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Original Research Article

TOXICITY STUDY, ANTIDIABETIC POTENTIAL AND EFFECT OF ETHANOL LEAF EXTRACT OF *TRICLISIA MACROPHYLLA* ON BODY WEIGHT AND HEMATOLOGICAL INDICIES IN ALLOXAN INDUCED DIABETES IN RATS

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ABSTRACT

This study investigated the toxicity, antidiabetic potential, and effects on body weight and hematological parameters of ethanol leaf extract of *Triclisia macrophylla* in alloxan-induced diabetic rats. A total of 51 adult male albino rats were used. 21 were used for acute toxicity testing and 30 for the antidiabetic study. The acute toxicity assessment followed a modified Lorke's method, administering oral doses ranging from 10 to 5000 mg/kg. The rats were monitored for signs of toxicity and mortality over 24 hours. For the antidiabetic study, the remaining 30 rats (weighing 106–150g) were divided into five groups. Diabetes was induced in groups 2 to 6 using a single intraperitoneal dose of 150 mg/kg alloxan monohydrate. Group 1 served as the normal control, while group 2 was the diabetic control. Groups 3, 4, 5, and 6 received treatments for 14 days with 3 mg/kg glibenclamide, and 200, 400, and 800 mg/kg of the plant extract, respectively. After inducing diabetes and administering various doses of the extract, no deaths were recorded, indicating a high safety profile (LD_{50} > 5000 mg/kg). The extract significantly reduced blood glucose levels ($p < 0.05$) and improved body weight, red blood cells, packed cell volume, hemoglobin, and white blood cell counts. The findings indicate that *T. macrophylla* leaf extract possesses strong antidiabetic activity and may be effective in managing diabetes-related hematological complications. Further studies are recommended to explore its effects on biochemical parameters and to identify the bioactive compounds responsible for its pharmacological effects.

Keywords: Alloxan, Antidiabetic, Diabetes, Toxicity, Triclisia macrophylla

INTRODUCTION

Diabetes mellitus (DM) a metabolic disease usually characterized by chronic hyperglycemia resulting from abnormalities in insulin secretion and/or action (Uloko *et al*., 2018; Kim, 2019) Diabetes mellitus is among the leading causes of global death and Its complications include damage to the brain, heart, kidney and the limbs (Adijat *et al*., 2021). 50% of diabetic patients are oblivious to it especially in countries where poor healthcare, unhealthy diet, sedentary lifestyle and poverty persist (Adeleye, 2021). Diabetes statistics has reached 451 million adults worldwide as at 2017, with a projected increase of up to 693 million by the year 2045 (IDF, 2017). Diabetes contributes to huge amount of the global health expenditure in the world. In Africa, it is estimated that more than 25 million people are affected by diabetes, with about 69.2% diabetic cases undiagnosed and the number is projected to be more than 40 million by 2045 (WHO, 2017).

A pooled DM prevalence of 5.77% observed in meta-analysis suggests that 11.2 million Nigerians (1 out of every 17 adults) are living with the disease (Adijat *et al*., 2021).

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International Diabetes Federation (IDF, 2017) had reported the prevalence of DM among adults aged 20-69 years in Nigeria to be 1.7% though, some researchers claimed that prevalence figures reported by the IDF was grossly under-reported the true burden of DM in Nigeria (Adijat *et al*., 2021; Uloko *et al*., 2018). However other researchers have reported prevalence ranging from 2% to 12% across the country (Uloko *et al*., 2018; Adeleye, 2021). There has been a progressive increase in the prevalence of diabetes mellitus in Nigeria (Adeleye, 2021). However, the current anti diabetic therapies are expensive and not easily accessible by patients from poor household. These synthetic therapies also present undesirable effects underlie the need for novel therapeutic approaches (*Umanath and Lewis 2018*). Phytochemicals which represent a rich source of plant-derived compounds and molecules that is of pivotal importance possessing therapeutic potential. Bioactive compounds like flavonoids, tannins, phenols, and alkaloids in medicinal plants play a vital role to normalize some pathological changes in the body system (Khan, *et al*., 2019). Currently, herb derived phytochemicals are emerging as promising drug candidates in the prevention and treatment of various metabolic disorders, particularly hyperglycemia and dyslipidemia (Zhao *et al*., 2019).

