



Research Article

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ANTIHYPERGLYCEMIC, ANTIHYPERLIPIDEMIC AND ANTIOXIDANT EFFECT OF *HEDYOTIS LESCHENAULTIANA* DC ON ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

The aim of this study was to investigate the effect of ethanol extract of whole plant of *Hedyotis leschenaultiana* (EEHL) as antihyperglycemic, antihyperlipidemic and antioxidant effect in alloxan induced diabetic rats. Diabetes was induced in wistar albino rats by administration of alloxan monohydrate (150mg/kg). The EEHL at a dose of 150 and 300mg/kg of body weight was administered at single dose per day to diabetes induced rats for a period of 30 days. The effect of EEHL on blood glucose, insulin, urea, creatinine, HbA_{1c}, serum protein, albumin, globulin, serum enzymes [serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP)], serum lipid profile, [total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C)] and lipid peroxidation (LPO), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione (GSH) were measured in the diabetic rats. The EEHL elicited significant reduction of blood glucose ($p < 0.01$), lipid parameters except HDL-C, serum enzymes and LPO and significantly reduced insulin ($p < 0.01$), HDL-C, SOD, CAT, GPx and GSH at the dose of 300mg/kg was compared with the standard drug glibenclamide. From the above results, it is concluded that ethanol extract (300mg) of *Hedyotis leschenaultiana* whole plant possesses significant antihyperglycemic, antihyperlipidemic and antioxidant effect in alloxan induced diabetic rats.

Keywords: *Hedyotis leschenaultiana*, Alloxan, Insulin, HbA_{1c}, HDL-C, LPO, SOD, GSH.

INTRODUCTION

Diabetes is a major worldwide health problem predisposing to markedly increased cardiovascular mortality and serious morbidity and mortality related to the development of neuropathy. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, abnormal insulin secretion, altered metabolism of lipids and carbohydrates¹. It is becoming the third "killer" of health of mankind along with cancer and cardiovascular diseases². The prevalence of diabetes mellitus is expected to reach up to 4.4% in 2030 and the occurrence was found to be high in India, China and USA¹. Among all the cases of diabetes, type 2 diabetes was found to be more prevalent³. Diabetes is usually accompanied by increased production of free radicals or impaired antioxidant defenses. Maritime *et al*⁴ reported that oxidative stress plays a major role in the pathogenesis of diabetes. Disturbance of the antioxidant defense system in diabetes involve enhancement of lipid peroxidation, alteration in antioxidant enzymes⁵.

In spite of the presence of known antidiabetic medicine in the pharmaceutical market, remedies from medicinal plants are used to treat this diseases⁶ successfully. Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic one⁷. Based on the WHO recommendations, hypoglycemic agents of plant origin used in traditional medicine are important.

The genus *Hedyotis* finds a prominent place in different Indian system of medicine. The different ethnic communities in India have used different species of *Hedyotis* in the treatment of various ailments⁸. The present study deals with antidiabetic

effect of ethanol extract of the whole plant of *Hedyotis leschenaultiana* on alloxan induced diabetic rats and also to evaluate protein metabolite, liver enzyme level changes, lipid profile and antioxidant potential in alloxan induced diabetic rats. The effect produced by this drug on different parameters was compared with those of glibenclamide, a reference drug.

MATERIALS AND METHODS

Collection of plant material

Whole plant of *Hedyotis leschenaultiana* DC was collected from Kothagiri, Nilgiri Biosphere Reserve, Western Ghats, Tamil Nadu. The plant samples were identified with the help of local flora and authenticated by Botanical Survey of India, Southern Circle, Coimbatore, Tamil Nadu, India. A voucher specimen (VOCB4062) of collected plants was deposited in the Ethnopharmacological Unit, PG & Research Department of Botany, V.O. Chidambaram College, Thoothukudi District, Tamil Nadu.

