



The Effect of *Anisopus mannii* on Blood Glucose Levels of Normal and Diabetic Wistar Rats

Darlington, Akukwu ^a, Catherine, Akukwu ^a, Ugochukwu, Aguwa ^{b*}, Ambrose, Agulanna ^b, Obatawwe, Ukoba ^c, Izuchukwu, Okonkwo ^d, Somadina, Okeke ^b, Matthew, Nwankwo ^e, Doris, Ogbuokiri ^b, Paul, Demshimeno ^f and Adline, Aguwa ^d

^a David Umahi Federal University of Health Sciences, Uburu, Ebonyi State, Nigeria.

^b Anatomy Department, Nnamdi Azikiwe University, Nnewi Campus, Nigeria.

^c Delta State University Teaching Hospital, Abraka, Nigeria.

^d Nnamdi Azikiwe University Teaching Hospital Nnewi, Nigeria.

^e Abia State University, Uturu, Nigeria.

^f Public Health Emergency Operation Centre Yola Specialist Hospital, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/112943>

Original Research Article

Received: 01/12/2023

Accepted: 06/02/2024

Published: 13/02/2024

ABSTRACT

Diabetes mellitus, a chronic metabolic disorder of carbohydrate, lipid and protein metabolism is characterized by persistent elevation of fasting blood glucose due to insufficient or complete

*Corresponding author: E-mail: us.aguwa@unizik.edu.ng, usaguwa@gmail.com;

cessation of insulin synthesis or secretion and / or peripheral resistance to insulin action. One is considered diabetic when his/her fasting blood glucose level falls between 160-200mg/dl. Conventional drugs used for the management of diabetes mellitus are expensive and produce side effects on different patients, hence the need for a more natural remedy. *Anisopus mannii* stem was collected from a bush in Yola, Adamawa State, Nigeria and identified by a taxonomist in the Department of Biological Sciences, Nnamdi Azikiwe University Awka. Fifty-five adult male Wistar rats weighing 200-250g were procured from physiology department, Nnamdi Azikiwe University and used for the work; 25 were used for acute toxicity test and 30 were used for the experiment proper. The rats were acclimatized for two weeks before the experiment began. They were fed with commercial Grower's Mash (Livestock feed, Nigeria Ltd.) and provided clean tap water *ad-libitum*. It was observed that, at 600mg/kg, the hypoglycemic and anti-diabetic effect of the *Anisopus mannii* stem aqueous extract was comparable to glibenclamide, a conventional drug used in managing diabetes mellitus, with a duration of action that extended for up to 18 hours. The possible mechanism of action of *Anisopus mannii* stem aqueous extract may be via increased peripheral utilization and decreased intestinal absorption of glucose in diabetic rats and, may be with stimulation of insulin release in normal rats. Isolation of the active principle(s) constitutes area of further research. Aqueous extract of *Anisopus mannii* stem have hypoglycemic and anti-diabetic activities and thus justifying its use by traditional herbalist in the management of diabetes mellitus. These effects could be attributed to the presence of saponins, flavinoids in the extract.

Keywords: *Diabetes mellitus; blood glucose; Anisopus mannii; glibenclamide.*

1. INTRODUCTION

"Diabetes mellitus is a serious endocrine syndrome characterized by persistent elevation of fasting blood glucose due to insufficient or complete cessation of insulin synthesis or secretion and / or peripheral resistance to insulin action" [1]. "This syndrome causes disorder of carbohydrate, lipid and protein metabolism, which if kept unchecked, results in complications such as heart disease, stroke, kidney disease, retinopathy, ulceration and gangrene of the extremities in the long run" [2]. "Diabetes mellitus is a chronic metabolic disorder of carbohydrate, lipid and protein metabolism characterized by persistent elevation of fasting blood glucose due to insufficient or complete cessation of insulin synthesis or secretion and / or peripheral resistance to insulin action" [1]. "A patient is considered diabetic when his or her fasting blood glucose level falls between 160-200mg/dl" [3].

"Type 1 diabetes is characterized by absolute insulin deficiency in the body as a result of decreased beta cells of islet of Langerhans of the pancreas" [4]. "Insulin deficiency becomes so low that the required concentration which normally prevent lipolysis and ketogenesis cannot be sustained and treatment requires insulin exogenously and hence otherwise referred to as insulin-dependent diabetes (IDDM). Type 2 diabetes which is the most common form of diabetes occurs due to a combination of

defective insulin secretion and peripheral insulin resistance. There is however, enough endogenous insulin to prevent ketosis and the patient may survive without insulin therapy, hence it is referred to as non insulin- dependent diabetes (NIDDM). Gestational diabetes usually affects pregnant subjects and it shares the characteristic of both Type 1 and 2 diabetes"[5].

