IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB)
ISSN: 2455-264X, Volume 4, Issue 5 (Sep. – Oct. 2018), PP 14-25
www.iosrjournals.org

Pharmacological evaluation of *Streblus asper* Lour. (Shakhotaka) extract with special reference to Antioxidant and Hypoglycemic activities

Pratima Kumari[1], Santwana Rani[2], Aman Kumar[3] and Baidyanath Kumar[4]
[1] Research Scholar, Department of Botany, College of Commerce, Arts and Science (Patliputra University), Patna- 800020
2Associate Professor, Department of Botany, College of Commerce, Arts and Science (Patliputra University), Patna- 800020
[3]Additional Professor, Department of FMT, IGIMS, Patna- 800014
[4]Visiting Professor, Department of Biotechnology, Patna Science College, (Patna University), Patna- 800005
Corresponding Author: Baidyanath Kumar

Abstract: *Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by absolute or relative deficiency of insulin secretion with or without varying degree of insulin resistance. Sedentary life style and obesity are two major epidemiological determinants of diabetes mellitus. In the present investigation hypoglycemic and antioxidant efficacy of methanol extract of Streblus asper of family Moraceae was tested on STZ induced mice diabetic models. The results clearly indicated that the diabetic control (DC) mice presented a significant lowering of body weight ($p<0.001$) when compared with the normal control (NC) mice. The DC mice showed a significantly ($p<0.001$) higher level of glucose (+279%), when compared with their normal control counterparts. Diabetic mice of all the three groups (DT_{150}, DT_{250} and DT_{500}) showed a reduction in glucose levels, when compared to the DC ones. The results clearly indicated that the methanol extract of Streblus asper is antidiabetic in nature due to the presence of different types of active phytochemicals.*

The role of oxidative stress in the patho-physiology of diabetes and its associated complications are well known. The antioxidant system plays an important role in defending the cells against oxidants generated during metabolic processes and thus prevents the tissues from toxic response of the oxidants. The methanol extract of Streblus asper exhibited anti diabetic property as well as increased the levels of enzymatic and non enzymatic anti oxidant entities along with reduced MDA levels. The methanol extract of this plant did not exhibit any toxicity in the present study and thus it was concluded that the extract possesses antidiabetic as well as antioxidant properties without any adverse effect.

Key Words: *Antioxidant activities, Diabetes mellitus, Streblus asper, Streptozotocin, Mice*

Date of Submission: 15-09-2018 Date of acceptance: 30-09-2018

I. Introduction

Diabetes mellitus (DM) is the third leading disease, after heart attack and cancer affecting almost every organ in the human body [1] and is also called silent killer. This is a metabolic disorder of multiple etiologies [2] characterized by absolute or relative deficiency of insulin secretion with or without varying degree of insulin resistance [3, 1].

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia with an elevated fasting (>110mg/dL of blood) and post prandial (> 130mg/dL of blood) plasma glucose level. According to WHO (2006) diagnosis a fasting plasma sugar of >126mg/dL and post prandial plasma sugar value of > 200mg/dL is considered as diabetes mellitus. There are two major forms of diabetes mellitus namely Type-1, characterized by diminished production of insulin due to degeneration of pancreatic B- cells, and Type-2, the multifactorial syndrome characterized by either hypo secretion of insulin or insulin insensitivity or sometimes both. Sedentary life style and obesity are two major epidemiological determinants of diabetes mellitus. The current therapy of this disorder includes exogenous insulin administration (particularly in case of Type-1 diabetes mellitus), and oral hypoglycemic agents (for Type-2DM) which includes Metformin, Pioglitazone, Sulphonylurea etc. which may have adverse effects in diabetic subjects. Multiple risk factors for diabetes have been identified [4] (WHO, 2006). The greatest risk is impaired glucose tolerance, a precursor of diabetes. Thus, a number of type 2 diabetes prevention trials have included subjects with impaired glucose tolerance. These trials compared intensive lifestyle modifications (e.g., diet, exercise and weight loss), OHAs and placebo controls [5, 6]. Ayurvedic treatment known as *Apatarpana* (balanced diet with restricted calories) and *Santarpana* (highly nutritious, high-

calorie diet intended to increase weight) are recommended for patients with type 2 and type 1diabetes, respectively [7].
Diabetes mellitus has been classified into some other specific types:

Maturity- onset diabetes of the young (MODY): This subgroup is a relatively rare monogenic disorder characterized by non- insulin- dependent diabetes with autosomal dominant inheritance and an age at onset of 25 years or younger. Patients are nonobese, and their hyperglycemia is due to impaired glucose- induced secretion of insulin.

Diabetes due to mutant insulin: This is a very rare subtype of nonobese Type- 2 diabetes. Since affected individuals were heterozygous and possessed one normal insulin gene, diabetes was mild, and showed autosomal dominant genetic transmission.

Diabetes due to mutant insulin receptors: In more than 40 people with diabetes, defects in one of their insulin receptor gene have been observed.

Diabetes mellitus associated with a mutation of mitochondrial DNA: Diabetes due to a mutation of mitochondrial DNA that impairs the transfer of leucine or lysine into mitochondrial proteins has been described. Most patients have a mild form of diabetes that responds to oral hypoglycemic agents. Two- thirds of patients with this subtype of diabetes have a hearing loss, and a smaller proportion had a syndrome of myopathy, encephalopathy, lactic acidosis, and stroke- like episodes (MELAS).

Obese Type- 2 patients: The most common form of diabetes is secondary to extra pancreatic factors that produce insensitivity to endogenous insulin. When an associated defect of insulin production prevents adequate compensation for this insulin resistance, nonketotic mild diabetes occurs. The primary problem is a “target organ” disorder resulting in ineffective insulin action that can secondarily influence pancreatic B cell function.