Preparation of plant extract for antidiabetic activity

The whole plant of *H. leschenaultiana* were cut into small pieces, washed and dried at room temperature; the dried whole plant was powdered in a Wiley mill. Hundred grams of powdered whole plant was separately packed in a Soxhlet apparatus and extracted with ethanol. The ethanol extract was concentrated in a rotary evaporator. The concentrated ethanol extract of the whole plant was used for antidiabetic activity. The extract was subjected to qualitative test for the identification of various phytochemical constituents as per the standard procedures^{9,10,11}.

Animals

Normal healthy male Wistar albino rats (180-240g) were housed under standard environmental conditions at temperature (25±2 °C) and light and dark (12: 12 h). Rats were fed with standard pellet diet (Goldmohur brand, MS Hindustan lever Ltd., Mumbai, India) and water *ad libitum*. The study was carried out as per IAEC approval No. 1012/C06/CPSEA-Corres-2008-2009.

Acute toxicity study

Acute oral toxicity study was performed as per OECD-423 guidelines¹² (acute toxic class method), albino rats (n=6) of either sex selected by random sampling were used for acute toxicity study (OECD, 2002). The animals were kept fasting for overnight and provided only with water, after which the extracts were administered orally at 5 mg/kg body weight by gastric intubations and observed for 30 days. If mortality was observed in two out of three animals, then the dose administered was assigned as toxic dose. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for higher doses such as 50,100, and 2000 mg/kg body weight.

Induction of experimental diabetes

Rats were induced diabetes by the administration of simple intra peritoneal dose of alloxan monohydrate (150 mg/kg)¹³. Two days after alloxan injection, rats screened for diabetes having glycosuria and hypoglycemia with blood glucose level of 200-260 mg/100 ml were taken for the study. All animals were allowed free access to water and pellet diet and maintained at room temperature in plastic cages.

Experimental design

In the present investigation, a total of 30 rats (24 diabetic surviving rats and 6 normal rats) were taken and divided into five groups of 6 rats each. Group I: Normal untreated rats Group II: Diabetic control rats Group III: Diabetic rats given ethanol extract of *H. leschenaultiana* whole plant (150 mg/kg body weight) Group IV: Diabetic rats given ethanol extract of *H. leschenaultiana* whole plant (300 mg/kg body weight) Group V: Diabetic rats given standard drug glibenclamide (600 µg/kg body weight).

Biochemical analysis

The animals were sacrificed at the end of experimental period of 30 days by decapitation. Blood was collected, sera separated by centrifugation at 3000g for 10 min. Serum glucose was measured by the O-toluidine method¹⁴. Insulin level was assayed by Enzyme Linked Immunosorbant Assay (ELISA) kit¹⁵ Urea estimation was carried out by the method of Varley¹⁶; serum creatinine was estimated by the method of Owen *et al.*¹⁷. Glycosylated haemoglobin (HBA₁C) estimation was carried out by a modified colorimetric method of Karunanayake and Chandrasekharan¹⁸. Serum total cholesterol (TC)¹⁹, total triglycerides (TG)²⁰, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C)²¹, high density lipoprotein cholesterol (HDL-C)²² and phospholipids²³ were analyzed. Serum protein²⁴ and serum albumins were determined by quantitative colorimetrically method by using bromocresol green. The total protein minus the albumin gives the globulin, serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) was measured spectrophotometrically by utilizing the method of Reitman and Frankel²⁵. Serum alkaline phosphatase (ALP) was measured by the method of King and Armstrong²⁶. Lipid peroxidation (LPO)²⁷, Glutathione peroxidase (GPx)²⁸, reduced glutathione (GSH)²⁹, superoxide dismutase (SOD)³⁰ and catalase (CAT)³¹ were analysed in the normal, diabetic induced and drug treated rats.

Statistical analysis

The data was analyzed using student's t-test statistical methods. For the statistical tests *p* values of less than 0.001, 0.01 and 0.05 was taken as significant.

RESULTS

The phytochemical screening of ethanol extract of whole plant of *H. leschenaultiana* revealed the presence of alkaloid, catechin, coumarin, flavonoid, tannin, saponin, steroid, phenol, glycoside, terpenoid and xanthoprotein.