"Recent statistics shows that the global epidemic of diabetes mellitus is still on the increase and especially worse in developing countries notwithstanding all efforts made in research" [6]. "About 120 million people are affected globally and this figure is likely to increase by the year 2025" [5][7]. "In the animal population, diabetes is also becoming an increasingly common medical condition for pets affecting 1 in every 400 dogs and cats each year" [8][9]. "Despite several efforts, diabetes remains a major problem whose prevalence is now assuming pandemic proportion" [10]. "The WHO Expert Committee on diabetes had recommended continued evaluation of folkloric method of managing the condition because of high mortality and morbidity arising from its attendant complication and drawbacks associated with the use of conventional anti-diabetic agent" [11]. Therefore the search for natural agents to curb and manage diabetics continues to be a concern to scientists. This is because, compared with synthetic drugs; anti-diabetic agents derived from plants are frequently less toxic with fewer side effects [11]. Thus, in many countries, it is

traditional to use plants to control diabetes [12] [13].

Among the several indigenous plants used in the local management of diabetes in Nigeria is *Anisopus mannii* commonly called *sweet killer* or *destroying sweetness*. *A. mannii* is a strong climber used traditionally as anti-diabetic and aphrodisiac. It is also used traditionally in the treatment of fever and cough. The plant is reported to have anti-bacterial property [13]. This work is designed to investigate the effect of *Anisopus mannii* on blood glucose levels of normal and diabetic Wistar rats.

“Blood sugar is the amount of glucose in blood which is usually expressed in millimol/litre (mmol/L) or milligram per deciliter (mg/dl). Maintenance of blood glucose within narrow limits needs to be very finely and efficiently regulated” [14]. “This is important because it is essential to have continuous supply of glucose to the red blood cells, renal medulla and especially the brain which has an obligatory requirement for glucose” [15]. “In humans, a normal person maintains blood glucose value between 70-110mg/dl. Following meal, there is post-prandial rise in blood glucose but does not usually rise above 140mg/dl due to prompt secretion of insulin. Hyperglycemia results when the pancreas does not release enough insulin (Type 1 diabetes) or tissue resistance to respond to the effect of insulin (type 2 diabetes)” [14]. “Blood glucose levels below 50mg/dl is regarded as hypoglycemia which occurs when glucose in the body is used up, when glucose release in the blood stream is slower than is needed or when excessive amount of insulin (as occur in tumour of the pancreas) is released into the blood stream” [16][17]. “Hypoglycemia even for a short while is fatal while hyperglycemia in the long-run leads to life-threatening complications as seen in diabetic patients” [15].

“Cardinal symptoms of diabetes include glucosuria which results when the glucose levels in the blood exceed the renal threshold, and due to osmotic effect, more water accompanies glucose in the urine giving a clinical picture of polyuria. To compensate the loss of water, thirst centre is activated giving a clinical sign of excessive water intake (polydipsia). Excessive food intake (polyphagia) without corresponding weight gain to compensate for loss of glucose and protein is seen” [18]. “The important differential diagnosis for weight loss is diabetes mellitus, tuberculosis, hyperthyroidism, cancer and acquired immunodeficiency syndrome

(AIDS). Often the presenting complaint may be chronic recurrent infection such as boil and abscess. Any person with recurrent infection should be investigated for diabetes. When glucose level in the extra cellular fluid is increased, bacteria gets good nutrition for multiplication, at the same time, macrophage function of the host is inefficient due to lack of glucose utilization. Inadequate control of plasma glucose concentration can also lead to long term complication such as vascular diseases like atherosclerosis in medium-sized vessel with plaque formation and consequent intravascular thrombosis. If this condition occurs in coronary artery, myocardial infarction results” [15].

2. MATERIALS AND METHODS

2.1 Plant Collection and Identification

Fresh stem and leaves of *Anisopusmannii* were collected from a bush in Yola, Adamawa State, Nigeria and identified by a taxonomist in the Department of Biological Sciences, Nnamdi Azikiwe University Awka.

