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Research Article
Hypolipidemic and Hypocholesterolemic Effect of *Elephantopus scaber* in Streptozotocin Diabetic Rats

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Abstract

Background and Objective: *Elephantopus scaber* (Asteraceae) is widely used in traditional system of medicine to treat diabetes and its complications in India. The parts of this herb have been used traditionally for the treatment of a number of diseases in many countries. This plant has been reported to possess several biological properties. This study aims to investigate the anti-cholesterolemic potential of *Elephantopus scaber*, a plant already reported to possess antidiabetic activity. **Methodology:** The present study was conducted to investigate the effect of various extracts of the chosen plant roots on serum lipids in STZ induced diabetic rats. *Elephantopus scaber* methanol, hexane and acetone extracts (150 mg kg^{-1} b.wt.) were administered orally for 60 days to streptozotocin (STZ) (60 mg kg^{-1} b.wt.) induced male diabetic wistar rats. Humulin and glibenclamide were also administered for 60 days to streptozotocin (STZ) (60 mg kg^{-1} b.wt.) induced male diabetic wistar rats. On the 61st day, the animals were sacrificed and the blood collected was tested for cholesterol, LDL, HDL and VLDL, respectively. **Results:** Data was analyzed using analysis of variance and student's t-test and a level of $p<0.05$ was considered statistically significant. Administration of the different extracts of *E. scaber* brought about a significant reduction in serum cholesterol, LDL, VLDL and triglycerides and increase in the HDL-cholesterol in diabetic rats. **Conclusion:** Hence, this study proves the protective and restorative effect of *E. scaber* in reverting the lipid alterations and complications of diabetes. Due to such attributes, *E. scaber* can be a source of potent drug to mitigate the complications of diabetes.

Key words: Diabetes, *Elephantopus scaber*, streptozotocin, HDL, VLDL, LDL

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Competing Interest: The author has declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The quality of life depends on the health status of an individual. The hallmark of diabetes is the presence of hyperglycemia. Because the metabolic syndrome occurs in most people with type 2 diabetes, its presence likely accounts for most of the increased incidence of CVD in type 2 diabetes. According to the World Health Organization, the burden of chronic diseases, including Coronary Heart Disease (CHD), cancers, diabetes and obesity contributed 59% of the 56.5 million deaths reported worldwide[1]. With CHD ranking number one as the main contributor to morbidity and mortality worldwide, there is a significant interest in identifying plants that have cardioprotectant and cardiotonic activity, as well as the phytochemicals responsible for these activities. Artherosclerosis is a major cause for coronary heart disease in humans. Many recent studies have indicated that oxidative modification of Low Density Lipoprotein (LDL), endothelial dysfunction and inflammation are involved in the pathogenesis of artheroclerosis. Although in vitro studies have provided important insights into potential mechanisms by which glucose might damage arterial cells or play a role in atherogenesis, these studies suffer from the shortcoming that they usually examine a single mechanism in isolation and often provide different results from those obtained with *in vivo* studies. Emergence of Cardio Vascular Disease (CVD) is on the increase and experimental studies indicate that high serum level of low density lipoprotein cholesterol (LDL-C) is associated with the cause CVD[2]. There are reports about the increase of CVD due to changes in lifestyle. Although several drugs as statins, fibrates, nicotinic acid and resins are available to lower blood cholesterol level, they exhibit a lot of side effects. Hence, there is a greater demand for safer alternatives. It is known that several plants possess hypoglycemic activity. Though these reports are available, yet their combined activity on diabetes and its associated CVD has not been much discussed. Hence, experiments on animal models are required to validate the combined effect of the plant and thus the current work was undertaken.

Though different types of oral hypoglycemic agents are available along with insulin for the treatment of diabetes mellitus, they have prominent side effects and are found toxic on prolonged treatment[3,4]. As the knowledge of heterogeneity of this disorder increases, there is a need to look for more efficacious agents with lesser side effects. Because of their perceived effectiveness, minimal side effects in clinical experience and relatively low costs, herbal drugs are prescribed widely even when their biologically active compounds are unknown[5].

Plants used in folk medicine have provided a rich source of drugs for many diseases, including cancer. In traditional system of medicines such as Chinese medicine and Ayurveda, the use of *E. scaber* for treating various illness have been well documented. Using the ethnobotanical approach and bioassay-guided fractionation, several compounds with biological activity were isolated and identified from the plant. Many of these isolations were based on the uses of the agents in traditional medicine which showed pharmacological activities including antiviral, anti-cancer, anti-tumour, anti-diabetic, anti-microbial, anti-inflammatory, anti-oxidant and hepatoprotective effects[6].

MATERIALS AND METHODS

Plant collection and extract preparation: *Elephantopus scaber* (whole plants) (ES) was collected from Palode, Thiruvananthapuram district, Kerala, India during rainy season. The plant parts that were chosen for the study had been washed and air-dried and powdered. About 500 g of *E. scaber* plants yielded 190 g powder. The dried residues were stored in air-tight containers for further use. The procedure was repeated with acetone and hexane, respectively.

