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The effect of ethanolic Acalypha Wilkesiana extract on blood sugar, sodium, potassium levels in alloxan-induced diabetic and salt-induced hypertensive Wistar rats

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Abstract

Diabetes Mellitus and hypertension often occur simultaneously. Hypertension affects approximately 70% of patients with diabetes, and the risk of cardiovascular disease in diabetic patients is three times higher than that in healthy individuals. The study was aimed at investigating the problem of diabetes and hypertension, and a possible remedy for it. Twenty-five (25) male wistar rats were assigned into five (5) groups of five (5) rats each. Group A served as negative control, and received water and feed only. Group B served as the positive control, and received alloxan160 mg/kg BW+ salt-loaded diet. Group C-E received alloxan 160 mg/kg BW+ salt-loaded diet + 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW of ethanolic acalypha wilkesiana (EAW) respectively. All administrations were given orally twice daily for 21 days. At the end of the treatment, blood samples were collected to estimate blood glucose, insulin, sodium, and potassium levels. Results are presented as mean±SEM, and were analysed using One-way ANOVA, statistical significance was considered at ($P \leq 0.05$). The results showed decrease in blood glucose levels and increase in insulin levels in groups C, D, and E compared to group B. There was also a decrease in sodium ion levels, and a concomitant increase in potassium ion levels in all wistar rat treatment groups when compared to group B. In summary, the results showed improved blood sugar, insulin, sodium, and potassium ion levels following EAW administration. It is therefore concluded that EAW administration was effective in improving diabetic and hypertensive complications in wistar rats.

Keywords: Acalypha Wilkesiana; Diabetes Mellitus; Insulin; Sodium; Potassium; Hypertension.

1. Introduction

Diabetes mellitus (DM) is a syndrome characterized by elevated blood glucose levels resulting from alterations in the metabolism of carbohydrates, lipids, and proteins [1]. DM characterizes metabolic issues that are mostly frequent global issues, with hyperglycemia in the blood being the main issues of concern. This is due to inappropriate pancreatic insulin secretion or low insulin-directed fostering of glucose by target cells [2]. Hypertension (HTN), also known as high blood pressure is a long-term medical condition in which the blood pressure in the arteries is persistently elevated [3]. Hypertension is also characterized by high plasma sodium ion, and low plasma potassium level [4]. Salt intake has been linked to the development and management of hypertension. Excessive consumption of salt can lead to fluid retention and increased blood pressure, exacerbating the condition [5].

DM and HTN often occur simultaneously. Hypertension, one of the independent risk factors for cardiovascular disease (CVD), affects approximately 70% of patients with diabetes, and the risk of CVD in diabetic patients is three times higher

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than that in healthy individuals [6]. Medicinal plants have long been acknowledged for their potential therapeutic properties in managing various health conditions, including diabetes and hypertension.

Acalypha wilkesiana, commonly known as copperleaf plant, Irish petticoat, and Jacob's coat [7], is an example of a medicinal plant with reported traditional uses in different cultures. It belongs to the family Euphorbiaceae and is native to tropical regions [8]. Research findings by Isirima and Uahomo [9], Odoh et al. [10], and Iyamu et al. [11] have revealed significant decrease in blood glucose levels following administration of *A. wilkesiana* leaf extract in alloxan-induced diabetic rats. Furthermore, Atef and Al-Attar [12] revealed that *A. wilkesiana* leaf extract has hypoglycemic effect in streptozotocin-induced diabetic wistar rats, in a way similar in action to the standard drug glibenclamide. Study findings of Ikewuchi et al. [13], reported a significant decrease in sodium and potassium ion levels in wistar rats administered the aqueous leaf extract of *A. wilkesiana.* Studies by Omage and Azeke [14] and Ibrahim et al. [15] also reported substantially lower sodium and potassium levels in wistar rats administered EAW. Ikewuchi et al. [16] in a study on the effect of EAW on urinary excretion of Na^+, reported an increase in urinary excretion of sodium and a concomitant decrease in plasma sodium concentration, with no change in urinary potassium excretion.

In this study, the focus is on evaluating the effects of *Acalypha wilkesiana* extract on various parameters related to diabetes and hypertension as a complication, such as blood sugar level, serum insulin level, serum sodium level, and serum potassium level. No drug has been documented to be effective in managing both diabetes and hypertension as a complication, hence the relevance of this study. The study utilizes alloxan monohydrate (AMH), a chemical compound known to induce diabetes in animal models, as well as high salt loading to induce hypertension, in order to explore the effects of the extract in a controlled experimental setting. By investigating these parameters, the aim is to assess the potential of *Acalypha wilkesiana* as a medicinal plant for managing diabetes and hypertension when they occur together.

