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**EFFECT OF ORAL ADMINISTRATION OF AQUEOUS
LEAF EXTRACT OF POLYALTHIA LONGIFOLIA ON
THE LIVER, KIDNEY AND SERUM ELECTROLYTES
OF ALLOXAN INDUCED MALE WISTAR RATS**

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Abstract: The effects of aqueous leaf extracts of Polyalthialongifolia (Mast Tree) for the management of rats induced with alloxan were investigated. Thirty male wistar rats were used for this research. They were divided into six groups of five rats each. Group 1, normal control (not induced and not treated); group 2, positive control (induced but not treated); group 3, induced and administered with metformin (100mg/kg); group 4, induced and given 100mg/kg of the extract; group 5, induced and treated with 200mg/kg of the extract, and group 6, induced and treated with 300mg/kg of the extract for fourteen days. The serum and tissue (kidney and liver) of the rats were obtained for biochemical analysis. The result showed a reduction in serum glucose levels at day's interval (0, 5, 10, and 15). There were a significant decrease in the activities of serum enzymes, and a marked increase at the tissue enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) and also a reduction in the levels of serum urea, uric acid and creatinine of the treated groups when compared with the control groups ($p < 0.05$). Serum electrolytes (calcium, sodium, phosphorus and chloride) also increases upon treatment when correlated with the control groups. Urea, creatinine and uric acid increases when assayed at the renal level as compared with the control groups. Thus, aqueous extracts of P.longifolia restores the activities of serum and tissue enzymes, level of renal markers as well as serum electrolytes towards normalization. The overall results is an indication of hypoglycemic, hepato and renal protective effects of the extracts.

Keywords: Alloxan, Polyalthialongifolia (mast tree), metformin, tissue enzymes, biochemical analysis.

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1. INTRODUCTION

Diabetes mellitus (DM) is a disease condition that is characterized by derangement of carbohydrate, protein and lipid metabolism (Bharathiet al., 2014). Insulin insensitive diabetes or non-insulin dependent diabetes (NIDD) is a metabolic disease characterized by persistent hyperglycemia (Riyaphanet al., 2017). It has been published as a metabolic disorder that arises from increase in postprandial glucose (PPG) levels due to insufficiency of insulin secretion or insulin resistance (Gerich, 2013). Insulin resistance (IR) may be a consequence of insensitivity of its receptors such as insulin receptor signal-1 (IRS-1) and as such, it does not diffuse into its target site of action thus, leading to postprandial hyperglycemia (PPHG). Diabetes is common in European and Africa continents. It is caused by varied interactions between environmental and genetic factors. Its pandemic effect is responsible for the increased mortality rate among the ages of 18 and above (WHO, 2014; ADA, 2011).

Several studies have been undertaken to explain the possible biochemical mechanisms involve in the causes of diabetes mellitus. Hyperglycemia and lipoprotein disorders which are the hallmark of diabetes mellitus have been considered as the principal cause of diabetes complications (NICE, 2015). These conditions are hypothesized to damage cell membranes, which results from

elevated generation of reactive oxygen species (ROS). Oxidative stress that results from ROS production has been associated in various diseases such as cancer, aging, diabetes, autoimmune diseases, cardiovascular disease, liver diseases and neurological degenerative disorder (Li et al., 2015). The release of oxygen free radicals during cellular metabolism and exposure to certain environmental factors, including lifestyle appears to play an important role in the causes of diabetes mellitus (Mayuret al., 2010; Assiset al., 2017).

Phytomedicine, regarded as herbal medicine has become a conventional existence worldwide (Prabhakaret al., 2014). Recently, it has been published that more than 80% of the world population is dependent on herbal medicine (Chandaet al., 2017). Plants have been used for the management of diabetes mellitus (DM) chiefly in developing countries where most people have limited resources and do not have access to current treatment. In Nigeria, quite a lot of plant species have been reported to possess medicinal properties and engaged in treatment of many ailments (Ighodaroet al., 2012). Research have shown that phytochemicals isolated from plant sources have been used for the preclusion and treatment of cancer, heart disease, diabetes mellitus, and high blood pressure (Daisy et al., 2009). Antioxidants assuage in cells stress caused by oxidation, thereby

help in the prevention and treatment of many diseases of humans. The exploration of herbal drugs as potent source of antioxidants has attracted much attention in recent times. Plant nutrients rich in polyphenols due to their affinity for enzyme protein, have been published to cause effects similar to insulin in the utilization of glucose and acts as good inhibitors of key enzymes like alpha-amylase and alpha-glucosidase associated with diabetes mellitus and lipid peroxidation (LPO) in tissues. Studies have also shown that the bioactivity of polyphenols in plant extracts is linked to their antioxidant scavenging activity and many of these plants possess hypoglycemic properties (Riyaphanet al., 2017).

