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REGULAR ARTICLE

HYPOGLYCEMIC ACTIVITIES OF AQUEOUS AND METHANOL LEAF EXTRACT OF *HYBANTHUS ENNEASPERMUS* AND *PAQUETINA NIGRESCENS* ON NORMAL AND ALLOXAN INDUCED DIABETIC FEMALE SPRAGUE DAWLEY RATS

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SUMMARY

Objective: Glycemic activities of aqueous and methanol leaf extracts of two medicinal plants commonly used by Traditional Birth Attendants in antenatal care in southwest Nigeria were investigated in 105 adult male Sprague Dawley rats. The two plants are *Hybanthus Enneaspermus* (HE) and *Parquetina nigrescens* (PN). The study was carried out in four phases which are; dose response effect of the extracts on fasted whole blood glucose, effects of the effective doses on OGTT on OGTT, 2weeks prophylactic study of the ED of the aqueous extracts on OGTT and study of the effects of the ED of the extracts on alloxan induced diabetes.

Design: The 85 rats used for the hypoglycemic study was grouped into Control, Aqueous leaf extract of PN (PNaq) treated, Methanol leaf extract of PN (PNmeth) treated, Aqueous leaf extract of HE (HEaq) treated and Methanol leaf extract of HE (HEmeth) treated group. Each group except the control has 4 sub groups of five rats each. The animals were fasted over night (12hrs), and fasting blood glucose level taken as well as blood glucose level after oral administration of the graded doses of each plant extract every thirty minutes for twelve hours, using a standardized one touch glucose meter. The animals were allowed free assess to water throughout the period of the experiment.

Results: The effective hypoglycemic dose (EHD) for HE(aq) and HE(meth) was obtained at 80mg/kg and 180mg/kg body weight respectively. This gave a percentage reduction of whole blood glucose level of 44.15 ± 0.46 at 7hrs and 44.94±0.32 at 10hrs respectively. On the other hand, the EHD of PN (aq) and PN (meth.) was obtained at 80mg/kg body weight and 160mg/kg body weight respectively. This also gave a percentage whole blood glucose reduction of 46.59±0.35 at 4hrs and 48.03±0.44 at 9hrs respectively. A total number of 30 rats were further used to check for the effect of the EHD of the extracts on Oral glucose tolerance test (OGTT). All animals in this test were giving 1.75g/kg body weight of glucose after 12hrs fasting along with the corresponding effective dose of the extracts. HEaq gave a similar hypoglycemic result as Glibenclamide a standard hypoglycemic drug while all others shows different degree of hypoglycemic effects.

Conclusion: The potential hypoglycemic activities of the aqueous leaf extracts of PN and HE could be of benefit in its use by the Traditional Birth Attendants in South west Nigeria in correcting Gestational diabetes. But care must be taking in its indiscriminate use to prevent a situation of energy deprivation both for the mother and the developing fetus.

Keywords: Glycemic activities, *Hybanthus Enneaspermus*, *Parquetina nigrescens*, oral glucose tolerance test.

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1. Introduction

Diabetes mellitus is a universal problem affecting human societies at all stages of development. It is a condition where sufficient amount of insulin is either not produced or the body is unable to use the insulin that is produced, leading to excess glucose in the blood [1]. Insulin is the hormone that enables glucose uptake and utilization by the body cells for energy supply. The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes and an estimated 1.1 million people died of this disease condition in 2005 alone. [2].The three basic types of Diabetes mellitus are Type I (insulin dependent diabetes, IDDM), Type 2 diabetes (Non insulin dependent diabetes NIDD) and Gestational diabetes (GD). Gestational diabetes is a condition in which the blood glucose of a previously non-diabetic woman becomes elevated during pregnancy. When not properly controlled, it can lead to severe complications over time. It usually results in macrosomia, respiratory distress and sometimes stillbirth [3, 4].

