ISSN 2582-6441 [Online]
RESEARCH JOURNAL OF PHARMACY AND LIFE SCIENCES
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RJPLS
An International Peer Reviewed Journal

Research Article

Evaluating the antihyperglycemic potential of *Justicia adhatoda* in dibetic rat

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ARTICLE INFO

Date of submission: 16-09-2025
Date of Revision: 02-10-2025
Date of acceptance: 30-10-2025

Key Words:
Diabetes mellitus, Hypoglycaemic activity, Streptozotocin, Phytochemical screening

ABSTRACT

Diabetes mellitus is a long-term metabolic disease that affects several organ systems and is typified by persistent hyperglycaemia brought on by either insulin resistance, decreased insulin production, or both. Even if traditional antidiabetic treatments successfully lower blood sugar, long-term use of them may have negative side effects and not stop the illness from getting worse. As a result, research into medicinal plants with bioactive phytoconstituents as supplemental or alternative therapeutic agents is growing. The current study set out to assess the phytochemical makeup and hypoglycaemic potential of *Justicia adhatoda's* ethanolic leaf extract. Following shade drying and powdering, the plant material underwent a series of solvent extractions and qualitative phytochemical screenings. Evaluating the extract's ability to decrease glucose in experimental animal models was the primary goal of the investigation. Streptozotocin was used to produce diabetes in rats, and oral glucose tolerance tests and blood glucose measurement in both normal and glucose-loaded animals were used to assess hypoglycaemic activity in contrast to a common antidiabetic medication. The extract has several bioactive components and had notable glucose-lowering effects. According to these results, *Justicia adhatoda* shows promise as an antidiabetic and might be a good option for more pharmacological testing and safety research.

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INTRODUCTION

Diabetes mellitus is a disease that people have to live with for a time. It is a problem with the way the body uses food for energy [1]. Diabetes mellitus happens when the body does not make insulin or when the insulin does not work properly. This disease is very common. It is getting more common all the time. That is why it is a problem for public health. When people have Diabetes mellitus they have much sugar in their blood for a long time [2]. This causes problems with the way the body uses proteins, fats and carbohydrates. It can hurt the organs. If people do not take care of their Diabetes mellitus it can cause problems. These problems can make life worse. Even kill people. Some of these problems are heart disease, problems with the eyes problems with the kidneys and problems, with the nerves [3]. Diabetes mellitus is closely linked to these complications. Most diabetes cases are type 2 diabetes. A sedentary lifestyle, obesity and genetic factors are all linked to type 2 diabetes [4]. Type 2 diabetes happens when the pancreas does not make insulin and the body's cells do not respond well to insulin. There are medicines available to manage blood sugar levels, including insulin and oral medications [5]. However long-term use of these medicines can cause side effects make it hard for patients to stick to their treatment and may not stop the disease from getting worse or prevent its consequences [6]. Because of these limits people are now more interested in ways of treatment like using herbs that can help lower blood sugar [7]. For a time, traditional healthcare has used herbal remedies to treat diabetes and other diseases related to metabolism [8]. Plants contain substances that have shown different helpful activities, such as helping the body absorb more glucose making insulin work better stopping carbs from being digested and fighting against antioxidants [9]. Medicinal plants are very promising for creating more effective treatments, for diabetes because of these properties. We need to figure out if traditional medicinal herbs are really good for us and safe to use [10]. To do this we have to study them to see what they can do and if they have any bad effects. We looked at the leaves of the *Justicia adhatoda* plant because it has been used for a time to help people feel better [11,12]. *Justicia adhatoda* leaves have things in them that can affect our bodies and might even help control things like diabetes. We still need to do more research, on *Justicia adhatoda* to make sure it is safe and to see if it really works to help people with diabetes [13].

