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Anti-hyperglycemic and Anti-hyperlipidemic effects of Hydroethanol Leaf and Stem Extracts of *Vitex doniana* in Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author FOA designed the study, carried out the investigation and prepared the original draft; author REJ managed analysis of the study, participated in the investigation; author DOA performed the statistical analysis, managed the literature searches; author SMS wrote the protocol, participated in the investigation and analysis of data. All authors read and approved the final manuscript.

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ABSTRACT

Anti-hyperglycemic and anti-hyperlipidemic effects of hydroethanolic leaf and stem extracts of *Vitex doniana* on alloxan induced diabetes in rats was evaluated. Thirty (30) male rats were assigned to five (5) groups of six (6) rats each as follows: Group I served as normal control rats and were fed with standard feed and water *ad libitum*, Group II was induced with diabetes by single intraperitoneal injection of freshly prepared alloxan [150 mg/kg body weight (BW)] to overnight fasted rats but received no treatment, Group III-V were induced with alloxan and treated with 5 mg/kg BW standard drug glibenclamide, 300 mg/kg BW leaf extract and 300 mg/kg BW stem extract of *Vitex doniana* respectively. The results revealed that the leaf and stem extracts had anti-hyperglycemic activity similar to glibenclamide. Analysis of lipid profile showed that whereas alloxan induced increase in the concentration of total cholesterol, low density lipoprotein and triglycerides, hydroethanolic leaf and stem extracts caused a significant decrease ($p<0.05$) in the these biomarkers compared to the control. The outcome of this study portrayed that hyperglycemia and hyperlipidemia caused by the alloxan can be mitigated by administration of extracts of *Vitex doniana*.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder, characterised by sustained increased levels of blood sugar ensuing from either a deficiency in insulin production or inability to utilise insulin and consequently, distortion in carbohydrate, protein and lipid metabolism [1]. Diabetes mellitus is characterised by recurrent urination, increasedthirst and appetite [2]. Other associated problems are diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death [3]. Long-standing complications of DM include cognitive impairment and sexual dysfunction, cardiovascular ailment, chronic kidney disease, stroke, nerve damage, damage to the eyes and ulcer of the foot [4].

Based on reports by the World Health Organisation (WHO), DM can be categorized into three broad types namely, type 1 which is result of inability of pancreas to produce adequate insulin due to loss of beta cells. Type 2 typified by resistance to insulin, a situation that causes inability of cells to properly respond to insulin. The third type which is called gestational diabetes occurs in pregnant women; typified by high blood glucose levels in pregnant women without a history of diabetes [2].

According to Vos et al. [5] and IDF Diabetes Atlas [6], up to 8.8% of the adult population globally comprising of 463 million people had diabetes in 2019 and 90% of the cases were type 2 diabetes. Trends projects that the rates will continue to increase and increases an individual's chances of dying early [2]. In 2019, diabetes contributed to an estimated 4.2 million deaths, which made it the 7th leading cause of death worldwide [7]. The estimated comprehensive financial cost of expenditures related to diabetes in 2017 was US$727 billion in the United States [8].

Many drugs are presently available for the management and treatment of diabetes, however, the search for natural plant products to control and treat diabetes continues to be heartbeat of the researchers. This is in part due to the side effects that accompany the use of synthetic drugs as well as the high cost of such drugs [9]. In addition, plant based remedies have been reported to be available and affordable, non-toxic and are the first line of treatment for many of the world's population [10,11].

Vitex doniana belong to the family of Verbenaceae, a deciduous tree with a weighty round crown and a distinct bole up to 5m. The plant is called Black plum in English, Dinya in Hausa, Ikoriri in Yoruba, Ucha koro in Igbo [12], Ejiji in Igala and Ozunchi in Ebira. It has many medicinal uses which consist of treatment against mental diseases, rheumatoid arthritis, gastrointestinal disturbance, urinary disorders, and as tranquilizer and anthelmintic [13]. The study by Kilani [14] established the antibacterial activity of the stem bark of *Vitex doniana* and evaluated its efficacy in managing gastroenteritis infections and dysentery. Njoku et al. [13] using alloxan-induced diabetic rats, demonstrated the antidiabetic potential of the leaf extracts of *Vitex doniana*. *Vitex doniana* is used in treatment and management of hypertension, liver illnesses, hemiplegia, infertility, cancer, anodyne, febrifuge stiffness, conjunctivitis, measles, rash, leprosy, backache, and rachitis [15]. Previous reports have reported the abundance of flavonoids, tannins, saponin, sterols and triterpenes, phenols cardiac glycosides, and high concentrations of iron, potassium, sodium, phosphorus, calcium and sulphur in extracts of *Vitex doniana* [13]. The ethanolic and aqueous leaf extracts has been shown to have potentials for the regeneration of pancreatic islet in diabetic rats induced with streptozotocin [16]. This present study was designed to investigate the anti-hyperglycemic and anti-hyperlipidemic effects of 80 % ethanol extracts from leaf and stem bark of *Vitex doniana*.

