

Hypoglycemic and antihyperglycemic activity of aqueous extract of *Justicia Schimperiana* leaves in normal and streptozotocin-induced diabetic mice

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ABSTRACT

Background: Non-communicable diseases like diabetes mellitus are becoming major health problem these days. There is an increasing demand by patients to use the natural products (plants) with anti-diabetic activity due to the severe side effects associated with the use of insulin and oral anti-diabetic drugs. One such plant is *Justicia Schimperiana* which has been traditionally used for the treatment of diabetes mellitus. The aim of this study was, therefore, to evaluate hypoglycemic and antihyperglycemic activities of aqueous extract of *Justicia Schimperiana* leaves in normal and streptozotocin-induced diabetic mice, respectively and to carry out acute toxicity test.

Methods: Two doses (200 mg/kg and 400 mg/kg) of the aqueous leaf extract of *Justicia Schimperiana* were administered to normal glucose loaded and diabetic mice to study blood glucose lowering effect. Acute oral toxicity test was also performed as per Organization for Economic Cooperation and Development (OECD) guideline-425 (limit test). Statistical analysis of the data were carried out using both Student's t test and one-way ANOVA followed by Dunnett's test to compare results between doses, among treatment and control groups and to compare results before and after treatment.

Results: Aqueous extract of *Justicia Schimperiana* (200mg/kg and 400mg/kg, p.o.) showed significant tolerance ($P < 0.05$) to oral glucose load at 1 and 2 hrs after glucose load. The extract also produced significant ($P < 0.05$) blood glucose reduction at 4 hours after its administration in normoglycemic mice. The extract at 400mg/kg dose level produced significant ($P < 0.05$) reduction in blood glucose level at 2, 3 and 4 hours of treatment in streptozotocin (45 mg/kg) induced diabetic mice. Acute oral toxicity studies of aqueous extract of *Justicia Schimperiana* leaves in rats showed no death or signs of toxicity at the dose of 2000 mg/kg indicating the safety nature of the extract.

Conclusion: The results of the experiments showed that aqueous extract of *Justicia Schimperiana* has significant antihyperglycemic activity in streptozotocin induced diabetic mice and improvement in glucose tolerance and slight hypoglycemic activity in normal mice justifying the traditional claim for its use in diabetes.

Key words: *Justicia Schimperiana*; Streptozotocin; hypoglycemic and antihyperglycemic activities

INTRODUCTION

Diabetes mellitus is a major global health problem. World health organization (WHO) estimated the number of cases of diabetes worldwide to be about 347 million [1]. Most common cause for this abnormality is obesity and the associated metabolic syndrome [2,3]. WHO projects that diabetes will be the 7th leading cause of death in 2030 [1].

Diabetes exerts a significant burden in developing countries especially in Sub-Saharan region, and this is expected to increase due to economic growth, adoption of 'western' lifestyles and their accompanying risk factors – smoking, high-fat diets, lack of exercise [4]. Many diabetic patients face significant challenges accessing diagnosis and treatment, which contributes to the high mortality and prevalence of complications observed [5]. In Ethiopia, prevalence of diabetes is increasing and estimated to be 2% nationally related to lifestyle changes and the resulting surge in obesity [6]. Estimated number of cases of diabetes in Ethiopia to be 1,386.64 and more than one-third, but only less than half, of diabetic patients receive standard diabetes care [6,7].

A large number of plants have proved their efficacy in the management of diabetes especially hyperglycemia [8,9]. For example, the popular hypoglycemic drug glucophage (metformin) is derived from *Galega officinalis* [10].

Justicia Schimperiana is a plant belonging to the family acanthaceae. This plant called locally as ‘sensel or smiza’ in Amharic, ‘umuga’ in Oromifa and used for many diseases locally like stomach-ache and burning [11], constipation [12], skin lesion [13], tooth ache [14], Scabies [15] and crude extract of *justicia schimperiana* exhibited antibacterial activity against *Niesseria gonorrhoea* and *Shigella flexineri* [16].