The limitations of currently available pharmacological agents for control of blood glucose have stimulated research on novel antidiabetic agents with different mechanism of action [5]. There are so many published works on the usefulness of medicinal plants in management of Non insulin dependent diabetes [6, 7, 8, 9, 10]. *Hybanthus enneaspermus* and *Parquetina nigrescens* (PN) are two major medicinal plants whose leaves are used by Traditional birth attendants (TBAs) in the antenatal care in South west states of Nigeria. The TBAs claimed that the administration of the leaf extract of the plant prevents the development of such diseases conditions as gestational diabetes as well as development of macrosomnia in fetus. They also claimed that the administration of the leaf extract boost hematological parameters and make delivery safe.

Parquetina nigrescens (PN) is a shrub commonly found in secondary forest and around villages. It is distributed from Senegal to Nigeria in West Africa. It is a perennial plant with twining stems and a base tapering 10-15cm long and 6-8cm broad. It has smooth long stems on which are located the leaves. Its flower grows from its side branches having whitish outside and inner reddish colouration. The fruit is composed of two parts; an outer woody and an inner softer part. It housed the featherlike seed. *Parquetina nigrescens* is called Kwànkwánín tsa tsumbe in Hausa north Nigeria, and Ogbo in Yoruba South west Nigeria. *Hybanthus enneaspermus* is also a shrub growing in a well-watered area of the rain forest. It grows to about 6cm coiling and crawling round in its colony. It has tiny leaves that adorn the twig like stems. It is known as 'Abiwere in Yoruba land , south west Nigeria.

There are several reports on the medicinal activities of the two plants. Hemalatha et al (2003) [11] reported the anticonvulsant and free radical scavenging activity of the aqueous and ethanol extract of the HE, while Weniger et al (2004) [12] reported the antiplasmodial activity. Tripathy et al (2005) [13] reported the curative effect of the extract of *Hybanthus enneaspermus* on Jaundice. Sahoo et al (2006) [14] and Awobajo et al (2009a) [15] have both reported the antimicrobial activities of HE on some organism of importance to female reproductive tract while Oluwafemi and Debiri (2006) [16] have reported the antimicrobial potential of extract of PN. Datte et al (1996) [17] also reported the spasmogenic action of methanol extract of *Parquetina nigrisence* on pregnant rat myometrium. Datte at al (1999) [18] reported that the extract of *Parquetina nigrescens* on pregnant rat myometrium. Datte at al (1999) [18] reported that the extract of *Parquentina nigrescens* exert a sympathomimetic effect on isolated portal vein smooth muscle. Agbor and Odetola (2005) [19] reported a significant increase in erythrocyte indices such as red blood cell count,

hemoglobin concentration, and hematocrit in rats after acute blood loss.

This research work therefore was designed to investigate the hypoglycemic activities of two medicinal plants used by Traditional Birth Attendants in pre and post natal care in the southwest Nigeria using female Sprague Dawley rats.

2. Materials And Methods

Plant materials

The leaf of *Hybanthus enneaspermus* and *Parquetina nigrescens nigrescens* plants were harvested from a semi forest in Ijebu-ode Ogun state Nigeria. Taxonomic identity of the plants was confirmed by a taxonomist, Dr. O. A. Ugbogu, Chief Research Officer at the Forest Research Institute of Nigeria (FRIN) and voucher no for each of the leaf (*Parquetina nigrescens* FHI. NO. = 108223 and *Hybanthus enneaspermus* FHI NO.= 108226) deposited at the Forest herbarium, Ibadan. The leaves were oven dried and extraction carried out using Soxhlet extractor, while phytochemical analysis and lethal dose determination of the plant extracts have earlier been reported [20]. The crude extract was filtered first through cotton wool, then through Whatman filter paper No 42 (125 mm) and the filtrate store under -4^{0}C until used.

Animal grouping drug and extract administration

This work was divided into four phases. The first phase was the dose response effect of the graded doses of the extracts on whole blood glucose level while the second phase was the effect of the effective dose (ED) on oral glucose tolerance test. The third stage was the prophylactic study of two weeks administration of the ED of the aqueous leaf extracts on whole blood glucose. The fourth phase studied the effect of administration of the ED of the leaf extracts on whole blood glucose level in alloxan induced diabetes in rats. Female Sprague Dawley rats were used in this experiment. The animals used were authenticated by Dr. I.A.Taiwo at the Department of cell Biology and genetics, University of Lagos.