2. MATERIALS AND METHODS

2.1 Chemicals and Drugs

Diagnostic kits from Randox Diagnostics (UK) were purchased for total cholesterol (TC), creatinine, high density lipoprotein (HDL), urea and triglyceride (TG). Alloxan was procured from Sigma (St. Louis, Germany). Accu-check Glucometer was a product of Roche Diagnostics (Germany). Glibenclamide and other chemicals used in this work were of analytical grade.

2.2 Plant Collection, Identification and Processing

Leaves and stem of *Vitex doniana* were sourced from Anyigba, Nigeria, and identified at the Biological Sciences Department of Kogi State University Anyigba, Nigeria and the voucher

specimen was deposited in the department's herbarium with Voucher No. 33;230. The plant parts were washed, dried at room temperature and pulverized using a blender. The pulverized plant sample was soaked in 80% ethanol for 24 hours before filtration. Rotary evaporator was used to concentrate the filtrate.

2.2.1 Phytochemical analysis

Qualitative phytochemical analysis was carried out according to methods of Sofowora [17], Trease and Evans [18] and Harbone [19].

2.2.2 Experimental animals

Male experimental rats whose average weight was 160 g were used for the study. The rats were housed in the Animal Care Facility of Biochemistry Department, Kogi State University Anyigba, Nigeria. The animals were acclimatization for seven days preceding the experimentation. During the period, the rats were fed standard (pelletized grower's mash) commercial feed and water *ad libitum*.

2.2.3 Induction of diabetes

The rats were fasted overnight after which freshly prepared alloxan (150 mg/kg body weight) was injected intraperitoneally. Forty-eight hours after induction, the fasting blood glucose level of the animals were determined, and animals whose blood glucose level were greater than or equal to 250 mg/dL were considered diabetic.

2.2.4 Experimental design

Animals that survived the alloxan-diabetes induction were allocated into five groups comprising of five rats each as indicated thus: Group I comprised of normal control rats, Group II were the diabetic untreated rats, Group III were diabetic rats (DR) treated with 5 mg/kg BW glibenclamide, Group IV were diabetic rats treated with 300 mg/kg BW leaf extracts of *Vitex doniana*, and the final Group V comprised of diabetic rats treated with 300 mg/kg BW stem extracts of *Vitex doniana*. Animals were treatment as stated above for 21 days. All animal groups were offered standard feed and water *ad libitum.*

2.2.5 Biochemical assays

The fasting blood glucose level of the experimental animals was monitored by the glucose oxidase method, aided by an Accu-check glucometer. On the 22nd day of experimentation, the rats were sacrificed. Plain bottles were used for the collection of blood samples. Following the manufacturer's instructions (Randox Diagnostic kits), biochemical assays were carried out to determine the levels of total cholesterol (TC), creatinine, high density lipoprotein (HDL), urea and triglyceride (TG).

2.3 Statistical Analysis

Statistical analyses were carried out to determine Mean values, Standard Deviations and Analysis of Variance using the Graphad Instat Software. Variations between mean values were considered significant at $p<0.05$.