2. Materials and method

2.1. Study Area

This study was conducted in the Department of Human Physiology, Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus, Okofia, Anambra State, Nigeria.

2.2. Ethical Approval

Ethical approval for this study was obtained from the Animal Research Ethics Committee, Nnamdi Azikiwe University, Awka (NAU-AREC) for laboratory animal care and use. The ethical approval number for the study is NAU/CHS/NC/FMBS/701. Rats handling and treatments conform to these guidelines.

2.3. Materials

Twenty-five (25) male wistar rats, Accu check glucometer with glucose oxidase enzyme specific sticks, ultrasensitive rat insulin ELISA Kit by Novus Biologicals Limited with ELISA assay reader, the Roche electrolyte analyzer, standard cages with water can, laboratory chow (Jos, Nigeria), *Acalypha wilkesiana* leaf, Sodium Chloride (salt), absolute ethanol (JHD Chemicals, Guangdong China), Alcohol, distilled water, oral cannula, automatic Water distiller (SZ-1 Search Tech Instrument), (Olympus XSZ-107BN), heparinized capillary tube, haematocrit centrifuge, chloroform, electronic weighing balance (M-Metallar M311), 2ml hypodermic sterile syringe, and animal weighing balance (Camry LB11).

2.4. Methodology

2.4.1. Experimental Animals and Design

A total of twenty-five (25) male wistar rats weighing between 130-190g were obtained from a private farm in Nnewi, Anambra State, and housed at the Animal House of College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Nigeria. The rats were acclimatized for a period of two weeks before the commencement of the experiment. They were then assigned into five (5) groups (5 rats/group): Group A: served as the negative control group and received distilled water and feed. Group B served as the positive control for diabetes and hypertension, and received single intraperitoneal dose of alloxan 160 mg/kg BW and 8% Nacl: 92% feed only. Group C-E received single intraperitoneal dose of alloxan 160 mg/kg BW, 8% Nacl: 92% feed, and *A. wilkesiana* extract at 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW respectively.

The rats were treated with 8% NaCl per 92% feed for a period of 4 weeks, thereafter alloxan (160 mg/kg BW) single intraperitoneal dose. *Acalypha wilkesiana* extract was given orally twice a day for 3 weeks. 24 hours after the last

administration, the animals were sacrificed by cervical dislocation, and blood was collected via ocular puncture for determination of serum insulin level, serum sodium level, and serum potassium level.

2.4.2. Collection and Preparation of Plant Extracts

Acalypha wilkesiana leaves were collected from moist, shrub-growing areas in Okofia, Nnewi, Anambra State. They were further authenticated by the Department of Botany, Faculty of Biosciences, Nnamdi Azikiwe University, Awka. The authentication voucher number is NAUH-241[A].

2.4.3. Extraction Procedure

The crude ethanolic extract of *Acalypha wilkesiana* was prepared according to Omage et al [17]. The leaves were picked, and air-dried completely. The dried leaves were then pulverized into fine powder and weighed. 200 grams of the pulverized leaves was soaked in 800 ml of ethanol for 72 hours (3 days), and was occasionally stirred using a magnetic stirrer to ensure proper mixture of the vessel content. The extract was filtered through a cotton plug and the filtrate was then concentrated with a rotary evaporator under reduced pressure to obtain crude extract.

2.4.4. Blood Glucose Estimation

Blood was collected via vein puncture, using 22G needles for determination of blood glucose level on the day 7, 14 and 21 after diabetes induction. Blood glucose level was measured using the Accu check glucometer with glucose oxidase enzyme specific sticks. The blood sample was then placed on the glucose strip and inserted into the glucometer, and results read from the screen in 15 seconds.

2.4.5. Serum Insulin Estimation

Animals were sacrificed on the 21st day after mild anesthesia with diethyl ether. Blood for serum insulin measurement was collected via ocular puncture. It was then centrifuged at 3000 rpm for 10 minutes, and the serums separated and stored in the refrigerator until analysed. Ultrasensitive rat insulin ELISA Kit manufactured by Novus Biologicals Limited, with ELISA assay reader was used in estimation of serum insulin level.