The impact of repeated oral administration of *H. leschenaultiana* whole plant extract and glibenclamide on normal and diabetic rats were shown in Table 1. The fasting plasma glucose (FPG) levels remain practically the same before and after the treatment with vehicle (saline only) in case of normal control rats. Whereas, in diabetic control rats fasting plasma glucose level rises gradually in 2 weeks after treatment with vehicle (saline only). Moreover, after 2 week treatment with most effective dose (300 mg/kg body weight) of *H. leschenaultiana* whole plant extract decreases FBG significantly from 232.84 mg/dl to 87.66±1.84 mg/dl. This sharp fall of fasting plasma glucose level was a clear evidence of significant antidiabetic effect of *H. leschenaultiana* whole plant extract.

Table 2 shows the levels of blood glucose, plasma insulin, urea, creatinine and glycosylated haemoglobin of normal and experimental rats. There was a significant elevation in blood glucose, urea, creatinine and glycosylated haemoglobin levels, while the plasma insulin level decreased significantly (*p*<0.01) in alloxan induced diabetic rats (Group II) when compared with normal rats (Group I). Administration of whole plant of *H. leschenaultiana* (Group III and IV) and glibenclamide (Group V) tends to bring the parameters significantly towards the normal. The effect of whole plant extract, at the dose of 300 mg/kg body weight was highly significant in restoring normal.

The levels of total protein, albumin, globulin, and liver marker enzymes such as SGPT, SGOT and ALP in the serum of diabetic rats are presented in Table 3. The diabetic rats (Group II) had decreased levels of serum total protein, albumin, globulin and elevated level of liver marker enzymes such as SGPT, SGOT and ALP when compared with normal control rats (Group I). After treatment with whole plant extracts of *H. leschenaultiana* (150 & 300mg/kg body weight) and glibenclamide (Group III, IV & V), total protein, albumin, globulin, and liver marker enzymes were brought back to near normal levels.

Table 4 shows the levels of TC, TG, HDL -C, LDL-C, VLDL-C, PL and LDL / HDL in the serum of diabetic rats. The diabetic rats had elevated levels of serum TC, TG, LDL-C, VLDL-C and PL and decreased level of HDL-C as compared with normal control rats. Diabetic rats treated with whole plant extract of *H. leschenaultiana* and glibenclamide reversed serum lipid profiles to near normal levels.

The activities of LPO, GPx, GSH, SOD and CAT in the serum of alloxan induced diabetic rats were depicted in Table 5. In the present study, the alloxan induced diabetic rats had shown increased activities of LPO, and decreased activities of SOD, CAT and GPx in the serum. Treatment with *H. leschenaultiana* and glibenclamide showed reversal of all these parameters to near normal levels.

Table 1: Effect of *H. leschenaultiana* (EEHL) whole plant extract on blood glucose level of normal, diabetic induced and drug treated rats at different time intervals

Groups	Blood glucose level in mgs/dl				
	0 day	1 week	2 week	3week	4 week
Group I	77.68±3.56	82.54±0.94	83.26±1.98	92.68±2.56	87.22±4.84
Group II	229.45±4.67	234.22±5.41**	226.59±2.94**	219.29±5.14**	228.14±5.85**
Group III	243.63±8.39	214.65±6.34**	128.63±4.54 ^{aa}	112.63±4.82 ^a	98.38±6.56 ^{aa}
Group IV	232.84±6.56	132.14±4.36** ^a	101.55±3.64 ^{aa}	98.11±0.93 ^{aa}	87.66±1.84 ^{aa}
Group V	214.14±7.56	148.63±5.65 ^{aa}	116.38±4.84 ^{aa}	104.56±0.84 ^{aa}	93.98±2.56 ^{aa}

Each Value is SEM of 6 animals * $p < 0.05$; ** $p < 0.01$ Significance between normal control vs diabetic induced control, drug treated group ^a $p < 0.05$; ^{aa} $p < 0.1$ diabetic induced control vs drug treated group; ns: not significant

