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Study of anti-diabetic activity of alstonia scholaris (L) R.BR. root extract

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***Abstract*---**Complementary therapies are being investigated extensively in the treatment of chronic disorders like diabetes mellitus (DM). The anti-diabetic efficacy of a methanol extract of Alstonia scholaris root on normoglycemic, glucose-loaded, and streptozotocin (STZ)-induced diabetic rats was investigated in this work. Single and multiple doses of Alstonia scholaris root extracts at 200 mg/kg and 400 mg/kg were given to normoglycemic, glucose-loaded, and streptozotocin-induced diabetic rats. At various points following administration, blood sugar levels were measured. One-way analysis of variance (ANOVA) and Dunnett's t-test were used to statistically analyse the data. Significant was defined as a p value of less than 0.05. In normoglycemic rats, the extract reduced blood glucose levels by 6.3 percent ($p < 0.01$) and 7.12 percent ($p < 0.01$) after 8 hours at doses of 200 mg/kg and 400 mg/kg body weight, respectively. The decline in blood sugar levels in STZ-induced diabetic rats was 44.28 percent ($p < 0.01$) and 56.66 percent ($p < 0.001$), respectively, at the same dosage level. During the research, the reference medication was glibenclamide. Thus, the hypoglycaemic activity of Alstonia scholaris root extract suggests that it could be used to generate a new herbal medication for diabetes treatment.

***Keywords*---**complementary therapies, diabetes mellitus, alstonia scholaris, streptozotocin, glibenclamide.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterised by insufficient insulin production or use [1, 2]. Insulin is the hormone responsible for glucose uptake and utilisation by cells in the body, and DM is indicated by hyperglycemia, or persistently elevated blood sugar levels [3-5]. Polyuria, polydipsia, and polyphagia are the three Ps that characterise it symptomatically. Diabetes has a large impact on low- and middle-income countries, according to recent reports [6]. With an estimated 72.96 million cases, India is second after China in terms of prevalence. In 2030, it is predicted that the global rate will rise by 25% [6, 7]. High blood pressure and impaired lipoprotein metabolism are common in diabetics. Atherosclerotic cardiovascular, peripheral artery, and cerebrovascular disorders are also common in patients with diabetes [4, 5, 8].

Plants have been used in traditional medicine spanning thousands of years. Around 800 plants have been identified to have anti-diabetic properties [9]. To reduce the weight of conventional drugs, underdeveloped countries use traditional medicine to manage diabetes. Herbal medications also have less or no negative effects and are readily available [10-12]. Alstonia scholaris, sometimes known as 'Devil's Tree,' is an Indian natural plant. It is a member of the Apocynaceae family and thrives in both deciduous and evergreen forests as well as the plains. The species A. scholaris and A. venenata are well-known for their therapeutic potential [13]. The bioactive components found in the leaf, stem, and root barks of A. scholaris have been extensively studied. The bark of A. scholaris has been shown to have anti-diabetic and anti-hyperlipidemic properties in streptozotocin-induced diabetic rats [14]. Aqueous methanol extract of dried leaves of A. scholaris has been reported to have potent α-glucosidase inhibitory action [15]. In light of the bark and leaf extracts' possible anti-diabetic effect, this study investigates the same in the plant's root extract.

Materials and Methods

Plant Material

Alstonia scholaris (L.) R.Br. roots were harvested in the month of October in the Mohana block of Odisha's Gajapati district. The plant was recognised, and the specimen was conserved in the herbarium.

Drugs and Chemicals

Glibenclamide pill (Daonil; Emcure- Sanofi India Ltd.) was acquired from the local market and Streptozotocin was procured from Sigma life science (Mumbai). Dr. Morpen Glucometer was used to measure blood glucose levels (Model NoBG-03).

Preparation of Extract

To remove any foreign debris, the roots were rinsed under running tap water and sun dried for 10-15 days. The roots were then pulverised and stored in a polythene bag for future use. Soxhlet extraction was used to extract the powdered

material with methanol. The liquid extract was concentrated under vacuum to produce dry extract, which was then kept in a desiccator.

