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Antihyperglycemic effects of the methanol leaf extract of *Diaphananthe bidens* in normoglycemic and streptozotocin-induced hyperglycemic rats

Anaga Aruh Ottah*, Onuoha Augustine, Igboeli Okechukwu Obiora, Ezeja Maxwell

[1]*Department of Veterinary Physiology and pharmacology, University of Nigeria Nsukka, Enugu State, Nigeria*
[2]*Department of Veterinary Physiology, Pharmacology and Biochemistry, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria*

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ABSTRACT

Objective: To evaluate the methanol leaf extract of *Diaphanathe bidens (D. bidens)* (AFZEL. EX SW) SCHLTR for antihyperglycemic activity in order to confirm it antidiabetic potential. **Methods:** *D. bidens* was extracted by cold maceration for 48 h and concentrated in vacuo to yield *D. bidens* extract (DBE). Hyperglycemia was induced by intraperitoneal administration of streptozotocin (75 mg/kg). Oral glucose tolerance test was done with 2 g/kg glucose load in normal rats. DBE (150, 300 and 600 mg/kg) was administered orally, while tolbutamide (100 mg/kg, p.o.) was used as the standard reference drug. Blood glucose levels determined using ACCUCHEK glucose auto-analyzer. The acute toxicity and phytochemical studies were also carried out. **Results:** DBE (600 mg/kg) and tolbutamide (100 mg/kg) significantly (P<0.05, 0.005) reduced blood glucose levels of rats between 120 and 480 min post administration in normal rats. In the streptozotocin-induced hyperglycemic rats, DBE (150, 300, 600 mg/kg) caused significant (P<0.001)dose- and time- dependent reduction in the blood glucose levels by 1.7%, 22.8% and 43.4%, respectively at 480 min compared to the negative control group. DBE (600 mg/kg) reduced the blood glucose level of rats by 1.2% in the oral glucose tolerance test when compared with the normal saline treated group. The acute toxicity test showed that DBE was safe at the doses used and the phytochemical screening revealed the presence of saponins, steroids, tannins and terpernoids. **Conclusions:** D. bidens extract possess antihyperglycemic activity which may be mediated through pancreatic and extra-pancreatic pathways, thereby justifying it folkloric use.

1. Introduction

Diabetes mellitus is a group of metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both[1]. The disease has now become an epidemic with a world wide incidence of about 5% of the population and now kills more than AIDS[2]. The international diabetes, federation has predicted that the number of individuals with diabetes will increase from 240 million in 2007 to 380 million in 2025 with 80% of the disease burden in low and middle income countries[3].

The two main types of diabetes include: the insulin dependent diabetes mellitus whose main characteristics is deficiency of insulin resulting from loss of insulin producing beta cells of the islets of Langerhans in the pancreas and the non-insulin dependent diabetes mellitus which is due to either insulin resistance or reduced sensitivity coupled with relatively reduced insulin secretion which in some cases become absolute[4] and this globally is the commonest form[5].

The treatment of diabetes currently is based on various oral hypoglycaemic drugs along side insulin[6]; however, synthetic hypoglycaemic agents are associated with serious side effects which include: hematological effects, coma, disturbances of the liver and kidney functions and in addition they are not suitable for use during pregnancy[7]. These side effects lead to the search for alternative remedies which may produce similar degree of efficacy with little or no adverse effects. Ethnobotanical information indicates that more than 800 plants are used as traditional remedies for the treatment of diabetes due to their effectiveness, less side effects and relatively low cost[8].

Diaphananthe bidens (*D. bidens*) (AFZEL. EX SW) SCHLTR

*Corresponding author: Dr. AO Anaga. Department of Veterinary Physiology and Pharmacology. University of Nigeria, Nsukka. Enugu State, Nigeria.
Tel: +2348063831206
E-mail: aruhanaga@yahoo.com

is an epiphyte and belongs to the family Orchidaceae with tough wiry stems. It attains several metres in length which makes the plant become gracefully pendulous from the branches of foot-hill forest trees, free flowing with salmon pink, yellowish pink or white flowers[9]. The common names include wax orchid (English), "Ikori" (Yoruba Tribe in Nigeria) and "Bombins" (Sierra Leone)[9,10]. Little is known about the medicinal properties of this plant; however, the natives in South Eastern Nigeria use the leaf decoction as a remedy for diabetes mellitus, inflammatory conditions and for management of asthmatic conditions.