Table 2: Effect of *H. leschenaultiana* (EEHL) whole plant extract on the insulin, blood glucose, urea, creatinine and glycosylated haemoglobin level of normal, diabetic induced and drugs treated rats

Parameter	Insulin (MIU/ml)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	HbA _{1c} (%)
Group I	19.84±0.84	77.54±2.81	14.68±0.98	0.64±0.11	4.33±0.15
Group II	7.29±0.73***	214.39±8.56***	31.62±1.31*	1.52±0.93 ^{ns}	10.88±0.24**
Group III	10.22±0.86*	148.14±2.52*	27.54±1.84 ^{ns}	1.13±0.56	8.03±0.11
Group IV	19.54±0.93 ^{aa}	103.56±1.94 ^{aa}	21.33±0.85 ^a	0.97±0.33	7.36±0.39 ^a
Group V	21.86±1.38 ^{aa}	96.08±0.84 ^{aa}	16.62±0.73 ^{aa}	0.61±0.14 ^a	6.79±0.22 ^a

Each Value is SEM of 6 animals * $p < 0.05$; ** $p < 0.01$ Significance between normal control vs diabetic induced control, drug treated group; ^a $p < 0.05$; ^{aa} $p < 0.1$ Significance between diabetic induced control vs drug treated group ns: not significant

Table 3: Effect of *H. leschenaultiana* (EEHL) whole plant extract on the protein, albumin, globulin, SGOT, SGPT and ALP level of normal, diabetic induced and drug treated rats

Groups	Parameters					
	Protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	SGPT (u/l)	SGOT (u/l)	ALP (u/l)
Group I	8.36±0.31	4.46±0.14	3.90±0.31	27.56±5.9	21.34±1.97	163.99±2.54
Group II	5.89±0.12*	3.61±0.64	2.28±0.13	181.63±4.83**	214.66±3.91**	224.54±8.4**
Group III	7.56±0.14	4.06±0.33	3.50±0.24	56.84±5.62*	74.64±1.37*	113.87±2.13*
Group IV	8.14±0.93	4.93±0.14	3.21±0.11	39.61±3.98	30.55±2.16	108.14±3.63
Group V	8.04±0.81	4.81±0.17	3.23±0.18	31.66±4.82	34.69±2.89	102.27±2.86

Each Value is SEM of 6 animals * $p < 0.05$; ** $p < 0.01$ Significance between normal control vs diabetic induced control, drug treated group;

Table 4: Effect of *H. leschenaultiana* (EEHL) whole plant extract on the TC, TG, LDL-C and PL in the plasma of normal, diabetic induced and drug treated rats

Groups	Parameter					
	TC (mg/dl)	TG(mg/dl)	LDL-C (mg/dl)	VLDL (mg/dl)	HDL (mg/dl)	PL (mg/dl)
Group I	114.63±3.46	68.4±3.64	50.33±2.56	13.68±0.94	50.62±2.63	170.02±3.64
Group II	178.55±2.86**	121.63±5.76*	129.67±4.91**	24.33±1.43 ^{ns}	24.55±2.61*	226.90±5.91*
Group III	128.54±2.64 ^{aa}	70.23±4.36 ^a	65.83±3.68 ^a	14.05±1.14	48.60±1.63 ^a	182.40±4.36 ^{ns}
Group IV	126.11±1.94 ^{aa}	78.33±2.42 ^a	58.81±3.16 ^a	15.67±1.68	51.63±2.6 ^{aa}	180.24±3.94 ^a
Group V	134.66±2.04 ^a	81.24±1.84 ^a	68.75±4.08 ^{ns}	16.25±1.93	49.66±1.54 ^a	187.85±2.68 ^{ns}

Each Value is SEM of 6 animals * $p < 0.05$; ** $p < 0.01$ Significance between normal control vs diabetic induced control, drug treated group;

^a $p < 0.05$; ^{aa} $p < 0.1$ diabetic induced control vs drug treated group; ns : not significant

Table 5: Effect of *H. leschenaultiana* (EEHL) whole plant extract on serum LPO, GPX, GSH, SOD and CAT in the normal, diabetic and drug treated rats