Animals: Male adult Wistar strain albino rats (100-150 g) bred in the laboratory of Animal Medicine, Centre for Animal Health Studies, Tamilnadu Veterinary and Animal Sciences University, Madhavaram, Chennai, Tamilnadu, India were used. All the animals were kept and maintained under laboratory conditions of temperature (22+2°C), humidity (45+5%) and 12 h day: 12 h night cycle and were allowed free access to food (standard pellet diet-Sai Durga Feeds and Foods, Bangalore, India) and water *ad libitum*.

Induction of diabetes: Diabetes mellitus was induced in the rats by single intraperitoneal injection of freshly prepared STZ (60 mg kg^{-1} b.wt.) in 0.1 M citrate buffer (pH 4.5) in a volume of 1 mL kg^{-1} b.wt. Diabetes was developed and stabilized in these STZ treated rats over a period of 7 days. After 7 days of STZ administration, rats with fasting blood glucose levels of 280-350 mg dL^{-1} were considered diabetic and included in the study.

Administration of extracts: The plant extracts were poorly soluble in water, hence a suspension of the required quantity of the plant extracts was prepared in 0.1% Carboxy Methyl Cellulose (CMC) (1 mL kg^{-1} b.wt.).

The different extracts of both the plants were administered by force-feeding. This was executed by inserting

a baby oral feeding tube, which was connected to a syringe containing the extract, into the gastric region of the rat. The animals were fasted 30 min before and after treatment to ensure maximum bioavailability[7]. One week after the induction of diabetes, rats with blood glucose>300 mg dL^{-1} were subjected to fasting for 16 h. One week after the induction of diabetes, rats with blood glucose>300 mg dL^{-1} were subjected to fasting for 16 h. They were divided into different groups, with 6 rats in each group. Methanol, acetone and hexane extracts of the plant ranging from 50-500 mg kg^{-1} b.wt., were administered to the animals and blood glucose was estimated at the end of 5 h after the oral administration of the extract[8]. The lowest dose that brought about the maximum anti-hyperglycemic effect for the plant was given through oral intubations for the repeated administration, which was 150 mg kg^{-1} b.wt. The selected dose of the plant extracts (the dosage arrived at after preliminary study for the different extracts) was given daily till completion of the experiment (i.e., 60 days). One week after induction of diabetes in albino rats, the fasting blood glucose levels of fasted rats were measured[9]. Rats with blood glucose >300 mg dL^{-1} were included in the study. They were divided into 7 groups, with 5 rats in each group:

- **Group 1:** Normal rats treated with vehicle alone (Carboxy Methyl Cellulose (CMC) 0.1%; 1 mL kg^{-1} b.wt.)
- **Group 2:** The STZ treated diabetic control-diabetic control group was given distilled water everyday through oral intubations
- **Groups 3-5:** The STZ induced diabetic rats treated with methanol, acetone and hexane crude extracts of ES
- **Group 6:** The STZ induced diabetic rats treated with 0.6 mg kg^{-1} glibenclamide
- **Group 7:** The STZ induced diabetic rats treated with 0.3 IU kg^{-1} humulin for 60 days

Blood testing: Blood was collected from diabetic and treated rats on the 0, 15, 30 and 60th days for biochemical estimations. Blood samples were collected as per the procedure of Kamtchouing *et al.*[10] by cutting the tip of the tail. Serum was assayed either immediately or stored[11] at -20°C. The serum was subjected to several biochemical tests as analysis of lipid profile, which included estimation of total cholesterol (Diagnostic kit-Beacon Diagnostics, Kabilpore, Navsari, India), estimation of triglycerides (Diagnostic kit-Bio Systems, Costa Brava, Spain), estimation of serum HDL-cholesterol (Diagnostic kit-Beacon Diagnostics, Kabilpore, Navsari, India)[12].

Acute toxicity studies: Acute oral toxicity study was performed as per Organization for Economic Co-operation and Development (OECD) guidelines 420. Wistar albino rats of either sex (150-200 g) were used for the study and administered a limit dose of 2000 and 5000 mg kg^{-1} of the hydroalcoholic combined plant extract and animals were observed for mortality and clinical signs for the 1st h, then hourly for 3 h and finally periodically until 48 h. All of the experimental animals were maintained under close observation for 14 days and the number of rats that died within the study period was noted. Behavioural and neurological changes such as tremors, convulsions, salivation, diarrhoea, sleep, lacrimation and feed behaviour in drug treated rats were observed for sign of acute toxicity.