Based on these traditional uses, this present study was undertaken to investigate the antihyperglycaemic activities of the methanol leaf extract of *D. bidens* with the aim of establishing its efficacy and the pharmacological basis for its folkloric use.

2. Materials and methods

2.1. Plant collection and identification

The fresh leaves were collected from Ede Oballa in Nsukka Local Government Area, Enugu State, Nigeria and were identified by a Taxonomist, Mr. AO Ozioko of Bioresources development and conservation programme (BDCP) Aku Road, Nsukka and a voucher specimen (BDCP/H.8910) deposited in the University of Nigeria Nsukka herbarium for reference.

2.2. Extraction of plant material

Cold maceration extraction method was used for the extraction of the plant materials. The fresh leaves of the plant were cut into tiny pieces, dried under mild sunlight and pulverized into a coarse powder of about 1 mm in diameter. Two hundred grammes (200 g) of the pulverized material were macerated in 750 mL of 80% aqueous methanol for 48 hours with intermittent shaking at 2 hours interval. The extract was filtered using Whitman filter papers (No.1) and later concentrated in vacuo using rotary evaporator at 40℃ and 210 milibar and a freeze dryer. The yield was calculated and the crude extract labeled as D. bidens extract (DBE) was stored in a refrigerator at the temperature of 10℃ until time of use.

2.3. Experimental animals

Adult male Wistar albino mice (22-31 g) and rats (150-180 g) of either sex from the Laboratory Animal Unit of Faculty of Veterinary Medicine, University of Nigeria, Nsukka were used for the experiments. The animals were kept in stainless steel cages and clean drinking water provided ad libitum while they were fed with standard commercial pelleted feed (Vital Feed® Nigeria). The temperatures varied between 27-30℃ and relative humidity of about 55%-60% with 12-h light-dark cycle and adequate ventilation maintained in the animal house. Ethical conditions governing the conducts of experiments with life animals as stipulated by Ward and Elsea[11] were strictly observed. Also, the experimental protocol was approved by the institution's ethical committee.

2.4. Acute toxicity test

The method of Lorke[12] was employed in this study. Briefly, 25 mice of both sexes were randomly grouped into 5e groups (A-E) of five mice per group and were dosed with 100, 200, 500 and 1 000 and 2 000 mg/kg of DBE orally by gastric gavage. The animals were given feed and water ad libitum and were observed over a period of 48 h for signs of toxicity and mortality.

2.5. Effect of DBE on blood glucose levels of normoglycaemic rats

Twenty five (25) adolescent albino rats of either sex were grouped into 5 of 5 rats per group after 18 h fast and treated as follows: Group 1 (negative control group) received 10 mL/kg of normal saline, group 2 (positive control) received tolbutamide (100 mg/kg) while groups 3, 4 and 5 received 150, 300 and 600 mg/kg of DBE, respectively. Blood samples were collected from each of the rats through tail snip at 0 min, 30, 60, 120, 240, 360 and 480 min. The blood glucose levels was measured using auto analyzer (AccuCheck Advantage II®) glucose kit[13].

2.6. Effect of DBE on streptozotocin-induced hyperglycaemic Rats

2.6.1. Induction of hyperglycemia

The modified method of Dash *et al*[13] was used for this study. The rats were weighed and fasted for 18 h and allowed free access to clean drinking water ad libitum. Hyperglycaemia was induced by intraperitoneal injection of 75 mg/kg streptozotocin (STZ) in citrate buffer (pH 4.5). Hyperglycaemia was confirmed in the STZ-treated rats 48 h later by measuring fasting blood glucose levels (18 h fast) using auto analyzer (AccuCheck Advantage II®)) glucose kit with blood collected from the tail vein. Rats with fasting blood glucose levels above 350 mg/dL were considered hyperglycaemic and included in the study.