Groups	Parameters				
	LPO (nanomol/mg protein)	GPX (u/mg protein)	GSH (u/mg protein)	SOD (u/mg protein)	CAT (u/mg protein)
Group I	1.93±0.051	596.46±21.41	34.83±1.88	489.26±16.27	81.27±1.94
Group II	4.13±0.026**	306.89±18.27**	16.91±0.93*	263.85±18.46**	51.18±1.38**
Group III	2.64±0.014 ^{ns}	454.68±14.16 ^a	27.33±1.14 ^{ns}	279.36±16.91**	73.29±1.56 ^{ns}
Group IV	2.04±0.031 ^a	579.11±15.37 ^{aa}	31.74±1.24 ^{aa}	419.17±15.64 ^a	86.59±2.50 ^{aa}
Group V	1.98±0.054 ^{aa}	565.35±10.94 ^{aa}	35.22±2.01 ^a	463.55±16.26 ^a	79.94±1.86 ^a

Each Value is SEM of 6 animals * $p < 0.05$; ** $p < 0.01$ Significance between normal control vs diabetic induced control, drug treated group ^a $p < 0.05$; ^{aa} $p < 0.01$ diabetic induced control vs drug treated group; ns : not significant

DISCUSSION

The present study was aimed to investigate the antihyperglycemic activity of ethanol extract of *H. leschenaultiana* whole plant (EEHL) in alloxan induced diabetic rats. The results of the study revealed that EEHL at doses 150 and 300mg/kg significantly normalized elevated blood glucose level and restored serum biochemical parameters towards normal values.

Hyperglycemia was observed after 3 days of alloxan induction. Treatment with EEHL in alloxan induced diabetic rats started reducing blood glucose levels in a dose dependent manner after 7 days and made them normoglycemic after 28 days. The antihyperglycemic effect of EEHL at a dose of 300mg/kg was found to be comparable to the effect exerted by the reference drug glibenclamide.

In the present study, the oral administration of EEHL whole plant decreased blood glucose level in diabetic rats. It has been reported that using medicinal plant extract to treat alloxan induced diabetic rats results in activation of β -cells and insulinogenic effects. EEHL may also have brought about hypoglycemic action through stimulation of surviving β -cells of islets of langerhans to release more insulin. This was clearly evidenced by the increased levels of plasma insulin in diabetic rats treated with EEHL. Since the percentage fall in plasma glucose levels was different in models with varying intensity of hyperglycemia, it implies that the antihyperglycemic effect of that plant is dependent on the dosage of diabetogenic agent, which in turn leads to β -cell destruction³². A number of other plants have also been observed to exert hypoglycemic activity through insulin release stimulatory effects^{33,34,35}.

The alloxan induced diabetic rats are associated with increases in serum urea and creatinine levels, when compared to control rats. EEHL were administered orally to rats for thirty days and this reversed the levels of urea and creatinine to near normal. Administration with glibenclamide, the standard diabetic drug also decreased the levels of urea and creatinine to some extent.

Glycosylated haemoglobin is an indicator of the progression of diabetes. Therefore glycosylated haemoglobin was measured in the control and diabetic rats. The increase of glycosylated haemoglobin serves as a marker to know the induction of diabetes. The treatment of EEHL in diabetic rats maintained the original levels of glycosylated haemoglobin equal to that of control ones.

The rats treated with alloxan, developed hepatic damage which was evident from the increase in the enzyme activities. Pretreatment with EEHL and glibenclamide resulted in a decrease of transaminase activities in alloxan treated rats. The serum GPT and GOT levels increased as a result of metabolic changes in the liver, such as administration of toxin, cirrhosis of the liver, hepatitis and liver cancer including diabetes³⁶. Similarly in the present study, it was observed that the levels of SGPT and SGOT in alloxan induced diabetic rats were elevated. It may be due to leaking out of enzymes from the tissues and migrating into the circulation by the adverse effect of alloxan³³. SGPT and SGOT were used as markers to assess the extent of liver damage in alloxan induced diabetic rats. In this study, the EEHL whole plant regulated the activity of SGPT, SGOT and ALP in livers of rats intoxicated with alloxan. The effect of glibenclamide on the recovery of hepatic enzyme activity in serum was very similar to that of the earlier study³⁷.