RESULTS AND DISCUSSION

Administration of the different extracts of *Elephantopus scaber* brought about a significant reduction in serum cholesterol, LDL, VLDL and triglycerides and increase in the HDL-cholesterol in diabetic rats (Table 1). The acetone extract of *E. scaber* was more effective in decreasing the serum lipids than the other extracts. This hypolipidemic effect may be due to an increase in insulin secretion that ultimately led to a decrease in the synthesis of cholesterol and fatty acids as seen in Table 1. Abnormalities in lipid profile are one of the most common complications in diabetes mellitus, which is found in about 40% of diabetic[13]. Insulin deficiency or insulin resistance is associated with hypercholesterolemia and hypertriglyceridemia[14]. Diabetes induction causes increase in the cholesterol, triglycerides, LDL and VLDL[15]. The level of serum lipids is usually elevated in diabetes mellitus and such an elevation represents the risk factor for coronary heart disease[16,17]. High levels of total cholesterol and, more importantly LDL-cholesterol, in blood are major coronary risk factors[18]. The abnormal high concentration of serum lipids in the diabetic subjects is due, mainly, to the increase in the mobilization of free fatty acids from the peripheral fat depots, since insulin inhibits the hormone sensitive lipase. Insulin deficiency or insulin resistance may be responsible for dyslipidemia, because insulin has an inhibitory action on HMG–CoA reductase, a key rate-limiting enzyme responsible for the metabolism of cholesterol-rich LDL particles. Acute insulin deficiency initially causes an increase in free fatty acid mobilization from adipose tissue. This results in increased production of cholesterol-rich LDL particles[19]. Administration of soluble dietary fibre fraction of *Trigonella foenum graecum* to diabetic rats lowered total cholesterol. Benwahhoud *et al.*[20] reported that aqueous extract of *Suaeda fruticosa* brought

Table 1: Effect of crude extracts of *Elephantopus scaber* on serum lipid levels in hyperglycemic rats

Parameters	CHOL (mg dL^{-1})	TRIGLY (mg dL^{-1})	HDL (mg dL^{-1})	LDL (mg dL^{-1})	VLDL (mg dL^{-1})
Normal	89.34±0.14	66.27±0.44	59.34±0.29	78.20±0.25	21.6±0.21
Diabetic (STZ-60 mg kg^{-1} b.wt.)	201.60±0.20	149.26±0.26	14.68±0.25	144.26±0.24	47.6±0.22
Diabetic+humulin (0.3 IU kg^{-1} b.wt.)	90.27±0.11	72.60±0.18	52.34±0.17	86.60±0.11	20.7±0.19
Diabetic+glibenclamide (0.6 mg kg^{-1} b.wt.)	98.32±0.13	76.49±0.23	49.20±0.18	92.40±0.17	22.7±0.20
Diabetic+ESM (150 mg kg^{-1} b.wt.)	99.78±0.9	79.54±0.18	50.70±1.4	92.61±0.52	25.62±0.2
Diabetic+ESA (150 mg kg^{-1} b.wt.)	98.40±0.2*	76.82±0.62*	54.00±1.0*	86.48±0.2*	22.7±0.17*
Diabetic+ESH (150 mg kg^{-1} b.wt.)	104.40±0.8	80.71±0.26	49.92±1.6	92.81±0.95	23.45±0.8

Values are Means±SD of 6 rats, *p<0.001, CHOL: Cholesterol, TRIGLY: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein and VLDL: Very low density lipoprotein

about a significant reduction in plasma cholesterol in diabetic rats, while it was reported that root of *Withania somnifera,* when administered to diabetic patients, brought about a significant decrease in serum cholesterol[21]. The crude extract of leaves of *Moringa oleifera* (1 mg g^{-1}) given with high fat diet for a period of 30 days led to decrease in cholesterol levels in serum, liver and kidney. The presence of phytosterol and β-sitosterol in the leaf is presumably the bioactive component with cholesterol lowering property[22].

Significant lowering of total cholesterol and rise in HDL-cholesterol is a very desirable biochemical state for prevention of atherosclerosis and ischaemic conditions. Several studies show that an increase in HDL-cholesterol is associated with a decrease in coronary risk and most of the drugs that decrease total cholesterol also decrease LDL-cholesterol[23]. Though several reports have demonstrated high cholesterol lowering effect by various plants, yet our report of hypolipidemic effect of *E. scaber* is significant since the lowering of cholesterol, triglycerides, LDL and VLDL and increase of HDL values were similar and comparable to the effect of glibenclamide and humulin as shown is Table 1. No behavioural and neurological changes such as tremors, convulsions, salivation, diarrhoea, sleep, lacrimation and feed behaviour in drug treated rats were observed and hence the non toxicity of the plant extract was established by no morphological and behavioural changes in the extract fed rats. This report confirms the traditional use of *E. scaber* for diabetes and its associated CVD. Further studies are underway to establish the exact mechanism of action.

CONCLUSION

The complications of diabetes are more dangerous and increase in cholesterol may lead to cardio vascular disease. Arthrosclerosis is a common disorder due to increase in lipid, especially seen as a diabetic complication. Hence the restoration of the lipid profile by *E. scaber* comparable to the control, suggests the use of the plant as an effective drug possessing anti-hypolipidemic effect.

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