Chronic Complications of Diabetes:

Diabetes mellitus is associated with late clinical manifestations that include a number of pathologic changes that involve small and large blood vessels, cranial and peripheral nerves, and the lenses of eye. These lesions lead to hypertension, renal failure (nephropathy), blindness (retinopathy), autonomic and peripheral neuropathy, amputations of the lower extremities, myocardial infarction, and cerebrovascular accidents.

The Clinical Practice Guidelines for the Prevention and Management of Diabetes recommends a target glycosylated hemoglobin (HbA_{1c}) concentration of 7.0% or less for all patients with diabetes and, for those in whom it can be safely achieved, a target HbA_{1c} concentration in the normal range, usually ≤ 6.0% [4] (WHO, 2006). Although nonpharmacologic therapy (e.g., diet, exercise and weight loss) remains a critical component in the treatment of diabetes, pharmacologic therapy is often necessary to achieve optimal glycemic control. Orally administered antihyperglycemic agents (OHAs) can be used either alone or in combination with other OHAs or insulin. Various classes of OHAs are now available that target the different pathophysiologic factors contributing to diabetes: α-glucosidase inhibitors to delay intestinal carbohydrate absorption [8, 9, 10], biguanides to target hepatic insulin resistance [11,12, 13, 14, 15], insulin secretagogues to increase pancreatic insulin secretion[16, 17, 18, 19, 20], insulin sensitizers or thiazolidinediones which function as ligands for the peroxisome proliferator-activated receptor gamma (PPARγ) to target adipocyte and muscle insulin resistance[21, 22, 23, 24, 25, 26, 27, 28], and intestinal lipase inhibitor or orlistat to inhibit fat absorption and promote weight loss in obese patients [29, 30, 31, 32].

Despite excellent potencies, these synthetic antidiabetic drugs had presented unwanted therapeutic profiles, marked by fluid retention, hypoglycemia at higher doses, liver problems, lactic acidosis, weight gain and potential cardiac hypertrophy. There is also evidence that hyperglycaemia per se has deleterious effects on beta cell function and insulin action (glucotoxicity). Thus, a concerted effort to search more effective drugs for T2DM has become the need of the time in terms of efficacy as well as safety due to the undesirable side effects of synthetic drugs.

Oxidation process is one of the important route for production of free radicals and these high energy molecules may abruptly interfere with the normal metabolic activities of the body causing immense damage to the normal tissues [33, 34]. There is a close relationship between diabetes and oxidative stress and it has been observed that the free radicals are produced in the form of ROS (reactive oxygen species) which cause mitochondrial DNA mutation thus resulting in hypoglycemic memory [35]. Free radicals generated during diabetes interfere with vital organ tissues and may lead to cardiovascular complications, diabetic nephropathy, diabetic retinopathy, erectile dysfunction and diabetic neuropathy [36]. Several plants are known for their efficacy to overcome these complications by enhancing the *in vivo* anti oxidant defense and provide protection against oxidative tissue damage [37]. The SOD (Superoxide dismutase), CAT (Catalase), Vitamin E and C are some of the antioxidants which provide protection to the diabetic tissues [38] and their level of defense can be assessed by measuring the MDA concentration which is the end product of lipid peroxidation [39].

Over the past 25 years, 50% of prescription drugs have been developed from natural products and their derivatives. These medicines have emerged as unique, safe, effective, and relatively inexpensive remedies producing minimal or no side effects with tall claims of efficacy as add on therapy [40]. Herbal drugs with antidiabetic activity can be classified into four categories according to their mode of action. The first group has insulinomimetic effect and includes plant like *Momordica charantia* (bitter gourd) [41]. Second group acts on the β-cells to increase the production of insulin and include plants like *Allium cepa* (onion) and *Pterocarpus marsupium* (Vijaysaar) [42]. The third one enhances glucose utilization in diabetic patients and includes plants like *Gingiber officinale* (ginger), *Cyamospsis tetragonalobus* (Gower plant) and *Grewia asiatica* (phalsa). They increase the viscosity of gastrointestinal contents, slow gastric emptying and act as a barrier to diffusion [42]. Fourth group act by miscellaneous mechanisms and include plants like *Euphorbia prostrata*, *Fumaria parvia*, *Panax ginseng* and *Phyllanthus embelica*. They may alter the fiber content and thereby altering the rate and speed of absorption of glucose from the gut [42].

Streblus asper Lour (Family: Moraceae) is a small tree which is indigenous to tropical countries such as India, Sri Lanka, Malaysia, the Philippines and Thailand. It is known by various names, e.g. Bar-inka, Berrikka, Rudi, Sheora, Koi, Siamese rough bush and Tooth brush tree [43]. In India it is known by its several vernacular names, the most commonly used ones being Shakhotaka (Sanskrit), Siora (Hindi), Sheora (Bengali) and Piray (Tamil) [44]. It is used traditionally in leprosy, piles, diarrhea, dysentery, elephantiasis [45] and cancer [46]. It is a rigid shrub or gnarled tree; branchlets tomentose or pubescent. Leaves are 2–4 inch, rigid, elliptic, rhomboid, ovate or obovate, irregularly toothed; petiole 1/12 inch. Male heads globose, solitary or 2-nate, sometimes androgynous; peduncle short scabrid, flowers minute. Female flowers longer peduncled. Fruit pisiform; perianth yellow. It is found in the drier parts of India, from Rohilkund, eastward and southwards to Travancore, Penang and the Andaman Islands [47]

The pharmacognostical studies of its stem bark as well as its root bark have been carried out [48, 49]. It finds place in the Ayurvedic Pharmacopoeia of India [50] and has also been described in some monographs [51], but none have described the complete chemistry and pharmacology of this important ethnomedicinal plant. Therefore, we aimed to compile an up-to-date and comprehensive review of *S. asper* that covers its traditional and folk medicinal uses, phytochemistry and pharmacology.

