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EFFECT OF AQUEOUS EXTRACT OF *Tapinathus bangwensis* ON SOME DIAGNOSTIC ENZYMES IN ALLOXAN-INDUCED DIABETIC WISTAR RATS

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ABSTRACT

This study investigated the effect of aqueous Tapinathus bangwensis on some diagnostic enzymes in alloxan induced diabetic wistar rats. The effect of plant extract were monitored on the serum concentrations as amylase (AMYL) aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), Lactate dehydrogenase (LDH) and creatinine kinas (CK) enzymes. Group 1 constitute the normal control which received only feed and water, group 2 received 50mg/kg citrate buffer. Alloxan was dissolved in 0.1M citrate buffer solution, PH 4.5. Group 1 constitute the normal control which received only feed and water, group 2 received 50mg/kg citrate buffer. Group 3 was administered alloxan solution and allowed free access to feed and water. Group 4-6 received 50mg/kg of citrate buffer and were also administered with the aqueous extract of Tapinanthus bangwensis at a dose of 250mg/kg and referred to as normal treated, concentration 1(NT conc-1), concentration 2 (NT con-2) and concentration 3 (NT conc- 3) respectively. Group 7-9 were administered 50mg/kg alloxan and different grades (5%, 7% and 10%) respectively of the aqueous extract. Blood, liver and pancreatic tissue samples were collected into appropriately labelled sample bottles and analysed. Blood, liver and pancreatic tissue samples were collected into appropriately labelled sample bottles and analysed. Result of the blood analysis showed that diagnostic enzymes were elevated significantly ($p<0.05$) in the group 3 rats. Oral administration of 250mg/kg aqueous Tapinathus bangwensis extract to group 7, 8 and 9 of 50mg/kg, 70mg/kg and 100mg/kg respectively significantly ($p<0.05$) decreased many of these biochemical alterations in a dose dependant manner. 100mg/kg administration of the extract showed the highest effect in lowering the elevated parameters followed by 70mg/kg administration. 50mg/kg had the least lowering effect. AMYL decreased in group 7, 8 and 9 respectively. Similarly, the respective decreases in group 7, 8 and 9 were for AST, ALT, LDH and CK. Histopathological results of the pancreas and liver also conformed to these chemical pathological results.

KEY WORDS: ***Tapinathus bangwensis, Awolowo leaf, Aqueous extract, intraperitonially, citrate buffer, lowering effect, enzymes***

INTRODUCTION

Many of the plant species growing throughout the world have medicinal values with active constituents that have a direct action on the body (Uahomo et al., 2022). They are used both in herbal and conventional medicine and offer benefits that pharmaceutical often lack helping to combat illness and support the bodies effort to regain good health (Singh et al., 2007).

World Health Organisation (WHO) and Food and Agricultural Organisation (FAO) studies indicate large scale uses of plant material as medicine against a variety of human ailments. With improved screening techniques and genomic investigations now in progress to target biomolecules of plant origin for treatment of a range of lethal and morbid human diseases, promising results have been emerging from these research programmes (Sofowora et al., 2013).

Onay-Ucar et al. (2006) have demonstrated that *Tapinathus bangwensis* has radical scavenging activity and thus protect against radical generation in cells. This research investigates the effect of aqueous extract of *Tapinathus bangwensis* on alloxan-induced diabetic Wistar rats. The purpose is to find out if *Tapinathus bangwensis* which has been known to lower serum enzymes during liver disease (Omoedu et al., 2008) can

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be used for the management of liver disease through the reduction of some diagnostic enzymes.

MATERIALS AND METHODS

Preparation of plant materials

The plant used for this work is *Tapinathus bangwensis*. The plant was found in the University of Port Harcourt where it was found hemi-parasitizing on specie of orange (*Citrus aurantium*) orchard located on the right side of the front of the Vice Chancellors lodge at the Delta Park of the university. The leaves which were used for this work were carefully plucked off, thoroughly washed and air dried for 24 days until a constant weight was obtained.

