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Antidiabetic and antihyperlipidemic effect of *Euphorbia hirta* in streptozotocin induced diabetic rats

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ABSTRACT

The present study was aimed to evaluate the anti diabetic activity potential of *Euphorbia hirta* leaves against streptozotocin (STZ) induced experimental rats. Ethanolic extract of *E. hirta* leaves was administered to streptozotocin induced rats. Glibenclamide was used as a standard drug. Blood glucose levels were determined after oral administration of a dose of *Euphorbia hirta* (400 mg/kg b. wt) in diabetic groups. Blood glucose levels were determined on 0, 7th, 14th and 21st day after oral administration of ethanolic extracts of *E. hirta* (400 mg/kg). An ethanolic extract of *Euphorbia hirta* was found to reduce blood sugar in streptozotocin induced diabetic rats. Reduction in blood sugar could be seen from 7th day after continuous administration of the extract. The effect of extracts of *Euphorbia hirta* on serum lipid profile like total cholesterol, triglycerides, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL) were also measured in the diabetic and non diabetic rats. There was significant reduction in total cholesterol, LDL cholesterol, VLDL cholesterol and improvement in HDL cholesterol in diabetic rats. These results indicated that *Euphorbia hirta* possesses significant hypoglycemic and antihyperlipidemic effect.

Key words: Glibenclamide, Antihyperlipidemic, *Euphorbia hirta*, Streptozotocin.

INTRODUCTION

Every year the number of diabetic patients is growing alarmingly all over the World. Diabetes is a chronic disease characterized by derangement in carbohydrate, fat, protein metabolism. Most of the hypoglycemic agents used in allopathic medicines are reported to have side effects in the long run. Therefore, there is a need to search for effective and safe drugs for diabetes [1]. The use of herbal medicines for the treatment of diabetes mellitus has gained importance throughout the world. The World Health Organization also recommended and encouraged this practice especially in countries where access to the conventional treatment of diabetes is not adequate. There is an increased demand to use natural products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents [2,3].

It has a long history of uses by indigenous and tribal people and in Ayurvedic or natural herbal medicines [4]. *E. hirta* belongs to the plant family Euphorbiaceae and genus *Euphorbia*. It is a slender- stemmed, annual hairy plant with many branches from the base to top, spreading upto 40 cm in height, reddish or purplish in color. Leaves are

opposite, elliptic-oblong to oblong-lanceolate, acute or subacute, dark green above; pale beneath, 1-2.5 cm long, blotched with purple in the middle, and toothed at the edge. The fruits are yellow, three-celled, hairy, keeled capsules, 1-2 mm in diameter, containing three brown, four-sided, angular, wrinkled seeds [5].

E. hirta has been studied by various workers and a number of active constituents have been isolated. Afzelin (I), quercitrin (II), and myricitrin (III) have been isolated from the ethanolic extract of *E. hirta*. The chemical investigation of *E. hirta* has led to the isolation of rutin (IV), quercitin (V), euphorbin-A (VI), euphorbin-B (VII), euphorbin-C (VIII), euphorbin-D (IX), 2, 4, 6-tri-O-galloyl- β -D-glucose, 1, 3, 4, 6-tetra-O-galloyl- β -D-glucose, kaempferol, gallic acid, and protocatechuic acid. *E. hirta* also contains β -amyrin, 24-methylenecycloartenol, β -sitosterol, heptacosane, nonacosane, shikmic acid, tinyatoxin, choline, camphol, and quercitol derivatives containing rhamnose and chlophenolic acid. The plant is useful in the treatment of fever, diarrhoea, diabetes, urinary disease, dyspepsia, depilatory [6].

The aim of this investigation was to ascertain the scientific basis for the use of this plant in the management of diabetes and hyperlipidemic, using streptozotocin induced diabetic rats.

MATERIALS AND METHODS

Materials: The leaves of *Euphorbia hirta* was collected from Indian Institute of Integrative Medicine, (Medicinal garden), Jammu and Kashmir, India, during the months of May 2011. The species was identified and authenticated by botanist Dr. S. N. Sharma, Department of Taxonomy, I.I.I.M (CSIR), Jammu, India and a voucher specimen was deposited in the Herbarium of Department of Botany, IIM Jammu

Animals: Male Wistar rats of body wt. 180–200 g were obtained from central animal house, Indian Institute of Integrative Medicine (CSIR). The animals were fed on standard pellet diet (Hindustan Lever, Mumbai, India) and water ad libitum. The rats used in the present study were maintained in accordance with guidelines of the CPCSEA, India and the study approved by the ethical committee.

