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Antidiabetic Effect of *Helicteres isora* Root in Streptozotocin Induced Diabetic Rats

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Abstract

The anti hyperglycemic and hypolipidemic activities of butanolic extract of *Helicteres isora* root were investigated in streptozotocin induced diabetic rats along with its *in vitro* free radical scavenging activity. The butanolic extract was tested for its antidiabetic activity in streptozotocin-induced diabetes at an oral dose of 125 and 250 mg/kg by acute and chronic dosing. Treatment with butanolic extract of *H. isora* roots at dose of 125 and 250 mg/kg caused reduction of blood glucose by 29.49 and 32.23% respectively, within 1-hour time after oral treatment. Chronic administration of the butanolic extract at a dose of 125 and 250 mg/kg significantly reduced the blood glucose level by 41.38 and 54.18%, respectively on day 10. Whereas glibenclamide (5 mg/kg) caused a significant reduction of 26.94% in plasma glucose levels. Both butanolic extract at 250 mg/kg and glibenclamide had significantly lowered the triglyceride and total cholesterol levels. The decrease in triglyceride and total cholesterol levels could be through its control of hyperglycemia. Besides, the butanolic extract was also tested for its antioxidant activity by using diphenyl picryl hydrazyl radical assay method and it was found to effectively scavenge the free radical *in vitro* with an the IC_{50} of 26 µg/ml. The total phenol content of butanolic extract was found to be 480 mg GAE/gm of the extract. Butanolic extract of *H. isora* root at a dose of 250 mg/kg caused significant hypoglycemic and hypolipidemic activity in streptozotocin induced diabetic rats and hence can be considered as a potent anti diabetic agent. Effective dose can be concluded as 250 mg/kg.

Keywords: *Helicteres isora*; Roots; Antidiabetic activity; Streptozotocin induced diabetes; Free radical scavenging activity

Introduction

Diabetes mellitus is a chronic condition characterized by high blood glucose due to an absolute or relative lack of insulin [1]. It ranks highly among the top ten disorders causing mortality throughout the world. It is a syndrome resulting from variable interaction of hereditary and environmental factors. In modern medicine still there is no satisfactory therapy available to cure diabetes mellitus although insulin therapy, oral hypoglycemic agents, restricted diet, exercises either singly or in combination constitute a major regime of therapy available for the present day diabetic patients. In a large number of cases, treatment with traditional medicine in the form of plant extracts has been reported to give remarkably good results.

Helicteres isora Linn., belongs to the family Sterculiaceae, is a sub deciduous large shrub or small tree and commonly known as East Indian Screw tree. Traditionally the juice of roots is claimed to be useful in cough, asthma, diabetes, stomach problems and intestinal infections [2-4]. The presence of cucurbitacin B and isocucurbitacin B was reported in roots [5]. The presence of antihyperglycemic properties in the butanolic extract of the roots of *H. isora* has been reported by us in glucose tolerance test [6] and alloxan induced diabetic rats [7]. The percentage reduction in blood glucose level is found to be 32 and 48 in glucose tolerance test and alloxan induced diabetic rats respectively at an oral dose of 250 mg/kg. Chakrabarti *et al.* (2002) reported a significant reduction in plasma glucose and insulin levels by 62 and 61% respectively at 300 mg/kg in insulin resistant and diabetic db/db mice [8]. Aqueous extract of the bark showed antidiabetic and hepatoprotective effect on Streptozotocin (STZ) induced diabetic rats [9]. The roots were reported to possess significant anti-inflammatory and antinociceptive properties [10,11].

The antihyperglycemic and hypolipidemic activity of *H. isora* root aqueous ethanol and butanolic extracts were reported in alloxan induced diabetic rats at a dose of 250 mg/kg body weight. The beneficial effects of these extracts were supported from histological examination of the liver, pancreas and kidney. Following the treatment with both extracts, the degenerative changes caused by alloxan in pancreatic cells were restored, particularly with the butanolic extract [12]. These results suggest *H. isora* root possesses antidiabetic principles and can be useful in the treatment of diabetes. However to develop an antidiabetic agent, the substance is required to be tested in various experimental models to determine the efficacy of the drug.