Polyalthia is a large genus of shrubs and trees found in tropic and subtropic regions. It belongs to the family of Annonaceae and *Polyalthialongifolia* is commonly known as mast tree. It is referred as Aranamaram in Malayalam. It is a medium-sized tree with lanceolate leaves, 1 to 1.5cm broad, originally grown in Srilanka and now grows in tropical parts of India on road sides and gardens for their beautiful appearance. It is found to have a unique place in the traditional medicinal practice of Indian Ayurvedic System (IAS) and has been worthy to be successful for the treatment of various diseases like cancer, ulcer, inflammation and hepatotoxicity (Jothyet al., 2012). Ethanolic extract of *P. longifolia* showed a high percentage inhibition

of alpha-amylase and alpha-glucosidase, key enzymes in diabetic coma (Gayathri and Jeyanthi, 2013). This study focuses on the use of locally sourced phytomedicine or decoction (extracts of *Polyalthialongifolia*) to lower postprandial glucose levels and also evaluate the effects on the hepatocyte and renal functions.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Adult male Wistar albino rats of three to four months weighing between 100-200g were obtained from the animal house, Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. They were fed with grower mash obtained from Dutch Farm Limited, Abraka and water ad libitum. They were acclimatized for one week. Thereafter, they were induced with Alloxan monohydrate, which causes diabetic coma.

2.2 Chemicals

Alloxan monohydrate and all other reagents used for this study were obtained from Alpha Chimika, Mumbai, China.

2.3 Collection and Identification of Plant Material

The plants were collected from Abraka, Ethiope East Local Government Area, Delta State and identified at the Department of Botany, Delta State University, Abraka.

2.4 Preparation of Extract

The plants were washed to remove contaminants and air-dried for about three weeks. Thereafter, they

were grinded to fine powder using Waren blender. 900g of powdered solute (Polyalthialongifolia pulverized leaves) was soaked in 3600ml (3.6L) of distilled water in a ratio 1:4. It was macerated after 48hrs to obtain the crude extract. This was followed by filtration using Whatman No110 filter paper. The purified crude was then concentrated using a vacuum rotary evaporator at reduced temperature (50oC) and bathed at 40oC. This yielded a dark brown concentrated extract of 63g (7%W/W). The obtained crude extract was packaged in an airtight plastic container and stored at 4oC until when required for use.

2.5 Induction of Diabetes

The rats were starved for 12 hours and induced intraperitoneally at a dosage of 150mg/kg Alloxan monohydrate solution. Prior to their induction, the fasting blood glucose level (FBGL) was determined using glucometer to ascertain the glucose levels. The Alloxan monohydrate solution was prepared by dissolving 4g of Alloxan in 100ml of normal saline. This corresponds to a stock solution of 40mg/ml. After 72 hours of induction, hyperglycemic conditions of $\geq 200\text{mg/dl}$ were confirmed using a glucometer (Iweala et al., 2013).

2.6 Experimental Design (ED)

A total of thirty (30) rats were used for this research. The rats were divided into six (6) groups of five (5) rats each as follows. The blood glucose level was taken every four days.

Group 1: Normal Control (NC)
Received Distilled Water

Group 2: Positive Control (PC)
Received Distilled Water

Group 3: Treated with known drug at 100mg/kg (Metformin)

Group 4: Treated with Aqueous Extract Polyalthialongifolia (F1, 100mg/kg)

Group 5: Treated with Aqueous Extract Polyalthialongifolia (F2, 200mg/kg)

Group 6: Treated with Aqueous Extract Polyalthialongifolia (F3, 300mg/kg)

The treatments lasted for a period of fourteen (14) days after which they were sacrificed.

2.7 Collection of Sample

The rats were sacrificed by cervical dislocation or decapitation and blood sample was collected using 5ml syringe from each rat. Samples were emptied into anticoagulant containers to prevent clotting (plasma enzymes). Some of the samples were equally placed in universal containers (serum enzymes). The tissues (liver and kidney) were homogenized and assayed for biochemical parameters. Tissue organelles of the hepatocyte and kidney were collected, rinsed with cold saline and 0.5g each was homogenized in 4.5ml of phosphate buffer using a homogenizer (mortar and pestle) at cold temperature. The homogenate was then placed on a plane tube and centrifuge and the resultant supernatant were the used for various biochemical analysis. The tubes were spinned at 3000rev/mins for 10mins. Samples that were not analyzed were refrigerated at 4°C and -4°C for preservation. The serum was

analyzed for the following biochemical parameters.

