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ANTIHYPERGLYCEMIC AND ANTIHYPERLIPIDEMIC ACTIVITY OF ROOT EXTRACTS OF *ERYTHRINA VARIEGATA* IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT

Hypoglycemic and hypolipidemic activity of alcohol and aqueous root extracts of *Erythrina variegata* Linn. is evaluated in streptozotocin induced diabetic rats. Diabetes was induced into albino Wistar rats by intraperitonial administration of streptozotocin (STZ, 50mg/kg). Blood samples were collected from overnight fasted normal and diabetic rats on 0^{th}, 7^{th}, 14^{th} and 21^{st} days of treatment. Hypoglycemic activity was evaluated by measuring serum glucose level and glycosylated haemoglobin level after dosing with 300 mg/kg and 600 mg/kg of both the extracts. Hypolipidemic activity was evaluated by measuring various biochemical parameters like total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein, high density lipoprotein and phospholipids. The results showed that the extracts significantly ($P<0.001$, $p<0.01$) reduced fasting blood glucose of streptozotocin diabetic rats in a dose-related manner, when compared to control and standard (Glibenclamide 500µg/kg). Both the extracts also have a significant recovery in the levels of parameters measured in lipid profile, when compared to control and standard group. Hence this plant may be a potential source for the isolation of new orally active agent(s) for diabetic mellitus. The present investigation established pharmacological evidence to support the folklore claim that it is used as hypoglycemic and hypolipidemic agent.

KEYWORDS: *Erythrina variegata*, Streptozotocin, Glibenclamide, Diabetes.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting approximately 10% of the global population. Besides hyperglycemia, several other factors including dislipidemia or hyperlipidemia are involved in the development of micro and macro vascular complications of diabetes which are the major causes of morbidity and death.[1] The increasing incidence of the disease worldwide may be due to sedentary life style, unhealthy diet, obesity and other predisposing risk factors.[2] It is projected to become of the world's main disablers and killers, as the number of people with diabetes multiplies worldwide. The disease has taken an ever increasing share of national and international healthcare budgets.[3]

Currently, the available therapy for diabetes includes insulin and various oral anti-diabetic agents such as sulfonylureas, metformin, etc. These drugs are used as monotherapy or in combination to achieve better glycemia control. However, in the indigenous system of medicine good numbers of plants are mentioned for the cure of diabetes and some of them have been experimentally evaluated and active principles were isolated. WHO has also recommended the evaluation of the effective use of plants, because of the modern drugs are not safe. The synthetic hypoglycemic agents used in clinical practices have serious side effects like haematological effects, coma, disturbances of liver and kidney. Compared with synthetic drugs, drugs derived from plants are frequently considered to be less toxic with fewer side effects.[4] In the present scenario, the demand for herbal products is growing exponentially throughout the world and major pharmaceutical companies are currently conducting extensive research on plant material for their potential medicinal value.[5]

The main objective of the study was to assess the hypoglycemic and hypolipidemic potential of roots of Indian coral tree *Erythrina variegata* belonging to the family Leguminosae. It is known as "Dadap" in Hindi.[6] The plant grows in tropical low lands with moderate rainfall approximately 1000-1500mm. It is a medium sized deciduous ornamental small tree with prickly stem and branches. Leaves are alternate, compound, trifoliate, entire margin, lanceolate stipules and leaflets are commonly triangular medium to light green, heart shaped. Flowers are large; emerge in dense, orange red colour. Flowering is normally followed by lavish production of seeds. The pods are thick and black in colour. Each pod contains 5-10 reniform seeds. These are glossy brown in colour.[7]

Different parts of the plant have been used as traditional medicine in nervine sedation, opthalmia, asthma, epilepsy and skin diseases. The bark of the plant is astringent, febrifuge,

