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Hepatotoxic and Antidiabetic Potentials of Aqeuous Bark Extracts of *Ficus asperifolia* on Normal and Alloxan-Induced Diabetic Albino Rats

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Authors' contributions

This research was conducted by the first author, BPO. The second author, TOJ carried out the qualitative phytochemical screening on the plant while the last author, OSO helped with the statistical analysis.

Research Article

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ABSTRACT

Aim: The aim of this research was to evaluate the antidiabetic effect of aqueous bark extract of *Ficus asperifolia* on alloxan-induced diabetic rats and also to investigate its toxicity potential on the liver of albino rats.
Place and Duration of Study: The research was carried out in the Department of Science Laboratory Technology, Faculty of Natural Sciences, University of Jos, Nigeria between June, 2011 and September, 2011.
Methodology: *F. asperifolia* bark was pulverized and percolated in distilled water. The mixture was filtered after 48 hours extraction using Whatman No 1 filter papers. The resulting filtrate was concentrated on a water bath and the concentrate used for the preparation of the doses used (i. e. 400mg, 800mg and 1200mg/Kg body weight). Alloxan-induced diabetic rats were treated with the different doses of the extract for 7 days and their fasting blood glucose concentration tested every day for 7days. The animals were sacrificed 24 hrs after the 7th day administration and their serum used for the analysis of Total Cholesterol, Triglyceride, High Density Lipoprotein, Low Density Lipoprotein and Very

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Low Density Lipoprotein. Rats were also treated with the different doses for 1, 7 and 21 days. They were sacrificed 24 hours after the administration days. Their serum were collected and used for the analysis of Alanine Aminotransferase, Aspartate Aminotransferase, Total Cholesterol and Albumin.

Results: Administration of aqueous bark extract of *F. asperifolia* caused a significant reduction (*P*= .05) in blood glucose concentration in alloxan-induced diabetic rats. Serum Total Cholesterol, Triglyceride, Low Density Lipoprotein and Very Low Density Lipoprotein Concentrations were also significantly decreased (*P*= .05) in the diabetic rats while High Density Lipoprotein was significantly increased (*P*= .05). Liver marker enzymes Aspartate Aminotransferase and Alanine Aminotransferase serum activities and serum Total protein were significantly increased (*P*= .05) in the treated animals when compared to the control group. Serum albumin concentration also fluctuated significantly (*P*= .05) following extract administration.

Conclusion: Results available from this study shows that aqueous bark extract of *F. asperifolia* possesses antidiabetic properties but also possesses hepatotoxic effects at the doses tested.

Keywords: Hepatotoxic; antidiabetic; Ficus asperifolia; aminotransferase; aqueous.

1. INTRODUCTION

Diabetes is a heterogeneous group of metabolic disorders characterized physiologically by deficiency in insulin or insulin activity and clinically by hyperglycemia or impaired glucose tolerance and other manifestable disorders [1]. Globally, there is an increase in the incidence and prevalence of type 2 diabetes. It was estimated in the year 2000 by the World Health Organization that 171 million people had diabetes, representing 2.8% of the world's population at the time, and also predicted that this number will increase to 366 million (4.4%) by 2030 [2]. Diabetes often results to complications which characteristically affect the kidneys, eyes, reproductive organs, nervous system, etc [3]. The rate of occurrence of diabetic neuropathy has been on the rise [4]. The underlying causes of diabetic complications have been attributed to hyperglycemia which results in oxidative stress, alterations in enzyme activities, protein glycosylation and several structural changes [5]. Current therapies though provide good glycemic control, do little in preventing complications. They are not just unaffordable and inaccessible especially in less developed and developing countries; but are also associated with side effects. Thus, it is of utmost necessity to continue looking for new, more efficacious and less toxic drugs. In recent times, scientists have been working to find a lasting solution to the threat that diabetes poses to mankind. The development of traditional or alternative medicine has taken the centre stage. Herbs are being scientifically scrutinized to determine their constituents, isolate their medicinal principles and discard their toxic components.