2.8 Determination of Blood Glucose Level (BGL)

Blood glucose level of experimental animals was determined at week 0 (before administration) and subsequent weeks and the last day of experiment. This were checked using glucometer.

2.9 Determination of Biochemical Parameters

Determination/Estimation of liver enzymes, lipid profile and kidney function were carried out using the Prietesteasylab Biochemistry analyzer. It measures theoretical densities of samples and it uses algorithm to calculate results, which are used for biochemical investigations. It has direct access to stored programs. The analyzer can analyze the following parameters.

Glucose, Urea, Creatinine, Hemoglobin, Cholesterol, SGPT (ALT), SGOT (AST), Albumin, Total Protein, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, Uric Acid ,Triglycerides, Urea UV Amylase, Gamma GT , Phosphorus , Micro Protein , Calcium Ars. III, Calcium OCPC, HDL Cholesterol and Chloride were assayed using Prietesteasylab Biochemical analyzer.

2.10 Statistical Analysis

The data was analyzed using a computer software (SPSS version 21) and compared using Bonferroni test. The results are represented as Mean \pm SEM.

3. RESULTS

Values with different alphabet superscript in the same column indicates a significant difference

($p < 0.05$), while values with the same alphabet superscript in the same column indicates no significant difference ($p > 0.05$).

3.1 Blood glucose level

There were reduction in blood glucose level of the rats administered aqueous extract *P. longifolia* when compared with the normal, positive and the groups given known drug metformin at 100mg/kg (fig.1).

3.2 Activities of serum liver markers (ALT, AST and ALP)

There were a significant difference ($p < 0.05$) in the activities of serum ALT and AST when compared with the control groups. Similarly, there were slight decrease although not statistically significant ($p > 0.05$) in the activities of serum ALP of the treated groups when compared with the control groups (table 1).

3.3 Activities of tissue liver markers (ALT, AST and ALP)

There were a significant increase in the activities of tissue AST and ALP of the treated groups as compared with the control groups. There were no observed difference in tissue ALT of the groups treated with 100mg and 200mg/kg of the extracts when compared with the normal control hence, restoration of liver integrity (table 2).

3.4 Levels of serum renal parameters (Urea, Creatinine and Uric acid)

There were a significant difference ($p < 0.05$) in the levels of serum urea, creatinine and uric acid of the groups given aqueous leaf extracts of *P. longifolia* when compared with the control groups (table 3).

3.5 Levels of tissue renal markers (Urea, Creatinine and Uric acid)

There were slight increase in the levels of tissue creatinine and uric acid of the treated groups when compared with the control groups. There were significant increase in tissue urea of the treated groups when related with the various control groups (table 4).

3.6 Levels of serum electrolytes

(Na⁺, Ca²⁺, P and Cl⁻)

There were no statistical difference in the levels of serum Na⁺, Ca²⁺, P and Cl⁻ of the treated groups when correlated with the normal control. However, when compared with the positive control there were observed significant difference. This is an indication of restoration of renal function towards normalization (table 5).

Table 1: Activities of Liver Marker Enzymes in the Serum

Groups	ALT	AST	ALP
NC	33.55±1.19 ^a	45.30±1.98 ^a	53.10±1.56 ^{ab}
PC	12.45±0.26 ^b	29.60±0.53 ^b	40.85±0.43 ^a
DRUG	17.00±0.41 ^c	22.88±1.01 ^c	47.40±3.22 ^a
F1	24.25±0.96 ^d	30.90±0.54 ^b	58.75±0.59 ^{ab}
F2	24.75±0.95 ^d	37.75±0.48 ^d	69.45±1.03 ^b
F3	22.50±0.96 ^d	36.63±0.55 ^d	38.47±8.95 ^a

Key: NC= Normal control; PC; Positive control; Drug= 100mgKg-1 Metformin; F1=100mgKg-1P. longifolia; F2=200mgKg-1P. longifolia; F3=300mgKg-1P. longifolia

Table 2: Activities of Liver Marker Enzymes in the Liver

Groups	ALT	AST	ALP
NC	16.50±1.37 ^a	37.16±0.33 ^a	44.40±1.59 ^a
PC	22.31±3.21 ^a	51.23±2.67 ^b	47.18±2.46 ^a
DRUG	14.91±1.42 ^a	44.70±0.47 ^{bc}	36.95±0.75 ^b
F1	15.44±0.41 ^a	33.76±1.56 ^a	64.25±0.85 ^c
F2	17.60±1.61 ^a	49.19±2.05 ^b	70.55±0.91 ^c
F3	21.14±1.11 ^a	41.23±0.30 ^{bc}	54.73±1.64 ^d