Other species are also used in traditional medicine of Ethiopia like *acanthus semi*, *dicliptera laxata*, and *J.valica* [17]. Around wolayta *Justicia Schimperiana* leave macerate is claimed to have antidiabetic activity and there is no study has tested the traditional claim. Thus, the present study aimed to evaluate hypoglycemic and antihyperglycemic activities of aqueous extract of *Justicia Schimperiana* leaves in normal and streptozotocin-induced diabetic mice and also to undertake acute toxicity study.

METHODES

Drugs, chemical, and instruments

Streptozotocin, obtained from biochemistry department, was used to induce hyperglycemia/diabetes on mice. Glibenclamide (Daonil®) was used as a standard hypoglycemic drug. Prodigy® glucose analyzer was used to check the blood glucose level.

Experimental animals

Healthy adult Swiss Albino mice of both sexes weighing 25-35g were used in this study. The animals were obtained from the Ethiopian Health and Nutrition Research institute (EHNRI). The animals were housed in standard cages and kept under standard condition. Mice's were acclimatized for a period of 2-3 days before the experiment given a standard diet and tap water *ad libitum*.

Collection of plant materials

Sufficient amount of *Justicia Schimperiana* leaves were collected from southern Ethiopia part particularly around wolayta sodo. The plant material was authenticated by the National Herbarium, Department of Biology, Addis Ababa University and voucher specimen (JS01/12) was deposited.

Preparation of the extract

Six hundred grams of air dried under shade and coarsely powdered (by using mortar and pistol) leaves of *Justicia Schimperiana* were macerated with cold water for 3 days in Erlenmeyer flasks with occasional shaking. The liquid extract was separated from the mark by using muslin cloth and the extraction and the procedure was repeated three times[18].

After clarification of the liquid extract by filtration with whatman filter paper no.1, it was frozen in refrigerator overnight and then freeze dried in a lyophilizer at - 40 °C and vacuum pressure 200mbar to obtain freeze dried powder aqueous extract.

Induction of experimental diabetes

Diabetes was induced in mice by intraperitoneal (i.p.) injection of streptozotocin (STZ) dissolved in 0.1 M cold citrate buffer (pH = 4.5) at a dose of 45 mg/kg body weight. Diabetes was confirmed by determining fasting blood glucose level on the third day post administration of streptozotocin [19]. Animals showing blood glucose levels > 200 mg/dl 48 h after STZ treatment to overnight fasted mice were considered diabetic [20].

Pharmacological evaluation

Oral glucose tolerance test (OGTT)

OGTT and dose optimization was undertaken based on the method described by chika and Bello (2010) with slight modification. Normal fasted mice were randomly assigned to four groups (comprising of six animals each). Two groups were administered 200mg/kg (AEJS200) and 400mg/kg (AEJS400) of aqueous leaf extract of *Justicia Schimperiana*. The other two groups served as negative (administered normal saline) and positive controls (administered 5 mg/kg of glibenclamide dissolved in N/S). Thirty minutes following each administration, 2.5 g/kg of glucose solution was administered to each animal. Blood sugar levels were measured, for each animal, at 30 min, 1 h and 2 h intervals following glucose administration [21,22].

Assessment of the hypoglycemic activity of *Justicia Schimperiana* in normoglycemic mice

Hypoglycemic effects of aqueous extract were determined on four randomized groups of normal fasted mice for 4 hours, but allowed free access to water. Two groups were administered 200mg/kg (AEJS200) and 400mg/kg (AEJS400) and the other two were given 5 mg/kg of glibenclamide and N/S. Subsequently, blood sugar levels were assessed at 1 h, 2 h, 3 h and 4 h intervals by using glucose oxidase-peroxidase reactive strips and a glucometer [21].