2.6.2. Experimental design

Hyperglycaemic rats were randomly divided into 5 groups of 5 rats each. The fasting blood glucose levels of the rats in each group were determined using the same method as above representing the fasting blood glucose level at 0 min and then treated as follows[13]:

Group 1 (negative control) rats received 10 mL/kg normal saline;Group 2 (positive control) rats received 100 mg/kg tolbutamide; Group 3, 4 and 5 (test groups) rats were given 150, 300 and 600 mg/kg of DBE, respectively, all by gastric gavage. The blood glucose levels of the rats were tested at 0, 60, 120, 180, 360 and 480 min after administration of drug and DBE using auto analyzer described as above.

2.7. Effect of DBE on oral glucose tolerance test in normoglycaemic rats

This study was done using the modified method of Aslan *et al*[14].

Briefly, ten (10) albino Wister rats were divided into 2 groups of 5 rats each and fasted for 18 h. Group 1 rats were given normal saline 10 mLl/kg, while group 2 rats were treated with 600 mg/kg of DBE by gastric gavage. The blood glucose level of each of the rats was measured immediately after treatment, 30 minutes later the rats were given glucose load at the dose of 2 g/kg per os. Blood samples were then collected by tail snip from the rats at 0 min (immediately after glucose load), 30, 60, 120 and 180 min and the blood glucose levels measured using auto analyzer as above.

2.8. Phytochemical spot tests of DBE

The phytochemical spot tests were done using the method of Harbourne and Trease and Evans[15,16].

2.9. Data analysis

The results were presented as mean ± SEM and were analyzed using one-way analysis of variance (ANOVA). The differences between the means were separated by LSD PostHoc analysis and values of $P<0.05$ were considered statistically significant.

3. Results

3.1. Plant extraction

The methanolic leaf extract of *D. bidens* was greenish black in colour which was odourless and the yield was 1.63% w/w dry matter.

3.2. Acute toxicity test

The animal clustered together following the administration of D. bidens and 2 deaths were recorded at the dose of 2 000 mg/kg at the 10th h after DBE administration.

3.3. Effect of D. bidens on normoglycaemic rats

The effect of the DBE on the glucose levels of normoglycaemic rats is presented in Table 1. The result showed that there was an increase in blood glucose level by 44.4% at the 8th hour in the normal saline treated group (negative control). Tolbutamide and DBE at the dose of 600 mg/kg caused a time dependent and various levels of significant ($P< 0.05-0.005$) reduction of blood glucose levels of the rats.

The blood glucose levels of the rats were reduced DBE (600 mg/kg) from (89.70±6.50) mg/dL to (47.43±1.70) mg/dL at the 8th hour representing 47.1% reduction while the reference drug tolbutamide caused a reduction of the blood glucose levels from (109.36±4.60) mg/dL at 0 min to (43.15 ±7.60) mg/dL at the 240 min representing 60.5% reduction but there was a rise to (95.16±9.20) mg/dL at the 8th hour representing 13.0% reduction.

At the doses of 150 and 300 mg/kg of the extract, the blood glucose levels of the rats were increased by 14.6% and 12.8%, respectively.

3.4. Induction of hyperglycemia

After 48 h of intraperitoneal injection of 75 mg/kg streptozotocin, the rats showed clinical signs of polyuria, polydipsia, weight loss (data not included) and hyperglycemia which were typical of diabetes mellitus.

3.5. Effect of DBE on STZ- induced hyperglycaemic rats

The result of the effect of DBE on mean blood glucose level in STZ-induced hyperglycaemia is presented in Figure 1. The result showed that the blood glucose levels of group 1 (negative control) were increased from 445.04418.54 at zero min to 485.85±23.55 at the 480th min representing 8.4% increase. Generally, DBE caused a significant ($P<0.001$) dose and time dependent reduction in the blood glucose levels of the rats 150, 300 and 600 mg/kg, reducing the mean blood glucose levels by 1.7%, 22.8% and 43.4%, respectively at the 480th min when compared to the negative group. The reference drug tolbutamide (100 mg/kg) stabilized the blood glucose level throughout the period of the study (Figure 1).