Animals and Approval Status

For anti-diabetic investigations, healthy adult albino Wister rats weighing 150-200 grammes were chosen. The animals were kept in an animal house in big, sanitary polypropylene cages. The latter was well ventilated, with a room temperature of 25°C and a 12-hour light/dark cycle. During the trial, the animals were fed a conventional chow diet and free access to water. Cleaning using antibacterial treatments maintained the laboratory tidy and sanitary. The husk that the animals slept on was autoclaved and disinfected. Before the animals were kept, the cages were sterilised and furnished with feeding water bottles. In order to prevent infection in diabetic animals, proper cleanliness was required. The IAEC of Dadhichi College of Pharmacy, Sundergram, Cuttack, Odisha, authorised the experimental protocol for the animal experiments.

Preparation of Test Extract

The methanol extract suspension was made with distilled water and Tween-40. This was utilised in animal testing.

Acute Oral Toxicity Study of Extract

Prior to the experiment, both sexes of Swiss albino mice were fasted overnight. The research followed OECD criteria from 2000. The extract was given to the mice at doses of 1000, 2000, 3000, and 4000 mg/kg body weight (b.w.). To avoid any decrease of test extract absorption caused by eating, food was postponed for another 3-4 hours following drug administration. Individual animals were critically evaluated at least once during the first 30 minutes of medication, then every 24 hours for the first 24 hours and then every 72 hours. If anybody died, it was documented. Miller and Tainter [16] were used to compute the LD50. A screening dose of one-tenth (1/10th) of the fatal dose was used [17]. The rats were kept under constant observation for the following profiles:

- Behavioural: alertness, restlessness, irritability, and fearfulness
- Neurological: spontaneous activities, reactivity, touch response, pain response, and gait
- Autonomic: defecation and urination
- Up to a dose of 4000 mg/kg b.w., no mortality was recorded. As a result, the doses of 200 and 400 mg/kg were chosen for anti-diabetic activity testing.

Evaluation of Anti-diabetic Activity of Extract

In normoglycemic, glucose-loaded, and streptozotocin-induced single dosage and multi-dose treated hyperglycemic rats, the anti-diabetic efficacy of the methanol extract of A. scholaris root was evaluated.

- **Evaluation of Activity on Normoglycemic Animals [18]:** The rats were placed into five groups of six rats each and denied food for 12 hours before to

the test. Blood was obtained from the tip of the tail at the conclusion of the fasting period, which was taken as zero time (0 h), and the fasting blood glucose level was estimated. The control animals in Group I were given only solvent (distilled water + Tween 40, 2 ml/kg b.w.). Glibenclamide (10 mg/kg b.w.) was given to Group II (standard group) animals. The test group animals, Group III and IV, were given oral solutions of methanol extract of A. scholaris (200 and 400 mg/kg, b.w.). The blood glucose level was measured at 0, 1, 2, 4, 6, and 8 hours after the test extracts and standard were administered. Blood was drawn from the animals' tail veins, and blood glucose levels were determined using glucose oxidase-peroxidase reactive strips and a glucometer.

- **Evaluation of Activity on Glucose-loaded Animals (OGTT):** The oral glucose tolerance test was carried out according to Shirwaikar's method [19]. Rats were starved for 16 hours before and during the experiment in this approach. The rats were split into four groups of six. Group I got solvent treatment (distilled water + Tween 40, 2 ml/kg). Glibenclamide (10 mg/kg b.w.) was given to Group II (standard group) animals. Groups III and IV were given suspensions of A. scholaris methanol extract (200 and 400 mg/kg b.w., respectively). 30 minutes after the vehicle, standard, and test extracts were given, glucose (3g/kg) was given. At 0, 1, 2, and 4 hours after glucose delivery, blood was collected from the animal's tail vein. Glucose oxidase-peroxidase reactive strips and a glucometer were used to determine the blood glucose level.
- **Evaluation of Activity on Streptozotocin-induced Diabetic Animals (Single-Dose) [18]:** The effect of extracts on blood glucose levels was investigated in diabetic rats produced by streptozotocin (STZ). STZ, freshly dissolved in citrate buffer (pH 4.5) and administered intraperitoneally at a dose of 65 mg/kg body weight, was used to induce diabetes. The rats were separated into five groups, each with six rats, and fasted for 12 hours while having free access to water. Six healthy rats were given only solvent treatment and served as solvent controls. The following therapies were given orally:
  - Group-I solvent control (distilled water + Tween 40, 2 ml/kg b.w.)
  - Group-II diabetic control (distilled water + Tween 40, 2 ml/kg b.w.)
  - Group-III glibenclamide (10 mg/kg)
  - Group-IV methanol extract (200 mg/kg)
  - Group-V methanol extract (400 mg/kg)
  - The blood glucose level was estimated at 0, 1, 2, 4, 8 and 10 h following the treatment.
- **Evaluation of Anti-hyperglycaemic Activity of Extract on STZ-induced Diabetic Animals (Multi-dose):** The rats were placed into eight groups, each with six animals (n=6), and fasted for 24 hours. Diabetes was induced by injecting 65 mg/kg body weight of STZ freshly mixed in citrate buffer (pH 4.5) intraperitoneally just before usage [20]. Six healthy rats were given only solvent treatment and served as solvent controls. The injection of a 5% glucose solution for 24 hours reversed STZ-induced hypoglycemia [21]. Blood glucose levels were assessed 72 hours after STZ treatment, and rats with blood glucose levels more than 220 mg/dl were declared diabetic and employed in this investigation. The solvent control group (distilled water + Tween 40, 2 ml/kg b.w.) received simply the solvent. Diabetic control group II (distilled water + Tween 40, 2 ml/kg body weight). The standard group,

