Research Article

Evaluation of the Antidiabetic Activity of the Ethanolic Extract of *Allmania nodiflora* Leaves in Wistar Albino Rats Subjected to Streptozotocin-Induced Hyperglycemia

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder characterized by insufficient insulin production by the pancreas and is currently considered incurable. Various plants are traditionally used to treat it, including *Allmania nodiflora*, commonly used in Asian medicine to manage diabetes.

Objective: To evaluate the antidiabetic activity of ethanolic extract of leaves of *Allmania nodiflora* against streptozotocin-induced hyperglycemia in Wistar albino rats.

Method: Experimentally, type II diabetes was induced in rats by an i.p. injection of STZ at a dose of 50 mg/kg. Blood glucose levels of streptozotocin-induced hyperglycemia in Wistar albino rats were monitored after administering *Allmania nodiflora* leaves extract (100, 200, and 400 mg/kg) to diabetic rats for 21 days. Fasting plasma glucose levels, serum lipid profiles, and changes in body weight were evaluated. In contrast, liver glycogen levels and pancreatic TBARS levels were evaluated additionally in diabetic rats.

Results: The diabetic groups treated with the ethanolic leaf extract were compared with standard Glibenclamide. The study's findings support the antidiabetic claims of *Allmania nodiflora*.

Conclusions: The results suggest that the leaf extract of *Allmania nodiflora* possesses antidiabetic activity, which is a potential source for isolating new orally active agents in treating diabetes and its associated complications.

Keywords: *Allmania nodiflora*, Glibenclamide, Antidiabetic activity, Streptozotocin.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder, characterized by hyperglycemia resulting from variable interactions of dietary and environmental problems. Today, it is a vulnerable endemic problem all over the globe.[1,2] It is an age-long, serious heterogeneous disorder characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, and proteins, and an increased risk of complications from vascular diseases.[3]

Continuing deterioration of endocrine control exacerbates metabolic disturbances and leads primarily to hyperglycemia.[4] Diabetes Mellitus (DM) is characterized by chronic metabolic dysregulation, leading to a cascade of secondary pathophysiological alterations in various organ systems. These alterations significantly impact the well-being of individuals with DM and contribute substantially to the burden on the healthcare system.

It is frequently associated with the development of microvascular and macrovascular diseases such as neuropathy, nephropathy, and cardiovascular and cerebrovascular diseases.[5]Several oral hypoglycemic drugs are available for managing diabetes since it is incurable but they suffer from generally inadequate efficacy and several serious adverse effects.[6,7] Hence, the exploration of plant-based sources for various applications represents a promising area of research. While not a new concept, it has gained renewed interest in recent years. The World Health Organization (WHO) plays a significant role in promoting the rigorous scientific evaluation of medicinal plants to ensure their safety and efficacy.[8]They have the potential to impart therapeutic effects in complicated disorders like diabetes and its complications.

Allmania nodiflora (Family: Amaranthaceae), is an annual herb, rising to 10 cm-15 cm tall, leaves are linear 1.5-6.5 mm long, 0.3-2.5 cm wide, carried on 2-10 mm long stalks. Flower heads are globose, become elongated with a margin with green or purple midvein, and apex long acuminate 4-5 mm. Fruits are enclosed in persistent perianth, pale green with a diameter of 3-3.5 mm. Seeds are 1.5-2mm in diameter.

The flowering season of the *Allmania nodiflora* plant is May-June. In the present study, the plant profile and its ethnopharmacology will be focused on. Various parts of *Allmania nodiflora* are found to possess useful medicinal properties, such as antimicrobial, anti-inflammatory, antioxidant, and hepatoprotective activity [9,10] Hence the present study was carried out to evaluate the antidiabetic activity of Ethanolic Extract of leaves of *Allmania nodiflora* against streptozotocin-induced hyperglycemia in Wistar albino rats.

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2. MATERIALS AND METHODS

2.1. Collection & authentication of plant material

Leaf of *Allmania nodiflora* was chosen for examination and obtained from the nearby area of our college. Plant material was taxonomically recognized (voucher specimens No. 45) and authenticated by Dr. N M Ganesh Babu, Associate Professor, Heading Centre for Herbal Gardens, the University of Trans-Disciplinary Health Sciences & Technology, Bangalore 560064, Karnataka, India.

2.2. Preparation of Plant Extract

The collected leaf samples were cleaned manually with tap water, cut into small pieces, and dried under shade. The dried material was ground into fine powder by using a mixer grinder. The powdered material was successfully extracted with 70 % ethanol by using the Soxhlet apparatus for six hours. The percentage yield of the extract was 9.58 %.[11]

2.3. Phytochemical screening

The extracts of the plant material were screened for the presence of alkaloids, carbohydrates, phenols, gums and mucilage, flavonoids, steroids, proteins, tannins, and saponins using standard qualitative methods.