Streblus asper is a well known ethnomedicinal plant which is also used in Ayurveda [52, 53, 54, and 55]. Its use in the Indian traditional folk medicine is also well documented.

Streblus asper is a rich source of cardiac glycosides. Reichstein and co-workers [56, 57] have isolated more than 20 cardiac glycosides from the root bark of *S. asper* and were able to structurally characterize ∼15 such compounds, mainly as a result of the application of degradative techniques, namely kamloside, asperoside, strebloside, indroside, cannodimemoside, strophalloside, strophanolloside, 16-*O*-acetyl-glucogitomethoside, glucogitodimethoside, glucogitodimethoside, glucokamloside, sarmethoside and glucostrebloside. The other glycosides reported from the roots include β-sitosterol-3-*O*-β-D-arabinofuranosyl-*O*-α-L-rhamnopyranosyl-*O*-β-D-glucopyranoside[58] (Chaturvedi and Saxena, 1984), lupanol-3-*O*-β-D-glucopyranosyl-[1-5]-*O*-β-D-xylofuranoside[59] (Chaturvedi and Saxena, 1985) and vijaloside, i.e. periplogenin-3-*O*-β-D-glucopyranosyl-[1-5]-*O*-β-D-xylopyranoside [60].

From the stem bark of this plant, α-amyrin acetate, lupeol acetate, β-sitosterol, α-amyrin, lupeol and diol [61], strebloside and mansonin [62] have been isolated. A pregnane glycoside named sioraside [63] has also been isolated. *n*-Triacontane, tetraiacontan-3-one, β-sitosterol, stigmasterol, betulin and oleanolic acid were identified from the aerial parts[64]. An unidentified cardenolide [65], β-sitosterol, α-amyrin and lupeol were isolated from root bark and leaves [66].

Biologically Active compounds of *S. asper*

The volatile oil [67] from fresh leaves of *S. asper* was obtained in 0.005% yield as a brown liquid. The major constituents of the volatile oil were phytol (45.1%), α-farnesene (6.4%), *trans*-farnesyl acetate (5.8%), caryophyllene (4.9%) and *trans*-*trans*-α-farnesene (2.0%). The other constituents were α-copaene, β-elemene, caryophyllene, geranyl acetone, germacrene, δ-cadinene, caryophyllene oxide and 8-heptadecene.

Several workers have reported the different biological activities of *S. asper* in various *in vitro* and *in vivo*test models. Different parts of his plant have been found to exhibit cardiotonic [68], antifilarial [69, 70, 71, 72, 73, 74], anticancer [75, 76, 67], antimicrobial [77, 78, 79, 85, 84], anti-allergic [80], insecticidal [81, 82] and antiparasitic [83] activities. Besides these, *S. aspera* is most useful in oral hygiene because its leaf extract is active against *Streptococcus mutans* which is associated with dental caries [77, 79, 78, 79, and 85]

The isolation and formulation of active constituents from *S. asper* along with their pharmacological evaluations are the need of the modern therapeutics. Therefore the present investigation has been undertaken to evaluate the antioxidative and antihyperglycemic efficacy of methanol extract of *Streblus asper*.

II. Materials and Methods

Methanol extract of *Streblus asper* was used for assaying antioxidative and hypoglycemic activities in Streptozotocin induced mice diabetic models. Plants of *S. asper* were collected from campus of College of Commerce, Patna and identified following relevant monographs of Indian Pharmacopoeia (2012). Freshly harvested plant materials (root, stem, leaves and flowers) were washed under running tap water blotted with filter paper and was dried in the shade at room temperature. The dried plant sample (2.6 kg) was then soaked with absolute methanol under reflux condition for the methanolic extract preparation. The sample was then homogenized with extraction buffer and the supernatant collected after three rounds of extraction. The solvent was evaporated under reduced pressure in a rotary evaporator at 40 ^{0}C. To this thick paste colloidal silicon dioxide was added and dried in vacuum tube dryer. The obtained methanol extract was stored in deep freezer at -20^0 C until further test.

Significant insights into the etiology of diabetes in human have been gained from the study of animal models. The albino mouse is an excellent model for study of human diabetes. Therefore all mice used in this study were in the albino genetic background. Adult albino mice weighing around 17–20 gram with 6.5 ± 0.5 cm length are selected for experiments. The mice were housed in shoe-box type cages under good hygienic conditions in the departmental animal house during experimental period. The mice were allowed to acclimatize for 15 days in an environmentally controlled room under standard environmental conditions (21±2°C, 55±5%Relative humidity, 12 hr Light: Dark cycle).

The mice were fed on diet consisted of wheat grains-1Kg, Choker wheat-250gm, Gram grains-250gm, Maize grains-250gm, Soybean grains-250gm, Sundrop oil-50gm, Milk powder-2 table spoon and Jaggery-50gm. This diet provided carbohydrate 48.3%, crude protein 23.5%,crude fat5.9% crude ash5.9% and crude fiber 3.9% (W/W).

In each cage one pellet of feed per mice was given. The diet was palatable to the animal as evidenced by feeding success. It has been observed that an adult mice normally intakes 4 to 5 gram of diet per day. The daily food consumption of the mice varied depending upon the physiological and health status of the mice as well as the environmental temperature. The consumption of food increased considerably when the mice were pregnant or at lactating stage and decreased considerably with the dose-duration and increased temperature in summer.

The animal model for the present study was based on multiple administration of low dose of freshly prepared streptozotocin (STZ). For induction of diabetes, initially the normal mice were kept 24 hours without food and water. The weight of normal mice was determined. Diabetes was induced by multiple intra-peritoneal injection of freshly prepared STZ solution in 0.05 M sodium citrate (pH 4.5) at the dose of 35 mg/kg body weight followed by an hour of fasting. The mice were then allowed to access the respective food and water *ad libitum*. Mice with fasting blood glucose level of 200 mg/dl (7.8 mmol/l) or higher were considered to be diabetic and were used in the study. A parallel set of control mice (non-diabetic) were injected with citrate buffer only.

