Effect of *Artocarpus altilis* fruit based-diet on liver and kidney function indices on alloxan-induced diabetic rats

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Abstract.
BACKGROUND: The prevalence of diabetes mellitus continues to increase alarmingly in spite of years of intensive research. The need to explore alternative therapy such dietary and phytotherapy has been gaining attention in the management/treatment of diabetes mellitus.
OBJECTIVE: The present research work was carried out to investigate the biochemical indices in the liver and kidney of alloxan-induced diabetic rats fed with *Artocarpus altilis* fruit based-diet.
METHODS: Diabetes was induced by a single intraperitoneal injection of alloxan (150 mg/kg) in albino rats. A total of thirty two albino rats (*Rattus norvegicus*) were grouped into four; control (non-diabetic rat), diabetic untreated rats, diabetic rats administered with metformin daily and diabetic rats fed with *Artocarpus altilis* fruit based-diet groups. Biochemical indices in the serum, liver and kidney were determined.
RESULTS: The results shows significant ($P < 0.05$) decrease in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, urea, creatinine and lipid peroxidation of diabetic fed with *Artocarpus altilis* fruit based-diet. Also diabetic rats fed with *Artocarpus altilis* fruit based-diet demonstrated significant increase ($p < 0.05$) in albumin and total protein concentrations as well as antioxidant enzymes activities when compared with diabetic untreated rats and diabetic rats administered with metformin daily.
CONCLUSION: The results obtained in this study demonstrated that consumption of *Artocarpus altilis* fruit based-diet may ameliorate the liver and kidney function indices of alloxan-induced diabetic rats.

Keywords: *Artocarpus altilis* fruit, alloxan, liver and kidney functions, diabetic rats

1. Introduction

Diabetes is a chronic condition associated with abnormally high levels of sugar in the blood that result from defects in insulin secretion, or action, or both [1]. It is characterized by hyperglycemia, glucosuria and several micro-vascular and macro-vascular complications [2, 3]. The term "diabetes", when used alone, generally refers to diabetes mellitus and not a rare, unrelated disease called diabetes insipidus.

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Diabetes develops when the pancreas fails to produce sufficient quantities of insulin [4]. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism [5]. The incidence of diabetes has reached an epidemic proportion worldwide. It is estimated that about 2.8% of the world's population suffer from diabetes, according to World Health Organisation [6]. This rapid increase in the incidence of the disease is associated with rapidly changing lifestyle and environmental factors [7].

Diabetes mellitus was classified based on whether or not the patient is insulin dependent/ independent. Insulin dependent diabetes mellitus is also called Type I diabetes mellitus; it is usually characterized clinically by abrupt onset of symptoms and dependence on injected insulin to sustain life. Insulin independent diabetes mellitus or Type II diabetes mellitus is the second subclass of diabetes, frequently present with minimal or no symptoms referable to the metabolic aberrations of diabetes [5]. The high blood glucose level that accompanies type I diabetes mellitus and Type II diabetes mellitus can cause serious health complications including ketoacidosis, kidney failure, heart disease, stroke, blindness etc.

There is yet no effective cure for diabetes. The currently available drugs as well as insulin used in managing disease are associated with several undesirable side effects [8]. Also their high cost has led to search for plants and diets with normoglycemic properties in the management of diabetes [9, 10]. The use of herbal medicine and diets are widespread throughout the world. Many medicinal plants have been confirmed to have hypoglycaemic properties. The hypoglycaemic properties of plants used in management of diabetes are reported to be due to their content of flavonoids, glycosides, alkaloids, plant polysaccharides and other bioactive compounds [11]. Some of them include *Pterocarpus massupum* (Indian Kino), *Allium sativium* (Garlic), *Carica papaya* (unripe fruit), *Trigonella foerum* (Fenugreek), *Aloe barbadensis miller* etc. [12].

Artocarpus altilis has been believed to be endowed with medicinal usefulness. It is an herbaceous perennial plant of the moraceae family and it is grown widely in tropical, pacific, Caribbean and African countries. *Artocarpus altilis* is a good source of antioxidants, carotenoids, fiber, copper, thiamine, niacin, calcium, iron and magnesium [13]. It has been shown that senescence leaves were used to prepare tea to reduce blood pressure, and it is also thought to control diabetes, treat liver diseases and fevers and has antioxidant and antitumor effects [13]. Although, the anti-diabetic effectiveness of *Artocarpus altilis* fruit is acclaimed traditionally, there is no proven scientific evidence to ascertain this. It is therefore imperative to investigate the effect of *Artocarpus altilis* fruit based-diet on liver and kidney function indices of alloxan-induced diabetic rats.

