

In-vivo potential of *Musa paradisiaca* Linn. (Stmn.) in streptozotocin-induced diabetic rats

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Abstract

Objective: *Musa paradisiaca* belonging to family Musaceae is a well-known herb having many pharmacological properties including antidiabetic activity. In ancient text, Basavaraju was reported the stamen of this plant as antidiabetic agent in a dietary recipe. The main aim of this study was to explore the *in-vivo* antidiabetic property of its stamen. **Materials and Methods:** Aqueous extract of *M. paradisiaca* stamen (AqMP, 100, 200, and 400 mg/kg, p.o.) was evaluated for hypoglycemic effect in normoglycemic rats and consequences on oral glucose tolerance test (OGTT) by measuring the tail blood glucose concentrations. Further, blood glucose level was measured after 7th, 14th, and 21th days in streptozotocin-nicotinamide (STZ 65 mg/kg, i.p. and NDA 110 mg/kg, i.p.) induced-diabetic rats treated with AqMP and reference drug glibenclamide (5 mg/kg, b.w. p.o.). **Results:** The result with normoglycemic rats shows that the AqMP (400 mg/kg, p.o.) did not have any hypoglycemic effect, and it effectively control the blood glucose level in OGTT within 30-60 min after glucose (2 g/kg) administration without causing any hypoglycemic effect. Moreover, the drug (400 mg/kg, p.o.) was also found to be effective in controlling the blood sugar level in STZ-NDA induce diabetic rat as compare to glibenclamide. **Conclusion:** The study shows that the drug exhibit significant *in-vivo* antidiabetic potential as well as support its traditional use in diabetes.

Key words: Antidiabetic, Basavaraju, hypoglycemic, *Musa paradisiaca*

INTRODUCTION

Diabetes is the heterogeneous group of metabolic disorders characterized by glucosuria and hyperglycemia. Regardless of the etiology, diabetes progresses through several clinical stages. Currently, in India, the number of people with diabetes is around 40.9 million, and this ratio is expected to rise to 69.9 million, in 2025.^[1] India has emerged as the diabetic capital of the world. Approximately 3.2 million deaths occur due to diabetes, and its complications were reported by the International Diabetes Federation.^[2] This is approximately 6.8% of the total global mortality. Basically, diabetes develops due to a diminished production of insulin (in Type 1) or resistance to its effects (in Type 2). Primary symptoms of diabetes results in excessive thirst, unexplained weight loss, excessive urine production, increased fluid intake, blurred vision, lethargy, and changes in energy metabolism. As disease progresses, complications such as ketoacidosis,

nephropathy, retinopathy, neuropathy, cardiovascular disease, and other microvascular damages may occur. A range of therapeutic agents is available to control hyperglycemia. Insulin and other oral hypoglycemic drugs such as thiazolidinediones, biguanides,^[3] pioglitazone, glipizide, and metformin, etc., are frequently used to treat diabetes mellitus (DM). However, these synthetic hypoglycemic drugs are usually associated with side effects such as gastrointestinal discomfort, nausea, and a metallic taste. High cost and poor availability of drugs in many rural populations particularly in developing countries also contribute in the progress of disease. Therefore, safe and effective medicines/therapies are

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still in search from alternative sources *viz.* Ayurveda, yoga, acupuncture, and other traditional system of medicines. A number of medicinal plants are used to treat disorders^[4-6] such as diabetes, arthritis, liver diseases, dyslipidemia, etc. worldwide. Drugs from natural sources are usually less toxic and with minimal side effects which are a major drawback with allopathic drugs. The pharmaceutical and scientific organizations are doing a lot of research for identification of active compounds from these plants. The antidiabetic potential of *Azadirachta indica* A. Juss, *Coccinia indica* Wight and Arn, *Gymnema sylvestre* R. Br., *Mangifera indica* L., *Zingiber officinale* Roscoe, *Curcuma longa* L., *Embllica officinalis* Gaertn., *Trigonella foenum graecum* L., and *Swertia chirayita* Roxb. Ex Fleming H. Karst.^[7] were scientifically established previously.