Dose response effects of graded doses of the extracts to fasted whole blood glucose level

Fifty non pregnant female Sprague Dawley rats weighing between 140 – 160 grams were used for the first phase of the experiment. They were randomly divided into six groups namely, Control rats (received only the vehicle), HEaq, HEmeth, PNaq, and PNmeth treated group. The extract treated groups were further sub divided into four subgroups of five rats each. The subgroups were administered the graded dose of the extracts. The doses used for HEaq was 40mg/kg, 60mg/kg, 80mg/kg and 120mg/kg body weight while that of HEmeth was 80mg, 120mg, 160mg and 180mg/kg body weight . Also the doses used for PNaq was 60mg, 80mg, 120mg and 180mg/kg body weight while the doses for PNmeth was 80mg, 120mg, 160mg and 180mg/kg body weight. The extract was constituted using distilled water and administered orally using sterilized oral dosing needle to the different groups of animals after 12hours fasting.

Phase 2: The second phase of the experiment was carried out on twenty female non diabetic rats divided into four groups namely Control, HEaq (received the ED), HEmeth (received the ED), PNaq (received the ED), PNmeth (received the ED) a dose of glucose (1gram/kg body weight) [21] was administered to the different group of rats after 12hours fasting while the basal and 2hourly whole blood glucose level was monitored thereafter. The treated groups received in addition to the glucose load the effective doses of the various leaf extracts obtained from phase 1 of the experiment.

Prophylactic study

The third phase was a prophylactic study on only the aqueous leaf extracts of PN and HE. The twenty female Sprague Dawley rats were divided into four groups of five rats each, namely Control, PNaq, HEaq and Glibenclamide administered group. The

extract treated groups were prior treated with the ED of the extracts for two weeks while the control received only water. All animals were fasted for 12hours before the day for the OGTT. On the day for the OGTT, the basal whole blood glucose level was recorded and a glucose load of 2g/kg body weight [22] was administered orally. The extract treated groups received corresponding ED of the leaf extracts and Glibenclamide group received 0.5mg/kg body weight of glibenclamide. All drugs and extracts were administered orally using a sterilized oral dosing needle. The whole blood glucose was thereafter monitored 2hourly till a reduction was recorded in the whole blood glucose level.

Study on Alloxan induced diabetic

The twenty female Sprague Dawley rats used for this study were randomly divided into five groups namely Control, Diabetic untreated, Diabetic HEaq treated, Diabetic PNaq treated and Diabetic Glibenclamide treated group. On the day of the OGTT, the animals were fasted overnight and the basal whole blood glucose level measured before loading them with glucose orally at a dose of 2g/kg body weight [23]. The extracts were thereafter administered to extract treated groups at the effective hypoglycemic doses. The glibenclamide treated group was administered 0.5mg/kg body weight of glibenclamide orally along with the glucose load. Whole blood glucose change was monitored thereafter 2hourly for 12hours.

Induction of Diabetes in rats

Diabetes was induced by intraperitoneal administration of 120mg/kg body weight of alloxan-monohydrate prepared in normal saline. Alloxan monohydrate was procured from sigma Andriach Germany and was injected after 12hours fasting. Diabetes was achieved after 48hours of administration of alloxan and rats with whole blood glucose above 250mg/dl were recruited for this study.

Blood glucose monitoring

The animals were fasted for 12hrs before the commencement of the experiment while being allowed free access to water. Blood samples were collected from the tail vein from each rat after carefully cleaning of dirt with distilled water. The fasting blood glucose level as well as the blood glucose level after oral administration of each of the extracts was monitored using a blood glucose monitor (One touch) [24]. The blood glucose was recorded 1hrs or 2hrly after the treatment.

All animals used were obtained from the rat colony of the Animal house of the College of Medicine University of Lagos, Nigeria and authenticated by Dr. I.A. Taiwo of the Department of cell Biology and genetics of the University of Lagos. The weights rage between 140 – 160 grams. Rules guiding animal handling and experimentation were observed in all the care and experimental procedures in this work. Glibenclamide was obtained from May & Baker Nigeria Ltd.

