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Antihyperglycemic and Antihyperlipidemic Effects of Aqueous and Ethanolic Leaf Extracts of *Vitex doniana* in Streptozotocin-induced Diabetic Rats

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ABSTRACT

This study evaluated the effect of aqueous and ethanolic leaf extracts of *Vitex doniana*, against Streptozotocin (STZ) induced diabetic Wistar rats. Diabetes was induced with a single dose of Streptozotocin (60 mg kg⁻¹ b.wt. i.p), followed by treatment with aqueous and ethanolic leaf extracts of *V. doniana* (100 and 200 mg kg⁻¹ b.wt./day each), while metformin (25 mg kg⁻¹ b.wt./day) was used as standard drug. The body weights and blood glucose levels were determined at the end of every week. Serum lipid profile was determined at the end of the experiment and the treatments were carried out for twenty-one days, after which the animals were sacrificed by humane decapitation. The results showed that significant difference (p<0.05) in Fasting Blood Glucose (FBG) between the diabetic treatment groups and Diabetic Control (DC) was observed at day fourteen, which remained consistent until the end of the experiment. All Diabetic treatment groups showed significant reduction (p<0.05) in triacylglycerol and cholesterol compared to the diabetic control group. Aqueous extract treatment groups significantly increased (p<0.05) the HDL-cholesterol compared to the diabetic control group while ethanolic leaf extract treatment groups showed no significant difference (p>0.05) in HDL-cholesterol compared to diabetic control group. All diabetic treatment groups reduced LDL-cholesterol, except 100 mg kg⁻¹ b.wt. aqueous extract and 200 mg kg⁻¹ b.wt. ethanolic extract. There was a decrease in body weights in all diabetic treatment groups. These results suggest that aqueous and ethanolic leaf extracts of *V. doniana* possess antihyperglycemic and antihyperlipidemic activity in STZ-induced diabetic rats.

Key words: *Vitex doniana*, fasting blood glucose, diabetes, extract, treatment

INTRODUCTION

Diabetes is a group of metabolic alterations characterized by hyperglycemia resulting from defects in insulin secretion, action or both. It is a major degenerative disease in the world today, affecting at least 15 million people and having complications which include hypertension, atherosclerosis and microcirculatory disorders (Ogbonnia *et al.*, 2008). Research has shown that prevalence of diabetes is higher in developed countries than in the developing countries in the mid '90s (King *et al.*, 1998). At present, however, China, India and the USA have the highest cases of diabetes (Hu, 2011). However, it has been estimated that the number of adults with diabetes will increase to 300 million by the year 2025 (King *et al.*, 1998) and the world health organization predicts that the number will reach 366 million or more by the year 2030 (Wild *et al.*, 2004). It is

worrying to note that the major part of this numerical increase is expected to occur in developing countries where there is rapid urbanization, nutrition transition and increasingly sedentary lifestyles (Hu, 2011). Although, there is paucity of data on the prevalence of diabetes in Nigeria and other African countries, available data suggest that diabetes is emerging as a major health problem in Africa, including Nigeria (Mbanya *et al.*, 1996). It is the fourth leading cause of death in the most developed countries and there is substantial evidence that it is epidemic in many developing and newly industrialized nations. Patients with uncontrolled diabetes mellitus usually experience heart failure which indicates that hyperglycemia may be responsible for the disease (Okutan *et al.*, 2005). Hyperglycemia produces symptoms of polyuria, polydipsia and polyphagia. It is also associated with long term damage and failure of various organs such as eyes, kidney, liver, nerves, heart and blood vessels. Diabetes mellitus is associated with alteration in the plasma lipid and lipoprotein profile (Betteridge, 1997).

Although, several chemotherapeutic agents are currently used in the treatment and management of diabetes, the search for plant-based products for the control of diabetes continues. This could be attributed to the draw backs in the use of the chemotherapeutic agents such as cost, hypoglycemia, weight gain, gastrointestinal disturbances and liver toxicity (Prasad *et al.*, 2009). Unlike chemotherapeutic agents, however, herbal remedies have been reported to be non-toxic, accessible and affordable and represent the first line of treatment available for many of the world's population (Irudayaraj *et al.*, 2012; Okpara *et al.*, 2007).

