

Anti-diabetic activity of aqueous extracts of *Vitexdoniana* leaves and *Cinchona calisaya* bark in alloxan – induced diabetic rats.

ABSTRACT

Vitexdoniana and *Cinchona calisaya* are tropical medicinal plants endowed with important pharmacological properties. The effects of aqueous extracts of *Vitexdoniana* leaves and *Cinchona calisaya* bark on alloxan-induced diabetes mellitus in Wistar albino rats were evaluated. Diabetes mellitus was induced by a single intraperitoneal (i.p) injection of 150.0 mg/kg body wt of alloxan. The aqueous extracts of *V. doniana* leaves and *C. calisaya* bark were administered intraperitoneally to four diabetic groups at doses of 50.0 and 100.0 mg/kg body wt. The actions of the extracts were compared with that of the standard oral hypoglycaemic agent, glibenclamide. Both extracts caused significant ($p < 0.001$) decreases in blood sugar levels of the rats at all the tested doses. At 50.0 mg/kg wt. *V. doniana* leaf extract produced 82.9% reduction in blood sugar level (i.e from 492.8 to 84.5 mg/dl) after four days of daily injection whereas *C. calisaya* caused 64.4% decrease. Unlike *C. calisaya* bark, *V. doniana* at both doses tested, was more potent than the reference drug, glibenclamide (0.3mg/kg. wt.). The anti-diabetic activity of *V. doniana* did not vary with the dose, whereas the observed effect of *C. calisaya* was dose – dependent. *C. calisaya* exhibited higher anti-diabetic activity at a lower dose of 50.0 mg/kg body wt. Both medicinal plants therefore possess valuable anti-diabetic property. Their effects on the anti-oxidant status were also investigated. Phytochemical screening of both extracts showed the presence of saponins, flavonoids, alkaloids, cardiac glycosides, tannins, and carbohydrates.

Keywords: Anti-diabetics, *Vitex*, *Cinchona*, Hypoglycaemic, Anti-oxidant.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia together with biochemical alterations of glucose and lipid metabolism (Pari *et al.*, 2002). This chronic disorder arises as a result of insufficient production of the pancreatic β -cells hormone insulin or inadequate utilization of insulin. Two major types of diabetes mellitus reported to increase mortality and morbidity are the type I commonly known as insulin – dependent diabetes mellitus (IDDM) and type 2, also called non-insulin – dependent – diabetes mellitus (NIDDM).

At least 80% of Africans depend on herbal medicine for their health care (Iwuet *et al.*, 1999; Kilani, 2006; Ajose, 2007; Okwu and Uchegbu, 2009). The high cost, low availability, uncertainty of use during pregnancy and undesirable side effects of synthetic drugs have been some of the factors leading to a preference for hypoglycaemic drugs of plant origin, which are believed to be suitable for chronic

treatments (Berger, 1985; Okigbo and Mmeko, 2006). Herbal preparations with anti-diabetic potentials are growing in popularity.

Vitexdoniana (Verbanaceae) is a perennial forest plant widely distributed in tropical West Africa. In ethnomedicine, *V. doniana* leaf is employed in the treatment of stomach and rheumatic pains, inflammatory disorders, diarrhoea and dysentery (Agunnuet *al.*, 2005; Iwuekeet *al.*, 2006). Likewise *Cinchona calisaya* (Rubiaceae) commonly known as quinine bark, is one of the famous rain forest plants which are now widely cultivated in many tropical countries for their medicinal and commercial values. Extracts of *C. Calisaya* bark have been reported to possess anti-malarial (Bareness *et al.*, 2006) and anti-parasitic (Rojas, 2006)

In Nigeria, from information available from the indigenous traditional healers, *V. doniana* leaves and *C. Calisaya* bark are useful in the management of diabetics (personal communication), although these medicinal properties have not been established scientifically.