anti-bilious and anthelmintics. The bark and leaves are used in many traditional medicines, including paribhadra, an Indian preparation said to destroy pathogenic parasites and relieve joint pain. The leaves are used in fever and inflammation. The Juice of the leaves is mixed with honey and ingested to kill tapeworm, roundworm and threadworm. The juice of the leaves is also used to relieve ear ache and toothache. The roots are used as bronchitis, febrifuge and as an insecticide. The roots are also used in the treatment of cancer, convulsions and to treat pimples. It has the reputation to stimulate lactation and menstruation and is used as laxative, diuretic and expectorant. Although many compounds have been reported from the genus, *Erythrina*, previous phytochemical investigations with *E. variegata* revealed the occurrences of orientanol B, erycristagallin, cristacarpin, sigmoidin K, 2-(γ,γ-dimethylallyl)- 6a-hydroxyphaseollidin, erystagallin A, eryvarins A and B, bidwillon B, eryvarins F and G, alpinum isoflavone, isococculinine, decarbomethoxyerymelanthine, erysodienone, erythritol, erysodine, erysovine, stachydrine, sterols, fixed oils and fatty acids.[8,9,10] Hypoglycemic and hypolipidemic activity of alcohol and aqueous root extracts of *Erythrina variegata* has been studies in alloxan induced diabetic rats.[11] In the current literature, there is not much data concerning the effect of *Erythrina variegata* in streptozotocin induced diabetic rats. Therefore, the present study has been planned to investigate the effect of extracts in streptozotocin induced diabetic rats and to compare it with diabetic untreated and glibenclamide as a reference standard.

2. MATERIALS AND METHODS

2.1. Drugs and Chemicals

The following drugs and chemicals were used in the experiment: Streptozotocin was purchased from Sigma Aldrich chemical Co, Bangalore, India and Glibenclamide was purchased from Bal Pharma, Bangalore, India. Diagnostic kits of Glycosylated haemoglobin was purchased from Coral Clinical System, Goa, India and diagnostic kits of cholesterol, phospholipids, triglycerides, HDL, VLDL and LDL were purchased from Span diagnostics Ltd., Surat, India and rest all other reagents and chemicals were of analytical grade.

2.2. Plant Material

The roots of *Erythrina variegata* were collected from the vicinity of Tirunnelveli (Tamil Nadu, India). Taxonomic identification was carried out by V. Chelladurai, Research Officer-Botany (Retired scientist-CCRAS). A voucher specimen (JCNagar) was deposited in the herbarium of the department of Pharmacognosy in the college for future reference.

The collected roots were washed thoroughly in tap water to remove any unwanted matter and then dried under shade for two to three weeks. After complete drying, roots were pulverized into coarse powder. The powder stored in airtight container in cool & dark place to prevent deterioration by elevated temperature, light and moisture.

2.3. Preparation of Crude Extracts

Coarsely powdered, shade dried roots of *Erythrina variegata* was charged into a soxhlet apparatus and successive hot extraction was carried out using ethanol (70% v/v) for 24 h. The liquid extract was concentrated in rotary flash evaporator at a temperature not exceeding 50ºC (yield 6.5% w/w). The alcohol extract was formulated as a suspension in distilled water using 2% v/v Tween-80 as suspending agent for animal studies.

The aqueous extract was prepared by maceration method. The coarsely powder of roots kept with chloroform water for 24h. The macerate was filtered and filtrate concentrated in rotary flash evaporator (yield 9.6% w/w). Aqueous extract was prepared by dissolving in distilled water for animal studies. The extracts were preserved in desiccators for further experiments.

2.4. Animals Used

Swiss albino mice weighing 20-30g and albino rats (Wistar strain) weighing 170±10g of either sex were used for the study. The animals were procured and housed in the animal house at least 2 weeks prior to the study, for acclimatization. Animal house was well maintained under standard hygienic conditions, at a temperature (15-20±5°C), room humidity (60%±10%) with 12 h day and night cycle with food and water *ad libitum*. All the pharmacological experiments were as per CPCSEA (Committee for the Purpose of Control and Supervision on Experiments on Animals) norms after obtaining approval of the Institutional Animal Ethics Committee (Reg.No.870/ac/08/CPCSEA).