V. doniana is widely used in Nigerian traditional medicine. It is used as medication for infertility, liver disease, anodyne, stiffness, leprosy, backache, hemiplegia, conjunctivitis, rash, measles, rachitis, hypertension, cancer, febrifuge etc. (Burkill, 2000; Sofowora, 1993). It also has significant analgesic and anti-inflammatory activities mediated through sequential inhibition of the enzymes responsible for prostaglandin synthesis from arachidonic acid (Iwueke *et al.*, 2006). Research report by James *et al.* (2010) on the hepatoprotective ability of aqueous leaf and stem extract of *V. doniana* showed that it was effective against carbon tetrachloride induced liver injury in rats. The anti-hypertensive effect of extract of stem bark of *V. doniana* has been reported by Ladeji *et al.* (1997). Extracts of stem bark of *V. doniana* have also demonstrated some level of *in vitro* trypanocidal activity against *Trypanosoma brucei brucei* (Atawodi, 2005). In addition, the aqueous and ethanolic leaf extracts demonstrated some level of pancreatic islet regeneration in Streptozotocin-induced diabetic rats (Okpe *et al.*, 2014). However, to the best of our knowledge, no work has been carried out to investigate the ability of the plant to lower blood glucose. Thus, the present study investigated the antihyperglycemic and antihyperlipidemic effects of the aqueous and ethanolic leaf extracts of *V. doniana* in Streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Plant samples collection and identification: Fresh leaves of *Vitex doniana* were collected from Ankpa, Kogi State, Nigeria in the month of April 2011. The plant was identified and authenticated at the Herbarium unit, Biological Sciences Department, Ahmadu Bello University Zaria, Nigeria, where a voucher specimen (900076) was deposited for future reference.

Experimental animals: Adult albino rats (140-220 g) of both sexes were obtained from the laboratory animal house, Department of Pharmacology, ABU, Zaria. The approval of the Ahmadu Bello University Animal Ethical Committee was obtained with an ethical number ABU/AEC/10167/2011. The animals were acclimatized for 2 weeks under standard environmental

conditions. The temperature and humidity were maintained at 25°C and 50%, respectively. Dark and light cycles were maintained at 12 h each. They had access to grower's mash (Vital feed, Grand Cereal Plc, Bukuru, Jos, Plateau State) and water *ad libitum*.

Preparation of plant sample: The collected plant leaves were rinsed in clean water and shade dried at room temperature for two weeks. The dry leaves were ground into powder using pestle and mortar. The powder obtained was then used to prepare extracts.

Aqueous extraction: To 100 g of powdered plant material, 500 mL portion of distilled water was added and then boiled in a conical flask for 2 h. After the set time, the suspension was filtered using cloth with fine pore and the filtrates were then concentrated in a crucible using a water bath set at 45°C and the weight of the sample taken. The concentrated extracts were then stored in an air tight sample bottle in a refrigerator until required for analysis.

Ethanol extraction: Five hundred grams of the powdered plant material was soaked in 2.5 L of 70% ethanol at room temperature in a conical flask for 72 h. After the set time, the suspension was filtered using cloth with fine pore and the filtrates were then concentrated in a crucible using a water bath set at 45°C and the weight of the sample taken. The concentrated extracts were then stored in an air tight sample bottle in a refrigerator until required.

Lethality (LD₅₀) test: The mean Lethal Dose (LD₅₀) of the aqueous and ethanolic extracts were determined in albino rat (weighing 150-200 g) using the method described by Lorke (1983).

Induction of diabetes: Diabetes was induced by a single intraperitoneal injection of Streptozotocin at 8°C (Sigma Chemicals Co., St. Louis U.S.A.) (60 mg kg⁻¹ body weight in 0.1 M citrate buffer pH 4.5) into 16-18 h fasted rats (Katsumata *et al.*, 1993). The Streptozotocin treated rats were kept for the next 24 h on 5% glucose solution bottles in their cages to prevent initial drug induced hypoglycemic mortality (Dhandapani *et al.*, 2002). After 96 h of Streptozotocin-injection, blood samples were collected by tail snip method and the sugar level of each animal determined. All rats with fasting blood glucose concentration of greater than 200 mg dL⁻¹ (11.1 mmol L⁻¹) were considered hyperglycemic (Burcelain *et al.*, 1995) and were selected for the experiment.

Animal grouping and treatment: The study was conducted in diabetic animals using the leaves extracts at an increasing dosage of 100 and 200 mg kg⁻¹ b.wt. by oral cannula.

