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Original Article

Antidiabetic and Antidyslipidemic Activities of the Aqueous Extract of *Cochlospermum planchonii* Leaves in Streptozotocin-Induced Diabetic Rats

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Abstract

Background: Diabetes mellitus is considered one of the 5 principal causes of death in the world and is recognized as a global public health issue because of its multifactorial facets affecting essential biochemical processes in the body. This study investigated the antidiabetic and antidyslipidemic activities of the aqueous extract of *Cochlospermum planchonii (C. planchonii)* leaves in streptozotocin (STZ)-induced diabetic rats.

Methods: Thirty adult female rats (*Rattus norvegicus*) weighing 153±3.41g were randomized into 6 groups of 5 animals each. STZ-induced diabetic rats were orally administered 50, 100, and 200 mg/kg body weight of the extract, respectively, once a day, and their blood glucose levels as well as variations of diabetes-associated biomarkers including alpha amylase, glucose-6-phosphate dehydrogenase (G6PDH), and lipid profile by the extract were monitored for 21 days. The results were expressed as means±SEMs and compared with repeated measures using SPSS, Data Editor, version 16.0.

Results: The aqueous extract of *C. planchonii* leaves significantly reduced the blood glucose level in a dose-dependent manner, with the highest dose producing a 74.52% reduction after 21 days of administration, which compared significantly ($P<0.01$) with the control and metformin-treated groups. Similarly, STZ-induced diabetic mediated alterations in the serum lipids were significantly ($P<0.01$) restored by the extract. In addition, the aqueous extract of *C. planchonii* leaves significantly attenuated the decrease in the activity of G6PDH and the increase in the activity of α-AMY in the liver of the STZ-induced diabetic rats.

Conclusions: Overall, the aqueous extract of *C. planchonii* leaves could be used to manage diabetes and other related complications.

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Keywords ● *Cochlospermum planchonii* ● Plant Leaves ● aqueous extract ● Streptozocin ● Diabetes Mellitus ● Rats

What's Known

- Decoction of the aqueous leaf extract of *Cochlospermum planchonii* has been employed in folk medicine in Nigeria and other West African countries for the treatment of various kinds of diseases (e.g., infertility, diabetes mellitus, premenstrual pain, jaundice, hepatitis, worms, and bilharziasis) as well as other social and religious uses.

What's New

- Oral administration of the aqueous extract of *Cochlospermum planchonii* demonstrated hypoglycemic potential by reducing the blood sugar level in STZ-induced diabetic rats.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from deficiencies in the production of insulin, insulin action,

or a lack of both.[1] It is considered a modern-day prevalent condition and is rightly known as a global public health issue. This pandemic is characterized by excessive blood glucose due to the absence of insulin or by the ineffectiveness of the insulin produced to control the blood glucose level in animals.[2] Its complications cause debility in its sufferers and lead to numerous hospitalizations and huge financial burden.[3] Dineshkumar et al.[4] reported that the total number of people with diabetes was anticipated to be about 366 million in 2030. Chronic diabetes is associated with long-term damage, dysfunction and failure of organs, sexual inadequacies, loss of body weight, retinopathy, and nerve damage among others.[5] Presently, several classes of drugs such as insulin secretagogues, biguanides, thiazolidinediones, and α-glucosidase inhibitors are available but their use is linked with side effects.[6] Therefore, it is necessary to find an alternative in herbal medicines for the management of the disease because they are readily available, less expensive, and safer. One of the numerous herbal preparations used in the management and treatment of DM in Nigeria is the decoction of the aqueous extract of the leaves of the *Cochlospermum planchonii* (*C. planchonii*) plant.

C. planchonii (Cochlospermaceae) is referred to as "Ghehutu" or "Feru" among the Yorubas and as "Oboyo" among Ekiti people in Western Nigeria. It is a bushy-plant with bright yellow flowers of about 50 cm in height. This plant occurs widely throughout the tropical regions of the world, and the most common species in this family *(Cochlospermaceae)* are either mesophytic or xerophytic, growing primarily in drier climates.[7] The plant has been employed in folk medicine in Nigeria and other West African countries for the treatment of the different kinds of diseases as well as other social and religious uses which include the treatment of infertility, DM, and premenstrual pain as well as the management of jaundice,[8,9] elimination of worms, bilharziasis, and hepatitis in Senegal.[10] The bark of this plant is commonly used by the Ekiti people in Western Nigeria as rope.

Despite the acclaimed antidiabetic role of the leaves of *C. planchonii* in folklore medicine, it has not been documented scientifically. Therefore, the present study aimed to investigate the antidiabetic properties of the aqueous extract of *C. planchonii* leaves and to determine the pharmacological bases for its use in traditional medicine for the management of DM.