2. Materials and methods

2.1. Sources of materials

2.1.1. Plant material and authentication

Artocarpus altilis fruits (breadfruit (Fig. 1) were purchased at Ikere market, Ikere- Ekiti, Ekiti State, Nigeria. Authentication and identification of the fruit was carried out at the Department of Plant Science, Ekiti State University, Ado-Ekiti, Ekiti State.

2.1.2. Chemicals

Albumin, bilirubin, total protein, urea, creatinine and all enzymes assay kits used were produced from Erba Diagnostics Mannheim, Germany. Alloxan and all other chemicals used were obtained from Sigma.

2.1.3. Experimental animals

A total of thirty two (32) Albino rats (Rattus norvegicus) with an average weight of 120-180 g were obtained from the animal house of the Department of Biochemistry, Afe Babalola University, Ado-Ekiti, Ekiti State.

Fig. 1. Breadfruits (*Artocarpus altilis* fruit).

2.1.4. Induction of diabetes

A single dose of 150 mg/kg (intraperitonial) of alloxan monohydrate was dissolved in normal saline (0.9%) and injected into the albino rats. The confirmations were carried out at 48 hours. Rats with blood glucose level $\geq$250 mg/dl were selected for this study.

2.1.5. Processing of the Artocarpus altilis fruit

Artocarpus altilis fruit (breadfruit) was peeled, to remove the seed. The fruit flesh was washed with distilled water and oven-dried at 60°C until its dried (to obtain a constant weight), thereafter the fruit flesh was pulverized into powder using an electric blender. This was used for various analyses.

2.1.6. Animal grouping

The animals were grouped into four (4):

Group A: Control (rats) fed with yam flour based-diet.
Group B: Diabetic untreated rats fed with yam flour based-diet.
Group C: Diabetic rats fed with yam flour based-diet administered metformin daily.
Group D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 1
Composition (g/100 g) of the Formulated Diets

Ingredients	Control	Group 1	Group 2	Group 3
Artocarpus altilis fruit	–	–	–	57.6
Yam flour	57.6	57.6	57.6	–
Cellulose	6	6	6	6
Soya beans	25	25	25	25
Soya beans oil	6	6	6	6
*Vit/Minerals	5	5	5	5
D-methonine	0.4	0.4	0.4	0.4

*Vitamin/ Mineral mix: Vitamin A 4,000,000 i.u; Vitamin D3, 800,000 i.u; Tocopherois, 400 i.u; Vitamin K_3 800 mg, Folacin, 200 mg; Thiamine, 600 mg; Riboflavin 1,800 mg; Niacin, 6000 mg; Calcium pathothenate, 4 mg; Biotin, 8 mg; Manganese, 30,000 mg, Zinc, 20,000 mg; Iron, 8,000 mg; Choline chloride 80,000 mg; Copper, 2,000 mg; Iodine, 480 mg; Cobalt, 80 mg; Selenium, 40 mg; BHT, 25,00 mg.

2.1.7. Formulation of experimental diets

The composition of the experimental diets (g/100 g) is presented in Table 1. Each component of the experimental diets were weighed, thoroughly mixed and packed into airtight containers.

2.1.8. Collection and treatment of blood samples

After three weeks of feeding, the animals were anaesthetized with diethyl ether and sacrificed by simply incising the jugular vein, the blood samples were collected into plain sample bottles.

2.1.9. Preparation of serum

The blood samples were allowed to stand at room temperature for 30 minutes to form clot after which it was centrifuged at 1000 g (gravity) for 15 minutes. After centrifugation, the clot forms sediment at the bottom of the centrifuge and the supernatant which is the serum was collected using a Pasteur's pipette. The serum, thus obtained were appropriately labeled and stored in a freezer at -5°C until required for further analysis.

2.2. Preparation of tissue homogenates

2.2.1. Isolation and homogenization of tissues

After sacrifice, the rats were dissected in order to isolate the tissues of interest (liver and kidney). The isolated tissues were cleansed with cotton wool to remove blood stains, weighed and immediately stored in ice cold 0.25 M sucrose solution. The liver and kidney was cut with a clean scalpel, then subjected to homogenization using Teflon homogenizer in ice-cold 0.25 M sucrose solution (1 : 5 w/v). The homogenates were stored in the freezer until required for further analysis.