The mice were grouped into six categories viz., Normal control (NC), Diabetic Control (DC), Diabetic Treated (DT_{150}), Diabetic Treated (DT_{250}), Diabetic treated (DT 500) and Diabetic Treated (DT_{RZG}). NC received only citrate buffer solution. DC group was STZ induced which received citrate buffer only. DT_{150}, DT250 and DT500 received 150mg/Kg, 250mg/Kg and 500mg per Kg of body weight of methanol extract respectively. DT_{RGZ} received Rosiglitazone at a dose of 2mg/Kg of body weight. All the mice were fed with common pellet diets for 2 weeks after arrival, and then randomly divided into two groups. One group continued to receive common pellet diets and constituted the normal group; the other was fed with diets high in fat and fructose, in order to induce type-2 diabetes. All the mice had free access to food and water.

For the experiment, the mice were divided into five groups having six mice in each group: DC group (diabetic control mice), NC group (non-diabetic control mice) and three DT group (diabetic mice treated with three different doses of extract as well as Rosiglitazone 2mg/ kg body weight). Body weights were recorded weekly during the experimental period. Treatment with extracts was started after one week of STZ treatment, which was considered as the 1st day of treatment. Blood samples were taken after 8 hrs fasting from the retro-orbital sinus vein prior to the administration of test substances or the buffer and 4 weeks after the treatment under mild ether anesthesia and allowed to clot for 30 minutes at room temperature. Blood samples were centrifuged at 3000 rpm for 20 minutes. Serum was separated and stored at -20°C until biochemical estimations were carried out.

The fasting blood glucose levels of animals were analyzed aseptically by puncturing their tail veins and blood glucose recorded with the help of Glucometer. At the end of thirty days drug treatment, the blood from each animal was drawn aseptically by puncturing the retro orbital vein. The *in-vivo* anti oxidant parameters such as lipid peroxidation viz MDA, SOD, catalase and GSH were evaluated in serum / RBC, liver, heart, kidney tissues of various experimental groups following the methods of Ohkawa et al. 1979 [86], Marklund & Marklund (1974) [87], Sinha (1972) [88] and Moron et al. (1979) [89] respectively. Whereas, the Glycosylated hemoglobin, serum Glutamate-Oxaloacetate Transaminase (SGOT), serum Glutamate-Pyruvate Transaminase (SGPT), Albumin and Globulin were estimated by using the kits obtained from Span diagnostics.

All experiments were carried out in replicates of five and results were statically analyzed by mean ± S.E and by one-way ANOVA. The levels of significance was fixed between p<0.05 – p<0.001. The results obtained have been presented in Table- 1- 7; Figure- 1 and 2.

Table-1: Showing body weight changes in mice during and after treatment of methanol extract of *Streblus asper*

Non Diabetic Normal Control (NC)	Day 0	Day7	Day15
	19.75±2.75	22.25±2.41	25.55±2.25
Diabetic Mice			
Diabetic Control (DC)	**12.25±1.16**	**10.35±0.75**	**9.45±1.35**
***S. asper* extract (150mg/Kg) (DT_{150})**	**12.35±2.14***	**14.15±1.75***	**15.35±1.65***
***S. asper extract*(250mg/Kg) (DT_{250})**	**12.75±1.85***	**14.25±2.35***	**15.65±2.65***
***S. asper* extract (500 mg/Kg) (DT_{250})**	**12.65±1.63***	**15.35±2.37***	**16.75±2.67***
Rosiglitazone (2mg/Kg) (DT_{RGZ})	**12.85±3.74***	**15.85±3.91***	**16.65±1.84***

significant as compared to control; n=6 in each group

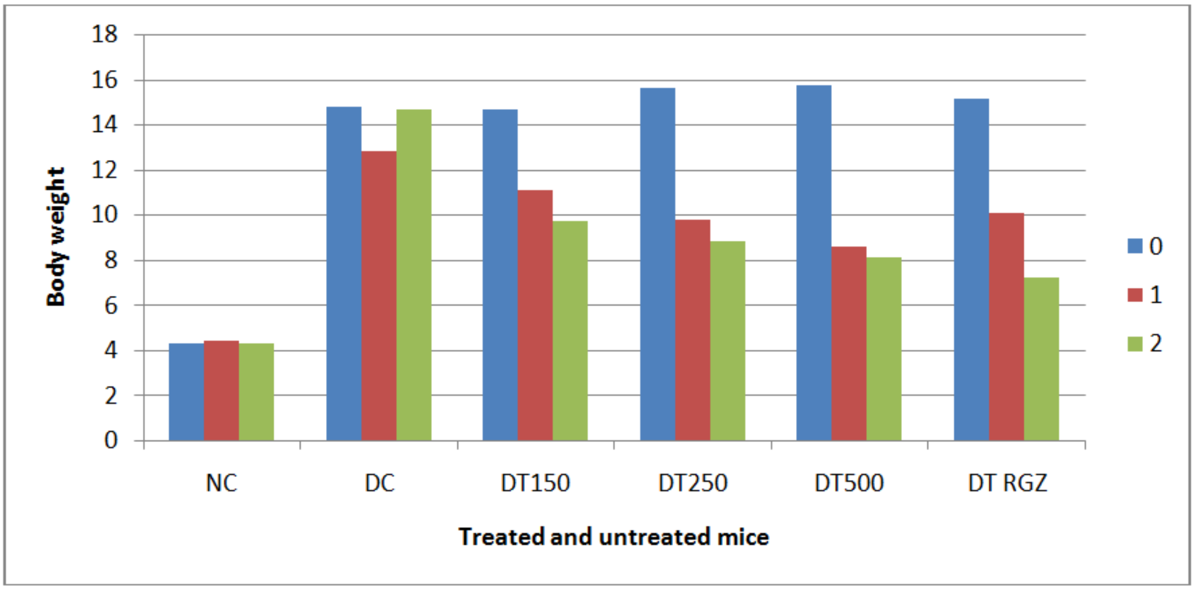

Fig- 1: Body weight changes in mice during and after treatment of methanol extract of *Streblus asper* after zero, 7 and 15 days of treatment