The mechanism of induction of diabetes by alloxan and streptozotocin are quite different. Hence the present study has been carried out to assess the effect of butanolic extract in streptozotocin induced hyperglycemia for its hypoglycemic and hypolipidemic properties at two different dose levels of 125 and 250 mg/kg body weight. *In vitro* antioxidant and total phenolic content were estimated.

Materials and Methods

Plant material

H. isora roots were collected from the Srisailam forests, Andhra

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Pradesh (A.P), India. Dr. S.T. Ramachandrachari, Taxonomist, Kama Reddy Degree College, Kama Reddy, A.P, India performed the botanical identification. A voucher specimen [HI/ RT/09] is being maintained in the Phytochemistry and Pharmacognosy Department of G. Pulla Reddy College of Pharmacy, Hyderabad. The roots were cleaned, cut and air dried and grounded into powder. The dried powder material was passed through sieve number 60 and stored in an air tight container.

Preparation of butanolic extract of *H. isora* roots

The dried root powder (5 kg) of *H. isora* was extracted with 80% aqueous ethyl alcohol at room temperature by maceration for seven days. To the concentrated ethanolic extract, 500 ml water was added and fractionated with chloroform, ethyl acetate and butyl alcohol. The yields of chloroform, ethyl acetate, butanol and left over aqueous extracts were 0.48, 0.25, 0.90 and 0.55% w/w respectively. The butanolic extract was used in the present study.

Animals

Male Wistar albino rats (160-180 g) were used for the study and procured from M/S. Mahaveer Agencies, Hyderabad. They were fed with standard diet (Hindustan lever, India) and water *ad libitum*. Animals were maintained in standard environmental conditions throughout the experiment during quarantine period. Animals described as fasted have been deprived of food for 16 h but had been allowed free access to water. The experiment was carried out according to the Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA) guidelines and the Institutional Animal Ethics Committee approved all the procedures.

Induction of diabetes

Diabetes was induced by single *intraperitoneal* injection of STZ (Sigma-Aldrich, Milwaukee, WI, USA) at a dose of 65 mg/kg in 0.1 M citrate buffer. Since STZ is capable of producing hypoglycemia as a result of massive pancreatic insulin release, rats were treated with 10% glucose solution. Five days later blood samples were drawn and glucose levels were determined to confirm the development of diabetes (>250 mg/dl).

Effect of *H. isora* root extract on STZ induced diabetic rats [13,14]

The fasted diabetic rats were divided into four groups each containing 6 animals. Control rats (Group I) received distilled water orally, while the butanol extract at a dose of 125 and 250 mg/kg were given orally to the animals of II and III groups. Group IV animals served as positive control and received glibenclamide (5 mg/kg). Group V served as normal group which received distilled water. 100 µl of blood samples were collected just prior to and at 1, 3 and 5 h after drug administration from retro orbital puncture. Plasma was separated and glucose levels were measured by glucose oxidation method using commercially available diagnostic kits (Span Diagnostics, India).

The action of *H. isora* roots was also tested after a longer duration of treatment [15]. The diabetic rats were divided into 4 groups of 10 rats each. Group I served as untreated diabetic control and received distilled water. Group II and III animals received *H. isora* butanolic extract 125 and 250 mg/kg, respectively as a fine aqueous suspension orally. Group IV animals served as positive control and received glibenclamide orally at a dose of 5 mg/kg. Group V served as normal group and received distilled water. Treatment was continued for 10 consecutive days, once daily. Blood samples were collected just prior to and on days 1 and 10 of extract administration. Plasma samples were used to measure glucose, total cholesterol, triglycerides and urea levels (Span Diagnostics, India).