The groupings are as follows:

Group 1: Normal rats not induced with STZ

Group 2: Diabetic control rats, intoxicated with 60 mg kg⁻¹ b.wt. of STZ

Group 3: Diabetic rats treated with an oral dose of ethanolic extract (100 mg kg⁻¹ b.wt./day)

Group 4: Diabetic rats treated with an oral dose of ethanolic extract (200 mg kg⁻¹ b.wt./day)

Group 5: Diabetic rats treated with an oral dose of aqueous extract (100 mg kg⁻¹ b.wt./day)

Group 6: Diabetic rats treated with an oral dose of aqueous extract (200 mg kg⁻¹ b.wt./day)

Group 7: Diabetic rats treated with metformin (25 mg kg⁻¹ b.wt./day)

Sub-chronic studies/collection and treatment of samples: The extracts were reconstituted in distilled water and administered orally on daily basis. The extracts groups were treated with either 100 or 200 mg kg⁻¹ b.wt., while the diabetic control and the normal were given distilled water for a period of 21 days. At the end of 21 days, the fasting blood glucose level of all the animals were taken, the animals were weighed and the animals were anaesthetized using chloroform and bled by cardiac puncture 24 h after the last treatment. The blood sample was collected in specimen bottles, allowed to clot and the serum separated by centrifugation at 3000× g for 10 min and then subjected to biochemical parameters analysis.

Biochemical analysis: The fasting blood glucose levels were determined based on glucose oxidase/oxidase principle, as described by Clark and Lyons (1962) using a digital glucometer (Accu-Chek Advantage II) after fasting the rats for 12 h. The packed cell volume was assayed according to the method described by Schalm *et al.* (1975). The serum levels of total cholesterol, triacylglycerol and HDL-c were determined by enzymatic method as described by Stein (1978), while the serum levels of LDL-c was measured according to the protocol of Friedewald *et al.* (1972).

Statistical analysis: Results are presented as Mean±Standard Deviation (SD). Within groups comparisons were performed by the analysis of variance (ANOVA) (using SPSS 17.0 for windows Computer Software Package). Significant differences in means between groups were compared using the Duncan's new multiple range test, a probability level of less than 5% (p<0.05) was considered significant.

RESULTS

Effect on glycemia: The effect of daily doses of aqueous and ethanolic leaf extract of *Vitex doniana* on blood glucose levels of Streptozotocin-induced diabetic rats are presented in Table 1. There was no significant difference (p>0.05) in Fasting Blood Glucose (FBG) between the diabetic treatment groups and Diabetic Control (DC) group on days zero and seven. However, at day fourteen, diabetic treatment groups have significantly lower (p<0.05) fasting blood glucose which continued until the end of the experiment (day 21). It is important to mention that there is no significant difference (p>0.05) in fasting blood glucose between the diabetic group treated with extracts and the standard drug (Metformin) treated group.

Table 1: Effect of aqueous and ethanolic leaf extracts of *V. doniana* on Fasting Blood Glucose (FBG) level of Streptozotocin-induced diabetic rats

Groups (n = 5)	Fasting blood glucose level (mg dL ⁻¹)			
	0 day	7th day	14th day	21st day
N	90.8±11.6 ^a	91.8±9.6 ^a	91.2±5.6 ^a	90.6±9.7 ^a
DC	406.6±106.3 ^b	420.0±20.1 ^b	438.0±48.4 ^b	441.0±64.1 ^c
DE-100	406.0±122.7 ^b	343.4±110.9 ^b	235.0±82.2 ^b	195.4±91.8 ^b
DE-200	416.8±90.4 ^b	342.0±62.0 ^b	267.2±37.2 ^b	217.2±32.5 ^b
DA-100	415.2±83.6 ^b	367.2±44.8 ^b	283.6±42.6 ^b	226.8±53.4 ^b
DA-200	412.6±67.7 ^b	387.4±66.6 ^b	293.6±32.7 ^b	246.8±53.1 ^b
D-Std	407.0±59.4 ^b	357.2±42.1 ^b	270.2±32.4 ^b	223.8±67.0 ^b

Values are presented as Means±SD of five replicate determinations. Values with different superscripts down the column are significantly different from each other at p<0.05, N: Normal rats, DC: Diabetic control rats, DA-100: Diabetic rats + Aqueous extract (100 mg kg⁻¹), DA-200: Diabetic rats + Aqueous extract (200 mg kg⁻¹), DE-100: Diabetic rats + Ethanolic extract (100 mg kg⁻¹), DE-200: Diabetic rats + Ethanolic extract (200 mg kg⁻¹) D-Std: Diabetic rats + Metformin

Table 2: Effect of aqueous and ethanolic leaf extracts of *Vitex doniana* on the lipid profile of Streptozotocin-induced diabetic rats

