Available online on 15.07.2016 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
An International Peer Reviewed Journal
Open access to Pharmaceutical and Medical research

RESEARCH ARTICLE

ANTIDIABETIC AND HYPOLIPIDEMIC EFFECT OF METHANOL EXTRACT OF *STEREOSPERMUM COLAIS* FRUIT IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Received 12 June 2016; Review Completed 30 June 2016; Accepted 30 June 2016, Available online 15 July 2016

ABSTRACT:

Objective: To assess the antidiabetic and hypolipidemic properties of *Stereospermum colais* Fruit.

Methods: Acute toxicity test was done to check the toxicity of *Stereospermum colais* fruit methanol extract at three dose levels was administered orally to streptozotocin (STZ) (40 mg/kg bw) induced diabetic rats for 15 days. The various parameters were studied including body weight, fasting blood glucose levels, plasma insulin, lipid profile, glycogen content, glycoslylated hemoglobin (HbA1c) and serum marker enzymes levels in normal, treated and diabetic rats. Histochemical analysis of pancreas was also carried out in normal treated and diabetic rats.

Results: The treatment group with the extract at three dose levels showed a significant increase in the liver, muscle glycogen and serum insulin level and a significant decrease in fasting blood glucose, glycosylated hemoglobin levels and serum marker enzyme levels. The total cholesterol and serum triglycerides levels were also significantly reduced and the high density lipoprotein level was significantly increased upon treatment with the *Stereospermum colais* Fruit methanol extract. Histochemical study of pancreas also confirmed the biochemical findings. Acute toxicity studies revealed the non-toxic nature of the *Stereospermum colais* Fruit methanol extract. **Conclusions:** The results of the experiments presented here suggest that methanol extract of *Stereospermum colais* Fruit exerts significant antidiabetic and hypolipidaemic effect in STZ induced diabetic rats.

Keywords: *Stereospermum colais, Antidiabetic, Hypolipidemic, Fruit, streptozotocin.*

INTRODUCTION:

Diabetes mellitus (DM) has been defined as a chronic disease with persistently elevated blood glucose concentration, leading to acute r long term complications [1]. Globally, DM presents enormous and increasingly important public health issues. The prevalence of DM in all age groups was estimated to be 2.8% (170 million) in 2000 and the rate is expected to rise to 4.4% (366 million) in 2030[2]. The pharmacological agents currently used for treatment of type 2 diabetes include sulfonylureas, biguanide, thiazolidinedione and alpha glycosidase inhibitors. These agents, however, have restricted usage due to several undesirable side effects and fail to significantly alter the course of diabetic complications. Renewed attention to alternative medicines and natural therapies has stimulated new waves of research interest in traditional practices, and there is a need to look for more efficacious agents with lesser side effects. Presently, there is growing interest in herbal remedies due to the side effects associated with oral hypoglycemic agents for the treatment of diabetes mellitus [3, 4].

Stereospermum colais (Buch.-Ham.ex Dillw.) is commonly known as Mabberley, belonging to the family of Bignoniaceae. It is normally found in India, Myanmar, and Sri Lanka; in the Western Ghats- South, Central and south Maharashtra Sahyadris. In spite of its many uses (diarrhoea, cough, asthma, hiccough, bleedings, hyperacidity, vomiting, fever, general debility, rheumatism, malarial fever, wounds, burning sensation, heart disease), the antidiabetic, antiperoxidative and radical scavenging activities of this species have not been assessed, and its chemical composition is scarcely known[5, 6].

However, there are no reports on the antidiabetic activity of the plant. Hence this study was undertaken to evaluate the anti-diabetic activity of methanol extract of *Stereospermum colais* Fruit in sterptozotocin (STZ) induced diabetic rats.

MATERIALS AND METHODS:

Plant material:

The Fruits of *Stereospermum Colais* were collected from Pathnur Ghat, Taluka Ardhapur, District Nanded, Maharashtra, India. Plant materials were authenticated from Dr. Arvind S Dhabe Dr, Babasaheb Ambedkar Marathwada University, Aurangabad. Collected plant material was dried in tray dryer at 55^{o}C for 24 h and powdered. Herbarium was prepared according to International curatorial practices. Specimen was given a number by the plant identifying authority is 0780 (reference number Bet/2010-11).

Preparation of extracts:

The whole plant of *Stereospermum colais* Fruit was washed thoroughly with water to remove the soil particles, and then was air dried and powdered. One kilogram of plant material was extracted with methanol solvent (2.5 L for each time). The filtrate was concentrated under reduced pressure at 40 ^{o}C and the extract was stored in a refrigerator at 4 ^{o}C for use in subsequent experiments.