Experimental design

MATERIALS AND METHOD

Collection and Authentication of Plant Material

Fresh leaves of *Justicia adhatoda* were collected from the local region of Balasore. The collected plant material was thoroughly washed with water to remove adhering debris and shade-dried at room temperature. A herbarium specimen was prepared and submitted for botanical identification and authentication by I. P. Padhy, Department of Pharmacognosy, Royal College of Pharmacy and Health Sciences. The authenticated plant material was stored in an airtight container for further experimental use.

Chemicals and Apparatus

Analytical-grade ethanol and petroleum ether were used as extraction solvents. The extraction and processing were carried out using a Soxhlet apparatus, heating mantle, condenser, round-bottom flask, beakers, glass rods, and rotary vacuum evaporator.

Induction of diabetes using streptozotocin

Thirty numbers of rats, weighing 160-200 gm, procured from the animal house were used for the present study [14]. After 7 days of acclimatize, rats were fasted for 12hr (free access to water). All rats of the challenged group (24 rats) were injected intraperitoneally with 60 mg/kg of STZ in 0.1 M citrate buffer, pH 4.5, while rats in the control group (6 rats) were injected with only the 0.1 M citrate buffer solution [15]. After administration of STZ the animals were free access to food and water. The development of hyperglycemic condition in rats was confirmed by estimation of serum glucose level [16]. After two days of STZ injection, the rats were fasted for 12hr (free access to water) and treated with D-glucose (2 gm/kg, p.o.). The blood glucose levels at 0 min (before glucose treatment) and 120 min (after the glucose treatment) were determined by using Glucometer and glucose testing strips. Rats with blood glucose level ≥ 140 mg/dl at 0 min and ≥200 mg/dl at 120 min were considered to be diabetic and included in the study.

Preparation of Plant Extract (Successive Extraction)

The shade-dried leaves were coarsely powdered and subjected to successive solvent extraction using a Soxhlet apparatus. Approximately 50 g of the powdered material was initially defatted with petroleum ether (60–80 °C). After defatting, the marc was dried and extracted with 500 mL of ethanol by continuous hot percolation for 72 h. The obtained extract was filtered and concentrated under reduced pressure using a rotary evaporator at controlled temperature (50–60 °C). The concentrated extract was stored in a refrigerator until further analysis [17].

Preliminary Phytochemical Screening

The ethanolic extract was subjected to qualitative phytochemical screening using standard methods to identify major secondary metabolites. The extract was tested for alkaloids, carbohydrates, glycosides, anthraquinones, saponins, gums and mucilage, proteins, tannins, phenolic compounds, triterpenoids, flavonoids, coumarins, steroids, sterols, and fixed oils. These tests were performed to determine the phytochemical composition of the extract [18].

Pharmacological study

Oral Glucose Tolerance Test

The oral glucose tolerance test (OGTT) evaluates the ability to respond appropriately to a glucose challenge. It is a sensitive test to detect disturbances of glucose metabolism, especially when casual and fasting plasma glucose (FPG) test give ambiguous results. After acclimatization for 7 days in the departmental laboratory, the OGTT was performed in overnight fasted normal rats as per the method described by Jaraldet al., 2008.The rats were randomly divided into five groups of six rats each and administered different drugs as per the schedule given in Table 1.

Anti-hyperglycemic activity was studied in glucose overloaded hyperglycemic rats. The rats were fasted for 12hr (free access to water) and administered the different drugs to respective groups as per the schedule. Zero minute blood sugar level was determined from overnight fasted animals. After 30 min of the drug treatment (p.o.), the rats of all groups were orally fed with glucose 4 gm/kg. Blood glucose concentration was determined after 30, 60, 90 and 120 min of glucose loading. The blood samples were collected from the tail tips of rat and glucose concentration was measured by using Glucometer and Glucometer strips.

Hypoglycaemic Study in Normal Fasted Rats

The hypoglycemic activity was performed in overnight fasted normal rats as per the method described by Jaraldet al., 2008.After acclimatize for 7 days in the departmental laboratory, the rats were randomly divided into four groups of six rats each and administered the drugs as per the schedule given in the Table-3. The hypoglycemic activity was studied in normal rats. The rats were fasted for 12hr (free access to water) and administered the different drugs to respective groups as per the schedule. Zero min blood sugar level was determined from overnight fasted animals i.e. before oral administration of drug. The blood glucose concentration was also measured after 30, 60, 90 and 120 min of oral administration of drug. The blood samples were collected from the tail tip of the rats and measured the glucose concentration by using glucometer.

