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AUTHORS: Fidelis OKOLAFOR, Frederick EKHAISE

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Effect of a Tropical Plant (*Hunteria umbellata*) in the Management of Streptozotocin Induced Diabetes Mellitus and other Physiological and Biochemical Functions in Wistar Rats

Fidelis Ifeakachukwu OKOLAFOR^{1*}, <u>Frederick Osaro EKHAISE</u>²

¹Department of Science Laboratory Technology, Faculty of Life Sciences, University of Benin ²Department of Microbiology, Faculty of Life Sciences, University of Benin, Nigeria Te: +2347034191830 *Corresponding author: fidelis.okolafor@uniben.edu

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Abstract

Hunteria umbellata seeds, leaves and root are used as decoctions in Western and Southern part of Nigeria for the treatment of blood related ailments. The antidiabetic effect of Hunteria umbellata extracts (aqueous and methanol) on hematological, lipid profile and biochemical parameters in streptozotocin-induced diabetes in female Wistar rats was studied. The qualitative phytochemical screening of the seed extracts was determined using standard chemical methods. Twenty five Wistar rats weighing between 117 g and 170 g were shared into five groups of five animals per group for the physiological studies. All treatment groups were administered 500 mg/kg per body weight of *H. umbellata* extracts. Group I; normal control, Group II; negative or diabetic control, Group III; metformin + streptozotocin (STZ), Group IV; aqueous extract of *H. umbellata* + STZ and Group V; methanol extract of H. umbellata + STZ. Diabetes was induced with 55 mg/kg body weight STZ. Qualitative phytochemical screening of aqueous and methanol seed extracts of *H. umbellata* revealed the presence of secondary metabolites such as saponins, phytate, oxalate, anthraquinones, cyanogenic glycoside, phenols and alkaloids were recorded highest concentrations in both extracts. The hypoglycaemic studies of methanol extract revealed significant (p<0.005) reduction on the fasting blood glucose levels of experimental animals for Group V compared to moderate reduction in Group III. Group IV recorded increase in the blood glucose levels of Wistar rats. The haematological parameters were not significant (p>0.05) for all treatment groups. Group V recorded significance (p<0.05) amount of high density lipoproteins (HDL), total cholesterol (CHOL), triglyceride (TRIG) and low density lipoproteins (LDL) while CHOL was significant (p<0.05) for Group III. The biochemical parameters were within safe limit. The methanol extract of H. umbellata possesses the potentials for the managements of blood glucose levels and other physiological and biochemical functions compared to conventional drug (Metformin).

Key Words: Antidiabetic, Phytochemical screening, Streptozotocin, Wistar rats, Hunteria umbellata

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1. Introduction

Diabetes mellitus (DM) is a chronic and endocrine disorder caused by inherited and/or acquired deficiency in the production of insulin by the pancreas (Selvaraju et al., 2013). The prevalence of DM is increasing across the world. In 2011, it was estimated that over 346 million people lived with DM worldwide (WHO, 2011). Nearly 80% of deaths due to DM occur in low and middle income countries

particularly in sub-Saharan Africa. Medicinal plants are known to possess bioactive components that may be used in the treatment and management of illness and disease condition in traditional medicine practice as a result of high cost of orthodox drugs and low potency of some orthodox drugs. Hunteria umbellata K. Schum, is a tree with a height of about 15 - 22 m belonging to the family Apocynaceae. The leaves of H. umbellata are broad, abruptly acuminate and broadly lineate (Gurib-Fakim, 2006). The plant is grown mostly in Southern parts of Nigeria, Ghana and the rainforest regions of Cameroon (Aderele et al., 2020). Many dialects in Nigeria have different names for the plant such as Osu (Edo), Erinor abeere (Yoruba, Southwest) and Nkpokiri (Igbo, Southeast). H. umbellata have been reported to be used for traditional medicine for the treatment of various ailments (Reynolds and Sofowora, 1984; Keay et al., 1989). The trees of H. umbellata are used as ornamental plants in Southern part of Nigeria where it is planted for shades and decoration and guarded jealously by owners from human scavengers. Localities in Western and Southern part of Nigeria apply the leaves, seeds and root of *H. umbellata* with other plants mixed with coconut water as decoctions for the treatment of fever, blood pressure, piles, headache and other body related ailments. The stem of the plant are used as chewing stick, due to the cleansing effect derived from its use as an alternative to tooth brush. Many researchers have reported the medicinal uses of *H. umbellata* such as treatment of ulcers, diabetes mellitus and dysmenorrhoea (Oboh et al., 2017).

