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Antidiabetic Activity of Aqueous Leaves Extract of Sesbaniasesban (L) Merr. In Diabetic Rats

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ABSTRACT
Objective: To investigate the antidiabetic property of Merremiaemarginata (M. emarginata) Burm. F. plant in streptozotocin induced diabetic rats.
Methods: The dose dependent effects of 28 days oral treatment with methanol extract (100, 200 and 400 mg/kg) from the plant of M. emarginata on blood glucose level, body weight, insulin, total hemoglobin, glycosylated haemoglobin (HbA1C), total protein, serum urea, serum creatinine and carbohydrate metabolizing enzymes were evaluated in streptozotocin induced diabetic rats. Histology of pancreas was also studied.
Results: A significant decrease in blood glucose, serum urea and serum creatinine and significant increase in body weight, insulin and protein level were observed in diabetic rats treated with M. emarginata. Treatment with M. emarginata resulted in a significant reduction of HbA1C and an increase in total hemoglobin level. The activities of carbohydrate metabolizing enzymes such as hexokinase were significantly increased whereas glucose-6- phosphatase, fructose-1, 6-bisphosphatase were significantly decreased by the administration of M. emarginata in diabetic rats. Histology of diabetic rats treated with M. emarginata showed the pancreatic -cells regeneration.
Conclusions: These findings suggest that M. emarginata has potent antidiabetic activity in streptozotocin induced diabetic rats.
Keywords: Merremiaemarginata Diabetes mellitus Carbohydrate metabolizing enzymes Histology Antidiabetic effect Streptozotocin Blood glucose Insulin.

I. INTRODUCTION

Sesbaniasesban (L) Merr. is a small perennial tree with woody stems, yellow flowers and linear pods belongs to the family Fabaceae. Seed and bark are used as astringent, emmenagogue, in menorrhagia, spleen enlargement and diarrhea. The pods and leaves contain campesterol and beta-sitosterol. Flowers contain cyanidin and delphinidinglucosides. Pollen and pollen tubes contain alpha-ketoglutaric, oxaloacetic and pyruvic acids. Leaves are used as antihelmintic and also useful in diabetes, colic and skin diseases. Seeds are stimulant, emmenagogue, astringent and also useful in diarrhea. Reports suggest that previous phytochemical investigations of the plant led to the isolation of oleanolic acid, stigmasta-5,24- diene-3-ol-3-0-β- D- galactopyranoside, fatty acids and amino acids. Various types of lignins are composed of guaiacyl, syringyl and P-hydroxyphenylpropane building units and also anti-tumor principal, kaempferoltrisacharide. However, the literature indicates that there is no specific evidence to support the antidiabetic effect of Sesbaniasesban. The present study investigates the action of aqueous extract of Sesbaniasesban leaves in the STZ-induced diabetic rats to ascertain the scientific basis for the use of this plant in the treatment of diabetes.

II. MATERIALS AND METHODS

Collection of plant material

The leaves of Sesbaniasesban were collected during July 2008 from the Mahatma PhuleKrishiVidyapeeth, Rahuri, Maharashtra, India. The leaves were identified by Dr. P.G.Diwakar, Joint Director, Botanical Survey of India, Pune. A voucher specimen (KS GSS12) has been kept in herbarium, in Botanical Survey of India, Pune Maharashtra.

Preparation of test sample

Sesbaniasesban leaves were cut into small pieces and were allowed to dry in the shade. About 100 g of the dried powdered material was hot extracted at 60o C for 6 hr using 1 L of water. The water extract was filtered and evaporated for dryness under vacuum, which yielded a sticky material (yield: 7.5% w/w).

Preliminary phytochemical screening

The preliminary phytochemical screening of aqueous extract of the Sesbaniasesban leaves

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was carried out for qualitative identification of type of phytoconstituents present. The presence of various phytoconstituents viz. steroids and terpenoids (LeibermannBurchard test), alkaloids (Dragendroffs test), tannins and phenolics (Ferric chloride test), flavonoids (Shinoda test), Sugars (Fehling solution test), amino acids (Ninhydrin test), etc. was detected by usual methods prescribed in standard texts.