2.2.2. Enzyme assay and measurement of serum metabolites

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by the method described by Reitman and Frankel [14]. Alkaline phosphatase (ALP) activity was assayed by para-nitrophenyl phosphate (PNPP) method of Wright et al. [15]. Serum albumin was assayed as described by Doumas et al. [16]. Serum protein concentration was determined using Biuret reagent as described by Gornall et al. [17]. Serum bilirubin was determined by the method of Sherlock [18]. Serum creatinine was determined by Bartels and Bohmer [19] method. Serum urea concentration was assayed as described by Fawcett and Scott [20]. Lipid peroxidation was determined by measuring the thiobarbituric acid reactive substances (TBARS) present in the test sample which is produced during lipid peroxidation according to the method of Varshney and Kale [21], the malondialdehyde (MDA) level was calculated according to the method of Adam-Vizi and Seregi [22]. Catalase (CAT) activity was determined as described by Sinha [23]. Superoxide dismutase (SOD) activity was determined by the method described by Misra and Fridovich [24] and gluthathione peroxidase (GPx) was carried out according to the method describe by Rotruck et al. [25].

2.2.3. Histopathological studies

Tissues (liver and kidney) were fixed in 10% formalin. They were dehydrated in ascending grades of ethanol, cleared in xylene, and processed to paraffin blocks, sectioned (5 μm thick) and stained with Hematoxyline and Eosin stain. They were examined using light microscopy for demonstration of tissues pathological changes including atrophy, cell destruction and necrosis [26].

2.2.4. Statistical analysis

All data were expressed as the mean of seven replicates $\pm$ standard error of mean (S.E.M). Statistical evaluation of data was performed by SPSS version 16, using one way analysis of variance (ANOVA), followed by Dunett's posthoc test for multiple comparism. Values were considered statistically significant at $p < 0.05$ (confidence level = 95%) [27].

3. Results

Tables 2, 3 and 4 show the activities of ALT, AST and ALP respectively in the tissues and serum of the experimental rats. There was significant increase ($p < 0.05$) in the diabetic untreated rats fed with yam flour based-diet (group B) when compared with the control rats (group A), diabetic rats fed with yam flour based-diet and administered metformin (group C), and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D). However, the values obtained for group A, C and D were not significantly different ($p > 0.05$) from each other.

Table 2

Effect of *Artocarpus altilis* Fruit Based-diet on ALT Activity (U/L) in Serum and Tissues Homogenates of Alloxan-Induced Diabetic Rats

Groups	Serum	Liver	Kidney
A	23.12 ± 0.12^a	200.10 ± 0.10^a	60.10 ± 0.01^a
B	38.40 ± 0.05^b	600.00 ± 2.00^b	100.00 ± 1.10^b
C	23.40 ± 0.50^a	204.00 ± 0.05^a	64.10 ± 1.10^a
D	23.20 ± 0.10^a	203.00 ± 0.12^a	62.10 ± 1.00^a

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 3

Effect of *Artocarpus altilis* Based-diet on AST Activity (U/L) in Serum and Tissues Homogenates of Alloxan-Induced Diabetic Rats

Groups	Serum	Liver	Kidney
A	13.84 ± 1.45^a	100.11 ± 1.10^a	40.21 ± 0.05^a
B	27.21 ± 0.01^b	400.14 ± 0.11^b	84.21 ± 0.10^b
C	14.02 ± 1.64^a	108.00 ± 0.20^a	44.10 ± 0.01^a
D	14.28 ± 1.12^a	104.20 ± 0.50^a	42.98 ± 0.10^a

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 4

Effect of *Artocarpus altilis* Fruit Based-diet on ALP Activity (UI) in Serum and Tissues Homogenate of Alloxan-Induced Diabetic Rats

Groups	Serum	Liver	Kidney
A	100.66 ± 1.01^a	430.00 ± 2.01^a	826.00 ± 2.01^a
B	240.08 ± 0.10^b	602.00 ± 1.34^b	928.00 ± 1.20^b
C	104.01 ± 1.10^a	426.00 ± 3.10^a	821.00 ± 1.20^a
D	102.02 ± 0.10^a	428.00 ± 2.14^a	824.00 ± 2.00^a

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 5 shows the serum concentrations of albumin, total protein, globulin and bilirubin in the experimental rats. Albumin, total protein and globulin shows a significant decrease ($p < 0.05$) in the diabetic untreated rats fed with yam flour based-diet (group B) when compared with the control rats (group A). However there was a significant increase ($p < 0.05$) in diabetic rats fed with yam flour based-diet and administered with metformin (group C) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D) when compared with the control rats (group A).

In addition, Table 5 also shows a significant increase ($p < 0.05$) in total and conjugated bilirubin in the diabetic untreated rats fed with yam flour based-diet (Group B) when compared with the control rats (group A) diabetic rats fed with yam flour based-diet administered with metformin (group C) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D) while group A, C and D were not significantly different ($p > 0.05$) from one another.