3. RESULTS AND DISCUSSION

The study being reported investigated the effects of hydroethanolic extracts of leaf and stem of *Vitex doniana* on hyperglycemia and dyslipidemia induced by alloxan in rats. Preliminary phytochemical analysis of the extracts disclosed the existence of tannins, phenolic compounds, flavonoids, saponins and terpenoids. The results complement those of Aiwonegbe et al. [20] and Agbafor & Nwachukwu [21] that reported the phytochemical analysis of acetone and methanol fruit pulp extracts of *Vitex doniana* and hydroethanol leaf extract of *Vitex doniana* respectively. Other plants reported to be rich in phytochemicals have demonstrated enormous medicinal value [22]. Blood glucose of the diabetic rats was monitored for 21 days so as to determine the effect of the plant extracts on alloxan induced hyperglycemia. As expected, hyperglycemia continued in the diabetic rats unabated as compared to the normoglycemic rats. However, animals administered glibenclamide, leaf or stem extracts of *Vitex doniana* showed progressively decreasing Fasting Blood Glucose level from the second day post induction until day twenty-one (Fig. 1). This outcome shows that hydroethanol extracts of *V. doniana* possess compounds with anti-hyperglycemic properties. Some related studies have proposed mechanisms of action of anti-hyperglycemic plants. These include but not limited to modulation of enhanced secretion of insulin from the β-cells of the pancreas, uptake of glucose by improvement of insulin sensitivity, and as well as direct insulin-mimetic effects [23,24].

Dyslipidemia is a common complication of diabetes. In fact, dyslipidemia can result in other clinical conditions that affect the cardiovascular system [25,26]. Sharma et al. [27] and Arvind et

al. [28] reported that insulin deficiency may lead to the accumulation of triacylglycerol and total cholesterol in diabetics. It has been established that there is direct relationship between diabetes and hyperlipidemia. According to Mc Kenney et al. [29], hypertriglyceridemia and hypercholesterolemia are autonomous key risk factors that, alone or synergistically can stimulate the development or promote the progression of coronary artery diseases.

Screening antidiabetic plants based on their ability to maintain a healthy variety of blood lipids is common practice among ethnopharmacologists. In this study, the effect of hydroethanolic extracts from leaves and stem of *Vitex doniana* on dyslipidemia was evaluated in diabetic rats. Fig. 2a-d shows the effect of the extracts on total cholesterol, high density lipoprotein, low density lipoprotein and triglycerides respectively. Alloxan induced significant increase ($p<0.05$) in the concentration of total cholesterol (TC), low density lipoprotein (LDL) and triglycerides (TAG) whereas the high density lipoprotein (HDL) levels decreased compared to normal control rats. The extracts were more effective at reducing the concentration of TC and LDL than the standard antidiabetic drug glibenclamide ($p<0.05$). In contrast, only the stem extract group showed significant decrease in TAG level ($p<0.05$). The hypocholesterolemic property of the extracts may be due to but not limited to the following mechanisms: inhibition of absorption of cholesterol from the intestine owing to development of complexes with compounds like saponins and glycosides, inhibition of HMG-CoA reductases, or the stimulation of cholesterol-7-alpha-hydroxylase, the enzyme responsible for the conversion of cholesterol into bile acids [30]. A decrease in TAG level may have occurred due to reduced lipogenesis, improved lipolytic activity by inhibition of the lipogenic enzyme or the hormone-sensitive lipase [31], or by the stimulation of lipoprotein lipase as seen with some anti-diabetic plants [32,33] which exhibit hypoglycemic properties as observed in this study.

The findings of this work also revealed significant variations in the lipid profile of animal groups treated with either leaf or stem extracts. For instance, leaf extract was significantly better at decreasing LDL level and increasing HDL level ($p<0.05$) while the stem extract significantly lowered the total cholesterol and TAG when compared with the group administered leaf extract. These points to the fact that the extracts used for the study modulate dyslipidemia via diverse pathways.