Preparation of the leaves extract: The shade dried leaves were powdered to get a coarse granule. About 250 g of dried powder were extracted with 90% ethanol by continuous hot percolation, using soxhlet apparatus.

The resulted dark – brown extract was concentrated up to 100 ml on Rota vapour under reduced pressure. The concentrated crude extracts were lyophilized in to powder and used for the study.

Toxicity studies: The animals were divided into six groups separately and were treated orally with ethanolic extracts of *E. hirta* at 100, 200 and 400 mg/kg, body weight doses. The animals were continuously observed for 1 hr., then frequently for 14 days. The parameters observed were grooming, hyperactivity, sedation, loss of righting reflex, respiratory rate and convulsion [7,8].

Streptozotocin-induced diabetic rats: Streptozotocin (STZ), obtained from Indian Institute of Integrative Medicine, Jammu was dissolved in ice-cold normal saline immediately before use. Diabetes was induced in rats by intraperitoneal (i.p) injection of streptozotocin at a dose of 50 mg/kg [9]. Forty eight hours after streptozotocin administration, blood samples were drawn from tail and glucose levels determined to confirm diabetes. The rats were divided into 4 groups as follows; first group served as normal control, received food and water. Second group served as diabetic control, received 0.5 ml of 5% Tween 80; third group served as (diabetic control), received glibenclamide (0.5 mg/kg p.o.), and fourth groups, (diabetic rats) received 400 mg/kg, body weight of ethanolic extracts of *E. hirta*. The treatment was continued daily for 28 days. Blood drop was collected from the tail for glucose estimation, just before drug administration on 1st day and 1 h after sample administration on days 7, 14, 21 and 28 (Table 1).

Biochemical parameters: The biochemical parameters were determined on day 28 after the animals were sacrificed by cervical dislocation. Triglycerides, cholesterol, HDL-cholesterol, and LDL-cholesterol were estimated from the serum by using standard kits [10-12].

Statistical evaluation: Results of estimation of biochemical and functional parameters have been reported as mean value \pm SEM. The variation in a set of data has been estimated by performing one way analysis of variance

(ANOVA). Individual comparisons of group mean values were done using Dunnett's test (Sigma stat 3.5). $P < 0.05$, $P < 0.01$ and $P < 0.001$ were considered statistically significant.

RESULTS

Toxicity studies: In performing preliminary test for pharmacological activity in rats, ethanolic extract did not produce any significant changes in the behavioral or neurological responses upto 400 mg/kg body weight. Acute toxicity studies revealed the non-toxic nature of the ethanolic extracts of *E. hirta*. The result obtained from the LD50 study indicates that ethanolic extract of *E. hirta* is safer to use in animals even at a dose of 400 mg/kg p.o.

Antidiabetic Effects: Effect of ethanolic extract of *E. hirta* on serum glucose levels in diabetic rats depicted in (Table 1). In animals treated with streptozotocin (50 mg/kg i.p) (Group II), a significant increase in serum glucose level was observed on 7th, 14th, 21st and 28th day when compared with normal rats (Group I). Group III received glibenclamide (0.5 mg/kg p.o.) showed decrease in serum glucose level when compared with diabetic control rats (Group II). After the oral administration of ethanolic extract of *E. hirta* in diabetic control rats, a significant reduction in blood glucose level was observed on the 7th, 14th, 21st, and 28th day compared with diabetic control rats (Group II).

Table 1: Anti-hyperglycemic activity of *Euphorbia hirta* extract on STZ induced diabetic rats

Groups	0 Day	After 7 Day	After 14 Day	After 21 Day	After 28 Day
Normal control	73.39	99.98	89.78	82.75	75.46
	±	±	±	±	±
Diabetic control	292.54	281.11	271.66	270.19	278.92
	±	±	±	±	±
Glibenclamide (0.5mg/kg)	286.34	231.56	177.33	142.87	95.55
	±	±	±	±	±
<i>E. hirta</i> Extract(400mg/kg)	7.56***	10.21***	9.54***	8.44***	10.22***
	±	±	±	±	±
	284.98	242.33	183.33	152.33	113.23
	±	±	±	±	±
	8.32***	9.55***	7.88***	9.21***	9.22***

Values are expressed as mean ± SEM (Number of animals, n=6); significantly different at * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.05$, when compared with glucose control group.