Table 6 shows the serum concentrations of creatinine and urea in the experimental rats. There was a significant increase ($p < 0.05$) in diabetic untreated rats fed with yam flour based-diet (group B) when compared with the control rats (group A), whereas there was a significant decrease in diabetic rats fed with yam flour based-diets administered with metformin (group C) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D) when compared to diabetic untreated rats fed with yam flour based-diet (group B).

Table 7 shows lipid peroxidation in the tissue homogenates of the experimental rats. There was a significant increase ($p < 0.05$) in the diabetic untreated rats fed with yam flour based-diet (group B) when compared with the control rats (group A), however there were no significant difference between control rats (group A), diabetic rats fed with yam flour based-diet and administered with metformin (group C) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D) of the liver. Meanwhile the kidney shows a significant increase

Table 5

Effect of *Artocarpus altilis* Fruit Based-diet on Albumin, Total Protein, Globulin, Total and Conjugated Bilirubin in serum of Alloxan-Induced Diabetic Rats

Groups	Albumin(g/l)	Total protein(g/dl)	Globulin(g/l)	Total Bilirubin(mg/dl)	Conjugated Bilirubin(mg/dl)
A	26.40 ± 0.02^a	54.62 ± 1.14^a	28.22 ± 0.05^a	14.80 ± 0.06^a	4.20 ± 1.01^a
B	10.50 ± 0.05^d	21.30 ± 1.10^d	10.80 ± 0.03^d	28.75 ± 2.40^b	12.16 ± 2.30^c
C	28.20 ± 1.00^b	73.20 ± 4.10^b	45.00 ± 0.06^b	15.40 ± 1.80^a	5.84 ± 1.40^b
D	32.40 ± 1.03^c	96.40 ± 3.10^c	64.00 ± 2.10^c	14.95 ± 1.20^a	5.28 ± 1.00^b

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 6

Effect of *Artocarpus altilis* fruit Based-diet on Creatinine and Urea in Serum of Alloxan-Induced Diabetic Rats

Groups	Creatinine (mg/dl)	Urea (mg/dl)
A	45.10 ± 2.00^a	12.03 ± 1.10^a
B	60.40 ± 2.50^d	28.00 ± 0.13^d
C	48.40 ± 0.05^c	19.04 ± 2.01^c
D	42.40 ± 2.40^b	14.10 ± 1.40^b

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 7

Effect of *Artocarpus altilis* Fruit Based-diet on Lipid Peroxidation (MDA)

($\times 10^{-5}$ nmol/ml) of Alloxan-Induced Diabetic Rats

Groups	Liver	Kidney
A	1.08 ± 1.10^a	0.06 ± 1.50^a
B	4.89 ± 2.10^c	1.63 ± 2.00^c
C	1.10 ± 2.01^a	0.12 ± 1.40^b
D	1.06 ± 1.50^a	0.08 ± 1.00^a

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

Table 8

Effect of *Artocarpus altilis* Fruit Based-diet on antioxidant enzymes in Liver and Kidney of Alloxan-Induced Diabetic Rats

Groups	CAT (unit/mg protein)		SOD (m/mg protein)		GPx (m/ml)	
	Liver	Kidney	Liver	Kidney	Liver	Kidney
A	342 ± 1.10^a	186 ± 2.10^a	588.41 ± 3.00^a	246.10 ± 1.64^a	429.01 ± 2.00^a	146.00 ± 1.20^a
B	142 ± 1.20^c	84 ± 1.01^c	238.00 ± 2.10^c	108.20 ± 2.00^c	120.40 ± 2.50^c	94.20 ± 2.00^c
C	268 ± 2.10^b	142 ± 3.10^b	568.00 ± 2.00^b	242.01 ± 1.50^b	401.10 ± 2.00^b	142.00 ± 2.00^b
D	340 ± 5.00^a	182 ± 4.00^a	584.00 ± 4.20^a	248.00 ± 2.50^a	426.00 ± 3.00^a	144.01 ± 2.00^a

Each value is a mean of seven determination $\pm$ SEM. Values with different superscripts along the column are significantly different ($p < 0.05$). A: Control (rats) fed with yam flour based-diet. B: Diabetic untreated rats fed with yam flour based-diet. C: Diabetic rats fed with yam flour based-diet and administered metformin daily. D: Diabetic rats fed with *Artocarpus altilis* fruit based-diet.

($p < 0.05$) in diabetic untreated rats fed with yam flour based-diet (group B) and diabetic rats fed with yam flour based-diet and administered with metformin (group C) when compared with the control rats (group A) but no significant difference between control rats (group A) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D).