2.4. Animals

Male Wistar albino rats weighing 150-200 g were obtained from the Animal House of Aditya Bangalore Institute of Pharmacy Education and Research (ABIPER). All animals were housed under standard laboratory conditions (temperature:(20 ±2*°C, relative humidity:65%, 12:12 light/dark cycle) with water ad libitum access to standard rodent chow and water throughout the experiment.* The experimental protocol was approved by the Institutional Animal Ethical Committee of Aditya Bangalore Institute of Pharmacy Education &Research, Bangalore (Project proposal no. 60/1611/CPCSEA). Studies were carried out according to current CCSEA regulations.

2.5. Acute toxicity study of the extract

An acute toxicity test was done on plant extracts after the animals had fasted overnight while only taking water. The weight of each Wistar rat was recorded before administering the extract. Randomly the animals were divided into control and treatment groups, each group consisting of six rats. The control group received only the (normal saline) and each treatment group received orally the Ethanolic extracts of *Allmania nodiflora* in a dose of 5mg/kg, 50mg/kg,300 mg/kg,1000 mg/kg, 2000 mg/kg. Animals were monitored for signs of overt or suspected toxicity and/or behavioral alterations throughout the study, like restlessness, tremor, diarrhea, loss of weight, and paralysis at regular intervals for the first four hours after administering the extract, and then they were observed daily for two weeks for any change in general behavior and/or other physical activities.[12]

2.6. Induction of experimental diabetes

Thirty-six Wistar albino rats (180-200 g) were fasted overnight with access to water only. Following the fast, diabetes was induced via a single intra-peritoneal (i.p) injection of streptozotocin (STZ) dissolved in 0.1 M citrate buffer (pH 4.5) at a dose of 50 mg/kg body weight. Seventy-two hours after STZ administration, diabetes was confirmed by measuring fasting blood glucose levels from the tail vein puncture using a glucometer. Only animals exhibiting fasting blood glucose levels exceeding 250 mg/dL after 2 days of STZ induction were considered diabetic and included in the subsequent study.

2.7. Experimental design

Rats were randomly allocated into 6 groups (n=6). Group 1 which served as negative control received normal saline (10 ml/kg), group 2 was diabetic control, group 3 served as standard, group 4 (low dose of extract 200mg/kg), group 5 (medium dose of extract 200mg/kg), and group 6 (high dose of leaf extract 400mg/kg).

2.8. Determination of blood glucose level

Fasting blood glucose levels were determined using biochemistry analyzer (GOD POD method) in all experimental rats initially to determine the diabetic status and thereafter every week during the 21-day study period. Blood was obtained by snipping the tail of the rat with the help of a sharp razor and glucose was determined using a glucometer.

2.9. Serum lipid profile estimation

At the end of 21 days, blood was collected from the inferior vena cava, serum was separated for determination of parameters like total cholesterol, HDL- cholesterol and triglycerides.

2.10 Liver glycogen estimation

The liver of individual animals was homogenized in 5% w/v trichloroacetic acid and its glycogen content was determined.

2.11. Glycosylated hemoglobin determination:

At the end of 21 days, blood was collected from the retro-orbital plexus and subjected to the determination of glycosylated hemoglobin.

Statistical Analysis

All the values are expressed as mean ± standard error of the mean (S.E.M) for groups of six animals, each data was analyzed by One-way Analysis of Variance (ANOVA) and compared by using Dun net's multiple test.

3. RESULTS

3.1. Phytochemical screening

The main chemical constituents found in this plant are alkaloids, carbohydrates, glycosides, flavonoids, saponins, tannins, and steroids [13,14]

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3.2. Acute oral toxicity study

Ethanolic extract of *Allmania nodiflora* leaves was studied for acute toxicity at doses of 5mg/kg, 50mg/kg, 300 mg/kg, and 2000 mg/kg as per OECD 423. A guideline Dose of 2000 mg/kg showed toxic symptoms; hence it is considered an LD_{50} cutoff value [15]

3.3. Anti-Diabetic Activity

The effects of different doses of ethanolic extracts of *Allmania nodiflora* on blood glucose (mg/dl), serum total cholesterol & triglycerides (mg/dl) were investigated within control and streptozotocin-induced diabetic rats. Glibenclamide (10 mg/kg) was used as a standard anti-diabetic agent [16]

