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Evaluation of antihyperglycemic and antioxidant properties of *Streblus asper* Lour against streptozotocin-induced diabetes in rats

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ABSTRACT

Objective: To evaluate antidiabetic and antioxidant role of methanol extract of *Streblus asper* (*S. asper*) root bark in Wistar rats. **Methods:** Diabetes was induced in rats by single intraperitoneal injection of streptozotocin (STZ, 65 mg/kg body weight). Three days after STZ induction, the diabetic rats were treated with *S. asper* orally at dose of 200 and 400 mg/kg body weight daily for 15 days. Glibenclamide (0.25 mg/kg, orally) was used as reference drug. The fasting blood glucose levels were measured on every fifth day during the 15-day treatment. Serum biochemical parameters such as serum glutamate pyruvate transaminase, serum glutamate oxaloacetate transaminase, serum alkaline phosphatase, total cholesterol total protein and serum triglycerides were estimated. Antioxidant properties were assessed by estimating liver and kidney thiobarbituric acid reactive substances, reduced glutathione and catalase. **Results:** *S. asper* in STZ-induced diabetic rats, at doses of 200 and 400 mg/kg bw produced reduction in blood glucose levels when compared with the STZ control group. Serum biochemical parameters antioxidant levels were significantly restored toward normal levels in *S. asper* treated rats as compared with STZ control. **Conclusions:** The present study infers that the methanol extract of *S. asper* root bark demonstrated remarkable antidiabetic activity in STZ-induced diabetic rats. The potential antidiabetic action is plausibly due to its underlying antioxidant role.

1. Introduction

Diabetes mellitus (DM) is a chronic disease caused by inherited or acquired deficiency in production of insulin by the pancreas or by the ineffectiveness of the produced insulin. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves. Regions with greatest morbidity potential are Asia and Africa, where DM rates could rise two to three-fold than the present rates. Treatment of type 2 diabetes mellitus (T2DM) patients with sulfonylureas and biguanides is always associated with side effects[1]. So, many herbal medicines have been recommended for the treatment of diabetes. Traditionally plant based medicines are used throughout the world for a range of diabetic presentations[2].

T2DM is more common because of increasing obesity and reduced activity levels, environmental and psychosocial stress factors, as well as malnutrition and increased xenobiotic intakes. In the past few decades, T2DM has rapidly increased in the world. T2DM is mainly characterized by the increased morbidity and mortality from cardiovascular diseases. DM is also associated with a high risk of atherosclerosis and renal, nervous system and ocular complications[3]. Oxidative stress is the imbalance between the generation of reactive oxygen species (ROS) and the body defense mechanisms. Environmental pollutants, toxic habits (drugs, smoking, and/or alcohol), inadequate nutrition, excess solar radiation, large exposure to toxic substances (fertilizers and pesticides), drug metabolism (side effects) and a high physical or psychical stress are the most common exogenous factors originating ROS in human body[4]. Oxidative stress has also been implicated in the pathogenesis of diabetes, micro and macro vascular complications and cancer[5].

Streblus asper (*S. asper*) Lour (Moraceae) is a medicinal plant commonly found in most areas of Southern Asia such as India, Bangladesh, Sri Lanka, Malaysia, Philippines and Thailand. It has a reputation for its claim on healing properties and used for specific ailments[6]. In fact, based

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on India's indigenous knowledge, the plant is traditionally used for a wide range of specific ailments including leprosy, piles, diarrhoea, dysentery, elephantiasis, cancer and other conditions[6]. The Marma tribes in Bangladesh have used the root juice of *S. asper* to treat irregular menstruation and to promote delayed menstruation[6].

Phytochemical investigation of *S. asper* Lour shows the presence of cardiac glycosides[7], glycosides, pregnane glycoside named sioraside from the roots[8] and from the stem bark of this plant, α-amyrin acetate, lupeol acetate, β-sitosterol, α-amyrin, lupeol and diol have also been isolated[9-18]. Due to the presence of high level of glycosides the present study attempts to report the antidiabetic and antioxidant properties of *S. asper* root bark in streptozotocin-induced diabetic rats.