Chemicals:

Sterptozotocin was obtained from Hetero Drugs, Hyderabad, India. Kits to estimate total cholesterol, triglycerides and HDL-cholesterol kit was purchased from Merck, Mumbai, India. All other chemicals were of analytical grade.

Preliminary phytochemical screening of the extract:

The preliminary phytochemical analysis was carried out for the *Stereospermum colais* Fruit methanol extract (SC methanol extract) using standard phytochemical methods[7].

Animals:

Healthy adult Wister albino rats with body weight around (170±5) g at 60-70 days from birth and raised in the animal house at Oriental College of pharmacy, Navi Mumbai were used for the study. Housed individually in polypropylene cages, maintained under standard conditions in 12 h light and 12 h dark cyle at (25±3) ^{o}C, the rats were fed with standard rat pellet diet (Pranav Agro Industry Ltd., Maharashtra) and water. The study was approved by the animal ethical committee of the institute **(1185/A/08/CPCSEA)**.

Acute toxicity study:

Healthy adult Wister albino rats of either sex starved overnight were divided into five groups (*n*=6) and were orally fed with the SC methanol extract in increasing dose levels of 100 mg/kg bw, 500 mg/kg bw, 1 g/kg bw, 3 g/kg bw and 5 g/kg bw[8]. The animals were observed continuously for 2 h under the following profiles[9] (a) Behavioral profile: Alertness, restlessness, irritability and fearfulness; (b) Neurological profile: spontaneous activity, reactivity, touch response, pain response and gait; (c) Autonomic profile: defecation and urination. After a period of 24 and 72 h they were observed for any lethality or death.

Oral glucose tolerance test (OGTT):

The oral glucose tolerance test was performed in overnight (18 h) fasted normal rats[10]. Rats divided into three groups (*n*=6) were administered drinking water, SC methanol extract at 50, 100, and 200 mg/kg, respectively. Glucose (2 g/kg) was fed 30 min after the administration of extracts. Blood was withdrawn from the retro orbital sinus under ether inhalation at 30, 60 and 120 min of glucose administered and glucose levels were estimated using a glucose oxidase-peroxidase method[11].

Induction of diabetes mellitus:

Diabetes mellitus was induced in overnight fasted adult Wister strain albino rats weighing (170±5) g by single intraperitoneal injection of freshly prepared STZ at dose of 40 mg/kg bw in o.1M citrate buffer (pH=4.5). After seven days of STZ administration, blood glucose level was determined. Rats with blood glucose level above 200 mg/dl were considered diabetic and induced in the study.

Experimental design:

In the experiment a total of 36 rats (6 normal; 30 STZ diabetic surviving rats) were used. The rats were divided into six groups of six rats each.

Group I: Normal control rats; Group II: Diabetic control rats; Group III: Diabetic rats treated with SC methanol extract at dose of 50 mg/kg bw; Group IV: Diabetic rats treated with SC methanol extract at dose of 100 mg/kg bw; Group V: Diabetic rats treated with SC methanol extract at dose of 200 mg/kg bw; Group VI: Diabetic rats treated with Glibenclamide at dose of 600 µg/kg bw. The extract was dissolved in 2% tween 80 solutions and administered orally in Group III, Group IV and Group V for two weeks.

At the end of the study, the animals were euthanized between 0900-1100 h to minimize diurenal variation. Fasting blood glucose level was estimated by glucose oxidase-peroxidase method. The assay of insulin in the plasma of normal and diabetic rats was performed by enzyme-linked immunosorbent assay (ELISA) method. The glycogen level of liver and skeletal muscles was measured by anthrone method[12]. Glycosylated hemoglobin was estimated by the method of Sudhakar and Pattabiraman, 1981[13]. Lipid profile [total cholesterol, high density lipoprotein (HDL), cholesterol and triglyceride] levels in serum were determined according to the instructions of the manufacturer (Merck, Mumbai, India). Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) was determined by the method of Reitman and Frankel, 1957[14].

Histological studies:

After blood sampling for the biochemical analysis, the animals were scarified, quickly dissected. Small slices of pancreases were taken and fixed in 10% formalin.

The specimens were dehydrated in ascending grades of ethanol. Cleared in xylene and embedded in paraffin wax. Sections of 6 µm in thickness were prepared and stained with haematoxylin and eosin and subjected to microscopical examination[15].

