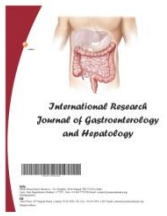

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Antidiabetic Potential of Alkaloid Extracts from *Vitex doniana* and *Ficus thonningii* Leaves on Alloxan-induced Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The growing number of diabetes coupled with the harsh side effects of some synthetic drugs has led to the increasing search for alternatives which are relatively cheap with minimal side effects.
Aim: This study sought to investigate the antidiabetic potential of alkaloid extracts from *Vitex doniana* and *Ficus thonningii* leaves on alloxan-induced diabetic rats.
Methods: Fresh leaves of *V. doniana* and *F. thonningii* were obtained from a local market Nkwagu in Abakaliki local government area of Ebonyi State. They were washed thoroughly in running water to remove contaminants. They were separately air-dried at room temperature for two weeks. The dried leaves were pulverized to fine granules using manual grinder. Crude alkaloid was extracted using standard method. The acute oral toxicity of both plants was determined. Diabetes was induced in forty male rats intra peritoneally with alloxan at a dose of 120 mg/kg body weight. The

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rats were grouped into eight groups of five animals per group: Groups 1 and 2 were treated with 200 and 400 mg/kg body weight of *V. doniana* respectively, groups 3 and 4 were treated with 200 and 400 mg/kg body weight of *F. thonningii* respectively, group 5 was treated with 100 mg/kg of *V. doniana* + 100 mg/kg of *F. thonningii*, group 6 was treated with 200 mg/kg of *V. doniana* + 200 mg/kg of *F. thonningii*, group 7 animals were not induced with alloxan and untreated (normal control) while group 8 were induced with alloxan but not treated (diabetic control). The extracts were administered to the animals orally for 30 days. The animal's blood sugar levels and lipid profile were assayed using standard methods.

Results: Both extracts significantly reduced blood glucose level when compared with those of diabetic control at $p<0.05$. The extracts also favourably perturbed the lipid profile of animals.

Conclusion: The present study suggests that both *V. doniana* and *F. thonningii* leaves be potent antidiabetic property. They could also reduce the risk of obesity and hypertension due to its hypolipidemic effect.

Keywords: Vitex doniana; Ficus thoningii; blood glucose concentration; lipid profile; antidiabetic potential.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by ineffectiveness of insulin produced. Such a deficiency results in increased concentration of glucose in the blood, which in turn damages many of the body's systems in particular the blood vessels and nerves [1]. As the number of the people with diabetes multiplies worldwide, the disease has taken an ever-increasing share of national and international health care budgets. It is projected to become one of the world's main disablers and killers within the next 25 years. Regions with greatest potential are Asia and Africa, where DM rates could rise to two-to-three-folds compared with the present rates. Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes.

Alkaloids, widely existing in natural plants, are compounds containing nitrogen atoms. Most alkaloids are pharmacologically active ingredients in many medicinal plants due to their significant physiological activity. Many alkaloids can be extracted from natural plant materials and purified by modern separation techniques [2]. Recent studies showed that simple alkaloid extracts have efficacy against viruses including *herpes simplex* [3] and human immunodeficiency virus (HIV) and tumors [4].

Vitex doniana, a member of Verbenaceae family is a medium-sized deciduous tree with a heavy rounded crown and a clear bole up to 5m. It is widely distributed in the Eastern and Western parts of Nigeria. The plant commonly called Black plum (English), Dinya (Hausa), Oriri (Yoruba), and Ucha koro (Igbo), is a deciduous ever green tree, usually 4-8 metres high occasionally up to 15 metres with a dense rounded crown [5]. Medical applications include treatment against mental illness, rheumatism, as anthelmintic` and tranquilizer, gastrointestinal disturbance, urinary ailments and so on [6]. Also Kilani [7] have assessed the stem bark of *V. doniana* for antibacterial activity and establish its efficacy in the management of dysentery and gastroenteritis infections. The root is used for treatment of gonorrhea, and women drink a decoction of it for backaches [6]. Phytochemical analysis of the various parts of the plant extract revealed the presence of saponin, tannins, phenols cardiac glycosides, flavonoids, sterols and triterpenes as well as high concentration of sodium, Potassium, Calcium, Iron, Phosphorus and Sulphur [8].