There are many plants used in folk medicine for the treatment of diabetes, one of which is *F. asperifolia* (sand paper tree). It is a small or average size tree, terrestrial or epiphyte which can reach 20m in height and belongs to the Moraceae family [6]. It is one of the many highly medicinal plants with a variety of uses which include its use as anti-tumors, anti-cancer, diuretic, abortificient, ecobolics and menstrual cycle/ general pain reliever [6]. There are claims that it is also used for the management of diabetes by the Igala tribe of Kogi State, Nigeria. *F. asperifolia* is found across African countries like Senegal, Uganda, Tanzania, Natal (South Africa), Madagascar and Cameroon [6]. It is also reported

to be found in Michika, Hong and Song Local Government Areas of Adamawa State [7], Toro Local Government Area of Bauchi State and Omala Local Government Area of Kogi State [8] all in Northern Nigeria.

The aqueous stem extract of *F. asperifolia* is reported to possess hypoglycemic and hypolipidemic properties on diabetic rats but significantly raised serum transaminases activities [8]. It has also been published that the leaf of *F. asperifolia* contained a higher protein, crude fibre and Mineral content than most Nigerian vegetables [7]. Phytochemical screening of the aqueous leaf extract of *F. asperifolia* have detected the presence of alkaloids, saponins, tannins, cardiac glycosides, terpenes, steroids, balsam and phenol [9]. The aim of this work is to ascertain the truth in the antidiabetes claim and also the toxicity potential of the plant in rats, thus contributing to the search for an affordable drug for diabetes treatment without a side effect.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Experimental animals

Eighty- five male albino rats weighing 200-250g were obtained from the Animal Holding Unit of Benue State University, Markurdi, Nigeria. The rats were housed in standard cages and allowed to acclimatize to animal house conditions for 7 days. They were allowed free access to normal rat pellet and tap water. Rats were divided into 2 major groups; the first group used for diabetes study contained 25 rats which were grouped into A, B, C, D and E representing Diabetic Control, Normal Control and Diabetic groups treated with 400mg/Kg, 800mg/Kg and 1200mg/Kg body weight doses respectively. Blood glucose concentration was taken for a period of 7days after which the rats were sacrificed and their serum used for lipid profile determination.

The second group of animals contained 60rats and were used for toxicity study. They were divided into 4 groups W, X, Y and Z. Group W which served as the control was orally administered with $1cm^3$ of distilled water while groups X, Y and Z were orally administered with 1 cm^3 of extract to give the required dose of 400, 800 and 1200 mg/kg body weight respectively. The animals were sacrificed 24 hours after extract administration for 1, 7 and 21 days.

2.1.2 Plant material

F. asperifolia bark was obtained from Icheke village, Omala Local Government Area of Kogi state, Nigeria by June, 2011.The plant was properly identified at the Department of Forestry, Ministry of Agriculture and Natural Resources, Lokoja, Kogi State, Nigeria.

2.1.3 Assay kits

Assay Kits for Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were products of Randox Laboratories, United Kingdom. All other reagents used were of analytical grade and were all prepared in all glass distilled water.

2.2 Methods

2.2.1 Qualitative phytochemical screening of *Ficus asperifolia* bark

Qualitative phytochemical screening was carried out on the aqueous extract of *F. asperifolia* bark. The method described by [10] was used for detecting alkaloids, tannins, phlobatannins, cardiac glycosides and anthraquinones. Phenolics and flavonoids were detected using the method described by [11] while saponins were detected using the method described by [12].

2.2.2 Preparation of aqueous bark extract of *Ficus asperifolia*

F. asperifolia bark was first weighed after which it was cut into pieces and oven dried at 40^0C to constant weight. The dried bark was ground to powder using an electric grinding machine. 200g of the powder was percolated in 1000cm^3 of distilled water and stirred properly. The mixture was then kept in a refrigerator for 48 hours to allow for proper extraction. It was thereafter filtered using Whatman No. 1 filter paper and the filtrate concentrated on a water bath at 80^0C to give a yield of 17g representing a percentage yield of 8.5%. The concentrate was then used for the preparation of the different doses.