2.5. Acute Toxicity Studies

These studies were carried out to study the acute toxic effects and determine minimum lethal dose of the drug extracts. Swiss albino mice of either sex weighing between 20-30 g fasted overnight, were used for the study. Each extract was orally administered at doses of 30, 100, 300, 1000 and 3000 mg/kg body weight to separate groups of mice. Subsequent to administration of drug extracts, the animals were observed closely for the first three hours, for any toxic manifestations, like increased motor activity, salivation, clonic convulsions,

coma and death. Subsequently observations were made at regular intervals for 24 hours. The animals were under further investigation up to a period of 1 week.[12]

2.6. Induction of Diabetes Mellitus

In the present work streptozotocin (50 mg/kg) dissolved in 0.1M-citrate buffer (pH 4.5) was used to induce hyperglycemia in overnight fasted animals by intraperitonial injection. The fasting blood glucose levels were determined after 48 hours of streptozotocin administration.[13] Rats having blood glucose level above 200 mg/dl were selected for the study. Diabetic rats were divided in six groups; each group comprised of six rats.[14]

Group 1 - Normal control.
Group 2 - Positive control-Untreated streptozotocin diabetic rats.
Group 3 - Standard- Streptozotocin diabetic rats treated with glibenclamide (500µg/kg, p.o.).
Group 4 - Streptozotocin diabetic rats treated with aqueous extract (300mg/kg, p.o).
Group 5 - Streptozotocin diabetic rats treated with aqueous extract (600mg/kg, p.o).
Group 6 - Streptozotocin diabetic rats treated with alcohol extract (300mg/kg, p.o).
Group 7 - Streptozotocin diabetic rats treated with alcohol extract (600mg/kg, p.o).

Doses of aqueous extract, alcohol extract, standard drug and normal saline were calculated according to the body weight of each animal. Suspension of extracts, standard drug and normal saline were administered orally to each animal using stainless steel feeding needle fitted on a plastic syringe. The treatment schedule was once daily for 21 days and animals were fed on laboratory diet of pellet chow and water *ad libitum*. They were fasted for 18 h prior to blood withdrawal.

2.7. Determination of Hypoglycemic Activity

Blood samples were collected by orbital sinus puncture under mild ether anaesthesia. Serum was separated by centrifuging blood at 6000rpm for 15 minutes. Serum glucose estimation was performed on 0^{th}, 7^{th}, 14^{th} and 21^{st} day by end point method using Autochem Nexgen semi autoanalyzer (Span diagnostics, Surat, India) with the help of glucometer (Glucochek, Surat, India). On 21^{st} day estimation of glycosylated hemoglobin was also performed using UV- visible spectrophotometer (Systronic 2203) with the help of Glycohemoglobin reagent kit (Coral Clinical System, Goa, India).

2.8. Determination of Hypolipidemic Activity

Blood samples were collected by orbital sinus puncture under mild ether anaesthesia on 21st day from the start of treatment. Serum was separated and analyzed for various biochemical parameters – Cholesterol, Triglycerides, HDL, LDL, VLDL and Phospholipids by using various kits (Span diagnostics Ltd., Surat, India).

2.9. Statistical Analysis

The data obtained were statistically analyzed by one way analysis of variance (ANOVA) and expressed as mean ± S.E.M. followed by Tukey Kramer Multiple Comparison Test using instat software.

3. RESULTS

3.1. Acute Toxicity Studies

Acute toxicity study revealed the nontoxic nature for both the extracts. There was no mortality and no toxic reactions found at any of the doses tested until the end of the study period. As per OECD guidelines, therapeutic range was considered between 1/10 to 1/5 times of LD_{50}. Accordingly, 300 mg/kg and 600 mg/kg BW doses for both the extracts were selected for determination of pharmacological studies.

3.2. Hypoglycemic Activity

Hypoglycemic activity of aqueous and alcohol extracts of *Erythrina variegata* were evaluated in streptozotocin induced diabetic rats. Administration of streptozotocin increases the serum glucose level in normal rats. The effects of extracts and glibenclamide on serum glucose level in diabetic rats are depicted in table 1. The fall in serum glucose levels of the extracts and glibenclamide treated groups were compared with that of positive control (diabetic untreated) group. Both aqueous and alcohol extracts showed significant hypoglycemic effect in comparison with positive control group on 7th day itself. The continuous treatment for three weeks leads to a dose dependent fall in serum glucose level. The dose of 600mg of both the extracts decreases the serum glucose level towards normal level. The concentrations of serum glycosylated haemoglobin level in diabetic rats are depicted in table 2. The concentration of serum glycosylated haemoglobin level also found significant when compared to positive control group.