2. Materials and methods

2.1. Plant material and extract preparation

The whole plant of *S. asper* Lour (Moraceae) was collected from West Bengal, India, during the month of March 2010 and identified by Mr. Shyam from Botanical Survey of India, Howrah, West Bengal, India. A voucher specimen (No.-CNH/I-I/ (29/2010/Tech.II) has been preserved at our Phytotherapy and Pharmacology laboratory for future reference. Air-dried root bark (500 g) material was powdered by a mechanical grinder and extracted with methanol by using Soxhlet extraction apparatus[19]. Then the solvent was completely removed under reduced pressure and stored in a vacuum dessicator (yield 9.80%). The methanol extract of *S. asper* was used for the present study.

2.2. Animals

Adult male Wistar albino rats (170-200 g) were housed in a clean polypropylene cage with not more than four animals per cage and maintained under conditions of (25 ± 2) ℃ with 12/12 h dark/light cycle. They were fed standard dry pellet diet (Hindustan Lever, Kolkata, India) and water *ad libitum*. The animals were acclimatized to laboratory conditions for one week prior to the experiment. All procedures described were reviewed and approved by the University Animal Ethics Committee (367001/C/CPCSEA), Jadavpur University.

2.3. Drugs and chemicals

Trichloroacetic acid (TCA) was obtained from Merck Ltd., Mumbai, India. Thiobarbituric acid (TBA), streptozotocin (STZ), 5, 5′-dithio bis-2-nitro benzoic acid (DTNB), phebnazine methosulfate (PMS), nicotinamide adenine dinucleotide (NADH) and reduced glutathione (GSH) were from SISCO Research Laboratory, Mumbai, India; potassium dichromate, glacial acetic acid were from Ranbaxy, Mumbai; and glibenclamide (Diabeta) were from Eli Lilly, India. All the other reagents were of analytical reagent grade obtained commercially.

2.4. Acute toxicity

The acute oral toxicity of alcoholic extract of *S. asper* in male Swiss albino mice was studied as per OECD guidelines 423[20]. The test sample was found to be safe up to a dose of 2000 mg/kg bw.

2.5. Oral glucose tolerance test

The oral glucose tolerance test was performed in overnight fasted normal rats. Rats were divided into three groups (n=6). Group I served as normal control and received distilled water (5 mL/kg bw, *p.o.*) and groups II and III received alcohol extract of *S. asper* at doses of 200 and 400 mg/kg bw, respectively. After these treatments, all groups received glucose (2 g/kg bw) orally. Blood was withdrawn from the tail vein just prior to and 30, 60, 120 and 240 min after oral glucose administration[21]. Blood glucose levels were measured using single touch glucometer (Accu-check, Roche Diagnostics, USA).

2.6. Induction of diabetes

Diabetes mellitus was induced in overnight fasted rats weighing (170-200 g) by a single intraperitoneal injection of STZ 65 mg/kg bw (in citrate buffer 0.01 M, pH 4.5). The injection volume was prepared to contain 65 mg/mL and injected as 0.1 mL/100 g of animal. After 3 days, blood glucose levels were measured and hyperglycemic (≥ 225 mg/dL blood glucose level) animals were taken for the investigation[21].

2.7. Experimental design and testing of fasting blood glucose level

The rats were divided into five groups (n=6). Except group I, which served as normal non-diabetic control. Group II served as diabetic (STZ) control. Groups III and IV received alcohol extract of *S. asper* (200 and 400 mg/kg bw, *p.o.*, respectively), and group V received reference drug glibenclamide (0.25 mg/kg b.w., *p.o.*) daily for 15 days. Fasting blood glucose was measured on day 0, 5, 10 and 15 by using a one-touch glucometer. At 24th hour of the last dose, blood was collected from overnight fasted rats from all animals in each group by cardiac puncture for estimation of serum biochemical parameters *viz.* serum glutamate pyruvate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SALP), total protein and total cholesterol. Then the rats were sacrificed by cervical dislocation for the study of liver and kidney for antioxidant parameters like lipid peroxidation, reduced GSH and CAT[22].

2.8. Body weight

Body weight of rats from each group was measured on day 1, 5, 10 and 15. Weight was measured using standard digital weight balance to get accuracy.

2.9. Estimation of serum biochemical parameters

Collected blood was used for the estimation of serum biochemical parameters *viz.*, SGOT, SGPT, SALP, total cholesterol, serum triglyderides and total protein using standard kit method (Span Diagnostic Ltd. India).

