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Research Article
Anti-Diabetic Potential of *Alstonia scholaris* Bark Extract Against Streptozotocin-Induced Diabetes Mellitus

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Abstract

Background and Objective: Traditionally different parts of *Alstonia scholaris* are well known for their widespread medicinal properties. In this study anti-diabetic potential of ethanolic extract of *Alstonia scholaris* bark extract (ASEE) was performed against streptozotocin-induced diabetes in rats. **Materials and Methods:** Animals were categorized into five groups (n = 6) with a treatment period of 30 days. The 1st group was given saline and 2nd group was treated with streptozotocin (50 mg kg^{-1}) and were considered normal control and diabetic control, respectively. The third group was treated with glibenclamide 5 mg kg^{-1} (standard drug), 4th and 5th groups were treated with 200 and 400 mg kg^{-1} doses of ASEE and termed as high and low doses, respectively. Before administration of treatment, all the groups except normal control were intraperitoneally injected with streptozotocin (50 mg kg^{-1}) to induce diabetes. Blood sugar level was evaluated on weekly basis and 24 hrs after the last treatment different biochemical parameters and histopathological examinations were carried out to determine the anti-diabetic potential of ASEE. **Results:** Upon treatment with ASEE, a dose-dependent significant improvement in blood glucose level and serum lipid profile was observed when compared to control groups. Histopathological findings revealed improvement in the regeneration of β-cell of the pancreas in extract-treated rats. **Conclusion:** Ethanolic extract of *Alstonia scholaris* bark possesses anti-diabetic potential in an animal experimental model in a dose-dependent manner.

Key words: *Alstonia scholaris* bark extract, streptozocin, glibenclamide, diabetes mellitus, anti-diabetic, lipid profile

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

INTRODUCTION

Diabetes mellitus (DM) is defined as a metabolic disorder, characterized by the presence of excess glucose levels in the blood with disruption in carbohydrate, fat and protein metabolism caused due to deficiency in the secretion of insulin, inadequate insulin action or both[1]. In 2000, 171 million people were known to have been affected with diabetes, it is estimated that by 2030, the total number may rise to 366 million[2].

Synthetic treatment available for treating diabetes often presents with numerous side effects. Diabetic management through agents without side effects continues to be a problem in the medical field. Herbal medicines are gaining popularity due to their effectiveness and apparent safety profile. People have been using herbal medicines since ancient times for the diagnosis, control and management of diverse diseases[3]. 21,000 plants are used worldwide for medicinal purposes by the World Health Organization (WHO). India being the world's largest manufacturer of herbal medicines, 150 of the 2,500 species are commercially utilized on a large scale basis[4].

Alstonia scholaris belonging to the family Apocynaceae[5] is well regarded for various medicinal properties including wound healing, anti-oxidant, hepatoprotective, antimicrobial, antidiarrhoeal, anti-plasmodic and anticancer activities. Apart from these scientific uses, other traditional uses of the bark are astringent, laxative, cardiotonic, digestive, antipyretic, galactagogue and stomachic. It is also used in abdominal disorders, malarial fever, dyspepsia, dysentery, skin diseases, leprosy, tumours, bronchitis, asthma, helminthiasis, tumours, pruritus and cardiopathy[6,7]. Almost all the parts of the plant like leaves, stems and bark the whole plant showed remarkable biological effects due to the occurrence of different potential active constituents such as phenolic compounds, different other flavonoids and alkaloids. Triterpenoids like lupeol linoleate, lupeol palmitate, alpha-amyrin linoleate, alkaloids like alstonidine, alstonine, alstovenine, chlorogenic acid, detain, ditamine, echitamine, echitamine chloride, echicaoutchin, echicerin, echitein, echitenin, pilocarpine, o-methylmacralstonine, reserpine alstonine and lupeol steroids like beta-sitosterol, noriridoids like scholareins are majorly responsible for reported activities[8]. Till now no study has been designed for the anti-diabetic potential of *Alstonia scholaris* bark. Hence, this study was designed to investigate the protective activity of ethanolic extract of *Alstonia scholaris* bark against streptozotocin-induced diabetes in rats.

MATERIAL AND METHODS

Study area: This study project was carried out concurrently at Yenepoya Pharmacy College and Research Centre, Mangaluru, Karnataka, India and Srinivasa College of Pharmacy, Valachil, Mangaluru, Karnataka, India, from August, 2018 to June, 2020.