Furthermore, Table 8 revealed no significant difference ($p > 0.05$) in CAT, SOD and GPx in the liver and kidney of control rats (group A) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D). But there was a significant decrease ($p < 0.05$) in the diabetic untreated rats fed with yam flour based-diet (group B) when compared with the control rats (group A), diabetic rats fed with yam flour based-diet and administered metformin (group C) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D) in CAT, SOD and GPx. While there was a significant decrease ($p < 0.05$) in diabetic rats fed with yam flour based-diet and administered with metformin (group C) when compared with control rats (group A) and diabetic rats fed with *Artocarpus altilis* fruit based-diet (group D).

3.1. Histological changes of Artocarpus altilis fruit based-diet in liver and kidney of alloxan-induced diabetic rats

Histopathological studies of the liver and kidney of control rats showed normal histology (Figs. 2a/3a). For the diabetic untreated rats fed with yam flour based-diet, portal congestion, periportal cellular infiltration and vacuolar degeneration of hepatocytes was observed (Figs. 2b/3b). The diabetic rats fed with yam flour based-diet

a Control

b Diabetic untreated

c Diabetic treated with metformin

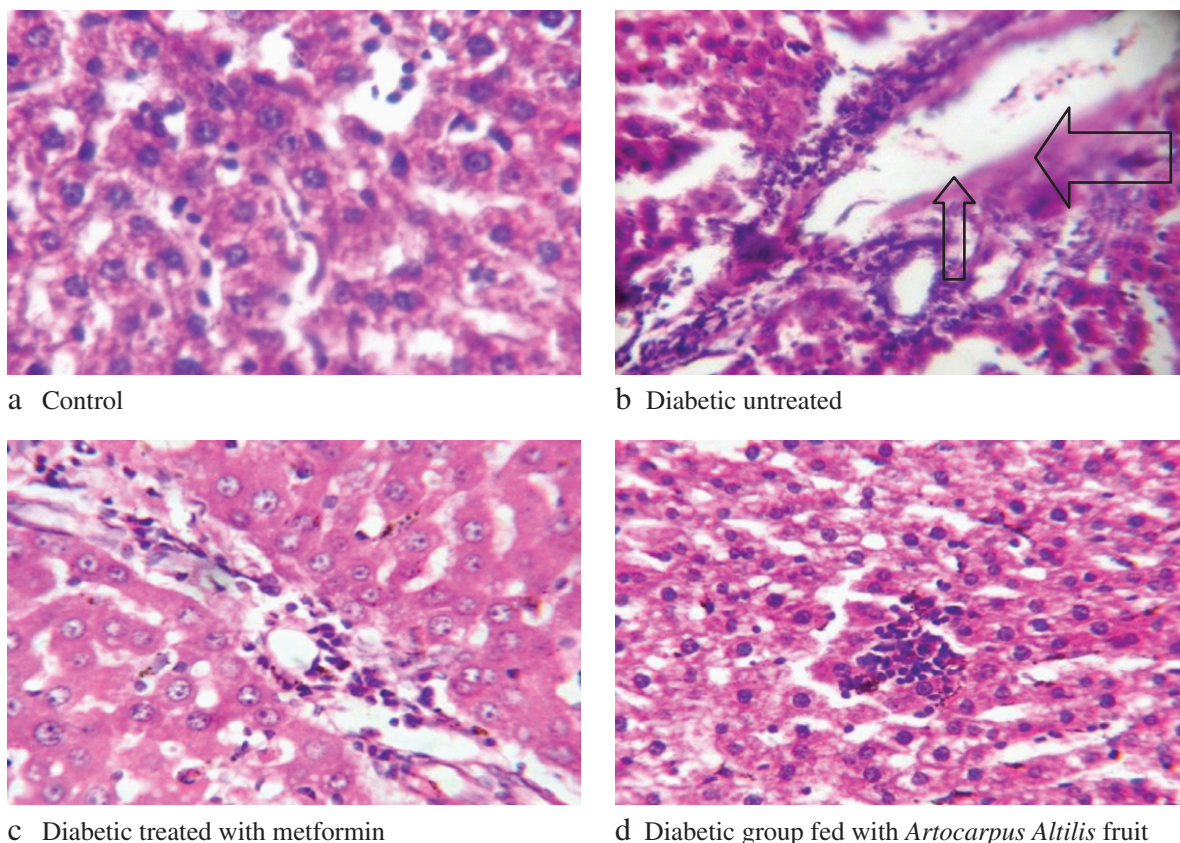d Diabetic group fed with *Artocarpus Altilis* fruit

Fig. 2. Changes in histology of Alloxan-Induced Diabetic Rats livers. Arrows: shows portal congestion, periportal cellular infiltration, and vacuolar degeneration of hepatocytes.

and administered with metformin also showed almost normal liver histology (Figs. 2c/3c) while the diabetic rats fed with *Artocarpus altilis* fruit based-diet showed normal liver histology (Figs. 2d/3d).