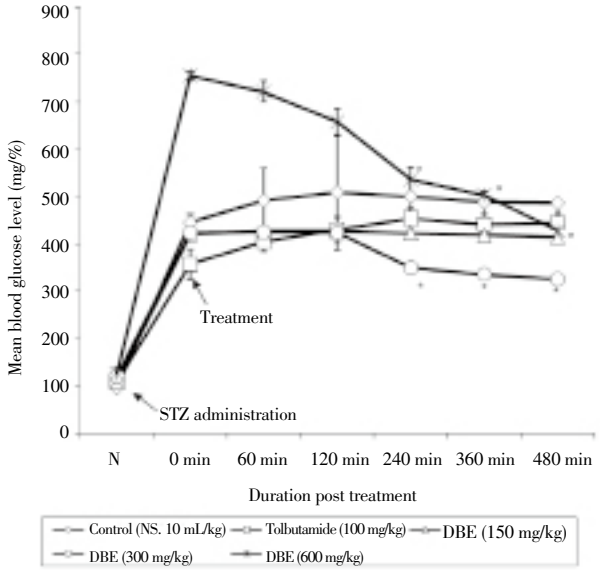

Figure 1. Effect of DBE on blood glucose level in STZ induced hyperglycaemic rats.
*: $P<0.05$ compared with 0 min.

Also the extract at the doses of 300 and 600 mg/kg caused various levels of reduction ($P<0.01-P<0.001$) of the mean blood glucose levels from 240-480 min, while at the dose of 150 mg/kg DBE though there was reduction in the blood glucose levels of the rats, it was not statistically significant ($P>0.05$) and that was observed in 360 min after administration of DBE.

3.6. Effect of DBE on oral glucose tolerance test in normoglycaemic Rats

Figure 2 shows the result of the effect of DBE on oral

Table 1
Effect of DBE on the mean blood glucose levels of normoglycemic rats(mg/dL).

Group	Treatment	Fasting blood glucose level						
		0 min	30 min	1 h	2 h	4 h	6 h	8 h
1	Normal saline(10 mL/kg)	48.11±6.40	56.52±5.30	63.62±7.90	68.11±6.30	64.25±14.90	80.19±16.80	86.70±15.80
2	Tolbutamide (100 mg/kg)	109.36±4.60	57.42±6.10*	56.42±12.60**	52.90±12.50**	43.15±7.60**	71.78±7.00	95.16±9.20
3	DB extract (150 mg/kg)	82.90±6.70	84.00±4.60	86.80±8.00	88.40±4.30	86.80±4.30	101.60±5.20	96.00±8.12
4	DB extract (300 mg/kg)	78.91±1.60	96.53±15.30	87.64±6.40	113.45±21.60	126.18±42.30	83.64±7.70	90.46±11.70
5	DB extract (600 mg/kg)	89.70±6.50	77.71±3.20	71.12±3.20*	73.43±3.30*	57.43±7.00**	53.71±6.40**	47.43±1.70**

*$P < 0.05$; ** $P < 0.005$ when compared to negative control group.

glucose tolerance test in normal rats. After 30 min of glucose load, there was about a two folds increase in the mean blood glucose levels of the rats in the two groups. This was followed by a gradual decrease resulting in 30.4% and 29.2% reduction by the extract (600 mg/kg) and normal saline, respectively at the 180 min after administration.

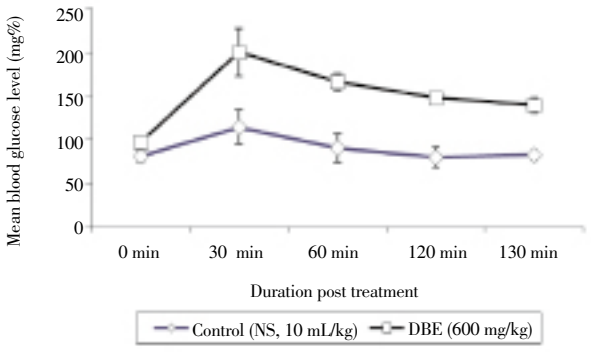

Figure 2. Effect of DBE on oral glucose tolerance test in normal rats.