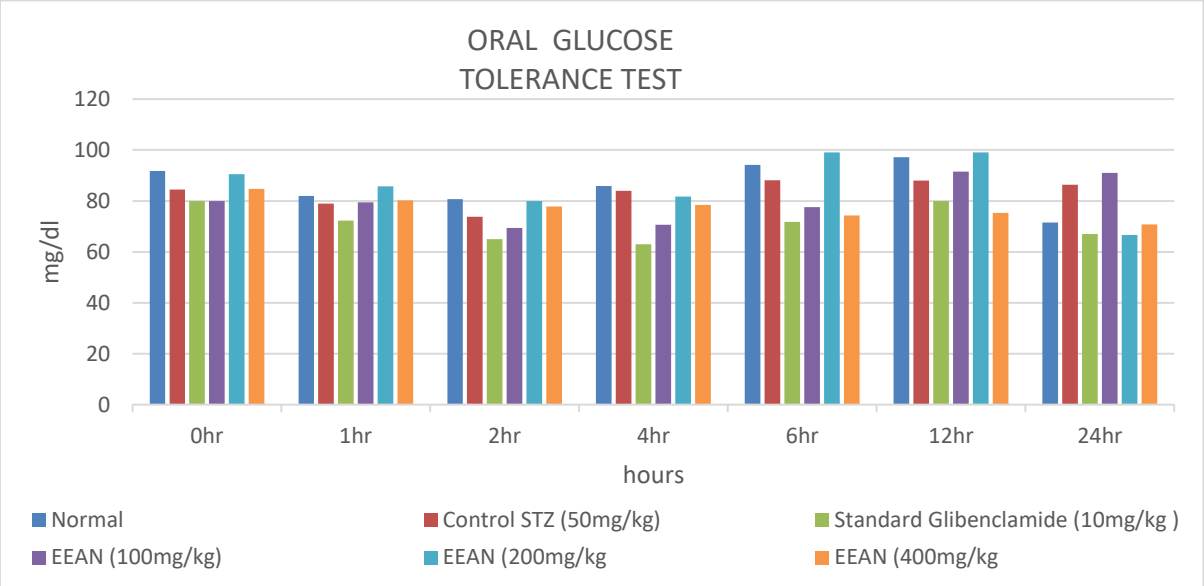
Effects of Ethanolic extracts of *Allmania nodiflora* on Serum Glucose Level:

A decrease in blood glucose level was observed in animals treated with *Allmania nodiflora* at 0, 1, 2, 4, 6, 10, 16, and 24th hr.

Allmania nodiflora extract (100mg/kg, 200 mg/kg, and 400 mg/kg) demonstrated a notable blood glucose-lowering effect at the 4-hour time point. Notably, the high dose (400 mg/kg) displayed a greater blood glucose-lowering capacity compared to the lower dose. Interestingly, the blood glucose levels in the Glibenclamide-treated group were comparable to those observed in the normal control rats. This significant reduction in peak blood sugar levels within 4 hours suggests the anti-diabetic potential of *Allmania nodiflora* extract in this rat model. Furthermore, these results indicate a potential improvement in glucose tolerance, which could be attributed to the extract's possible insulin-mimetic activity, potentially restoring a delayed insulin response.

Compared to diabetic control animals, both standard and plant extract-treated groups exhibited significantly reduced blood glucose levels. Notably, treatment with *Allmania nodiflora* at a dose of 400 mg/kg body weight and Glibenclamide at 10 mg/kg body weight reversed hyperglycemia induced by STZ to normoglycemic levels after two weeks of continuous administration.

Figure 1: Effect of Ethanolic extract of *Allmania nodiflora* on fasting serum glucose level (OGTT) in STZ-induced diabetic rats. (In hours)



All the values are mean ± SEM, n=6, ns= not significant, one-way Analysis of Variance (ANOVA) followed by Dunett's multiple comparison test.

Table 1: Effect of Ethanolic extract of *Allmania nodiflora* on fasting serum glucose level (OGTT) in STZ-induced diabetic rats.

Treated group	Fasting serum blood glucose level (OGTT)						
	0hr	1hr	2hr	4hr	6hr	12hr	24hr
Normal	91.00±0.73	82.00±2.0	80.67±1.85	85.83±1.07	94.1±1.13	97.17±1.07	71.5± 1.17
Control STZ (50mg/kg)	84.50±0.76	79.00±0.57	73.83±1.13	84.00±0.96	88.17±0.94	85.67±0.8	86.33±4.4
Standard Glibenclamide (10mg/kg)	80.00±0.76	72.33±1.45	65.00±1.52	63.00±1.93	71.83±1.51	80.00± 1.18	67.00±2.38
EEAN (100mg/kg)	80.00±1.23	79.50±1.11	69.33±1.30	70.67±0.88	77.50±1.17	91.50±1.11	77.17±5.63
EEAN (200mg/kg)	90.50±1.52	85.67±0.88	80.00± 1.18	81.7±0.94	99.00±0.73	99.00±1.53	66.67± 3.64
EEAN (400mg/kg)	84.67±3.21	80.17±3.36	77.83± 4.16	78.50±3.86	74.33±3.71	75.33±1.89	66.00± 7.13