Key: NC= Normal control; PC; Positive control; Drug= 100mgKg-1 Metformin; F1=100mgKg-1P. longifolia; F2=200mgKg-1P. longifolia; F3=300mgKg-1P. longifolia

Table 3: Levels of Urea, Creatinine and Uric acid in the Serum

Groups	Urea	Creatinine	Uric Acid
NC	18.30±1.06 ^a	2.33±0.34 ^a	3.30±0.15 ^a
PC	39.75±0.62 ^b	1.93±0.05 ^{ab}	4.53±0.05 ^{bd}
DRUG	24.50±1.71 ^a	1.45±0.13 ^b	3.73±0.12 ^{ab}
F ₁	26.15±0.43 ^{bc}	2.08±0.05 ^{ab}	6.20±0.08 ^c
F ₂	31.10±0.61 ^{bc}	2.05±0.06 ^{ab}	5.40±0.15 ^{cd}
F ₃	32.98±5.68 ^{bc}	1.95±0.10 ^{ab}	5.45±0.52 ^{cd}

Key: NC= Normal control; PC; Positive control; Drug= 100mgKg-1Metformin; F1=100mgKg-1P. longifolia; F2=200mgKg-1P. longifoliaF3=300mgKg-1P. longifolia

Table 4: Levels of Kidney Function Parameters in the Kidney

Groups	Urea	Creatinine	Uric Acid
NC	43.15±1.89 ^{ab}	2.25±0.09 ^a	5.55±0.17 ^{ab}
PC	47.18±2.46 ^{ad}	2.93±0.05 ^a	6.33±0.13 ^a
DRUG	36.13±1.75 ^b	2.90±0.39 ^{ab}	5.00±0.39 ^b
F ₁	64.35±0.89 ^c	3.75±0.10 ^b	5.50±0.21 ^{ab}
F ₂	70.80±0.67 ^c	2.95±0.06 ^a	5.73±0.11 ^{ab}
F ₃	53.98±1.45 ^d	3.35±0.22 ^a	5.68±0.22 ^{ab}

Key: NC= Normal control; PC; Positive control; Drug= 100mgKg-1Metformin; F1=100mgKg-1P. longifolia; F2=200mgKg-1P. longifoliaF3=300mgKg-1P. longifolia

Table 5: Levels of Serum Electrolytes

Groups	Na ⁺	P	Ca ²⁺	Cl ⁻
NC	134.50±1.71 ^a	5.13±0.20 ^a	6.80±0.45 ^a	88.50±4.91 ^a
PC	154.00±3.19 ^b	4.25±0.10 ^b	12.50±1.65 ^b	115.50±2.22 ^b
DRUG	141.75±4.44 ^{ac}	5.27±0.03 ^a	6.25±0.48 ^a	88.00±1.78 ^a
F ₁	156.75±1.38 ^b	4.80±0.08 ^a	10.00±0.41 ^c	98.25±2.02 ^{ac}
F ₂	152.50±1.04 ^{bc}	6.20±0.18 ^c	10.10±0.42 ^c	98.25±2.02 ^{ac}
F ₃	156.75±1.50 ^b	5.28±0.11 ^a	10.25±0.48 ^{cb}	102.75±1.11 ^{bc}

Key: NC= Normal control; PC; Positive control; Drug= 100mgKg-1 Metformin; F1=100mgKg-1P. longifolia; F2=200mgKg-1P. longifolia F3=300mgKg-1P. longifolia

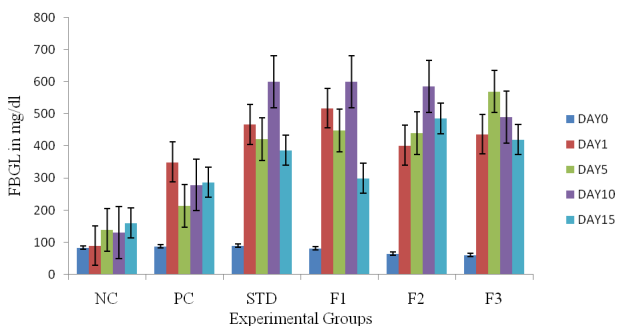


Figure 1: Glucose chart showing the changes in blood glucose levels in every four days interval. FBGL in mg/dl.