Table 1: Schedule of drug administration in different groups of OGTT

Groups	Treatment groups	Treatments and Dose
Group-I	Normal control	Distilled Water (5 ml/kg)
Group-II	Glucose loaded Control	Distilled Water (5 ml/kg) + Glucose (4 mg)
Group-III	Standard	Glibenclamide (5 mg/kg) + Glucose (4 mg)
Group-IV	EEJA-200	EEJA (200 mg/kg) + Glucose (4 mg)
Group-V	EEJA-400	EEJA (400 mg/kg) + Glucose (4 mg)

Table 2: Schedule of drug administration in different groups of hypoglycemic activity study

Groups	Treatment groups	Treatments and Dose
Group-I	Normal Control	Distilled Water (5 ml/kg)
Group-II	Standard	Glibenclamide (5 mg/kg)
Group-III	EEJA-200	EEJA (200 mg/kg)
Group-IV	EEJA-400	EEJA (400 mg/kg)

Table 3: Table represents Streptozotocin Induced Diabetic Rats

Groups	Treatment Groups	Treatments
Group 1	Normal control	No diabetic rat received distillation water 5ml/kg
Group 2	Diabetes control	Diabetic rat received distilled water 5ml/kg
Group 3	Standard	Diabetic rat given Glibenclamide, 5 mg/kg
Group 4	EEJA – 200	Diabetic rat given EEJA 200mg/kg
Group 5	EEJA - 400	Diabetic rat given EEJA 400mg/kg

Streptozotocin Induced Diabetic Rats

In adult rats, 60 mg/kg is the most common dose of streptozotocin (STZ) to induce insulin dependent diabetes [19], but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40 mg/kg may be ineffective (Katsumata et al., 1992). In general, rats are considered diabetic if tail blood glucose concentrations in fed animals are greater than 200–300 mg/dl, 2 days after STZ injection.

Fasting Serum Glucose Estimation

Glucose is the major carbohydrate present in blood. Its oxidation in the cells is the source of energy for the body. Increased levels of glucose are found in diabetes mellitus, hyperparathyroidism, pancreatitis and renal failure. A drop of blood was collected from the tail vein of rats for the estimation of blood glucose concentration by using glucometer and glucometer strips on 0 day, 7th day and 14th day [20].

Statistical analysis

Differences among treatment group means were assessed by one-way ANOVA (nonparametric), followed by Bonferroni's multiple comparison test (Graph pad prism, 5.04 versions) and group means were significantly different at 5% level of significance, P < 0.05. The values were expressed as mean ± SEM.

Phytochemical Studies:

The ethanol extract of Justica adhatoda obtained from the above extraction process were analyzed for different phytoconstituents present in it by the method of qualitative phytochemical analysis. Preliminary qualitative phytochemical screening of EEJA showed the presence of alkaloids, phenolics, tannins, saponins, triterpiniods, flavones and flavonoids. As flavones and flavonoids are responsible for most of pharmacological activity by their antioxidants activity, further in-vivo study was carried out. The results are as follows.

Table 4: Presence of Phytochemicals in EEJA

Sl.no	phytoconstituents	presence/absence
1	Alkaloid	+
2	Carbohydrates	+
3	Glycoside	+
4	Tannins	+
5	Protein and amino acid	-
6	Gums and Mucilage	+
7	Flavones and Flavonoids	+
8	Saponins	-
9	Steroids and Sterols	+
10	Triterpinoids	+
11	Quinine	+
12	Volatile oil	-

Oral Glucose Tolerance Test

The antihyperglycemic effect in glucose loaded hyperglycemic rats in OGTT. The glucose concentration was estimated at 0, 30, 60, 90 and 120 minutes after glucose loading and results are recorded in table 5 and 6. There was a significant rise in the blood glucose level of the control animals and at the end of two hours, the glucose level declined. The EEJA exhibited significant antihyperglycemic effect at 200 and 400 mg/kg dose levels after glucose load, compared to control group animals.