The aim of this study is, therefore, to investigate these acclaimed values of these forest plants. Oxidative stress, caused by imbalance between the production of reactive oxygen species (ROS) and a biological system's ability to readily detoxify or scavenge released reactive intermediates, has been implicated by many researchers in the pathogenesis of some chronic conditions such as Alzheimer's disease, Parkinson's disease, diabetes mellitus (David *et al.*, 2005), rheumatoid arthritis and neurodegeneration (Valko, *et al.*, 2007). In view of this, the effects of the extracts of the two plants on some anti-oxidant mechanisms of the body were also studied. Phytochemical analyses of the extracts were also carried out.

2.0 Material and Methods

2.1 Plant material.

Fresh leaves of *V. doniana* and *C. calisaya* bark were collected from Abagana, Anambra State, Nigeria. The plants were identified and authenticated at the International Centre for Ethnomedicine and Drug Development (INTERCEDD).

2.2 Experimental animals

Forty adult male albino rats (Wistar) weighing between 100.0 – 175. 0g were purchased from the Department of Veterinary Medicine, University of Nigeria, Nsukka. The animals were housed in standard animal cages, fed with commercial feed and water, *ad libitum*, and acclimatized for 7 days.

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2.3 Chemicals.

Alloxan monohydrate, adrenaline and thiobarbituric acid were manufactured by Sigma, Germany. All other chemicals used in our studies were of analytical grade.

2.4 Preparation of extracts.

Five hundred grammes each of dried and pulverized *V. doniana* leaves and *C. calisaya* bark were macerated twice in 2.0L of distilled water for 18 ± 1 h. Filtrations were done using cheese cloth and then Whatman No. 1 filter paper. Combined filtrates were evaporated in a water bath at 80°C . The crude extracts obtained (36.4% and 21.7% yields for *V. doniana* and *C. calisaya* respectively) were stored in the refrigerator and used for the experiments.

2.5 Determination of extracts' effects on alloxan – induced diabetes mellitus.

Forty adult male albino rats (Wistar) were weighed and their base line blood sugar levels recorded using a glucometer (Accucheck Active). A single dose intraperitoneal injection of alloxan (50.0 mg/kg body wt.) was given to thirty-five rats, whereas five rats served as the negative control group. Glucose solution (75%) was used to prevent the initial hypoglycaemia usually caused by alloxan. Two days after alloxan administration, the blood sugar levels of the rats were recorded and the diabetic rats (with blood sugar levels $\geq 250.0\text{mg/dl}$) were divided into six groups of five animals each according to their body weights. Four test groups received daily treatment with the aqueous extracts of *V. doniana* leaves and *C. calisaya* bark at the doses of 50.0 and 100.0mg/kg body wt each whereas the remaining animals served as the untreated diabetic (positive control) group. [The reference group (five rats) were treated with glibenclamide (0.3 mg / kg. wt).Extracts and drugs were solubilized in distilled water and tween -80 respectively and the duration of treatment was four days. The animals were sacrificed on the last day and blood samples were collected for anti-oxidant enzymes assays.

2.6 Superoxide dismutase (SOD) activity assay.

Whole blood SOD activity was assayed utilizing the method of Okpuzor *et al.*,2009. Whole blood (1.0ml) was diluted in 9.0ml of distilled water to make a one in ten dilution of the blood. An aliquot of 0.2 ml of diluted blood was added to 2.5 ml of 0.05 M sodium carbonate buffer (pH 10.2) and left to equilibrate in the spectrophotometer and the reaction was started by addition of 0.3ml of freshly prepared 0.3mM adrenaline to the mixture which was quickly mixed by inversion.