Assessment of the hypoglycemic activity of *Justicia Schimperiana* in diabetic mice

Confirmed diabetic mice were randomly grouped into four groups (n-6). Two groups were administered 200mg/kg (AEJS200) and 400mg/kg (AEJS400) of the extract, the other two groups were given glibenclamide

(5 mg/kg) and N/S. Following the administration, Blood samples were collected via tail vein by excision and glucose levels were determined at an hourly interval for 4 h by touch glucometer [21].

Acute oral toxicity study

Acute oral toxicity test was performed as per OECD (Organization for Economic Cooperation and Development) guideline-425 (limit test) [23]. Five female albino rats (one animal in each step) were randomly selected. The animals were kept fasting for 4 hours providing only water. Aqueous extract of *Justicia Schimperiana* leaves were administered orally at a dose of 2000 mg/kg. The rats were observed continuously for the first 4 hrs and then periodically up to 24 hrs for toxic manifestations like: drowsiness, restlessness, writhing, convulsion, piloerection and mortality if any. The rats were observed for two weeks.

Data analysis and Management

Data were analyzed using IBM SPSS version 20 for windows software. Statistical analysis of the data were carried out using both Student's t test and one -way ANOVA followed by Dunnett's test to compare results between doses, among treatment and control groups and to compare results before and after treatment. The results were expressed as mean \pm S.E.M and considered statistically significant at 95% confidence level or P value < 0.05 .

Ethical consideration.

The study protocol was submitted to and official permission was accepted from the ethics committee of the department of pharmacology, school of medicine and the animals were handled, treated and sacrificed based on the requirement.

RESULTS

Percentage yield of crude extract

The percentage yields of aqueous extract 600g powdered *Justicia Schimperiana* leaf were found to be 10 (w/w).

Oral glucose tolerance test in normal mice

Administration of glucose (2.5g/kg, p.o.) produced significant change in blood glucose level of normal, overnight fasted, mice. Treatment with glibenclamide (5mg/kg, p.o.) improved glucose tolerance significantly ($P < 0.05$) at 1/2hr, 1hr and 2hr after the glucose load. Aqueous extract of *Justicia Schimperiana* (200mg/kg and 400mg/kg, p.o.) showed significant tolerance ($p < 0.05$) to oral glucose load at 1 and 2 hrs after glucose load as compared to normal control group (Table 1).

Hypoglycemic activity of *Justicia Schimperiana* extract in fasting normal mice

Fasting blood glucose test in normal mice showed that aqueous extract of *Justicia Schimperiana* (400mg/kg, p.o.) produced significant ($P < 0.05$) blood glucose reduction only at 4 hours after administration. Whereas glibenclamide (5 mg/kg, p.o.) revealed significant reduction throughout the time as compared with normal control (Table 2).

Antihyperglycemic activity of *Justicia Schimperiana* extract in fasting diabetic mice

The effect of aqueous extract of *Justicia Schimperiana* on fasting blood glucose level in diabetic animals is presented in table 3.

A significant ($P < 0.05$) reduction in blood glucose level was observed with aqueous extract of *Justicia Schimperiana* (400mg/kg, p.o.) at 2, 3 and 4 hours after its administration as compared with the control.

Acute oral toxicity study

There were no lethality or toxic reactions found at 2000 mg/kg dose level. The oral LD₅₀ of *Justicia Schimperiana* aqueous leaves extracts was greater than 2000 mg/kg.

DISCUSSION

Diabetes mellitus is an endocrine disorder characterized by hyperglycemia together with impaired metabolism of glucose and other calorogenics such as lipids and proteins, associated with absolute or relative deficiencies in insulin secretion and/or insulin action [24].

The fundamental mechanism underlying Persistent hyperglycemia involves over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues in diabetic patients. Treatment should aim to lower blood glucose to near-normal levels. There is an increasing demand by patients to use the natural products with anti-diabetic activity due to the severe side effects associated with the use of insulin and oral anti-diabetic drugs [2,25]. The search for effective and safe anti-diabetic lead molecule from plants is thus of great importance.

In Ethiopia, Non-communicable diseases like diabetes mellitus are becoming major health problem these days [6]. There are many traditionally used plants claimed to have antidiabetic effect in this country. One such plant is *Justicia Schimperiana* which has been traditionally used for the treatment of diabetes mellitus.