Animals

Healthy adult male albino wistar rats (150-200 g), in house breed at the animal house of M.E.S. College of Pharmacy, Sonai, India were used for the study. Rats were housed in polypropylene cages lined with husk in standard environmental conditions. (temperature 25±2o C; relative humidity 55±10%; and 12:12 light:dark cycle,) The rats were fed on a standard pellet diet (Amrut rat and mice feed, Sangli, India) ad libitum and had free access to water. The experiments were performed after approval of the protocol by the Institutional Animal Ethical Committee (IAEC) and were carried out in accordance with the current guidelines for the care of laboratory animal.

Acute toxicity studies

Acute toxicity study was carried out for the Sesbaniasesban by adapting fixed dose method of CPCSEA, OECD guidelines no 420. Thirty fasted male albino mice were weighed (25-30 g, 10 weeks old), grouped into A, B, C, D, E, and F with five animals each. Group A animals served as control and received distilled water, while groups B, C, D, E and F were orally administered 500, 1000, 1500, 2000, and 2500 mg/kg body weight of SSAE in distilled water, respectively, using orogastric tubes. The animals were observed at 2, 6, 24 and 48 hr after extract administration to detect changes in autonomic or behavioral responses. Mortality was observed for 24 hrs.

Effect of aqueous extract in normoglycemic rats

The rats were divided into four groups of 6 animals (n=6) each. Group I served as control and received distilled water. Group II served as standard control, received glibenclamide (0.25 mg/kg b.w.). Group III and IV received 250 and 500 mg/kg SSAE orally. Blood glucose levels were determined at 0, 1, 2, 3 and 4 hr following treatment by retro-orbital plexus of the eye under mild ether anesthesia.

Effect of aqueous extract on oral glucose tolerance test in STZ-induced diabetic rats (OGTT)

The rats were divided into five groups of 6 animals (n=6) each. Group I served as control and received distilled water. Group II served as diabetic control and received distilled water. Group III served as positive control, received glibenclamide (0.25 mg/kg b.w.). Group IV and V received 250 and 500 mg/kg SSAE orally. All the animals were given glucose (2 g/kg) 30 min after dosing. Blood samples were collected from the retro-orbital plexus of the eye just prior (0 hr) and 30, 60, 90, and 120 min. After the glucose loading, blood glucose levels were estimated.

Evaluation of antidiabetic activity

Induction of diabetes:

Diabetes was induced in rats by single intra peritoneal (i.p.) injectionof steptozotocin (STZ, Sigma chemical Co. USA) at a dose 60 mg/kg b.w. freshly dissolved in 0.1 M cold citrate buffer of pH 4.5; 48 hr later blood samples were collected and blood glucose levels were determined to confirm the development of diabetes. Those animals which showed hyperglycemia (blood glucose levels >240 mg/dl) were used in experiment.

Chronic treatment model

The rats were divided into five groups of 6 animals (n=6) each as below:

Group I- Normal control (received distilled water 10 ml/kg b.w., p.o.)

Group II- Diabetic control untreated (received distilled water 10 ml/kg b.w., p.o.)

Group III- Diabetic treated with standard drug glibenclamide (0.25 mg/kg/day, p.o.)

Group IV- Diabetic treated with SSAE (250 mg/kg/day, p.o.)

Group V-Diabetic treated with SSAE (500 mg/kg/day, p.o.)

For 30 days blood glucose levels and body weights were measured on 1st, 10th, 20th and 30th day of the study. Finally on day 30, blood was collected to estimate various parameters.

Estimation of plasma glucose, body weight and lipid profile

Every week, following overnight fasting (16 hr fasting with free access to water), the blood samples were withdrawn from the animals by retro-orbital puncture under light ether anesthesia. The plasma glucose estimation was done by the glucose

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oxidase/peroxidase (GOD/ POD) method using a standard kit obtained from Span Diagnostics, India. Body weight of all experimental animals was recorded using a digital weighing scale. The TG, TC and HDL levels were estimated (15) using standard kits obtained from Span Diagnostics, India VLDL = TG/5 LDL = TC − (HDL + VLDL).

Estimation of serum insulin

Serum insulin concentration was determined by radioimmunoassay kit done spectrophotometrically using standard kits (RIA provided by BRIT, BARC, India), The kit included human insulin as standard and 125Ilabelled human insulin antibody, which crossreacts similarly with rat insulin. Estimation of glycated hemoglobin After 30 days experimental period, the 12hr fasted rats were sacrificed by cervical decapitation, blood was withdrawn by retro orbital puncture under light ether anesthesia and the glycated hemoglobin was estimated.