2.4.6. Electrolyte Estimation

Blood sample for serum sodium and potassium estimation was collected in serum separating tube (SST) (plain tubes) via ocular puncture, and allowed to clot. The serum was separated by centrifugation using centrifuge at 3000 rpm for 10 minutes. The serum was separated from the clotted samples into serum tubes and then stored in the refrigerator for electrolyte estimation. The Roche electrolyte analyzer was used for the determination of sodium and potassium electrolytes.

2.5. Statistical Analysis

All data was entered and analyzed using statistical package for social science, SPSS version 25. One-way ANOVA was used to compare the means across groups, and bonferroni post-HOC test was used for multiple comparison tests. Results were expressed as mean ± SEM, and P values less than or equal to 0.05 was considered statistically significant.

3. Results

Table 1 Effect of ethanolic leaf extract of *Acalypha wilkesiana* on body weight in diabetic and hypertensive rats

	Initial body weight (g)	Final body weight (g)	T-value	P-value
	MEAN±SEM	MEAN±SEM		
Group A (control)	130.00±1.97	161.20±1.20	-30.59	0.000*
Group B (DM + HTN control)	190.67±0.33	136.67±0.66	128.17	0.000*
Group C (DM + HTN + 100 mg/kg of EAW)	136.33±0.88	165.67±1.20	-15.80	0.004*
Group D (DM + HTN + 200 mg/kg of EAW)	137.67±8.17	154.67±11.05	-4.20	0.052#
Group E (DM + HTN + 300 mg/kg of EAW)	139.50±2.10	146.00±2.27	-2.60	0.080#

Data was analysed using paired t-test and values were considered significant at $p \leq 0.05$. DM: diabetes mellitus, HTN: hypertension, EAW: ethanolic leaf extract of *Acalypha wilkesiana*; *: significant and #: not significant.

Table 1 showed a significant increase in the mean body weight in groups A; however, group B had significant decrease in the mean body weight while groups D and E had an increase in the mean body weight but showed no difference when the initial weight was compared to the final weight.

Table 2 Effect of ethanolic leaf extract of *Acalypha wilkesiana* on blood glucose level in diabetic and hypertensive rats

	Bloodglucose level (mg/dl) day 0	**Blood glucose level (mg/dl) day 7**	**Blood glucose level (mg/dl) day 14**	**Blood glucose level (mg/dl) day 21**
	MEAN±SEM	MEAN±SEM	MEAN±SEM	MEAN±SEM
Group A (control)	102.40±12.20	115.26±4.56	116.20±3.54	114.57±6.64
Group B (DM + HTN)	225.00±9.02*	280.00±14.12*	270.70±10.52*	259.63±10.50*
Group C (DM + HTN + 100 mg/kg of AW)	231.00±10.58	183.33±3.03*[a]	165.20±9.11*[a]	142.05±4.96*[a]
Group D (DM + HTN + 200 mg/kg of AW)	239.00±3.51	160.90±14.40*[a]	148.17±7.62*[a]	143.65±0.45*[a]
Group E (DM + HTN + 300 mg/kg of AW)	226.00±8.50	161.66±5.20*[a]	142.93±2.73*[a]	118.03±6.90*[a]
F-ratio	38.64	40.13	65.52	53.74

Data was analysed using ANOVA followed by post Hoc LSD multiple comparison and values were considered significant at *p≤0.05*. DM: diabetes mellitus, EAW: ethanolic leaf extract of *Acalypha wilkesiana*; *: significant when compared to group B, [#]: not significant when compared to group B. [a]: significant when compared to day 0, and [b]: not significant when compared to day 0.

Table 2 showed a mean increase in the blood glucose level in groups B, C, D, and E (*p=0.00, p=0.00, p=0.00, p=0.00*) when compared to group A at day 0 (48 hours after alloxan administration). At day 7, a significant decrease in the mean blood glucose was indicated in groups C, D, and E (*p=0.00, p=0.01, p=0.01*) when compared to group B. At day 14, the mean blood glucose level showed a significant decrease in groups C, D, and E (*p=0.00, p=0.01, p=0.00*) when compared to group B. At day 21, a significantly lowered mean blood glucose level was shown in groups C, D, and E (*p=0.01, p=0.02, p=0.01*) when compared to group B.