The efficacy and safety of such claimed plant medicines need to be investigated. The present study was done in an attempt to confirm the claim for the anti-diabetic effect of *Justicia schimperiana* leaves.

In this study, the hypoglycemic and antihyperglycemic activity of the aqueous extract of *Justicia Schimperiana* leaves in normal and diabetic mice, respectively were investigated using three models. Hypoglycemic activity was investigated by oral glucose tolerance test and blood glucose lowering on fasted normal mice, whereas antihyperglycemic activity was investigated on diabetic mice.

The oral glucose tolerance test and study on normal mice with doses of 200mg/kg and 400mg/kg revealed that aqueous extract of *Justicia Schimperiana* has capacity to lower blood glucose levels. The extract also exhibited a marked antihyperglycemic activity in streptozotocin induced diabetic mice. It is well documented that anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood [2].

The significant oral glucose tolerance observed with oral administration of aqueous extract of *Justicia Schimperiana* (200mg/kg and 400mg/kg) at 1 and 2 hr of glucose load shows that the extract decreases blood glucose. The blood glucose lowering effect may be due to a decrease in glucose absorption, increased peripheral glucose utilization and glycolysis, decrease in glycogenolysis and gluconeogenesis. Significant oral glucose tolerance seen in lower (200mg/kg) as well as in higher (400mg/kg) doses employed could indicate aqueous extract of *Justicia Schimperiana* has got appreciable glucose absorption decrement and postprandial glucose lowering like *Trigonella foenum-graecum* as reported by Madar (1984) which slow absorption of carbohydrate and inhibit glucose transport in gut.

The aqueous extract of *Justicia Schimperiana* at the dose of 400mg/kg body weight showed significant blood glucose reduction in streptozotocin induced diabetic mice after 2, 3 and 4 hours of treatment indicating that the extract may stimulate insulin secretion and peripheral glucose utilization as suggested by Erah *et al* (1996). The aqueous extract of *Justicia Schimperiana* at the dose of 400mg/kg body weight showed significant hypoglycemic activity in normal mice only at 4 hour after its administration. The same dose, however, showed the maximum anti-diabetic activity 1 h after treatment, which is similar to the report of Kesai *et al* (2005) on *Murraya Koenigii* and Sharma *et al* (1996) on *Cinnamomum tamala*, *Terminalia pallid* [26] though insignificant hypoglycemic effect.

Many secondary metabolites isolated from different plant species have been expected to have potent hypoglycemic, antihyperglycemic and glucose suppressive effects. These secondary metabolites include flavonoids [19,27], sterols/triterpenoids [28], alkaloids and phenolics [25,29]. Effects might be achieved by facilitating insulin release from pancreatic β -cells, inhibiting glucose absorption in gut, stimulating glycogenesis in liver and/ or increasing glucose utilization by the body [30]. Apart from lowering blood glucose effect, these phytochemicals are known to regenerate the damaged beta cells and stopping oxidative stress on beta cells in experimental diabetic rats [31,32].

As reported by Mekonnen *et al* (2006) *Justicia Schimperiana* contains alkaloids, phenols and terpenoids. Any of these secondary metabolites may, therefore, be responsible for the observed glucose suppressive and antihyperglycemic activity of the crude extract. However, there is a need of bioactivity guided investigation to isolate the lead compound responsible for anti-diabetic activity and to establish the possible mechanism(s) of action.

The acute oral toxicity studies of aqueous extract of *Justicia Schimperiana* leaves in rats showed no death or signs of toxicity at the dose of 2000mg/kg indicating the safety nature of the extract.

Even though the hypoglycemic effect observed in normal mice might indicate hypoglycemia to be one of the side effects of the extract, oral glucose tolerance test and antihyperglycemic study indicate more of the desirable effect. Future isolation, characterization and structure activity modification of the responsible active constituent of the plant extract may pave new treatment approach for diabetes mellitus.