Statistical analysis:

One-way ANOVA and Students t-test (SPSS program; version 11.5) were carried out to compare the data with the level of significance set at $P \leq 0.05$.

RESULTS:

Phytochemical analysis of SC methanol extract revealed the presence of Carbohydrate, Proteins, Sterols, Saponin, Coumarins, Lipid and flavonoids. The simple quantitative analysis of the extract was based on the intensity of colour change.

Acute toxicity studies showed the non-toxic nature of the SC methanol extract. There was no lethality or any toxic reactions found at any of the doses selected until the end of the study period. In OGTT, SC methanol extract, from 30 min onwards showed significant reduction in plasma glucose levels (Table 1).

Table 2 showed the changes in body weight of experimental rats at zero and final day of treatment. Significant decrease in body weight of diabetic control rats were observed when compared with normal control rats. However, significant increase in body weight was observed in SC methanol extract treated groups in dose dependent manner when compared with diabetic control rats.

Inductions of diabetes in the experimental rats were confirmed by the presence of a high fasting blood glucose level. The effect of the SC methanol extract on the fasting blood glucose level normal and STZ induced diabetic animals were presented in table 3. At the end of 15th day study SC methanol extract at 200 mg/kg bw treated group reduced the fasting glucose level significantly (46.32%) when compared with diabetic control.

Tables 4 and 5 showed the effect of SC methanol extract on serum insulin, glycosylated hemoglobin and liver and muscle glycogen content. Administration of SC methanol extract to diabetic rats for 15 days significantly increased the levels of serum insulin, liver glycogen content, muscle glycogen and significant decrease was observed in glycosylated hemoglobin when compared with diabetic control.

Table6 showed increased level of total cholesterol, triglycerides and decreased level of HDL-cholesterol in diabetic rats compared to normal control. Administration of SC methanol extract for 15 days significantly reduced the total cholesterol, triglycerides levels and significantly increased the HDL-cholesterol level when compared with diabetic rats.

The Table 7 showed the effect of administration SC methanol extract on serum marker enzymes. The concentration of SGOT, SGPT and ALP was increased in diabetes condition when compared with normal control. Administration of SC methanol extract and glibenclamide was found to keep the levels near to normal values.

Table 1: Effect of the SC methanol extract on OGTT in normal rats (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Blood glucose (mg/dL)			
		0 min	30 min	60 min	120 min
I	Control + 2g/kg bw glucose	67.65±2.41	146.04±1.42**	132.59±1.29	122.68±1.88
II	SC 50mg/kgbw + 2g/kg bw glucose	65.97±1.28	133.79±0.84**	117.54±1.09**	102.16±1.88**
III	SC 100mg/kgbw + 2g/kg bw glucose	64.79±1.27	127.01±1.17**	111.56±1.09**	95.34±0.86**
IV	SC 200mg/kgbw + 2g/kg bw glucose	65.14±1.18	122.63±1.56**	101.66±0.90**	75.83±1.76**
V	Glibenclamide 600µg/kg bw + 2g/kg bw	65.82±1.27	122.46±1.05**	112.68±1.22**	79.15±1.12**

** Values deviate significantly from diabetic control; ** Values deviate very significantly ($P \leq 0.05$) when compared with diabetic control values.*

Table 2: Effect of oral administration of SC methanol extract on body weight in STZ induced diabetic rats after 15 days (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Body weight (g)	
		0 day (g)	15th day (g)
I	Normal control	161.93±4.42	167.59±0.29
II	Diabetic control	167.04±6.84	138.54±1.09
III	Diabetic+ SC (50mg/kgbw)	166.01±2.17	171.56±2.09**
IV	Diabetic+ SC (100mg/kgbw)	148.63±2.56	164.66±3.90*
V	Diabetic+ SC (200mg/kgbw)	149.46±0.85	166.68±1.22**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	158.46±1.75	175.68±2.22**

** Values deviate significantly from diabetic control; ** Values deviate very significantly from diabetic control group ($P \leq 0.05$).*

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 3: Effect of oral administration of SC methanol extract on plasma glucose levels in STZ induced diabetic rats (Mean ± SEM).

