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IN VIVO ANTIDIABETIC EFFECT OF A COMBINATION OF ETHANOL EXTRACT OF *FICUS CAPENSIS* AND *CNIDOSCOLUS ACONITIFOLIUS* LEAVES IN ALLOXAN-INDUCED DIABETIC RATS

Ezeigwe Obiajulu Christian*[1], Obayuwana Erhunmwense Ann[1], Iloanya Ebele Lauretta[1], Enemchukwu Benneth Nnanyelugo[2], Oguazu Chinenye Enoch[1], Anyaoku Ijeoma Cynthia[1], Ekwunoh Peter Okwukwe[3], Akpata Ebere Immaculata[4]

[1]Department of Applied Biochemistry, Faculty of Biosciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.
[2]Department of Science Laboratory Technology, Akanu Ibiam Federal Polytechnic, Unwana, P.M.B. 1007 Afikpo, Ebonyi State, Nigeria.
[3]Department of Biochemistry, Chukwuemeka Odumegwu Ojukwu University Uli, Anambra State, Nigeria.
[4]Department of Applied Biochemistry, Faculty of Applied Natural Sciences, Enugu State University of Science and Technology, Enugu State, Nigeria.

***Corresponding Author: Dr. Ezeigwe Obiajulu Christian**
Department of Applied Biochemistry, Faculty of Biosciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

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ABSTRACT

Aim and Objectives: The antidiabetic effect of a combination of ethanol extracts of *Ficus capensis* and *Cnidoscolus aconitifolius* leaves was studied in alloxan-induced diabetic rats. **Materials and Methods:** Fasting blood glucose levels were checked using One Touch glucometer and test strips. The lipid profile and liver function test of the experimental rats were determined using standard diagnostic test kits. **Results**: The result obtained showed a significant (p<0.05) reduction in the blood glucose levels of the experimental groups treated with the extract combination compared with the diabetic untreated group as well as the group treated with the standard drug, metformin. A significant (p<0.05) decrease in total cholesterol (TCHOL), low density lipoprotein (LDL), triglycerides (TRIG) and very low-density lipoprotein (VLDL) levels with a significant (p<0.05) increase in the levels of the high-density lipoprotein (HDL) were recorded in the extract treated experimental groups compared with the diabetic untreated group. Also, a significant (p<0.05) decrease in the levels of the various liver function test parameters, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and direct bilirubin (D.BIL) were recorded in the groups treated with the combined ethanol extracts of *F. capensis* and *C. aconitifolius* leaves compared with the diabetic untreated group. **Conclusion**: It can be concluded from the result obtained that the combined extracts of *F. capensis* and *C. aconitifolius* leaves possess antidiabetic effect without altering the lipid profile and liver function parameters of the experimental animals. These results suggest that the ethanol extract of a combination of *F. capensis* and *C. aconitifolius* leaves will be beneficial in the treatment and management of diabetes mellitus.

KEY WORDS: Diabetes, Alloxan, *Ficus capensis, Cnidoscolus aconitifolius*.

INTRODUCTION

All over the world today, one of the main health concerns is diabetes mellitus (DM). Diabetes mellitus is a metabolic disorder in the endocrine system associated with increased levels of blood glucose referred to as hyperglycaemia, over a long period of time resulting from abnormalities in resistance to insulin action and inadequate insulin secretion or both.[1][2][3] Information from the World Health Organization (WHO) showed that Nigeria has the largest number of people who are diabetic.[4] Shockingly, diabetes mellitus is not prevalent in rural communities alone. The case of its high incidence varies from 0.65% in rural Mangu of Northern Nigeria to 11% in Lagos which is an urban city situated in the Southern region of Nigeria.[5] It was also reported that the likelihood of diabetic patients in Nigeria is not less than 1.05 million persons and only about 198,000 managing their condition and about 225,000 Nigerians unaware of their state, with the incidence being on the increase in both males and females after the peak age of 45 years.[6] Experts propose that the number of people suffering from diabetes mellitus will be on the increase by 64% by the year 2025, which projects the fact that a whooping number of about 53.1 million citizens will be

living with the disorder.[7] The incidence of diabetes mellitus in adults as at 2010 was 285 million (6.4%) and it is said to be on the increase by 2030.[8][9]