2.10. Estimation of liver and kidney antioxidant parameters

Lipid peroxidation, *i.e.*, thiobarbituric acid reactive substances (TBARS) was estimated and expressed as mM/100 g of tissue. Reduced GSH was determined and expressed as mg/100 g of tissue[22]. CAT activity was assayed and expressed as μ moles of H_2O_2 decomposed/min/mg of tissue[22].

2.11. Statistical analysis

All results are expressed as the Mean ± SEM. The results were analyzed for statistically significance by one-way analysis of variance (ANOVA) followed by Dubnnett's test using Graph Pad InStat version 5 (Graph Pad Software, USA).

3. Results

3.1. Acute toxicity

The test samples were found to be safe up to a dose of 2 000 mg/kg orally.

3.2. Oral glucose tolerance test

Glucose loading to the normal rats increased serum glucose levels from 65.26 ± 6.33 to 146.76 ±0.08 at 60 min and returned to normal at 240 min. Alcoholic extract of *S. asper* administration improved glucose tolerance significantly ($P < 0.01$) in a dose dependent manner at 120 min (Table 1). The effect of alcoholic extract of *S. asper* on glucose tolerance remained statistically significant ($P< 0.01$) at 240 min at the higher dose (400 mg/ kg).

3.3. Fasting blood glucose level

The body weights of normal and diabetic rats were summarized in Table 2. The final body weights were significantly ($P< 0.001$) decreased in the STZ control group when compared with the saline control group. The observed data showed an improvement of body weight after treatment with the alcoholic extract of *S. asper* with respect to STZ-control group. Administration of alcoholic extract of *S. asper* in STZ-induced diabetic rats, at the doses of 200 and 400 mg/kg bw produced a significant reduction in blood glucose levels when compared with the STZ-control group (Table 3).

3.4. Estimation of serum biochemical parameters

Biochemical parameters like SGOT, SGPT, SALP, total cholesterol and triglycerides in STZ control group were significantly ($P<0.001$) elevated as compared to normal control group. Treatment with alcoholic extract of *S. asper* significantly ($P<0.001$) reduced the serum biochemical parameters towards normal values in a dose dependent manner. Total protein was found to be significantly decreased in STZ control group as compared to normal control group ($P<0.001$) and alcoholic extract of *S. asper*

Table 1
Effect of *S. asper* on oral glucose tolerance test (Mean ± SEM, n=6).

Group	Treatment	Blood glucose (mg/dL)				
		0 min	30 min	60 min	120 min	240 min
I	Normal control	65.26 ± 6.30	110.50 ± 6.00	146.76 ± 0.08	121.34 ± 0.70	74.66 ± 0.12
II	*S. asper* (200 mg/kg)	63.27 ± 4.20	109.00 ± 5.30	135.43 ± 0.23	105.50 ± 0.26	68.46 ± 0.26
III	*S. asper* (400 mg/kg)	62.56 ± 4.10	105.00 ± 0.33	129.63 ± 0.80***	101.60 ± 0.05***	66.50 ± 0.40

***$P< 0.001$ compared to normal control at 60 min and 120 min, respectively.

Table 2
Effect of *S. asper* on body weight (g) (Mean ± SEM, n=6).

Group	Treatment	Day 0	Day 5	Day 10	Day 15
I	Normal saline (5mL/kg)	178.10 ± 0.50	179.85 ± 4.20	179.50 ± 0.28	180 ± 1.20
II	STZ (65 mg/kg)	187.23 ± 1.32	160.54 ± 2.36	160.50 ± 0.22	116.25 ± 1.56***
III	STZ + 200 mg/kg *S. asper*	170.35 ± 1.69	164.38 ± 0.38	164.56 ± 0.20	147.36 ± 0.21##
IV	STZ + 400 mg/kg *S. asper*	172.05 ± 0.80	168.46 ± 0.25	168.68 ± 0.35	150.45 ± 1.37###
V	STZ + 0.25 mg/kg glibenclamide	185.33 ± 9.50	176.50 ± 6.40	176.39 ± 0.26	163.76 ± 3.30##

***$P<0.001$ compared with normal saline control on corresponding day, ##$P<0.01$ and ###$P<0.001$ compared to STZ control group on corresponding day.

Table 3
Effect of *S. asper* on fasting blood glucose on STZ induced diabetic rats (Mean ± SEM, n=6).