2.2.3 Induction of diabetes

Animals were subjected to fasting for 12 hours. They were then administered with a single intraperitoneal dose of 150mg/kg body weight dose of alloxan monohydrate in saline solution. Normal rats received the same volume of 0.9%w/v saline solution through the same route. The animals were returned to their cages after injection and allowed free access to food and water. After 4 days, the fasting blood glucose concentrations were measured from tail blood samples by using a One Touch Ultra® glucometer (Lifescan; Johnson & Johnson, Milpitas, CA, USA). Animals with blood glucose concentrations above 180mg/dl were used for the experiment [13]. Extract administration started 4 days after alloxan administration once hyperglycemia was confirmed.

2.2.4 Serum preparation

The rats were sacrificed under light anesthesia (diethyl ether). Their blood was collected into sample bottles without anticoagulants by puncturing of their jugular veins. The blood was allowed to stand for 10 minutes to clot. Serum was then collected using a Pasteur pipette.

2.2.5 Measurement of enzyme activities, liver function indices, blood glucose concentration and lipid profile

Aspartate aminotransferase (AST) (EC 2.6.1.1) and Alanine aminotransferase (ALT) (EC 2.6.1.2) activities were assayed at 546nm by the method of [14]. Serum Total Protein concentration was determined at 540nm using the Biuret method [15]. Serum total and conjugated bilirubin were analysed at 540nm [16]. Serum albumin determination was done at wavelength 639nm [17]. The blood glucose levels were determined by the glucose-oxidase method [18]. Serum triglycerides, total cholesterol and HDL were estimated by enzymatic colorimetric end point methods using Span diagnostic reagent kit. LDL and VLDL were obtained by calculations using the formula provided in cholesterol diagnostic kit booklet.

2.2.6 Statistical analysis

Data are expressed as mean of 5 replicates± Standard Deviation (SD). The obtained data were subjected to statistical analysis using the IBM® Statistical Package for Social Sciences (SPSS) software version 17.0. Significant differences were determined by one way analysis of variance (ANOVA) and Post Hoc multiple comparisons was done using Duncan's multiple range test. Significance level was set at (*P*= .05).

2. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Qualitative phytochemical screening results

Table 1 shows the qualitative phytochemical screening of aqueous bark extract of *F. asperifolia.* Flavonoids, Alkaloids, Cardiac glycosides, Resin and Terpens/Steroids were detected while Tannins, Saponins, Balsam and Phenols were not detected.

Table 1. Qualitative Phytochemical Screening of Aqueous Bark Extract of *F. asperifolia*

Phytochemicals	Status
Flavonoids	+
Alkaloids	+
Tannins	-
Saponins	-
Cardiac Glycosides	+
Balsam	-
Phenol	-
Resin	+
Terpenes/Steroids	+

Key: += Present, -= Absent

3.1.2 Blood glucose concentration

The effect of oral administration of aqueous bark extract of *F. asperifolia* on blood glucose concentration of diabetic rats is presented in Table 2. Administration of Alloxan monohydrate led to a significant increase (*P*= .05) in blood glucose concentration of the experimental animals when compared with the control group. However, treatment with the various doses of the extract reduced significantly (*P*= .05) the blood glucose concentration in all the treated rats when compared to the diabetic untreated group. The reduction in blood glucose concentration observed was not to normal levels. However, diabetic rats treated with the 1200mg/kg dose for 5, 6 and 7 days and those treated with the 800mg/kg dose for 6 days had blood glucose concentrations closest to those of normal control rats.