Fig. 1. *Vitex doniana* leaves [5]

Ficus thoningii, also known as common wild fig is an evergreen tree with a rounded to spreading, dense crown; it can grow 6 - 21 metres tall [9].

The plant often begins life as an epiphyte, growing in the branch of another tree; as it grows older it sends down aerial roots which, when they reach the ground quickly form roots and become much thicker and more vigorous. They supply nutrients to the fig, allowing it to grow faster than the host tree. The aerial roots gradually encircle the host tree, preventing its main trunk from expanding, whilst at the same time the foliage smothers the foliage of the host. Eventually the host dies, leaving the fig to carry on growing without competition. It eventually becomes a stilt-rooted, banyan-like tree with multiple ascending trunks and massive wide-spreading branches [10]. The bark is important in local medicine, and it is used in treating colds, sore throat, dysentery, wounds, constipation, nosebleed and to stimulate lactation. Extracts of the bark are used in baths as a treatment of nervous illnesses, tuberculosis, paralysis and leprosy. The latex is used for wound fever [11]. The milky latex is dropped into the eye to treat cataracts. An infusion of the root and fibre is taken orally to help prevent abortion. The powdered root is taken in porridge to stop nose bleed.

Fig. 2. *Ficus thoningii* leaves [10]

Diabetes mellitus is a chronic disease with serious health complications and is now one of the most common non-communicable diseases globally. It is the fourth leading cause of death in most developed countries. Recently, there has been a growing interest in anti-diabetic agents from natural products especially those derived from plants. The interest in anti-diabetic agents has been focused on plants used in traditional medicine because they may be better treatment than currently used synthetic drugs. Therefore, this study sought to investigate the anti-diabetic properties of alkaloid extracts from *V. doniana* and *F. thonningii* leaves on alloxan-induced diabetic rats.

2. MATERIALS AND METHOD

2.1. Extraction of Alkaloid from the Plants

Fresh leaves of *V. doniana* and *F. thonningii* were obtained from a local market Nkwagu in Abakaliki local government area of Ebonyi State. They were identified by Prof. F. N. Mbagwu, a plant taxonomist at the Department of Plant Science and Biotechnology, Imo State University, Owerri, Nigeria. They were washed thoroughly in running water to remove contaminants. They were separately air-dried at room temperature for two weeks. The dried leaves were pulverized to fine granules using manual grinder. Crude alkaloid was extracted according to [12]. Five hundred grams (500 g) of each plant leaf sample was weighed separately into a 250 ml beaker and 200 ml of 10% acetic acid in ethanol was added and covered and allowed to stand for 6 hrs. This was filtered with Whatman filter paper No.1. The extract was concentrated on a water bath to one-quarter of the original volume. Concentrated ammonium hydroxide was added to the extract drop wisely until the precipitation was complete. The whole solution was allowed to settle and the precipitate was collected and washed with dilute ammonium hydroxide and then filtered. The separate residues were further tested using Dragondoff's reagent which gave an orange colour solution to confirm the presence of alkaloid. The extracts were dried and stored in the refrigerator for further analysis.

2.2 Acute Oral Toxicity Studies (LD_{50})

The acute oral toxicity study was conducted using the limit doses test of up and down procedure according to organization for economic and cultural development [13,14]. Fifteen Wistar rats weighting between 150 and 200 g were used for this experiment. They were acclimatized for 7 days and grouped into 5 of 3 rats each. Animals in group A were administered 1000 mg/kg *V. doniana*, those in group B were administered 3000 mg/kg *V. doniana*, those in group C were administered 1000 mg/kg *F. thoningii*, those in group D were administered 3000 mg/kg *F. thoningii*, while those in group E were administered 1500 mg/kg *V. doniana* + 1500 mg/kg *F. thoningii*. They were observed for 48 hours, and thereafter for 7 days. Animals were weighed daily and recorded. They were observed for signs of acute toxicity, weight changes, morbidity and mortality. The behavioral changes and other changes observed in the experimental rats were recorded according to

Organization for Economic Co-operation and Development [13] guidelines.