4. Discussion

The measurement of the activities of various enzymes in the tissues and body fluids plays a significant role in disease investigation and diagnosis [28]. This enzymes activities in the tissues are often used as 'marker' to ascertain early toxic effects of administered foreign compounds (like alloxan) to experimental animals [29]. Tissue enzyme assay can also indicate tissue cellular damage long before structural damage can be picked up by conventional histological techniques [30].

ALT and AST are cytosolic enzymes involved in the transfer of amino group from α-amino to α-keto acids. They are also involved in the biochemical regulation of intracellular amino acid pool. These enzymes are highly concentrated in the liver and kidney and are only found in the serum in significant quantities when the cell membrane becomes leaky and even completely ruptured [31, 32] indicating tissue injury or organ dysfunction.

ALT as a liver cytosol enzyme is more specific to the liver, a rise only occurs in liver diseases [33]. The liver also contains considerable amount of AST, where it is associated with liver parenchyma cells. AST is important

a Control

b Diabetic untreated

c Diabetic treated with metformin

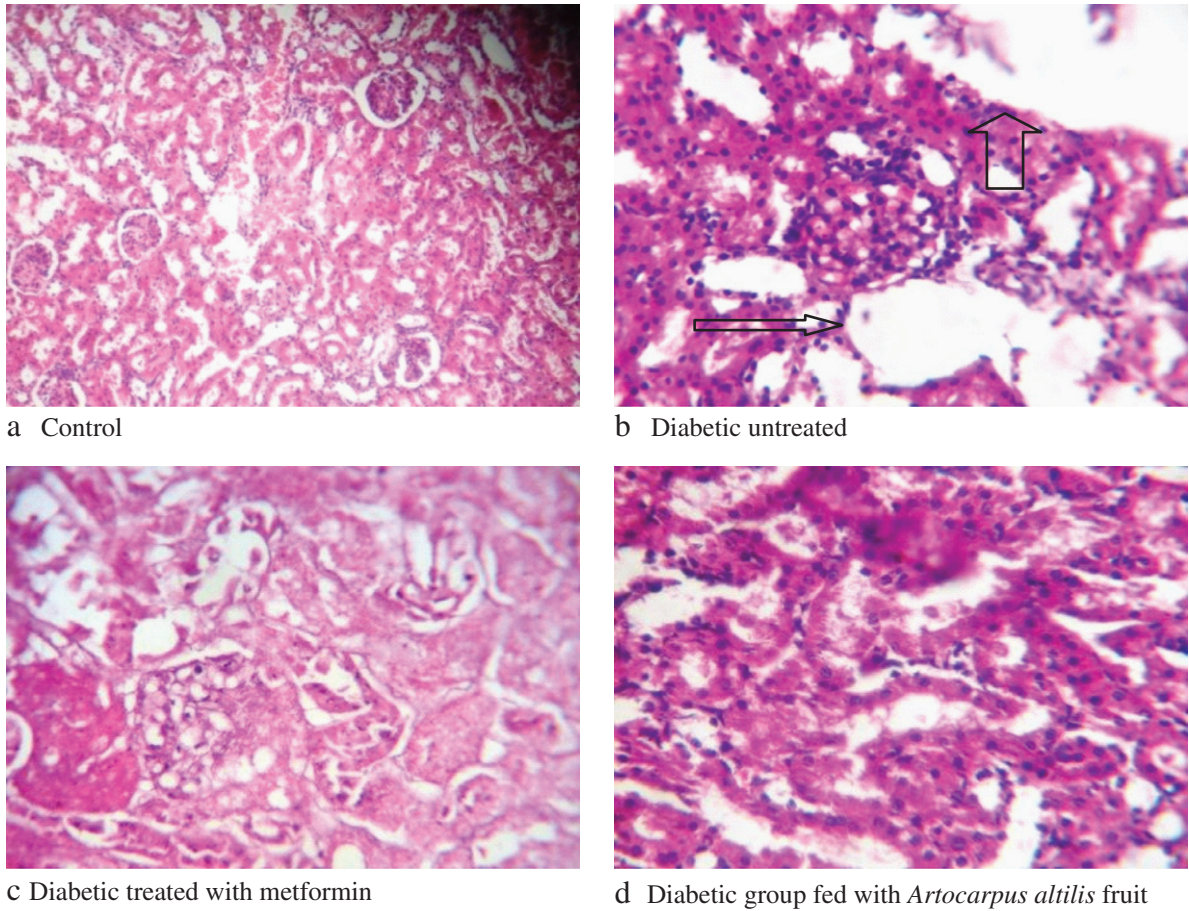d Diabetic group fed with *Artocarpus altilis* fruit