Table 2. Effect of administration of aqueous extract of *F. asperifolia* Bark on Blood Glucose Concentration of Alloxan-Induced Diabetic Rats

Days	A	B	C	D	E
1	183.00±6.60^{a}	86.67± 6.51^{b}	140.00±8.19^{c}	148.67±17.95^{c}	148.68±17.95^{c}
2	184.00±6.00^{a}	107.33± 7.51^{b}	145.00±5.00^{c}	140.67±18.99^{c}	149.33±15.50^{c}
3	183.50±4.60^{a}	101.33 ±3.51^{b}	150.00±8.66^{c}	136.33±17.44^{c}	147.67±13.32^{c}
4	185.00±4.70^{a}	101.33 ±3.79^{b}	131.00±3.61^{c}	127.67±17.26^{c}	138.33±14.47^{c}
5	183.80±5.30^{a}	99.00 ±3.61^{b}	113.00±4.36^{c}	126.33±7.37^{d}	118.67±20.11^{bcd}
6	184.50±4.90^{a}	98.43 ±3.31^{b}	118.33±2.52^{c}	106.00±13.75^{bc}	103.00±24.33^{bc}
7	186.00±2.80^{a}	97.67 ±3.30^{b}	120.00±3.46^{c}	114.33±8.08^{c}	110.67±18.01^{bc}

Values are means of 5 replicates± Standard Deviation; Values carrying superscripts different from the control along the row are significantly different at (P= .05). Concentrations are expressed in mg/dL. A represents Diabetic Control, B represents Normal Control while C, D and E represent Diabetic groups treated with 400mg/Kg, 800mg/Kg and 1200mg/kg b. wt. dose respectively.

3.1.3 Lipid profile

Table 3 shows the effect of administration of the aqueous bark extract of *F. asperifolia* on lipid profile concentrations of diabetic albino rats. There was a significant increase (*P*= .05) in the concentrations of Triglyceride (TG), Total Cholesterol (TC), Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL) and a significant decrease (*P*= .05) in High Density Lipoprotein (HDL) concentration in all the animals following alloxan administration. Administration of the aqueous bark extract caused a significant reversal (*P*= .05) of that feat although not to normal levels.

Table 3. Effect of administration of aqueous extract of *F. asperifolia* bark on lipid profile of Alloxan-induced diabetic rats

Parameters	A	B	C	D	E
TG	149.10±8.26^{a}	13.67±1.53^{b}	62.00±7.00^{c}	78.33±5.68^{d}	44.00±6.56^{e}
TC	125.11±10.85^{a}	58.67±2.52^{b}	91.67±8.50^{c}	96.67±7.09^{c}	89.80±7.09^{d}
HDL	10.26±3.92^{a}	55.00±3.00^{b}	46.67±5.13^{bc}	53.00±6.08^{b}	42.67±5.51^{c}
LDL	85.00±4.70^{a}	1.33 ±0.79^{b}	31.00±3.61^{cd}	27.67±7.26^{d}	38.33±4.47^{c}
VLDL	29.84±1.62^{a}	2.73±0.31^{b}	12.40±1.40^{c}	15.67±1.14^{d}	8.80±1.31^{e}

Values are means of 5 replicates± Standard Deviation; Values carrying superscripts different from the control along the row are significantly different at (P= .05). Concentrations are expressed in mg/dL. A represents Diabetic Control, B represents Normal Control while C, D and E represent Diabetic groups treated with 400mg/Kg, 800mg/Kg and 1200mg/kg b. wt. dose respectively.

3.1.4 Serum alanine aminotransferase and aspartate aminotransferase activities

Table 4 represents the effect of the extract on serum Alanine and Aspartate transaminase activities. All the animals that were administered with the various doses of the extract showed a significant increase (*P*= .05) in serum Alanine and Aspartate activities when compared to the control animals. The concentration of the enzymes increased with increases in extract concentrations and days of extract administration.