The reference cuvette contained 2.5ml buffer, 0.2ml of distilled water and 0.3ml of substrate (adrenaline. The increase in absorbance at 480mm was monitored at 30 seconds interval for 150 seconds

2.7 Determination of catalase activity.

Serum catalase activity was determined according to Beer and Sizer (1952) as reported by Usoh *et al* .,2005, by measuring the decrease in absorbance at 240nm in a uv recording spectrophotometer by monitoring the decomposition of H₂O₂ as described by Aebi (1984). The reaction mixture (3.0ml) contained 0.1ml of suitably diluted serum in phosphate buffer (50.0mM, PH 7.0) and 2.9ml of 30.0mM H₂O₂ in phosphate buffer.

An extinction coefficient for H₂O₂ at 240nm of 40M M-l cm-l was used for the calculation. The specific activity of catalase was expressed as moles of H₂O₂ reduced / min / mg. protein .

2.8 Determination of lipid peroxidation.

The method of Biye and Aust (1978) as described by Usoh *et al*.,2005 was employed. Serum (0.4ml) aliquots were collected into the test-tubes and were mixed with 1.6 ml of 0.25N HCL, 0.5ml of 15.0% TCA (trichloroacetic acid) and 0.5ml of 0.375% of TBA (thiobarbituric acid). The reaction mixtures were then placed in 100°C boiling water for 15 minutes, cooled and centrifuged at 3000 rpm for 10minutes. The optical densities of the supernatants were recorded at 532nm against a reagent blank which contained only distilled water.

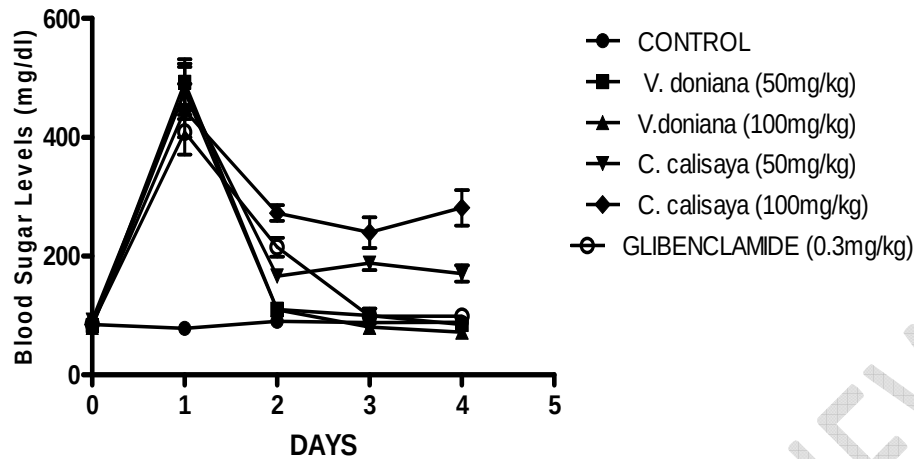
2.9 Phytochemical analyses.

Phytochemical screening was carried out according to established procedures by Sofowora (1980) and Cuiled (1982) for the presence of alkaloids, flavonoids, saponins tannins, cardiac glycosides and carbohydrates.

3.0 RESULTS

3.1 Anti-diabetic activity of the extracts. Intraperitoneal administration of alloxan (150.0 mg/kg) increased the average blood sugar levels of the animals (by up to 396.0%). Daily administration of 50.0mg/kg wt of aqueous extract of *V. doniana* caused a decrease of 82.9% (from 492.8 ± 38.60 to 84.5 ± 6.8mg/dl) in the average blood sugar levels. Increasing the dose of the extract to 100.0mg/kg wt. did not increase the efficacy of the extract. Aqueous *C. calisaya* bark extract at the tested doses, 50.0 and 100.0 mg/kg reduced the blood glucose levels by 64.4 and 36.9% respectively(see Fig.1). Unlike *C. calisaya*, the extract of *V. doniana* was more potent than the

