Antihyperanaemic and antihyperlipidemic activities of *Artocarpus altilis* fruit based-diet on alloxan-induced diabetic rats

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**Abstract**

In West Africa especially in Nigeria uses of *Artocarpus altilis* fruit (breadfruit) have been used traditionally in the management of diabetes mellitus and its complications. This study was designed to investigate the effect of the *Artocarpus altilis* fruit (breadfruit) based-diet on fasting blood glucose level, haematological parameters and serum lipid profiles in alloxan-induced diabetic rats. In this study, the in vitro antioxidant parameters were determined on aqueous extract of the *Artocarpus altilis* fruit, while in the in vivo study thirty-two albino rats (*Rattus norvegicus*) were used and grouped into four: control, diabetic untreated rats, diabetic rats administered with metformin daily and diabetic rats fed with *Artocarpus altilis* fruit based-diet. All rats except those in control group were induced intraperitonially with a single dose of 150 mg/kg of alloxan. The aqueous extract of the *Artocarpus altilis* fruit contained total phenol, total flavonoid, DPPH, FRAP and Fe\(^{2+}\) chelation. Administration of alloxan significantly increased (p<0.05) fasting blood glucose, LDL and VLDL with significant reduction (p<0.05) in all the haematological parameters and HDL. The feeding of the diabetic rats with *Artocarpus altilis* fruit based-diet significantly ameliorated all these effects to normal. Therefore, the results suggest that consumption of *Artocarpus altilis* fruit based-diet by diabetic rats ameliorated antihyperanaemic and antihyperlipidemic complications.

**Introduction**

Diabetes mellitus is a disorder characterized with hyperglycaemia due to deficiency in insulin secretion and/or insulin action. It is the most common serious metabolic disease in the world, affecting millions of people worldwide (Nelson and Cox, 2010). Diabetes mellitus comprises of three major types (Nelson and Cox, 2010). Type I diabetes also called juvenile onset diabetes is usually detected in childhood. This type of diabetes, the body makes little or no insulin and daily injection of insulin is needed. The exact causes are unknown but genetics, viruses, and autoimmune problems may be involved (Naik, 2011). The symptoms of type I diabetes as reported by Murray et al. (2009) are fatigue, increased thirst and urination, nausea, at times vomiting and weight loss despite increased appetite. Type II diabetes, commonest type of diabetes, observed mainly in adulthood, but nowadays young people are increasingly being diagnosed with this disease. In this case the pancreas does not produce enough insulin to maintain the normal blood glucose levels (Alemzadeh and Wyatt, 2010). The occurrence of obesity, sedentary living and failure to exercise exacerbating this type of diabetes, coupled with symptoms such as blurred vision, fatigue, increased appetite, thirst and urination (Alemzadeh and Wyatt, 2010). Gestational diabetes which is the third type of diabetes, with high fasting blood glucose levels, this condition may develops at any time during pregnancy in non-diabetic individuals. Women who have it are at high risk of type II diabetes and cardiovascular disease later in life (Naik, 2011).

Management of diabetes mellitus, focus on making available sufficient amount of insulin in the body system. This relies mainly on dietary measures which include the uses of traditional plant therapies, before insulin therapy was introduced in 1922 (Ekeanyanwu et al., 2012). A number of plants have been acclaimed for antidiabetic properties worldwide as reported by Ekeanyanwu et al. (2012). This became more apparent following WHO (1994) recommendations regarding the needs to develop and evaluate better pharmacological agents for improving insulin secretion, enhancing insulin sensitivity, preventing beta cells destruction, promoting beta cells regeneration and interrupting pathways leading to various complications of diabetes (World Health Organization, 1994). These

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recommendations, together with the cost and side effects of most orthodox hypoglycaemic agents, have stimulated an increasing demand for natural products with antidiabetic activities that have fewer side effects (Adoum et al., 2012). The most promising of such products are of plant origin (World Health Organization, 1994). The hypoglycaemic properties of these plants used by traditional medical practitioners may be due to their bioactive constituents (Bako et al., 2014). Example of plant that can be used for this purpose is Artocarpus altillis fruit, as reported by Ajiboye et al. (2016) where they assessed the uses of this plant based-diet on liver and kidney functions indices of alloxan-induced diabetic rats but other complications of diabetes mellitus like anaemia and lipidaemia were not addressed.

In vitro analyses
Total phenolic and flavonoid contents of Artocarpus altillis fruit were determined using the methods described by Singleton et al. (1999) and Miliauskas et al. (2004) respectively. The free radical scavenging ability of the Artocarpus altillis fruit extracts against 1, 1 – diphenyl – 2 – picrylhydrazyl (DPPH) free radical was measured using the method of Szabo et al. (2007). In addition, the determination of ferric reducing property and iron chelation assay were carried out the methods of Ali et al. (1996) and Puntel et al. (2005) respectively.

Experimental animals
Thirty two albino rats (Rattus norvegicus) were used in this study. They were obtained from the animal house of the Department of Biochemistry, Afe Babalola University, Ado-Ekiti, Ekiti State.

