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Evaluation of Anti-Diabetic and Hypolipidemic Activity of *Pseudarthria viscida* (Whole Plant) in Streptozotocin-Nicotinamide Induced Type II Diabetic Rats

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Abstract: To evaluate the anti-diabetic activity of ethanolic extract of *Pseudarthria viscida* whole plant on Streptozotocin - Nicotinamide induced type-II diabetes in rats. A crude extract of *Pseudarthria viscida* whole was prepared by Soxhlet extraction and the ethanolic extract was dried. At a dose of 100 mg/kg, 200mg/kg the extract was given for 14 days to evaluate the anti-hyperglycemic and anti-hyperlipidaemic activity in Streptozotocin - Nicotinamide induced diabetic rats. The blood glucose levels were determined at different times by glucose oxidase method. Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT) levels and lipid profile was also determined. Dosage of 100mg/kg and 200mg/kg of the extract significantly (P<0.001, P<0.01) decreased blood glucose levels and the decrease was found to be dose dependent. SGOT and SGPT levels were decreased (P<0.01, P<0.05). Lipid profile was also decreased significantly (P<0.01, P<0.05). In the present study the anti-hyperglycemic potential of *Pseudarthria viscida* was demonstrated in rats. It also has beneficial effects in diabetes associated complications.

Key words: Anti-Diabetic · Glibenclamide · *Pseudarthria viscida* · Streptozotocin · Nicotinamide Induced

INTRODUCTION

Diabetes mellitus is characterized mainly by abnormalities in carbohydrate, lipids and protein metabolism, due to defect in insulin secretion from pancreatic β-cells or insulin action or both. The number of people with type 1 and type 2 diabetes mellitus are dramatically increasing worldwide [1]. World health organization has estimated that several plants are known to have various medicinal applications in various cultures and WHO also estimated that about 4 billion people, 80% of the world population presently use herbal medicine in order to have a primary health care. More than 50% of all the drugs in clinical use in the world today have been Mellitus, 2003, most patients can be classified clinically as represented by the natural products and their derivatives and higher plants contribute not less than 25% [2].

Streptozotocin shows cytotoxic effect on entire pancreatic β-cell which leads to destruction of entire pancreatic β-cells. In order to partially protect the pancreatic β-cells and to develop a new model of diabetic syndrome in adult rats which appears closer to Non insulin dependent diabetic mellitus (NIDDM), a suitable dose of Nicotinamide is administered to rats 15min prior to Streptozotocin administration [3].

Pseudarthria viscida belongs to the family Fabaceae. It is commonly called as Salaparni and is sweet and bitter in taste, sweet in the post digestive effect and has hot potency. It alleviates all the three Doshas. It possesses heavy and oily attributes. It has antipyretic, aphrodisiac and rejuvenative properties and is used in the diseases like fever, bronchial asthma, hemorrhoids, edema, diabetes mellitus, diarrhea and tuberculosis [4].

The chemical constituents of the plant are Petrocarpanoids, Gangetin, Gangetinin and Desmodin. Seven alkaloids viz. N, N-dimethyltryptamine and its Nb-oxide, Hypaphorine, Hordenine, Candicine, N-methyltyramine and Phenylethylamine have been reported from roots [5]. A new antifungal Isoflavonoid, Phytoalexin, Desmocarpin, isolated together with Genistein, 2-hydroxygenistein, Dalbergioiden, Diphysolone and Kievitone from fungus – inoculated leaflets, its structure determined [6].

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MATERIALS AND METHODS

Collection of Plant Material: The plant material *Pseudarthria viscida* was collected from waste lands of Chittoor district during the month of April 2012 and authenticated by an expert taxonomist Dr. Madhavashetty, Department of Botany, Sri Venkateshvara University, Thirupathi andhra Pradesh, India.

Animals: Healthy Wistar albino rats of either sex aged between 2-3 months and weighing 150–200 g were used for the study which was procured from Mahaveera Enterprises, Hyderabad. Housed individually in polypropylene cages, maintained under standard conditions (12h light and 12h dark cycle, 25±30°C, 35–60% relative humidity), the animals were fed with standard rat pellet diet and water *ad libitum*. The experiments planned after the approval of Institutional Animal Ethical Committee (IAEC), Vaagdevi College of Pharmacy, Warangal andhra Pradesh, India.

Chemicals: Glibenclamide was obtained as a gift sample from Suzikem Drugs private limited, Hyderabad andhra Pradesh, India. Streptozotocin was purchased from Sigma Aldrich, Germany. Total cholesterol and HDL kit, triglycerides kit and other chemicals were procured from SS pharma, Hanamkonda andhra Pradesh, India.