2.3 Experimental Design

A total of 40 male albino rats with body weight ranging from 160 to 180 g were used for this study. They were acclimatized for seven days to Laboratory condition. They were kept in plastic cages and fed with commercial rat chow and supplied with water *ad libitum.* The rats were used in accordance with NIH Guide for the care and use of laboratory animals; NIPRD Standard Operation Procedures (SOPs). After the acclimatization period, the rats were injected with alloxan monohydrate dissolved in sterile normal saline in a dose of 120 mg/kg body weight intraperitoneally [15]. After 72 hours of the injection, rats with fasting blood glucose (FBG) at or above 200 mg/dL were considered diabetic.

2.4 Grouping of Animals

The animals were randomly assigned to 8 groups of 5 rats each, and treated as follows:

Group 1: Diabetic rats treated with 200 mg/kg body weight of *V. doniana* (VD_1).

Group 2: Diabetic rats treated with 400 mg/kg body weight of *V. doniana* (VD_2).

Group 3: Diabetic rats treated with 200 mg/kg body weight of *F. thonningii* (FT_1).

Group 4: Diabetic rats treated with 400 mg/kg body weight of *F. thonningii* (FT_2).

Group 5: Diabetic rats treated with 100 mg/kg body weight of *V. doniana* and100 mg/kg body weight of *F. thonningii* ($VD+FT_1$).

Group 6: Diabetic rats treated with 200 mg/kg body weight of *V. doniana* and 200 mg/kg body weight of *F. thonningii* ($VD+FT_2$).

Group 7: (Normal control) which received feed and water only.

Group 8: (Diabetic control) which was induced with alloxan without treatment.

Weight of animals was recorded at intervals. After 30 days of orally administering the animals daily with the plant alkaloid extracts, the animals were fasted overnight and sacrificed. Blood samples for biochemical analyses were collected through ocular puncture and gently dispersed into plain sample bottles. The Sera samples were obtained after clotting of the blood via centrifugation.

2.5 Determination of Blood Glucose Concentration

The blood glucose concentration were taken by sterilizing the tails of the animals with 10 % alcohol, and cutting the tails using scissors then allowing the blood to touch the test strip which was inserted into a calibrated glucose meter (One touch Glucometer, Acon Laboratory INC. San Diego, USA) according to the methods described by Airaodion et al. [16]. This gave direct reading after 5 seconds in mg/dL.

2.6 Determination of Lipids

Lipids were extracted and determined according to previously described methods [17,18].

2.7 Statistical Analysis

Data were subjected to analysis of variance using Graph Pad Prism (Version 6.0). Results were presented as Mean ± Standard Error of the Mean (SEM). One way analysis of variance (ANOVA) was used for comparison of the means. Differences between means were considered to be significant at $p<0.05$.

3. RESULTS

Response and effect on the body weight of rats treated for 7 days with 1000 $mgkg^{-1}$and 3000 mg kg^{-1} leaf extracts of *V. doniana* and *F. thoningii* is shown in Table 1. The results showed that the high doses induced progressive and sustained weight loss from 13.71%-16.84% after 7 days of oral administration (Table 1). The results showed that all rats treated with the 3000 mg kg^{-1} limit dose of the leaf extracts were hypo-reactive to external stimuli such as touch in the first 30 min to 1 hr post administration and subsequently became active and exhibited normal behavior throughout the 7 days observation period. The limit test dose of 3000 mg kg-1 did not cause any mortality or any major acute toxicity. Thus, the LD_{50} of the leaf extracts is greater than 3000 mg/kg.

