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Research Article
Effects of Ethanolic Leaf and Stem-bark Extracts of *Adansonia digitata* in Alloxan-induced Diabetic Wistar Rats

[1]Ojochenemi Ejeh Yakubu, [1]Chinedu Imo, [1]Christopher Shaibu, [2]John Akighir and [1]Daniel Simon Ameh

[1]Department of Biochemistry, Faculty of Pure and Applied Sciences, Federal University Wukari, P.M.B. 1020, Wukari, Taraba State, Nigeria
[2]Department of Biochemistry, University of Agriculture, Makurdi, Nigeria

Abstract

Background and Objectives: Diabetes mellitus has been a great worry to humanity and the scientific community and researchers have made it a point of challenge and responsibility to bring an end to the quantum of havocs posed by this monster. This study was carried out to evaluate the effects of ethanolic leaf extract and stem-back extract of *Adansonia digitata* (AD) on liver function, haematology and blood glucose level in alloxan-induced diabetic Wistar rats. **Materials and Methods:** Twenty-five Wistar rats were distributed into 5 groups of 5 animals each. The test animals were administered alloxan (150 mg kg^{-1}) intraperitoneally and were monitored for 72 h for the development of hyperglycemia. Group 1 served as normal control, group 2 served as diabetic control, while groups 3and 4 were diabetic rats treated orally with ethanolic leaf and stem-bark extracts of *Adansonia digitata* (100 mg kg^{-1}), respectively for 21days. Group 5 animals were diabetic rats treated with anti-diabetic drug (glibenclamide). **Results:** The result of this study indicated a reduced blood glucose level and a significantly ($p<0.05$) reduced liver function parameters evaluated in the alloxan-induced diabetic treated rats compared with the diabetic control rats. However, there was no specific pattern of increase/decrease in the haematological parameters. **Conclusion:** This study showed that alloxan-induced diabetes mellitus caused a possible liver disease condition and alteration of the haematological indices. However, administration of the AD leaves extract and AD stem-bark extract exhibited the ability of treating the inflammation and alterations caused by alloxan-induced diabetes.

Key words: *Adansonia digitata*, antidiabetic, haematology, hyperglycaemia, phytochemicals, phytomedicine, medicinal plant, preventive medicine

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Corresponding Author: Ojochenemi Ejeh Yakubu, Department of Biochemistry, Faculty of Pure and Applied Sciences, Federal University Wukari, P.M.B. 1020, Wukari, Taraba State, Nigeria Tel: +2348069078726

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Natural products especially of plant origin have been used for the treatment of various diseases promisingly for decades. In developing countries, herbal medicine is the source of new discoveries for the new drug leads towards various healthcare issues and synthesis of new formulations[1]. Traditional medicine when compared to other sources of drug discoveries had contributed immensely to many novel therapeutic compounds for preventive and curative medicine. Previous studies showed that secondary metabolites like polyphenols, terpenes and alkaloids possess anti-mutagenic and anticancer properties[1]. Medicinal plants have been of great sources of relief for debilitating challenges especially diabetes and other life threatening diseases. Phytochemicals such as saponins, tannins, essential oils, flavonoids, alkaloids and other chemical compounds, have been known for these preventive and curative properties. These complex chemical substances of different compositions are found as secondary plant metabolites in one or more of these plants and are useful for humanity[2]. In view of many diseases defiling drugs, health practices are now changing from curative to preventive medicine. Phytochemicals popular in preventive medicine are flavonoids, polyphenols, saponins, lignoids and vitamins. The knowledge of chemical constituents of plants would further be valuable in discovering the actual value of folkloric remedies[2]. Medicinal plants are widely used by the populations of underdeveloped countries as alternative therapy. In Africa, hundreds of plants are used traditionally for the management and control of diabetes mellitus. Unfortunately, only a few of such African medicinal plants have received scientific scrutiny[2].

Adansonia digitata L. also called the baobab tree in both English and French belongs to the family Malvaceae[3]. Baobab tree has multi-purpose activities and every part of the plant is reported to be useful[4]. The leaves, for instance are used as vegetable in preparation of soup, seeds are used as a thickening agent in soups, but they can be fermented and used as flavoring agent or roasted and eaten as snacks[5]. The pulp is either sucked or made into a drink, while the bark is used in making ropes. The different parts of the plant provide food, shelter, clothing and medicine, as well as sources for industrial raw materials[6,7]. Baobab tree provides income and employment to rural and urban households.