This study examines the antidiabetic effect of aqueous and methanol seed extracts of H. umbellata and its effect on hematological, lipid profile and biochemical parameters in streptozotocin-induced diabetes in female Wistar rats.

2. Material and Methods

2.1. Sample Collection and Identification

The seeds of *Hunteria umbellata* were purchased from Oshodi Markets in Oshodin Local Government Area, Lagos State in April 2015. The seeds were air dried for three weeks, after which the epicarps were removed and further air dried for another three weeks to obtain constant weight. The air drying was carried out to protect the bioactive components of the plant seed. The identification of the plant was carried out by Dr. E. I. Aigbokhan, of the Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, Benin City.

2.2. Preparation of Sample

The dried plant seeds of *H. umbellata* were pulverized using electronic grinder Lab. Mill (Model: Serial NO. 4745, Christy and Norris Ltd, England). The pulverized seeds were stored in air tight plastic container for experimental analyses.

2.3. Extraction of Plant Materials

400 g of the seeds were blended using a sterile grinder. The blended seeds were transferred into Pyrex flask containing 1.5 litres of aqueous (sterile distilled water) and non-aqueous solvent (methanol) and allowed to soak for 24 h for the aqueous and 72 h for the non-aqueous mixture. After 24 hr the mixture was macerated using a sterile cotton wool. At the end of extraction, the homogenate was filtered through а Whatman Filter Paper No. 1 using a glass The filtrates were labeled funnel. accordingly for subsequent use. The filtrates were concentrated using Water Bath at temperature of 80°C to dryness. The crude extract was obtained and stored for further analyses.

2.4. Percentage Yield

The percentage yield of *H. umbellata* was obtained using the methods of Kao (2018). The percentage yield was computed using the mathematical formula below:

$$\text{Yield }\% = \frac{W_2 - W_1}{W_0}$$

 W_2 = Weight of extract + container W_1 = Weight of container W_1 = Weight of container W_0 = Initial weight of sample before extraction

2.5. Qualitative Phytochemical components of *Hunteria umbellata*

The qualitative phytochemical analyses of the selected plant seeds were determined using the methods of Price (1985) and Thirumalai et al. (2011). All determinations were carried out in triplicates.

2.6. *In-vivo* Diabetic Study

Twenty five female Wistar rats weighing between 117 g and 170 g were shared into five groups of five animals per group. The animals were allowed to acclimatize for three weeks before administration of drugs. Freshly prepared solution of streptozotocin (STZ) (Sigma, USA), 55 mg/kg body weight in 0.1 mol/L of cold citrate buffer pH 4.1 was introduced into the overnight fasted animals by a single intra-peritoneal injection (Igbe et al., 2009). The control experimental animals were injected with distilled water. The animals were considered diabetic at the blood glucose level values above 250 mg/dL on the third day after STZ injection using a glucometer and acute test strip. The diabetic animals were treated for three weeks, while blood glucose levels were taken on a weekly basis.

2.7. Experimental Animal Grouping

Twenty five experimental animals of five animals per group were shared for experimentation as follows: **Group I**- Normal control (non-diabetic rats)

Group II- Negative control (diabetic without treatment)

Group III- Positive control (diabetic + 500 mg/kg body weight Metformin)

Group IV- Diabetic + 500 mg/kg body weight of aqueous seed extract of *H. umbellata.*

Group V- Diabetic + 500 mg/kg body weight of methanol seed extract of *H. umbellata.*

2.8. Extract Administration and Observation

Three days after induction of diabetes, experimental animal Groups III, IV, and V were treated with 500 mg/kg body weight standard drug (Metformin), 500 mg/kg body weight aqueous seed extract of *H. umbellata* and 500 mg/kg body weight methanol crude extract of *H. umbellata* respectively.

Group I (control) was administered distilled water at each treatment and Group II (negative control) was left untreated. Treatments (Aqueous and methanol seed extract of *H. umbellata*) were administered orally to the respective groups at a dose of 500 mg/kg.

2.9. Collection of Blood Samples and Plasma Preparation for Analysis

The experimental animals were sacrificed by anesthetizing the rats in enclosed container with chloroform. Blood samples were collected by ocular punctures into the abdominal aorta and the heart (Adeneye and Adeyemi, 2009). The blood was further centrifuged for 10 min at 3000 rpm using the centrifuge. The clear supernatants (plasma) collected were used for the estimation of lipid profiles and liver function tests.