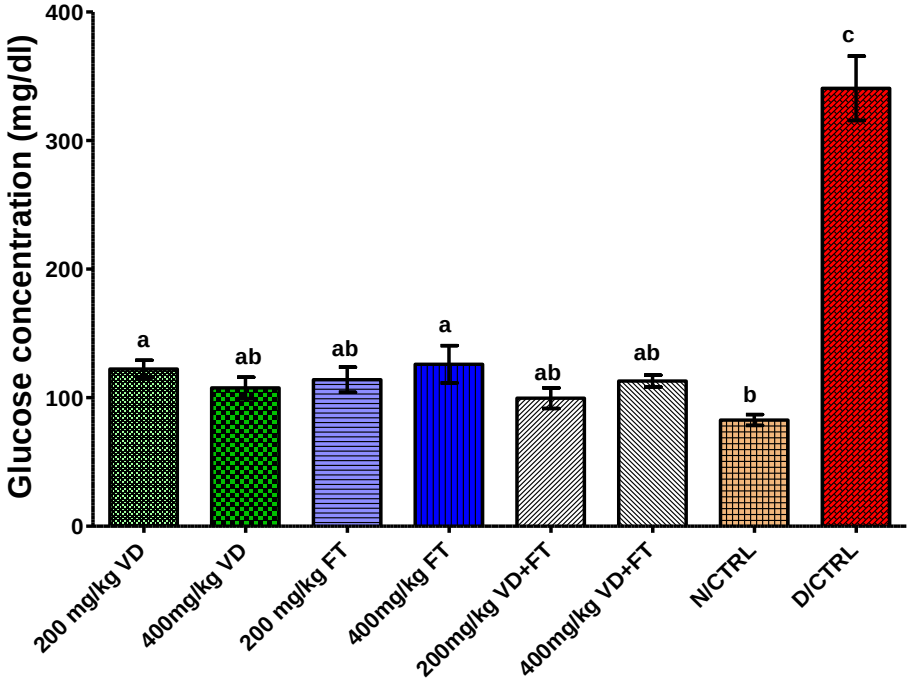

Fig. 3. Blood glucose concentration (mg/dL) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT)

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control.

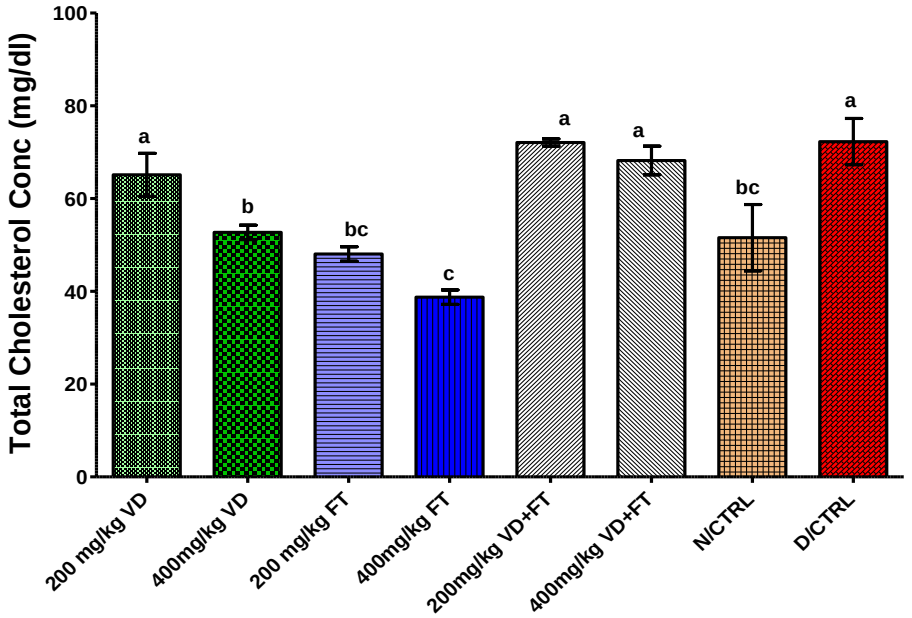

Fig. 4. Total cholesterol concentration (mg/dL) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT).

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control.