Group-III, received glibanclamide (10 mg/kg b.w.) by oral route once daily for 14 days. Methanol extracts of 200 and 400 mg/kg were given to groups IV and V, respectively. On the first, second, fourth, seventh-, and fourteenth-days following administration of the solvent, standard medication, and test extract, the blood glucose levels in the collected samples were measured [22].

Statistical Analysis

All of the data is presented as mean SEM. The test groups were compared to the diabetes control group. The data were analysed statistically using one-way analysis of variance (ANOVA) and Dunnett's t-test, with a p value of less than 0.05 considered significant.

Results

Evaluation of Activity on Normoglycemic Animals

At 200 mg/kg and 400 mg/kg b.w., respectively, the methanolic extract of Alstonia scholaris root supplied orally caused a 6.30 percent and 7.12 percent drop in blood glucose levels in normoglycaemic rats after 8 hours. At 10 mg/kg, the reference medication glibenclamide showed a reduction of 43.74 percent. When compared to 0 hour, the methanolic extract at a dose of 400 mg/kg resulted in a significant drop in blood sugar levels after 8 hours ($p < 0.01$). However, the pace of blood glucose reduction was extremely slow. It's possible that the methanolic extract of A. scholaris possesses hypoglycemic properties (Table 1).

Table 1
Hypoglycaemic activity of methanolic extract of roots of Alstonia scholaris (L.) R.Br. in normoglycemic rats

Groups and treatment	Blood glucose level (mg/dl)						
	0h	1h	2h	4h	6h	8h	Decrease at the end of 8 h (%)
Solvent control (2 ml/kg)	98.16 ± 0.60	97.66 ± 0.61	97.50 ± 0.76	96.83 ± 0.60	85.83 ± 0.60	93.33 ± 0.49	-
Glibenclamide (10 mg/kg)	92.83 ± 0.60	85.66 ± 0.66*	79.66 ± 0.88**	67.83 ± 0.79**	63.50 ± 0.76**	52.50 ± 0.84**	43.74
Methanolic extract (200 mg/kg)	94.73 ± 0.35	93.69 ± 0.69**	92.14 ± 0.59**	90.12 ± 0.84*	89.65 ± 0.69**	87.45 ± 0.71**	6.30
Methanolic extract (400 mg/kg)	94.46 ± 0.64	93.4 ± 0.66*	92.53 ± 0.81**	87.43 ± 0.56**	86.93 ± 0.67**	86.68 ± 0.51**	7.12

*The data were statistically analysed by one-way ANOVA test, followed by Dunnet's t-test. p values less than 0.05 were considered significant. *p<0.05; **p<0.01

Evaluation of Activity on Glucose-loaded Animals (OGTT)

The methanolic extract at dose levels of 200 mg/kg and 400 mg/kg b.w. recorded blood glucose levels of 106.30 mg/dl and 96.45 mg/dl, respectively, at the end of 4h in glucose-loaded animals. At 0 hours, the glucose levels were 94.56 mg/dl and 83.66 mg/dl, respectively. When compared to 0h, the methanolic extract exhibits a substantial drop ($p < 0.01$) in blood glucose levels at the end of 4 hours; the reference medicine glibenclamide has the same significance ($p < 0.05$). (Table 2).

