities of the above-mentioned enzymes [Table 3]. The hepatoprotective agent flavonoid present in plant extract might have involved in the reduced activities of AST[39] thereby inactivating cytosolic AST within the diabetic rat tissues through a glycation reaction.[40] In the plant extract treated diabetic rats, reduction in ALT and ALP activities may be due to the presence of flavonoids and tannins in the plant extract, which repairs the tissue damage induced by diabetic complications.[41] In a similar study Arise *et al*. had reported that *Acacia ataxacantha* root extract significantly decreased the activities of AST, ALT, and ALP in diabetic rats.[42]

Lipid profile

Cholesterol is an essential component of the cell membrane, which maintains proper membrane permeability and fluidity. Higher total cholesterol leads to higher risk for cardiovascular diseases.[43] Triglycerides are neutral fats and play an important role in metabolism as an energy source and transporter of dietary fat.[44] HDL is an antiatherogenic lipoprotein. It is good cholesterol because of its role in the prevention of atherosclerosis by transporting the cholesterol from peripheral tissues to the liver.[45] Low-density lipoprotein (LDL) is the bad cholesterol since it gets deposited on the walls of blood vessels. LDL is an important predictor of atherosclerosis and coronary heart disease.[46] VLDL is a type of lipoprotein made by the liver. It functions as the body's internal transport mechanism for lipids.[47]

The level of serum total cholesterol, triglyceride, LDL, and VLDL cholesterol was found to be significantly ($P < 0.01$) increased in diabetic rats when compared to the normal rats [Table 4]. This may be due to defects in insulin secretion/function and also due to the increase in the mobilization of free fatty acids from the peripheral depots.[48] The level of serum HDL was found to be significantly ($P < 0.01$) decreased in diabetic rats when compared to the normal rats [Table 4]. This may be related to insulin deficiency. Decreased insulin levels enhance lipoprotein lipase activity, thereby mobilizing fatty acid from the adipose tissue. Since HDL is involved in transporting the fatty acids from peripheral tissues, more levels of HDL are used up by the liver that might have caused a reduction in Group II diabetic rats.[49] Kabbaoui *et al*. had reported that there was an increase in the levels of serum total cholesterol, triglyceride, LDL, VLDL, and decrease in the HDL levels in diabetic rats.[50]

The serum total cholesterol, triglyceride, LDL, and VLDL levels were found to be significantly decreased in Group III ([$P < 0.05$]; [$P < 0.05$]; [$P < 0.05$]; [$P < 0.05$]) and Group IV ([$P < 0.01$]; [$P < 0.05$]; [$P < 0.01$]; [$P < 0.05$]) rats, when compared with diabetic rats. The glibenclamide-treated rats also showed a significant ($P < 0.01$) decrease in the above-mentioned lipid levels [Table 4]. This effect of plant extract on lipid metabolism might be due to the improvement in insulin levels.[51] The presence of flavonoids and saponins in the plant extract contributes to the reduction in serum total cholesterol, triglyceride, LDL, and VLDL levels.[52] The level of serum HDL was found to be significantly increased in Group III ($P < 0.05$) and Group IV ($P < 0.01$) rats, when compared to the diabetic rats [Table 4]. This might be due to increase in the activity of lecithin cholesterol acyltransferase, which may contribute to the regulation of blood lipids.[53] Flavonoids present in the plant extract are responsible for increasing the level of HDL.[54] In a similar study, Arise *et al*. had reported that *A. ataxacantha* root extract significantly decreased serum total cholesterol, triglyceride, LDL, VLDL, and increased serum HDL levels. No significant difference was found in the serum protein, glucose, urea, creatinine, liver marker enzymes, and lipid profile levels, when the normal rats were compared with plant extract alone treated rats.

CONCLUSION

The findings of the present study suggest that the hydroethanolic leaf extract of *A. catechu* (L.f) Willd possesses significant antihyperglycemic and antihyperlipidemic activities in STZ-induced diabetic rats. Further, the extract might be beneficial for future drug design and development so as to be effective for the management of diabetes mellitus.

ACKNOWLEDGMENT

The authors are thankful to Management of PSG College of Arts and Science, for the support of our work.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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Source of Support: Nil. **Conflict of Interest:** None declared.