Table-2: Showing effects of different doses of *Streblus asper* extract and Rosiglitazone on blood glucose levels in mice

Mice Groups	Blood glucose levels in (mmol/l) in four different weeks				
	Pretreatment	Post-treatment			
	0	1	2	3	4
Normal control (NC)	4.35±0.15**	4.45±0.16**	4.37±0.35**	4.45±0.17**	4.41±0.17**
Diabetic control (DC)	14.85±1.65*	14.85±1.50*	14.75±1.35*	14.92±1.50*	14.95±1.52*
S. asper extract (150mg/Kg) DT_{150}	14.75±1.40**	11.15±1.18*	9.75±2.09**	9.37±1.28**	9.17±1.79**
S. asper extract (250mg/Kg) DT_{250}	15.65±1.59**	9.85±1.38**	8.87±1.28**	8.45±1.74**	8.13±1.28**
S. asper extract (500mg/Kg)	15.75±1.59**	8.65±1.39**	8.15±1.42**	6.25±1.52**	5.45±1.51**
Rosiglitazone (2mg/Kg) DT_{RGZ}	15.15±1.42**	10.15±1.45**	7.25±1.28**	6.15±1.35**	5.95±0.97**

**p<0.05 as compared with normal control. **p<0.001 as compared with diabetic control.*

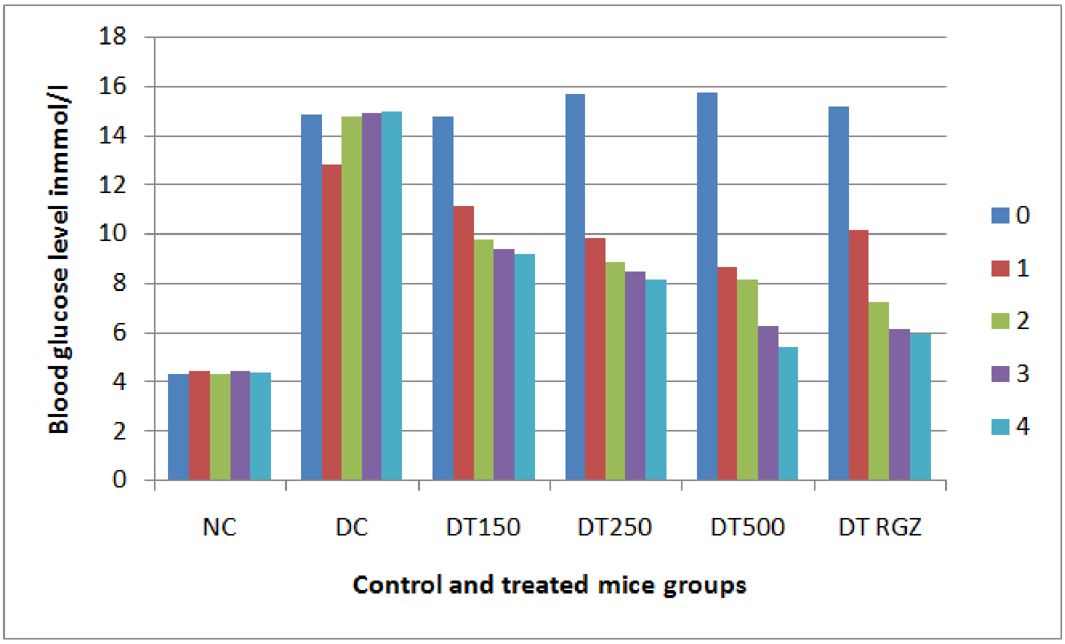

Fig- 2: Effect of different doses of *Streblus asper* extract and Rosiglitazone on blood glucose levels in mice after zero, 1, 2, 3 and 4 days of treatment

Table- 3: Showing effect of *Streblus asper* extract on Catalase, SOD, GSH and MDA activity in the liver of Diabetic mice (values in mean ± SD)

Parameters	Mice groups					
	NC	DC	Rosiglitazone (2mg/Kg) (DT_{RGZ})	*S. asper* extract (150mg/Kg) (DT_{150})	*S. asper* extract (250mg/Kg) (DT_{250})	*S. asper* extract (500mg/Kg) (DT_{500})
Catalase	93.55±4.31	27.65±7.25a***	42.00±9.75^{NS}	47.35±6.35b**	67.35±6.25b***, c***	70.65±11.75b***, c***
SOD	0.97±0.15	0.51±0.08a***	0.57±0.07^{NS}	0.71±0.07b***	0.81±0.05b***, c**	0.85±0.07b***, c**
GSH	54.75±5.21	30.65±3.75a***	33.15±3.15^{NS}	34.85±2.50^{NS}, b*	38.65±3.11b*	40.35±5.25b**
MDA	7.65±0.65	22.25±2.41a***	20.75±1.75^{NS}	19.75±1.15NS	18.17±2.75b**	16.65±2.45b**, c*

p Values (p = <0.05, **p<0.01, ***p<0.001) NS: Non Significant.*
Comparison : a: Diabetes vs Normal, b: Rosiglitazone, extract150,250,500 mg v/s diabetic.
c: extract 150,250,500 mg v/s Rosiglitazone. Catalase: nmol of H2O2 consumed/min/mg protein,
SOD: units/ min/mg protein, GSH : mg/ 100 gm tissue, MDA: nmol/mg protein.