Animals: For the main experimental work, thirty laboratory-bred Wistar Albino rats were employed, while ten albino mice were used for toxicity studies. The animals were kept in conventional animal facilities and given food and water daily. Before the animals were prepared for the experiment, they were given a 48 hrs acclimatization period in the laboratory. Before the start of the investigation, the experimental protocol was approved by the college's ethical committee (SCP/CPCSEA/F150/P10/2015).

Preparation of ethanolic extract: The bark part of *Alstonia scholaris* was collected in the month of July to August from in and around Mangalore City, Karnataka State, India. The plant part was taxonomically authenticated by Mr. Dinesh Nayak, Botanist (Green belt), Mangalore, Karnataka. The dried barks were pulverized into coarse powder at the plant mill. The powdered material was batch extracted by using ethanol as a solvent in the Soxhlet apparatus. *Alstonia scholaris* bark powdered material (150 g) was wrapped in a Soxhlet extractor and extracted utilizing ethanol as a 12-cycle solvent. In a heating mantle with thermostat control, the temperature was maintained. As a final extraction, a colourless solvent emerged in the siphon tube. The extract was absorbed using an evaporator rotating flash. The concentrated extract was then cleaned, weighed and the percentage production was calculated at room temperature. The extract percentage, colour and consistency were noted.

Phytochemical estimations of the extract: *Alstonia scholaris* bark extract (ASEE) was subjected to qualitative investigation to identify various phytochemical compounds like steroids, glycosides, terpenoids, flavonoids, alkaloids, saponins, gallic tannins, catecholic tannins, proteins and carbohydrates.

Dose selection: For 2 and 14 days, ASEE at a dose of 2000 mg kg^{-1} per p.o., was studied for acute toxicity and observed for behaviour, neurology and mortality profile. In the dosed groups of animals, there was no mortality, toxicity or behavioural changes and the extract had no negative impacts on health or caused any deleterious effects in rats. The study used a low dose that was 1:10 of the maximum safe dose and a high dose that was twice that low dose[9].

Streptozotocin-induced diabetic activity in rats

Experimental design: Wistar Albino rats of both sexes weighing about 150-200 g were categorized into five groups of six animals each with a treatment period of 30 days. Animals in 1st the group were treated with saline and 2nd group were treated with streptozotocin (50 mg kg^{-1}) and were considered normal and diabetic control, respectively. The 3rd group was treated with glibenclamide 5 mg kg^{-1} (standard drug) and 4th and 5th group animals were treated with 200 and 400 mg kg^{-1} doses of ASEE and termed as low and high doses, respectively.

Induction of diabetes mellitus: All animals except 1st group were given a single intraperitoneal streptozotocin injection (50 mg kg^{-1} b.wt.). After 2 days of streptozotocin administration, blood glucose levels were measured and animals with blood sugar levels greater than 200 mg dL^{-1} were chosen for the test[10].

Evaluation: Blood was drawn from the tail tip vein of fasted animals on days 1, 7, 14, 21 and 30 under mild anaesthesia. A single glucostix with a glucometer was used to assess fasting blood glucose levels. Blood was collected 24 hrs after the last treatment with serum separation at 3000 rpm for 10 min and the lipid profile such as LDL-cholesterol, HDL-cholesterol, triglycerides and cholesterol was estimated in a semi-autoanalyzer using the relevant agappe kit. The cervical dislocation method was used to sacrifice the rats. The liver and pancreas were removed for glycogen estimation and histopathological studies.

Histopathological analysis: Hematoxylin and eosin-stained sections of pancreatic tissue from each group were prepared and changes in histopathology were reported[11].

Statistics: The study's findings were statistically examined and presented as Mean±Standard error of the mean. The analysis was carried out using a One-way Analysis of Variance (ANOVA), followed by Tukey multiple comparison tests. A significant difference was indicated by a probability value of <0.05.

RESULTS

Preliminary phytochemical investigation: The ASEE's preliminary phytochemical analysis revealed the presence of alkaloids, flavonoids, gallic tannins, catecholate tannins, proteins, carbohydrates and saponins. The percentage yield of ASEE was found to be 18.48%.