Groups (n=6) Treatment	Treatment		Plasma glucose levels (mg/dL)	
		0 day (g)	7th day (g)	15th day (g)
I	Normal control	74.93±1.42	74.93±1.42	75.59±1.29
II	Diabetic control	211.04±3.84	234.04±2.84	248.54±2.09
III	Diabetic+ SC (50mg/kgbw)	207.01±1.17	186.01±2.17	166.56±2.09**
IV	Diabetic+ SC (100mg/kgbw)	209.63±1.56	166.63±1.56	145.66±2.90**
V	Diabetic+ SC (200mg/kgbw)	210.46±1.85	157.46±0.85	114.68±1.22**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	205.46±1.75	155.46±0.75	102.68±1.22**

*** Values deviate very significantly (P≤ 0.05) when compared with diabetic control values.*

Table 4: Effect of oral administration of SC methanol extract on plasma insulin levels in STZ induced diabetic rats (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Plasma Insulin (µU/mL)	
		Zero day	Final day
I	Normal control	128.93±0.42	131.59±1.29
II	Diabetic control	48.04±0.84	55.54±1.09
III	Diabetic+ SC (50mg/kgbw)	47.01±1.17	71.56±2.09**
IV	Diabetic+ SC (100mg/kgbw)	50.63±1.56	86.66±1.90*
V	Diabetic+ SC (200mg/kgbw)	51.46±1.85	114.68±1.22**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	50.46±1.75	115.68±0.22**

** Values deviate significantly from diabetic control; ** Values deviate very significantly (P≤ 0.05) when compared with diabetic control values.*

Table 5: Effect of oral administration of SC methanol extract on glycosylated hemoglobin, liver glycogen and muscle glycogen in STZ induced diabetic rats after 15 days (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Glycosylated hemoglobin (%)	Liver glycogen (mg/g wet tissue)	Muscle glycogen (mg/g wet tissue)
I	Normal control	4.00±0.13	54.05±0.93	7.53±0.14
II	Diabetic control	8.25±0.53	17.93±0.37	2.57±0.16
III	Diabetic+ SC (50mg/kgbw)	6.81±0.15*	23.23±1.27	3.39±0.13
IV	Diabetic+ SC (100mg/kgbw)	5.29±0.35*	29.53±0.45**	5.79±0.08**
V	Diabetic+ SC (200mg/kgbw)	4.79±0.27**	38.85±0.63**	7.47±0.17**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	4.33±0.25**	47.17±0.65**	8.49±0.19**

** Values deviate significantly from diabetic control; ** Values deviate very significantly (P≤ 0.05) when compared with diabetic control values.*

Table 6: Effect of oral administration of SC methanol extract on lipid profile in STZ induced diabetic rats after 15 days (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Lipid profile (mg/dL)		
		Total cholesterol	Triglyceride	HDL
I	Normal control	54.93±2.42	45.93±2.42	72.59±2.29
II	Diabetic control	116.04±3.84	134.04±6.84	28.54±1.09
III	Diabetic+ SC (50mg/kgbw)	107.01±2.17*	96.01±3.17**	71.56±3.09**
IV	Diabetic+ SC (100mg/kgbw)	98.63±1.56**	91.63±1.56**	74.66±2.90**
V	Diabetic+ SC (200mg/kgbw)	94.46±1.85**	79.46±5.85**	75.68±1.22**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	93.46±2.75**	111.46±1.75**	75.68±1.22**

** Values deviate significantly from diabetic control; ** values deviate very significantly (P≤ 0.05) when compared with diabetic control values.*

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 7: Effect of oral administration of SC methanol extract on serum marker enzymes in STZ induced diabetic rats after 15 days (Mean ± SEM).

Groups (n=6) Treatment	Treatment	Serum marker enzymes (µ/L)		
		SGOT	SGPT	ALP
I	Normal control	62.93±0.42	67.93±1.42	122.59±1.29
II	Diabetic control	153.04±2.84	156.04±1.84	243.54±1.09
III	Diabetic+ SC (50mg/kgbw)	123.01±1.17**	118.01±1.17**	171.56±1.09**
IV	Diabetic+ SC (100mg/kgbw)	95.63±0.56**	93.63±1.56**	138.66±0.90**
V	Diabetic+ SC (200mg/kgbw)	66.46±1.85**	75.46±2.85**	125.68±1.22**
IV	Diabetic+ Glibenclamide (600µg/kg bw)	64.46±1.75**	66.46±1.75**	125.68±2.22**

*** Values deviate very significantly (P≤0.05) when compared with diabetic control values.*

DISCUSSION:

The present study for the first time reports the antidiabetic and hypolipidemic effect of SC methanol extract in STZ induced diabetic rats. STZ in one of the most commonly used substances to induce diabetes in rats. This toxin causes the death of pancreatic β-cell by alkylation of DNA resulting in reduced synthesis and release of insulin. Furthermore, it has been shown to be involved in the fragmentation of DNA by means of production of reactive oxygen species[16, 17].