Table- 4: Showing effect of *Streblus asper* extract on Catalase, SOD, GSH and MDA activities in the cardiac tissue of Diabetic mice (values in mean ± SD)

Parameters	Mice groups					
	NC	DC	Rosiglitazone (2mg/Kg) (DT_{RGZ})	*S. asper* extract (150mg/Kg) (DT_{150})	*S. asper* extract (250mg/Kg) (DT_{250})	*S. asper* extract (500mg/Kg) (DT_{500})
Catalase	86.25±7.65	38.65±2.15a***	45.75±5.67^{NS}	50.75±3.41b*	54.65±5.71b**	59.25±7.45b**, c*
SOD	1.65±0.17	0.75±0.12a***	0.85±0.17^{NS}	0.88±0.15^{NS}	0.95±0.16bNS	0.98±0.25^{NS}
GSH	53.75±2.35	30.65±2.75a***	35.25±4.15^{NS}	38.45±2.75^{b*}	40.75±3.17b**	42.20±3.85b**, c*
MDA	0.85±0.15	2.75±0.16a***	2.35±0.25^{NS}	1..76±0.25b*	1.70±0.15b**	1.65±0.25b^{NS}

p Values (p = <0.05, **p<0.01, ***p<0.001) NS: Non Significant.*
Comparison : a: Diabetes vs Normal, b: Rosiglitazone, extract 150,250,500 mg v/s diabetic.
c: SAPE 100,200,500 mg v/s Rosiglitazone.
Catalase: nmol of H2O2 consumed/min/mg protein, SOD: units/ min/mg protein,
GSH : mg/ 100 gm tissue, MDA: nmol/mg protein.

Table- 5: Showing effect of *Streblus asper* extract on Catalase, SOD, GSH and MDA activities in the kidney of Diabetic mice (values in mean ± SD)

Parameters	Mice groups					
	NC	DC	Rosiglitazone (2mg/Kg) (DT_{RGZ})	*S. asper* extract (150mg/Kg) (DT_{150})	*S. asper* extract (250mg/Kg) (DT_{250})	*S. asper* extract (500mg/Kg) (DT_{500})
Catalase	46.35±4.35	21.00±2.60a***	22.15±2.65^{NS}	23.75±6.05NS	24.85±5.65NS	26.65±4.75NS
SOD	1.56±0.21	0.71±0.17a***	0.83±0.15^{NS}	0.89±0.21^{NS}	0.93±0.07NS	0.98±0.25^{NS}
GSH	21.75±4.15	9.35±1.05a***	10.25±1.85^{NS}	11.97±2.45^{NS}	12.85±1.95b*	16.15±1.75b**, c**
MDA	0.75±0.31	1.52±0.18a***	1.57±0.35^{NS}	1..53±0.15bNS	1.33±0.15b**	1.29±0.17b*

p Values (p = <0.05, **p<0.01, ***p<0.001) NS: Non Significant.*
Comparison : a: Diabetes vs Normal, b: Rosiglitazone, extract150,250,500 mg v/s diabetic.
c: extract150,250,500 mg v/s Rosiglitazone. Catalase: nmol of H2O2 consumed/min/mg protein,
SOD: units/ min/mg protein,GSH : mg/ 100 gm tissue, MDA: nmol/mg protein.

Table- 6: Showing effect of *Streblus asper* extract on Catalase, SOD, GSH and MDA activities in the Serum of Diabetic mice (values in mean ± SD)

Parameters	Mice groups					
	NC	DC	Rosiglitazone (2mg/Kg) (DT_{RGZ})	*S. asper* extract (150mg/Kg) (DT_{150})	*S. asper* extract (250mg/Kg) (DT_{250})	*S. asper* extract (500mg/Kg) (DT_{500})
Catalase	70.15±7.15	25.15±4.15a***	31.35±2.15^{NS}	31.75±3.35NS	35.15±6.65NS	40.25±7.15b**
SOD	2.55±0.25	1.40±0.13a***	1.45±0.15^{NS}	1.56±0.15^{NS}	1.62±0.17NS	1.90±0.15b**, c*
GSH	44.75±2.35	25.10±3.35a***	27.45±3.15^{NS}	30.95±3.05^{NS}	31.75±4.05b*	34.25±5.26b**
MDA	2.07±0.25	4.15±0.26a***	4.06±0.21^{NS}	4.03±0.15NS	3.85±0.25b**	3.15±0.41b**, c**

p Values (p = <0.05, **p<0.01, ***p<0.001) NS: Non Significant*
Comparison : a: Diabetes vs Normal, b: Rosiglitazone, extract150,250,500 mg v/s diabetic.
c: extract 150,250,500 mg v/s Rosiglitazone. Catalase: nmol of H2O2 consumed/min/mg
protein, SOD: units/ min/mg protein, GSH : mg/ 100 gm tissue, MDA: nmol/mg protein.

Table- 7: Showing effect of *Streblus asper* extract on serum biochemical profile in different groups of mice

Parameters	Mice groups					
	NC	DC	Rosiglitazone (2mg/Kg) (DT_{RGZ})	*S. asper* extract (150mg/Kg) (DT_{150})	*S. asper* extract (250mg/Kg) (DT_{250})	*S. asper* extract (500mg/Kg) (DT_{500})
SGOT (U/dL)	87.75±3.15	173.0±11.61***	156.35±8.51	151.25±9.75b**	144.25±6.15b**	140.75±8.85b**, c*
SGPT (U/dL)	50.45±2.75	80.00±4.45a***	71.85±5.25^{NS}	70.75±6.35^{NS}	65.45±9.75b**	60.35±7.55b**
Albumin (mg/dL)	4.45±0.25	6.92±0.35a***	6.15±0.45b*	6.65±0.55b**	6.01±0.51b***	5.75±0.35b***
Globulin (mg/dL)	3.45±0.17	3.67±0.17NS	3.57±0.25^{NS}	3.58±0.15NS	3.45±0.25NS	3.45±0.17NS
Glycosylated Haemoglobin (HbA1c)	7.61±0.15	13.55±0.65a***	12.52±1.65NS	10.35±0.48a*	10.65±0.41b**, c*	10.25±0.51b**, c*

