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Antidiabetic activity of *Pulicaria wightiana* extract in streptozotocin-induced diabetic rats

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ABSTRACT:

Aim: The present study was carried out to evaluate the antidiabetic activity of *Pulicaria wightiana* methanolic extract in streptozotocin induced diabetic rats for 21 days.

Results: The methanolic extract at high dose (400mg/kg) exhibited significant anti hyperglycemic activity than low dose (200mg/kg) in diabetic rats. The methanolic extracts also showed improvement in parameters like lipid profile as well as regeneration of β -cells of pancreas in diabetic rats.

Conclusion: Histopathological studies reinforce the healing of pancreas, by methanolic *Pulicaria wightiana* extract, as a possible mechanism of their antidiabetic activity.

Keywords: STZ, Antidiabetic, *Pulicaria wightiana*.

INTRODUCTION:

Diabetes mellitus (DM) is a chronic endocrine disorder, involving metabolic disorders of carbohydrate, fat, and protein. All forms of diabetes are characterized by a decrease in the circulating concentration of insulin (insulin deficiency) and a decrease in the response of peripheral tissues to insulin (insulin resistance) [1, 2]. In modern medicine no satisfactory effective therapy is still available to cure diabetes mellitus [3]. There is increasing demand by patients to use natural products with antidiabetic activity due to side effects associated with the use of insulin and oral hypoglycemic agents [4-6]. There are numerous traditional medicinal plants reported to have hypoglycemic properties such as *Allium sativum* (Garlic), *Azadirachta indica* (Neem), *Vinca rosea* (Nayantara), *Trigonella foenum* (Fenugreek), *Momordica charantia* (Bitter ground), *Ocimum sanctum* (Tulsi) [7]. *Pulicaria wightiana* (Family: Asteraceae)

commonly known as sontikli and distributed in various parts of India. Earlier phytochemical studies reveal the presence of Sesquiterpenoids, Diterpenoids and Flavonoids [8]. However there is no scientific report available on anti-diabetic activity of *Pulicaria wightiana*. Thus the present study is an attempt to test the antidiabetic activity of *Pulicaria wightiana*.

MATERIALS AND METHODS:

Plant Material:

The basic plant material of *Pulicaria wightiana* whole plant used for the investigation was obtained from local area of Kadapa, India. The plant can be identified authenticated by department of Botany SV University, Tirupathi.

Preparation of the extract:

The whole plant product was collected and dried under shadow. The shade-dried whole plant was subjected to

pulverization to get coarse powder. The coarsely powder whole plant (1 kg) of *P. wightiana* was used for extraction with methanol in soxhlet apparatus. The extract was evaporated to dryness under vacuum and dried in vacuum desiccator (15.5% w/w).

Animals:

Wistar albino rats of both sexes were used for the study. Before and during the experiment, rats were fed with standard diet (Pranav Agro, Mysore). After randomization into various groups and before initiation of experiment, the rats were acclimatized for a period of 7 days under standard environmental conditions of temperature, relative humidity, and dark/light cycle. Animals described as fasting were deprived of food and water for 16 hours ad libitum.

Oral Glucose Tolerance Test:

Rats were divided into four groups containing six animals in each group. All animals fasted before treatment. Group I was kept as control which received distilled water p.o., group II received standard drug, group III received methanolic extract 200mg/kg, and group IV received methanolic extract 400 mg/kg respectively. The rats of group III and IV were loaded with glucose (3g/kg, p.o.) 30 minutes after drug administration. Blood samples were collected from puncturing the retro orbital sinus on 0, 30, 90 and 150 minutes after loading glucose. Serum glucose level was measured immediately by using glucose estimation kit (Span Diagnostic Pvt. Ltd. Surat, India).

Experimental Induction of Diabetes:

Animals were allowed to fast for 12 h and were administered freshly prepared streptozotocin (STZ) (Himedia) at the concentration of 60 mg/kg bodyweight, i.p. in 0.1mol/L cold citrate buffer, pH 4.5 [18]. The STZ-treated animals were allowed to drink 5% glucose solution overnight to overcome drug-induced hypoglycemia. After 24 h of injection, fasting blood glucose level was checked, and animals with levels above 3.9 mmol/L were considered diabetic.