Table 2
Evaluation of methanolic extract of Alstonia scholaris (L.) R.Br. on blood glucose levels in glucose loaded animals (oral glucose tolerance test)

Groups and treatment	Blood glucose level (mg/dl)				
	0h	1h	2h	4h	Decrease at the end of 4 h (%)
Solvent control (2 ml/kg)	85.83 ± 0.30	140.50 ± 0.76	133.00 ± 0.36	124.33 ± 0.49	-
Glibenclamide (10 mg/kg)	79.66 ± 0.55	126.17 ± 0.44*	99.83 ± 0.54**	76.66 ± 0.76**	38.34
Methanolic extract (200 mg/kg)	94.56 ± 0.76	134.53 ± 0.74*	125.40± 0.86*	106.30 ± 0.71*	14.50
Methanolic extract (400 mg/kg)	83.66 ± 0.60	129.57 ± 0.66*	117.43 ± 0.23*	96.45 ± 0.23**	22.42

*All rats were loaded with glucose (2 g/kg p.o.) 30 minutes before extracts, glibenclamide or water. The data were statistically analysed by one-way ANOVA test, followed by Dunnet's t-test. p values less than 0.05 were considered significant. *p<0.05; **p<0.01

Evaluation of Activity on Streptozotocin-induced Diabetic Animals (Single-Dose)

The methanolic extract reduced blood glucose levels by 44.28 percent and 56.66 percent in STZ-induced diabetic rats when given orally at doses of 200 mg/kg and 400 mg/kg b.w., respectively, after 10 hours, whereas the conventional medication glibenclamide reduced blood glucose levels by 61.45 percent (Table 3).

Table 3
Effect of methanolic extract of Alstonia scholaris (L.) R.Br. on blood glucose levels in single dose treated streptozotocin-induced diabetic animals

Groups and treatment	Blood glucose level (mg/dl)						
	0h	1h	2h	4h	8h	10h	Decrease at the end of 10 h (%)
Solvent control (2 ml/kg)	87.66 ± 0.88	88.50 ± 0.99	89.83 ± 1.04	92.50 ± 1.08	89.33 ± 0.95	87.66 ± 1.02	-
Diabetic control	279.17 ± 0.70[b]	277.67 ± 0.76[a]	278.17 ± 0.70[b]	285.67 ± 0.88[a]	276.17 ± 0.60[c]	275.83 ± 0.74[d]	-
Glibenclamide (10 mg/kg)	266.83 ± 0.60**	218.67 ± 0.88*	190.33 ± 0.88**	147.17 ± 0.60**	63.50 ± 0.76**	106.33 ± 1.14***	61.45
Methanolic extract (200 mg/kg)	267.47 ± 0.59*	263.47 ± 0.41**	242.67 ± 0.74*	234.83 ± 0.89*	89.65 ± 0.69**	153.67 ± 0.60**	44.28
Methanolic extract (400 mg/kg)	268.63 ± 0.12**	261.19 ± 0.77**	236.57 ± 0.25*	193.30 ± 0.66*	86.93 ± 0.67**	119.53 ± 0.67***	56.66

*The data were statistically analysed by one-way ANOVA test, followed by Dunnet's t-test. p values less than 0.05 were considered significant. For solvent control vs diabetic control: [a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$.
In case of diabetic control vs all other groups: *$p<0.05$; **$p<0.01$; ***$p<0.001$

Evaluation of Anti-hyperglycaemic Activity of Extract on STZ-induced Diabetic Animals (Multi-dose)

The study's goal was to determine the test extract's long-term anti-diabetic impact. On the 14th day of therapy, the methanolic test extract reduced blood glucose levels by 45.15 percent and 66.15 percent, respectively, at doses of 200 mg/kg and 400 mg/kg b.w. The conventional medicine glibenclamide reduced the risk by 68.46%. From day 1 to day 14, the methanolic extract at 400 mg/kg causes a significant drop in blood sugar levels ($p < 0.01$). (Table 4).