Groups (n = 5)	Serum TC (mg dL ⁻¹)	Serum TAG (mg dL ⁻¹)	Serum HDL-c (mg dL ⁻¹)	Serum LDL-c (mg dL ⁻¹)
N	76.09±11.42 ^a	76.87±14.19 ^a	27.32±4.87 ^b	33.32±12.47 ^a
DC	150.07±8.30 ^c	132.33±12.26 ^b	16.49±2.21 ^a	107.11±7.15 ^c
DE-100	107.59±3.49 ^b	78.71±14.09 ^a	20.84±3.62 ^a	71.01±3.70 ^b
DE-200	115.33±18.79 ^b	98.49±8.79 ^a	19.58±1.98 ^a	76.05±19.23 ^{bc}
DA-100	120.75±21.72 ^b	85.29±15.35 ^a	26.52±7.74 ^b	76.17±17.98 ^{bc}
DA-200	123.17±10.90 ^b	87.90±15.95 ^a	24.03±1.98 ^b	81.56±7.25 ^b
D-Std	108.36±8.73 ^b	79.99±9.25 ^a	26.84±4.04 ^b	65.53±8.83 ^b

Values are presented as Means±SD of five replicate determinations. Values with different superscripts down the column are significantly different from each other at p<0.05, N: Normal rats, DC: Diabetic control rats, DA-100: Diabetic rats + Aqueous extract (100 mg kg⁻¹), DA-200: Diabetic rats + Aqueous extract (200 mg kg⁻¹), DE-100: Diabetic rats + Ethanolic extract (100 mg kg⁻¹), DE-200: Diabetic rats + Ethanolic extract (200 mg kg⁻¹), D-Std: Diabetic rats + Metformin, TC: Total cholesterol, TAG: Triacylglycerol, HDL-c: High density lipoprotein, LDL-c: Low density lipoprotein

Table 3: Effect of aqueous and ethanolic leaf extracts of *Vitex doniana* on body weight of Streptozotocin-induced diabetic rats

Groups (n = 5)	Mean initial body weight (g)	Mean final body weight (g)	Change value (g)	Change (%)
NC	131.8±3.24	142.8±3.85*	11.0±0.61	18.35
DC	141.8±5.84	130.4±3.59*	11.4±2.6	18.04
DE-100	144.2±4.35	140.2±4.39	4.0±0.40	12.77
DE-200	131.8±4.14	130.6±4.48	1.2±0.34	10.91
DA-100	153.6±6.54	152.0±7.01	1.6±0.47	10.59
DA-200	149.4±8.44	144.2±8.77	5.2±0.33	13.48
D-Std	160.0±11.15	156.8±5.77	3.2±5.38	12.00

Values are Means±SD of five replicate determinations. *Across the row shows significant change between the initial and final body weight at p<0.05, †Increase, ‡Decrease, N: Normal rats, DC: Diabetic control rats, DA-100: Diabetic rats + Aqueous extract (100 mg kg⁻¹), DA-200: Diabetic rats + Aqueous extract (200 mg kg⁻¹), DE-100: Diabetic rats + Ethanolic extract (100 mg kg⁻¹), DE-200: Diabetic rats + Ethanolic extract (200 mg kg⁻¹), D-Std: Diabetic rats + Metformin

Effect on lipids: A study of the effect of sub-chronic administration of aqueous and ethanolic leaf extract of *V. doniana* on lipid profile of Streptozotocin-induced diabetic rats is shown in Table 2. The STZ-induced diabetic Wistar rats treated with extracts and the standard drug showed significant reduction (p<0.05) in serum cholesterol compared to the diabetic control. Diabetic treatment groups showed significant reduction (p<0.05) in triacylglycerol compared to the diabetic control group. Ethanolic leaf extract treatment groups showed no significant difference (p>0.05) in HDL-cholesterol compared to diabetic control group. However, aqueous extract treatment groups significantly increased (p<0.05) the HDL-cholesterol compared to the diabetic control group. All diabetic treatment groups reduced LDL-cholesterol, however, there is no significant difference (p>0.05) between 100 mg kg⁻¹ b.wt. aqueous extract treated group and diabetic control group. Same was observed for 200 mg kg⁻¹ b.wt. ethanol extract treated group which is not significantly different (p>0.05) from diabetic control group.

Effect on body weight: Table 3 shows the body weight of diabetic rats treated with aqueous and ethanolic leaf extracts of *V. doniana* and Metformin for 21 days. Like the diabetic control group, we observed a decrease in body weights in all diabetic treatment groups. It is only the normal group that had an increase in body weight. However, the decrease in body weight is most visible in diabetic control group (-8.04).