Administration of 300mg/kg of aqueous extract showed 25.43%, 48.33%, 64.42% decline in glucose levels of experimental animals on day 7th, 14th, 21st respectively. The glycosylated

haemoglobin level also decreases 51.25%, when compared to diabetic control group. Administration of 600mg/kg of aqueous extract showed 32.16%, 50.27%, 65.23% decline in glucose levels of experimental animals on day 7th, 14th, 21st respectively. The glycosylated haemoglobin level also decreases 57.80%, when compared to diabetic control group. Administration of 300 mg/kg of alcohol extract showed 24.22%, 48.06%, 64.27% decline in glucose levels of experimental animals on day 7th, 14th, 21st respectively. The glycosylated haemoglobin level also decreases 53.75%, when compared to diabetic control group. Administration of 600mg/kg of alcohol extract showed 35.26%, 55.12%, 65.03% decline in glucose levels of experimental animals on day 7th, 14th, 21st respectively. The glycosylated haemoglobin level also decreases 58.15%, when compared to diabetic control group.

Table-1: Effect of aqueous and alcohol extracts of roots of *Erythrina variegata* on serum glucose level in streptozotocin induced diabetic rats.

Groups	Serum glucose level on			
	0th day	7th day	14th day	21st day
Normal control	120.24±3.21	116.99±2.15	120.76±1.84	120.95±2.40
Positive control	370.55±9.29	391.66±10.72	403.46±9.71	408.80±6.14
Std. (Glibenclamide)	374.47±11.83	240.32±11.85***	161.42±6.75***	124.80±4.37***
Aq. Ex. (300mg/kg)	393.13±9.97	293.13±9.10***	203.13±5.80***	139.85±4.77***
Aq. Ex. (600mg/kg)	375.79±9.01	254.93±9.76***	186.76±5.43***	130.65±2.84***
Alc. Ex. (300mg/kg)	381.04±8.95	288.73±9.53***	197.91±9.92***	136.11±3.37***
Alc. Ex. (600mg/kg)	373.22±7.59	241.62±6.79***	167.50±7.14***	130.51±3.38***

Std.- Standard, Aq. Ex.- Aqueous Extract, Alc. Ex.-Alcohol Extract.

Values expressed as Mean ± SEM. One way ANOVA (*** $p < 0.001$).

Tukey Kramer Multiple Comparison Test in comparison with diabetic control group.

Table-2: Effect of aqueous and alcohol extracts of roots of *Erythrina variegata* on glycosylated hemoglobin conc. on 21st day.

Groups	Glycosylated hemoglobin conc.
Normal control	4.06 ± 0.08
Positive control	11.59 ± 0.19
Standard (Glibenclamide)	4.18 ± 0.14***
Aqueous extract (300mg/kg)	5.65 ± 0.25***
Aqueous extract (600mg/kg)	4.89 ± 0.07***
Alcohol extract (300mg/kg)	5.36 ± 0.22***
Alcohol extract (600mg/kg)	4.85 ± 0.07***

Values expressed as Mean ± SEM. One way ANOVA (*** $p < 0.001$).

Tukey Kramer Multiple Comparison Test in comparison with diabetic control group.

3.3. Hypolipidemic Activity

The lipid profiles of normal control, positive control, glibenclamide and extracts treated diabetic rats are depicted in table-3 and 4. In streptozotocin induced diabetic rats there was a significant increase in total cholesterol, triglycerides, phospholipids, LDL-cholesterol, VLDL-cholesterol and significant decrease in HDL-cholesterol in serum, when compared to normal control. The extracts and glibenclamide treated rats were significantly decrease the total cholesterol, triglycerides, phospholipids, LDL-cholesterol, VLDL-cholesterol and increase the HDL-cholesterol on day 21. Both the extracts showed almost same effect on serum glucose level. In the diabetic untreated rats the lipid profile levels remained higher without much change during the study period of 21 days.

Table-3: Effect of aqueous and alcohol extracts of roots of *Erythrina variegata* on different parameter in streptozotocin induced diabetic rats on 21st day.