Determination of DPPH radical scavenging activity [16,17]

A commercially available and stable free radical DPPH (2, 2-diphenyl-1-picryl hydrazyl) soluble in methanol was used to evaluate the antioxidant potential of *H. isora*. DPPH in its radical form has an absorption peak at 517 nm, which disappears on reduction by an antioxidant compound. Different concentrations of the butanolic extract (10-100 µg/ml) were added to 2 ml of freshly prepared DPPH solution. Absorbance was measured at 517 nm, 1 h after the reaction started. The percentage inhibition of DPPH in the reaction medium (% Radical Scavenging Capacity) was calculated by comparison with the control. Curcumin was used as standard. From the obtained % Radical Scavenging Capacity (%RSC) values, the IC_{50} value was calculated which represents the concentration of the scavenging compound that caused 50% neutralization. IC_{50} value was obtained by linear regression method using % activity and concentration.

%RSC was calculated by the following formula:

%RSC = 100 x (ABLANK – ASAMPLE)/ABLANK

ABLANK – absorbance of the reagent blank

ASAMPLE - absorbance of the sample

Determination of total phenolic compounds

The total phenolic compounds in butanolic extract of *H. isora* root was determined by using Folin Ciocalteau Phenol Reagent method and absorbance was determined at 760 nm [18,19]. Gallic acid was used as standard. The total phenolic content in the extract was expressed as mg/gm of Gallic Acid Equivalents (GAE).

Statistical analysis

All values were expressed as mean ± SEM. Results were analysed statistically by using Analysis Of Variance (ANOVA) followed by Dunnett's test. Values of $p < 0.05$ were considered significant.

Results

The results of butanolic extract of *H. isora* root in STZ induced diabetic rats are presented in Table 1. The fasting blood glucose levels of diabetic rats were 260-290 mg/dl. The significant fall in blood glucose levels at both the test dose levels were observed from 1 h after the extract administration. The butanolic extract at a dose of 250 mg/kg showed highest blood glucose lowering action at 3 h (47%), while at 125 mg/kg dose the reduction is 39%. Treatment of diabetic rats with standard glibenclamide produced 15% reduction of blood glucose. In untreated diabetic animals the blood glucose levels did not change significantly.

Similar results were also observed upon sub chronic administration of *H. isora* root butanolic extract. The blood glucose levels of STZ alone treated group significantly increased from 76 to 305 mg/dl. During the course of 10 day treatment there was no

Table 1: Effect of *Helicteres isora* root extract on blood glucose levels in streptozotocin induced diabetic rats.

Group	Concentration (mg/dl)			
	Pre-treatment	After treatment		
	Initial	1 h	3 h	5 h
I Diabetic untreated	292.22 ± 1.43	290.93 ± 1.27	290.54 ± 1.66	292.99 ± 1.40
II Butanol extract 125 mg/kg)	286.58 ± 1.65	207.79 ± 2.20** (29.49%)	172.35 ± 3.44** (39.85%)	244.56 ± 0.3.67* (14.66%)
III Butanol extract (250 mg/kg)	273.99 ± 1.35	185.66 ± 3.19** (32.23%)	156.82 ± 2.38** (47.26%)	234.93 ± 4.30** (14.24%)
IV Gilbenclamide (5 mg/kg)	265.62 ± 1.00	227.33 ± 4.03** (14.41%)	227.46 ± 1.85** (15.11%)	218.75 ± 2.05** (17.26%)
V Normal	79.39 ± 1.12	79.84 ± 0.67	79.55 ± 0.91	79.77 ± 0.75

Values are mean ± S.E.M; *n*=6; *p < 0.05, **p < 0.01: are in comparison with the initial blood glucose levels of the rats in the respective group; Figure in parentheses indicate the % decrease in blood glucose.

Table 2: Effect of continued administration of *Helicteres isora* on glucose, total cholesterol, triglycerides and urea levels in streptozotocin induced diabetic rats.