Materials and Methods

Plant Collection

The leaves of *C. planchonii* used were collected in Amoyo town, Ilorin, Kwara State, Nigeria. The plant material was identified and authenticated against the voucher specimen (UIH 001/923) at the Herbarium of the University of Ilorin, where it was deposited.

Metformin (MET, 14.2 mg/kg bwt) was obtained from Qianjin Pharm. Co. Ltd., China, and streptozotocin (STZ) and sucrose were purchased from Sigma-Aldrich (St. Louis, MO, USA). Assay kits of high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), total cholesterol (TC), triglycerides (TG), and glucose-6-phosphate dehydrogenase (G6PDH) were the products of Randox Laboratory Ltd. Dinitrosalicylic acid was also obtained from BDA, Germany. All the other chemicals and reagents were of the analytical grade and were prepared in glassware.

Preparation of the Extract

The leaves were air dried at room temperature to a constant weight and crushed to powder using an electric blender (Philip Comfort Blender, mode HR1727, Holland). The powdered leaves of *C. planchonii* (200 g) were soaked with 2000 mL of distilled water for 12 hours with intermittent shaking, filtered using Muslin cloth, and dried in the oven at 40 °C to give a yield of 10.25%. The dried extract was stored in an air-tight container at 4 °C until further use.

Phytochemical Screening

The aqueous extract of *C. planchonii* leaves was subjected to various qualitative and quantitative phytochemical screenings to detect the presence of the following bioactive principles: alkaloids, steroids, anthraquinones, cardenolides, phenols, flavonoids, tannins, triterpenes, glycoside, and saponins.[11]

Laboratory Animals

Thirty adult female albino rats, weighing between 153 and 3.41 g, were used for this experiment. The animals were obtained from the Animal House of the Biochemistry Unit of the Department of Biosciences and Biotechnology, Kwara State University, Malete, Ilorin, Nigeria. They were acclimatized for 14 days to standard housing condition (temp 28–20 °C), relative humidity of 40% to 45%, and 12-hour light (12-h dark cycle). Water and rat pellets were provided *ad libitum*.

Induction of Diabetes

The animals were made diabetic by a single intraperitoneal injection of 65 mg/kg body weight of STZ in citrate buffer (0.01 M, pH 4.5) after 18 hours of fasting (without food, but with water). On the 2nd day of induction (48 h), blood samples (0.6 µL) were drawn from the vein of their tails and glucose levels were determined to confirm the induction of diabetes using a glucose oxidase-based commercial glucometer (Accu-Chek Active, Roche Diagnostic). Only animals with a blood glucose level >190 mg/dL were considered diabetic and were used for the study. The blood glucose level of the animals was also determined before the administration of STZ using the same procedure.

Animal Grouping and Extract Administration

The 30 female albino rats were randomly divided into 6 groups (A–F) of 5 animals each.

- Group A (non-treated nondiabetic rats) received 0.5 mL of distilled water.
- Group B (non-treated diabetic rats) received 0.5 mL of distilled water.
- Group C (diabetic rats treated with the standard drug) received 1 mL of 14.2 mg/kg bwt of MET.
- Group D (diabetic rats treated with the extract) received 1 mL of 50 mg/kg bwt of *C. planchonii*.
- Group E (diabetic rats treated with the extract) received 1 mL of 100 mg/kg bwt of *C. planchonii*.
- Group F (diabetic rats treated with the extract) received 1 mL of 200 mg/kg bwt of *C. planchonii*.

The experiment lasted for 21 days. The animals were handled humanely in accordance with the guidelines of the Ethics Committee of Kwara State University, Malete, Nigeria, and the research adhered strictly to the Principles of Laboratory Animal Care (NIH Publication, No. 85-23).

Determination of Blood Glucose

The method described by Ortiz-Andrade et al.[12] was applied with slight modifications. The animals were fasted for 12 hours overnight (between 7 pm and 7 am) with free access to water. The blood glucose level in the rats was monitored on days 0, 1, and alternate days until the 21st day using a glucose oxidase-based commercial glucometer (Accu-Chek Active, Roche Diagnostic).

Biochemical Analysis

G6PDH activity, TG, TC, VLDL, LDL, and HDL were measured spectrophotometrically by using commercially available diagnostic kits and reagents obtained from Randox Laboratories (UK). Protein concentration was determined via the method described by Lowry et al.[13] and alpha amylase (αAMY).[14]

Statistical Analysis

The results were expressed as means±SEMs and compared using repeated measurements. P≤0.05 were considered statistically significant. The statistical evaluation was carried out using SPSS, Data Editor, version 16.0.