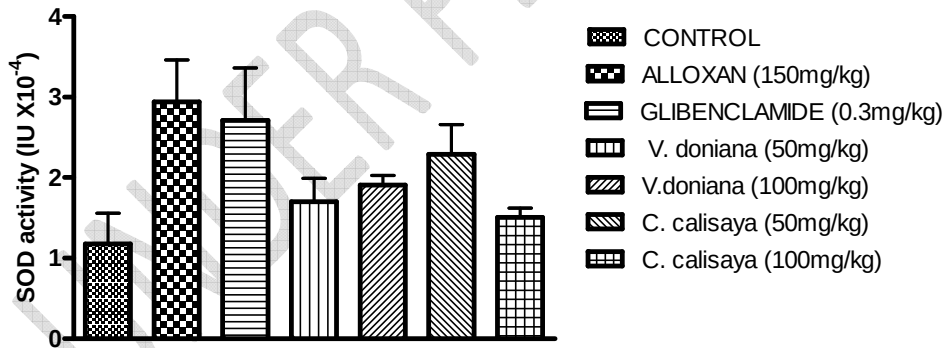
146 reference drug, glibenclamide(0.3mg/ kg wt.) at both doses tested.



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148 Fig. 1

149 3.2 Superoxide dismutase activity

151 There were significant ($p < 0.01$) elevations (up to 94.0%) in the activity of superoxide dismutase in all
152 the extract- treated diabetic rats compared to the control animals (Fig.2). Highest increase (130.0%)
153 was recorded in the rats treated with the standard oral hypoglycaemic agents, glibenclamide. The
154 effects of both *C. calisaya* and *V. doniana* extracts on SOD activity were dose –dependent.



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157 Fig. 2

3.3 Catalase activity.

When compared with the control, slight and insignificant ($p > 0,05$) decreases in serum catalase activity were caused by the treatment of the diabetic rats with *C. calisaya* extract (Fig.3). Glibenclamide and *V. doniana* extract (100.0mg/kg wt dose) significantly ($p < 0.01$) inhibited the action of this enzyme by 30.4%.

The effect of *V. doniana* extract was dose – dependent.

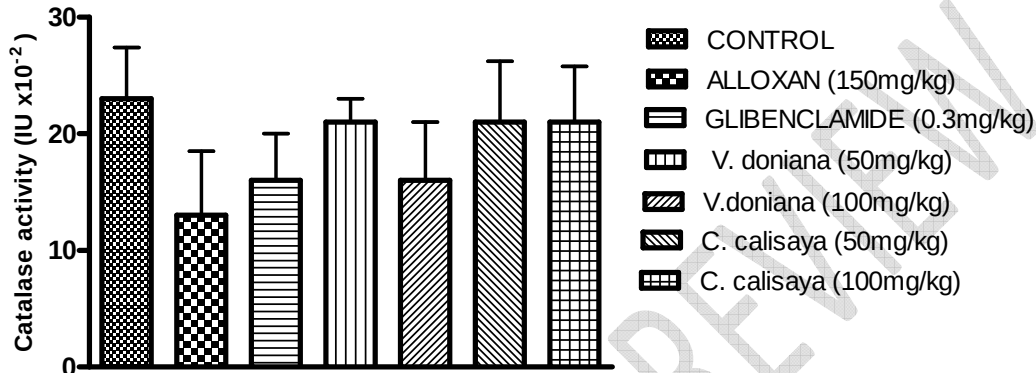


Fig. 3

3.4 Lipid – Peroxidation.

Malonyl aldehyde (MDA) levels were significantly higher ($p < 0.001$) in the serum of all the diabetic rats treated with the extracts of *C. calisaya* and *V. doniana* when compared with the control. The reference drug, glibenclamide 0.3mg/kg wt., caused the highest (up to 700%) increase in serum MDA levels of the rats. The effect of *C. calisaya* extract was more at a lower dose than at a higher dose, whereas varying the dose did not have any effect on the action of *V. doniana* on lipid – peroxidation (see Fig 3).