A significant reduction in serum protein ($p<0.05$), albumin and globulin were observed in alloxan induced diabetic rats, when compared to control and glibenclamide treated rats. On administration of EEHL to the diabetic rats, protein, albumin and globulin levels were found to be restored in normal. These results were in accordance with the effect of *Wattakaka volubilis* leaf in diabetic rats³⁸.

Alloxan induced diabetic rats showed ($p<0.05$; $p<0.01$) increased serum lipid profiles except HDL-C, when compared to normal rats. The glibenclamide and EEHL treated rats showed significant decrease in the content of lipid profiles, when compared to normal rats. Similarly HDL-C level decreased in alloxan induced diabetic rats when compared with normal rats. On administration of EEHL and glibenclamide to the diabetic rats, HDL-C level was found to be restored to normal. The level of serum lipid profiles are usually raised in diabetic rats in the present study and such elevation represents risk for coronary heart diseases³⁹. Lowering the serum lipid level through dietary or drug therapy seems to be associated with a disease in the risk of vascular disease⁴⁰.

Oxidation stress in diabetes mellitus has been shown to coexist with impairment in the endogenous antioxidant status⁴¹. A marked increase in the concentration of TBARS in alloxan induced diabetic rats indicated enhanced lipid peroxidation leading to tissue injury and failure of the endogenous antioxidant defense mechanisms to prevent over production of free radicals. Lipid peroxidation is usually measured in terms of TBARS as a biomarker of oxidative stress⁴². In the present study, it was observed that there was a significant ($p<0.01$) decrease in the TBARS levels of the EEHL treated rats in comparison with diabetic (alloxan) control rats.

Glutathione plays an important role in the endogenous non-enzymatic antioxidant system. It primarily acts as a reducing agent and detoxifies hydrogen peroxide in the presence of the enzyme glutathione peroxidase⁴³. The depleted reduced glutathione (GSH) may be due to reduction in GSH synthesis or degradation of GSH by oxidative stress in alloxan induced hyperglycemic rats. EEHL treatment significantly ($p<0.01$) elevated the serum reduced glutathione levels towards normal in diabetic rats. The results showed that the antihyperglycemic activity of EEHL was accompanied by enhancement in non-enzymatic antioxidant protection.

The destruction of superoxide radical or H_2O_2 by SOD or CAT would ameliorate alloxan toxicity, as would substances able to scavenge of hydroxyl radical. The altered balance of antioxidant enzymes caused by decrease in SOD, CAT activities may responsible for the inadequacy of antioxidant defense in combating ROS mediated damage. The decreased activities of CAT and SOD may response to increased production of H_2O_2 and O_2 by the autooxidation of glucose and non-enzymatic glycation⁴⁴. A reduced activity of SOD and CAT in serum has been observed during diabetes and this may result in a number of deleterious effects due to the accumulation of superoxide radicals and hydrogen peroxides⁴⁵. EEHL treated rats showed decreased lipid peroxidation, which is associated with increased activity of SOD and CAT. This means that the extract can reduce reactive oxygen free radicals and improve the activities of the serum antioxidant enzymes.

CONCLUSION

In the present study, the administration of EEHL to alloxan induced hyperglycemic rats demonstrated prominent reduction in blood sugar level, normalization of serum biochemical profile

including lipid contents, as compared to alloxan control rats. Also, EEHL treatment resulted in significant modulation of lipid peroxidation, endogenous non-enzymatic (GSH) and enzymatic (SOD and CAT) antioxidant and detoxification status. The bioactive component(s) responsible for the observed activities are not precisely known but it may be one or more of the phytochemical constituents established to be present in the whole plant extract. In the present study, the phytochemical screening reported that the presence of flavonoid in extracts which might be the constituents responsible for these activities. Further identification and isolation of these constituents may be fruitful.

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