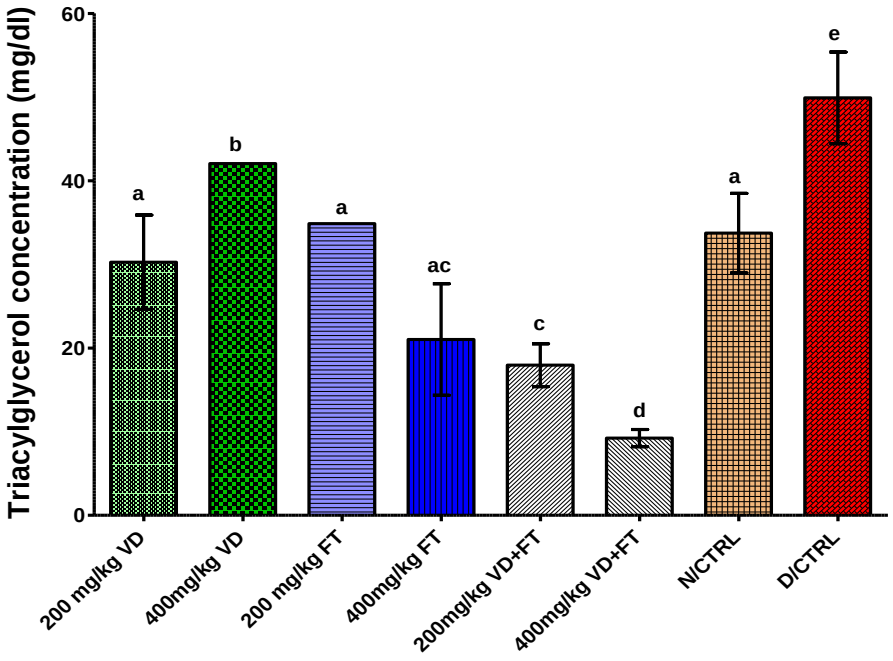

Fig. 5. Triglyceride Concentration (mg/dL) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT)

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control.

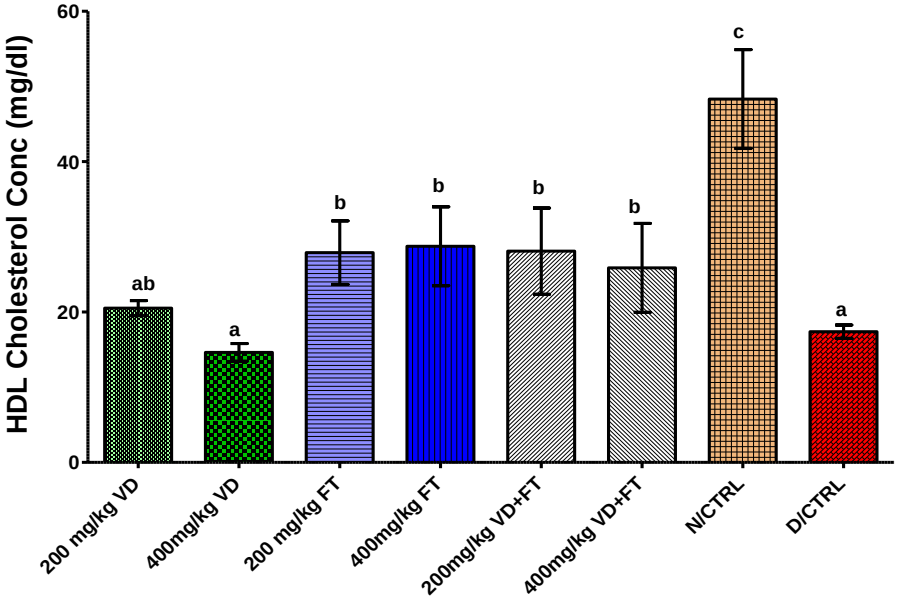

Fig. 6. HDL-Cholesterol Concentration (mg/dL) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT)

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control.

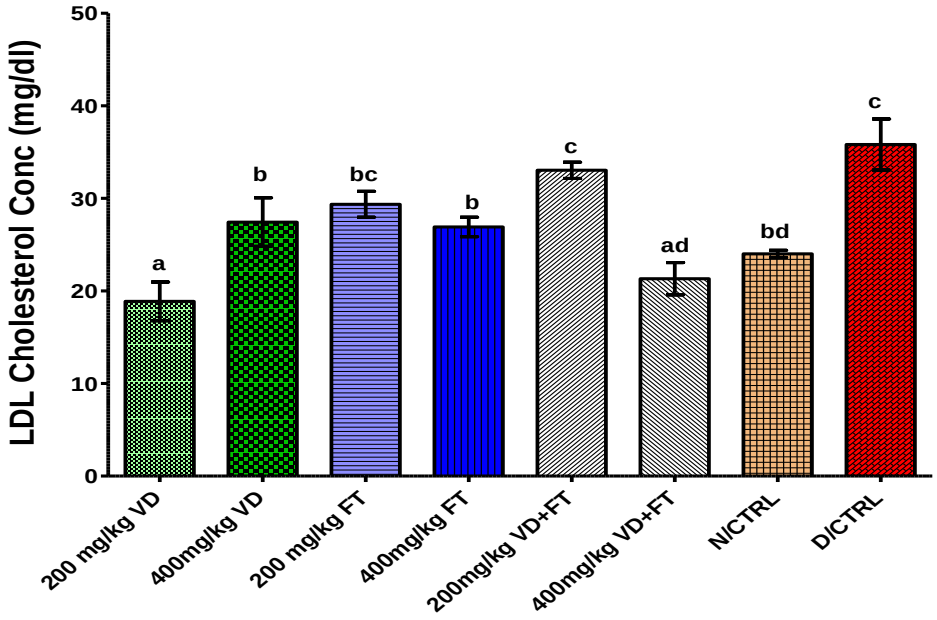

Figure 7: LDL-Cholesterol Concentration (mg/dL) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT)