All the values are mean ± SEM, n=6, ns= not significant, One-way Analysis of Variance (ANOVA) followed by Dunett's multiple comparison test, *p< 0.05 and **p<0.01, vs. control group and [a]p<0.001, vs normal group. EEAN- Ethanolic extract of *Allmania nodiflora*

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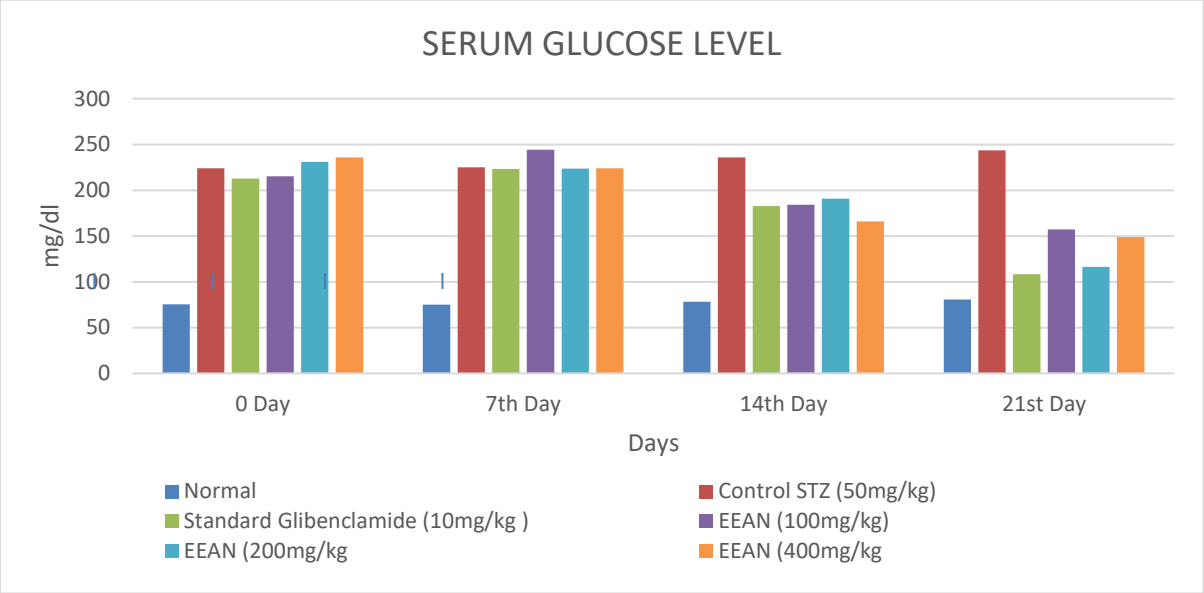
Figure 2: Effect of ethanolic extract of *Allmania nodiflora* on fasting serum glucose level (OGTT) in STZ-induced diabetic rats. (In weeks)



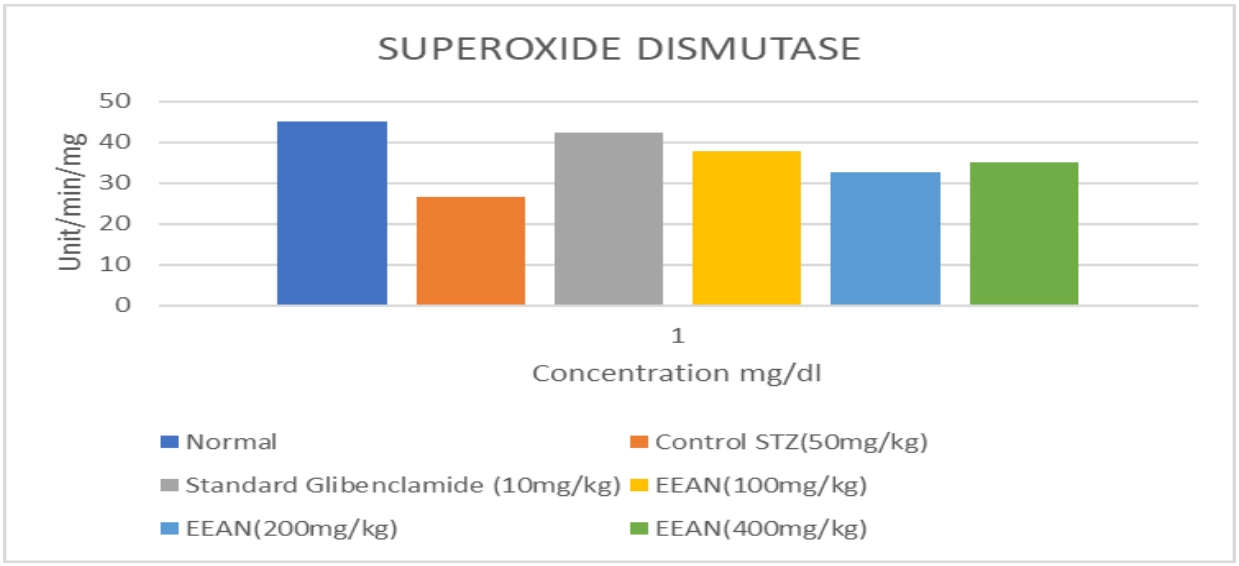
All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunett's multiple comparison test.