Estimation of liver glycogen

After 30 days experimental period, the 12hr fasted rats were sacrificed by cervical decapitation. The liver tissue (1 g) was collected, placed in a centrifuge tube containing 2 ml of KOH (300 g/L) after washing with saline water and heated for 20 min with occasional shaking. To this, a saturated solution of sodium sulphate (0.2 ml) was added and mixed thoroughly. The glycogen was precipitated by the addition of ethanol (5 ml). The precipitate was removed and dissolved in 10 ml of water. One ml of this solution was added to 1 ml of HCl (1.2 mol/l) and boiled for 2 hr. After 2 hr, the solutions were neutralized by NaOH (0.5 mol/l) using phenol red as indicator. The neutralized solution was diluted to 5 ml and transferred to a calorimeter tube and read at 620 nm after adjusting the calorimeter with the reagent blank. The glycogen content was expressed as mg/g of liver tissue.

III. STATISTICAL ANALYSIS

The results were expressed as mean± S.E.M. Statistical difference was tested by using one-way analysis of variance (ANOVA) followed by Dunnette's multiple comparison test. A difference in the mean p value <0.05 was considered as statistically significant.

IV. RESULTS

Preliminary phytochemical screening

Preliminary phytochemical screening revealed the presence of triterpenoids, carbohydrates, vitamins, amino acids, proteins, tannins, saponin glycosides and steroids.

Acute toxicity study

In the LD50 value determination, we observed that the SSAE was safe to use in animals and showed no mortality on 2500 mg/kg b.w. Therefore 2500 mg/kg dose was considered as a safe dose, 1/5th (500 mg/kg b.w.) and 1/10th (250 mg/kg b. mg/kg b.w.) of that was selected for all in vivo experiments as maximal dose.

Effect of aqueous extract in normoglycemic rats

The results from the study clearly indicated that there was no significant effect observed on normoglycemic rats when treated with the single dose of Sesbaniasesban aqueous extract (Table 1).

Effect of aqueous extract on oral glucose tolerance test in STZ-induced diabetic rats (OGTT)

The results from the study clearly indicated that the aqueous extract of Sesbaniasesban leaves at 250 and 500 mg/kg reduced the blood glucose level (hyperglycemia due to glucose load 2 g/kg p.o.) significantly and glibenclamide (0.25 mg/kg) after 60 min of oral administration, when compared to diabetic control (Table 2).

Table 1. Effect of aqueous extract of Sesbaniasesban leaves in normoglycemic rats

Group treatment (n=6)	**Fasting plasma glucose level (mg/dl) at (hrs)**				
	0	**1**	**2**	**3**	**4**
I Normal	95.00±0.73	94.16±0.65	92.50±1.05	91.83±1.07	91.33±0.49
II Glibenclamide	95.16±0.70	92.50±0.67	89.16 ±0.47*	88.50±0.67*	85.33±0.95**
III Aqueous extract	95.66±1.05	94.16±0.60	90.00±0.57	89.33±0.33	88.50±0.42*
IV Aqueous	94.83±1.01	93.83±0.79	90.66±0.91	89.83±0.70	88.62±0.42*

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extract					

* p<0.05, **p<0.01, Values are mean±SEM, n=6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test

Table 2. Effect of aqueous extract of Sesbaniasesban leaves on OGTT in stz-induced diabetic rats

Group treatment (n=6)	Fasting plasma glucose level (mg/dl) at (hrs)				
	0	1	2	3	4
I Normal	95.00±0.73	123.17±2.72	134.83±1.35	144.83±1.35	154.83±1.35
II Diabetic control	259.17±1.16	269.50±0.95	279.50 ±0.95	289.50±0.95	297.83±0.83
III Positive control	255.17±1.01	265.17±1.01*	275.17±1.01*	285.17±1.01*	265.00±1.15**
IV Aqueous extract	259.67±1.02	266.33±1.30	276.33±1.30	286.33±1.30	274.67±1.17*
V Aqueous extract	258.50±2.04	265.17±1.13*	275.37±1.13*	285.47±1.13*	265.17±1.13**

* p<0.05, **p<0.01, Values are mean±SEM, n=6, when compared with diabetic control by using one way ANOVA followed by Dunnette's multiple comparison test.