Anti-hyperlipidaemic activity: The lipid profiles in control and experimental rats are depicted in (Table 2) in STZ induced diabetic rats. The diabetic control rats (Group II) showed significant increase in serum triglycerides, total cholesterol, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) while increase in High density lipoproteins (HDL) when compared with normal (Group I). Standard glibenclamide (Group III) also reduced triglycerides, Total cholesterol, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and increased High density lipoproteins (HDL) when compared with normal (Group I). The ethanolic extract of *E. hirta* showed significant decrease ($p < 0.05$) in Total cholesterol, LDL, VLDL, Triglycerides and significant increase ($p < 0.05$) in HDL when compared with diabetic control group (Group II). All these effects were observed on day 28th. The present experimental result indicated that ethanolic extracts exhibited a potent blood glucose lowering properties in STZ diabetic rats.

Table 2: Antihyperlipidemic activity of *Euphorbia hirta* extract on STZ induced diabetic rats

Group Treatment/Dose	Lipid Profile (mg/dl)				
	Total Cholesterol	Triglyceride	HDL	LDL	VLDL
Normal control	88.35±2.01	70.33±0.44	38.99±1.22	40.54±2.11	18.21±1.33
Diabetic control	142.34±1.22	134.21±1.21	32.46±0.95	95.62±3.33	38.98±2.34
Glibenclamide (0.5mg/kg)	119.11±3.23*	93.54±3.24*	38.22±2.43*	54.88±3.44*	25.83±1.34*
<i>E. hirta</i> Extract(400mg/kg)	116.19±2.32*	95.68±2.48*	48.45±1.54*	56.98±3.76*	24.43±0.45*

Values are expressed as mean ± SEM (Number of animals, n=6); significantly different at * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.05$, when compared with glucose control group.

DISCUSSION

Diabetes mellitus is one of the leading causes of death, illness and economic loss all over the world. Insulin-dependent (Type I, IDDM) diabetes is characterized by juvenile onset and by absolute insulin deficiency. Non-insulin-dependent (Type II, NIDDM) diabetes is characterized by mature onset, by varying basal insulin levels and a frequent association with obesity. During study it was found that both extracts control significantly the blood glucose level on streptozotocin induced diabetic rats. The ethanolic extracts of leaves a significant reduction on blood glucose level in STZ-induced-diabetic rats as compared to the diabetic control group. The possible mechanism by which *E. hirta* brings about its hypoglycemic action in diabetic rat may be by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from the existing beta cells or by its release from the bound form.

We found an elevated blood glucose concentration accompanied by increase in total cholesterol, triglycerides, LDL, VLDL and decrease in HDL cholesterol in streptozotocin induced diabetic rats as compared to control animals. Oral administration of ethanolic extract of *E. hirta* normalized the levels of blood glucose. The potent antidiabetic effect of the plant extract suggests the presence of potent antidiabetic active principles, which produced antihyperglycemic effect in diabetic rats.

In recent years, considerable interest has been directed towards the investigation of plasma lipids and lipoproteins pattern in diabetes mellitus due to the fact that abnormal lipid level leads to the development of coronary artery disease in diabetic patients [13].

Reduced insulin secretion and defect in insulin function results in enhanced metabolism of lipids from adipose tissue to the plasma. Impairment in insulin sensitivity due to high concentration of lipids in the cells is responsible for the elevated cardiovascular risk in diabetes mellitus [14]. Thus, the altered lipid and lipoprotein pattern observed in diabetic rats could be due to defect in insulin secretion and/or action. Hypercholesterolemia and hypertriglyceridemia have been reported to occur in diabetic rats. Accumulation of cholesterol and phospholipids in liver due to elevated plasma free fatty acids has been reported in diabetic rats.

In the present study, ethanolic extract of *E. hirta* had significantly decreased total cholesterol, triglycerides, VLDL and LDL with increase in HDL which is having a protective function for the heart compared with diabetic control group.

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