Induction of diabetes by STZ leads to loss of body weight due to the increased muscle wasting and loss of tissue proteins[18]. Administration of SC methanol extract for 15 days significantly increased the body weight when compared with diabetic control in dose dependent manner. When SC methanol extract was administered to glucose loaded normal rats fasted for 18 h, hypoglycemia was observed after 30 min. The decline in blood sugar level reached its maximum at 2 h. The observed significant increase in the level of blood glucose and significant decrease in the level of plasma insulin in diabetic rats could be due to the destruction of pancreatic β - cells by STZ[19]. Oral capacity of SC methanol extract to decrease the elevated blood sugar to normal glycemic level is an essential trigger for the liver to revert to its normal homeostasis during experimental diabetes. The possible mechanism by which SC methanol extract bring about its hypoglycemic action in diabetic rats may be improving glycemic control mechanism and insulin secretion from remnant pancreatic beta cells in diabetic rats[20], as it is evidenced by the significant increase in the level of insulin in treated rats by SC methanol extract (200 mg/kg bw).

Phytochemical investigation of SC methanol extract reveals the presences of Carbohydrate, Proteins, Sterols, Saponin, Coumarins, Lipid and flavonoids. These principles are known to be bioactive for the management of diabetes. It is well known that certain flavonoids exhibit hypoglycemic activity and pancreas beta cell regeneration ability. Sterols have also shown to decrease blood sugar in experimental animal models[21]. Thus, the significant antidiabetic effect of aqueous SC extract may be due to the presence of more than one antihyperglycemic principle and their synergistic properties.

Insulin is the main regulator of glycogenesis in muscle and liver. The decrease of liver glycogen level observed in this study may be due to lack of insulin in diabetic condition or oxidative stress which may inactivate the glycogen synthetase[22]. The marked reduction in liver and muscle glycogen level is observed (15 days) in streptozotocin induced diabetic animals. Treatment with SC methanol extract remarkably increased the glycogen level in liver and muscle. In the view of glycogen level, there may be three possible ways of antidiabetic action; one possible way may be increased insulin level by preventing the inactivation of the glycogen synthetase and by synthesize the glycogen synthatase[23]. The typical characteristics of diabetes is the increase of serum glycated protein such as glycated hemoglobin (HbA1C), which is a parameter for glycemic control where glucose or other reducing sugars react with the amino residues of proteins to form Amadori products such as glycated hemoglobin[24]. Animals treated with SC methanol extract significantly decreased the glycosylated hemoglobin level which could be due to an improvement in insulin secretion from the remnant pancreatic beta cells in diabetic rats[25].

Since lipid abnormalities accompanying with premature atherosclerosis is the major cause of cardiovascular diseases in diabetic patients, therefore ideal treatment for diabetes, in addition to glycemic control, should have a favorable effect on lipid profile. Cardiovascular diseases are listed as the cause of death in 65% people suffering from diabetes[26-31]. From this point of view, it is encouraging that the 15 day treatment of SC methanol extract brought down the elevated level of lipid profile such as total cholesterol, triglycerides to near normal level. There was increase in HDL-cholesterol also, which was desirable feature.

HDL-cholesterol also, which was desirable feature. 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 [32]. Treatment of the diabetic rats with the SC methanol extract 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. These results are in agreement with those obtained by Eliza *et al*[33].

Histopathology studies also supported our findings. STZ was suspected to destroy pancreas partially. Diabetic rats showed reduced islet cells, which were restored to near normal upon treatment with the SC methanol extract. No such changes were found in the normal rats.

The findings of this study indicate that consumption of SC methanol extract exerts significant antidiabetic and hypolipidemic effect in STZ-induced diabetic rats. Histopathological studies of the pancreas of SC methanol extract treated diabetic rats show evidence of signs of regeneration of β-cells. Longer duration studies of S. Colais and its isolated compounds on chronic models are necessary to elucidate the exact mechanism of action so as to develop it as a potent antidiabetic drug.

CONFLICT OF INTEREST STATEMENT:

We declare that we have no conflict of interest.

ACKNOWLEDGEMENTS:

Authors thank, Department of Pharmaceutical Sciences, JJT University & Oriental college of Pharmacy, for providing facilities to conduct this research work.

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How to cite this article:
Imran MD, Khan M, Akhtar R, Ahmed S, Rageeb M, Antidiabetic and hypolipidemic effect of methanol extract of stereospermum colais fruit in streptozotocin induced diabetic rats, Journal of Drug Delivery & Therapeutics. 2016; 6(4):31-36