Groups	Changes in mg/dL level		
	Serum HDL	Serum LDL	Serum VLDL
Normal control	23.20± 0.91	33.99 ± 1.79	14.17 ± 0.61
Positive control	14.05± 0.47	74.83 ± 2.14	34.71 ± 1.84
Standard (Glibenclamide)	20.35±0.62***	37.78± 0.93***	17.85 ± 0.77***
Aqueous extract (300mg/kg)	16.94±0.38**	49.96±0.98***	25.94±1.55***
Aqueous extract (600mg/kg)	18.77± 0.36***	41.54±1.34***	20.03 ± 0.83***
Alcohol extract (300mg/kg)	17.05±0.41**	48.59±1.61***	25.91±1.32***
Alcohol extract (600mg/kg)	19.16±0.33***	40.65±1.10***	18.05±0.66***

Values expressed as Mean ± SEM. One way ANOVA (*** $p < 0.001$, ** $p < 0.01$).

Tukey Kramer Multiple Comparison Test in comparison with diabetic control group.

Table-4: Effect of aqueous and alcohol extracts of roots of *Erythrina variegata* on different parameter in streptozotocin induced diabetic rats on 21st day.

Groups	Changes in mg/dL level		
	Cholesterol	Triglycerides	Phospholipids
Normal control	93.42 ± 2.95	95.38 ± 2.45	156.42± 3.65
Positive control	212.41 ± 7.34	175.56± 3.46	249.15± 5.08
Standard (Glibenclamide)	126.09± 2.11***	116.10± 2.23***	168.20± 2.21***
Aqueous extract (300mg/kg)	144.88± 2.07***	137.23± 2.26***	185.97±3.40***
Aqueous extract (600mg/kg)	133.64± 2.74***	122.35± 2.34***	175.16±2.81***
Alcohol extract (300mg/kg)	140.94± 2.36***	136.12±2.86***	188.92±2.32***
Alcohol extract (600mg/kg)	128.27± 1.35***	123.68± 1.47***	174.06±2.94***

Values expressed as Mean ± SEM. One way ANOVA (*** $p < 0.001$).

Tukey Kramer Multiple Comparison Test in comparison with diabetic control group.

4. DISCUSSION

Type I diabetes mellitus is a chronic disease characters by high blood glucose level due to an absolute or relative deficiency or circulating insulin levels. Various types of oral hypoglycemic agents are available along with insulin for treating diabetes mellitus. It is generally accepted that sufonylureas including glibenclamide, produce hypoglycaemia by stimulating the pancreatic β-cells to release more insulin. Reducing hepatic insulin clearance, stimulate the release of somatostatin and suppressing the secretion of glucagon. Sulfonylureas have also been shown to suppress hepatic gluconeogenisis.[15,16]

The present study focused the scientific explanation about the hypoglycemic and hypolipidemic activity for both the extracts of roots of *Erythrina variegata* for the management of streptozotocin induced diabetes. Experimental animals were made diabetic using streptozotocin**.** Streptozotocin selectively destroys the pancreatic insulin secreting β-cells, leaving less active cells and resulting in a diabetic state. The fundamental mechanism underlying hyperglycaemia in diabetes mellitus involves the over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues and studies have shown that the level of blood glucose was elevated in STZ-induced diabetic rats.[17,18,19]

Lipid play an important role in the pathogenesis of complications involved with diabetes mellitus. The elevated level of serum cholesterol, LDL, VLDL, triglycerides and reduced level of HDL possess to be a rises of factor for developing microvascular complication leading atherosclerosis and cardiovascular diseases like coronary heart disease. The abnormal high concentration of serum lipid in diabetic mainly due to increased mobilization of free fatty acids from peripheral fat depots, since insulin inhibits the hormone sensitive lipase, insulin deficiency or insulin resistance may be responsible for dislipidimia.[5]

The present studies provide the introductory approach for the evaluation of its traditional preparations in order to scientifically validate the therapeutic use of *Erythrina variegata* in the control of diabetes as well as maintenance of various biochemical parameters.

5. CONCLUSION

Screening of Ayurvedic drugs/plants for biological activity assumes prime importance to establish physiological action of the drug. To obtain required evidence that will demonstrate

drug's safety and effectiveness for its proposed use, a carefully designed and progressive sequence of preclinical (animal) and clinical (human) studies are undertaken.

This study indicated that both of the extracts of *Erythrina variegata* have potential to decrease blood glucose level as well as improving hyperlipidaemia and to reduce the complications associated with experimental diabetes. This study also supports the folklore usefulness of this plant in the treatment of diabetes. It can be concluded that the roots of this plant could be further investigated for antidiabetic bioactive principles.

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