Preparation of aqueous extract of *Tapinanthus bangwensis*

Tapinathus bangwensis was collected with stalks. The fresh greenish leaves were carefully plucked off from the stalks and pedicle removed from each leaf. The leaves were thoroughly washed and spread out on a clean cardboard paper and kept at room temperature in a well aerated room. They were allowed to dry to constant weight after 24days. The dried sample was then pounded in a mortar with pistil. After pounding, the partially powdered sample was grounded in a manual grinding machine until a fine powder was obtained. Fifty grams of the powdered mistletoe was measured and dissolved in a 1 litre measuring cylinder containing 500ml distilled water. The mixture was thoroughly shaken for 10 minutes. The mixture was then stored at room temperature for twenty-four hours (Omeodu et al, 2008). The preparation was filtered using ten different pieces of white cloth. The filtrate was filtered two times through a Whitman No. 541 filter paper and stock was stored in a refrigerator at a temperature of 40^{o}C for 24 hours. 50mg/kg, 70mg/kg and 100mg/kg of the filtrate were then prepared from the stock solution and these three different concentrations were used to treat the test animals (Omeodu et al., 2008).

Experimental animals

The animals were divided into experimental groups of six (6) animals per group and each group was housed in a metabolic cage. They were provided with feeds and water ad libitum. The animal feeds were purchased from the Livestock Feeds, Choba, a division of Livestock Feeds Nigeria Limited. Ikeja, Lagos; while the water was supplied by the Water Treatment Plant, Choba Park, University of Port Harcourt. There was a total of (9) experimental group. All the rats weighed between 200g-300g and their average age was fourteen (14) months. The investigated animals consisted of nine groups with six animals per group (Table 1). Each animal was labelled with picric acid for easy identification on the head (HD), right hands (RH), right leg (RL), left hands (LH), left leg (LL) and tail (TL).

Table 1: Research Design

	Group 1 Normal control 1 (NC-1)	**Group 2** Normal control 1 (NC-2)	**Group 3** Normal diabetic control (NDC)	**Group 4** Normal treated control (NT-1)	**Group 5** Normal treated control (NT-2)	**Group 6** Normal treated control (NT-3)	**Group 7** Diabetic treated control (DT-1)	**Group 8** Diabetic treated control 2 (DT-2)	**Group 9** Diabetic treated control 3 (DT-3)
No of Rats	6	6	6	6	6	6	6	6	6
Treatment	Feed + H_2O Only *ad libitum*	Feed + H_2O *ad libitum* + citrate buffer	Feed + H_2O *ad libitum* + alloxan solution	Feed + H_2O *ad libitum* + citrate buffer 5% mistletoe solution	Feed + H_2O *ad libitum* + citrate buffer + 7% mistletoe solution	Feed + H_2O *ad libitum* + citrate buffer 10% mistletoe solution	feed + water *ad libitum* + alloxan + 5% mistletoe solution	Feed + water *ad libitum* +alloxan + 7% mistletoe solution	Feed + water *ad libitum*+ alloxan solution+ 10% mistletoe solution.

Group one animals were administered only feeds and water *ad libitim to* serve as general control group. Group two animals received citrate buffer solution in addition to feeds and water. Alloxan solution was administered to group three animals and allowed free access to feed and water. Before citrate and alloxan administration to group two and three respectively, the animals were fasted for 18 hours. This was the same for group 4 to 9 animals that received various treatments. Group four to six were administered with citrate buffer at 50mg/kg dose, while groups seven to nine were administered with alloxan solution at same 50mg/kg and then treated with *Tapinanthus bangwensis* solution at a dose of 250mg/kg with group seven receiving 50mg/kg of the *Tapinanthus bangwensis* extract, group eight receiving 70mg/kg and group nine 100mg/kg of the extract.