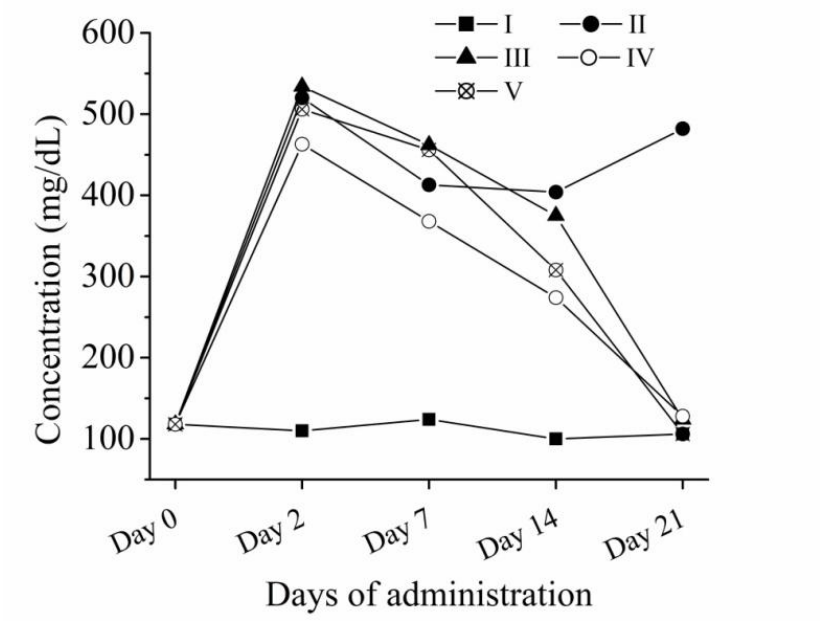

Fig. 1. Blood glucose concentration of diabetic rats treated with extracts of *Vitex doniana*

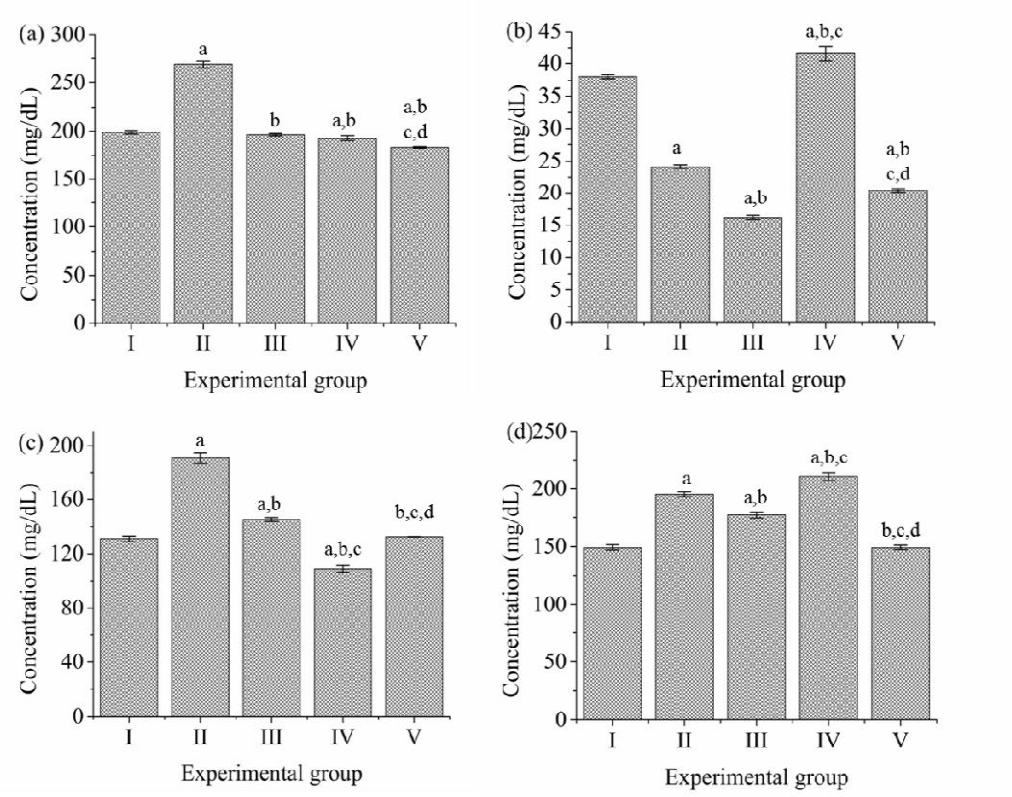

Fig. 2. Effect of leave extracts of *Vitex doniana* on concentration of total cholesterol (a), high density lipoproteins (b), low density lipoprotein (c) and triglycerides (d) in diabetic rats

[a]p<0.05 vs normal control; [b]p<0.05 vs untreated;[c]p<0.05 vs glibenclamide; [d]p<0.05 vs leave extracts of Vitex doniana; n=5

4. CONCLUSION

The study revealed that the extract of *Vitex doniana* is effective in treatment and management hyperglycemia and dyslipidemia associated with diabetes mellitus.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

For the use of number of rats employed in this work, ethical approval was given by the Kogi State University Ethical Clearance Committee

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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