CONCLUSIONS

The result of the present study indicates that aqueous extract of *Justicia Schimperiana* has significant antihyperglycemic activity in streptozotocin induced diabetic mice and improvement in glucose tolerance as well as slight hypoglycemic activity in normal mice and justifying the traditional claim for its use in diabetes.

The oral LD₅₀ of *Justicia Schimperiana* aqueous leaves extracts was greater than 2000 mg/kg.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AT and SG conceived the idea, drafted the proposal and involved in all implementation stages of the project and write up. EM reviewed the proposal, and involved in all implementation stages of the project and write up. All authors approved final version of the manuscript.

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Table 1: Effect of aqueous leave extract of *Justicia Schimperiana* on oral glucose tolerance test

Group	Treatment	Blood glucose concentration (mg/dl).			
		Normal fasting	½ hr	1 hr	2 hr
I	Control (normal saline)	94.17 ± 7.57	143.67 ± 8.50	146.67 ± 11.44	125.17 ± 11.95
II	Glibenclamide (5mg/kg)	105.17 ± 8.25	131.00 ± 7.71*	86.33 ± 11.61*	51.67 ± 11.34*
III	AEJS (200mg/kg)	104.17 ± 4.91	132.33 ± 8.51	100.67 ± 7.97*	83.00 ± 6.83*
IV	AEJS (400mg/kg)	109.00 ± 3.01	130.17 ± 4.77	108.67 ± 3.32*	85.50 ± 3.85*

Each value represents mean ± S.E.M, n=6 for each treatment,

* Represents statistical significance vs. control in respective hours (P < 0.05),

AEJS = Aqueous extract of *Justicia schimperiana*

Table 2: Effect of aqueous leave extract of *Justicia Schimperiana* on normal mice

Group	Treatment	Blood glucose concentration (mg/dl).				
		Normal fasting	1 hr	2 hr	3 hr	4hr
I	Control (normal saline)	102.17 ± 1.72	101.50 ± 1.75	100.00 ± 1.71	98.83 ± 1.92	92.50 ± 1.63
II	Glibenclamide (5mg/kg)	103.00 ± 6.99	86.00 ± 3.17*	85.50 ± 2.92*	84.33 ± 2.79*	80.17 ± 2.40*
III	AEJS (200mg/kg)	97.67 ± 3.17	96.83 ± 3.24	95.33 ± 3.30	94.67 ± 3.31	93.50 ± 3.44
IV	AEJS (400mg/kg)	102.33 ± 4.92	101.33 ± 4.69	98.33 ± 4.03	89.17 ± 3.14	82.33 ± 2.21*

Each value represents mean ± S.E.M, n=6 for each treatment,

* Represents statistical significance vs. control in respective hours (P < 0.05),

AEJS = Aqueous extract of *Justicia schimperiana*.

Table 3: Effect of aqueous leave extract of *Justicia Schimperiana* on diabetic mice

Group	Treatment	Blood glucose concentration (mg/dl).				
		Fasting	1 hr	2 hr	3 hr	4hr
I	Control (normal saline)	255.50 ± 9.33	255.00 ± 9.15	254.17 ± 9.31	253.17 ± 9.19	252.33 ± 9.21
II	Glibenclamide (5mg/kg)	238.67 ± 7.55	224.67 ± 6.17*	216.83 ± 2.55*	211.83 ± 4.01*	203.17 ± 5.91*
III	AEJS (200mg/kg)	265.33 ± 9.16	264.00 ± 9.02	261.67 ± 8.57	257.50 ± 9.24	249.83 ± 7.22
IV	AEJS (400mg/kg)	242.33 ± 5.08	239.33 ± 4.01	224.00 ± 2.66*	222.00 ± 2.11*	213.33 ± 6.25*

Each value represents mean ± S.E.M, n=6 for each treatment,

* Represents statistical significance vs. control in respective hours (P < 0.05), AEJS = Aqueous extract of *Justicia schimperiana*