2.2 Extract Preparation

The stem of the plant was air-dried to obtain a weight of 260g and then pulverized with mortar and pestle into a fine powder. The resulting powder was then extracted with distilled water using reflux method. The filtrate obtained was completely dried into a light green solid residue over a water bath, giving a yield of 25.6% (w/w). The extract was then stored in a water-tight and air proof container which was kept in the refrigerator until use. It is from this stock that a fresh solution is made each time it is desired.

2.3 Phytochemical Screening

The aqueous extract was screened for the presence of various photochemicals as follows; Test for Alkaloids was carried out according to the method of Meyer reported by [19]. Test for Tannins was carried out according to the method reported by [20][21]. Test for Carbohydrate was done using Molisch test as reported by Trease and Evans [22]. Test for Flavonoids was done according to the method of Brain and Turner (1975). Test for Saponins was done according to the method reported by Soforawa [20]. Test for Terpenes was done according to the method reported by Silva *et al.*, [21] Test for Cardiac glycoside (Salkowski's test) was carried out according to the method reported by Silva *et al.*,

[21]. Test for Steroids was done by Liebermann-Buchard's test reported by Silva *et al.*, [21]. Test for Anthraquinones was done using the Bornstranger's test) as reported by Trease and Evans [22].

2.4 Experimental Animals

Fifty-five (85) adult male Wistar rats weighing 200-250g were used for the work. The rats were procured from Department of Anatomy, Nnamdi Azikiwe University, and kept in a rubber cage in the department for two weeks for acclimatization before the experiment began. They were fed with commercial Grower's Mash (Livestock feed, Nigeria Ltd.) and provided clean tap water *ad libitum*.

2.5 Acute Toxicity Study

The arithmetic method of Karbar as modified by Aliu and Nwude (1982) was used for the acute toxicity study. Twenty-five (25) male rats were divided into five (5) groups of five (5) rats each labeled A–E. Group A received distilled water while groups B, C, D and E received the extract intraperitoneally at doses of 200, 400, 800 and 1600mg/kg body weight respectively.

2.6 Evaluation of Anti-Diabetic Effect of the Extract

A total of thirty (30) male diabetic rats weighing between 200 to 250g were used for the study. The rats were made diabetic by single intra-peritoneal administration of Alloxan Monohydrate (Sigma Chemical Co., St. Louis, U.S.A.) at a dose rate of 150mg/kg body weight dissolved in 0.1M freshly prepared cold citrate buffer of pH 4.5 (as described by Pari and Venkateswaran, [23]). Stable hyperglycemia was confirmed on the fifth day post Alloxan administration when the fasting blood glucose levels of the rats were greater than 180mg/dl. The rats were then divided into six (6) groups of five (5) rats each. Group A were administered distilled water while Group B received the standard drug (Glibenclamide) at 0.1mg/kg body weight. Groups C, D, E and F received 200, 400, 600, and 800mg/kg body weight of the extract respectively.

2.7 Blood Sample Collection and Glucose-Level Determination

Blood samples were collected from the tail vein by snipping 2cm of the tail with a scissors. Blood

glucose was determined by glucose oxidase method of Trindar [24], using One Torch Basic Glucose monitoring system (LifeScan Inc. Milpitas, California, USA) at 0 hour and at 1, 6, 12 and 18 hours post extract administration.

2.8 Statistical Analysis

Data obtained were presented as Mean \pm Standard deviation of 5 rats per group. Differences between means were compared using one-way analysis of variance (ANOVA). GraphpadInStat® (2003) computer statistical software package was used for the analysis and results were considered statistically significant at $P \leq 0.05$.

3.RESULTS

3.1 Phytochemical Screening

The result of the phytochemical analysis of stem aqueous extract of *A. mannii* as presented in Table 1 below indicates the presence of alkaloid, tannins, flavonoids, saponins, cardiac glycoside, terpenes, carbohydrate and steroids.

3.2 Acute Toxicity Studies

No rat died after administration extract at 200, 400 and 800 mg/kg doses. However, following the administration of 1600mg/kg four out of five rats died within one hour post-administration. The LD₅₀ was therefore calculated to be 1280 mg/kg as shown in Table 2.