Previously published biochemical analyses revealed that the leaves, the seed and the pulp from baobab tree are rich in nutrients[8,9]. Researches and reviews on baobab provided information on the species and their phytochemical composition[4]. Scientific reports have also revealed a great variation in values of nutritional composition of the plant part which may be dependent on parameters such as the quality of the sample, provenance of the sample, age of the sample, soil composition and structure[9].

This study was aimed at determining the effects of ethanolic leaf extract and stem-back extract of *Adansonia digitata* on liver function, haematology and blood glucose level in alloxan-induced diabetic Wistar rats with focus on deciphering the mechanisms and providing adequate information on the appropriate parts, solvent, methods, safety and efficacy of the plant parts.

MATERIALS AND METHODS

Study was conducted from May, 2018 to January, 2019.

Sample collection: Fresh leaves of *Adansonia digitata* were collected from the natural habitat of Gidan Adamu in Wukari, Taraba State, Nigeria: In the month of June, 2018. The specimen was identified in the Department of Biological Sciences, Federal University Wukari, Nigeria and was dried at room temperature before ground into a powder form for the experiment as described by Yakubu *et al.*[10].

Experimental animals: This animal experiment was approved by the Ethical committee of the Faculty of Pure and Applied Sciences, Federal University Wukari, with the approval number, FUW/FPAS/19/020. Twenty-five healthy male Wistar rats with an average weight 150-250 g were purchased from animal house of College of Health Science, Benue State University, Nigeria and transported to the Animal house of Department of Biochemistry, Federal University Wukari, Nigeria. They were acclimatized for 2 weeks and weighed prior to the commencement of the experiment[10].

Ethanolic extraction: The method of Yakubu *et al.*[10] was adopted for this protocol. One hundred grams (100 g) of pulverized sample each of leaf and stem-bark was weighed into a plastic container and filled with 400 mL ethanol (70%) and was allowed to stand for 24 h with occasional shaking, thereafter, filtered with Whatman No. 1 filter paper. The filtrate was concentrated using rotary evaporator under reduced pressure and concentrates transferred into air-tight container and preserved in the refrigerator at 4°C prior to administration. Before the administration, it was re-dissolved in normal saline.

Alloxanization: This was carried out as described by Yakubu *et al.*[11]. The animals were fasted overnight prior to induction and diabetes was induced in the male Wistar rats by intraperitoneal administration of alloxan (150 mg kg^{-1} b.wt.). After 72 h, the animals were tested and confirmed to be diabetic. The blood glucose concentrations of the animals were determined weekly using a glucometer (Accu-Check Active). Animals with extremely high fasting blood glucose level were considered diabetic and were used for the study.

Experimental design: The 25 male Wistar rats were distributed into 5 groups consisting of 5 animals each. Out of the 5 groups, 4 were made diabetic. The administration of the extracts was as described as follows:

Group 1 : Normal control
Group 2 : Diabetic control
Group 3 : Diabetic, treated with *Adansonia digitata* leaves extract (100 mg kg^{-1})
Group 4 : Diabetic, treated with *Adansonia digitata* stem-bark extract (100 mg kg^{-1})
Group 5 : Diabetic, treated with Glibenclamide (5 mg kg^{-1}). The treatments were given to the rats through oral route

Biochemical analysis

Fasting blood glucose determination: This was carried out as described by Yakubu *et al.*[11]. A drop of blood was collected through tail puncture from each of the over-night fasted rats on an assay strip and fasting blood glucose level was determined using Accu-Check active glucometer. This was carried out on weekly basis for 21 days (3 weeks).

Animal sacrifice and collection of blood samples: After the 21 days, the animals were starved overnight and sacrificed. Blood was collected from each of the animal through cardiac puncture and dispensed into 2 different types of tubes. The 1st part of the blood (dispensed into an anti-coagulant containing sample tube) was used for haematological analysis. The 2nd part of the blood (dispensed into a very cleaned plain tube) was allowed to clot for about 10 min and centrifuged at 4000 rpm for 10 min. The serum was separated from the clot and was used for the analysis of the selected indices of liver function.

Liver function tests: This was carried out as described by Imo *et al.*[12]. The serum biochemical examination was carried out using Vitros DT 60 Ã Chemistry Analyzer and the following parameters were measured, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin (BIL) and potassium (K).

Haematological analysis: The method of Imo *et al.*[12] was adopted. Using whole blood, the total red blood cell (RBC) count, haemoglobin (HB) concentration, white blood cell (WBC) count and platelet count were determined using Abacus 280 auto-haematology analyzer.