Diabetes is characterized by diabetic ketoacidosis, kidney failure, foot ulcers, hyperosmolar coma, eye damage, cardiovascular problems and non-ketotic hyperosmolar coma. The disease state results from the action of insulin and abnormalities in carbohydrate metabolism leading to increased levels of glucose in the blood accompanied by symptoms such as increased hunger, thirst, lethargy, glycosuria and polyuria.[10][11] One of the most effective methods for the induction of diabetes is by the use of alloxan.[12] It is a popular chemical diabetogenic agent used for the induction of type 1 diabetes mellitus in experimental animals.[13][14] It is a dangerous glucose analogue that tends to deposit itself in large quantity in the β-cells through the glucose transporter 2 (GLUT 2). Alloxan causes the production of reactive oxygen species (ROS) in the presence of intracellular thiols particularly glutathione in cyclic redox reaction generating a reduced product called dialuiric acid whose auto-oxidation leads to the production of superoxide radicals, hydrogen peroxide radicals which finally leads to the destruction of β-cells which possesses low antioxidant defence potential. It also acts by inhibiting the β-cell glucose sensor glucokinase.[15]

Ficus capensis (Moraceae) commonly referred to as cape fig tree, bush fig, fig of heaven, is of the mulberry family of plants and it is native to tropical Africa and cape island. It is a fast growing deciduous or evergreen tree,[16][17] with a height usually ranging from about 5-12 meters but can also reach up to 35-40 metres. The leaves are big in size which are alternate and spirally arranged, ovate to elliptic possessing irregularly serrated margins. Fresh foliage is very reddish and papery with the bark of the young trees being light greyish white in colour and smooth.[18] In Nigeria, it is grown in all parts of the country but more common to the middle belt (North-central) of Nigeria and it is locally referred to as "Ogbaikolo" in "Igala", "Opoto" in "Yoruba",[19]"Akoro" in"Nsukka", "Uwaryara" in "Hausa", "Rimabichehi" in"Fulani"and "Obada" in"Edo".[20] It is used as vegetable in soup and yam pottage in different parts of Nigeria (South-east) [21]. It is used for the treatment of dysentery, wound dressing.[22] circumcision wounds, leprosy, rickets, Oedema, epilepsy, gonorrhoea, respiratory disorders, infertility[23], and abortion[24] which scientific researches has shown its anti-sickling[25], blood boosting[26], antibacterial[27], anti-abortifacient[25], immune-stimulatory[28], profertility in treating azoospermia[29], antioxidant[30], antidiarrheal[31], and the leaves has been reported to possess certain phytochemicals such as tannins, terpenids, flavonoids, cardiac glycosides and the ability in reducing blood sugar levels in the ethanol leaf extract.[32]

Cnidoscolus aconitifolius which is widely used for the treatment of many diseases locally belongs to the "Euphorbiaceae" family of plants. Colloquially, the plant is known as Chaya. It is known by a number of names in the western part of Nigeria which includes: "Efo", "Iyanaipaja" and "Efo Jerusalem" and is commonly called "hospital too far" in the Niger Delta region because of its various uses in disease treatment traditionally.[33] Its roots and leaves have been taken as laxatives, diuretic, and circulatory stimulant to improve digestion, improve lactation and strengthen fingernails.[34] It has been prescribed for a number of ailments and they include: digestion, obesity, hemorrhoids, kidney stones, eye problem, atherosclerosis, gall stones and high cholesterol.[35] The anti-bacterial, anti-diabetic and ameliorative effects of various extracts of *Cnidiscolus aconitifolius* on anaemia and osmotic fragility induced by protein energy malnutrition have been reported[36][37][38], with its phytochemical composition including: phenol, flavonoid, alkaloids, terpenoids and saponin.[39]