Triclisia marcrophylla has been identified for its medicinal values to possess antibacterial activity and commonly used locally bay indigenes of Nsukka (eastern parts of Nigeria) for the treatment of gastrointestinal disorder. (Okorie and Ali, 2021). *Triclisia marcrophylla* is a species of plant in the menispermaceae family. It is commonly known as 'IsimEgied' by the annang people of Akwa Ibom state, Nigeria. It is a shrub occurring as climber growing in farmlands and forest (Udobi *et al.,* 2017). In cote d'lvoire, the root pulp of *T. macrophylla* is used to treat joint pains and epileptic attack. In democratic republic of congo, a decotion of the twig bark is used to treat malaria, while In Nigeria the plant is used in the treatment of malaria among the people of Awka ibom state and in treatment of diarrhea and other gastrointestinal disorders in Enugu State Okorie and Ali, 2021).

The present study investigated the ethanol leaf extract of *Triclisia macrophylla* for its toxicity, antidiabetic potentials and the effect of the plant extract on body weight and haematological indices in alloxan-induced diabetic rats.

METHODOLOGY

COLLECTION AND IDENTIFICATION OF PLANT MATERIALS

Fresh leaves of *Triclisia macrophylla* were collected from Ikot Akam Ibesit in OrukAnam Local Government Area of Akwa Ibom State and were authenticated by a plant scientist at the Department of Forestry, College of Natural Resources and Environmental Management, Michael Okpara University of Agriculture, Umudike.

PREPARATION OF PLANT EXTRACT

The collected leaves of *Triclisia macrophylla* were dried under shed within 14 days and were thereafter ground to powder. The powdered sample was soaked in 1 liter of ethanol and vigorously steered at intervals for 48 hours before filtration to obtain filtrate containing the extract in solution. The filtrate was concentrated to dryness in a hot air oven at low temperature (40^0C) to obtained a pasty dark green extract. The extract was preserved in the refrigerator until use.

EXPERIMENTAL ANIMALS

A total of 51 adult male albino rats (106-150 g) were used for the study. Twenty-one (21) were used for acute toxicity test while the remaining thirty (30) were used for the antidiabetic study. The animals were obtained from the laboratory animal production unit of the College of Natural Sciences, MOUAU. The animals were housed in aluminum cages and were exposed to standard environmental conditions with access to food and water but starved for 12 hours before commencement of experiment. International guidelines for care and use of laboratory animals were strictly adhered to (OECD, 2008).

DETERMINATION OF ACUTE TOXICITY (LD_{50}) VALUE OF THE EXTRACT

For the acute toxicity evaluation, the new Lorke's method used by Orieke *et al*., (2019) was adopted with little modification. Briefly, two stages were involved in the experiment. In the first stage, 9 albino rats were assigned to 3 groups (A, B and C) of 3 rats each and were treated with 10, 100 and 1000 mg/kg of the *Triclisia macrophylla* leaves extract respectively. The animals were thereafter monitored for the manifestations of toxicity signs and deaths within 24 hours. With zero mortality recorded, the study proceeded to the second phase which also involved the use of 9 rats assigned to 3 groups (A-C). Single treatment doses assigned to the groups were 1600, 2900 and 5000 mg/kg respectively. The animals were again monitored for toxicity signs and deaths within 24 hours. When no mortality was observed at the end of the period, the highest dose used (5000 mg/kg) was repeated on another set of 3 rats to serve as a confirmatory test and was observed within 24 hours and a further one week.

Acute toxicity values calculated using Lorke's formular stated as:

$LD_{50} = \sqrt{A \times B}$

A= Maximum dose that produced no mortality

B= Minimum dose that killed all animals in a group

TABLE IA: RESULTS OF LETHAL DOSE EVALUATION OF THE EXTRACT (PHASE 1 LD_{50} RESULTS)

Group	Dose (mg/kg)	Number of deaths	Observation
1	10	0/3	Animals were active and physically stable. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.
2	100	0/3	Animals were active and physically stable. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.
3	1000	0/3	Animals were active and physically stable. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.

TABLE IB: RESULTS OF LETHAL DOSE EVALUATION OF THE EXTRACT (PHASE 2 LD_{50} RESULTS)

Group	Dose (mg/kg)	Number of deaths	Observation
1	1600	0/3	Animals were active and physically stable. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.
2	2900	0/3	Animals were calm and physically inactive for about 25 minutes but regained physical activity thereafter. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.
3	5000	0/3	Animals were calm and physically inactive for about 3 hours, but regained physical activity thereafter. Signs of toxicity like agitations, roughness of hairs, depression, writhing reflexes and death were absent.