There was no significant difference found between the dose of 400 mg/kg of extracts and glibenclamide treated animals.

Hypoglycaemic Activity

In the hypoglycemic activity study glucose concentration was estimated at 0, 30, 60, 90 and 120 min after the drug administration and results were recorded in table 7 and 8. The hypoglycemic effect in fasted normal rats was evaluated. After 30 min. of drug administration up to the end of 2 hours the blood glucose levels of the standard animals were declined. The extract was showed hypoglycemic activity at 400 mg/kg dose level.

Table 5: Effect of different extracts on blood glucose concentration in glucose loaded rats

Groups	Mean blood glucose concentration (mg/dl) at different time				
	0 min	30 min	60 min	90 min	120 min
Normal control	86.83 ± 2.72	86.17 ± 2.51	88.67 ± 2.14	87.83 ± 3.74	84.33 ± 2.95
Glucose loaded Control	90.33 ± 3.63	148.17 ± 3.42[a]	161.83 ± 3.38 [a]	141.17 ± 3.66 [a]	126.17 ± 3.42 [a]
Standard	84.50 ± 3.77	112.83 ± 4.42***	93.17 ± 2.98***	78.83 ± 3.57***	68.83 ± 2.80***
EEJA-200	87.17 ± 3.39	127.67 ± 3.07*	134.67 ± 4.14***	112.67 ± 3.07***	101.17 ± 3.54***
EEJA-400	89.33 ± 1.78	#118.50 ± 3.21***	#107.83 ± 3.28***	#89.67 ± 3.20***	#80.50 ± 3.12***

*The results were expressed as Mean ± SEM, n=6.^{a}P< 0.001, ^{b}P< 0.01 and ^{c}P< 0.05; compared Normal control vs Glucose loaded control.***P< 0.001, **P< 0.01 and *P< 0.05; compared Standard and Test groups vs Glucose loaded control. '#'- Indicates there is no significant difference between standard and test drug at P< 0.05 significant level.*

Table 6: Percentage change in blood glucose concentration of different groups in glucose loaded rats

Groups	Percentage changes in blood glucose (mg/dl) at different time				
	0 min	30 min	60 min	90 min	120 min
Standard	6.46	23.85	42.43	44.16	45.44
EEJA-200	3.51	13.84	16.79	20.19	19.82
EEJA-400	1.11	20.02	33.37	36.48	36.20

Table 7: Effect of EEJA on blood glucose concentration in overnight fasted normal rats

Groups	Mean blood glucose (mg/dl) at different time				
	0 min	**30 min**	**60 min**	**90 min**	**120 min**
Normal Control	84.50 ± 2.88	86.33 ± 3.24	83.67 ± 2.72	82.67 ± 2.14	85.83 ± 3.04
Standard	83.17 ± 3.27	64.83 ± 3.75***	57.67 ± 2.74***	52.83 ± 2.27***	48.17 ± 2.21***
EEJA-200	84.67 ± 3.22	78.33 ±2.67*	74.83 ± 3.86**	77.17 ± 3.09	81.17 ± 3.22
EEJA-400	82.67 ± 3.17	77.33 ± 1.54*	76.83 ± 2.69*	73.67 ± 3.86*	72.33 ± 3.82*

*The results were expressed as mean ± SEM, n=6.v ***P< 0.001, **P< 0.01 and *P< 0.05; compared Standard and Test groups vs Normal control group.v '#'- Indicates there is no significant difference between standard and test drug atP< 0.05 significant level.*

Table 8: Percentage change in blood glucose concentration of different groups in overnight fasted normal rats