Preparation of Extracts: The Ethanolic extract of *Pseudarthria viscida* (EEPV) was prepared by Soxhlet extraction by taking 100g of the shade dried powder in 1000 ml of ethanol, followed by prior defattening with ether. The extract was filtered, concentrated, dried in vacuum (8% yield) and the residue stored in a refrigerator at 2-8°C for use in subsequent experiments [7].

Preliminary Phytochemical Screening: EEPV was subjected to phytochemical screening tests for the detection of reducing sugars, Alkaloids, Flavonoids, Anthraquinones, Tannins, Saponins and Sterols using conventional protocol [8-9].

Experimental Protocol: A total number of 30 rats were divided into five groups and each group six rats.

- Group I – Control, administered vehicle (distilled water).
- Group II – Diabetic control, administered Streptozotocin at a dose of 60 mg/kg body weight (b.w) + Nicotinamide 120mg/kg b.w.
- Group III – Standard, administered Glibenclamide at an oral dose of 10 mg/kg b.w
- Group IV – Administered ethanolic extract of *Pseudarthria viscida* at oral dose of 100 mg/kg b.w.
- Group V – Administered ethanolic extract of *Pseudarthria viscida* at oral dose of 250mg/kg b.w.

Induction of Hyperglycemia: Hyperglycemia was induced in overnight fasted adult Wistar strain albino male rats weighing 150–200 g by a single dose of 60 mg/kg Streptozotocin, 15 min after the intra-peritoneal (*i.p*) administration of 120 mg/kg of Nicotinamide. Streptozotocin (STZ) was dissolved in citrate buffer (pH 4.5) and Nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 hrs after administration. Rats with fasting blood sugar levels around 160 to 300 mg/dl were selected for the study. A Blood sample for glucose estimation from the experimental rats was collected by retro-orbital plexus technique using heparinized capillary glass tubes. The collected blood samples were centrifuged at a speed of 4000 rpm for 15 min to get plasma [10-12].

Assessment of Serum Glucose in Normoglycemic Rats: Overnight fasted normal rats divided into four groups (six rats / group) were administered with distilled water for control and EEPV for test groups at a dose of 100 mg/kg and 200 mg/kg respectively. Glibenclamide (10 mg/kg) was used as a standard drug. Blood was withdrawn from eye (retero-orbital plexus) at 0, 2, 4 and 6 hr from control and test group animals. The plasma was separated and blood glucose levels were determined by using Glucose Oxidase- Peroxidase (GOD-POD) method [13].

Oral Glucose Tolerance Test: The oral glucose tolerance test was performed in overnight fasted (16 hrs) normal rats. Rats divided into four groups (six rats/group) were administered distilled water for control and EEPV for test groups at a dose of 100 mg/kg b.w. and 200 mg/kg b.w. respectively. Glibenclamide (10 mg/kg) was used as a standard drug. Glucose (3g/kg b.w.) was fed 30 min after treatment. Blood was withdrawn by retero-orbital plexus at 0, 30, 60 and 120 min after the administration of glucose load and the plasma was estimated for glucose levels were determined by using GOD-POD method [14].

Assessment of Serum Glucose in Hyperglycemic Rats: Overnight fasted normal rats divided into five groups (six rats / group). Non-diabetic control group rats received distilled water. All other STZ – Nicotinamide diabetic rats

received EEPV (100 and 200 mg/kg, orally) and Glibenclamide (10 mg/kg, orally). The drugs were given every day for 14 days. Blood was withdrawn by retero-orbital plexus at 1st, 7th and 14th day after dosing and the plasma was estimated for glucose levels were determined by using GOD-POD method [15].

Biochemical Estimations: Blood glucose was determined by using GOD – POD method [16]. Total cholesterol estimated by CHOD / PAP method [17]. Triglycerides, HDL, LDL, VLDL estimated by GPO/PAP method [18]. Serum Glutamate Oxaloacetate Transaminase, Serum Glutamate Pyruvate Transaminase estimated by modified IFCC method [19].

RESULTS

Preliminary Phytochemical Screening: The preliminary phytochemical screening of Ethanolic extract of *Pseudarthria viscida* revealed the presence of reducing sugars, Alkaloids, Flavonoids, Tannins and Sterols.

Hypoglycemic Effect of EEPV: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on serum glucose levels in normal rats. Post GOD-POD test indicated that EEPV at 100 and 200 mg/kg exhibited significant reduction in the normal rats. The onset of hypoglycemic effect was observed significantly at 4th hour for 200mg/kg dose of the plant extract (Table 1).