In this contemporary time, there is a renewed interest in the use of medicinal plants for the treatment of diabetes due to its easy affordability and minimal or no side effects compared to the conventional drugs. One of the main goals in developing anti-diabetic drugs is in the reduction of the blood sugar level and at the same time reducing the side effects to the barest minimum which is important in the management of the disease. One of the main ways of treating the disease includes but not limited to insulin and oral antidiabetic agents such as sulfonylureas, biguanides and glinides. These drugs do not however go without side effects and thus research continues for hypoglycaemic agents with little or no side effects and medicinal plants have remained a huge help in therapeutics having important phytoconstituents and an important alternative in combating different diseases plaguing the society.[40] Thus, the purpose of this research is the quest to discover anti-diabetic agents with little or no side effects, hence the anti-diabetic effect of the combination of *Ficus capensis* and *Cnidoscolus aconitifolius* in alloxan induced diabetic rats.

MATERIALS AND METHODS

Sample Collection and identification

The leaves of *Ficus capensis* were collected at Ibeagwa Nike, Enugu East Local Government Area (L.G.A), Enugu State. The leaves of *Cnidoscolus aconitifolius* were collected at Umueze town, Nkanu West L.G.A, Enugu State, Nigeria. The samples were authenticated by a taxonomist in the Department of Botany, Nnamdi Azikiwe University, Awka, Anambra State. The voucher number of *F. capensis* is 164 while that of *C. aconitifolius* is 168. The voucher was deposited at the herbarium of the Department of Botany, Nnamdi Azikiwe University, Awka.

Preparation of the Ethanol Extracts of *F. capensis and C. aconitifolius*

The leaves were hand-picked, thoroughly washed and air dried at room temperature for four weeks. The dried leaves were ground into powder using Corona manual grinding machine. Exactly 300g of the ground leaves powder of *F. capensis* and *C. aconitifolius* were respectively soaked in 1 Litre of 80% ethanol for 24 hrs for complete extraction. The ethanol extraction was sieved and filtered using Whatman no 1(125mm) filter paper. The filtrates were dried using water bath at 50^0C. The two extracts were reconstituted with distilled water in the ratio of 1:1 and administered to the experimental subjects.

Test Animals

Male Wistar albino rats were purchased from Chris Animal Farms and Research Laboratory, Awka, Anambra State and used for the experiment. They were maintained and housed in cages in the Department of Applied Biochemistry Laboratory, Nnamdi Azikiwe University, Awka. They were allowed to acclimatize with the environment for one week before use. The animals were kept on Vital growers' mash pellets purchased from Vital Feed Distributor at Awka, Anambra state and fed *ad libitum*. At the end of one-week acclimatization period, the animals were weighed, grouped and labelled.

Study Design

A total of twenty-five (25) male wistar albino rats were randomized into five (5) groups (n=5) and used for the study. The blood glucose levels of the rats were checked before the administration of alloxan using One Touch Glucometer (Life Scan, USA) and test strips based on the method of Trinder.[41] The rats were grouped as follows: Group A was the normal control, Group B was the negative control (diabetic untreated), Group C was the positive control (standard drug-Gluformin) 100mg/kg b.w., Group D was administered 100mg/kg b.w. ethanol extract of a combination of *Ficus capensis* and *Cnidoscolus aconitifolius* leaves and Group E was 200mg/kg b.w. ethanol extract of a combination of *Ficus capensis* and *Cnidoscolus aconitifolius* leaves.

Determination of Weight

The weights of the experimental subjects were checked using electronic weighing balance. The weighs of the rats were monitored before, during and after the experiment to know whether the combination of the extracts have effect in the body weight of the experimental rats during the treatment period.