LD_{50}> 5000 mg/kg body weight

INDUCTION OF DIABETES AND EXPERIMENTAL DESIGN

The animals kept to fast overnight and diabetes was induced by intraperitoneal injection of freshly prepared solution of Alloxan Monohydrate (150mg/kg) in ice cold 0.9 % NaCl saline solution. Control rats were injected with normal saline alone, 72 hours later, rats with blood glucose level above 200mg/dl were considered diabetic and selected from the experiment.

The animals in all groups (except group 1) were made diabetic by a single intraperitoneal administration of alloxan monohydrate (150 mg/kg body weight) and were confirmed to be diabetic in a further 5 days via the determination of the glucose concentration of blood collected by tail snip using an Accu-chek® active glucometer (Roche)

and test strips. Animals with constant blood level above 200mg/dl were considered diabetic and were used for the study.

RESULTS

The groups were treated according to the order below:

Group 1: Normal control, **Group 2:** Diabetic control

Group 3: Diabetic treated with glibenclamide, 3 mg/kg body weight, **Group 4:** Diabetic treated with Extract, 200 mg/kg body weight, **Group 5:** Diabetic treated with Extract, 400 mg/kg body weight, **Group 6:** Diabetic treated with Extract, 800 mg/kg body weight

The extract was dissolved in water, 1:1. Treatment for the rats was oral and once daily and lasted for 14 days before animals were sacrificed by cervical dislocation for blood collection into sample bottles for hematology studies.

DETERMINATION OF HEMATOLOGICAL INDICES

The determination of various blood parameters such as RBC counts, Hb, PCV, WBC counts and platelets counts was done using automated hematology analyzer (Model BC-2300, Mindray, China) to evaluate the effect of the drugs on the blood count of the experimental animals.

TABLE II: ACUTE EFFECT OF THE EXTRACT ON BLOOD SUGAR LEVELS OF DIABETIC RATS

Group	Pre-induction blood sugar level (mg/dl)	Post-induction blood sugar level (mg/dl)	2 H Post-treatment blood sugar level (mg/dl)	4 H Post-treatment blood sugar level (mg/dl)	Percentage fall in blood sugar level
1	81.80±1.02	82.6±1.03	75.4±1.57	73.4±1.17	11.13
2	77.6±1.69[a]	283.0±9.12[a]	294.6±5.94[a]	304±6.10[a]	0.00[a]
3	79.8±1.69	296.6±13.20[a]	267.2±6.89[ab]	193±9.98[ab]	34.27[ab]
4	79.6±1.47	302.4±1.83[a]	288.4±0.60 [a]	240±6.98[ab]	20.66[ab]
5	83±1.52[b]	311.6±15.69[a]	272.6±12.49[ab]	221.6±13.15[ab]	28.89[ab]
6	80.8±0.73	304.8±10.98[a]	225.2±6.18[ab]	195.8±2.03[ab]	35.45[ab]

Group 1: Normal control; Group 2: Diabetic control; Group 3: Diabetic treated with glibenclamide, 3 mg/kg body weight; Group 4: Diabetic treated with Extract, 200 mg/kg body weight; Group 5: Diabetic treated with Extract, 400 mg/kg body weight; Group 6: Diabetic treated with Extract, 800 mg/kg body weight; Values are Mean±SEM of 5 determination (n=5). Values with superscript 'a' and or 'b' indicates significant difference ($p<0.05$) from the normal and diabetic control respectively.

TABLE III: SUB-ACUTE EFFECT OF THE EXTRACT ON BLOOD SUGAR LEVELS IN DIABETIC RATS

Group	Last acute phase (4H) blood sugar level (mg/dl)	Day 7 Post-treatment blood sugar level (mg/dl)	Day 14 Post-treatment blood sugar level (mg/dl)	Percentage fall in blood sugar level
1	79.6±2.01	80.6±1.66	77.8±0.73	5.77
2	305.8±6.61[a]	329.4±9.41[a]	360.8±32.89[a]	0.00[a]
3	188.0±8.07[ab]	143.2±3.76[ab]	125.2±2.63[ab]	57.38[ab]
4	239.2±7.30[ab]	222.6±3.36[ab]	190±6.71[ab]	37.15[ab]
5	214.8±15.65[ab]	168.4±7.01[ab]	141.4±2.62[ab]	54.23[ab]
6	194.6±2.46[ab]	152.6±3.16[ab]	134.6±3.47[ab]	55.48[ab]

Group 1: Normal control, **Group 2:** Diabetic control, **Group 3:** Diabetic treated with glibenclamide, 3 mg/kg body weight, **Group 4:** Diabetic treated with Extract, 200 mg/kg body weight, **Group 5:** Diabetic treated with Extract, 400 mg/kg body weight, **Group 6:** Diabetic treated with Extract, 800 mg/kg body weight, Values are Mean±SEM of 5 determination (n=5). Values with superscript 'a' and or 'b' indicates significant difference ($p<0.05$) from the normal and diabetic control respectively.