Musa paradisiaca (Family Musaceae), commonly known as banana, is a perennial tree-like herb, usually grown indigenously in the tropic and subtropic regions. It is commonly cultivated in the Maland region of Karnataka and distributed in Assam, West Bengal, Madhya Pradesh, Bihar, Gujarat, Maharashtra, Andhra Pradesh, and Tamil Nadu. The fruits are valued for its delicious taste and flavor. For several medicinal purposes, every part of this plant has been traditionally used in India. The plant was reported to possess antidiarrheal, antidysentery, antihelmentic, antiulcerative, antimicrobial, hypoglycemic, antihypertensive, diuretic, antilithiatic, wound healing, antimalarial, and anti-snake venom activity.^[8] Several phytoconstituents have been isolated from the different parts of the plant like catecholamines such as norepinephrine,^[9] serotonin, dopamine, acyl steryl glycosides such as sitoindoside I-IV and steryl glycosides such as myoinositol- β -D-glucoside, gentiobioside, sitosterol, indole compounds, tryptophan,^[10] pectin, tannin, starch, iron, crystallizable and non-crystallizable sugars, vitamin C, B-vitamins, albuminoids, fats, minerals salts and several flavonoids and related compounds (leucocyanidin, quercetin and its 3-ogalactoside, 3-O-rhamnosyl glucoside^[11] and 3-O-glucoside, have been found in the fruit pulp of *M. paradisiaca*.^[12]

In classical text, “Basavarajiyam” written by Shree Neelakantha Basava Raju, the stamen of the flower of *M. paradisiaca* is mentioned to cure *Mutra roga* (*Madhumeha*).^[13]

MATERIALS AND METHODS

Collection, Identification, and Authentication of Plant Part

The inflorescence was collected, and stamen was separated from flowers of *M. paradisiaca* in the month of June-July 2015 from Mondh, District Bhadohi (Uttar Pradesh) (25° 24' N, 82° 38' E longitude and altitude, 85 m ASL). A voucher with the specimen number (APRL/HERB/2015-16/04) was secure

at Ayurvedic Pharmacy Laboratory, Rajiv Gandhi South Campus, Banaras Hindu University, Barkachha, Mirzapur for further assistance in future.

Drugs and Chemicals

Glibenclamide, streptozotocin (STZ), and nicotinamide (NDA) were purchased from (Sigma-Aldrich Co. LLC., New Delhi, India). All the solvents and reagents of analytical grade were used in all experiments.

Animals

Charles foster albino rats weighing 160-200 g were used in the study. Rats were housed in polypropylene cages, lined soft wood shavings as bedding (renewed every 24 h), 12/12 h light/dark cycles, 50-60% relative humidity, and at temperature $22 \pm 2^\circ\text{C}$. The animals were fed with rat pellet diet and water *ad libitum* regularly. Rats were acclimatizing for 7 days before experimentation. Prior approval was obtained from the Animal ethical committee, Banaras Hindu University to carry out the work (Dean/2015/CAEC/1431).

Oral Toxicity Studies

The acute oral toxicity study was performed according to OECD guidelines 425.^[14] The animals were divided into 3 groups ($n = 6$), and aqueous extracts of *M. paradisiaca* (AqMP) treatments were given at a dose of (2 g/kg, 3 g/kg and 5 g/kg b.w.), respectively. The animals were observed for 14 days for any toxicity sign such as gross changes in mucous membranes, skin, eyes, fur, and behavior pattern, handling response, occurrence of any excretions, and secretions.

Experimental Design

Study on normoglycemic rats

Normoglycemic studies were carried out in overnight fasted normal rats. A total of 30 animals were divided into five groups of six rats each. The normal control group received only vehicle, and the standard group received reference drug glibenclamide while third to fifth group was administered with three different doses of the test drug, respectively. Blood samples were collected from tail vein before dosing and then at regular intervals of 1, 2, 4, and 6 h, respectively and subjected to fasting blood glucose (FBG) level with the help of commercially available simple one touch select glucometer based on glucose-oxidase-peroxide reaction.