Administration of *Tapinanthus bangwensis* extract

The *Tapinanthus bangwensis* solution was prepared into 5%, 7% and 10% by the process already stated by Omeodu et al. (2008). These three different preparations were fed only to groups 4, 5 and 6 respectively at a dose of 250mg/kg body weight of animal on daily basis. The treatment continued for twenty-one (21) days at the end of which all the nine groups were sacrificed by cervical dislocation method and their whole blood collected for analyses. Each of the animal's pancreas and liver were also collected and preserved in 10% formaldehyde.

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Sample collection for analyses

At the end of the twenty-one days of extract administration, the animals were sacrificed on the twenty second day. Each rat to be sacrificed was withdrawn from the cage and sacrificed by cervical dislocation (Okwakpam et al., 2020). Blood sample was then collected from the animal by cardiac puncture into appropriately labelled sample bottles, its pancreas and liver tissues were also collected into separate sample bottles and preserved in formaldehyde. These samples at the end of collection were quickly taken to the laboratory for analyses. The blood specimen was centrifuged at 5000rpm using MSE centrifuge to obtain plasma. The liver and pancreatic samples were prepared into slides and analysed at the anatomical histopathology, laboratory of the University of Port Harcourt Teaching Hospital.

Enzyme assays

The whole blood specimen was assayed for the alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Creatine kinase (CK) and α-Amylase (AMYL). AST and ALT activities were determined using measurement against reagent blank (Reittman and Frank, 1957). The method of estimation of serum ALP was described by Englehard et al. (1970) for the estimation of LDH, oxidoreductase catalyses the oxidation of L-lactate to pyruvate using NAD^+ as hydrogen acceptor, however the reaction equilibrium favours the pyruvate lactate direction at 37^0C (Bais and Philcox, 1994; Schuman et al., 2002). The method employed in LDH estimation is known as the OPTIMISED DG KC method (1972). The method of estimation of CK utilizes the optimised standard method recommended by the Deuutsche Gesselschaft fur klinishe chemie (Rec, Gscc (DG KC); 1997).

Statistical Analysis

Statistical package for social science (SPSS), version 23.0 was used for statistical analysis. Results were expressed as mean ± standard error of mean (SEM), (n=5) and statistically analyzed by a one-way analysis of variance (ANOVA) followed by a Turkey's multiple comparison test as a post-test. Analysis at $p \leq 0.05$ was considered to indicate statistical significance.

RESULTS

The results of the investigation shown on Table 2 indicated clearly that alloxan caused diabetes mellitus in the experimental animals where the group 3 animals had very high levels of the diagnostic enzymes (AST, AMYL, ALT, ALP and LDH). Values of the control animals were found to be within normal range for the parameters analysed. CK was only slightly elevated in the experimental animals as shown on Table 2.

Table 2: shows mean serum enzyme levels in alloxan induced diabetes treated with mistletoe extracts.

Group	α-Amylase	AST	ALT	ALP	LDH	CK
1	170.167^{d}	108.167^{fg}	32.500^{de}	146.670^{fg}	2571.700^{e}	6486.700^{c}
2	164.833^{de}	110.500^{fg}	33.333^{de}	167.000^{ef}	3123.300^{d}	6716.700^{c}
3	250.000^{a}	200.830^{a}	56.833^{a}	386.830^{a}	6293.300^{a}	77148.800^{abc}
4	157.833^{e}	118.667^{e}	34.333^{d}	178.170^{e}	3028.300^{de}	6970.000^{bc}
5	163.333^{de}	112.167^{ef}	30.167^{e}	128.330^{a}	2860.00^{de}	7016.700^{bc}
6	164.167^{de}	103.500^{a}	31.000^{e}	130.670^{a}	2800.00^{de}	6891.700^{bc}
7	235.167^{b}	181.000^{b}	51.167^{b}	355.000^{b}	5516.700^{b}	8416.700^{a}
8	212.500^{c}	172.000^{c}	48.333^{b}	311.83^{c}	5110.00^{bc}	8241.700^{ab}
9	205	148.667^{d}	42.167^{c}	273.50^{d}	4658.300^{c}	7616.700^{abc}
LSD	**9.148**	**8.025**	**3.172**	**27.556**	**456.050**	**1371.300**

Values are expressed as Mean ± Standard error of mean (SEM), n=5. Values with the same are not significantly different at ($p<0.05$).