Acute toxicity of *Alstonia scholaris* bark extracts (ASEE): It was found that with the dose of 2000 mg kg^{-1}, there was no sign of mortality and any other abnormal behaviour.

Antidiabetic activity: Throughout the study period, the fasting blood glucose level in the diabetic control group demonstrated a significant increase which was substantially decreased after daily administration of glibenclamide (5 mg kg^{-1}) (GLI). At 200 and 400 mg kg^{-1} doses, ASEE showed a significant dosage decline in FBG relative to 7th, 14th, 21st and 30th day diabetic control. The activity of *Alstonia scholaris* extracts against STZ induced diabetes was depicted in Table 1.

Impact of ASEE on blood cholesterol, triglycerides, HDL and LDL: The elevated levels of total cholesterol, triglycerides and low-density lipoprotein (LDL) were dose-dependently reduced by treatment with high and low doses of extract, when compared to the diabetic control group there was significantly elevated in high-density lipoprotein (HDL) was observed (Table 2).

Histopathological analysis: The pancreas of the normal control group revealed normal acini and normal cellular population in islets of Langerhans as well as the absence of damage to islets and hyperplasia (Fig. 1a). The diabetic control group reported severe damage and decreased size of the islets

Table 1: Effect of *Alstonia scholaris* extract on blood glucose level in STZ-induced diabetic rats

	Blood glucose level (mg dL^{-1})				
Groups	Initial	7th day	14th day	21st day	30th day
Normal control	87.50±1.78	86.01±3.08	88.01±5.22	86.05±6.36	85.58±1.248
Diabetic control	318.12±1.52$^{###}$	350.70±7.17$^{###}$	362.20±2.65$^{###}$	355.25±1.25$^{###}$	338.87±5.43$^{###}$
Glibenclamide (5 mg kg^{-1})	317.00±6.158	265.80±5.16**	208.50±10.2**	119.80±2.58***	109.20±4.1***
ASEE (200 mg kg^{-1})	322.85±3.95	301.20±5.57*	246.40±9.15**	211.90±8.65**	151.30±2.56**
ASEE (400 mg kg^{-1})	325.31±6.35	284.00±3.95*	224.80±1.24**	147.65±5.326**	130.5±1.501**

In all, values are expressed as Mean±SEM, n = 6 in one way, followed by the Dunnett's test, along with diabetic control $^{###}$p>0.05, *p<0.05, **p<0.01 and * **p<0.001