Table 4
Effect of methanolic extract of Alstonia scholaris (L.) R.Br. on blood glucose levels in multi-dose treated streptozotocin-induced diabetic animals

Groups and treatment	Blood glucose level (mg/dl)					
	Day 1	Day 2	Day 4	Day 7	Day 14	Decrease at the end of day 14 (%)
Solvent control (2 ml/kg)	91.16 ± 0.60	93.33 ± 0.95	90.83 ± 0.60	93.66 ± 0.66	89.33 ± 0.95	-
Diabetic control	280.17 ± 0.47[b]	282.50 ± 0.76[a]	302.50 ± 0.76[c]	317.33 ± 0.88[b]	337.67 ± 0.88[b]	-
Glibenclamide (10 mg/kg)	2667.67 ± 0.66*	253.33 ± 0.88*	236.33 ± 0.88**	172.33 ± 0.66**	106.50 ± 0.76***	68.46
Methanolic extract (200 mg/kg)	265.64 ± 0.88	269.45 ± 0.76*	263.82± 0.56*	254.35 ± 0.28*	185.19 ± 0.13**	45.15
Methanolic extract (400 mg/kg)	264.48 ± 0.76	257.16 ± 0.70	242.23 ± 1.05*	209.64 ± 0.66	114.29 ± 0.88**	66.15

*The data were statistically analysed by one-way ANOVA test, followed by Dunnet's t-test. p values less than 0.05 were considered significant. For solvent control vs diabetic control: [a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$.
In case of diabetic control vs all other groups: *$p<0.05$; **$p<0.01$; ***$p<0.001$

Discussion

Diabetes mellitus (DM) is one of the most serious health problems of the twenty-first century. In poor nations, type II diabetes affects between 87-91 percent of those diagnosed. Type I diabetes affects 7–12% of the population, whereas other kinds of diabetes affect the remaining 1-3 percent. The majority of cases of DM are now identified in children and adolescents. Accelerated socio-cultural changes, poor physical activity, more people living in cities, increasing sugar consumption, and low intake of fruits and vegetables are among the explanations [4, 5, 8]. In experiments, various chemical substances can cause diabetes. Streptozotocin is a glucosamine-nitrosourea molecule that damages pancreatic β-cells, resulting in decreased insulin production and, as a result, hyperglycemia [23]. Because the disease is chronic and persistent, it requires long-term treatment [24]. Until now, the pharmaceutical industry has provided us with both injectable (insulin) and oral hypoglycemic medicines, which have saved many lives [25]. In STZ-induced diabetes, sulfonylureas, particularly glibenclamide, are frequently employed to compare the efficiency of a variety of antihyperglycaemic agents [26]. The drug's oral hypoglycaemic impact was observed in normoglycemic rats, oral glucose-loaded rats, and STZ-induced diabetic rats in our investigation. The result in the third group could be explained by partial loss of β-cells by STZ, despite the fact that the pancreas was intact in the first two groups.

At doses of 200 mg/kg and 400 mg/kg, the root extracts of A. scholaris caused just a 6.3 percent and 7.12 percent reduction in blood sugar levels after 8 hours. The drop was most noticeable in STZ-induced diabetic rats, where it was 44.28 percent and 56.66 percent, respectively. Because diabetes is a chronic condition, medicines that have a long-term effect on blood sugar are favoured. The root extract of A. scholaris, like glibenclamide, was proven to have a continuous influence on blood sugar levels even after 14 days. Many indigenous medicinal plants have been effectively used to treat diabetes patients. Furthermore, drug-related side effects and problems have been recorded among habitual users. As a result, the use of indigenous ethno-medicinal plants is becoming more popular in India. Anti-diabetic medicinal plants frequently contain active compounds that can mimic the action of insulin or have a comparable impact on the β-cells of the pancreas, inducing them to produce and secrete insulin [27]. In our research, the efficacy of A. scholaris root extract to lower blood glucose levels was found to be promising.

Conclusion

The effect of a methanolic extract of A. scholaris roots on normoglycaemic, glucose-loaded, and STZ-induced diabetic rats is investigated in this work. The extract lowered blood sugar levels in STZ-induced diabetic rats, most likely via increasing insulin release from the pancreas' intact β-cells. As a result, there must be some active principles accountable for these effects, which require additional investigation in order to be identified. These findings suggest that the plant could be a source for developing novel oral anti-hyperglycaemic drugs.

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Authors' contributions

KBS, SJ and SKM conceived the idea. SJ performed the experiments. KBS, SJ and SKM analysed the data. All the authors made significant contributions in drafting the manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.
Ethical issues: The study was approved by the Institutional Animal Ethics Committee of Dadhichi College of Pharmacy.

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