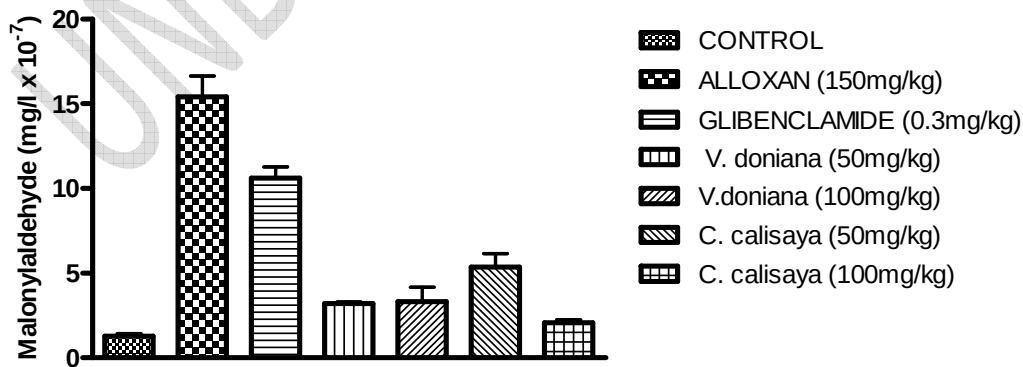


Fig. 4

3.5 Phytochemical analysis

Results of the phytochemical analyses revealed the presence of appreciable quantities of alkaloids, flavonoids, saponins, cardiac glycosides and carbohydrates in both extracts of *C. calisaya* bark and *V. doniana* leaves. Traces of tannins were observed.

Table1: Result of Phytochemical Screening

Phytochemical	Observation	
	<i>V. doniana</i>	<i>C. calisaya</i>
Alkaloids	++	++
Flavonoids	++	++
Saponins	++	++
Tannins	+	+
Cardiac glycosides	++	++
Carbohydrates	++	++

Where + represents **trace amount**, and ++ represents **intensely present**.

4.0 DISCUSSION.

Findings from our investigation revealed that there were significant ($p < 0.001$) decreases in the blood sugar levels of the diabetic rats treated with 50.0 and 100.0mg/kg body wt. doses of the aqueous extracts of *V. doniana* leaves and *C. calisaya* bark. Their actions were comparable to that of the standard anti-diabetic drug, glibendamide, at the dose of 0.3mg/kg wt. These observations suggest that both valuable forest plants possess anti-diabetic activity and therefore justify the traditional use of these plants in the management of the chronic disease diabetes mellitus. *C. calisaya* extract was more potent at a low dose (50.0mg/kg) which produced 64.4% decrease in blood sugar level than at a higher dose (100.0mg/kg) that gave 36.9% reduction. On the other hand, the anti-diabetic effect of *V. doniana* was not in any way influenced by the increase in dose (Fig. 1). This implies that both extracts do not exhibit cumulative effects on the sugar levels of the rats (Salahdeen *et al.*, 2004) probably because none of the processes involved in their absorption, distribution, metabolism, or elimination exhibit saturability.

Increased generation of free radicals together with reduced levels of body's endogenous antioxidant vitamins and enzymes are considered to be the main contributor to oxidative stress (EllnanWojtasek *et al.*, 2003). Free radicals' attack on membrane lipids, proteins and DNA is believed to be involved in many health disorders such as diabetes mellitus, cancer, neurodegenerative and inflammatory diseases (Charles and Brian, 2010; David *et al.*, 2005). The anti-oxidant enzymes include superoxide dismutase (SOD) and catalase. Superoxide dismutase generates H_2O_2 , while catalase consumes it. Precisely, catalase is the main regulator of H_2O_2 metabolism (Lazlo *et al.*, 2005).