2.10. Determination of Animal Body Weight

The initial weights of all the experimental animals in the different experimental groups were determined at the start of the experiment. Weekly weight measurements of the experimental animals were taken in all the groups and values recorded. The final weight measurement was carried out on the last day of the experiment. The differences in the weight in the various groups recorded accordingly (Bain et al., 2017).

2.11. Determination of Blood Glucose Level

The initial blood glucose of fasting Wistar rats before STZ induction was taken using a glucometer with acute test strip. The weekly blood glucose was taken in all groups of animals by pricking the tail of the rats and blood dropped on a strip fastened to the glucometer; this was carried out weekly for the three weeks study (Bain et al., 2017).

2.12. Haematological Study of Blood Samples of Experimental Animals

The serum obtained from the blood of the experimental animals were analysed for haematological parameter at the Department of Haematology, University of Benin Teaching Hospital (UBTH), Benin City, Nigeria. Blood samples was analysed for packed cell volume (PCV), haemoglobin level (Hb), total white blood cells count (TWBC) and differential white blood cells counts (DWBC) according to the methods of Trinder (1969).

2.13. Determination of Plasma Lipid Profiles

The plasma total protein (TP), total cholesterol (TG), triglyceride (TG) and HDL-cholesterol (HDL-Chol) were determined

according to the methods of Friedewald et al. (1972) using Randox Diagnostic kit. Low density lipoprotein-cholesterol (LDLChol) was calculated using formula adopted by Xing-Jiu et al. (2006).

2.14. Biochemical Analysis (Liver function test)

The liver function test was carried by digesting the plasma in Teco diagnostic (TC) kits and measured using the spectrophotometer. Plasma obtained from clotted blood samples from experimental animals were analyzed for alkaline phosphatase (ALP). Aspartate transaminase (AST) and alanine transaminase (ALT) was determined following the methods of Reitman et al. (1957) and Azwanida (2015).

2.15. Statistical Analyses

Data obtained were analyzed by one-way analysis of variance (ANOVA) using Student T-test to determine the significance differences in group results.

3. Results and Discussion

Medicinal plants have repeatedly been used as non-prescription medication for type 2 diabetes in rural areas in sub-Saharan Africa. Their potency may be due to several factors that are yet to be completely studied. *H. umbellata* is one medicinal plant that has been explored for its antidiabetic properties. The percentage yield of aqueous and methanol seed extracts of *H. umbellata* revealed highest solubility in aqueous (48.73 %) solvent compared to methanol (3.765%) (Table 1).

Table 1. Percentage yield profile ofaqueous and methanol crude extracts of *H.*umbellate

Solvent	W2 (g)	W1 (g)	W0 (g)	Yield %
Aqueous	493.41	298.5	400	48.73
Methanol	156.06	141.0	400	3.765
Methanol		141.0	400	3.76

W₀: Initial weight of sample before extraction,

W1: Weight of container,

W2: Weight of extract + weight of container

The result showed that the seed of H. umbellata was more soluble in polar solvent compared to non-polar solvent. The high percentage yield, with preserved integrities of the extracts is an indication that the method of extraction can be adopted as a standard method of extract preparation, using the common available equipment in our laboratories as alternatives to other standard equipment that are not readily available (Niranjan and Kanaki, 2008). phytochemical screening of Qualitative aqueous and methanol seed extracts of H. umbellata indicated presence the of secondary metabolites such as alkaloids. phenols, saponins, phytate, oxalate. anthraquinones (Table 2). It was reported that medicinal plants with hypoglycemic and antidiabetic effect usually contain high concentration of alkaloids and flavonoids (Murray et al., 1994). The result of Qualitative phytochemicals of *H. umbellata* in this study does not completely agree with this assertion. Alkaloids and phenol was highest compared to other secondary metabolites for aqueous and methanol extracts.

Table 2. Qualitative phytochemical screening
of aqueous and methanol crude extracts of H.
umbellata.