Table 2: Effect of Ethanolic extract of *Allmania nodiflora* (on fasting serum glucose level (OGTT) in STZ-induced diabetic rats. (In weeks)

Treated groups	**Serum glucose levels at weekly intervals mg/dl**			
	0 Day	**7th Day**	**14th Day**	**21st Day**
Normal	75.40±0.53	75.17±0.68	78.10±0.27	80.77±0.18
Control (STZ 50mg/kg)	224.0±0.37	225.1±0.36	236.0±0.21	243.5±0.25
Standard (Glibenclamide10mg/kg)	212.9±0.23	223.3±9.17	182.9±10.66	108.3±0.27
EEAN (100mg/kg)	215.2±0.22	244.3±9.86	184.1±19.76	157.2±0.22
EEAN (200mg/kg)	230.8±0.18	223.7±0.70	190.6±15.16	116.4±0.14
EEAN (400mg/kg)	236.0±4.86	224.0±3.34	166.0±3.08	148.8±1.15

All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunetts multiple comparison test, **p*< 0.05 and **p<0.01, ***p<0.001 vs. control group and [a]*p*<0.001, vs normal group;

Figure 3: Effect of Ethanolic extract of *Allmania nodiflora* on SOD (Superoxide dismutase) in STZ-induced diabetic rats



All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunetts multiple comparison test, **p<0.001vs***p<0.001 vs. control group and [a]p<0.001 vs shams operated normal

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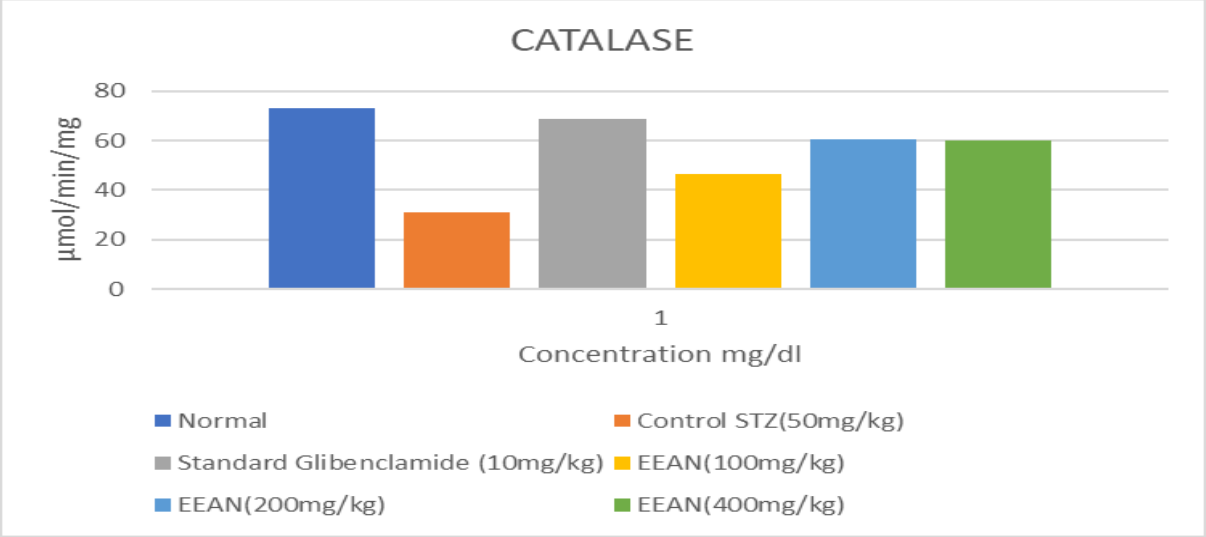
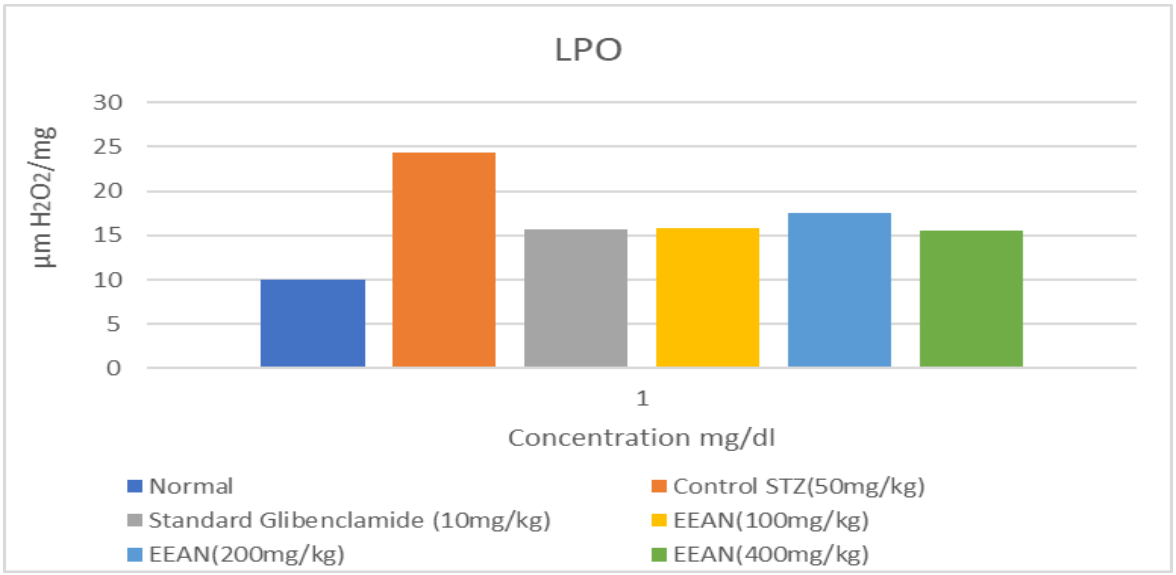
Figure 4: Effect of Ethanolic extract of *Allmania nodiflora* on catalase in STZ-induced diabetic rats