Induction of diabetes
A single dose of 150 mg/kg of alloxan monohydrate was dissolved in normal saline (0.9%) and induced into the already 12 hours fasted rats. Forty eight hours after the induction, the animals fasting blood glucose level was checked using Accu chek Glucometer. Only the animals with fasting blood glucose level ≥ 250 mg/dl was used in this study (Eyo et al., 2011).

Animal’s grouping
The animals were grouped into four (4): Group 1: Normal control placed on yam flour based-diet, Group 2: Diabetic untreated rats placed on yam flour based-diet, Group 3: Diabetic rats placed on yam flour based-diet and administered (14.2mg/kg) metformin daily, and Group 4: Diabetic rats placed on Artocarpus altillis fruit based-diet

Formulation of experimental diets
The composition of the experimental diet was as already described by Ajiboye et al. (2016).

Collection of blood
At the end of the experimental period, animals were anaesthetized with diethyl ether. The blood of each animal was collected through cardiac puncturing method and collected into EDTA and plain sample tubes for haematological and serum analysis respectively. The serum was obtained by centrifuging the blood at 3000 revolution per minutes for 15 minutes. The serum was then collected using a Pasteur’s pipette and stored in a freezer at -5°C until required for further analysis.
Haematological parameters determination
The following haematological parameters were analysed using automated hematologic analyzer: haemoglobin, packed cell volume, red blood cells, white blood cells, neutrophils, lymphocytes, mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentrations by employing the method of Dacie and Lewis (1991).

Serum lipid profile
The concentration of total cholesterol was carried out using the method described by Fredrickson et al. (1967). Tietz (1990) method was used in determining the concentrations of triacylglycerol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol.

Statistical analysis
The statistical evaluation of data was performed by SPSS version 20, with one way analysis of variance (ANOVA) and Dunett’s posthoc test for multiple comparison. The data were expressed as mean of five replicates ± standard error of mean (S.E.M) and values were considered statistically significant at p<0.05.

Results
Table 1 shows the present of total phenol, flavonoid and some in vitro antioxidant parameters such as; 1,1-diphenyl-2-picrylhydrazyl (DPPH), ferric reducing antioxidant properties (FRAP) and Fe²⁺ chelation in aqueous extract of Artocarpus altilis fruit. The blood glucose concentration was markedly increased in the diabetic rats before treatment; suggesting a diabetic state as shown in Table 2. At the end of the three weeks duration of the treatment, a significant reduction (p<0.05) was observed in group D when compared to diabetic untreated rats (Group B), whereas there were no significant difference (p>0.05) in control rats (Group A) when compared to group D.

Table 3 shows the effect of Artocarpus altilis fruit based-diet on haematological parameters in alloxan-induced diabetic rats. It shows that there was a significant decrease in all the haematological parameters in diabetic untreated rats (Group B) when compared to control (Group A), diabetic rats administered with metformin (Group C) and diabetic rats fed with Artocarpus altilis fruit based-diet (Group D).

The effect of Artocarpus altilis fruit based-diet on serum lipid profile parameters of alloxan-induced diabetic rats is presented in Table 4. Group B (diabetic untreated rats) shows a significant increase (p<0.05) in cholesterol, triglycerides, VLDL and LDL concentrations when compared to the control (Group A), diabetic rats administered with metformin (Group B) and diabetic rats fed with Artocarpus altilis fruit based-diet (Group D). Group B also shows a significant decrease (p<0.05) in HDL (good cholesterol) concentrations when compared to groups A, C and D.

Discussion
In this study, the presence of phenol and flavonoids alongside with ferric reducing antioxidant property (FRAP), 1,1-diphenyl-2-picrylhydrazyl (DPPH) and Fe²⁺ Chelation (Table 1) in the aqueous extract of Artocarpus altilis fruit. These concord with Wiley et al. (2011) that phenolics compounds and in vitro antioxidant parameters may be used to assess the antioxidant nature of a plant or animal samples in scavenging free radical. Gharib et al. (2013) reported that antioxidants reduce oxidative injury to cells by ameliorating the affected organs biomarkers caused by reactive oxygen species (ROS). This is because antioxidants can serve as free radical scavengers and singlet oxygen reducer (Gharib et al., 2013), which makes antioxidant rich food highly helpful to diabetes mellitus patients.

Diabetes mellitus is characterized by elevated level of oxidative stress, decreased level of antioxidant defences, haematology parameters and serum lipid profile abnormalities (Wali et al., 2013). Alloxan induces diabetes by damaging the insulin secreting cells of the pancreas leading to hyperglycaemia. The observation in this study correlates with the earlier research finding, in that the blood glucose levels significantly increased in
The normoglycaemic activity in diabetic rats fed with *Artocarpus altilis* fruit-based diet may be attributed to free radical scavenging of the fruit. Blood and blood components play vital role in maintenance of homeostasis. However, alteration in blood components may lead to severe diseases or disorders. Haematology is the study of the numbers, morphology of the cellular elements of the blood and the uses of these results in the diagnosis and monitoring of disease (Merck, 2012). Haematological studies are useful in the diagnosis of many diseases as well as investigation of the extent of damage to blood (Togun et al., 2007). The significant increase in all the haematological parameters in diabetic rats fed with *Artocarpus altilis* fruit-based diet (Table 3) demonstrated the anti-anemic activity of the diet and good blood compositions for the animals, probably due to oxidative stress suppressor of the diet (Isaac et al., 2013).