Induction of Diabetes Mellitus

The blood glucose levels of the rats were checked before the administration of alloxan using one touch Glucometer and test strips. The rats were then fasted for 16 hours, but with free access to water after which they received an intraperitoneal injection of alloxan 150mg/kg body weight. The rats were orally given 5% glucose solution after 2 hours to prevent hypoglycemia. The animals were allowed free access to food and water after alloxan administration. After 48 hours of the alloxan administration, blood was collected *Orbito-rectally* and their glucose levels were checked. Diabetes was confirmed to have been induced when the glucose level was observed to be far much higher than normal (above 200mg/dl).

Lipid Profile

The lipid profile (Total Cholesterol (TCHOL), Triglycerides (TRIG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were determined using Randox test kits).[42] [43] Low density Lipoprotein-Cholesterol (LDL-C) was calculated using a standard formula from Friedwald, *et al*.[44] The procedure used was according to the manufacturer's instructions.

Liver Function Test

Serum biochemical indices routinely estimated for liver functions, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase (ALP) and bilirubin were determined using Randox diagnostic kits. The procedures used were according to the manufacturer's instruction.

Statistical Analysis

Data obtained from the experiments were analyzed using the Statistical Package for Social Sciences (SPSS) software for windows version 23 (SPSS Inc., Chicago, Illinois, USA). All the data were expressed as Mean ± SEM. Statistical analysis of the results obtained were performed by using ANOVA and POST-HOC Tests to determine if significant difference exists between the mean of the test and control groups. The limit of significance was set at $p<0.05$.

RESULTS AND DISCUSSION

Results

Table 1: Weight of diabetic rats measured weekly expressed as mean ± SEM.

Groups	Initial Weight 0 week	Weight (g) 1st Week	Weight (g) 2nd Week
Normal Control	124.2 ±1.562	138.4 ±3.530	147.6 ±2.441
Diabetic untreated	127.4 ±0.678	122.8 ±1.158	121.3 ±0.882
100mg/kg Gluformin	126.4 ±0.748	110.3 ±4.732	117.5 ±4.425
100mg/kg Extract	131.4 ±1.327	119.0 ±0.577	127.0 ±2.739
200mg/kg Extract	134.4 ±2.015	123.0 ±2.683	132.0 ±2.121

The weight of the rats significantly (p<0.05) decreased after the induction of diabetes as can be seen from week one (table 1). The weights increased in week two as a result of treatment with the different doses of a combination of the ethanol extracts of *F. capensis* and *C. aconitifolius* leaves. Better recovery was observed in the groups treated with the extract combination compared to the group treated with standard drug.

Table 2: Glucose profile of diabetic rats treated with a combination of *F. capensis* and *C. aconitifolius.*

Groups	Initial	Day 0	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15
Normal Control	80.00± 3.082	76.80 ±1.715	80.00 ±3.873	72.20 ±1.319	75.40 ±1.363	73.40 ±5.988	75.00 ±2.8809	79.40 ±2.731	73.60 ±2.158
Diabetic untreated	75.00± 1.22	499.00 ±51.53	576.00 ±21.58	593.60 ±3.867	569.60± 15.92	522.00± 26.56	524.3 ±67.34	479.66 ±46.81	564.6 ±20.91
100mg/kg Gluformin	77.00± 3.781	438.0± 52.09	482.0± 14.35	399.0± 29.98*	295.50 ±53.68*	311.5± 90.94*	303.7± 37.31*	290.2± 48.81*	322.8± 22.85*
100mg/kg Extract	78.60 ±76.25	491.2 ±31.32	472.2± 44.73	346.5± 45.09*	229.5± 28.38*	350.5 ±84.35*	213.2± 69.06*a	275.5± 48.79*a	268.5± 23.52*a
200mg/kg Extract	76.60 ±5.853	417.2± 39.10	510.2± 38.66	472.8± 38.41	227.8± 65.39*	227.6± 31.24*a	209.2± 46.84*a	211.8± 38.20*a	215.0± 24.37*a