Effect of EEPV on Glucose Tolerance: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on oral glucose tolerance test (OGTT). This indicated that glucose load has caused significant sudden increase in glucose at 30 min to 1 hr after administration of EEPV at 100 and 200 mg/kg. A significant reduction in the serum glucose levels was observed at 120th min for 200mg/kg dose of the plant extract (Table 2).

Effect of EEPV on STZ – Nicotinamide Induced Hyperglycemia: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on STZ – Nicotinamide induced Hyperglycemia. This indicated that STZ – Nicotinamide has caused significant increase in serum glucose compared to control group. Treatment of Hyperglycemic rats with EEPV (100 and 200 mg/kg) exhibited significant reduction in the blood glucose. The 200 mg/kg dose of EEPV caused maximum reduction in the blood glucose from day 7 to day 14 (Table 3).

Effect of EEPV on Serum Lipid Profile: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on STZ – Nicotinamide induced diabetic rats. This indicated that the plant extract showed a significant reduction in the blood HDL, LDL, VLDL, Total cholesterol and Triglyceride levels (Table 4).

Effect of EEPV on Liver Enzyme Levels: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on liver function tests. EEPV 100mg/kg reduced SGPT levels alone, whereas EEPV 200 mg/kg significantly reduced both SGOT and SGPT levels (Table 5).

Effect of EEPV on Body Weights: One-way ANOVA followed by Dunnett's test showed significant effect of EEPV on the body weights of the diabetic rats. EEPV 100mg/kg and 200 mg/kg significantly increased the final body weights when compared to that of control group (Table 6).

DISCUSSION

This study was initiated with the objective of evaluating antidiabetic activity of EEPV in Streptozotocin-Nicotinamide induced diabetic rats. Oral administration of Ethanolic extract at 200mg/kg dose resulted in a significant fall in blood glucose level, 2 hours after a single dose of treatment in glucose loaded rats. Ethanolic extract was effective in depressing the peak value of blood sugar at 60 min after glucose loading. The extract producing its hypoglycemic activity by a mechanism independent from the insulin secretion, it may be by inhibition of endogenous glucose production or by the inhibition of intestinal glucose absorption.

Among the two doses of extract, 200mg/kg dose showed significant anti-hyperglycemic effect. As it is evident from the results that maximum reduction in the blood glucose levels were observed at 14th day of treatment. The fasting blood glucose of the group treated with 200mg/kg body weight extract lowered the glucose level from 210.34mg/dl to 142.06mg/dl and Glibenclamide from 196.5mg/dl to 110.3mg/dl representing 31.8% and 43.8% reductions respectively. The effect on the fasting blood glucose is dose dependent. The proposed mechanism of action may be by promoting regeneration of β-cells or by protecting the cells in pancreas from destruction, by restricting glucose load as well as by promoting unrestricted endogenous insulin action and further effect β-cells to release insulin and activate the insulin receptors to absorb the blood sugar. Regeneration of islet β-cells following destruction by Streptozotocin may be the primary cause of the recovery.

Table 1: Hypoglycemic effect of EEPV in normal rats.

	Blood glucose levels in mg/dl (Mean± S.D)			
	Time period (hrs)			
Groups	0	2	4	6
Control	72.41±4.87	78.62±5.93	75.86±3.77	77.24±1.68
Standard	71.72±3.37	65.51±3.08**	59.31±2.58***	62.75±2.58**
Test(100mg/kg)	72.41±4.87	72.41±3.08	64.13±3.15**	68.27±2.58*
Test(200mg/kg)	71.03±5.60	68.96±3.77*	62.75±4.57***	68.96±3.77*

Data represents mean ± S.D. (n=6). *P < 0.05, ** P < 0.01, *** P < 0.001 Significant compared to control, analyzed by one-way ANOVA followed by Dunnett's test. Parenthesis indicates %reduction in blood glucose.

Table 2: Effect of EEPV on glucose tolerance in normal rats

	Blood glucose levels in mg/dl (Mean± S.D)			
	Time period (min)			
Groups	0	30	60	120
Control	82.75±3.08	97.93±3.51	87.58±3.51	80.00±5.06
Standard	76.55±4.02	88.96±2.58*	75.86±3.77***	72.41±4.8***
Test(100mg/kg)	76.37±2.64	94.48±5.16	82.39±2.74	75.68±2.20
Test(200mg/kg)	73.79±5.16	95.30±4.62	81.37±3.56*	69.65±4.02**

Data represents mean ± S.D. (n=5). * P <0.05, *** P < 0.001 Significant compared to control, analyzed by one-way ANOVA followed by Dunnett's test.