Table 4. Effect of Administration of Aqueous Bark Extract of *F. asperifolia* on male rat Serum Alanine Aminotransferase and Aspartate Aminotransferase Activities

Days	W (Control)	X (400mg/kg)	Y (800mg/kg)	Z (1200mg/kg)
Serum Alanine Aminotransferase				
1	57.67±0.58^{a}	87.33±1.56^{b}	91.33±1.53^{c}	95.00±1.73^{d}
7	57.67±0.58^{a}	104.67±1.53^{b}	104.33±3.79^{b}	114.00±2.00^{c}
21	57.67±0.58^{a}	127.00±1.73^{b}	130.00±5.30^{bc}	135.00±2.65^{b}
Serum Aspartate Aminotransferase				
1	171.00±1.00^{a}	213.00±0.01^{b}	221.00±2.00^{c}	231.33±2.30^{d}
7	171.00±1.00^{a}	216.67±5.78^{b}	230.00±2.00^{c}	237.33±12.22^{c}
21	171.00±1.00^{a}	223.67±0.58^{b}	231.00±3.00^{c}	254.33±4.51^{d}

Values are means of 5 replicates± Standard Deviation; Values carrying superscripts different from the control along the row are significantly different at (P= .05). Enzyme activities are expressed in U/L.

3.1.5 Serum total protein and albumin concentrations

The effect of the extract on serum total protein and albumin is presented in Table 5. There was a significant increase (*P*= .05) in the serum total protein concentration for all the experimental animals in a dose-dependent manner. Experimental animals showed significant fluctuations (*P*= .05) in serum albumin concentration. Rats treated with the 400 and 1200mg/Kg body weight doses of the extract for 1 day showed a significant increase (*P*= .05) in serum albumin concentration while in the other animals, serum albumin concentration significantly decreased (*P*= .05).

Table 5. Effect of administration of aqueous bark Extract of *F. asperifolia* on male rat serum total protein and albumin concentrations

Days	W (Control)	X (400mg/kg)	Y (800mg/kg)	Z (1200mg/kg)
Serum Total Protein Concentration				
1	0.90±0.10^{a}	7.40±0.20^{b}	7.80±0.10^{c}	8.13±0.12^{d}
7	0.90±0.10^{a}	6.33±0.15^{b}	6.70±0.20^{c}	7.50±0.15^{d}
21	0.90±0.10^{a}	5.70±0.44^{b}	6.12±0.08^{b}	7.17±0.15^{c}
Serum Albumin Concentration				
1	3.43±0.21^{a}	3.67±0.58^{ab}	3.17±0.15^{a}	3.80±0.10^{b}
7	3.43±0.21^{a}	3.10±0.17^{ab}	2.94±0.15^{b}	3.37±0.58^{ab}
21	3.43±0.21^{a}	2.93±0.21^{bc}	2.37±0.41^{b}	3.16±0.15^{ac}

Values are means of 5 replicates± Standard Deviation; Values carrying superscripts different from the control along the row are significantly different at (P= .05). Concentrations are expressed in g/dL.

3.2 Discussion

3.2.1 Phytochemicals

Medicinal plants elicit their actions due to the presence of diverse chemicals contained in them. Qualitative phytochemical screening of aqueous bark extract of *F. asperifolia* detected the presence of Alkaloids, Flavonoids, Terpenes/Steroids, Resin and Cardiac glycosides. The phytochemicals which were detected in the aqueous bark extract of *F. asperifolia* were the same with those detected in its aqueous stem extracts [8]. Interestingly, qualitative phytochemical analysis of the aqueous leaf extract of this plant revealed the presence of Tannins, Saponins, Balsam and Phenols which were not detected in the plant's stem and

bark [9]. Previous researches have implicated Alkaloids and Flavonoids fractions from different plants to possess antidiabetic, antihyperglycemic and antihyperlipidemic properties [19-21]. The results obtained in this study agree with those from such previous experiments.