Analysis and presentation of results

The results were presented as Mean ± SEM and analysed using one way ANOVA. Percentage whole blood glucose change was also calculated while line graph was used for graphical representation.

Discussion and Conclusion

The use of medicinal plants in the management of diabetes is on the increase, especially plants with high content of insulin-like factors such as flavonoids [25], plants with high free radical scavenging property and many other plants acting through several other mechanisms among which are hepatoprotectve effects on pancreatic β-cells. We have earlier reported the presence of flavonoids and other phytochemical substances in the leaf extracts of both PN and HE [20]. In normoglycaemic rats, hypoglycaemic action of the leaf extracts of *Parquetina nigrescens* (PN) and, *Hybanthus enneaspermus* (HE) were observed to be dose dependent, with prolonged hypoglycaemia at the higher doses (Table 1, 2, 3, 4).

The aqueous extract of both extracts expressed their hypoglycemic effect at lower concentration while the methanolic extract showed hypoglycemic activities at relatively higher concentration (Table 1 and 3). A time course effect of the graded concentrations of the different extracts of HE and PN on reduction of the fasted whole blood glucose level revealed that the effective hypoglycemic doses of the aqueous and methanol leaf extract of *Hybanthus enneaspermus* are, 80mg/kg body weight (ED_{44}) at 7hours and 180mg/kg body weight (ED_{45}) at 10hours respectively. On the other hand, the effective hypoglycemic doses of aqueous and methanolic leaf extracts of *Parquetina nigrescens was* 80mg/kg b. wgt (ED_{47}) at 4hours and 160mg/kg body weight (ED_{48}) at 9hours respectively.

Table1. Dose-time response activities of oral administration of aqueous leaf-extract of *Hybanthus Enneaspermus* on whole blood glucose level in fasted non-diabetic, non gravid Sprague Dawley rats along with the percentage whole blood glucose change.

Time (hours)	Control		HEaq (40mg/kg)		HEaq (60mg/kg)		HEaq (80mg/kg)		HEaq (120mg/kg)	
	Blood glucose level mg/dl	%Change in blood glucose	Blood glucose level mg/dl	%Change in blood glucose	Blood glucose level mg/dl	%Change in blood glucose	Blood glucose level mg/dl	%Change in blood glucose	Blood glucose level mg/dl	%Change in blood glucose
0	70.60±0.25		89.00±0.55		82.20±0.80		82.40±0.93		70.20±0.49	
2	68.20±0.37	6.06±0.52	74.80±1.39	15.96±1.57	62.80±0.86	23.36±1.05	66.60±0.60	18.78±0.73	65.40±0.40	6.84±0.57
4	62.60±0.25	13.77±0.34	60.80±0.37	31.69±0.42	50.60±0.51	38.44±0.62	54.80±0.37	33.17±0.46	58.20±0.37	17.09±0.53
7	62.60±0.25	13.77±0.34	51.80±0.49	41.79±0.55	46.00±0.55	44.04±0.67	45.80±0.37	44.10±0.46*	55.80±0.20	20.51±0.29
8	64.40±0.25	11.30±0.34	54.40±0.25	38.88±0.28	46.20±1.20	43.80±1.46	48.80±0.37	40.49±0.46	45.00±0.63	35.90±0.90
12	67.20±0.37	7.44±0.52	70.60±0.40	20.67±0.45	62.60±0.81	23.84±0.99	62.40±0.68	23.90±0.83	77.80±0.66	-10.83±0.95

Highest percentage change in whole blood glucose level

Table 2. Dose-time response activities of oral administration of methanol leaf-extract of *Hybanthus Enneaspermus* on whole blood glucose level in fasted non-diabetic, non gravid Sprague Dawley rats along with the percentage whole blood glucose change.