Hyperglycaemia in diabetic patients is associated with alterations in glucose and lipid metabolism (Ajiboye et al., 2014). Diabetes mellitus has been recognized as a major risk factor for cardiovascular diseases (CVD), such as atherosclerosis, heart attacks, stroke (Mazumber et al., 2009). About 75% of deaths among men and 57% of death among women with diabetes are attributable to CVD (Muller, 2004).
the present study, *Artocarpus altillis* fruit based-diet was found to reduce the concentrations of cholesterol, triglycerides, VLDL and LDL with significant increase in HDL concentration (Table 4).

Disturbances in the regulation of the activity of the hormone-sensitive enzyme (lipase) by insulin due to its deficiency or absence has been ascribed to abnormal increase in serum lipid profiles (triglycerides, cholesterol, very low density lipoprotein and low density lipoprotein) in diabetic mellitus patients (Naik, 2011). This might be caused by the reactive oxygen species, prompted by destruction of beta islet cells (as a result of alloxan induction). Lipase is an enzyme which converts triglycerides to free fatty acids and glycerol while insulin is an hormone that inhibits hormone-sensitive lipase in adipose tissue (Murray *et al.*, 2009). Therefore, in the absence of insulin, the plasma level of free fatty acids increases. This is because in the liver, the free fatty acids are catabolized to acetyl CoA, and the excess acetyl CoA is converted to cholesterol, triglyceride and ketone bodies resulting in ketosis (Bako *et al.*, 2014). In addition, the high concentration of serum lipoprotein in the diabetic mellitus may also be due to increase in the mobilization of free fatty acids from the peripheral fat depots by glucagons in the absence of insulin (Bako *et al.*, 2014). This may promote the conversion of some fatty acids by liver into triacylglycerol, phospholipids and cholesterol that may be discharged into the blood as lipoproteins (Naik, 2011).

The presence study demonstrated that *Artocarpus altillis* fruit based-diet might promote the presence of insulin, inhibit hormone-sensitive lipase in the adipose tissue and hinder the mobilization of fatty acid from adipose tissue by glucagons. Furthermore, high levels of high density lipoprotein (HDL) have been reported by Khan *et al.* (2003) to be inversely related to the incidence of coronary heart disease. The high concentration of HDL on diabetic rats placed on *Artocarpus altillis* fruit-based diet may promote the removal of cholesterol from peripheral tissue to the liver for catabolism and excretion. These results demonstrated the normolipidaemia activity of the diet, which may be helpful in ameliorating CVD in diabetes mellitus patients (Andallu *et al.*, 2009). This may be attributed to inhibition of oxidative stress and lipid peroxidation by the diet, which promotes regeneration of pancreatic beta cells.

**Conclusion**

From this study, it can be concluded that the *Artocarpus altillis* fruit based-diet could be very useful in the management of diabetes, probably due to phenolic contents and *in vitro* antioxidant parameters in the fruit.

**Acknowledgement**

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**Table 4. Artocarpus altillis fruit based-diet on serum lipid profile (mmol/l) of alloxan-induced diabetic rats**

<table>
<thead>
<tr>
<th>Groups</th>
<th>HDL</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>VLDL</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>234.00±2.41*</td>
<td>348.00±2.40*</td>
<td>64.40±2.01*</td>
<td>29.27±1.10*</td>
<td>85.77±2.01*</td>
</tr>
<tr>
<td>B</td>
<td>150.10±2.10*</td>
<td>604.00±3.10*</td>
<td>126.00±2.10*</td>
<td>54.55±1.40*</td>
<td>399.35±5.60*</td>
</tr>
<tr>
<td>C</td>
<td>205.50±1.10*</td>
<td>378.00±4.00*</td>
<td>84.10±2.10*</td>
<td>38.23±2.00*</td>
<td>113.23±2.01*</td>
</tr>
<tr>
<td>D</td>
<td>268.00±2.20*</td>
<td>340.00±5.49*</td>
<td>82.40±2.00*</td>
<td>37.45±1.40*</td>
<td>34.55±2.50*</td>
</tr>
</tbody>
</table>

Column values with different superscripts are significantly (p<0.05) different
Each values is a mean of eight determination ± SEM
Legend: A = Control rats fed with yam flour based-diet, B = Diabetic untreated rats fed with yam flour based-diet, C = Diabetic rats administered with metformin daily and fed with yam flour based-diet, D = Diabetic rats fed with *Artocarpus altillis* fruit-based diet, HDL = High density lipoprotein, LDL = Low density lipoprotein, VLDL = Very low density lipoprotein
References


Publications.