Results

Phytochemical Constituents

The preliminary phytochemical screening of the aqueous extract of *C. planchonii* leaves revealed the presence of cardenolides, phenolics, cardiac glycosides, saponins, terpenoids, flavonoids, tannins, and alkaloids, while anthraquinones and steroids were not detected (table 1). The quantitative phytochemical profiling of the aqueous extract of *C planchonii* leaves showed that the extract contained 23.71%, 41.07%, and 5.94% of flavonoids, phenolics, and tannins, respectively (table 2).

Blood Glucose Level

The treatment of the STZ-induced diabetic rats with different concentrations of 50, 100, and 200 mg/kg body weight of the aqueous extract of *C. planchonii* leaves resulted in a reduction in the blood glucose level in the same manner as

Table 1: Qualitative phytochemical screening of the aqueous extract of *Cochlospermum planchonii* leaves

Phytochemicals	Status
Alkaloids	+
Tannins	+
Anthraquinones	-
Flavonoids	+
Glycosides	+
Cardenolides	+
Phenolics	+
Terpenoids	+
Steroids	-
Saponins	+

+=Detected; –=Not detected

Table 2: Quantitative phytochemical analysis of the aqueous extract of *Cochlospermum planchonii* leaves

Phytochemicals	%Composition
Flavonoids	23.71±1.23
Phenolics	41.07±2.91
Tannins	5.94±1.32

that with the standard drug, MET. Nevertheless, the highest dose (Group F) produced the highest (74.52%) reduction in the blood glucose level of the diabetic rats after 21 days compared with the other groups. However, the rats receiving 50 mg/kg body weight compared significantly ($P<0.01$) well with the MET-treated rats, which produced a 53.82% reduction in the level of blood glucose in the STZ-induced diabetic rats at the end of the experiment (figure 1).

Alpha Amylase and Glucose-6-phosphate Dehydrogenase Activities

Table 3 depicts the activities of hepatic α-AMY and G6PDH in the diabetic rats treated with the aqueous extract of *C. planchonii* leaves. The activities of α-AMY in the livers of the rats receiving the standard drug and the extract were significantly reduced, whereas those of G6PDH were significantly increased ($P<0.01$) compared with the untreated diabetic rats (controls, Group B). In addition, there was no significant difference in the activities of α-AMY between all the extract-treated rats, whereas there was a significant increase in the activities of G6PDH of all the extract-treated rats, with the animals treated with the highest dose having the highest activity of all the groups. Furthermore, there were significant differences ($P<0.01$) in the activities of both α-AMY and G6PDH of the extract-treated rats when compared with the standard drug, except for the activity of G6PDH in the diabetic rats treated with the least concentration (50 mg/kg bwt, Group D), which was not significantly different (table 3).

Lipid Profile

The increase in serum TC, TG, LDL, and VLDL with a corresponding decrease in HDL in the diabetic controls (Group B) was significantly upturned by the aqueous extract of *C. planchonii* leaves in a dose-dependent manner. There were significant reductions ($P<0.01$) in the lipid profile of the diabetic rats treated with the extract compared with the standard drug, MET (table 4).

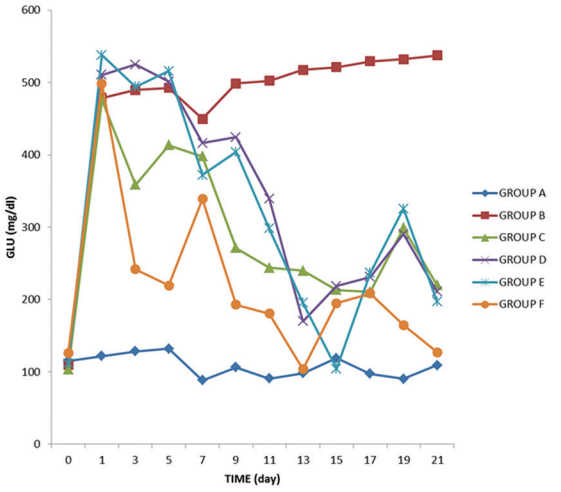

Figure 1: Antihyperglycemic effects of the aqueous extract of *Cochlospermum planchonii* leaves. A, B, C, D, E, and F are normal controls; diabetic controls; diabetics +14.2 mg/kg bwt of metformin; diabetics +50 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; diabetics +100 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; and diabetics +200 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves, respectively.