Group	Treatment	Dose (mg/kg)	Concentration (mg/dl)		
			Initial	Day 1	Day 10
Effect on glucose					
I	Diabetic untreated	---	305.41 ± 2.82	309.09 ± 2.94	310.21 ± 3.55
II	Butanol extract	125	319.09 ± 2.70	239.81 ± 2.67*** (24.84%)	185.43 ± 2.72*** (41.88%)
III	Butanol extract	250	307.47 ± 2.50	200.40 ± 3.43*** (34.82%)	140.88 ± 1.72*** (54.18%)
IV	Glibenclamide	5	311.47 ± 2.84	267.30 ± 3.37*** (14.17%)	227.54 ± 2.32*** (26.94%)
V	Normal	---	76.82 ± 1.34	78.55 ± 0.83	79.28 ± 1.14
Effect on total cholesterol					
I	Diabetic untreated	---	100.02 ± 2.37	95.01 ± 2.18	89.11 ± 2.07
II	Butanol extract	125	120.27 ± 1.46	118.79 ± 1.87 (2.06%)	115.03 ± 2.56 (4.35%)
III	Butanol extract	250	115.95 ± 1.72	107.57 ± 2.57 (7.22%)	90.83 ± 2.01*** (21.66%)
IV	Glibenclamide	5	105.57 ± 1.94	101.79 ± 1.87 (3.58%)	85.16 ± 2.31*** (19.33%)
V	Normal	---	59.68 ± 0.89	60.48 ± 0.77	62.06 ± 0.83

Values are mean ± S.E.M; n=10; *p < 0.05, **p < 0.01, ***p < 0.001: are in comparison with the initial blood glucose levels of the rats in the respective group; Figure in parentheses indicate the % decrease in the respective parameter.

significant change in the blood glucose levels of untreated diabetic animals. Continuous administration of butanolic extract was found to significantly decrease the blood glucose levels at both the test dose levels.

Effect on glucose

Continuous administration of butanolic extract of *H. isora* shows significant (p< 0.001) antihyperglycemic effect. The results are shown in Table 2. The plasma glucose levels markedly increased over 4-folds in diabetic control when compared to the normal rats on the initial and 10th day of the experiment. Ten days of daily treatment with butanolic extract of H. *isora* has shown a dose dependent fall in blood glucose by 41 and 54% at 125 and 250 mg/kg, respectively. Glibenclamide has produced 26% reduction in blood glucose levels on day 10. In untreated diabetic rats there was no significant difference of plasma glucose levels during the course of the experiment.

Effect on cholesterol

The effect of *H. isora* butanolic extract and glibenclamide on plasma total cholesterol is presented in Table 2. The total cholesterol levels were higher in untreated diabetic rats (100 mg/dl) compared to normal rats (59 mg/dl). Administration of butanolic extract at both the dose levels has produced a significant fall in total cholesterol. The decrease in total cholesterol in 250 mg/kg butanol extract (Group III) treated animals is significantly higher and percent decrease in total cholesterol was over four folds than 125 mg/kg (Group II) treated animals. In glibenclamide treated rats the decrease in cholesterol was found to be 19% on day 10.

Effect on triglycerides

Butanolic extract at a dose of 250 mg/kg produced a gradual decrease in triglyceride levels and the percent decrease in triglyceride on day 10 was 16, however there was no activity observed on triglycerides on treatment with 125 mg/kg butanolic extract. The activity exerted by glibenclamide and butanolic extract (250 mg/kg) was more or less significantly (p<0.001) same on day 10. Inter group comparison reveals that butanolic extract at a dose of 250 mg/

Table 3: Effect of continued administration of *Helicteres isora* on triglycerides and urea levels in streptozotocin induced diabetic rats.

Group	Treatment	Dose (mg/kg)	Concentration (mg/dl)		
Effect on Triglycerides			**Initial**	**Day 1**	**Day 10**
I	Diabetic untreated	-	120.66 ± 4.103	125.25 ± 3.89	130.84 ± 4.73
II	Butanol extract	125	120.42 ± 3.54	114.13 ± 3.55 (4.55%)	118.02 ± 3.78 (1.99%)
III	Butanol extract	250	130.84 ± 2.14	121.52 ± 3.30 (7.12%)	109.63 ± 2.48*** (16.21%)
IV	Glibenclamide	5	126.05 ± 3.64	111.52 ± 2.70** (11.52%)	105.34 ± 3.35** (16.42%)
V	Normal	---	75.57 ± 2.16	78.01 ± 2.48	80.60 ± 2.45
Effect on urea					
I	Diabetic Untreated	---	43.81 ± 2.72	44.16 ± 2.54	46.14 ± 3.33
II	Butanol extract	125	41.85 ± 2.92	38.99 ± 2.92 (6.83%)	34.73 ± 2.75 (17.01%)
III	Butanol extract	250	39.3 ± 2.17	31.94 ± 1.50* (18.72%)	29.15 ± 1.72** (25.82%)
IV	Glibenclamide	5	45.62 ± 2.91	42.71 ± 2.64 (6.37%)	39.08± 3.37 (16.73%)
V	Normal	---	26.49 ± 1.09	26.03 ±1.96	27.45 ± 1.76