Statistical analysis: Statistical analysis was carried out with the use of one-way analysis of variance (ANOVA) and further with Duncan multiple comparisons using Statistical Package for Social Sciences (SPSS), version 21. The result means were compared for significance at $p \leq 0.05$ and the group results presented as mean ± standard deviation (n = 5).

RESULTS

Liver function: The result showed significant ($p<0.05$) increase in the AST, ALT, ALP activities and bilirubin concentration in the diabetic control (group 2) compared with normal control (group 1). Treatment with the leaf and stem-bark extracts caused significant decrease in the levels of these parameters compared to the diabetic control. The result of K^+ showed no significant increase ($p>0.05$) in the diabetic control compared to the normal control. Treatment with the leaves and stem-bark extracts caused no significant decrease in the K^+ level compared to the diabetic control. There was no significant increase/decrease between effects elicited by the standard drug and the extracts (Table 1).

Haematological analysis: The results of WBC and RBC showed a decrease in the diabetic control compared to the normal control. Treatment of the diabetic rats with the extracts caused an increase in the levels of these parameters compared to the diabetic control. Similar pattern of observation was made for the lymphocyte concentration. The result of HCT showed a significant decrease in the diabetic control compared to the normal control. Treatment with the leaves and stem-bark extracts caused an increase in the HCT level compared to the diabetic control. There was an increase in the effect elicited by the standard drug compared with the extracts. The results of PLT and HB showed a significant ($p<0.05$) decrease in the diabetic control compared to the normal control, but treatment with the extracts and the standard drug caused an increase in the levels of PLT and HB when compared with the diabetic control (group 2) (Table 2).

Table 1: Concentrations of liver marker enzymes, bilirubin and potassium in diabetic rats treated with ethanolic leaves and stem-bark extracts of *Adansonia digitata*

Treatments	AST (U L^{-1})	ALT(U L^{-1})	BIL (µmol L^{-1})	ALP (U L^{-1})	K^+ (mmol L^{-1})
Normal control (group 1)	30.40±2.60^{a}	40.00±13.05^{a}	19.20±5.58^{a}	78.58±3.10^{a}	9.50±5.00^{a}
Diabetic control (group 2)	171.90±59.45^{d}	184.00±47.04^{d}	52.88±6.64^{c}	277.00±51.56^{e}	12.00±0.00^{a}
Diabetic+AD leaves extract (group 3)	68.10±3.60^{c}	117.00±34.30^{b}	41.26±9.22^{b,c}	181.25±24.21^{d}	9.01±5.00^{a}
Diabetic+AD stem-bark extract (group 4)	71.00±5.00^{c}	136.00±42.56^{c}	40.94±3.34^{b,c}	157.75±50.34^{c}	9.50±5.00^{a}
Diabetic+GLB (group 5)	50.20±2.60^{b}	100.00±27.05^{b}	35.74±1.34^{b}	121.05±4.01^{b}	9.61±3.00^{a}

Results are Mean±SD (n = 5), AD: *Adansonia digitata*, GLB: Glibenclamide, mean in the same column having different letters of the alphabet are statistically significant (p<0.05)

Table 2: Concentrations of haematological indices in diabetic rats treated with ethanolic leaves and stem-bark extracts of *Adansonia digitata*

Treatments	WBC (×10^9 L^{-1})	LYMP (×10^7 L^{-1})	RBC (×10^{12} L^{-1})	HB (g dL^{-1})	HCT (%)	PLT (×10^9 L^{-1})
Normal control (group 1)	6.43±0.20^{b}	8.29±0.32^{b}	7.61±0.63^{b}	11.40±0.72^{b,c}	37.72±4.32^{c}	85.00±9.37^{b}
Diabetic control (group 2)	3.23±1.70^{a,b}	2.56±0.53^{a}	4.31±0.37^{a}	6.31±0.67^{a}	15.20±1.37^{a}	56.00±16.45^{a}
Diabetic+AD leaves extract (group 3)	7.42±2.50^{b}	8.52±0.64^{b}	6.41±0.82^{b}	8.31±0.32^{b,c}	35.20±8.41^{b,c}	61.00±10.07^{a}
Diabetic+AD stem-bark extract (group 4)	5.65±1.43^{b}	3.76±0.02^{a}	5.37±0.29^{a,b}	9.10±0.50^{b,c}	31.16±4.32^{b}	93.00±17.90^{c}
Diabetic+GLB (group 5)	2.38±0.30^{a}	9.70±0.20^{b}	6.79±0.27^{b}	14.00±1.31^{c}	43.34±7.60^{d}	211.00±25.30^{d}