Hypoglycemic effect of the aqueous extract

The results from the study clearly indicated that the aqueous extract exhibited significant hypoglycemic activity in STZ-induced diabetic rats, whilst there was no significant effect observed on normoglycemic rats. However, at the end of 30 days of treatment, there was a 70.12 %, 64.96% and 68.09% (p<0.01) decrease of serum glucose levels with the glibenclamide and aqueous extract (250 and 500 mg/kg) respectively when compared with diabetic control after 30 days (Table 3).

Changes in body weight

At the end of 30 days treatment, the body weight of normal rats, aqueous extract and standard drug treated group increased significantly; whereas body weight of diabetic control group decreased (Table 4).

Changes of serum insulin, liver glycogen and glycolsylated hemoglobin

After 30 days treatment period it was observed that animals treated with aqueous extract showed a significant increase in the serum insulin level, liver glycogen level and decrease in glycosylated hemoglobin level as compared to serum insulin levels in normal groups (Table 5).

Table 3. Effect of aqueous extract of Sesbaniasesban leaves on serum glucose level

Group treatment (n=6)	**Fasting plasma glucose level (mg/dl)**			
	1st day	**10th day**	**20th day**	**30th day**
I Normal control	94.50±2.07	94.33±2.10	96.33±1.89	95.16±2.02
II Diabetic control	255.00±1.18	286.67±1.22	312.67±4.58	387.67±2.83
III Diabetic + glibenclamide (0.25 mg/kg)	255.67±1.33	265.67±1.33**	210.67±2.84**	115.83±1.53**
IV Diabetic + aqueous extract (250 mg/kg)	255.83±0.79	275.83±0.79**	235.83±0.79**	135.83±0.79**
V Diabetic + aqueous extract (500 mg/kg)	256.33±2.65	268.67±1.02**	223.67±2.01**	123.67±2.01**

* p<0.05,**p<0.01, Values are mean±SEM, n=6, when compared with diabetic control by using one way ANOVA followed by Dunnette's multiple comparison test.

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Table 4. Effect of aqueous extract of Sesbaniasesban leaves on body weight in stz-induced diabetic rats

Group treatment (n=6)	Changes in body weight (g) at (days)			
	0	10	20	30
I Normal	155.67±0.76	166.33±0.91	172.00±0.91	185.33±0.87
II Diabetic control	158.17±0.70	153.50±0.56	148.67 ±0.66	139.00±0.77
III Positive control	158.00±0.77	161.50±1.05**	163.33±0.80**	168.33±1.35**
IV Aqueous extract	163.33±5.04	166.83±0.94**	168.50±0.34**	175.17±1.37**
V Aqueous extract	158.67±0.49	165.33±1.70**	167.33±0.55**	173.50±1.14**

* p<0.05, **p<0.01, Values are mean±SEM, n=6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test.

Table 5. Effect of aqueous extract of Sesbaniasesban leaves on serum parameters after 30 days

Group treatment (n=6)	Serum insulin µU/ml	Glycosylated hemoglobin mg/g Hb	Liver glycogen mg/g
I Normal control	18.16±0.55	0.22±0.007	14.66±0.33
II Diabetic control	7.13±0.317.	0.58±0.009	7.16±0.60
III Diabetic + glibenclamide (0.25 mg/kg)	16.66±0.33**	0.25±0.007**	13.00±0.25**
IV Diabetic + aqueous extract (250 mg/kg)	13.33±0.33**	0.27±0.006**	11.41±0.37**
V Diabetic + aqueous extract (500 mg/kg)	15.33±0.33**	0.31±0.004**	12.58±0.23**

*p<0.05, **p<0.01, Values are mean±SEM, n=6, when compared with diabetic control by using one way ANOVA followed by Dunnette's multiple comparison test

Table 6. Effect of aqueous extract of Sesbaniasesban leaves on serum lipid profile after 30 days

Group	Cholesterol	LDL	HDL	VLDL	Triglycerides
Normal control	66.16±0.83	22.83±0.87	11.00±0.36	17.33±0.66	66.50±0.76
Diabetic control	95.33±0.71	97.33±0.49	9.83±0.30	22.16±0.30	114.33±1.47
Diabetic+glibenclamide (0.25 mg/kg)	69.66±0.66**	36.00±0.73**	13.83±0.47**	18.16±0.30**	76.50±0.76**
Diabetic+aqueous extract (250 mg/kg)	77.16±0.60**	48.33±0.42**	13.83±0.40**	18.66±0.21**	82.50±0.99**
Diabetic+aqueouse xtract (500 mg/kg)	70.83±0.60**	38.50±076**	14.83±0.30**	19.16±0.16**	77.50±0.84**