****p<0.001) NS: Non Significant. Comparison : a: Diabetes vs Normal, b: Rosiglitazone, extract150, 250,500 mg v/s diabetic. c: extract150,250,500 mg v/s Rosiglitazone.*

III. Results

Effect of Methanol Extract on Blood Glucose level in Mice

The whole plant extract of *Streblus asper* has been reported to be effective in alleviating diabetes mellitus through its antioxidant and insulin- potentiating activities. In the present investigation the effect of methanol extract of *Streblus asper* on body weight of mice was studied. The results clearly indicated that the diabetic control (DC) mice presented a significant lowering of body weight (p<0.001) when compared with the normal control (NC) mice (Table- 1 and Fig- 1). A significant gain in body weight was observed in the treated groups of diabetic mice (DT_{150}, DT_{250} and DT_{500}) as compared to the DC ones. The DT_{150}, DT_{250} and DT_{500} group showed an increase of about 30%, 40% and 48% in body weight respectively after 15 days of treatment. Contrary to this, DT_{RGZ} group mice showed an increase of 50% in body weight after 15 days of treatment (Table-1and Fig- 1).

The changes in the blood glucose levels before and after receiving the treatment in normal and diabetic mice have been presented in Table -2 and Figure 2. As expected, the DC mice showed a significantly (p<0.001) higher level of glucose (+279%), when compared with their normal control counterparts. Diabetic mice of all the three groups (DT_{150}, DT_{250} and DT_{500}) showed a reduction in glucose levels, when compared to the DC ones; nevertheless, the reduction was particularly evident in the DT_{250} and DT_{500} mice (−44%; p<0.001). When compared, the glucose levels of the DT_{250} and DT_{500}versus the DC group mice during the 4th week of treatment program, a significant lower value in the first was also found (−45% and -70%; p<0.001) respectively (Table-2 and Fig- 2). Nevertheless, this decline in the glucose levels was less evident in the DT_{150} mice (−38%) than in the DT_{250} and DT_{500}mice. In contrast to this, DT_{RGZ} group mice showed almost 70% decline in glucose level after 4-weeks of treatment program (Table -2 Fig- 2).

Effect of Methanol Extract on the antioxidants profile of Mice liver

A significant decreased activities of Catalase, SOD and GSH were observed along with decreased MDA levels in the liver of diabetic rats (p<0.001, Table- 3). There was no any significant alteration in the anti oxidant profile of the Rosiglitazone treated diabetic mice. On the other hand, the methanol extract treated group (DT150, DT250 and DT500) showed a significantly increased activities of the Catalase and SOD in the mice (p<0.05). Although 150 mg/kg body weight methanol extract treatment failed to improve the level of GSH and MDA but at the dosage of 250 mg/kg body weight and 500 mg/kg body weight showed a significant improvement (p<0.01). The Catalase and SOD activities of the 250 mg/kg body weight as well as 500 mg/kg body weight methanol extract treated diabetic animals were significantly higher than the Rosiglitazone treated rats (p<0.001). Further, the reduction in the MDA levels at the dose of 500 mg/kg methanol extract treated animals was significantly higher than the Rosiglitazone treated mice (p<0.05).

Effect of Methanol Extract on the antioxidant profile of diabetic cardiac muscles

A significant decrease (p<0.001) in the Catalase and SOD activities along with decreased GSH levels was observed in the cardiac tissues of diabetic mice. The levels of MDA was also significantly higher than the normal control (p<0.001, Table- 4). Methanol extract treatment significantly improved the Catalase activity and GSH levels while decreasing their MDA levels (p<0.05-p<0.01). Catalase activity and GSH levels in the 500 mg/kg body weight methanol extract treated diabetic hearts was found to be significantly higher than the Rosiglitazone treated animals (p<0.05). No significant changes in the SOD activities of cardiac tissues were observed in all the groups of diabetic animals.

Effect of Methanol Extract on the antioxidant profile of kidneys

Significantly decreased Catalase, SOD and GSH along with increased MDA levels were observed in the diabetic kidneys (p<0.001, Table- 5). Rosiglitazone treated mice could not exhibit any alteration in the antioxidant profiles of the kidneys. On the other hand, a significant improvement in the GSH (p<0.05) and MDA levels (p<0.01) of the 250 mg/kg body weight and 500 mg/kg body weight methanol extract treated animals were recorded. It was noticed that only 500 mg/kg body weight methanol extract treated diabetic mice exhibited significantly (p<0.01) better GSH levels even as compared with Rosiglitazone treated animals.

Effect of Methanol Extract on serum antioxidant profile

The GSH, SOD and Catalase levels in the serum of the diabetic mice was found to be significantly (p<0.001) reduced along with increased MDA level in these animals (Table- 6). Rosiglitazone and methanol extract treatment at 150 mg/kg body weight could not significantly improve these parameters but methanol extract of *S. asper* at the dose of 250 mg/kg body weight was able to exhibit significant alteration in the GSH content (p<0.05) along with decreased MDA level (p<0.01). On the other hand, methanol extract of *S. asper* at the dose of 500 mg/kg body weight significantly improved all the enzymatic and non enzymatic anti oxidant parameters and the values were significantly higher than the Rosiglitazone treatment (p<0.01).