3.7. Phytochemical screening

The phytochemical spot tests showed that the methanol leaf extract of *D. bidens* contains saponins, tannins, steroids and terpenoids.

4. Discussion

The present study was designed to investigate the antihyperglycaemic effects of the methanol leaf extract of D. bidens using normal and STZ-induced hyperglycaemic models in rats. The methanol leaf extract of *D. bidens* was greenish black in colour and gave a yield of 1.63% w/w dry matter. Acute toxicity test of the DBE in mice showed that there were signs of depression and clustering together which suggests the involvement of central nervous system. Mortality (40%) was recorded in 10 h after administration of the extract in the mice that received 2 000 mg/kg DBE. Based on this, the doses of DBE used in this study did not exceed 600 mg/kg.

STZ is a broad spectrum antibiotics glucosamine nitrosourea compound extracted from Streptomyces acromogens. STZ-induced hyperglycaemia is associated with the generation of reactive oxygen species causing oxidative damage[17] and causes the destruction of β-cells, resulting in the development an insulin dependent syndrome characterized by severe hyperglycaemia, polydipsia, insulinopenia and weight loss[18]; which is characteristic of type 2 diabetes mellitus or non-insulin dependent diabetes mellitus.

The results of this study demonstrated that tolbutamide (100 mg/kg) and DBE significantly ($P<0.05$, 0.005) reduced blood glucose level in normal rats when compared with the negative control. This effect commenced 30 min after drug administration and lasted till 4 h, while that of DBE started 1 h after extract administration and lasted throughout the duration of the study. Since DBE (600 mg/kg) caused 47% reduction in blood glucose level in normal rats, therefore individuals who use this plants for other folkloric reasons other than diabetes mellitus may stand the risk of hypoglycaemic coma.

Based on the finding above, STZ-induced diabetic model in rats was used to evaluate the antihyperglycaemic effect of DBE in rats. The therapeutic objectives are to normalize glucose-induced insulin secretion and restore glucose transport into insulin sensitive tissues[19]. DBE may be one of such plants that may restore insulin sensitivity in non-insulin dependent diabetes mellitus. Our findings showed that the hyperglycaemia was very severe (above 700 mg/dL) and DBE (600 mg/kg) able to reduced blood glucose level from 755.59 mg/dL at zero time to 427.78 mg/dL 8 h (about 57% reduction) after DBE administration. Also botanical products can improve glucose metabolism and the overall condition of individuals with diabetes not only by hypoglycaemic effects but also by improving lipid metabolism, antioxidant status and capillary function[20]. *D. bidens* leaf extract may have achieved its blood glucose lowering effects through one or a combination of the above mechanisms.

To confirm antihyperglycaemic effect of DBE, oral glucose tolerance test was conducted normal rats. Single dose of 600 mg/kg DBE used because it produced the highest antihyperglycaemic effect in STZ-induced hyperglycaemic study. DBE (600 mg/kg) significantly ($P<0.05$) decreased the blood glucose level between 2 and 3 h after glucose load. This shows that DBE-induced antihypergylcaemic property may involve pancreatic and extra-pancreatic mechanisms. Pancreatic involvement may be due to release of insulin from healthy pancreas in normal rats[21], while extra pancreatic pathway may be as a result of increased glucose utilization by the tissues and or reduced intestinal absorption of glucose[22-28].

The phytochemical screening showed that the methanol leaf extract of *D. bidens* contains sapponins, tannins, steroids and terpernoids. Tannins and flavonoids isolated from other antidiabetic plants have been found to stimulate secretion or possess insulin- like effects[29]. It is therefore possible that

the antihyperglycaemic activity of *D. bidens* leaf extract may be due to its phytoconstituents.

In conclusion, the use of DBE in folkloric medicine, thus, has a high scientific correlation with the data generated in this study, where DBE administered orally produced a significant decrease in the blood glucose levels in normoglycaemic and STZ induced-diabetic rat models and therefore suggests its antidiabetic potential and may have acted through other mechanism(s) other than direct effect on glucose uptake. However, more work should be carried out to determine the toxicity profile, isolate the bioactive compound(s) in the plant and to determine the exact mechanism(s) of action.

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