Values are mean±S.E.M; n=10; *p < 0.05, **p < 0.01, ***p < 0.001: are in comparison with the initial blood glucose levels of the rats in the respective group; Figure in parentheses indicate the % decrease in the respective parameter.

kg has reduced the plasma triglyceride levels significantly on day 10 indicating its antihypertriglyceridemic action following continuous daily administration for 10 days compared to animals receiving 125 mg/kg butanolic extract. In diabetic untreated group, increased triglyceride level was observed on day 10 (Table 3).

Effect on urea

Results pertaining to effect of butanolic extract on plasma urea levels are presented in Table 3. In untreated diabetic animals the urea levels were increased over 2 folds compared to the normal rats (26.49 to 43.81 mg/dl). Administration of butanolic extract for 10 days with 125 and 250 mg/kg caused a significant dose dependent fall in urea levels by 17 and 25%, respectively. Glibenclamide caused a non significant reduction of 16% in urea levels on day 10 of its oral administration.

Antioxidant activity and total phenolic content

The butanolic extract of *H. isora* was found to exhibit antioxidant activity in a concentration dependent manner. Stable free radical DPPH was effectively scavenged by butanolic extract and the inhibition was found to be dose dependent. The IC_{50} was found to be 26 µg/ml. The IC_{50} value of standard curcumin was found to be 8 µg/ml. The results are shown in Table 4. The total phenolic content in butanolic extract of *H. isora* roots was 480 ± 3.24 mg GAE/g of the extract.

Table 4: Effect of *Helicteres isora* root extract on DPPH Radical Scavenging Capacity.

Concentration mg/ml	DPPH Radical Scavenging Capacity	
	Percentage Inhibition	
	Butanolic Extract	Curcumin
10	-	64.49 ± 1.576
20	33.45 ± 2.55	76.08 ± 1.076
30	59.92 ± 1.51	73.91 ± 1.079
40	65.80 ± 1.306	74.27 ± 1.406
50	77.205 ± 0.668	73.91 ± 2.347
60	78.673 ± 0.765	75 ± 1.749
70	82.352 ± 1.607	72.82 ± 1.759
80	81.61 ± 1.793	71.73 ± 2.103
90	82.35 ± 1.113	72.1 ± 1.834
100	-	78.26 ± 3.178
IC_{50} Value	26 µg/ml	8 µg/ml

Values are mean ± SEM

Discussion

In traditional medicine *H. isora* roots are claimed to be useful in diabetes and is proved to be correct. The antidiabetic potential of *H. isora* root extracts of different polarities was investigated earlier in different models (glucose and alloxan induced diabetic rats). It was concluded that the butanolic extract of *H. isora* root possesses a significant antihyperglycemic [6] and hypolipidemic activity in glucose and alloxan induced diabetic rats [7,8]. Thus in the present investigation the potential of butanolic extract was further investigated at a dose of 125 and 250 mg/kg in streptozotocin induced diabetic rats. In order to substantiate the antidiabetic effect of *H. isora* root, we characterized the antihyperglycemic properties of butanolic extract by studying its effect on carbohydrate and lipid metabolism in STZ induced diabetic rats. The induction of diabetes by alloxan and streptozotocin are different [20]. As a result it is essential to know the antidiabetic activity in STZ induced diabetic rats.

The results of the present study indicate that *H. isora* butanolic extract was found to reduce the glucose, total cholesterol and urea levels at an oral dose of 250 mg/kg in STZ induced diabetic rats. The oral route of administration was preferred as it is simple and physiological. The continuous administration of butanolic extract of *H. isora* root (125 and 250 mg/kg) has produced a dose dependent fall in blood glucose by 41 and 54%, respectively on day 10. Glibenclamide has produced 26% reduction in blood glucose levels.