Table 3: Effects of the aqueous extract of *Cochlospermum planchonii* leaves on the activities of alpha amylase and glucose-6-phosphate dehydrogenase in the liver homogenate of streptozotocin-induced diabetic rats

Treatment	Alpha Amylase	Glucose-6-Phosphate Dehydrogenase
A	8.95 ± 1.42^{b}	161.90 ± 4.24^{e}
B	12.72 ± 0.12^{c}	66.81 ± 1.75^{a}
C	7.77 ± 0.86^{b}	128.90 ± 4.78^{b}
D	6.17 ± 0.47^{a}	126.30 ± 3.73^{b}
E	6.04 ± 0.18^{a}	136.04 ± 2.26^{c}
F	6.00 ± 0.72^{a}	972.50 ± 2.06^{d}

Values are expressed as the mean of 5 replicates±SEMs, values with different superscripts along the column are statistically different ($P<0.05$). A=Normal controls; B=Diabetic controls; C=Diabetics+14.2 mg/kg bwt of metformin; D=Diabetics+50 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; E=Diabetics+100 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; F=Diabetics+200 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves

Discussion

Plants have been known to be an exemplary source of drugs, and many currently available drugs have been directly or indirectly produced from medicinal plants.[5] Sulyman et al.[15] revealed that an extract from the plant can effectively reduce the glucose level in STZ-induced diabetic animals. *Cochlospermum spp.* are widely used by traditional medicine practitioners in Nigeria for the management of various ailments, and this health benefit has been documented in ethno-botanical reports and reviews.[5,16] The decoctions obtained from the tuberous roots of *Cochlospermum tinctorium,* a specie of *Cochlospermum*, are commonly and indifferently used by traditional healers to treat malaria and fevers.[16] *C. planchonii* has been previously shown to possess blood glucose-lowering effects in animal models.[5] However, there are no detailed scientific data to substantiate the antidiabetic properties of the aqueous extract of *C. planchonii* leaves, the common specie used among the traditional medicine practitioners

Table 4: Effects of the aqueous extract of *Cochlospermum planchonii* leaves on the lipid profile in the serum of the streptozotocin-induced diabetic rats

Group	TC	TG	LDL	VLDL	HDL
A	11.12±0.04^{b}	22.62±1.51^{b}	2.32±0.13^{b}	4.52±0.30^{b}	4.28±0.87^{c}
B	25.12±0.01^{e}	65.75±2.43^{e}	11.10±1.19^{e}	13.15±2.33^{d}	0.87±0.04^{a}
C	16.27±0.50^{d}	41.82±7.33^{d}	5.31±0.18^{d}	8.36±0.27^{c}	2.60±0.94^{b}
D	12.41±0.12^{c}	18.81±3.27^{a}	3.40±0.73^{c}	4.86±0.85^{b}	4.15±0.99^{c}
E	12.13±0.70^{c}	34.20±4.63^{c}	2.99±0.39^{c}	4.84±0.73^{b}	4.30±0.38^{d}
F	9.08±0.76^{a}	19.19±3.07^{a,b}	0.26±0.72^{a}	3.83±0.04^{a}	4.99±0.14^{c}

TC: Total cholesterol; TG: Triglyceride; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein; values are expressed as the mean of 5 replicates±SEMs, values with different superscripts along the column are statistically different (P<0.05). A=Normal controls; B=Diabetic controls; C=Diabetics+14.2 mg/kg bwt of metformin; D=Diabetics+50 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; E=Diabetics+100 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves; F=Diabetics+200 mg/kg bwt of the aqueous extract of *Cochlospermum planchonii* leaves

in the south west region of Nigeria. The phytochemical analysis of *C. planchonii* leaves revealed the presence of saponins, alkaloids, tannins, flavonoids, phenolics, glycosides, cardenolides, and terpenoids. These secondary metabolites may be responsible for various biological activities, including antidiabetic. A number of investigators have shown that the plant's polyphenolic compounds and a host of the other secondary metabolites of the plant possess hypoglycemic activities.[17-19]

Pancreatic β-cells are responsible for insulin production. STZ induces diabetes in animals by causing an almost complete destruction of pancreatic β-cells. Deficiency or massive reduction in insulin may cause hyperglycemia, which insulin only can reverse. The results of the present study indicated that the aqueous extract of *C. planchonii* leaves caused a significant reduction in the blood glucose level of diabetic rats. Similar reductions in the fasting blood glucose level of diabetic rats have been reported following the administration of medicinal plant extracts.[5,17-19] The observed reduction in the fasting blood glucose level may be attributed to high phenolics, a secondary metabolite found in the extract.[18] The results obtained from the present study showed that the reduction in postprandial glucose in the animals may have been associated with decreased glucogenic activity with a reduction in urea excretion or the inhibition of glycogenolysis as suggested by increased liver glycogen.[20]