Morphological Findings

The liver of normal/control rats showed liver parenchyma with general structures preserved including normal hepatocytes surrounded by sinusoids and containing Kupffer and red blood cells. Portal spaces were normal and no observed fatty degeneration or abnormal distribution of fibroblast at a magnification of x200. Morphological observation of the liver of group 3 animals shows vacuolated cytoplasm, lesions and a degenerative cytoplasm while those of groups 4-6 show normal architecture and groups 7-9 shows a gradual return to normal liver architecture in a dose dependent manner with group 7 having a close resemblance to group 3 with massive area of necrosis and group 9 having similar architecture to normal liver architecture of groups 1 and 2 animals.

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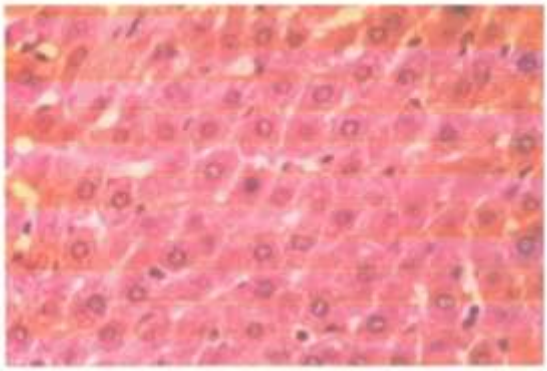

Plate 1: Showing Normal Liver architecture with clear sinusoids (Magnification x200)

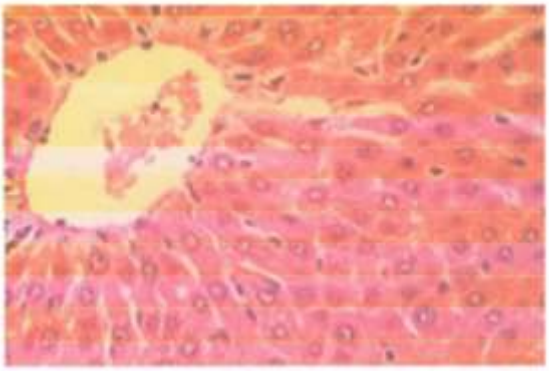

Plate 2: Showing vacuolated cytoplasm with degenerative Kuffers seen (Magnification x200)

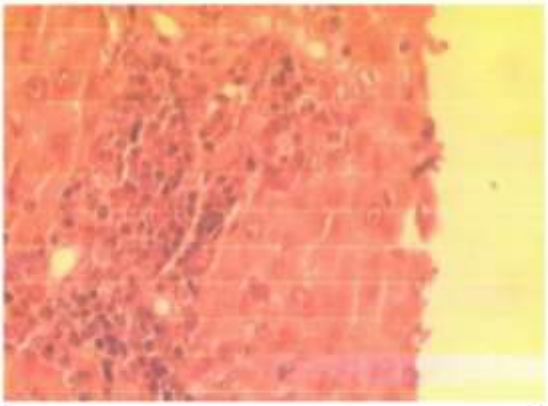

Plate 3: Showing massive area of necrosis with degenerative cytoplasm (Magnification x200)

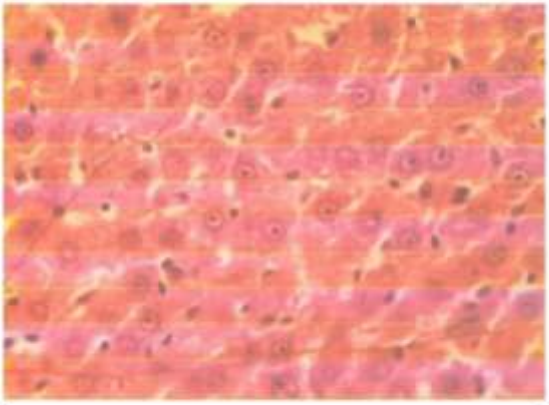

Plate 4: Showing only few areas of necrosis (Magnification x200)