Study on oral glucose tolerance test (OGTT)

OGT for test drug were carried out in 30 overnight fasted normal rats, which were divided into five groups of six rats each. The normal control group received only vehicle, and the standard group received reference drug glibenclamide (5 mg/

kg, p.o.) while group from third to fifth was administered with test drug (100 mg/kg, 200 mg/kg, and 400 mg/kg, b.w. p.o.), respectively. All the animals were challenged with glucose (2 mg/kg, p.o.).^[15] The blood glucose level was measured in the blood collected from the tail vein using glucometer at 0, 30, 60, 90, and 120 min after administration of glucose.

Study on STZ-induced diabetic rats

Diabetes was induced by STZ (65 mg/kg, i.p.) and NDA (110 mg/kg, i. p.)^[16] in overnight fasted normal rats. Blood glucose level was checked using glucometer after 72 h of STZ and NDA administration. Rats shown FBG >250 mg/dl were considered to be diabetic and were select for studies. Selected animals were divided into five groups ($n = 6$) as follows and 6 non diabetic animals serve as a normal control (Group-I).

Group-II: Diabetic control rats.

Group-III: Diabetic rats administered once with glibenclamide (5 mg/kg, b.w. p.o.)^[17] as the reference drug.

Group-IV-VI: Diabetic rats administered with the test drug.

Treatment was continued for 21 days. Plasma glucose level was measured in the blood collected from the tail vein before dosing (day 0) at regular intervals of 7th, 14th, and 21st days, respectively in all groups.

Statistical Analysis

All the values of the experimental results were expressed as mean \pm standard error of mean Two-way ANOVA followed by Bonferroni post-test was used to access effect

on normoglycemic, OGTT, and STZ-NDA induced diabetic rats.

RESULTS

Acute Oral Toxicity Study

At a maximum dose of 5000 mg/kg, AqMP did not show any toxicity as well as no behavioral changes were observed. Our findings revealed that AqMP was non-toxic to rats at 5000 mg/kg, dose. The 100, 200, and 400 mg/kg, b.w. p.o. dose of AqMP were selected through the pilot study for the antidiabetic study *in-vivo*.

Antidiabetic Study of AqMP

Effect on blood glucose levels in fasted normal rats

Table 1 demonstrates the effect of AqMP on overnight fasted rats. The result of two-way ANOVA suggests that there was a significant difference between the control group and treatment groups. Glibenclamide at the dose of (5 mg/kg, p.o.) significantly reduced the blood glucose level in rats when compared to a normal control group. However, AqMP in the entire tested dose did not show any hypoglycemic effect on normal rats.

OGTT

The effect of AqMP (100, 200, and 400 mg/kg, p.o.) on OGTT is illustrated in Table 2. Two-way ANOVA indicates that there were significant differences between experimental groups

Table 1: Effect of AqMP on normal rats

Time (h)	Normal	Standard drug	AqMP 100 mg/kg	AqMP 200 mg/kg	AqMP 400 mg/kg
0	112.09 \pm 0.88	109.19 \pm 0.68	110.63 \pm 0.83	108.72 \pm 0.70	109.85 \pm 0.79
1	108.01 \pm 0.90	98.49 \pm 0.34 ^a	107.15 \pm 1.04	105.67 \pm 1.03	105.60 \pm 1.23
2	108.31 \pm 1.11	73.20 \pm 0.49 ^a	107.83 \pm 1.18	107.04 \pm 1.23	105.49 \pm 1.15
4	107.55 \pm 0.80	65.98 \pm 1.04 ^a	106.03 \pm 0.83	104.95 \pm 0.87	104.02 \pm 1.92
6	109.23 \pm 1.14	86.39 \pm 0.65 ^a	105.85 \pm 1.17	104.50 \pm 0.78	103.81 \pm 1.42