αAMY is an enzyme which aids in the breakdown of starch to maltose by hydrolyzing bonds between glucose repeats. α-AMY is a metalloenzyme that is calcium-dependent. There are many digestive enzymes, and the most important one among them is pancreatic α-AMY, which acts as a catalysis in the reaction that involves the hydrolysis of the α-1,4 glycosidic linkages of starch, amylopectin, amylose, glycogen, and numerous maltodextrins and is also responsible for starch digestion.[21] The blood/brain barrier is impermeable to large molecules like starch and there is a need for glucose to reach the brain. Thus, to overcome this problem, α-AMY acts to cleave large starch molecules into smaller fragments of sugars in order to cross the blood/brain barrier. The excess conversion of starch to sugars by αAMY will eventually increase the sugar level in blood.[21] The hepatic α-AMY activities of the diabetic rats were repressed by the aqueous extract of *C. planchonii* leaves as well as the standard drug, MET. A decreased activity of this enzyme caused by the treatment of the rats with the extract and MET means that carbohydrate breakdown was hindered and this resulted in hyperglycemia.[22] Previous studies have demonstrated that the pharmacologically active components of plants such as vitamins, carotenoids, flavonoids, anthocyanins, and other phenolic compounds can reduce blood sugar by inhibiting α-AMY[23,24] and reducing numerous direct and indirect effects of various parameters which might be responsible for the development of diabetes.[25] The activity of G6PDH was significantly lower in the diabetic controls than in the treated diabetic and normal rats. G6PDH has also been found to decrease in the diabetic state.[26-28] This enzyme is located in the pentose phosphate pathway, a metabolic pathway that supplies reducing energy to cells (e.g. erythrocytes) by maintaining the level of the co-enzyme, nicotinamide adenine dinucleotide phosphate (NADPH). The decrease in the activity of this enzyme in the diabetic condition diminishes the reducing equivalent and increases oxidative stress,[29] leading to diabetic complications.[27] On the other hand, the hepatic G6PDH was boosted in the diabetic rats following the administration of the aqueous extract of *C. planchonii* leaves. The mechanism of the action of the aqueous extract of *C. planchonii* leaves is not yet known.

However, given its effects on α-AMY and G6PDH, the extract appears to increase the flux of glucose into the glycolytic pathway and hexose monophosphate shunt an alternative pathway of glucose metabolism to reduce the levels of glucose in blood. This will result in an increased production of the reducing agent, NADPH, with a concomitant decrease in oxidative stress.[29] This hypothesis is further supported by the decreased hepatic glucose level observed in the diabetic rats treated with the aqueous extract of *C. planchonii* leaves when compared with the untreated diabetic control rats.

Several studies have reported a rise in serum lipids such as TC and triacylglycerols, which is related to significant changes in lipid metabolism as a result of the induction of diabetes.[30,31] The aberrations in cellular cholesterol metabolism could be partly responsible for the alterations in serum cholesterol levels in diabetes as well as oxidative stress, which have been reported to increase the accumulation of lipids in cells.[31] The anomalies in lipid metabolism in diabetic conditions lead to variations not only in the levels of liver and serum lipids but also lipoproteins, which in turn play an important role in the manifestation of untimely and severe atherosclerosis, which affects patients with diabetes.[32] Thus, measurements of these parameters are essential to avert cardiac complications in diabetic conditions.[32] The major distinctive features of diabetic dyslipidemia are a high serum TG concentration and LDL cholesterol with corresponding low HDL cholesterol.[33] There is a need for therapeutic agents with both antidiabetic and anti-obese effects that will be of immense benefits.[34] The aqueous extract of *C. planchonii* leaves may serve these benefits. The administration of the standard drug and the aqueous extract of *C. planchonii* leaves led to a drop in TC, TG, LDL, and VLDL with a corresponding increase in HDL. Therefore, the aqueous extract of *C. planchonii* leaves shows that it may regulate lipid metabolism and prevent the upsurge of atherosclerosis and coronary artery disease.[35]

Conclusion

The findings from this study indicated that the oral administration of the aqueous extract of *C. planchonii* leaves demonstrated hypoglycemic potential in a dose-dependent manner comparable to the standard drug, MET. In addition, the aqueous extract of *C. planchonii* leaves mediated alterations in liver and serum TC, triacylglycerides, HDL, LDL, and VLDL in the STZ-induced diabetic rats. The study recommends that the aqueous extract of *C. planchonii* leaves may be used in the management of diabetes.

Conflict of Interest: None declared.

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