3.3 The Effect of *Anisopus mannii* Stem Aqueous Extract on Mean Blood Glucose Levels of Normal Rats

The result of the effect of *A. mannii* stem aqueous extract on blood glucose level of normal rats is presented in Table 3: After 1 hour post-extract administration, the group treated with 200mg/kg dose of the extract showed insignificant ($P > 0.05$) decrease in blood glucose level from zero hour value of 94.40 ± 7.0 to 90.80 ± 3.0 (9.4% decrease). At 6 hours post-extract administration, the blood glucose decreased significantly ($P > 0.05$) to 85.80 ± 9.0 (16.75% decrease). The blood glucose of the group at 12 and 18 hours significantly ($P > 0.05$) decreased to 65.20 ± 3.0 by (52.4%) and 59.0 ± 2.0 (68.4%) respectively.

Table 1. Phytochemical screening of *Anisopusmannii* Stem Aqueous Extract

S/No	Phytochemical constituent	Result
Test for Alkaloids	-with Dragendorff's reagent	+
	-with Mayer's Reagent	+
Test for Tannins	-Ferric chloride test	+
	-Lead ethanoate test	+
Tests for Carbohydrate	-General Molisch test	+
	-Barfoed test (Monoccharides)	+
	-Fehling test (Reducing sugar)	+
	-Standard test for ketones	+
	-Standard test for pentoses	+
Tests for Flavinoids	-Lead acetate test	+
	-Sodium hydroxide test	+
	-Ferric chloride test	+
	-Pew test	+
Test for Saponins	-Froth test	+
Test for Cardiac glycoside		+
Test for Terpenes and Steroids	-Lieberman-Burchard test	+
	-Salkowski test	+
Test for Anthraquinone	-Bournstrager test	-
	-Free and combined anthraquinone test	-

Table 2. Acute Toxicity Study Of *Anisopus manniin* Wistar Rats

Dose (mg/kg)	No of Animals	Dose Diff.	Death	Mean D (md)	md x Dd
Control	5	0	0	0	0
200	5	200	0	0	0
400	5	200	0	0	0
800	5	400	0	0	0
1600	5	800	4	2	1600

Key: Diff. = Difference

$$LD_{50} = LD_{1600} - Dd \times md / N$$

$$= 1600 - 1600/5$$

$$= 1280 \text{ mg/kg}$$

In 400mg/kg treated group, even at one hour, there was significant ($P>0.05$) decrease in blood glucose level from zero hour value of 101.4 ± 13 to 82.2 ± 3.0 (23.3%). At 6 hours, significant ($P>0.05$) decrease to 75.8 ± 5.3 (33.7%) was observed while at 12 and 18 hours, further drop to 61.4 ± 11.3 (65.1%) and 57.8 ± 10.9 (75.4%) were respectively recorded which was significantly ($P>0.05$) lower in comparison with the zero hour blood glucose value.

In 600mg/kg treated group, blood glucose level was significantly ($P>0.05$) reduced to 85.6 ± 11.2 (19%) after 1 hour of extract administration, and further significant ($P>0.05$) decrease to 80.6 ± 41 (26.7%), 55.8 ± 3.8 (83.1%) and 46 ± 6.2 (122%) were recorded at 6, 12 and 18 hours respectively.

Similarly, after 1 hour post-extract administration, blood glucose level decreased significantly ($P>0.05$) to 82.6 ± 6.6 (17.1%) in 800mg/kg

treated group and at ($P>0.05$) reduced to 66.2 ± 6.5 (46.2%), 44 ± 7.0 (120%) and 41.4 ± 3.8 (134%) respectively, after 6, 12 and 18 hours.

The control group has their blood glucose level maintained between 98.6 ± 2.0 and 116.20 ± 17 .

Numbers in bracket indicate percentage decrease (-) in blood glucose level when compared with zero hour blood glucose value.

3.4 The Effect of *Anisopusmannii* Stem Aqueous Extract on Mean Blood Glucose Levels of Diabetic Rats

The effect of *A. manniin* stem aqueous extract on mean blood glucose levels of diabetic rats is presented in Table 4. The mean blood glucose levels of rats treated with 200, 400, 600 and 800mg/kg of the extract at 0 hour were 257.6 ± 49.8 , 248 ± 73 , 313.2 ± 2.17 and 280.2 ± 58 mg/dl respectively.