Effect of Methanol Extracton the serum biochemical parameters

The levels of SGOT, SGPT, albumin and Glycosylated Hemoglobin were found significantly higher in the serum of the diabetic animals (p<0.001, Table- 7). On the other hand, Rosiglitazone treatment significantly improved the albumin levels in the diabetic mice (p<0.05). Similarly, methanol extract treated mice also showed significant control over all these parameters at different doses used in this study (p<0.05- p<0.001). The reduction in the serum SGOT activity at the dose of 500 mg/kg body weight methanol extract treated diabetic mice was significantly lower than that of the Rosiglitazone treated mice (p<0.05). The Glycosylated hemoglobin (HbA1C) levels in the 250 and 500 mg/kg body weight methanol extract treated mice were also significantly lower than the Rosiglitazone treated mice (p<0.05).

IV. Discussion

Phytochemicals from natural products possess potent antioxidant activities that are capable of prevention of the onset and/or progression of many human diseases by counteracting reactive oxygen species (ROS) [90, 91, 92, 93, and 107].

It is evident from the present study that the methanol extract of *Streblus asper* exhibited good anti diabetic property and prevented the loss of body weight under diabetic condition. Further methanol extract was able to prevent and improve the deteriorating antioxidants parameters in the tissues of the treated diabetic animals. These findings indicate a possible interrelationship of diabetes with deteriorating antioxidant profile and the efficacy of methanol extract against diabetes as with treatment marked alteration in the fasting blood glucose levels along with increased level of antioxidants was observed in these animals.

It has already been observed that oxidative stress can increase the levels of H_2O_2 (hydrogen peroxide) in the mesangial cells which may result in altered antioxidant profile in the serum [94]. In the present study, the reduction in the antioxidant profile of the diabetic mice may be due to the disease induction. In the present investigation decreased activities of Catalase, SOD and GSH in the liver were observed whereas, after the methanol extract treatment an increased activity of these parameters along with decreased blood glucose level in diabetic mice suggests a positive role of this drug in controlling the diabetes. SOD can detoxify superoxide radicals by converting it into hydrogen peroxide (H_2O_2) [95] which can be further decomposed into water and oxygen molecules by Catalase [96]. Thus, it appears that the methanol extract of *S. asper* may be acting through the same mechanism as marked alteration in the enzymes activities were observed after the treatment. On the other hand, increase MDA level was observed in the liver of diabetic mice. It is known that oxidative stress is associated with dyslipidemia which may cause oxidation of the LDL present in the serum leading to increased levels of MDA [97]. Thus, it appears that increased level of MDA in the present study may be due to the oxidative stress in diabetic mice and methanol extract of *S. asper* can control the oxidative stress, which is evident by decreased level of MDA as after the drug treatment. It is well known fact that free radicals are one of the major reasons for dyslipidemia and inflammation [98] and the anti inflammatory activity of *Sreblus asper* in macrophages [99] has already been reported which also supports our observation in the present study. A more or less similar antioxidant and hypoglycemic activities of *Streblus asper* has been observed in Streptozotocin induced diabetic rats by [100].

The presence of Lupeol in extract of *Streblus asper* has already been documented and Lupeol is well known for its anti oxidant and hypotensive activity [101]. Thus, it is evident from the present study that the potent *in-vivo* anti oxidant activity observed in different tissues after methanol extract treatment might be due to the presence of Lupeol. Further, 30 days of methanol extract treatment was very much effective and it was able to control the fasting blood sugar levels similar to Rosiglitazone thereby indicating that the action of methanol extract is slow but it acts over a period of time as compared with Rosiglitazone. The results clearly indicate that methanol extract of *S. asper* increased the activities of Catalase and SOD along with GSH and this in turn may have reduced the levels of MDA in the diabetic tissues because it is a tissue per-oxidation product. Lipid peroxidation has already been reported due to oxidative stress [102] in the tissue of diabetic rats and it seems possible that methanol extract may have influenced the hydroxyl radicals against lipid peroxidation.

Lupeol is known to reduce the elevated tyrosinase phosphatase 1B [103] and alpha amylase activities [104] during diabetes and thus the showed efficacy against different enzyme activities. The Assamese people (Northeastern India) customarily use the leaves of this plant to treat patients who urinate frequently at night and lose their weight. This weight protective action of *S. asper* looks very much justified as with methanol extract treatment marked alteration in the body weight of animals has been recorded which further proves its efficacy. Therefore the presence of Lupeol in extract may be responsible for *in- vivo* anti oxidant activity thereby protecting the vital diabetic tissues against diabetic complications.

Glycosylated hemoglobin (HbA1C) is often used to assess the control of hyperglycemia over a period of time and it is also related with coronary arterial diseases including diabetic cardio vascular complications [105]. An interrelationship was observed between the Glycosylated hemoglobin and serum albumin level in the type 2 diabetic patients along with cardio vascular complications [106].

V. Conclusions

In the present investigation it was found that methanol extract treatment could able to control the glycosylated hemoglobin suggesting its cardio protective nature. The level of SGOT, SGPT and albumin in serum was also altered after the methanol extract treatment which may be correlated with hepatoprotective, cardioprotectve and nephroprotective activities of methanol extract. Even though the existing anti diabetic molecules possesses better anti hyperglycemic activity but they fail to prevent insulin resistance due to their lack of anti oxidant potential. Therefore, under such circumstances herbal extracts like extract of *Streblus asper* can play a promising role by its anti diabetic and anti oxidant properties.

Acknowledgement

The author are thankful to Dr. Baidyanath Kumar, Visiting Professor, Department of Biotechnology, Patna Science College, Patna (PU), for providing necessary suggestion for the preparation of this research article.

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IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB) is UGC approved Journal with Sl. No. 4033, Journal no. 44202.

Pratima Kumari. " Pharmacological evaluation of Streblus asper Lour. (Shakhotaka) extract with special reference to Antioxidant and Hypoglycemic activities." IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB) 4.5 (2018): 14-25.