Table 3: Effect of EEPVon fasting blood glucose levels in diabetic rats.

	Blood glucose levels in mg/dl (Mean ± S.D)		
GROUPS	1st Day	7th Day	14th Day
Control	73.30±4.56	76.55±4.02	75.86±2.18
Diabetic control	272.41±3.08	277.24±3.51	279.31±3.08
Standard	196.55±5.93**	151.72±4.87**	110.34±4.87***
Test(100mg/kg)	228.96±6.39*	202.06±6.01*	177.93±7.10**
Test(200mg/kg)	210.34±2.14**	179.31±4.87**	142.06±2.58***

Table 4: Effect of EEPV on serum lipid profile in diabetic rats.

Groups	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	Total Cholesterol	Triglycerides (mg/dl)
Normal control	24.02±0.86	22.84±0.74	17.53±0.56	71.14±4.25	74.85±4.07
Diabetic control	10.94±0.86	99.32±2.38	22.74±0.63	167.02±5.28	179.42±5.21
Standard	33.82±1.14**	36.36±1.15**	18.44±0.40***	83.33±3.24***	88.22±3.35***
EEPV(100mg/kg)	23.92±3.59**	52.22±1.95**	19.31±0.46***	99.08±4.96***	105.13±4.33***
EEPV(200mg/kg)	26.91±1.04**	44.42±1.24**	18.63±0.42***	95.02±4.82***	95.11±4.46***

Data represents mean ± S.D. (n=5). ** P <0.01, *** P < 0.001, Significant compared to diabetic control analyzed by one-way ANOVA followed by Dunnett's test.

Table 5: Effect of EEPV on liver enzyme levels

Groups	SGOT(IU/ml)	SGPT(IU/ml)
Normal control	34.13±0.83	41.71±0.43
Diabetic control	75.10±0.52	88.53±1.82
Standard	35.12±2.88**	40.13±1.54**
EEPV(100mg/kg)	62.31±0.82	73.01±1.58*
EEPV(200mg/kg)	56.23±1.60*	68.15±1.42**

Data represents mean ± S.D. (n=5). ** P <0.001, * P < 0.05, Significant compared to diabetic control analyzed by one-way ANOVA followed by Dunnett's test.

Table 6: Effect of EEPV on body weight of various groups.

	Mean ± SD	
Group	Initial Weight	Final Weight
Control	219.35±3.77	250.35±3.98***
Diabetic Control	170.50±3.61	158.03±2.89
Standard(Glibenclamide)	173.31±7.63	200.64±8.73**
EEPV(100mg/kg)	170.33±3.82	180.81±3.92*
EEPV(200mg/kg)	173.82±4.66	194.11±6.88**

Data represents mean ± S.D. (n=5). * * P <0.01, * P < 0.05, Significant compared to diabetic control analyzed by one-way ANOVA followed by Dunnett's test.

Liver is the vital organ of metabolism, detoxification, storage and excretion of Xenobiotics and their metabolites. SGOT and SGPT are reliable markers of liver function. Treatment of the diabetic rats with Glibenclamide and extract caused reduction in the activity of these enzymes in plasma compared to the diabetic untreated group and consequently alleviated liver damage caused by STZ-Nicotinamide induced diabetes.

In this study, Ethanolic extract significantly recovered the levels of plasma lipid profile in treated diabetic rats when compared to untreated diabetic rats. From this result, it may be stated that the ethanolic extract leads to regeneration of the β-cells of the pancreas and potentiation of insulin secretion from surviving β-cells. The increase in insulin secretion and consequent decrease in blood glucose level may lead to inhibition of lipid peroxidation and control of lipolytic hormones [20].

The untreated diabetic rats gained weight at a much lower rate compared to control and extract treated groups. Administration of ethanolic extract of *Pseudarthria viscida* to diabetic (Group IV and V) rats resulted in an increase in body weight compared to diabetic rats (Group II). Results suggested that *Pseudarthria viscida* treatment has positive effect on maintaining body weights in diabetic rats. A gradual increase in body weights of Glibenclamide treated groups (Group III) was similar to that of normal control rats.

CONCLUSION

From our study, obtained results showing that the ethanolic extract of *Pseudarthria viscida* whole plant possess antidiabetic and anti-hyperlipidaemic activities in the Streptozotocin - Nicotinamide induced Type 2 diabetic rats.

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