*** *p*<0.05 Significant difference compared with the diabetic untreated. *a* p<0.05 Significant difference compared to 100mg/kg Gluformin (standard drug).**

The glucose profile of the various groups of experimental rats are represented in table 2. The result showed a significant (p<0.05) reduction in the blood glucose levels of the groups treated with the combined extracts (groups D and E) compared to the diabetes untreated group (group B) as well as a significant (p<0.05) reduction compared to the experimental group treated with a 100mg/kg body weight of the standard drug, gluformin with the highest reduction observed in the groups administered with 200mg/kg of the combined extracts.

Table 3: Lipid profile of diabetic rats treated with a combination of *F. capensis* and *C. aconitifolius.*

Groups	TCHOL (mg/dl)	HDL (mg/dl)	LDL (mg/dl	TRIG (mg/dl)	VLDL (mg/dl)
Normal Control	101.2 ±8.422	96.40 ±6.757	33.60 ±2.723	77.60 ±2.315	15.52 ±0.463
Diabetic untreated	199.0± 1.882	47.00 ±5.507	182.33 ±25.69	150.3 ±1.105	30.06 ±2.210
100mg/kg Gluformin	117.2 ± 3.682*	80.50 ±5.330*	52.45 ±3.893*	78.50 ±1.403*	15.70 ±2.807*
100mg/kg Extract	102.2 ±1.633*	67.75 ±1.099*	52.25 ±6.38*	88.75 ±6.088*	17.75 ±1.217*
200mg/kg Extract	106.4 ± 5.278*	83.60 ±3.501*	40.36 ±8.075*	84.80 ±10.38*	16.96 ±2.077*

*** P<0.05 Significant difference compared to diabetic untreated.**

The result showed an increase in total cholesterol (TCHOL), low density lipoprotein (LDL), triglycerides (TRIG) and very low-density lipoprotein (VLDL) levels with a decrease in the levels of the high-density lipoprotein (HDL) following the induction of diabetes (table 3). Upon treatment, it was observed that there was a significant (p<0.05) decrease in the total cholesterol (TCHOL), low density lipoprotein (LDL), triglycerides (TRIG) and very low density lipoprotein (VLDL) levels and a significant increase in the levels of the high density lipoprotein (HDL) in the treated experimental groups (groups C, D and E) as compared to the diabetic untreated group (group B).

Table 4: Liver function parameters of diabetic rats treated with a combination of *F. capensis* and *C aconitifolius* leaves.

Groups	ALT (U/L)	AST (U/L)	ALP (U/L)	T. BIL. (mg/dl)	D. BIL.(mg/dl)
Normal Control	9.800 ±0.374	12.20 ±1.428	93.60 ±3.187	6.300 ±0.0547	3.28 ±0.102
Diabetic untreated	27.33 ±1.453	34.67 ±2.603	178.3 ±6.89	13.201 ±1.539	11.80 ±0.1155
100mg/kg Gluformin	11.00 ±0.912*	11.75 ±1.377*	105.2 ±3.145*	7.225 ±0.125*	4.300 ±0.460*
100mg/kg Extract	8.500 ±0.645*	11.25 ±1.652*	139.5 ±5.85*	10.15 ±0.064*	6.025 ±1.993*
200mg/kg Extract	7.800 ±2.588*	9.000 ±0.894*	192.4 ±7.305	10.40 ±0.770	5.800 ±0.481*

*** P<0.05 Significant difference compared to diabetic untreated**

The result showed an increase in the liver function parameters as a result of the induction of diabetes (table 4). The alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (T.BIL.) and direct bilirubin (D.BIL.) concentrations were significantly (p<0.05) increased in the diabetic untreated group. A significant (p<0.05) decrease in these parameters were recorded in the group treated with 100mg/kg b.w of a combination of the

extract and the group treated with the standard antidiabetic drug.