Groups	Percentage change in blood glucose conc. at different time				
	0 min	**30 min**	**60 min**	**90 min**	**120 min**
Standard	1.56	29.05	45.63	52.39	58.55
EEJA-200	-0.20	9.27	10.56	6.65	5.44
EEJA-400	2.17	10.42	8.17	10.89	15.73

Table 9: Effect of different extracts on blood glucose conc. of diabetic rats

Treatment Groups	Blood glucose concentration (mg/dl) on different days		
	0	**7**	**14**
Normal control	83.69 ± 3.12	82.83 ± 2.99	84.35 ± 3.25
Diabetic control	238.15 ± 6.12	222.33 ± 5.42	216.6 ± 5.77
Standard	236.56 ± 5.21	161.33 ± 5.21*	123.36 ± 4.81*
EEJA-200	#243.15 ± 6.64	203.16 ± 4.53*	164.50 ± 4.38*
EEJA-400	#242.33 ± 4.94	#181.47 ± 4.28*	#144.17 ± 4.11*

*The results were expressed as mean ± SEM, n=6. P< 0.05; compared Normal control vs Diabetic control. *P< 0.05; compared Standard and Test groups vs Diabetic control group. '#'- Indicates there is no significant difference between standard and test drug at P< 0.05 significant level.*

Antidiabetic Study by Using Streptozotocin Induced Diabetic Rats

After 4 weeks of dietary manipulation, injection of STZ (35 mg/kg, i.p.) was significantly (p<0.001) increased serum glucose concentration, thus producing the frank hyperglycemia as compared to normal control rats. Blood glucose remained consistently elevated in diabetic control rats throughout the drug treatment period. Oral administration of glibenclamide (5 mg/kg) significantly (p<0.001) reduced glucose concentration 26.69% and 41.46% on 7th and 14th day respectively. The administration of EEJA200 mg/kg was reduced glucose concentration 9.48% and 22.73%; 400 mg/kg 17.96% and 33.16% on 7th and 14th day respectively. There were no significant differences found in glucose level between glibenclamide and 400 mg/kg of EEPM treated animals.

Glucose is the major carbohydrate present in blood. Its oxidation in the cells is the source of energy for the body. Increased levels of glucose are found in diabetes mellitus. Hence the results obtained from testing the glucose concentration of fasting rats are tabulated as follow.

Discussion

The current investigation showed that in experimental animal models, the ethanolic leaf extract had notable hypoglycaemic and antihyperglycemic effects. The extract may promote insulin activity or glucose utilization, as seen by the decrease in blood glucose levels seen in both normal fasting rats and oral glucose tolerance tests. The presence of bioactive phytoconstituents such alkaloids, flavonoids, tannins, and phenolic compounds found during initial phytochemical screening may be the cause of these effects. Numerous of these secondary metabolites are known to have antidiabetic benefits through mechanisms such as antioxidant activity, peripheral glucose absorption improvement, suppression of carbohydrate digestion, and stimulation of insulin secretion. The extract's medicinal potential is further supported by the observed glucose-lowering impact that is equivalent to that of the usual medication.

CONCLUSION

Over the past two decades, the interest in medicinal plants has grown enormously leading to routine scientific investigation of numerous plant extracts for their biological effects and potential therapeutic properties in human. A detailed investigation of plants used in local heath tradition and pharmacological evaluation of these plants and their taxonomical relatives can lead to development of invaluable plant drug for many dreaded diseases including diabetes mellitus. thus based on the background of diversified therapeutic values and uses in diabetes mellitus complications in folklore, the locally available plant *Justica adhatoda* were taken up for present investigation. The present study showed that the ethanolic heart wood extract of *Justica adhatoda* are able to produce a consistent reduction in serum glucose dose dependent manner. There were no significant differences found in the action between glibenclamide and 400 mg/kg of EEPM treated animals. The extract has also shown the presence of active constituents responsible for significant anti hyperglycemic supplement. Further investigation is expected to isolate and characterize the active principle of the extracts. Clinical evaluation will throw more light on clinical usefulness, safety and efficacy of this plant extract.

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