Time (hours)	Control		HEmeth (80mg/kg)		HEmeth (120mg/kg)		HEmeth (160mg/kg)		HEmeth(180mg/kg)	
	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change In blood glucose	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose
0	70.60±0.25		70.20±0.66		72.40±0.40		74.4±0.25		77.0±0.45	
1	70.60±0.25	2.76±0.34	65.00±0.32	7.41±0.45	72.0±045	0.55±0.62	74.6±0.25	-0.27±0.33	66.2±0.37	14.03±0.49
4	62.60±0.25	13.77±0.34	65.00±0.32	7.41±0.45	70.40±0.25	2.76±0.34	65.4±0.25	12.1±0.33	66.4±0.25	13.77±0.32
6	62.60±0.25	13.77±0.34	62.20±0.37	11.40±0.53	65.60±0.51	9.39±0.70	62.6±0.25	15.86±0.33	53.2±0.20	30.91±0.26
8	64.40±0.25	11.30±0.34	60.60±0.25	13.68±0.35	59.00±0.31	18.51±0.44	63.0±0.32	15.32±0.43	53.6±0.25	30.39±0.32
10	64.40±0.25	11.30±0.34	59.40±0.25	15.39±0.35	54.40±0.40	24.86±0.55	44.6±0.25	40.05±0.33	42.4±0.25	44.94±0.32*
12	67.20±0.37	7.44±0.52	43.00±0.45	38.75±0.64	46.00±0.32	36.46±0.44	34.4±0.40	53.76±0.54	43.6±0.25	43.38±0.32

Highest percentage change in whole blood glucose level

Table 3. Dose-time response activities of oral administration of aqueous leaf-extract of *Parquetina nigrescens* on whole blood glucose level in fasted non-diabetic, non gravid Sprague Dawley rats along with the percentage whole blood glucose change.

Time (hours)	Control		PNaq(60mg/kg		PNaq(80mg/kg)		PNaq(120mg/kg)		PNaq(180mg/kg)	
	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose	Blood Glucose level mg/dl	%Change in blood glucose
0	70.6±0.25		43.6±0.51		54.6±0.24		48.2±0.37		52.6±0.24	
1	70.6±0.25	2.76±0.34	44.6±0.24	0.82±0.42	45.4±0.24	26.71±0.72	52.0±0.32	0.00±0.00	38.0±0.32	18.93±0.50
3	62.6±0.25	13.77±0.34	51.2±0.37	8.42±0.33	43.0±0.32	32.39±0.35	49.0±0.32	37.87±0.66	41.8±0.37	33.33±0.42
4	62.6±0.25	13.77±0.34	37.8±0.49	34.0±0.69	45.4±0.24	46.50±0.35*	43.0±0.32	44.08±0.55	35.2±0.37	23.2±0.33
8	64.4±0.25	11.3±0.34	49.2±0.37	40.76±0.69	37.8±0.37	42.05±0.53	38.6±0.24	27.22±0.55	52.4±0.24	19.47±0.33
12	67.2±0.37	7.44±0.52	44.6±0.24	31.52±0.69	40.4±0.24	35.23±0.57	48.4±0.24	21.6±1.05	52.2±0.20	18.93±0.50

Highest percentage change in whole blood glucose level

Table 4. Dose-time response activities of oral administration of methanol leaf-extract of *Parquetina nigrescens* on whole blood glucose level in fasted non-diabetic, non gravid Sprague Dawley rats along with the percentage whole blood glucose change.

Time (hours)	Control		PNmeth(80mg/kg)		PNmeth(120mg/kg)		PNmeth(160mg/kg)		PNmeth(180mg/kg)	
	Whole blood glucose level (mg/dl)	%Change in blood glucose	Whole blood glucose level(mg/dl)	%Change in blood glucose	Whole blood glucose level (mg/dl)	%Change in blood glucose	Whole blood glucose level (mg/dl)	%Change in blood glucose	Whole blood glucose level (mg/dl)	%Change in blood glucose
0	73.60±0.25		71.20±0.37		70.20±0.20		71.20±0.37		70.80±0.37	
1	69.40±0.25	5.71±0.33	70.60±0.25	0.84±0.34	70.00±0.00	0.29±0.00	71.00±0.32	0.28±0.44	64.20±0.37	9.32±0.53
4	62.80±0.20	14.67±0.27	60.40±0.25	15.17±0.34	60.40±0.51	13.96±0.76	58.20±0.37	18.26±0.53	56.60±0.51	20.06±0.72
8	68.00±0.32	7.61±0.43	52.00±0.32	26.96±0.44	56.20±0.20	19.94±0.29	53.40±0.40	25.00±0.56	46.00±0.32	35.03±0.45
9	70.40±0.25	4.35±0.33	44.60±0.25	37.36±0.34	48.80±0.20	30.48±0.29	37.00±0.32	48.00±0.44*	46.00±0.32	35.03±0.45
10	70.40±0.25	4.35±0.33	48.00±0.55	32.58±0.77	56.60±0.25	19.37±0.35	40.20±0.20	43.54±0.28	40.40±0.25	42.93±0.34
12	70.20±0.20	4.35±0.33	52.00±0.32	26.97±0.44	60.80±0.37	13.39±0.53	45.20±0.49	36.52±0.69	50.60±0.40	28.53±0.56