Results are Mean±SD (n = 5), AD: *Adansonia digitata*, GLB: Glibenclamide, mean in the same column having different letters of the alphabet are statistically significant (p<0.05)

Table 3: Changes in body weight of diabetic rats treated with ethanolic leaves and stem-bark extracts of *Adansonia digitata*

	Body weight (g)		
Treatments	Week 0	Week 1	Week 2
Normal control (group 1)	127.50±3.54^{a,b}	135.50±2.12^{b,c}	142.50±3.54^{b,c}
Diabetic control (group 2)	114.00±19.80^{a}	104.52±14.85^{a}	100.23±21.21^{a}
Diabetic+AD leaves extract (group 3)	135.25±14.73^{b}	140.50±12.22^{c}	147.75±9.54^{c}
Diabetic+AD stem-bark extract (group 4)	125.25±20.20^{a,b}	127.25±17.33^{b}	136.25±20.47^{b}
Diabetic+GLB (group 5)	125.33±6.43^{a,b}	144.33±6.03^{c}	149.11±7.94^{c}

Results are Mean±SD (n = 5), AD: *Adansonia digitata*, GLB: Glibenclamide, mean in the same column having different letters of the alphabet are statistically significant (p<0.05)

Table 4: Fasting blood glucose concentrations (mg dL^{-1}) of diabetic rats treated with ethanolic leaves and stem-bark extracts of *Adansonia digitata*

Treatments	Week 0	Day 1	Week 1	Week 2	Week 3
Normal control (group 1)	80.00±2.44^{b}	74.00±5.66^{a}	77.50±7.78^{a}	69.50±1.41^{a}	73.00±2.44^{c}
Diabetic control (group 2)	63.50±11.33^{a}	198.00±84.85^{e}	267.50±6.36^{d}	280.50±21.92^{d}	263.50±11.33^{d}
Diabetic+AD leaves extract (group 3)	60.50±4.65^{a}	168.25±60.62^{d}	111.50±18.66^{b}	76.50±4.65^{b}	56.50±4.65^{b}
Diabetic+AD stem-bark extract (group 4)	57.50±5.44^{a}	131.75±5.85^{b}	85.25±11.79^{a}	77.00±4.24^{b}	47.30±5.24^{a}
Diabetic+GLB (group 5)	65.34±4.13^{a}	146.00±23.07^{c}	195.00±20.55^{c}	95.33±24.83^{c}	45.34±4.13^{a}

Results are Mean±SD (n = 5), AD: *Adansonia digitata*, GLB: Glibenclamide, mean in the same column having different letters of the alphabet are statistically significant (p<0.05)

Changes in body weight: There was an increase in body weight of rats in all the groups during the period of the experiment, except the diabetic control which decreased in body weight across the weeks (Table 3).

Fasting blood sugar: The result of fasting blood sugar (FBS) showed a significant increase (p<0.05) in the diabetic control compared to the normal control across the weeks. Treatment with the extracts and the GLB showed significant (p<0.05) decrease across the weeks compared to the diabetic control (Table 4).

DISCUSSION

The result of fasting blood sugar (FBS) showed a significant increase (p<0.05) in the diabetic control compared to the normal control across the weeks. Treatment with the extracts and the GLB showed significant (p<0.05) decrease across the weeks compared to the diabetic control as depicted in Table 4. Alloxan induces diabetes in experimental animals by destroying the beta cells of the Islet of Langerhans in the pancreas leading to reduction in the synthesis and release of insulin thereby inducing hyperglycemia[13]. Historical records provide a reservoir of basic information on the use of traditional medicine in the management of diabetes mellitus with plant part extracts[13-15]. One of such part is the stem-bark of *Adansonia digitata*. The result of this study (Table 4) showed that the extracts caused a significant (p<0.05) decrease in the blood glucose levels in Alloxan-induced diabetic Wistar rats. The mechanism by which the extracts exerted the hypoglycemic effect appear to be related to the presence of flavonoids among other secondary metabolites or bioactive chemical constituents found in the plant extracts as reported by Marles and Farnsworth[16] which may be an active

constituent in a group or as an individual responsible for the hypoglycemic activity of the plant extract. It has been worthy of note that flavonoids act as antihyperglycaemic agent by causing inhibition of renal glucose reabsorption through inhibition of the sodium-glucose symporters located in the proximal renal convoluted tubule[17]. Probably, this also may be a possible mechanism by which the plant extracts used in this study exerted its hypoglycemic effects in the diabetic animals and lend credence to the use of this plant in the management of diabetes mellitus.