The pancreas of the normal/control rats showed normal islets at magnification of, no inflammation or necrosis and no reduction in the number of cells. Morphological observation of the pancreas of the experimental animals also shows group 3 animals having extensive necrosis of islets and reduced number of cells. Group 4 – 6 have architecture close to the normal groups 1 and 2. While groups 7 – 9 shows reduction in necrosis of the islets in a dose dependent manner with group 7 (5% extract) having more necrosis than groups 8 and 9 administered with 7 and 10% extract respectively.

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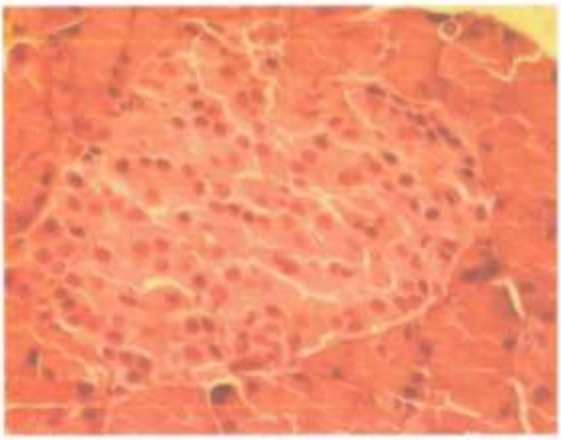

Plate 5: Showing the Pancreas with islets seen (Magnification: x200)

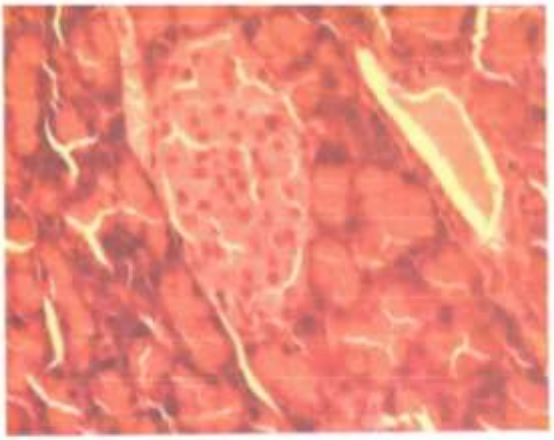

Plate 6: Showing Pancreas with extensive necrosis of islets and reduction in number of cells.

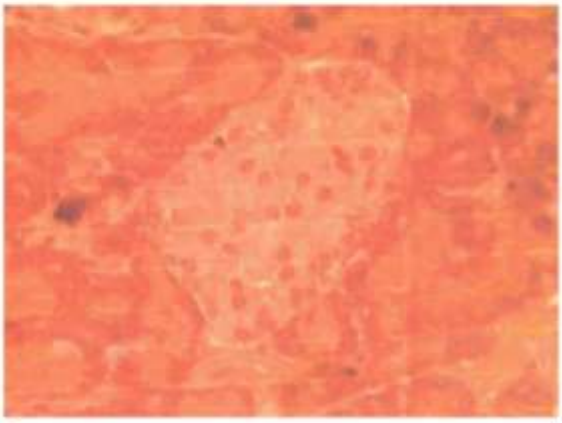

Plate 7: Showing Pancreas with enlarged islet cells (hyperplaxia) with patchy necrosis (Mag.: x200)