All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunetts multiple comparison test, **p<0.001vs***p<0.001 vs. control group and [a]p<0.001 vs shams operated normal

Figure 5: Effect of Ethanolic extract of *Allmania nodiflora* on LPO (Lactoperoxidase) in STZ-induced diabetic rats



All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunetts multiple comparison test, **p<0.001vs***p<0.001 vs. control group and [a]p<0.001 vs shams operated normal

Table 3: Effect of Ethanolic extract of *Allmania nodiflora* on in–vivo Anti-Oxidant Parameter from Liver Homogenate in STZ-induced diabetic rats

Treated Group	**SOD (Unit/min/mg)**	**Catalase (µmol/min/mg tissue)**	**LPO (µm of H_2O_2/mg tissue)**
Normal	44.87±0.66	72.33±0.81	9.972±0.27
Control (STZ 50mg/kg)	26.45±0.84	30.63±0.84	24.39±0.59
Standard (Glibenclamide10mg/kg)	42.23±0.37	69.71±0.74	15.64±0.38
EEAN (100mg/kg)	37.87±0.71	46.59±0.91	15.90±0.65
EEAN (200mg/kg)	32.64±0.94	60.57±0.82	17.53±0.58
EEAN (400mg/kg)	34.98±1.66	60.28±2.58	15.61±1.20

All the values are mean ± SEM, n=6, One-way Analysis of Variance (ANOVA) followed by Dunetts multiple comparison test, p<0.05, **p<0.01**, ***p*< 0.001 vs. control group and [a]*p*<0.001, vs Sham-operated normal