3.2.2 Blood glucose concentration

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Alloxan is known to destroy the insulin-producing β-cell of the pancreas [22]. In consonance with many previous studies, intraperitoneal administration of alloxan in this study also led to a significant rise in blood glucose concentration [23-25]. However, administration of the plant extract decreased significantly the blood glucose levels in the diabetic rats. This result is similar to that obtained in a previous study done on the aqueous stem extract of this plant. The aqueous stem extract reduced blood glucose concentration in diabetic rats to normal levels [8], a feat not achieved by the aqueous bark extract. In this study however, blood glucose concentration of the diabetic rats move closer to being normal after continuous administration of the higher doses of the extract (Table 2). This may be attributed to the ability of the extract to increase uptake of glucose from the blood. The presence of Alkaloids and Flavonoids in the extract might be responsible for the blood glucose level lowering effect observed in this study. These phytochemicals have been reported in several similar experiments to possess hypoglycemic properties [20,26]. The mechanism of action of these phytochemicals were however not checked in this study but may be attributed to insulin-mimicking potentials, ability to either regenerate dead β-cells or induce more insulin production from surviving ones.

3.2.3 Serum lipid profile

Diabetes is a metabolic disorder associated with malfunction of glucose and lipid metabolism. Hypertriglyceridemia is one of the major abnormalities found in diabetes with insulin deficiency [27]. Insulin inhibits the activity of hormone-sensitive lipase in the adipose tissue, thus reducing the release of free fatty acid and glycerol [28]. The deficiency of insulin in diabetes mellitus therefore causes excessive mobilization of chylomicrons and VLDL leading to hypertriglyceridemia [28]. In this study, there was a compromise of normal lipid metabolism following alloxan administration, where Total Cholesterol, LDL and VLDL significantly increased while HDL significantly decreased. Administration of the extract restored significantly lipid metabolism in the experimental animals although not absolutely (Table 3). The result obtained in this study is in consonance with those obtained in previous works done on *F. asperifolia.* In the first work done on the aqueous stem extract, there was a reduction in Triglyceride, Total Cholesterol, VLDL and LDL while HDL was increased [8]. In the other work done on the effect of the aqueous leaf extract on cardiac enzymes and lipid profile in normal albino rats, the extract at the same doses used in this experiment reduced serum Triglyceride, Total Cholesterol and LDL in a dose and days-dependent manner while HDL was also increased [9].These confirm the hypolipidemic effect of the extract. The extract might have enhanced excess lipid uptake from the blood and also inhibit lipolysis. The observed effect might also be attributed to the presence of flavonoids in the plant bark which possesses lipid-lowering activity by increasing LDL oxidation resistance [19].

3.2.4 Serum alanine aminotransferase and aspartate aminotransferase activities

The liver is liable to injury caused by xenobiotics [29]. Aspartate Aminotransferase and Alanine Aminotransferase are liver marker enzymes which are predominant in the liver but

present only in the serum in minute concentrations. Serum levels of transaminases amongst other ubiquitous enzymes are known to be elevated in many different disease states, including cancer, myocardial infarction, viral and toxic hepatitis and muscular dystrophy [30]. An increase in serum levels of these enzymes is suggestive of leakage from the liver or any of the other principal sources into the serum as a result of tissue membrane damage. In this study a drastic significant rise in serum levels of AST and ALT was observed following administration of the extract (Table 4). This may be attributed to the ability of the extract to cause deterioration of hepatocyte membranes consequently leading to enzyme leakage. This result is consistent with previous research done on the aqueous stem extract of *F. asperifolia* [8] and other xenobiotics [29,31,32].

3.2.5 Serum total protein and albumin concentrations

Serum Total Protein and Albumin are synthesized in the Liver and are thus used as indices for measuring the synthetic function of the Liver [33]. Albumin plays important roles which include maintenance of oncotic pressure, transport of fatty acids, drugs and unconjugated bilirubin amongst others. A compromise of normal albumin metabolism is therefore detrimental. In this study there was a significant rise in serum total protein concentration while serum albumin significantly fluctuated. The extract might have caused excessive production of protein far beyond what is required and also cause a compromise of the liver's function of maintaining protein homeostasis. Both results are suggestive of the toxic effect of the extract at the doses tested.

4. CONCLUSION

Results available from this study shows that aqueous bark extracts of *F. asperifolia* possesses antidiabetic properties but also possesses hepatotoxic constituents. Further studies should be carried out to isolate and separate the active principle(s) from the toxic component(s) for optimum use.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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