Highest percentage change in whole blood glucose level

The results of the administration of the extracts at their respective effective doses on Oral glucose tolerance test (OGTT) further revealed that the extracts prevented the sharp rise in whole blood glucose level after the glucose loading compare with the normal control rats that received equal volume of distilled water. Although, the hypoglycemic effects of both the aqueous and methanol leaf extract of HE and PN were not as potent as

glybenclamide a standard hypoglycemic drug, the degree of blood glucose reduction was found to be highest in HEaq, followed by PNaq, PNmeth and HEmeth when administered at their respective effective doses. The results of two weeks pre administration of the aqueous leaf extracts of PN and HE at their respective effective hypoglycemic doses on OGTT, showed similar hypoglycemic effect as ealier reported.

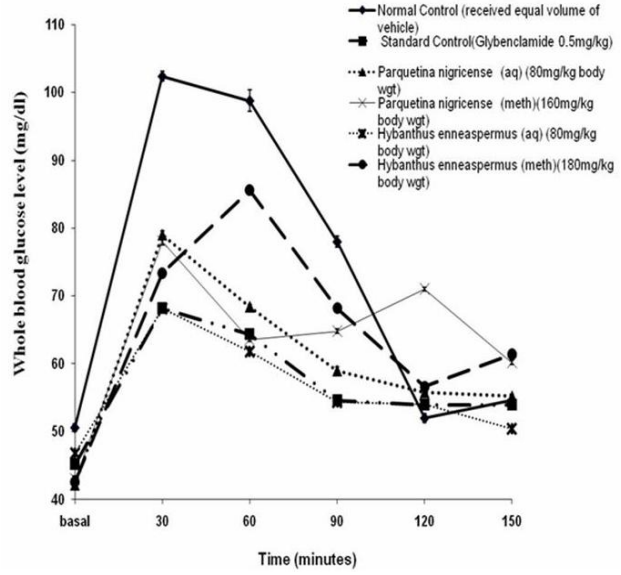

Fig. 1. Dose-time response curves for the oral administration of effective doses (ED) of aqueous and methanol leaf extract of Hybanthus enneaspermus and *Parquetina nigrescens* on whole blood glucose level after 1g/kg glucose load in an OGTT after a 12hours fast in non diabetic female Sprague Dawley rats

Oral administration of the effective doses of the leaf extracts of HE and PN to different groups of diabetic rats that were fasted for twelve hours further confirmed the hypoglycaemic potentials of the methanol leaf extracts of the two plants as well as the aqueous leaf extract of PN. All the plants extracts except HEaq reduced the whole blood glucose level in alloxan induced diabetic rats. Alloxan, a beta-cytotoxin, induces diabetes (alloxan diabetes) by damaging the insulin secreting cells of the pancreas. The destruction of β cells, results in decrease in endogenous insulin release, which paves the way for the decreased utilization of glucose by the tissue [26].