Parameters	mg/kg			
Parameters	Aqueous	Methanol		
Oxalate	9.9	3.7		
Phytate	6.6	2.3		
Tannins	0.2	0.3		
Flavonoids	0.0	0.3		
Saponins	12.8	6.4		
Alkaloids	20.8	19.0		
Phenols	8.1	26.7		
Cyanogenicglycoside	3.6	3.9		
Anthraquinones	8.4	7.7		

Experimental animals induced with STZ have been reported to produce a diabetic state that is characterized by loss of weight,

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polydipsia, polyuria, glucosuria, polyphagia, hypoinsulinaemia hyperglycemia and (Subash-Babu et al., 2007). The effect of H. umbellata extracts on the fasting body weight of experimental animals revealed weight changes in Group I, II and Group IV (Table 3). Group I recorded significant (p<0.002, p<0.001) increase in body weight compared to other treatment groups that received 55 mg/kg body weight STZ. Group II recorded significant (p<0.05) decrease for week 1 and 2. Group IV showed significant (p<0.05) decrease in weight for week 1 and week 2. Group III and V had no significant (p>0.05) difference in the body weight of experimental animals for 21 days treatment period. The decrease in body weight for Groups II and IV may be attributed to the underutilization of glucose due to the hyperglycemic action in both groups. This result is in agreement with the work of Muhd et al. (2012), who reported that the decrease in the body weight of diabetic rats may be due to catabolism of fats and protein.

Diabetes mellitus is a metabolic endocrine disorder which affects multiple organs, causing severe complications such as the destruction of 68 to 80 % beta cell of the islet of Langerhans (Adeneye et al., 2013). These destruction results in the increase in the blood glucose level (hyperglycemia). The fasting blood glucose level after STZ induction compared to fasting blood sugar level after three weeks treatments revealed normal blood glucose level for group 1 and hyperglycemia in Group II. Group III treated with standard drug (Metformin) recorded significant (p<0.05) decrease at week one and week three, while Group V (treated with methanol seed extracts of H. umbellata) recorded significant (p<0.05) decrease in blood sugar levels for week one and two and high significant (p<0.005) decrease for week three (Figure 1).

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Table	3.	Effects	of	Н.	umbellata	seed	extracts	on	the	fasting	body	weight	(FBW)	of
experi	mer	ntal anin	nals	S										

Group	FBW before STZ (g)	FBW after Week 1 (g)	FBW after Week 2 (g)	FBW after Week 3 (g)
Ι	147.7±6.86	164.7±8.09 ^{***}	$168.3\pm8.19^{**}$	175.4±8.03 ^{***}
II	134.0±6.15	123.6±4.38 [*]	121.6±3.94 [*]	122.8±2.96
III	139.5±5.62	133.3±6.64	135.3±6.73	138.4±10.8
IV	160.4±5.81	136.7±6.03 [*]	133.3±5.81 [*]	128.6±12.4
V	164.2±4.31	177.0±9.65	178.8±8.96	182.9±7.65

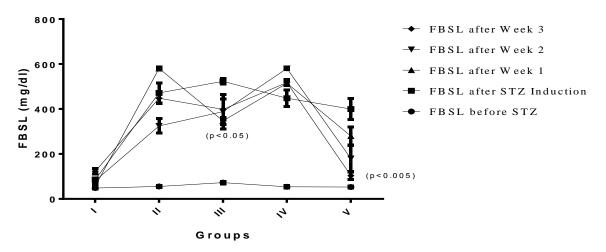
Body weight in Mean±SEM, n=5, Significance at 'p<0.05, "p<0.002, "p<0.001 compared to FBW before STZ induction, FBW: fasting body weight Group I: Normal control (no diabetes)

Group II: Negative control (induced 55mg/kg BW STZ)

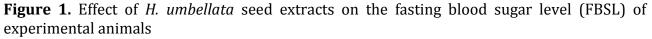
Group III: Positive control (55mg/kg BW STZ + 500mg/kg BW Metformin) Group IV:

55mg/kg BW STZ + 500mg/kg BW Aqueous extract of H. umbellata Group V: 55mg/kg BW

STZ +500mg/kg BW Methanol extract of H. umbellata



FBSL in Mean±SEM, n=5, Significance at ^{*}p<0.05, ^{**}p<0.005 compared to FBSL after STZ induction, FBSL: fasting blood sugar level Group I: Normal control (no diabetes) Group II: Negative control (induced 55mg/kg BW STZ) Group II: Positive control (55mg/kg BW STZ + 500mg/kg BW Metformin) Group IV: 55mg/kg BW STZ + 500mg/kg BW Aqueous extract of *H. umbellata* Group IV: 55mg/kg BW STZ + 500mg/kg BW Methanol extract of *H. umbellata*