The rise in blood glucose levels in STZ induced diabetic rats is accomplished by a rise in total cholesterol and triglyceride levels [15]. In the present study, significant increase was observed in our experiment in accordance with these studies. Under normal circumstances insulin activates the enzyme lipoprotein lipase and hydrolyses triglycerides [21]. In insulin deficient subjects it fails to activate the enzyme and causes hypertriglyceridemia. In the present study the butanolic extract at 250 mg/kg and glibenclamide at 5 mg/kg had significantly lowered the triglyceride levels which may be attributed to the increase in insulin production in STZ induced hyperglycemic animals by activation of the enzyme lipoprotein lipase. Thus the decrease in triglyceride levels could be through its control of hyperglycemia which is in agreement with earlier reports that with improved glycemic control following sulfonyl urea therapy there are decreased levels of serum triglycerides [22]. The treatment of animals with butanolic extract has shown a significant reduction in total cholesterol which indicates the roots of *H. isora* are useful in reducing diabetic complications of hypercholesterolemia and hyperglycemia which coexist in diabetic patients. The rise in blood glucose levels in diabetes is always accompanied by an increase in urea levels. The present study also indicates that *H. isora* can partially inhibit STZ induced renal toxicity as seen from blood urea levels.

Alloxan and STZ are chemical diabetogens widely used to induce experimental diabetes in animals. The cytotoxic action of both these diabetogenic agents is mediated by reactive oxygen species. However, the source of their generation is different in the case of alloxan and streptozotocin. Alloxan produces superoxide radicals which undergo dismutation to hydrogen peroxide. Thereafter highly reactive hydroxyl radicals are formed by the fenton reaction. With alloxan, the action of reactive oxygen species with the simultaneous massive increase in cystolic calcium concentration causes rapid destruction of β-cells.

Streptozotocin enters β-cells via a Glucose Transporter (GLUT 2) causing alkylation of DNA eventually leading to cell death and diabetes. Furthermore, STZ liberates toxic amounts of nitric oxide that inhibit aconitase activity and participates in DNA damage. As a result of STZ action, β-cells undergo destruction or necrosis [23].

Enhanced ATP dephosphorylation after STZ treatment supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals. Consequently hydrogen peroxide and hydroxyl radicals are generated and causes tissue injury. Thus the pancreas is especially susceptible to the action of STZ induced free radical damage where β-cells undergo destruction by necrosis. The butanol extract of *H. isora* root has effectively scavenged the stable free DPPH radical *in vitro*, indicating that administration of butanolic extract of *H. isora* root can reduce the levels of free radical as well as ameliorate the destruction of β-cells of pancreas and confirm the possibility that the major function of the extract is in protection of vital tissues including the pancreas, thus reducing the causation of diabetes in these animals.

Phytochemically, the butanolic extract of *H. isora* contained tannins, sterols and triterpenoids and their glycosides and carbohydrates [6]. Tannins are widely known for their antioxidant properties to scavenge the free radicals. The total phenolic content of butanolic extract is 480 mg GAE/g of the extract. The observed antihyperglycemic actrivity may be attributed to tannins because earlier reports reveal that a tannin epicatechin [24] and tannins of *Pterocarpus marsupium* [25] have pronounced antihyperglycemic activity by stimulation and regeneration of β-cells to secrete insulin.

Conclusion

The treatment with butanolic extract at a dose of 250 mg/kg of *H. isora* root caused significant antihyperglycemic and hypolipidemic activity in STZ induced diabetic rats. These results confirmed our earlier reports on the alloxan induced antidiabetic properties. The effective dose of *H. isora* can be concluded as 250 mg/kg. Thus the butanolic extract of *H. isora* root can be considered as a potent antidiabetic agent. Estimation of insulin level and insulin receptor may give more insight into the mechanism of antidiabetic activity shown by the butanolic extract. The active ingredient in the extract which is exactly responsible to reduce the blood sugar is not known at present.

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