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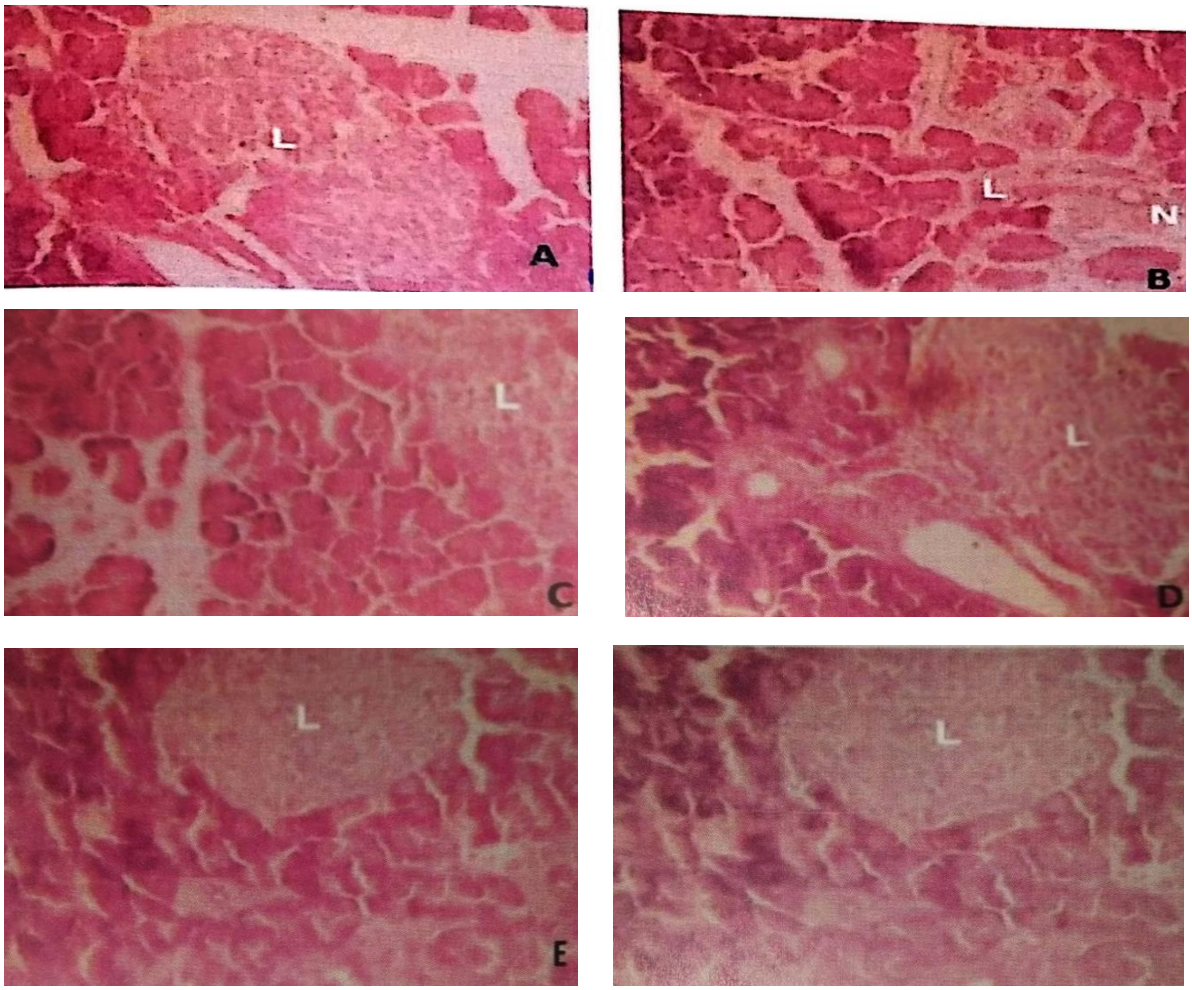

Figure 6: Microphotographs of pancreas tissue examined by routine hematoxylin-eosin of STZ-treated animals.

A: Normal group, B: Control group (STZ 50mg/kg), C: Glibenclamide 10mg/kg, D: EEAN 100mg/kg, E: EEAN 200 mg/kg, F: EEAN 400 mg/kg.

Histopathology of Pancreas

The histopathological changes were observed in the control and experimental group rats. The control rat's pancreas showed the normal appearance of islet cells [17] The STZ treated rats showed vacuolization, necrotic changes, and reduced islet cells of pancreas damage was observed. Oral administration of Ethanolic extract of *Allmania nodiflora* at the dose of 100, 200, and 400 mg/kg body weight to STZ-treated rats showed markedly reduced extent of necrosis, vacuolization, and reduced islet cells of the pancreas. In the reference group, i.e., STZ with Glibenclamide, pancreas architecture was similar to that observed in the control rats. The maximum curative effect against STZ-induced diabetic aberrations was achieved with the 400 mg/kg body weight.[18]

4. DISCUSSION

The acute toxicity test of *Allmania nodiflora* in mice produced no death or signs of toxicity even at the dose of 2000 mg/kg which shows that the extract was well tolerated and the test doses safe in the animals. Oral administration of Ethanolic extract of *Allmania nodiflora* showed significant hypoglycemic effects $p<0.01$) against STZ-induced diabetes in rats. The extract significantly lowered the levels of blood glucose [19]

The antidiabetic activity of *Allmania nodiflora* was evaluated in STZ-induced diabetic rats by testing its effect on fasting blood glucose levels using an autoanalyzer (AccuCheckActive®) glucose kit. The fasting blood glucose test is a routine carbohydrate metabolism test that measures the concentration of glucose (sugar) in the blood plasma after an overnight fast (typically 8-12 hours)[20] During this fasting state, the body undergoes gluconeogenesis, a metabolic process stimulated by the hormone glucagon. Glucagon acts on the liver to convert glycogen stores into glucose, which is then released into the bloodstream to maintain blood sugar levels. Under normal physiological conditions, the body maintains glucose homeostasis through insulin secretion from pancreatic β-cells. This hormone facilitates cellular glucose uptake, effectively lowering blood glucose levels. However, in diabetes mellitus, this regulatory mechanism is impaired, resulting in chronically elevated blood glucose (hyperglycemia). Alloxan/STZ are both of the usual substances used for the induction of diabetes mellitus and have a destructive effect on the beta (β) cells of the