Fig. 3. Changes in histology of Alloxan-Induced Diabetic Rats kidneys. Arrows: shows portal congestion, periportal cellular infiltration, and vacuolar degeneration of nephrocytes.

in the diagnosis of heart and liver damage caused by heart attack, drug toxicity, or infection although, it is not as specific as liver marker enzyme as ALT. The increase in the serum AST and ALT as indicated in alloxan-induced diabetes produced an alteration in hepatic function, and this may be due to the leakage of the named enzymes from the liver cytosol into the blood stream [34] while a general decrease in ALT and AST may perhaps suggests that the experimental diet confer protection on the liver tissues against injury, damage or disease, which are often the direct cause of elevation of the enzymes in the blood stream [35].

This study shows that diabetic rats fed with *Artocarpus altilis* fruit based-diet decreased serum and tissue homogenates activities of ALT and AST (as shown in Tables 2 and 3 respectively). *Artocarpus altilis* fruit is a good source of antioxidants, carotenoids, fiber, copper, thiamine, niacin, calcium, iron and magnesium. It is also believed to be useful in managing liver diseases, fevers etc. [36]. Therefore this reduction can be attributed to the protective effect of *Artocarpus altilis* fruit.

Also, an increased activity of ALP (membrane bound enzyme) is a well known diagnostic indicator of liver injury and it is considered the bio-markers for liver functions. At the end of this study, diabetic rats fed with *Artocarpus altilis* fruit based-diet were observed to have a significant decrease in the ALP activities (Table 4). This may indicate hepatoprotective and renoprotective abilities of the diet. Meanwhile elevated ALP activities in

the diabetic untreated rats is an indication of pathological processes which could be liver impairment or kidney dysfunction as described by Bogin et al. [37]. The fact that the enzyme activities were maintained in the serum and tissue homogenates of the diabetic rats fed with *Artocarpus altilis* fruit based-diet implies that the compounded diet has no membrane labializing effect on these organs.

Total protein, albumin and globulin are plasma proteins (Table 5) that measure synthetic function of the liver. They help in maintaining blood osmotic pressure. Hypoproteinaemia is the deficiency of protein in the plasma, partly due to excessive excretion or muscle wasting. The induction of alloxan in Wistar rats has displayed this effect, as illustrated by the significant decrease in the total serum proteins. This was reversed by consumption *Artocarpus altilis* fruit based-diet by the diabetic rats.

Albumin which is manufactured by the liver can be used to assess the health status of liver. It is the major protein present within the blood. Low serum albumin has also been associated with low protein intake. Albumin serves in the maintenance of osmotic pressure of the blood and body fluids, and transport of inorganic anions, fatty acids, and drugs [38]. Therefore, decrease in serum albumin level would affect the metabolism of these substances that are transported by it [39]. Any effect that negatively affects albumin content would be expected to have a deleterious impact on total plasma proteins as in massive hepatic necrosis, chronic cirrhosis and other disorders with significant destruction or replacement of liver cells. In this study there was an observable depletion of albumin in the diabetic untreated rats fed with yam flour based-diet when compared to the control rats; this is in agreement with hypoalbuminemia observed in diabetes [40]. Hypoalbuminemia is a common problem in diabetic animals and is generally attributed to the presence of diabetic nephropathy. However diabetic rats fed with yam flour based-diet administered with metformin and diabetic rats fed with *Artocarpus altilis* fruit based-diet showed a significant ($p < 0.05$) increase in the concentration level of albumin (Table 5).

Also, this study shows a significant decrease ($p < 0.05$) of globulin in the *Artocarpus altilis* diabetic untreated rats. This may due to decrease in total protein and albumin levels in diabetic rat. Previous studies have reported that induction of alloxan have a negative effect on the serum total proteins, albumin and globulin leading to a decrease in their concentration [41]. Whereas, consumption of *Artocarpus altilis* fruit based-diet by diabetic rats tend to normalize the decrease in serum total protein, albumin and globulin levles.