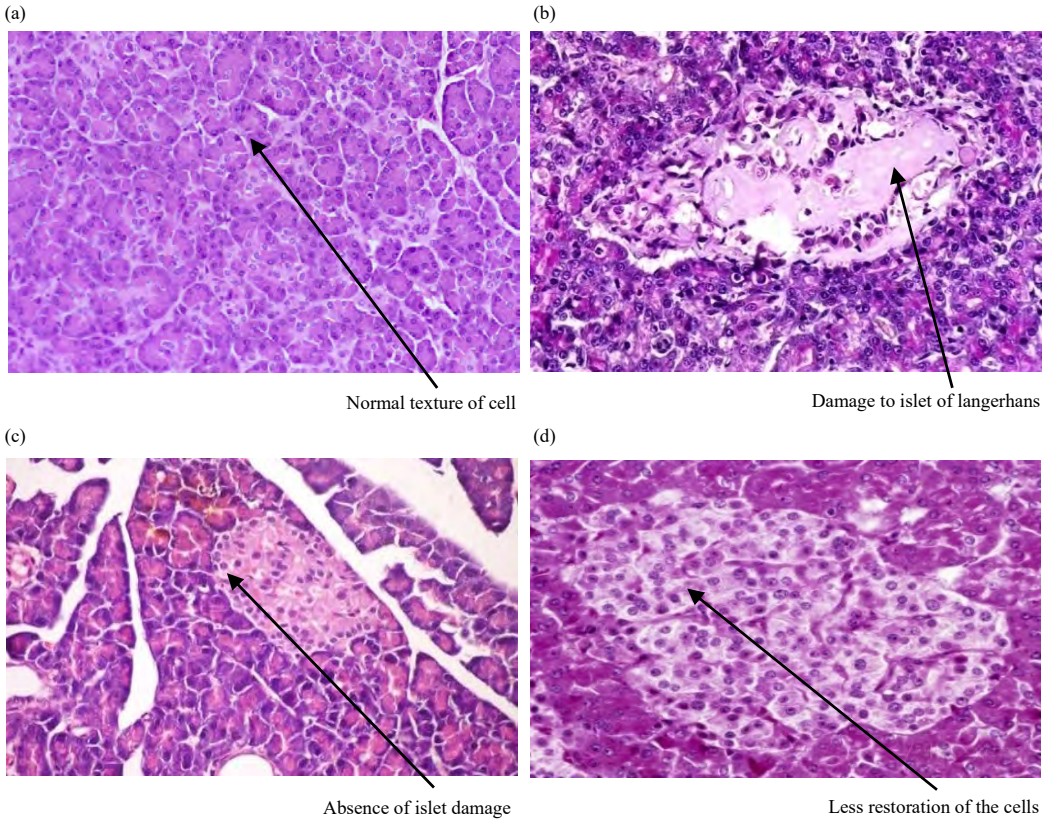

Fig. 1(a-d): Microscopic study of a section of rat pancreas (H and E, ×400), (a) Normal control group (normal texture of cell), (b) Diabetic control (extensive damage to the islets of Langerhans and reduced islet size), (c) Glibenclamide (restoration of the normal cellular population size of islets of Langerhans and absence of islet damage and presence of hyperplasia) and (d) ASEE 400 mg kg^{-1} (ASEE treated groups showed dose-dependent restoration of islets of Langerhans cell)

Table 2: Effect of ASEE on serum cholesterol, triglycerides, HDL and LDL in STZ induced diabetic rats

	SERUM			
	Cholesterol	Triglycerides	HDL	LDL
Normal control	68.23±2.153	58.58±0.05	48.51±1.54	47.19±3.217
Diabetic control	151.5±0.124	110.26±1.69	16.86±8.12	114.21±1.58
Glibenclamide (5 mg kg^{-1})	89.8±1.59***	64.40±3.254***	42.19±4.25***	61.32±2.68***
ASEE (200 mg kg^{-1})	118.3±0.258*	98.00±6.18**	31.57±3.51*	87.68±1.951*
ASEE (400 mg kg^{-1})	105.6±6.12**	82.80±893**	36.85±0.24**	75.21±2.68**

Values are expressed as Mean±SEM (n = 6), One way ANOVA followed by Dunnett's test, *p<0.05, **p<0.01, ***p<0.001, when compared diabetic control group, HDL: High-density lipoprotein and LDL: Low-density lipoprotein

of Langerhans (Fig. 1b). The standard drug (glibenclamide) treated group exhibited complete restoration of the normal cellular population, size of islets of Langerhans and the absence of islet damage and presence of hyperplasia (Fig. 1c). ASEE treated groups showed dose-dependent restoration of islets of Langerhans cells especially high doses of ASEE demonstrated significant protection from diabetic pancreatic injury (Fig. 1d).

DISCUSSION

The current study was designed to investigate the antidiabetic potential of *Alstonia scholaris* bark extract against the streptozotocin-induced diabetic rat. It was found that the ethanolic extract of *Alstonia scholaris* bark (ASEE) showed significant anti-diabetic properties against streptozotocin-induced diabetes in rats. The mechanism

behind the diabetic induction involves entry via a GLUT2 and triggers the alkylation of DNA into beta cells. DNA damage contributes to poly ADP-ribosylation activation, a process that is considered more fundamental than DNA damage for the STZ's diabetogenicity. NAD+ and ATP are depleted as a result of poly ADP-ribosylation. Administration of STZ leads to improvement in ATP dephosphorylation mediated xanthine oxidate substrate formation that generates free radicals including hydroxyl radicals, hydrogen peroxide and superoxide substances. The STZ also participates in DNA damage by inhibiting aconitase activities by releasing toxic levels of nitric oxide. Beta cells are destroyed by necrosis as a result of the STZ activity[12,13]. The STZ therapy caused a considerable increase in blood glucose levels in this study due to the extensive destruction of pancreatic cells. Glibenclamide treated, low and high ASEE dose treated groups showed a significant reduction in blood glucose levels. The GLI a sulphonylurea derivative is effective in retaining the functioning of Islet β-cells in diabetic rats. The pharmacological action is therefore to induce insulin synthesis and secretion by the β pancreatic cells. This drug will reduce insulin-independent glucose production from the liver[14]. The plants like glycyrrhiza glabra and catharanthus roseus were extensively used in the treatment of diabetes[15,16]. In these plants, the phytoconstituents responsible for the treatment of diabetes were found to be indole alkaloids, flavonoids, triterpenoids and saponins. *Alstonia scholaris* plant also contains indole alkaloids, flavonoids, saponins, tannins and triterpenoids which may be accountable for the associated anti-hyperglycemic activity of ASEE. Earlier studies on the phytochemical components of this plant demonstrated the existence of secondary metabolites and had shown hypoglycemic and hypolipidemic effects of the phytochemistry, such as saponins[17], alkaloids[18], flavonoids[19], tannin[20] and terpenoids[21]. In other words, these effects may be due to their action similar to insulin[22]. Diabetes mellitus causes insulin deficiency, metabolic disorders of carbohydrates, lipids and protéins to boost adipose tissue lipolysis. Therefore, diabetes mellitus contributes to the liver, hyper cholesterol and high blood pressure. Increased triglycerides also increase the free fatty acid level and its oxidation, both disrupting glucose metabolism and the utilization of insulin and degrading the action leading to hyperglycemia growth[23].