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pancreas[21]The cytotoxic action of STZ is mediated by reactive oxygen species with simultaneous massive increase in cytosolic calcium concentration leading to rapid destruction of β cells. This results in a decrease in endogenous insulin secretion which paves the way for the decreased utilization of glucose by body tissues and consequently, the elevation of blood glucose levels, decreased protein content, and increased levels of cholesterol and triglycerides[22]

This study presents a preliminary evaluation of the antidiabetic potential of an ethanolic extract from *Allmania nodiflora*. In streptozotocin (STZ)-induced diabetic rats, the extract administration resulted in a dose-dependent reduction in fasting blood glucose (FBG) levels. STZ is known to induce diabetes by damaging pancreatic β-cells, likely mediated by the generation of cytotoxic free radicals. These free radicals primarily target pancreatic cell DNA, leading to fragmentation. The administration of an ethanolic extract of *Allmania nodiflora* to glucose-loaded, fasted (18 hours) normal rats resulted in a reduction in blood glucose levels observed after 2 hours, with the maximum decrease occurring at 24 hours. This oral glucose tolerance test (OGTT) suggests potential blood sugar lowering effects. In our study design, diabetic control rats exhibited a significantly elevated fasting blood glucose level at the end of the 21-day experimental period compared to baseline levels. Interestingly, treatment with the extract in diabetic rats led to a significant decrease in fasting blood glucose levels and a corresponding increase in serum insulin levels. These observations suggest a possible hypoglycemic mechanism for the *Allmania nodiflora* extract, potentially involving the potentiation of insulin action in plasma. This effect could be mediated by either increased pancreatic insulin secretion from existing beta cells or by enhanced release of insulin from a bound form.

An alternative mechanism for the observed hypoglycemic effect may involve the potential dietary fiber content of the ethanolic extract of *Allmania nodiflora*. Dietary fibers are known to play a beneficial role in glycemic control by delaying the rate of carbohydrate absorption from the intestine. This mechanism can be particularly advantageous for individuals with type 2 diabetes, where impaired insulin action often leads to postprandial hyperglycemia (high blood sugar after meals).

Lipoprotein lipase (LPL) is an enzyme responsible for triglyceride hydrolysis under normal physiological conditions. Diabetes mellitus can impair LPL activation, leading to hypertriglyceridemia (elevated blood triglycerides). Dietary fibers are known to exert cholesterol and triglyceride-lowering effects. Therefore, the significant improvement in serum lipid profiles observed in the extract-treated groups might be attributed to the potential fiber content within *Allmania nodiflora*.

Streptozotocin (STZ)-induced diabetes is typically associated with weight loss due to increased muscle wasting and protein breakdown. The liver serves as a vital organ for the metabolism, detoxification, storage, and excretion of xenobiotics (foreign chemicals) and their metabolites. Serum levels of enzymes like SGOT, SGPT, and ALP have established markers of liver function. STZ-induced diabetes is known to cause liver necrosis (cell death). The observed increase in plasma activities of SGOT, SGPT, and ALP in diabetic rats likely reflects leakage of these enzymes from damaged liver cytosol (fluid within cells) into the bloodstream, indicating the hepatotoxic (liver-damaging) effect of STZ, Treatment with the ethanolic extract of *Allmania nodiflora* in diabetic rats resulted in a significant decrease in plasma activity levels of these enzymes compared to the untreated diabetic group. This suggests a potential hepato-protective role of the extract, potentially alleviating liver damage caused by STZ-induced diabetes. The observed reduction in enzyme activities in extract-treated diabetic rats suggests a possible hepatic protective role of the extract in preventing diabetic complications.

5. CONCLUSION

In conclusion, the result of the present study indicates that the Ethanolic extract of *Allmania nodiflora* may have an active principle(s) that exerts anti-diabetic properties. This justifies the traditional use of this plant in the treatment of diabetes mellitus. Plant extract of the title plant possesses almost equipotent anti-diabetic activity when compared with reference standard Glibenclamide. However, more efforts are still needed for the isolation, characterization, and biological evaluation of the active principle(s) of *Allmania nodiflora.*

6. CONFLICT OF INTEREST

The authors declare no conflict of interest.

7. ACKNOWLEDGEMENT

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