TABLE IV: EFFECT OF THE EXTRACT ON BODY WEIGHT CHANGES OF DIABETIC RATS

Group	Initial body weight (g)	Final body weight (g)	Body weight gain (g)	Percentage weight gain
1	106.48±1.51	132.56±0.97	26.08±0.58	24.54
2	111.94±1.90	107.52±1.57[a]	0.00[a]	0.00[a]
3	113.84±3.54	121.94±1.63[ab]	8.1±1.93[ab]	7.352[ab]
4	113.76±3.43	120.32±1.82[ab]	6.56±1.63[ab]	5.972[ab]
5	117.68±3.31	124.2±3.77[ab]	6.52±0.74[ab]	5.518[ab]
6	115.72±1.73	123.76±1.53[ab]	8.04±0.23[ab]	6.964[ab]

Group 1: Normal control, **Group 2:** Diabetic control, **Group 3:** Diabetic treated with glibenclamide, 3 mg/kg body weight, **Group 4:** Diabetic treated with Extract, 200 mg/kg body weight, **Group 5:** Diabetic treated with Extract, 400 mg/kg body weight, **Group 6:** Diabetic treated with Extract, 800 mg/kg body weight, Values are Mean±SEM of 5 determination (n=5). Values with superscript 'a' and or 'b' indicates significant difference ($p<0.05$) from the normal and diabetic control respectively.

TABLE V: EFFECT OF THE EXTRACT ON HAEMATOLOGICAL PARAMETERS IN DIABETIC RATS

Group	RBC ($x10^6/mm^3$)	PCV (%)	Hb (g/dl)	WBC ($x10^3/mm^3$)	PLT ($x10^3/mm^3$)
1	6.916±0.09	44.00±0.55	14.88±0.29	9.062±0.05	358.20±8.53
2	4.226±0.04[a]	31.40±0.24[a]	10.24±0.11[a]	7.792±0.04[a]	449.00±4.55[a]
3	5.326±0.05[ab]	38.80±0.49[ab]	12.68±0.16[ab]	8.146±0.03[ab]	378.20±2.92[ab]
4	5.668±0.12[ab]	40.60±0.60[ab]	13.82±0.09[ab]	8.524±0.08[ab]	378.40±8.95[ab]
5	5.718±0.18[ab]	41.40±0.68[ab]	14.08±0.18[ab]	8.702±0.05[ab]	358.80±4.58[b]
6	5.728±0.04[ab]	42.60±0.24[b]	14.04±0.04[ab]	8.518±0.12[ab]	342.00±2.51[b]

Group 1: Normal control, **Group 2:** Diabetic control, **Group 3:** Diabetic treated with glibenclamide, 3 mg/kg body weight **Group 4:** Diabetic treated with Extract, 200 mg/kg body weight, **Group 5:** Diabetic treated with Extract, 400 mg/kg body weight, **Group 6:** Diabetic treated with Extract, 800 mg/kg body weight. Values are Mean±SEM of 5 determination (n=5). Values with superscript 'a' and or 'b' indicates significant difference ($p<0.05$) from the normal and diabetic control respectively

DISCUSSION

Glycemic homeostasis referred to the control of glucose within living organisms. Diabetes mellitus often compromises this balance, leading to complications and changes in hematological indices. These complications contribute to co-morbidity and mortality. Therapeutic agents like medicinal plants' ability to restore glycemic balance and biochemical parameters is crucial for their antidiabetic function and relevance. The result shows that the plant's leaf extract demonstrated a significant antidiabetic action on the animals by bring to near normal the levels of some parameters to a concentration similar to the normal control (group 1), these values which comparatively differ significantly ($p<0.05$) with the untreated diabetic control (group 2). The acute toxicity assessment (Table I) revealed a high safety profile for the ethanol leaf extract, with no mortality recorded across all test groups. This result agreed with the existing literature strongly suggesting appreciable medicinal potentials of *Triclisia macrophylla* in treatment of different ailment (Udobi *et al.,* 2017; Okorie & Ali, 2021).