*p<0.05, **p<0.01, Values are mean±SEM, n=6, when compared with diabetic control by using one way ANOVA followed by Dunnette's multiple comparison test

Lipid profile

Lipid profile of animals treated with aqueous extract showed significant reductions (p<0.01) of 19.06% and 25.70% CHL (cholesterol), 50.34% and 60.44% LDL, 15.79% and 13.53% VLDL (Very Low density lipoproteins) and 27.84% and 32.21% TG after treatment with aqueous extract of Sesbaniasesban leaves (250 and 500 mg/kg), respectively when compared with diabetic control rats. Also there was a significant (p<0.05) increase of HDL in the treated diabetic rats. In case of untreated diabetic rats, there was a fall in HDL level (Table 6).

V. DISCUSSION

STZ induced diabetic rats are one of the animal models of type 1 diabetes mellitus. It is well known for its selective pancreatic islet beta cell cytotoxicity and has been extensively used to induce type 1 diabetes in experimental rat model.

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Glibenclamide is often used as a standard antidiabetic drug in STZ induced diabetes to compare the efficacy of variety of hypoglycemic drugs.

This study showed that Sesbaniasesban produced a marked decrease in blood glucose at 250 and 500 mg/kg in diabetic rats after 30 days of treatment. The antidiabetic effect of S. sesbanmay be due to increased release of insulin from the existing cells of pancreas. Further, the antihyperglycemic activity of S. sesban was associated with an increase in plasma insulin level, suggesting an insulinogenic activity of the plant extracts. The observed increase in the level of plasma insulin indicates that S. sesbanstimulates insulin secretion from the remnant beta cells or from regenerated beta cells. In this context, a number of other plants have also been reported to exert hypoglycemic activity through insulin release stimulatory effect. Decreased body weight observed in diabetic control rats in comparison to normal rats indicates that loss of body weight is a result of excessive breakdown of tissue proteins. Treatment with S. sesbanimproved body weight to a certain extent, indicating that control over muscle wasting resulted from glycemic control. This suggests the hypoglycemic effect of S. sesbanin diabetic rats.

Increased non enzymatic glycosylation is one of the possible mechanism linking hyperglycemia and vascular complications of diabetes. During diabetes, the excess glucose present in the blood reacts with hemoglobin to form HbA1C. In the present study, the diabetic rats had shown higher level of HbA1C compared with those in normal rats, indicating their poor glycemic control. S. sesbantreated diabetic rats significantly decreased the level of HbA1C and increased total hemoglobin which might be the result of an improvement in the glucose metabolism.

Kondeti et al have reported that STZ induced diabetic rats account for the observed decrease in the total protein content. Increased urea production in diabetes might be due to enhanced catabolism of both liver and plasma proteins. S. sesbantreatment has appreciably normalized the content of protein and urea. In response to STZ treatment, creatinine was increased in the serum, suggesting an impairment of kidney functions. S. sesbanshowed a clear improvement in kidney functions, perhaps due to the antioxidant properties.

Hexokinase is the rate-limiting glycolytic enzyme that is severely impaired during diabetes. The activities of both glucose-6-phosphatase and fructose-1, 6-bisphosphatase are increased in the liver during the diabetic condition. Treatment with S. sesban has appreciably normalized the activity of these enzymes. In the diabetic rats, treatment with S. sesbanresulted in normalizing the pancreatic histoarchitecture quite appreciably. An increase in the number of beta cells in the islets showed that they were regenerated. Also, the increase in secretory granules in the cells indicates that the cells were stimulated for insulin synthesis. A decrease in the number of secretory granules, nuclear shrinkage and pycnosis, swelling of mitochondria, hypertrophied cytoplasmic organelles such as Golgi and endoplasmic reticulum have been observed in the beta cells of STZ induced diabetic rats.

In conclusion, the present study shows that the methanol extract of S. sesbanhas potential antidiabetic action in STZ induced diabetic rats and the effect was found to be more similar to the reference drug glibenclamide.

VI. CONCLUSION

In conclusion, it can be stated that the aqueous leaves extract of Sesbaniasesban has beneficial effects in reducing the elevated blood glucose level and lipid profile of STZinduced diabetic rats, but has no effect on normal rats. Thus justifying the claim made by ayurvedic classics.

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