DISCUSSION

The induction of alloxan caused a significant (p<0.05) decrease in the body weight of the experimental animals. Treatment with a combination of the ethanol extracts of *F. capensis* and *C. aconitifolius* for a period of two weeks increased the weight of the rats compared with the group that was diabetic untreated. However, treatment with the combined extract restored their body weights. Diabetes is usually associated with glycogenolysis, lipolysis, gluconeogenesis which eventually leads to muscle wasting and loss of tissue protein. The combined extract was seen to reverse this alteration thereby leading to the restoration of their body weights and this study correlates to the report documented involving treatment with the standard, glibenclamide (an antidiabetic drug) which upon use for treatment restored the body weight of the experimental animals just as in this present study.[45-49]

The blood glucose levels of the treated experimental rats were observed to significantly (p<0.05) reduce during the administration of the extracts compared to both the group treated with the standard drug and the untreated group with a continued increase in the blood glucose level of the untreated group. This thus shows that the extract possesses hypoglycemic property and this may be due to the individual hypoglycemic potential of each of the plant extract. This study agrees with earlier studies on *Cnidoscolus aconitifolius* and *Ficus capensis* by.[50] [51] [52] Presently, this is the first research that has studied the antidiabetic effect of both plants as a combination. There is no recorded report of the use of the combined extracts of *Ficus capensis* and *Cnidoscolus aconitifolius* leaves. The antidiabetic effect of the combination of the extracts may be due to their phytochemical constituents such as flavonoids, saponins and tannins as these phytochemicals have long been implicated as hypotensive, antihypercholesterol, cardiac depressant properties as well as blood glucose reducing agents which is probably achieved by the stimulation of insulin release from the pancreatic β-cells.[53] [54] [50]

The disorder also results in secondary complications that stems from hypercholesterol and triglyceride[55] and its management and treatment has been a major problem especially the case of elevated levels of triglycerides upon alloxan induction. An elevated level of TCHOL, LDL, VLDL and TRIG was observed with a decrease in HDL after the induction of diabetes. This observation before treatment agrees with the report of Akah *et al.*[55] on the effect of alloxan induced diabetes on lipid profile parameters. Report has it that increased levels of TRIG, LDL, VLDL has been associated with heart disease. But upon treatment, the combined extract led to a significant (p<0.05) reduction in the levels of TRIG, TCHOL, LDL, VLDL with a subsequent increase in HDL. This agrees with the report of the effect of *Ficus capensis* and *Cnidoscolus aconitifolius* on lipid profile which may be due to the saponin content which has been shown to have immense significance as an antihypercholesterol.[56] [57]

The liver is an organ involved in a lot of metabolic processes and as such prone to xenobiotic induced damages because of its importance in the metabolism of xenobiotics. The liver contains a lot of enzymes which include AST, ALT and ALP and their levels are used to decipher the functional status of the liver and as such serves as biochemical markers of the liver [55]. The result from the study showed an increase in these liver enzymes as well as D.BIL and T.BIL upon induction of diabetes indicating an abnormality in the functionality of the liver. Treatment with the combined extracts caused a significant (p<0.05) reduction in these parameters tested for compared to the diabetic untreated group. This agrees with the report of Mordi and Akanji which showed that *C. aconitifolius* has no hepatotoxic effect.[56]

CONCLUSION

Conclusively, results gotten from the study, revealed that the combined ethanol extract of *F. capensis* and *C. aconitifolius* leaves has antidiabetic effect and normalizes the lipid profile and liver function parameters in alloxan-induced diabetic rats. This suggests that the combined extract is beneficial and has a great potential in correcting sugar, lipid and liver abnormalities associated with diabetes and thus could be used in the management and treatment of diabetes mellitus.

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