DISCUSSION

The relationship between diabetes and hyperlipidemia is a well-recognized phenomenon. Hypercholesterolemia and hypertriglyceridemia are independent major risk factors that, alone or together can accelerate the development of coronary artery disease (McKenney *et al.*, 2001). When rats are injected with Streptozotocin, they provide an animal model of insulin-dependent diabetes mellitus (Gandhi *et al.*, 2011). The intraperitoneal administration of STZ (60 mg kg⁻¹ b.wt.) selectively destroys the insulin secreting β -cells of the pancreas by breaking the DNA strand, resulting in decreased endogenous insulin release, causing activation of poly (ADP-ribose) polymerase (PARP) resulting in reduction of cellular NAD⁺ and cell death (Bolzan and Bianchi, 2003). In this present study, there was severe hyperglycemia in the experimental rats as a result of Streptozotocin induction in albino rats.

The results of the present findings demonstrated that aqueous and ethanolic leaf extracts of *V. doniana* induced significant reduction in Fasting Blood Glucose (FBG) level in Streptozotocin-induced diabetic rats suggesting that the extract can be used to reduce heart failure (Okutan *et al.*, 2005). This is in agreement with earlier reports by Murali *et al.* (2002). Some mechanisms proposed for the antihyperglycemia of plant extract include direct insulin-mimetic effect, enhanced secretion of insulin from the β -cell of the pancreas, or increased tissue uptake of glucose by enhancement of insulin sensitivity (Nandhini *et al.*, 2004; Ogawa *et al.*, 2005; Kim *et al.*, 2006).

Dyslipidemia is a metabolic disorder that constitutes a crucial risk factor of atherosclerosis and cardiovascular disease. Diabetes progresses with alteration in the serum lipid profile which can result in dyslipidemia (Betteridge, 1997; Durrington, 2003). It has been demonstrated that insulin deficiency in diabetes mellitus leads to accumulation of lipids such as total cholesterol and TGs in diabetic patients (Sharma *et al.*, 2011). In uncontrolled diabetes mellitus, increase in total cholesterol, triglyceride, LDL and VLDL cholesterol with decrease in HDL-cholesterol which contributes to coronary artery disease has been observed (Arvind *et al.*, 2002). The STZ-induced diabetic rats showed increase in the cholesterol, LDL cholesterol and triglyceride concentrations. Administration of our extracts and metformin reduced the total cholesterol, triglyceride, LDL cholesterol and improved HDL cholesterol level which is in agreement with the works of Twajj and Al-Badr (1988). This effect is of significant value since serum lipids profile is an important risk factor to many diseases like diabetes, hypertension, etc (Ghosh *et al.*, 2006). The hypocholesterolemic activity of the extracts may be due to a number of mechanisms: Inhibition of HMG-CoA reductases, stimulation of Cholesterol-7-alpha-hydroxylase which converts cholesterol into bile acids, or inhibition of cholesterol absorption from the intestine due to formation of complexes with compounds such as glycosides and saponins (Chen *et al.*, 2004). A reduction in triacylglycerol level may be due to decreased lipogenesis, increased lipolytic activity by inhibition of hormone-sensitive lipase or the lipogenic enzymes (Pari and Venkteswaran, 2004) or activation of lipoprotein lipase as have been proposed for some anti-diabetic plants (Al-Shamaony *et al.*, 1994; Ahmed *et al.*, 2001; Sharma *et al.*, 1997) exhibiting hypoglycemic activity as observed in this present study.

Loss of body weight is a major consequence of diabetes in rats (Ramachandran *et al.*, 2012). The loss of body weight could be due to dehydration and catabolism of fats and protein (Rajkumar *et al.*, 1991). The improved body weight obtained in this research is in agreement with the work of Ambika *et al.* (2013). The prevention of loss in body weight by the extracts may be due to increasing glucose uptake in peripheral tissues or inhibition of catabolism of fat and protein by

good glycaemic control (Ambika *et al.*, 2013). A similar effect of *Artemisia herba-alba* on body weight of diabetic rats has been observed by Twaij and Al-Badr (1988) and Ramachandran *et al.* (2012). We also observed a significant reduction in food and water intake in the extract treated groups, whereas an increased in food and water intake was observed in the diabetic control.

CONCLUSION

The results of the present study show that aqueous and ethanolic extracts of *V. doniana* leaves have antihyperglycemic effect on STZ-induced albino Wistar rats. Since, many antidiabetic drugs do not correct dyslipidemia, the observed hypolipidemic effect of the plant extract in these STZ-induced diabetic rats, makes *V. doniana* quite important in the management of cardiovascular complications associated with diabetes.

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