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control

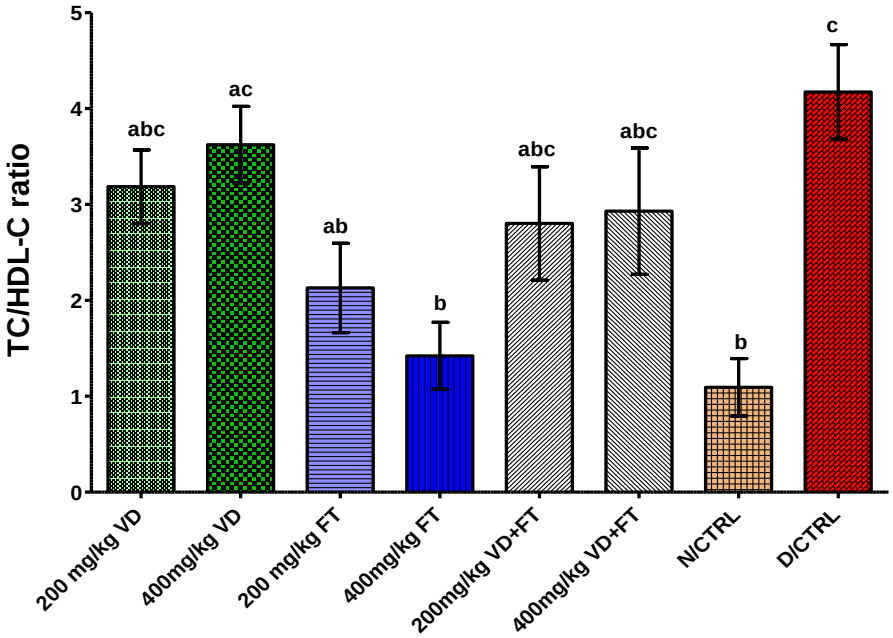

Fig. 8. Total cholesterol/HDL-cholesterol concentration of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT).

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control.

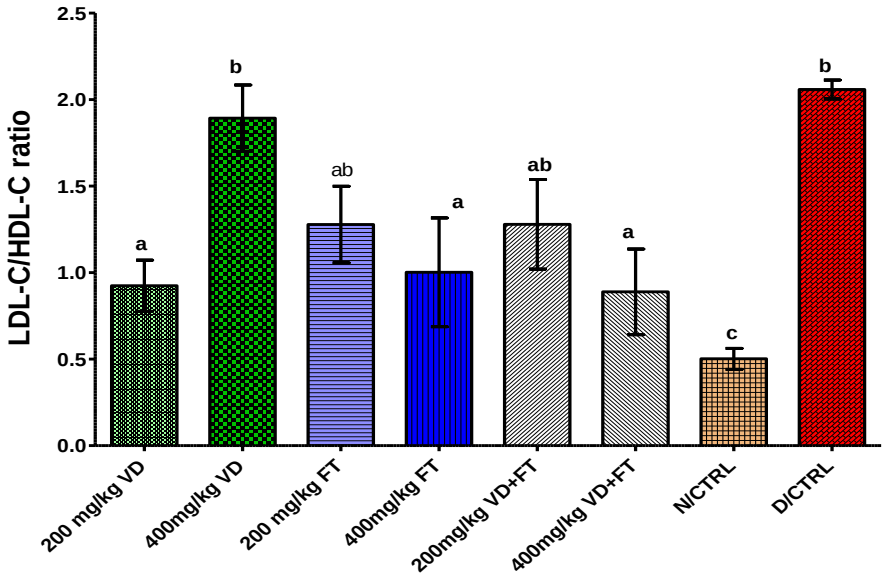

Fig. 9. LDL-Cholesterol/HDL-cholesterol concentration of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT).