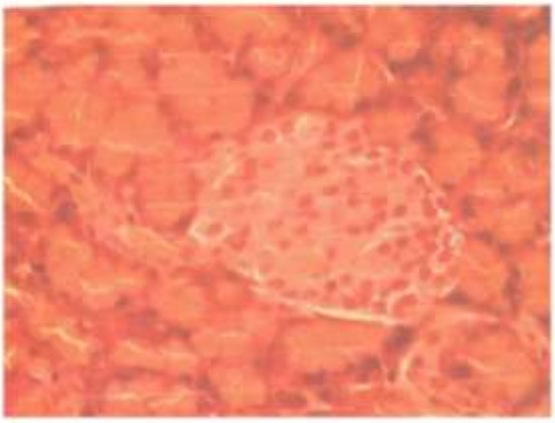

Plate 8: Showing Pancreas with patchy necrosis with few inflammatory cells seen (Mag.: x200)

DISCUSSION

Several researchers on African medicinal plants have reported significant success with minimal or no side effect (Prout, 1974). The work of Swason-Flatt et al. (1989) has lent credence to this present work.

In this study, we observed that alloxan given to the experimental rats at 50mk/kg induced diabetes mellitus in them. Serum amylase level was marked by raised liver function enzymes (AST, ALT and ALP) were elevated in the serum of the animals. LDH showed significant elevation of serum level, CK was only sparingly raised in the serum of the experimental animals. Belfiore et al. (1973) have documented the diagnostic enzymes whose activities are increased in diabetics and hence can be a good tool in the treatment and, management of diabetes mellitus.in all experimental groups, ALT, AST, ALP, and LDH were significantly ($p<0.05$) elevated. AMYL and CK were also observed to be raised in serum. Elevated serum amylase levels often accompany acute pancreatitis (Yegneswaran and Pitchmoni, 2010; Pieper-Bigelow et al., 1990). This elevation may also be caused by other conditions such as pancreatic tumours, diabetic ketoacidosis, and kidney dysfunction (Collen et al., 1990). Warshaw et al. (1977) reported that S-type not P-type amylase is responsible for the serum amylase elevation in diabetes. Treatment of the test rats with 50mg/kg alloxan, elevated the serum levels of hepatic enzymes. ALP showed the greatest elevation with 163% increase compared with the control group, while ALT had the lowest serum elevation of 76%. AST had an increase in serum of 80% compared with the control group.

This trend was also observed in the study by Rajangam et al. (2009) where AST, ALT and ALP were released into the serum during chemical assault like alloxan (Crook, 2006). These serum AST elevations were significantly ($p<0.05$) decreased on treatment of the animals with the *Tapinanthus bangwenses* extracts. Diabetic concentration 1 (group 8) treatment lowered the serum AST by 15%. The histopathological examination result also conformed to this finding. Similar results were obtained for ALT and ALP, LDH and CK. Following the elevation of these serum enzymes on the treatment with alloxan solution, oral administration of 250mg/kg body weight significantly lowered the serum ALT

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in a dose dependant manner. 10% extract had the highest lowering capacity of 26% compared to the 15% and 10% lowering effects of group 8 (7% mistletoe solution) and group 7 (5% mistletoe solution) respectively.

These changes in enzyme activities reflect the change in the metabolism in which the enzymes are involved. Transaminase activity is increased in the absence of insulin due to availability of amino acis in the blood of diabetics and are responsible for the increased gluconeogenesis and ketogenesis (Gokce and Haznedarogly, 2008; Batran et al., 2006)

The increase observed in ALP levels in this study agreed with the work of Prince at al. (1997). This increase was lowered by treatment of extracts of mistletoe by 8% (group 7), 19% (group 8) and 2% (group 9), thus showing a dose dependent effect. Similarly, the serum elevations of LDH on treatment with alloxan significantly lowered by extract administration. 10% extracts (diabetic treated concentration 3 (DT conc-3)) showed the greatest effect of 26% lowering, while diabetic treated concentration 1 (DT conc-1) had the lowest reduction of 12%. This study observed no significant ($p>0.05$) change in creatinine kinase level.

CONCLUSION

This study was able to establish the diabetogenicity of alloxan as seen in the diagnostic enzyme concentrations which were elevated. Therefore, this study has shown that extract of African mistletoe is insulinogenic and thus can be a good anti-diabetic agent as it can improve most of the altered biochemical and physiological parameters observed during diabetes mellitus.

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