Group IV recorded increase blood sugar levels for the three weeks treatment period, indicating that the aqueous extract of the plants does not possess antidiabetic properties. The levels of blood glucose for Group IV treated with methanol seed extracts of *H. umbellata* were more statistically significant compared to Group III treated with standard drug due to the reduction in blood glucose levels. The result of this study confirmed that methanol extract of *H. umbellata* may best be used in the management of diabetic condition as a result of its reducing tendencies of blood sugar level of diabetic experimental animals compared to the Metformin. The result of this study correlates with several authors' findings (Adeneye and Adeyemi. 2009a; Adeneye and Adeyemi, 2009b; Adeneye and Crooks, 2015, Kakade et al., 1972) who reported significant reduction of blood glucose levels of streptozotocin-induced diabetes mellitus in experimental animals treated with methanol extract of *H. umbellata*. The examination of blood serum is a good way of assessing the health status as it plays a vital role in physiological, nutritional and pathological status of individuals (Ayinde et al., 2010; Ashafa et al., 2009). Hematological parameters are used to determine the extent of deleterious effect on blood constituents of animals (Rees, 2007; Adesokan and Akanji, 2010). It is used to explain blood related functions of chemical compounds/plant extract (Onoja et al., 2018). The mean hematological parameters for all groups showed no significance (p>0.05) (Table 4).

Three weeks observation may not be enough to allow for hemolysis of blood. Therefore, longer weeks of monitoring may be encouraged to ascertain the actual effect of the plant extract on hematological parameters. This result contradicts the report on the significant reduction of hematological parameters of alloxaninduced diabetics (Ogbera et al., 2009; Dave et al., 2019). Diabetes mellitus (DM) has been reported to be associated with

cardiovascular morbidity and this may partly be explained by the abnormal lipid profile which is sometimes a feature of DM (Han et al., 2012). The study of the effect of H. umbellata on the lipid profile of streptozotocin-induced experimental animals showed lipid profile parameters such as HDL, CHOL and LDL in all experimental groups (Table 5). Group V recorded significance (p<0.05) amount of HDL, CHOL, TRIG and LDL while CHOL was significant (p<0.05) for Group III. Other lipid profile parameters in this study showed no statistical significance (p>0.05). The high cholesterol level may be attributed to the presence of hypertension for diabetic conditions which however mav be contributory factor in the prevalence of dyslipidemia in type 2 DM. This result agrees with the reports of Harris (2005) and Kyoungho et al. (2014), who reported that high cholesterol presence in plasma of diabetic experimental animals treated with plant extract confirms the rise in blood pressure for animals that are diabetic.

Table 4. Effects of *H. umbellata* seed extracts on the hematological parameters of experimental animals

Parameters	Unit of measurement	Group I	Group II	Group III	Group IV	Group V
WBC	(×10³/ul)	12.83±4.64	6.240±0.44	7.140±1.01	17.63±8.01	8.600±0.45
LY	%	50.50±10.6	45.26±9.25	51.32±3.91	48.80±14.1	49.00±2.35
МО	%	6.533±0.81	9.700±1.62	9.540±1.07	7.533±0.49	7.367±0.58
GR	%	42.97±10.8	45.02±8.06	39.14±3.11	43.67±15.4	43.63±1.78
RBC	(×10 ⁶ /ul)	5.873±0.44	6.398±0.164	6.504±0.33	4.933±0.71	5.803±0.27
Hgb	g/dl	12.97±0.94	13.40±0.47	15.20±0.36	11.00±1.19	13.00±0.65
PCV	%	38.67±1.37	40.70±1.18	41.46±1.97	34.97±2.64	38.43±1.87
PLT	(×103/ul)	797.3±63.2	300.8±106	422.8±148	539.0±27.5	752.7±55.1

Hematological parameters in Mean±SEM, n=5, not Significance at p>0.05, WBC: White blood cells, LY: Lymphocytes, MO: Monocytes/Macrophages, GR: Granulocytes, RBC: Red blood cells, Hgb: Hemoglobin , PCV: Packed cell volume, PLT: Platelets,

Group I: Normal control (no diabetes), Group II: Negative control (induced 55mg/kg BW STZ), Group III: Positive control (55mg/kg BW STZ + 500mg/kg BW