Bilirubin is a waste product, which is the principle pigment in bile. It is derived from the breakdown of haemoglobin. After several degradation steps, the free bilirubin becomes bound by albumin and is transported through the blood to the liver. It is removed from the blood by the liver; hence it is a good indicator of liver function. A low concentration of bilirubin is found in normal plasma hence elevated bilirubin concentration in the blood is either by increased production of bilirubin or decreased liver uptake (as a result of liver disease) or due to an abnormally high peripheral breakdown of haemoglobin, termed haemolysis. Cheesebrough [42] reported that a rise in the concentration of serum bilirubin indicate or suggests liver damage since the liver serves as an excretory unit rather than a distributing unit for bilirubin. Total billirubin and conjugated billirubin are formed through breakdown of red blood cells by hepatocytes and used to access extent of hepatocellular damage [43].

In this study, it was observed that diabetic rats fed with *Artocarpus altilis* fruit based-diet demonstrated significant reduction in the levels of total and conjugated bilirubin (Table 6). It has been reported that when a toxicant is induced it leads to hyperbilirubinaemia (high level of bilirubin) which is often the first and sometimes the only manifestation of a liver disease [44] characterized with diabetes mellitus.

Serum creatinine and urea are useful clinical tool in assessing renal function. They are established markers of glomerular filtration rate (GFR). Though creatinine is a more sensitive index of kidney function compared to urea level. This is because creatinine fulfils most of the requirements for a perfect filtration marker [45]. Creatinine is also helpful in recognizing when there is an acute drop in kidney function, thus creatinine is used in monitoring disease progression [46].

With respect to kidney function, serum creatinine and urea elevation are evidence of acute kidney dysfunction [47]. Researcher also posited that high urea levels in diabetes could be attributed to a fall in the filtering capacity of the kidney thus leading to accumulation of waste products within the system [48]. The result of this work (Table 6) suggests that *Artocarpus altilis* fruit based-diet may have little or no nephrotoxic substances. The

significant increase observed in the serum creatinine and urea levels of diabetic untreated rats might due to increase synthesis from the damaged pancreatic cells caused by reactive oxygen species generated by alloxan induction.

Lipid peroxidation is a characteristic of diabetes. The increase of free radicals in diabetic condition is suggested to be due to increase lipid peroxidation [49] and damage of antioxidant defence system as a result of increased production and/ or decreased activities of antioxidant enzymes [50]. Elevated lipid peroxide is commonly based on concentration of thiobarbituric acid reactive substances (TBARS) and decreased activity of antioxidant molecules in diabetic rats could probably be associated with oxidative stress and decreased antioxidant defence potential [51].

In the present study, as shown in Table 7, *Artocarpus altilis* fruit based-diet was found to reduce levels of lipid peroxidative damage in diabetic rats. This may be attributed to antioxidative potential of the diet. The increase in lipid peroxidation was observed in alloxan-induced diabetic groups due to the generation of free radicals [52].

It is well known that SOD, CAT and GPx (Table 8) play an important role as protective enzymes against free radical formation in tissue [53]. SOD protects tissues against oxygen free radicals by converting the superoxide radical into hydrogen peroxide and molecular oxygen, while catalase catalyses the detoxification of hydrogen peroxide, preventing damage to cell membranes and other biological structures. Consumption of antioxidants rich diet might stimulate cell survival by strengthening the defence systems and also exerting scavenging effects on the generated free radicals thereby protecting the cells [59]. This may be the reason behind significant increase in all the antioxidant enzymes activities of diabetic rats fed on *Artocarpus altilis* fruit based-diet. The superoxide radicals produced during diabetes mellitus damage the essential components of extracellular matrix, lipoproteins and DNA. The activity of the SOD decreased significantly in the liver of alloxan-induced diabetic animals due to increased oxidative stress.

The histopathology evaluation of the liver and kidney shows that the liver of the diabetic untreated rats fed with yam flour based-diet was markedly damaged, probably due to oxidative damage by alloxan induction while diabetic rats fed on *Artocarpus altilis* fruit based-diet demonstrated normal liver and kidney structure, which compared favourably with normal control. The protective effect of the diet as observed in the result may be linked to its antioxidants.

5. Conclusion

From the results of this study, it can be deduced that diabetic rats fed with *Artocarpus altilis* fruit based-diet produces heptoprotective and renoprotective effects. It did not have any adverse effects on the liver and kidney functions and protected the organs against oxidative stress by altering the increased levels of lipid peroxidation and enhanced activities of CAT, SOD and GPx. Therefore, *Artocarpus altilis* based-diet may be useful in the management of diabetes mellitus.

Ethical approval

All applicable Afe Babalola University guidelines for the care and use of animals were properly followed (ABUAD/034).

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Conflict of interest

The authors declare no conflict of interest.

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