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control

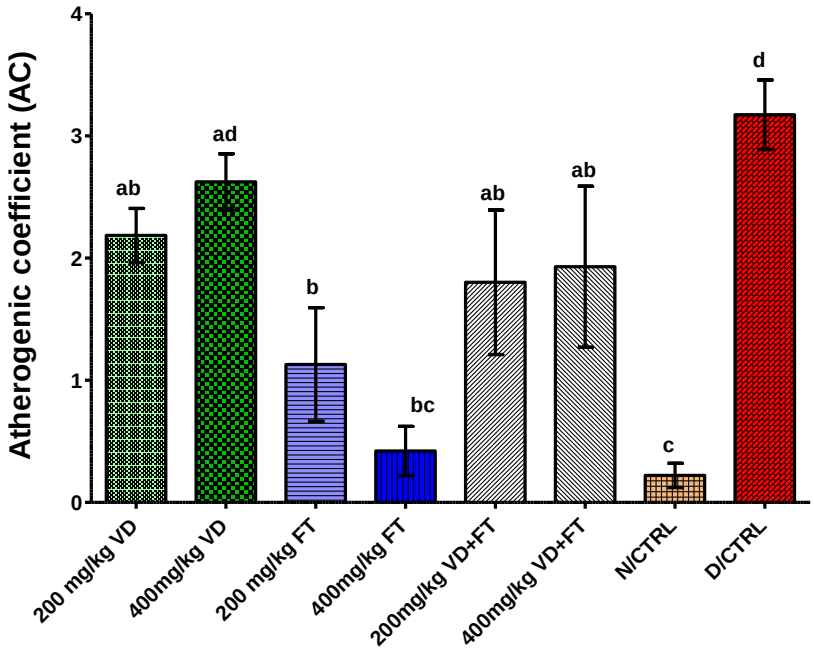

Fig. 10. Atherogenic Coefficient (AC) of diabetic albino rats administered single and combined doses of alkaloid extracts of *V. doniana* (VD) and *F. thoningii* (FT).

Results are presented as mean ± standard deviation. Bars bearing different letter(s) are statistically significant (p<0.05)

Legend: VD = V. doniana, FT = F. thoningii, N/CTRL = Normal Control; D/CTRL = Diabetic Control

Table 1. Acute oral toxicity of rats exposed to *V. doniana* and *F. thoningii*

Animal groups	Treatment	Changes in body weight from day 0 to day 7 (%)	Number of death recorded
A	1000 mg/kg of *V. doniana*	16.14	0
B	3000 mg/kg of *V. doniana*	13.73	0
C	1000 mg/kg of *F. thoningii*	13.71	0
D	3000 mg/kg of *F. thoningii*	16.84	0
E	1500 mg/kg of *V. doniana* + 1500 mg/kg of *F. thoningii*	15.50	0

4. DISCUSSION

The results of acute toxicity study indicated that the LD_{50} of the leaf extracts of *V. doniana* and *F. thoningii* is greater than 3000 mg/kg body weight (Table 1). The limit test dose is primarily used in situations where the experimenter has information indicating that the test material is likely to be non-toxic or of low toxicity [13]. Thus, the non-lethal effects produced with the high doses of this extracts is an indication that the leaf extracts of *V. doniana* and *F. thoningii* are relatively safe on acute oral exposure. It can therefore be concluded that *V. doniana* and *F. thoningii* leaf extracts is non-toxic which is in agreement with Bruce [19] and American Society for Testing and Materials [20], that any chemical substance with LD_{50} estimate greater than 3000-5000 mg/kg (oral route) could be considered of low toxicity and safe. OECD [13] also recommended the use of limit test dose with LD_{50} greater than 5000 mg/kg (oral route) as having low acute oral toxicity. This implies that the leaf extracts of both plants are relatively safe.