Table 3. The Effect of *Anisopus mannii* Stem Aqueous Extract on Mean Blood Glucose Levels of Normal Rats

Time post –treatment (hours)	Treatment dose(Mg/kg)				
	0	1	6	12	18
Control	116.2±17	115.8±16 (-0.3%)	111.8±8.0 (-4%)	109.8±6.0 (-5%)	98.6±2.0 (-17%)
200	94.4±7.0	90.8±3.0 (-9.4%)	85.8±9.0* (-16.7%)	65.2±3.0* (-52.4%)	59±2.0* (-68.4%)
400	101.4±13	82.2±3.0* (-23.3%)	76±6.0* (-33.4%)	61.4±11* (-61-5%)	57.8±10* (-75.4%)
600	102.2±8.0	85.6±11* (-19%)	80.6±4.0* (-26.7%)	55.8±3.8* (-83.1%)	46±6.2* (-122%)
800	96.8±9.0	82.6±6.0* (-17.1%)	66.2±6.5 (-46.2%)	44±7.0* (-120%)	41.4±3.8* (-132.7%)

$X = \text{Mean} \pm \text{SD}$

* = significantly ($P < 0.05$) lower than zero hour blood glucose value

Table 4. The Effect of *Anisopus mannii* Stem Aqueous Extract on Mean (X) Blood Glucose Level of Diabetic Rats

Time post –treatment (hours)	Treatment dose (mg/kg)				
	0	1	6	12	18
Diabetic untreated	225.8±51	226.4±65(17.9%)	294.2±53 (23.2%)	309±49 (26.9%)	331.6±57 ^a (31.9%)
Glibenclamide	235.8±41	147.8±39 (-59.5%)	102.6±29* (-129.8%)	77.6±16* (-2034%)	58.8±11* (-301%)
200	257.6±49	204.4±03 (-26.1%)	167.6±28* (-53.6%)	114.4±23* (-125.2%)	126.6±43* (-104.4%)
400	248±73	160.8±39 (-54.1%)	132.4±42* (-87.3%)	101.2±24 (-145%)	108±16* (-129.6%)
600	313.2±72	170.2±45 (-84%)	140.6±44* (-122.7%)	100±21* (-213.2%)	177.2±35* (-76.7%)
800	280.2±58	149±25 (-88%)	125.6±43* (-123%)	85.9±25* (-226%)	100.2±14* (-179%)
Control	116.2±17	115.8±16 (-0.3%)	111.8±8 (-4%)	109.8±6 (-5%)	98.6±20 (-17%)

$X = \text{Mean} \pm S$

* = significantly ($P < 0.05$) higher than zero hour blood glucose value

After 1 hour, the blood glucose level of rats treated with 200mg/kg of the extract significantly decreased to 204.2 ± 30 (26.15% decrease). The blood glucose levels of the same rats significantly ($P < 0.05$) decreased to 167.6 ± 28 (53.6% decrease), 114.4 ± 23 (125% decrease) and 126.2 ± 43 (104% decrease) at 6, 12 and 18 hours post-extract administration respectively.

The groups treated with 400mg/kg body weight of the extract had their blood glucose level significantly ($P < 0.05$) decreased to 160.8 ± 39 (54.1%), 134.4 ± 42 (87.31%), 101.2 ± 24 (145%) and 108 ± 16 (129.6%) at 1, 6, 12 and 18 hour(s) post-extract administration respectively.

The blood glucose levels of rats administered 600mg/kg also significantly ($P < 0.05$) decreased from zero hour value to 170.2 ± 45 (84%), 140.6 ± 44 (122.7%), 100 ± 21 (213.2%) and 177.2 ± 6 (76.7%) at 1, 6, 12 and 18 hours after extract administration.

In 800mg/kg treated group, all the values of blood glucose levels were also significantly ($P > 0.001$) reduced from zero the hour value at 1, 6, 12 and 18 hours blood samples were taken to 149 ± 25.6 (88%), 125.6 ± 22.43 (123%), 85.9 ± 25 (226%) and 100.2 ± 14 (179%) in the respective hours.

The group of diabetic rats treated with Glibenclamide (standard drug) had their blood glucose level significantly ($P < 0.01$) reduced from zero hour blood level of 235.8 ± 41 at 1 hour to 149.8 ± 39 (58.9%), but decreases were significant ($P > 0.001$) at 6, 12 and 18 hours to 102.6 ± 29 (129%), 77.6 ± 16 (204.6%) and 58.8 ± 11 (301%) respectively.

The diabetic untreated group had their blood glucose levels increased between 225.8 ± 50 and 331.6 ± 57 throughout the experiment. The control group had their blood glucose levels maintained between 98.6 ± 2 and 116.2 ± 17 .

Numbers in bracket indicate percentage decrease (-) in blood glucose when compared with zero hour blood glucose value.