Group	Treatments	Fasting blood glucose level (mg/dL)			
		Day 0	Day 5	Day 10	Day 15
I	Normal saline (5 mL/kg)	73.50 ± 0.19	75.48 ± 0.14	75.50 ± 0.35	74.85 ± 0.19
II	STZ (65 mg/kg)	356.00 ± 0.12***	354.00 ± 0.25***	400.70 ± 0.10***	391.00 ± 0.12***
III	STZ + 200 mg/kg *S. asper*	401.80 ± 2.50	267.70 ± 3.50##	218.50 ± 2.30###	168.50 ± 1.30###
IV	STZ + 400 mg/kg *S. asper*	400.30 ± 3.90	252.80 ± 2.10##	196.20 ± 3.90###	140.30 ± 1.30###
V	STZ + 0.25 mg/kg glibenclamide	294.50 ± 1.10###	278.00 ± 3.90##	179.20 ± 2.60###	111.20 ± 0.80###

***$P<0.001$ compared with normal saline control, ##$P<0.01$ and ###$P<0.001$ compared with STZ control group.

Table 4
Effect of *S. asper* on serum biochemical parameters in STZ induced diabetic rats (Mean ± SEM, *n*=6).

Group	Treatment	SGOT (IU/L)	SGPT (IU/L)	SALP (U/L)	Total protein (g/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
I	Normal saline (5 mL/kg)	25.10 ± 0.23	28.36 ± 0.30	150.00 ± 0.60	9.10 ± 0.10	66.32 ± 0.12	85.14 ± 0.60
II	STZ (65 mg/kg)	36.60 ± 1.35	39.00 ± 0.20	256.12 ± 0.36	5.90 ± 0.47	186.00 ± 0.21***	198.00 ± 0.10***
III	STZ + 200 mg/kg *S. asper*	33.20 ± 1.60	38.21 ± 0.60***	242.70 ± 0.35***	7.15 ± 0.21	150.28 ± 0.47***	141.01 ± 0.20***
IV	STZ + 400 mg/kg *S. asper*	30.20 ± 0.10	38.00 ± 0.10***	242.30 ± 0.10***	8.14 ± 0.32	139.10 ± 0.78***	138.00 ± 0.32***
V	STZ+ 0.25 mg/kg glibenclamide	27.50 ± 0.20	36.12 ± 0.30***	236.00 ± 0.14***	8.12 ± 0.31	110.61 ± 0.10***	121.00 ± 0.89***

***P<0.001 compared with normal saline control.

treatment restored the total protein content towards normal as compared with STZ control group (Table 4).

3.5. Estimation of tissue antioxidant parameters

The level of TBARS, GSH and CAT activities in liver and kidney of experimental diabetic rats are shown in Figure 1. There was a significant elevation of TBARS in liver and kidney in STZ group when compared to the saline control group. It was found that the administration of alcoholic extract of *S. asper* significantly decreased TBARS levels in liver and kidney, which is an indication of the inhibition of oxidative damage of hepatic and renal tissues. There was a significantly decreased (P<0.001) level of GSH and CAT in the STZ-control group as compared with the saline control group. Administration of alcoholic extract of *S. asper* significantly (P<0.001) increased the GSH and CAT level in the liver and kidney of STZ-induced diabetic rats in a dose dependent manner.

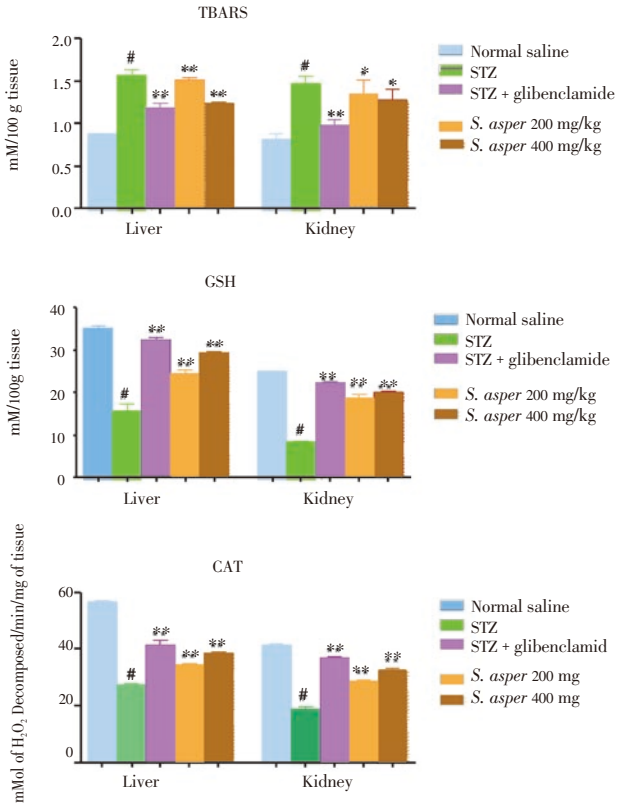

Figure 1. Effect of *S. asper* on antioxidant properties. Values are expressed as Mean ± SEM (*n*=6); #P<0.001 compared STZ control with normal saline control. *P<0.01 and ***P<0.001 compared with STZ control.