Metformin) Group IV: 55mg/kg BW STZ + 500mg/kg, BW Aqueous extract of H. umbellata Group V: 55mg/kg BW STZ + 500mg/kg BW Methanol extract of H. umbellata

		mg/dL		
Group	HDL	CHOL	TRIG	LDL
Ι	138.68±15.01	155.89±14.69	66.667±12.13	36.720±16.35
II	158.83±9.058	140.75±9.948	92.436±18.87	38.854±14.84
III	140.75±21.74	*199.50±18.66a*	107.56±28.07	39.150±17.89
IV	124.24±24.32	184.46±4.780	91.877±37.61	49.250±19.39
V	103.39±17.00a*	194.49±12.29*	46.497±32.51a*	81.803±19.19a*

Table 5. Effect of *H. umbellata* on the Lipid profile of streptozotocin-induced diabetic experimental animals

Lipid profile in Mean±SEM, n=5, Significance at ^{a*}p<0.05 with respect to normal control, ^{*}p<0.05 with respect to negative control, HDL: High density lipoproteins, CHOL: Total cholesterol, TRIG: Triglyceride, LDL: Low density lipoproteins Group I: Normal control (no diabetes), Group II: Negative control (induced 55mg/kg BW STZ)

Group III: Positive control (55mg/kg BW STZ + 500mg/kg BW Metformin) Group IV: 55mg/kg BW STZ + 500mg/kg BW Aqueous extract of H. umbellata Group V: 55mg/kg BW

STZ +500mg/kg BW Methanol extract of H. umbellata

The liver plays a major role in the regulation of carbohydrate homeostasis as a result of the hepatocellular glycogen accumulation which leads to hepatomegaly and liver enzyme abnormalities poorly in controlled diabetes patients (Han et al., 2012). Liver function tests (LFTs) are used in clinical practice to screen potential damage to liver, monitor the progression of known disease, and monitor the effects of potentially hepatotoxic drugs (Harris, 2005). Type 2 DM have been reported to be associated with higher incidence of abnormal LFT compared the to

individuals without diabetes, elevated ALT being the most common abnormality (Harris, 2005). The study on the effect of *H. umbellata* on the liver function test of streptozotocin-induced diabetic animals revealed the mean liver enzymes in this study such as ALT, AST, ALP for all experimental groups (Table 6). ALT showed significance (p<0.05) decrease for Group V while AST and ALP were not statistically significant for Group I to group IV. The result of ALT, ALP and ALP for Group I to Group V were within safe limits (Kyoungho *et al.*, 2014; Harris, 2005).

Table 6. Effect of *H. umbellata* on the liver function test of Streptozotocin-induced diabetic experimental animals

U/L				
Group	ALT	AST	ALP	
Ι	20.617±2.70	24.633±3.87	80.820±12.3	
II	22.137±0.95	29.460±5.22	119.59±29.9	
III	29.419±3.46	25.800±2.56	74.794±15.2	
IV	25.264±3.39	19.980±2.05	64.610±2.97	
V	13.373±4.25*	28.333±2.11	42.467±6.09	

Liver enzymes in Mean±SEM, n=5, Significance at *p<0.05 with respect to normal control, *p<0.05 with respect to negative control, ALT: Alanine transaminase, AST: Aspartate Aminotransferase, ALP: Alkaline phosphatase,

Group I: Normal control (no diabetes), Group II: Negative control (induced 55mg/kg BW STZ), Group III: Positive control (55mg/kg BW STZ + 500mg/kg BW Metformin) Group IV: 55mg/kg BW STZ + 500mg/kg BW Aqueous extract of *H. umbellata* Group V: 55mg/kg BW STZ + 500mg/kg BW Methanol extract of *H. Umbellata*

4. Conclusion

Failure of over the counter drugs in the management of patients with high blood sugar level (diabetes) has continued to draw attention to research into medicine plants as alternative to orthodox drugs. Medicinal plants possess phytochemical compounds depending of the extracting solvent used. The result of this study showed positive antidiabetic properties, significant physiological and biochemical functions on Wistar rats administered with methanol seed extract of *H. umbellate*. The methanol extract of *H. umbellata* possesses the potentials for the managements of blood glucose levels in experimental animals compared to Metformin. Attention should be drawn to proper utilization of medicinal plants in the management of diabetes condition in sub Saharan Africa.

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Author Contribution

Fidelis Ifeakachukwu OKOLAFOR carried out the research and wrote the manuacript

Frederick Osaro EKHAISE suppervised the project, did the editing of manuscript

Conflicts of Interest

There were no conflicts of interest in the course of this research.

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