Two-way ANOVA followed by Bonferroni post test revealed that there was a non-significant difference between control group and treatment group. ^a $P < 0.05$, compared to normal control. AqMP: Aqueous extract of *Musa paradisiaca*

Table 2: Effect AqMP on oral glucose tolerance test in normal rats

Time (min)	Normal	Standard drug	AqMP 100 mg/kg	AqMP 200 mg/kg	AqMP 400 mg/kg
0	114.29 \pm 0.71	112.03 \pm 0.68	110.63 \pm 0.83	109.28 \pm 0.63	100.43 \pm 0.31
30	161.01 \pm 2.10	143.33 \pm 2.58 ^a	165.32 \pm 1.63	157.83 \pm 3.85	158.00 \pm 5.23
60	153.60 \pm 2.55	106.20 \pm 0.49 ^a	152.23 \pm 1.09	140.10 \pm 2.81 ^a	127.25 \pm 4.25 ^a
90	138.13 \pm 3.08	81.98 \pm 1.04 ^a	135.39 \pm 1.47	112.43 \pm 6.23 ^a	104.02 \pm 0.87 ^a
120	114.45 \pm 5.13	71.39 \pm 0.65 ^a	105.89 \pm 1.13	101.96 \pm 1.30 ^a	102.00 \pm 2.59 ^a

$P < 0.05$, compared to normal control. ^a $P < 0.05$, compared to Glibenclamide. (Two-way ANOVA followed by Bonferroni post-test). AqMP-Aqueous extract of *Musa paradisiaca*

after treatment. Animals treated with AqMP (400 mg/kg), and glibenclamide showed a significant decrease in blood glucose level when compared to normal control animals. The administration of AqMP significantly prevented the increase in blood glucose levels without causing any hypoglycemic effect. The maximum effect of AqMP was observed at 30, 60, 90, and 120 min after the oral glucose administration.

Effect on FBG level of STZ-NDA induced diabetic rats

Table 3 shows the effect of AqMP (100, 200 and 400 mg/kg, p.o.) on the STZ-NDA induced diabetic rats. Two-way ANOVA reveals that there were significant differences in the experimental groups. A significant increase in the level of blood glucose was observed in STZ-NDA treated rats when compared to normal control rats ($P < 0.05$). Administration of AqMP significantly reduced the FBG levels on 7th, 14th, and 21th days as compared to diabetic control. Treatment of diabetic rats with glibenclamide also significantly reduced the increased blood glucose level, and all the doses of tested drug were dose dependent.

DISCUSSION

Diabetes is a worldwide problem, in which the number of patients is increasing every year. It is reported that diabetes was the 16th leading cause of mortality. In this study, the extracts show no effect on blood glucose levels during the tests period of 6 h when compared to the controls group while glibenclamide causes hypoglycemia in animals. This observation suggests that in acute conditions the AqMP is less likely to cause hypoglycemia in normal individual. This result supports the view of *Acharya Basavaraju* that stamen of *M. paradisiaca* can be used by the diabetic patient as a dietary recipe (prepared with the test drug and *Godhum* (*Triticum aestivum*)).

For decades, the OGTT has been sustaining basis for diagnosing diabetes. Tolerance of non-diabetic rats to an oral glucose challenge in either the absence or presence of AqMP and glibenclamide was shown in Table 2. After glucose loading, the FBG level reached to its peak value after 15 min and the treatment with reference drug and AqMP shows the good tolerance tendency against Glucose. Many animal models are