4. Discussion

STZ is an antibiotic obtained from *Streptomyces achromogenes*, which enters pancreatic β cells via the glucose transporter GLUT2 and causes alkylation of deoxyribonucleic acid in DNA. Its toxicity depends on the potent alkylating properties combined with the synergistic action of nitric oxide and reactive oxygen species that contribute to DNA fragmentation. As the result of STZ action, pancreatic β cells are destroyed by necrosis[23]. Treatment with alcoholic extract of *S. asper* in STZ-induced diabetic rats started reducing fasting blood glucose levels in a dose dependent manner after 5 to 7 days and made them normoglycemic after 15 days. The antihyperglycemic effect of *S. asper* alcoholic extract at dose of 400 mg/kg was found to be comparable to the effect exerted by the reference drug (glibenclamide) at a dose of 0.25 mg/kg. Induction of diabetes with STZ is associated with a characteristic loss of body weight, which is due to increased muscle wasting and loss of tissue proteins[24]. Diabetic rats treated with alcoholic extract of *S. asper* showed significant improvement in body weight as compared to STZ control animals; hence alcoholic extract of *S. asper* exhibited a marked effect in controlling the loss of body weight of diabetic rats.

Oxidative stress in diabetes mellitus has been shown to coexist with impairment in the endogenous antioxidant status and removal of oxidative damage molecules by activating antioxidant enzymes such as CAT, gluthathione S-transferase (GST), glutathione peroxidase (GPx), etc. These antioxidants are able to resist oxidative stress by scavenging free radicals, inhibiting lipid peroxidation and increasing GSH and CAT activity[21].

Elevation of serum biomarker enzymes such as SGOT, SGPT, SALP, total cholesterol, serum triglyderides was observed in diabetic rats indicating impaired liver function, which is obviously due to hepatocellular necrosis. The decreased total protein content in STZ-induced diabetic animals also substantiated the hepatic damage by STZ. Diabetic complications such as increased gluconeogenesis and ketogenesis may be due to elevated transaminase activities[22]. The 15-day treatment with alcoholic extract of *S. asper* restored all the above mentioned hepatic biochemical parameters towards normal levels in a dose dependent manner.

Lipid peroxidation is usually measured through a catabolite malondialdehyde (MDA) in terms of TBARS as a marker of oxidative stress[22]. A marked increase in the concentration of TBARS in STZ-induced diabetic rats indicated enhanced lipid peroxidation leading to tissue

injury and failure to scavange the formation of excess free radicals. Alcoholic extract of *S. asper* showed the ability to prevent STZ-induced increased TBARS levels, suggesting that alcoholic extract of *S. asper* inhibited lipid peroxidation and improved the pathological condition of diabetes.

GSH is one of the abundant tripeptide non-enzymatic biological antioxidants present in the liver and kidney. It plays an important role in detoxification and in the protection of cellular constituents against reactive oxygen species[22]. Treatment with alcoholic extract of *S. asper* elevated the reduced level of GSH, thus protecting the liver and kidney form oxidative stress induced by STZ.

CAT is a heme-containing enzyme widely distributed in the peroxisomes or microperoxisomes of all animals tissues. This enzyme catalyzes the decomposition of H_2O_2 to water and oxygen and thus protects the cell from oxidative damage[22]. It was found that the CAT activity was decreased in STZ-induced diabetic rats. Alcoholic extract of *S. asper* supplement in diabetic rats showed normalization of CAT, preventing oxidative injury of the liver and kidney.

From the present study it could be concluded that alcholic extract of *S. asper* possess potent antioxidant properties due to the presence of glycosides. Possibly by virtue of its augmenting the endogenous antioxidant mechanism *S. asper* has shown antihyperglycemic activity in STZ induced diabetic rats.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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