4. DISCUSSION

Many plants used ethno-pharmacologically in managing various disease conditions with little or no scientifically proven information on its efficacy, are now being investigated [13][25]. *Anisopus mannii* was investigated in this study for hypoglycemic and anti-diabetic property. Acute toxicity studies employing parenteral route showed a high LD_{50} value of 1250mg/kg (*i.p*)

indicating the safety profile of the extract. In another work, oral administration of aqueous stem extract of *A. mannii* at a dose limit of 3000mg/kg did not produce any sign of toxicity or death [11]. According to Clarke and Clarke [25], substance with oral LD_{50} of 1000 mg/kg body weight and above can be considered as being safe or of low toxicity.

Preliminary phytochemical analysis of the aqueous extract of the plant revealed the presence of alkaloids, tannins, flavinoids, saponins, carbohydrate, terpenes cardiac glycosides and steroids. Most of these constituents are known in literature to have hypoglycemic and anti-diabetic properties. The natural compounds with anti-diabetic activity with decreasing frequency of occurrence are complex carbohydrate, alkaloids, glycopeptide, terpenoids, and amines, steroids, flavinoids and lipids [26]. Complex carbohydrates have been documented [27][28][29] to have hypoglycemic activity in both normal and induced hyperglycemic rat. Several experimental studies have demonstrated that flavinoids possess many biological and pharmacological properties that include both hypoglycemic and anti-diabetic effect [30]. Saponins have also been reported to have hypoglycemic and anti-diabetic effects which are useful in the management of diabetes mellitus [31][32][33]. Presence of these phytochemicals can therefore explain the hypoglycemic and anti-diabetic potentials observed in *A. mannii* stem aqueous extract.

Assay methods used in the screening of plants for hypoglycemic activity are varied and not directly comparable. In-vivo techniques include animals with normoglycemia or induced hyperglycemia (alloxan, streptozotocin, various hormones, or surgery) and diabetic human subjects [34]. In this study, Alloxan was used for inducing experimental animal model of insulin-dependant diabetes mellitus. A single dose of alloxan (150mg/kg body weight *i.p*) was administered to rats which reliably establish diabetes within 5 days post-induction as evidenced by significant elevation of fasting blood glucose. Literature shows that alloxan induces diabetes by selectively destroying pancreatic beta cells involved in the synthesis, storage and release of insulin [35][8][36].

Dose dependant response in blood glucose lowering effect for both normal and alloxan-induced diabetic rats was observed in this study. At a dose rate of 200mg/kg, there was insignificant decrease in blood glucose in both

normal and diabetic rats at 1 hour post-extract administration, but at 6, 12 and 18 hours, the decrease were significant. At higher doses of 400, 600 and 800mg/kg, the effect was significantly observed even at 1 hour post extract administration and persisted for up to 18 hours. The anti-diabetic mechanisms involved in hypoglycemic activity mentioned in the literature by various researchers include reduction in intestinal absorption of glucose [37][38][39], regeneration of pancreatic beta cells and insulin release [40][41], combination of induced insulin release and increased peripheral uptake of glucose [42] and increased peripheral utilization of glucose as well as glycogen synthesis [42]. Since Alloxan permanently destroys pancreatic beta cells and the extract lowered blood glucose of diabetic rats, such a glucose-lowering effect may be accounted for, in part by decrease in rate of intestinal absorption and in part, due to peripheral glucose utilization or enhanced glycogenic processes with concomitant decrease in glycogenolysis and gluconeogenesis [43,44]. In normal rats, increased insulin release may also be responsible.

5. CONCLUSION

In conclusion, it was observed that, at a dose rate of 600mg/kg, the hypoglycemic and anti-diabetic effect of the *Anisopus mannii* stem aqueous extract was comparable to a conventional drug (glibenclamide) used in managing diabetes mellitus, with a duration of action that extended for up to 18 hours. The possible mechanism of action of *Anisopus mannii* stem aqueous extract may be via increased peripheral utilization and decreased intestinal absorption of glucose in diabetic rats and may be with stimulation of insulin release in normal rats. Isolation of the active principle(s) constitutes area of further research. Aqueous extract of *Anisopus mannii* stem therefore has hypoglycemic and anti-diabetic activities and thus justifying its use by traditional herbalist in the management of diabetes mellitus. These effects could be attributed to the presence of complex carbohydrate, saponins and flavinoids present in the extract.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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