Though hypoglycaemic potential of *Adansonia digitata* stem-bark extract in alloxan-induced diabetic Wistar rats has been established, there is paucity of information about the anti-hyperglycaemic effect of the leaves widely consumed and used in the management of diabetes mellitus in Hausa land, Nigeria[17]. Flavonoids and glycosides stimulate the secretion of insulin in β-cells of pancreas[18]. It is also possible that the leaves and stem-back extracts stimulated the secretion of insulin in the test animals. In this study however, it was observed that *Adansonia digitata* extracts reduced the negative effect and tends to bring about normalcy in the parameters, this was compared with the observation with anti-diabetic drugs (glibenclamide) in diabetic rats and the non-diabetic rats.

Elevated levels of serum liver enzymes have been associated with diabetes mellitus[19]. Non-alcoholic hepatosteatosis have been implicated as the major cause of elevated serum liver marker enzyme in diabetics, although it is also rarely caused by glycogenic hepatopathy: A disease condition associated with excess glycogen stored in the liver[19]. Results from this study showed a significant increase in serum liver marker enzymes (ALT, AST, ALP) in the diabetic control (Table 1) when compared with the normal control group indicating a possible liver disease condition which may have been caused by the alloxan-induced diabetes mellitus[20]. Administration of AD leaves extract and AD stem-bark extract decreased the elevated serum liver marker enzymes. This may be attributed to the presence of free radical scavenging antioxidants in the extracts[21]. There was also a decrease in the level of serum bilirubin after treatment with AD leaves extract and AD stem-bark extract: Further indicating the ameliorative effects of the extracts on liver disease caused by alloxan-induced diabetes. However, diabetic rats treated with GLB had a higher reduction in the biochemical parameters above. There was no significant difference in K^+ concentration among the groups.

Research evidences have revealed alterations in haematological indices arising from glycation of haemoglobin, fibrinogen, prothrombin and other blood clotting proteins due to persistent hyper glycaemia[22]. This study showed a significant decrease in RBC, HB and HCT in the diabetic control when compared with the normal control (Table 2). This may be due to decreased production of erythropoietin[23]. Treatment with AD leaves extract and AD stem-bark extract raised the RBC count, HB concentration and HCT and compares to a good extent with the use of GLB in this study. A reduced PLT and LYMP count was also observed in the diabetic control rats. The reduction may have been caused by diabetes induced inflammation of vital organs and bone marrow neuropathy[24-26]. There was a reduction in the WBC count in the diabetic control rats. The WBC and LYMP count were however, stabilized better upon the administration of AD leaves extract suggesting that the extract exhibited the potential of treating inflammation caused by alloxan-induced diabetes. Haematological and biochemical indices have been reported to be a reliable parameter for the assessment of health status of animals[27]. *Adansonia digitata* extracts produced an elevation on the reduced levels of haematological parameters in the diabetic control rats.

There was a progressive loss of body weight of the diabetic control rats when compared with the normal control (Table 3). This is in tandem with reports of Hamden *et al.*[28], Virdi *et al.*[29] and Berredjem *et al.*[30]. Loss of weight may be attributed to utilization of fat and proteins as alternative source of energy and dehydration[30,31]. There was however weight gain in rats treated with AD leaves extract and AD stem-bark extract[32].

This result implies that the leaf of *A. digitata* has antioxidant effects especially using the solvent in question which supports it use in folklore medicine. This study is limited to laboratory animals; it is yet to be validated clinically on human subjects. Hence, further studies are required to validate the safety and isolation of compounds responsible for these effects and the possible mechanisms involved.

CONCLUSION

The result obtained in this study indicated that *A. digitata* leaves and stem-bark extracts possess the potential to be used in the management of diabetes mellitus by being able to reduce the negative effects of alloxanization as elucidated by the different parameters under consideration in this study. The presence of certain phytochemicals such as flavonoids, alkaloids, saponins, glycosides and phenolics may have helped to overcome the negative effects of the alloxan in the diabetic rats.

SIGNIFICANT STATEMENT

This study discovered the medicinal importance of *A. digitata* that can be beneficial for the management of diabetes mellitus and related diseases/complication with emphasis on the method and specificity of solvents for the extraction of the active principles. This study will help the researcher, drug designers and developers to uncover the critical areas like solvent and method of extraction, dosage and route of administration which many researchers were not able to explore. Thus a new theory/mechanism on this plant may be arrived at.

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