The table also showed a significant decrease in blood glucose levels on day 7 in group C, D, and E *(p=0.00, p=0.01, p=0.01)* when compared to day 0 of the same group. At day 14, there was a significant decrease in blood glucose levels in groups C, D, and E *(p=0.00, p=0.01, p=0.00)* when compared to day 0 of the same group. At day 21, a significantly lowered blood glucose level was shown in groups C, D, and E *(p=0.00, p=0.00, p=0.00)* when compared to day 0 of the same group.

Table 3 Effect of ethanolic leaf extract of *Acalypha wilkesiana* on insulin level in diabetic and hypertensive rats

	Insulin level (µIU/ml) day 21
	MEAN±SEM
Group A (control)	5.00±0.58
Group B (DM + HTN)	3.33±0.33[#]
Group C (DM + HTN + 100 mg/kg of EAW)	6.67±1.76[#]
Group D (DM + HTN + 200 mg/kg of EAW)	6.66±1.67[#]
Group E (DM + HTN + 300 mg/kg of EAW)	8.00±0.58*
F-ratio	2.43

Data was analysed using ANOVA followed by post Hoc LSD multiple comparison and values were considered significant at *p≤0.05*. DM: diabetes mellitus, EAW: ethanolic leaf extract of *Acalypha wilkesiana*; *: significant and [#]: not significant.

Table 3 showed that the mean insulin level decreased in group B (*p=0.31*) when compared to A, but had no significance. Groups C, D, and E (*p=0.06, p=0.07, p=0.02*) had an increase in the mean insulin level when compared to group B, but significance was indicated in group E while groups C and D showed no difference.

Table 4 Effect of ethanolic leaf extract of *Acalypha wilkesiana* on sodium and potassium ion level in diabetic and hypertensive rats

	Sodium ion (meq/L) day 21	**Potassium ion (meq/L) day 21**
	MEAN±SEM	MEAN±SEM
Group A (control)	136.40±1.15	5.53±0.35
Group B (DM + HTN)	142.56±6.8#	6.60±0.94*
Group C (DM + HTN + 100 mg/kg of EAW)	125.86±1.15*	7.47±0.56#
Group D (DM + HTN + 200 mg/kg of EAW)	136.03±4.16#	7.13±0.06#
Group E (DM + HTN + 300 mg/kg of EAW)	131.87±4.54#	7.43±0.28#
F-ratio	2.17	2.27

Data was analysed using ANOVA followed by post Hoc LSD multiple comparison and values were considered significant at *p≤0.05*. DM: diabetes mellitus, EAW: ethanolic leaf extract of *Acalypha wilkesiana*; *: significant and #: not significant.

Table 4 when subjected to statistical analysis showed an increase in the mean sodium ion level in group B compared to A (*p=0.32*). Groups C, D, and E (*p=0.02, p=0.29, p=0.10*) had a decrease in the sodium ion level compared to group B but significance was indicated in group C, while groups D and E showed no difference. The potassium ion level showed an increase in group B compared to A (*p=0.18*), groups C, D, and E (*p=0.27, p=0.49, p=0.29*) had an increase compared to group B but had no significance.

4. Discussion

DM is a chronic non- communicable disease that is assuming global epidemic. Hypertension, on the other hand, is one of the independent risk factors for cardiovascular disease (CVD), affecting approximately 70% of patients with DM, and the risk of CVD in diabetic patients is three times higher than that in healthy individuals [6]. The study investigated the effect of *Acalypha wilkesiana* on blood sugar levels, serum insulin levels, serum sodium levels, and serum potassium levels, in diabetic and hypertensive wistar rats.

The study findings showed that the intake of EAW at 100, 200, and 300 mg/kg BW revealed a significant increase in the mean body weight in group C, while group D and E showed no difference in the mean body weight when the initial weight was compared to the final weight. This could be because the rats used for the experiment were young, and still growing.