The study showed that the plasma triglycerides, total cholesterol and LDL in the diabetic control group were increasing, with a decrease in HDL cholesterol. Potential ASEE extracts can reduce triglyceride and cholesterol levels in diabetics and in turn help to prevent diabetic complications, thus increasing lipid metabolism. The ASEE in a dose-dependent manner witnessed antihyperlipidemic properties, as evidenced by a significant increase in high-density lipoprotein level, triglyceride and level of cholesterol however a significant decrease in LDL. This may be due to the presence of some of the potent phytoconstituents such as saponins and flavonoids. Saponins have also been shown to boost the activity of lipoprotein lipase, resulting in a reduction in total cholesterol[24]. Flavonoids may have an antihyperlipidemic effect by increasing the activity of lecithin acyltransferase, a protein that regulates blood lipids by integrating free cholesterol into HDL and then transferring it back to LDL and VLDL, which are then taken back by liver cells[25].

Histopathological studies of the pancreas also supported current findings. The vehicle control group showed exocrine acini and cellular populations in the islet of langerhans are normal in the pancreas and absence of damage to islets of normal rats. But in the diabetic positive rat islets were extensively damaged and the size of the islet is reduced. normal cellular size of the islet of Langerhans was completely restored and there was an absence of islet damage in the GLI treated group. The diabetic group treated with drug extract showed normal cellular population size of the islets of Langerhans in a dose-dependent manner and an absence of islet damage. The mechanism of the anti-diabetic effect of the extract may be because of the increased consumption of glucose by peripheral tissues[26] or because the enhanced metabolic regulations for glucose enhance the susceptibility of insulin target tissues[27].

Although bark extract of *Alstonia scholaris* may have a direct antidiabetic effect by enhancing carbohydrate consumption or improving insulin receptor sensitivity, its antioxidant potential is an important factor that has to be investigated. As a result, in future research, we recommend estimating antioxidant activity and oxidative indicators in serum or tissue homogenate. Furthermore, elucidating the molecular mechanism of antidiabetic potential as well as investigating the relevant phytochemicals will help to validate our findings.

CONCLUSION

Finally, the *Alstonia scholaris* ethanolic extract demonstrated significant anti-diabetic potential. This activity of *Alstonia scholaris* may be related to the presence of alkaloids, triterpenoids and flavonoids in the herbal extract. More research is needed to characterize the extract and determine which phytoconstituents are responsible for the reported action. Nonetheless, the findings of this study will be useful for future researchers, particularly those interested in the herb's clinical applications.

SIGNIFICANCE STATEMENT

Diabetes mellitus is becoming more common in both developed and developing countries. Although the currently available synthetic medications are effective, there have been reports of intolerable side effects. When administered over a long period, most herbal remedies are relatively safe and effective. The anti-diabetic efficacy of an ethanolic extract of *Alstonia scholaris* bark extract (ASEE) was investigated utilizing a standardized diabetic experimental model. The study found that *Alstonia scholaris* has Anti-diabetic action that is dose-dependent. The findings could provide scientific support for the traditional belief that this herb has anti-diabetic properties. However, before these findings can be used in clinical settings, they must be validated in human participants.

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