Acute effect of the plant extract on blood sugar levels of diabetic rats (Table II) showed a significant fall over 20, 28 and 35% fall at 200, 400 and 800mg/kg bw respectively. Confirming that treatment of the animals with the leaf extracts resulted to a dose-dependent significant reduction ($p<0.05$) in the blood glucose concentration. Table II shows that the glucose concentration of the untreated diabetic rats (group 2) increased significantly ($p<0.05$) compared to normal control (group 1). Glucose level of diabetic rats treated with 200, 400 and 800mg/kg body weight of the extracts decreased significantly compared to the untreated diabetic rats (group 2). Similarly, sub-acute effect of the extract on blood sugar levels in diabetic rats (table III) demonstrated a significant decrease (over 50% fall) in blood glucose level of the treated rats after 14 days of treatment. This result suggests that the extract possess antidiabetic potential which may be attributed to the chemical constituents of the extracts. Udobi *et al.* (2017) had reported the presence of tannins, flavonoids, alkanoids terpenes, saponins and other constituents in *Triclisia macrophylla* leaf. However, the actual mechanism by which the plant extract brings about its antidabetic effect has not been fully elucidated. It could be suggested that the plant extract might have exerted its action on the beta cells of the Islet of Langerhans in the pancrease of the animals since Alloxan induces diabetes in experimental animals by destroying the beta cells of the Islet of Langerhans in the pancrease leading to reduction in the synthesis and release of insulin hence inducing hyperglycemia.

Diabetes is associated with the characteristic loss of body weight which is due to increased muscle wasting and due to loss of tissue proteins (Asuzu-Samuel & Karibo, 2024). In the diabetic control group, the results revealed a progressive body weight loss (table IV) in the untreated diabetic rats (group 2) when compared to the normal control (group 1). Loss of weight may be due to the loss in muscle and adipose tissues which further resulted from excessive breakdown of tissue protein and fatty acids occasioned by the observed decrease in plasma insulin concentration (Asuzu-Samuel & Karibo, 2024). In diabetic animals, lack of insulin facilitates inhibition of protein synthesis and promotes degradation which increases amino acid levels in the blood to be subsequently used for gluconeogenesis (Qian *et al*., 2015).

The body weights of rats in group 2 decreased significantly ($p<0.05$) when compared to group 1. But when treated with the plant extract, a significant increase in body weight was observed when compared to group 2 diabetic animals. Similar loss of weight in diabetic animals had been previously reported by Mestry, *et al.* (2017) in STZ-diabetic rats. The weight gain observed after treatment with the plant extract suggests that the extract is beneficial in preventing muscle wasting, adipose tissue degradation and protein turn over.

Table V shows the haematological indices of alloxan-induced diabetic rats treated with ethanol leaf extract of *Triclisia macrophylla*. Red blood cells RBC, Packed cell volume PCV, Hemoglobin Hb and White blood cell WBC in the diabetic untreated (group 2) contrasted with the normal control (group1) in significant decrease. In the same way, RBC, PCV Hb and WBC showed a significant increase ($p<0.05$) in all test groups when compared to the untreated group 2. Table V also showed a significant increase in platelet PLT level in untreated diabetic group 2 compared to all test groups. During pathological conditions such as diabetes, the body system is challenged leading to alteration of hematological indices (Mansi & Lahham, 2008). The reduction in RBC, PCV and Hb level could be as a result of oxidative stress generated in the course of diabetes leading to destruction of the red blood cells. It has also been reported that, ingestion of medicinal plants or drugs can alter the normal hematological values (Ajagbonna *et al*., 1999). However, the results of this study suggest that plant leaf extract contain appreciable antioxidants which prevented further disruption of the red blood cells, it could further be suggested that the plant extract are capable of normalizing hematological abnormalities associated with diabetes mellitus thus could be prescribed as adjunct to dietary therapy and main therapy for diabetes mellitus. In agreement with Enechi *et al*. (2023) the significant decrease in the levels of RBC, PCV Hb and WBC observed in the diabetic animals were significantly increased to near normal level following administration of the leaf extract. The decrease in RBC, PCV Hb and WBC values as observed in the diabetic animals is an indication of abnormal hemoglobin synthesis, failure of blood osmoregulation, and plasma osmolarity (Stookey *et al*., 2007). Following administration of the extract, the level of RBCs and its related indices were appreciably improved. This gives an indication that leaf extract can stimulate the formation or secretion of erythropoietin, which stimulates stem cells in the bone marrow to produce red blood cells.

CONFLICT OF INTEREST

No conflict of interest was reported.

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