The study findings showed that administration of EAW at 100, 200, and 300 mg/kg BW resulted in significantly improved blood glucose levels in all wistar rat treated groups when compared to the diabetic and hypertensive control group. There was also significantly improved blood glucose levels in all wistar rat groups on day 7, 14, and 21 when compared to day 0 of each group in all the diabetic and diabetic + hypertensive groups. The anti-diabetic action of EAW is likely due to the presence of alkaloids and saponins present in the extract, which stimulate insulin release from β-cells of pancreatic islets. It has been shown that alkaloids obtained from leaves of *Acanthus montanus* administered intraperitoneally at doses of 100, 200, and 400 mg/kg BW demonstrated hypoglycemic activity in alloxan-induced diabetic rats [18]. Work on total saponins from the seeds of *Entada phaseoloides* showed significant decrease in fasting blood glucose level in type 2 diabetic rats [19]. This study findings are in line with the study conducted in mice by Al-Attar [12], Isirima and Uahomo [13] using aqueous leaf extract of *A. wilkesiana,* and Iyamu et al. [12] using the ethanolic leaf extract of *A. wilkesiana.* Atef and Al-Attar [14] revealed that *A. wilkesiana* leaf extract had hypoglycemic effect in streptozotocin-induced diabetic wistar rats.

Insulin in this study was improved. The study revealed that the administration of EAW extract at 100, 200, and 300 mg/kg BW lead to increase in insulin levels in all wistar rat groups on day 21, which was significant at the highest dose (300 mg/kg BW) of the extract. The significantly improved blood glucose levels as seen on day 7, 14, and 21, in this study could also be attributed to a possible concomitant improvement in insulin levels during those days. The increase in insulin therefore in this study has the potential to improve blood glucose level in diabetics by acting through the

insulin receptors in the liver, pancreas, and skeletal muscles. The increase in insulin levels following administration of EAW could be attributed to the presence of flavonoids. Flavonoids isolated from antidiabetic medicinal plants are shown to stimulate peripheral glucose uptake and regulate the activity and/or expression of the rate-limiting enzymes involved in carbohydrate metabolism pathway by acting as insulin secretagogues or insulin mimetics [20]. Flavonoids isolated from *Pterocarpus marsupium* has also been shown to cause in vitro pancreatic β-cell regranulation and found to enhance insulin release and conversion of proinsulin to insulin [21]. It is also suggested that the hypoglycemic activity of EAW could result from its mineral/trace elements composition: zinc, which is required in all aspects of insulin metabolism, synthesis, secretion, and utilization. There is a high zinc excretion rate in diabetic patients, and zinc supplementation was shown to improve insulin levels in both type 1 and type 2 DM [22]. A study also showed that zinc intake regulates insulin receptors and extends insulin action [23].

Hypertension is characterized by high plasma sodium and low plasma potassium level [4]. Following administration of EAW, there was a decrease in the sodium ion level in groups C, D, and E when compared to group B, which was significant in group C. The potassium ion level showed no significant increase in all wistar rat treated groups when compared to group B. The decrease in Na^+ levels following EAW administration may be beneficial in the maintenance of homeostasis or regulation of arterial blood volume, important in hypertensive conditions associated with electrolyte imbalance, especially those associated with sodium and potassium electrolytes. One of the likely reasons for the reduction in Na^+ following administration of EAW, which is also a hypotensive property can be attributed to flavonoids, which are highly present in *A. wilkesiana.* A study revealed that regular consumption of flavonoids reduces the onset or progression of many cardiovascular diseases, especially hypertension [24]. Generally, the EAW leaf extract reduced serum sodium level and increased serum potassium levels in rats that were both diabetic and hypertensive. This implies that it could be a K^+-sparing diuretic, and may either act by inhibiting aldosterone directly, or affect the Na^+-K^+ pump activity in the body. Oladunmoye [25] reported that the mechanism of antimicrobial activities of *Acalypha wilkesiana* is through the release of Na^+-K^+ pumps. This point is further strengthened by the fact that EAW contains flavonoids, a family of compounds that are known to interact with the Na^+-K^+ pumps [26]. The effect observed in this study may therefore be beneficial in the management of hypertension associated with sodium and potassium electrolyte imbalances.

5. Conclusion

The study revealed that the administration of EAW showed therapeutic efficacy on blood glucose levels and insulin levels in the diabetic and hypertensive wistar rats. Furthermore, the study documented decreased sodium ion levels and a concomitant increase in potassium ion levels following EAW administration. Overall, therapeutic efficacy was indicated by the effect of EAW at low doses on blood glucose level, insulin level, sodium, and potassium ion concentration of all diabetic and hypertensive wistar rats, demonstrating high hypoglycemic effects, and mild to moderate hyperinsulinemic and anti-hypertensive effects at the same low doses.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval for animal experimentation of this work was obtained from Nnamdi Azikiwe University Animal Research Ethics Committee (NAU-AREC), Nnewi. The Ethical Approval Number is: NAU/CHS/NC/FMBS/701.

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