Increased plasma lipid peroxidation and superoxide dismutase activity in type 2 diabetes mellitus have been well documented (Marjani, 2005; Akalin *et al.*, 2008). Alloxan induces experimental diabetes mellitus in animals by enhancing the generation of H_2O_2 through the reaction of alloxan and reduced glutathione *in vitro*, as well as decreasing the catalase enzyme activity (Kazunori *et al.*, 2009). The higher SOD activity seen in diabetes mellitus in response to the increased generation of H_2O_2 may be attributed to an adaptive mechanism in the tissues (Akalin *et al.*, 2008).

Results of our studies showed that superoxide dismutase activity and plasma lipid peroxidation were significantly higher ($p < 0.01$ and $p < 0.001$ respectively) in all the diabetic rats compared to the control (Figs: 2 and 4). Lower catalase activity was observed (Fig. 3).

These observations corroborate previous reports by other researchers (Marjani, 2005; Akalin *et al.*, 2008; Ebuehi *et al.*, 2009) that many species of the herbal plants produce their pharmacological actions by restoring the oxidant – antioxidant balance of the body.

Treatment of the diabetic rats with either the standard oral hypoglycaemic drug, glibenclamide or the hypoglycaemic *V. doniana* and *C. calisaya* extracts caused increases in the activity of SOD and lipid peroxidation when compared with control, but the increases were lower than that produced by

243 alloxan.. Significant ($p < 0.01$) inhibition of catalase enzyme activity was elicited by glibenclamide.

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245 Our observations have, therefore, clearly indicated that alteration of the oxidants – antioxidants
246 imbalance may be part of the mode of action of these anti-diabetic extracts of *V. doniana* and *C.*
247 *calisaya*. It has been reported that many plants with hypoglycaemic action may act on blood glucose
248 through inhibition of endogenous glucose production (Eddouks, *et al.*, 2003), or interference with
249 gastrointestinal glucose absorption (Musabayane *et al.*, 2006); some may have insulin – like
250 substances (Gray and Flatt., 1999); some may inhibit insulinase activity and some may increase
251 secretion of insulin from the β - cells of the pancreas (Trivedi *et al.*, 2004; Yadai *et al.*, 2008), while
252 others may increase active β - cells' population in the pancreas by activating regeneration of these
253 cells (Shannugasundaram *et al.*, 1999; Jelodar *et al.*, 2007). All these mechanisms are yet to be
254 investigated in order to elucidate the exact mechanism(s) of action of *V. doniana* and *C. calisaya*
255 extracts.

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257 Results of the qualitative phytochemical analyses showed that both extracts contained appreciable
258 quantities of alkaloids, flavonoids, saponins, cardiac glycosides and carbohydrates whereas trace
259 amounts of tannins were observed (Table. 1). One or more of these phytochemicals could be
260 contributing to the observed activities of the extracts (Edeoga *et al.*, 2005).

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262 In conclusion, it is evident from our findings that the aqueous leaf extract of *V. doniana* and *C.*
263 *calisaya* bark possess strong anti-diabetic activity against alloxan-induced diabetes mellitus,
264 alteration of the oxidants – antioxidants imbalance created by alloxan may be contributing to their
265 anti-diabetic activity. Subsequent work should focus more on the elucidation of their mechanisms of
266 action, as well as isolation and characterization of the active ingredients.

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FIGURE CAPTIONS

Figure 1: Effects of aqueous extracts of *C. calisaya* bark and *V. doniana* leaves on blood glucose levels in alloxan – induced diabetic rats. Both extracts caused significant reductions in blood glucose levels at all the tested doses.

Figure 2: Superoxide dismutase activity in extracts' treated – diabetic rats. Both extracts reduced alloxan – induced increases in superoxide dismutase activity.

Figure 3: Catalase enzyme activity in extracts' treated – diabetic rats. The extracts decreased the activity of this serum enzyme.

Figure 4: Malonylaldehyde concentrations in extracts ' treated – diabetic rats. Increased concentrations of malonylaldehyde were observed when compared with the control group. But extracts produced lesser increases relative to alloxan.