available for the investigations of DM, in which STZ induce diabetes is most frequently used.^[17-20] It is a toxin obtained from *Streptomyces achromogenes*. Intraperitoneal (i.p.) administration of STZ accumulates in pancreatic β -cells of the islets of Langerhans via the glucose transporter 2 (GLUT2) and release Nitric oxide (NO). The STZ rapidly destroy the β -cells through DNA alkylation and NO which reduces the synthesis of insulin, expression of GLUT-2 and inhibits the release of insulin, ultimately diabetes established. The combination of NDA and STZ mildly enhanced the blood glucose level in STZ-NDA-induced Type 2 diabetic rats without showing any effect on body weight. The NDA act as antioxidant having ability to inhibit the release of NO by which it protects the β -cells from any cytotoxic action caused by STZ.^[21,22] Free radical mediated cytotoxicity to β -cells lowers the insulin level which leads to a disturbance in glucose metabolism. Reduction in glucose oxidation and adenosine triphosphate (ATP) formation results in the inhibition of insulin secretion^[23,24] due to which hyperglycemic condition resist.

The standard drug glibenclamide inhibits ATP-sensitive potassium channels in pancreatic beta cells which cause the depolarization of cell membrane, calcium influx, the opening of voltage-gated calcium channels and stimulate the insulin release, finally activate the insulin secretory machinery. Other studies show that the drug having glycogen deposition action on the synthesis of glycogen phosphorylase enzyme level and GLUT2.^[25-27] Besides this action, glibenclamide has also increases the level of fructose 2, 6-biphosphate levels which reduce the rate of glucose formation from a mixture of lactate/pyruvate.^[28] Moreover, the drug was also reported for the promotion of glucose uptake and utilization by the tissues, especially skeletal muscle cells during a hyperglycemic challenge^[29] as well as inhibition of glucose production from different sources in the body.^[30]

The optimum dose (400 mg/kg) of aqueous extract of stamen had no relevant effect on FBG level in the first week of treatment, but it was seen that the level of blood glucose was notably reduced after 3 weeks of treatment. In previous research, it was reported that saponins and tannins having antidiabetic activity.^[31] The AqMP does not cause hypoglycemia, but it surely lowers the blood glucose level in OGTT and STZ-induced diabetic rats. Previously, there are various phytochemical have been reported such as alkaloids, tannins, saponins, phenols in the *M. paradisiaca* plant.^[32]

Table 3: Effect of AqMP on the blood glucose level of STZ-NDA induced diabetic rats

Time (day)	Normal control	Diabetic control	Standard drug	AqMP 100 mg/kg	AqMP 200 mg/kg	AqMP 400 mg/kg
0	98.65±1.99	273.79±1.37 ^a	312.59±0.97 ^{ab}	294.69±0.95 ^{ab}	303.73±0.69 ^{ab}	284.55±0.49 ^{ab}
7	97.00±2.45	295.29±1.49 ^a	184.16±0.91 ^{ab}	234.01±1.00 ^{ab}	173.14±0.084 ^{ab}	146.81±0.43 ^{ab}
14	97.56±5.23	310.18±0.72 ^a	125.61±1.09 ^{ab}	183.10±8.89 ^{ab}	134.16±0.73 ^{ab}	110.77±0.43 ^{ab}
21	98.05±3.76	247.49±1.59 ^a	92.60±2.03	164.75±0.71 ^{ab}	116.21±0.56 ^{ab}	90.72±0.42 ^b

^a $P < 0.05$, compared to normal control; ^b $P < 0.05$, compared to diabetic control. (Two-way ANOVA followed by Bonferroni post-test). AqMP-Aqueous extract of *Musa paradisiaca*

In preliminary phytochemical screening, we found that there was a presence of alkaloids, tannins, saponins, and phenolics in the extract of stamen of *M. paradisiaca*. Saponin shows potent hypoglycaemic activity *in-vivo*. It stimulates the insulin secretion, regenerate beta cells, and activate those enzymes which are necessary for utilization of glucose^[31] Tannin also might have antidiabetic property as well as antioxidant potential.^[33,34]

CONCLUSION

On conclusion, this study reveals that the stamen of *M. paradisiaca* maintains the elevated blood glucose level and act as a better antidiabetic activity. The presence of various chemicals such as saponins, tannins, and phenols supports its potent activity.

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