The use of plants in the treatment of diseases and in particular diabetes mellitus is as old as man [21,22]. This is because plants have been shown to contain some potent bioactive compounds with anti-diabetic properties [23,24,25]. In this study, diabetes established on the basis of fasting blood glucose concentration in the treated rats on the 5^{th} day of the experiment formed baseline values. The results indicated that daily oral administration of *V. doniana* and *F. thoningii* alkaloid extracts for 30 consecutive days significantly ($p<0.05$) lowered the fasting blood glucose (Fig. 3). The fasting blood glucose lowering effect of the plant extracts was dose dependent, with all doses however, showing high levels of potency. The observed anti-diabetic effects of *V. doniana* and *F. thoningii* alkaloid extracts is an indication that the extracts contain bioactive phytochemicals with potent anti-diabetic properties. The results compared favourably with the fasting blood glucose lowering effects of *Corchorus olitorius* [23], *Vernonia amygdalina* [26], *Barleriaprionitis* [27], *Parkia biglobosa* [16], *Withania coagulans Dunal* [28], *Talinum triangulare* [25], *Dorstenia picta* [29], *Telfairia occidentalis* [30], *Ceiba pentandra* [31] and *Carica papaya* [32] among others. In normal rats the extract could be acting via increased insulin secretion or increased peripheral utilization of glucose but in the *in vivo* type II diabetes model created in this study the alkaloid extracts may have lowered the concentration of fasting blood glucose level probably by increasing the peripheral utilization of glucose in the diabetic rats [32,33].

Diabetes mellitus affects serum lipid profiles leading to complications with severe consequences [34]. High levels of total cholesterol and more importantly LDL-Cholesterol in blood are major cardiovascular risk factors [35]. Insulin deficiency causes an increase in free fatty acid mobilization from adipose tissues which results in increased production of cholesterol rich LDL particle and dyslipidaemia [34]. The results showed that *V. doniana* and *F. thoningii* alkaloid extracts significantly brought down the elevated total cholesterol, triacylglyerol and LDL-cholesterol levels after 30 days of treatment, but increased the HDL level in the diabetic treated rats to levels comparable to those of the normal control group. In recent times, there has been a decline in the prevalence of artherosclerosis and artherosclerosis-related deaths possibly due to effective management of the risk factors that predispose to this disorder. Lowering of serum lipid concentrations, particularly LDL is therefore considered as one of the strategies that can delay the on-set of chronic disorders associated with hyperlipidemia in humans [16,30]. Herbal extracts are often used in folk medicine to improve the lipid profile of humans [25,26].

In the present study, the effects of alkaloid extracts of *V. doniana* and *F. thoningii* on the

lipid profile of alloxan-induced diabetic rats revealed that these plants could improve lipid profile of animals, particularly total cholesterol and LDL cholesterol. This was deduced from the fact that the serum concentrations of these fractions in the treated diabetic rats were significantly lower when compared with those of the normal and diabetic control animals at $p<0.05$. On the other hand, HDL-cholesterol concentration was significantly ($p<0.05$) elevated in the plants' alkaloid treated groups. Dietschy et al. [36], reported that plasma clearance of LDL particles is mediated primarily by LDL receptors, a large complement of which is expressed by the liver and that LDL becomes atherogenic when they are modified by oxidation reaction [35]. Biochemically, *V. doniana* and *F. thoningii* alkaloid extracts might be inducing rapid catabolism of low-density lipoprotein cholesterol through hepatic receptors for final elimination in the form of bile acids as has been previously suggested [37].

HDL is beneficial in hyperlipidaemic conditions [25,26]. It is often referred to as good cholesterol [32]. It exerts an atherogenic effect by counteracting LDL oxidation and facilitating the translocation of cholesterol from the peripheral tissues to liver for catabolism [35]. LDL plays a crucial role in the development of atherosclerotic lesions, progress of fatty streaks and ulcerated plagues. In this present study, administration of alkaloid extracts from *V. doniana* and *F. thoningii* leaves resulted in a significant hypolipidaemic effect. The significant reduction of LDL cholesterol and increase in HDL concentration are indicative of a lowered atherogenic index (A.I) (Fig. 10), and a reduced LDL/HDL ratio in the treated rat groups. A.I is commonly used as an index to evaluate the risk for atherosclerosis. The result of this study is in accord with the findings of Igwe et al. [35] who reported that elevation of HDL and lowering of A.I are important in reduction of the risk for atherosclerosis.

5. CONCLUSION

The present study proved that both *V. doniana* and *F. thonningii* leaves are potent antidiabetic agents. They could also reduce the risk of obesity and hypertension due to its hypolipidemic effect.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal ethic Committee approval has been collected and preserved by the author**.**

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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