Experimental Design:

Five groups of rats, six in each received the following treatment schedule. Group I: Normal (distilled water). Group II: STZ treated control (60 mg/kg.i.p). Group III: STZ (60 mg/kg.i.p) + Standard drug, Glibenclamide (5mg/kg, p.o), Group IV: STZ (60 mg/kg.i.p) + *Pulicaria wightiana*. Whole plants extract (200mg/kg, p.o), Group V: STZ (60 mg/kg.i.p) + *Pulicaria wightiana*. Whole plants extract (400mg/kg, p.o). Whole plant extracts and standard drug glibenclamide (5mg/kg) and saline were administered with the help of feeding cannula.

Biochemical Estimations:

Blood samples were collected from puncturing the retro orbital sinus on initial day, 7th, 14th & 21st day. Serum glucose level was measured immediately by using glucose estimation kit (Span Diagnostic Pvt. Ltd. Surat, India). The lipid profiles (total cholesterol, TG, HDL, and LDL) for all the four groups of animals were performed using commercially available kits. Glycogen content of liver was measured according to Van method [9].

Histopathological Studies

The whole pancreas from each animal was removed after sacrificing the animal and was collected in 10% formalin solution, and immediately processed by the paraffin technique. Sections of 5 μ thickness were cut and stained by haematoxylin and eosin (H & E) for histological examination.

Statistical Analysis.

All the values were expressed as mean $\pm$ standard error of mean (S.E.M.) and analyzed for ANOVA and post hoc Tukey's t-test. Differences between groups were considered significant at $P < 0.05$ levels.

RESULTS:

The effect of methanolic extract of *Pulicaria wightiana* (400 mg/kg and 200 mg/kg) on glucose tolerance test are shown in Figure 1. The supplementation of *Pulicaria wightiana* showed significant hypoglycemic effect after 90 minutes of treatment. The anti-hyperglycemic effect of the extracts on the fasting blood sugar levels of diabetic rats is shown in Table. 1 & Figure 2. Administration of STZ (60 mg/kg, i.p.) lead to 1.5 fold elevation of fasting blood glucose levels, which was maintained over a period of 4 weeks. Daily treatment of *Pulicaria wightiana* lead to a dose dependent and significant ($P < 0.001$) fall in blood sugar levels. STZ treatment will increase the serum enzymes levels such as cholesterol, triglycerides, LDL and decrease the HDL level, but glibenclamide (5mg/kg) and whole plant extract of *Pulicaria wightiana* reversed the above STZ induce changes (Table 2). There was a significant increase in glycogen content of liver ($P < 0.001$) with *Pulicaria wightiana* or glibenclamide treatment as compared to diabetic control (Table 3). Histopathological studies (Figure 3) showed normal acini and normal cellular population in the islets of Langerhans in pancreas of control rats (Group I). Extensive damage to the islets of Langerhans and reduced dimensions of islets (Group II), restoration of normal cellular population size of islets with hyperplasia by glibenclamide (Group III) were also shown. The partial restoration of normal cellular population and enlarged size of β -cells with hyperplasia were shown by methanolic extracts (Figure 1. Group IV & Group V).

Table 1: Effect of MPW on Glucose levels in diabetic rats

Group	Treatment	Serum glucose (mmol/L) (Mean $\pm$ SEM) on			
		Initial day	7 th day	14 th day	21 st day
I	Normal (Distilled water)	5.24 $\pm$ 0.69	5.26 $\pm$ 0.72	5.26 $\pm$ 0.61	5.24 $\pm$ 0.85
II	Control STZ (60 mg/kg, i.p)	5.26 $\pm$ 0.61	24.90 $\pm$ 1.22	27.44 $\pm$ 1.3 ^{###}	21.60 $\pm$ 0.24 ^{###}
III	Standard Glibenclamide (5 mg/kg, p.o.) + STZ	5.28 $\pm$ 0.69	24.30 $\pm$ 1.19	10.70 $\pm$ 1.31 ^{***}	5.46 $\pm$ 0.006 ^{***}
IV	Low dose Methanolic extract (200 mg/kg, p.o) + STZ	5.24 $\pm$ 0.68	24.28 $\pm$ 1.19	16.72 $\pm$ 1.36 ^{***}	7.10 $\pm$ 0.05 ^{***}
V	High dose Methanolic extract (400 mg/kg, p.o) + STZ	5.25 $\pm$ 0.71	24.20 $\pm$ 1.00	10.58 $\pm$ 1.33 ^{***}	5.47 $\pm$ 0.26 ^{***}

Values are expressed as means $\pm$ S.E.M. n=6, ^{###} = P<0.001 when compared to normal group (G-I), ^{***} = P<0.001 when compared to diabetic control group (G-II)