Key: DAY 0: Fasting blood glucose level (FBGL) before induction. DAY1: FBGL after induction. DAY5: FBGL after four days of treatment. DAY10: FBGL after nine days of treatment. DAY15: FBGL after sacrificing; STD: Drug (Metformin).

4. DISCUSSION AND CONCLUSION

Diabetes is a non-communicable disease that is prevalent among the world population (WHO, 2014). Measurement of serum enzymes help in the diagnosis and prognosis

of various diseases (Nelson and Cox, 2005). The amount of serum enzymes gives an inkling of damage in the liver. This study adduce that in alloxan induced diabetic rats, treatment with aqueous leaf extracts of Polyalthialongifolia may probably

assuage oxidative stress caused by liver and kidney damage . High serum glucose levels, (figure 1) observed after induction of the rats with alloxan and gradual decrease in glucose levels upon treatment with different concentrations of the plant extract was in accordance with the work of Assiset al. (2017) who used streptozotocin to induce rats.

The same biochemical mechanism was observed in table 1, where the activities of serum alanine aminotransferase, aspartate aminotransferase in all the treated groups reduced significantly and slight increase in the activities of alkaline phosphatase except at 300mg/kg where there was a significant reduction when compared with the control groups (table 1). The marked reduction in the activities of ALP as shown in table 1 may be an indicator of hepatoprotective effect of aqueous leaf extracts of *Polyalthialongifolia* at 300mg/kg. This result is similar to what was reported on treatment with *Ipomoea batatas* (Ogunrinola et al., 2015; Balamuruganveluet al., 2014).

The biochemical trend in the activities of liver tissue markers was observed to be inverse with the activities in the serum. There was a slight increase in the activities of tissue enzymes (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) of the treated groups when compared with the normal control (table 2). However, the observed increased in enzyme activities in the liver may be due to

the restoration of the liver integrity caused by the presence of some phytochemicals present in the plant extract.

The levels of serum urea, creatinine and uric acid (table 3) also significantly decreased at 100mg and 200mg/kg of the treated groups when compared with positive control ($p < 0.05$) except at 300mg/kg of the extract. This is in line with methanolic extracts of *Polyalthialongifolia* that has been reported to reduce serum urea, creatinine and uric acid (Chanda et al., 2012). The reduction observed may be due to the presence of the following secondary metabolites; phenol, saponin, tannin and alkaloid (Gayathri et al., 2015). There was significant increase in the levels of tissue urea when compared with the control groups. However, slight increase was observed in the levels of tissue creatinine and uric acid when compared with the control groups (table 4). This is consistent with the report of Omoniwa et al. (2012). Again this could be a restoration of renal integrity upon treatment with aqueous extracts of *P. longifolia*.

The result of serum electrolytes showed no significant difference ($p > 0.05$) in the levels of serum sodium ion (Na^+) of the treated groups when compared with the control groups. Slight reduction was observed in the levels of serum Ca^{2+} , P and Cl^- when compared with the control groups (table 5). This may probably due to the restoration of ion channels in the membrane

upon administration of the extract. The hepatoprotective and renal function restoration of aqueous leaf extracts of *Polyalthialongifolia* is mainly the antioxidants present in the leaf. This is similar to the reports on the treatment with ethanolic leaf extracts of *Polyalthialongifolia* (Khan et al., 2013; Omonkhuat et al., 2014).

Oral administration of metformin at 100mg/kg, showed a marked decrease in serum levels of electrolytes; Na⁺, Ca²⁺, P and Cl⁻ as compared with the different dosage of the extracts. However, at 300mg/kg of the extract, activities of serum enzymes were close to normal when compared with metformin (table 1).

Finally, aqueous leaf extracts of *Polyalthialongifolia* is able to reduce postprandial glucose levels by restoring the distorted frame work of the liver and kidney of allonizedwistar rats.

In conclusion, diabetes is a life threatening disease requiring urgent attention and management. Diet and lifestyle factors contribute to the endemic nature of this disease. The use of aqueous leaf extracts of *Polyalthialongifolia* is devoid of side effects associated with the known drugs for diabetes, and its

availability at affordable cost makes it a perfect alternative for the management of diabetes. Similarly, the presence of the following secondary metabolites; phenol, saponin, tannin and alkaloid may be responsible for the antidiabetic activities of the extract. Isolation and purification of the phytochemicals present in the plant should be carried and further subjected to investigation in animal models. Furthermore, more study should be done on increase of dosage from 300mg/kg to between 400mg and 700mg/kg which appears to be better for the treatment of diabetes.

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