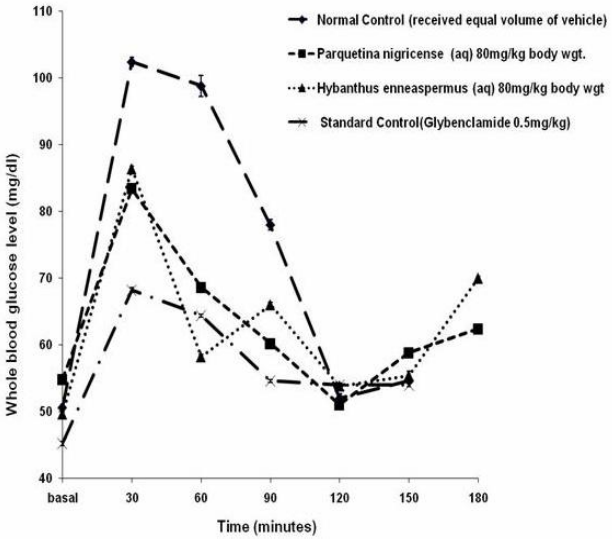

Fig. 2. Whole blood glucose level during Oral glucose tolerance test on rats treated for two weeks with aqueous leaf extracts of Hybanthus enneaspermus and Parquetina nigrescens at their respective hypoglycemic effective doses after 1.75g/kg glucose load compared with control that received equal volume of distilled water and rats administered Glibenclamide orally (0.5mafterg/kg body weight) after 12hours fast.

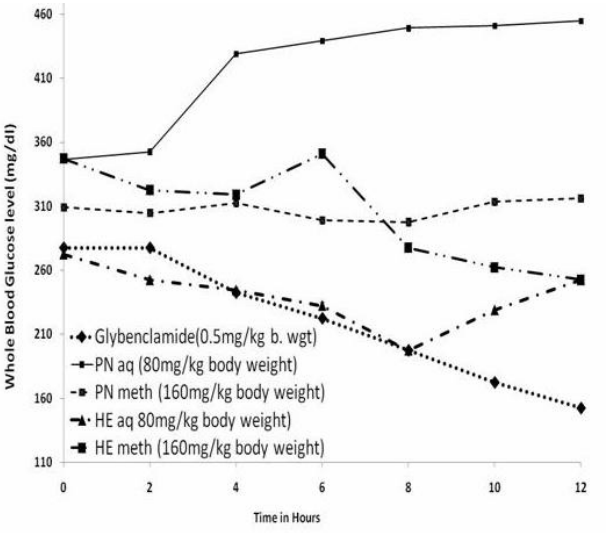

Fig. 3. Activities of aqueous and methanol leaf extracts of *Paquetina nigrisense and Hybanthus enneaspermus* given orally at their corresponding effective doses to alloxan induced diabetic female Sprague Dawley rats on fasted whole blood glucose compared with Glibenclamide (0.5mg/kg).

Conclusion

The results of these findings clearly showed that both the aqueous and methanol leaf extracts of *Hybanthus enneaspermus* and Paquetina *nigrisence* possessed hypoglycemic activities. This hypoglycemic activity was clearly demonstrated in OGTT. This in a way may explain possible benefits of the effect of the extracts as it is been used by Traditional Birth Attendants during antenatal care in combating pregnancy related diseases among which is gestational diabetes. However, further work will be required to unravel the mechanism of hypoglycemic activities of the leaf extracts of the two plants apart from the possibilities of the hypoglycemic activities of the flavonoids found in abundant in the two plants.

Table 5.Tables of changes in fasted whole blood glucose level after administration of the effective doses of each of the aqueous and methanol leaf extracts of *Parquetina nigrescens* and, *Hybanthus enneaspermus* and the Glybenclamide in alloxan induced diabetic Sprague Dawley rats.

Group	2hrs	4hrs	6hrs	8hrs	10hrs	12hrs
Glybenclamide (0.5mg/kg body weight)	0.00	-35.00	-55.00	-80.00	-105.00	-125.00*
PN aq (80mg/kg body weight)	6.00	82.50	92.50	102.50	104.50	108.00
PN meth (160mg/kg body weight)	-4.50	3.50	-10.00	-11.50*	4.50	7.00
HE aq 80mg/kg body weight)	-20.00	-28.00	-40.00	-75.00*	-43.50	-20.00
HE meth (160mg/kg body weight)	-24.50	-28.00	4.00	-69.50	-85.00	-94.50*

* Highest change in fasted whole blood glucose level.

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