Table 2: Effect of MPW on serum Lipid profile

Group	Treatment	Serum markers (Mean $\pm$ SEM)			
		Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
I	Normal (Distilled water)	55.62 $\pm$ 4.456	36.49 $\pm$ 3.320	35.40 $\pm$ 5.556	12.91 $\pm$ 1.671
II	Control STZ (60 mg/kg, i.p)	274.26 $\pm$ 13.96 ^{###}	140.37 $\pm$ 15.58 ^{###}	10.26 $\pm$ 2.337 ^{###}	235.86 $\pm$ 14.10 ^{###}
III	Standard Glibenclamide (5 mg/kg, p.o.) + STZ	59.92 $\pm$ 4.472 ^{***}	48.22 $\pm$ 4.489 ^{***}	41.385 $\pm$ 3.401 ^{***}	8.89 $\pm$ 1.500 ^{***}
IV	Low dose Methanolic extract (200 mg/kg, p.o) + STZ	60.50 $\pm$ 4.437 ^{***}	50.58 $\pm$ 2.177 ^{**}	38.5 $\pm$ 5.590 ^{***}	11.88 $\pm$ 1.108 ^{***}
V	High dose Methanolic extract (400 mg/kg, p.o) + STZ	56.53 $\pm$ 4.774 ^{***}	44.23 $\pm$ 2.74 ^{***}	39.09 $\pm$ 3.72 ^{***}	10.590 $\pm$ 1.315 ^{***}

Values are expressed as means $\pm$ S.E.M. n=6, ^{###} = P<0.001 when compared to normal group (G-I), ^{***} = P<0.001 when compared to diabetic control group (G-II)

Table 3: Effect of MPW on liver glycogen

Group	Treatment	Liver glycogen (mg/g) (Mean $\pm$ SEM) on 21 st day
I	Normal (Distilled water)	16.53 $\pm$ 0.1
II	Control STZ (60 mg/kg, i.p)	8.12 $\pm$ 0.12 ^{###}
III	Standard Glibenclamide (5 mg/kg, p.o.) + STZ	15.28 $\pm$ 0.9 ^{***}
IV	Low dose Methanolic extract (200 mg/kg, p.o) + STZ	12.98 $\pm$ 1.1 ^{***}
V	High dose Methanolic extract (400 mg/kg, p.o) + STZ	14.58 $\pm$ 0.4 ^{***}

Values are expressed as means $\pm$ S.E.M. n=6, ^{###} = P<0.001 when compared to normal group (G-I), ^{***} = P<0.001 when compared to diabetic control group (G-II)

OGTT

Figure 1: Effect of methanolic extract of *Pulicaria wightiana* on glucose tolerance test.

GLUCOSE

Figure 2: Effect of methanolic extract of *Pulicaria wightiana* on glucose levels

Figure 3: Histopathological studies of pancreas: Group I (Control), Group II (STZ 60mg/kg), Group III (STZ + glibenclamide (5mg/kg), Group IV (STZ + Whole Plant 200mg/kg), and Group V (STZ + Whole Plant 400mg/kg)

DISCUSSION:

The present study discusses the antidiabetic effect of the methanolic extract of *Pulicaria wightiana* on streptozotocin-induced diabetic rats. Insulin-dependent diabetes mellitus (IDDM) is a disease caused by progressive destruction of the insulin secreting β -cells. Streptozotocin (STZ) is most commonly used to induce diabetes in rats. STZ selectively destroys the pancreatic cells that secrete insulin, which causes less active pancreatic cells and produces diabetes mellitus [10].

From the results of the present study, it appears that insulin producing cells are still functioning and the stimulation of insulin release could be responsible for most of the metabolic effects. The medicinal plant compounds may have mechanisms acting as insulin-like effect, improving insulin sensitivity, augmenting glucose-dependent insulin secretion, and stimulating the regeneration of islets of Langerhans in pancreas of STZ-induced diabetic rats.

Presence of phenolic compounds such as alkaloids, flavonoids, and tannins in *Pulicaria wightiana* was noticed in preliminary phytochemical analysis. We hypothesized that *Pulicaria wightiana* can be attributed to their insulin-trophic effect that enables the reduction of blood glucose levels due to their antidiabetic effect. The possible mechanism of action of *Pulicaria wightiana* extract treated groups could be potentiating the pancreatic secretion of insulin from β -cells of islets, as was evident by significantly lowering the level of glucose [11].

Conflict of Interests

The authors declare no conflict of interests.

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