

Original Research Article

Cardiotoxic Effect of Aqueous Extract of *Dialium guineense* Stem Bark in Wistar Rats

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Abstract: *Aim:* To investigate the cardiotoxic effect of aqueous extract of *D. guineense* stem bark in Wistar rats. *Materials and Methods:* Wistar rats (n = 35) weighing 160 to 180 g were randomly assigned to seven groups (5 rats per group). One group served as control, while rats in the remaining groups received varied doses of extract (200 - 5000 mg/kg body weight, bwt) for 28 days. Indices of cardiac function were measured. *Results:* Percentage increases in body weights of rats treated with aqueous extract of *D. guineense* stem bark were significantly reduced, relative to the control group ($p < 0.05$), but there were no significant differences in the relative heart weights among the groups ($p > 0.05$). Treatment with the extract did not elicit any significant differences in the activities of lactate dehydrogenase (LDH), creatine kinase (CK) and aspartate aminotransferase (AST) as well as cardiac malondialdehyde (MDA) level among the groups ($p > 0.05$). In all instances, the basal activities of the measured indices of cardiac function were not significantly different from the values after treatment ($p > 0.05$). Moreover, the extract did not significantly alter the normal architecture of rat heart. *Conclusion:* Aqueous extract of *D. guineense* stem bark is not toxic to the heart and could be included in herbal medicine for the treatment of diseases.

Keywords: Cardiac function, Cardiotoxicity, Creatine kinase, *Dialium guineense*, Histology.

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INTRODUCTION

Drug-induced cardiotoxicity, a serious consideration in drug development, is a major toxic effect induced by various kinds of drugs [1]. Although anticancer agents are most renowned for their cardiotoxicity, other therapeutic drug classes have unpredicted effects on cardiac function. However, cardiotoxicity induced by neurological and chemotherapeutic agents, constitutes a major problem since the toxicity may become obvious only after long-term accumulation of the drug or its metabolites [2]. Evaluation of drug-induced cardiotoxicity risk is considered a crucial component of standard preclinical assessment of new chemical entities [3]. Cardiotoxicity continues to top safety concerns principally because of lack of sufficient knowledge of the underlying mechanisms [4]. Cardiovascular adverse effects can lead to cardiac arrhythmias [5].

Drug-induced cardiotoxicity, in the form of cardiac muscle dysfunction that may progress to heart failure, represents a major adverse effect of some common traditional antineoplastic agents, biological monoclonal antibodies, tyrosine kinase inhibitors, antiretroviral drugs, and illicit drugs such as alcohol, cocaine, methamphetamine, ecstasy, and synthetic cannabinoids [6-8].

Herbal medicines derived from plant sources are being increasingly utilized to treat a variety of clinical diseases [9]. Their popularity is increasing and at least one-quarter of patients with different diseases use botanicals. The World Health Organization (WHO) estimates that 80 percent of the population of some Asian and African countries presently uses herbal medicine for some aspects of primary health care [10, 11]. Medicinal herbs have proven beneficial effects [12-16].

Dialium guineense (Velvet Tamarind) is a medicinal plant used in folklore medicine for the treatment of infections such as diarrhea, severe cough, bronchitis, wound, stomachaches, malaria fever, jaundice, ulcer and hemorrhoids [17]. It is a tall, tropical, fruit-bearing tree, belonging to the *Leguminosae* family, and has small, typically grape-sized edible fruits with brown hard inedible shells. In Africa, it grows in dense forests along the southern edge of the Sahel [18]. The plant grows naturally in West African countries, Central African Republic, and Sudan [18]. In Nigeria, it is known by different names: *Icheku* (Igbo), *Awin* (Yoruba), *Tsamiyarkurm* (Hausa) and *Amughen* (Bini) [19]. Extracts of the plant are reported to be rich in important phytochemicals [20, 21]. At present little or nothing is known about the adverse effect of extracts of *D. guineense* stem bark on rat heart. The aim of this study was to investigate the cardiotoxic effect of aqueous extract of *D. guineense* stem bark in Wistar rats.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals and reagents used in this study were of analytical grade and they were products of Sigma-Aldrich Ltd. (USA).

Collection of Plant Material

The stem barks of *D. guineense* were obtained from Auchu, Edo State, Nigeria and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria (No. UBH_p330).

Plant Extraction

The stem bark was washed and shade-dried at room temperature for a period of two weeks and crushed into small pieces using clean mortar and pestle. A portion (500 g) of the powdered stem bark was soaked in 5000 mL of distilled water. The resultant aqueous extract was filtered with a muslin cloth and freeze dried via lyophilization [21].

Experimental Rats

Adult male Wistar rats (n = 35) weighing 160 – 180 g (mean weight = 170 ± 10 g) were obtained from the Department of Anatomy, University of Benin, Benin City, Nigeria. The rats were housed in metal cages under standard laboratory conditions: temperature of 25 °C, 55 – 65 % humidity and 12-h light/12-h dark cycle. They were allowed free access to rat feed (pelletized growers mash) and clean drinking water. The rats were acclimatized to the laboratory environment for one week prior to commencement of

the study. Standard experimental protocol was followed for this study.

Experimental Design

The rats were divided into 7 groups (5 rats per group): Group I served as control, while rats in groups II - VII received graded doses of extract (200 - 5000 mg/kg bwt) for a period of 28 days. Blood samples were collected before treatment and served as basal samples. At the end of the 28th day the rats were fasted overnight and euthanized. Blood sample collected in heparin containers was centrifuged at 3000 rpm for 10 min to obtain plasma which was used for biochemical analysis.

Cardiac Function Tests

Cardiac function tests (CFTs) such as AST, CK and LDH were performed in plasma [22 - 24].

Determination of Lipid Peroxidation in Rat Heart

Malondialdehyde (MDA) level was measured in heart homogenate [25].

Histological Examination of Rat Heart

Cut portions of the heart were sectioned and fixed in 10 % formalin for 48 h, and thereafter dehydrated using graded concentrations of ethanol. Just before embedment in paraffin, the specimens were cleared three times with xylene. Serial sections of exactly 4 µm thickness were stained with haematoxylin and eosin (H & E) according to standard protocol. Histopathological examination was performed under light microscopy. In each H and E section, exactly 25 circular tubules were measured in two axes drawn perpendicular to each other with the aid of an image analyzer (Image Proplus, version 3.0).

Statistical Analysis

Numerical data are expressed as mean ± standard error of mean (SEM, n = 5). Statistical analysis was performed using SPSS (version 20). Groups were compared using Duncan multiple range test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Percentage Weight Increase and Relative Organ Weight of Rats

Percentage increases in body weights of rats treated with aqueous extract of *D. guineense* stem bark were significantly reduced, relative to the control group ($p < 0.05$). However, there were no significant differences in the corresponding relative heart weights among the groups ($p > 0.05$; Table 1).

Table 1: Comparison of Percentage Weight Increase and Relative Organ Weight of Rats

Groups	% Increase in weight	Relative organ weight (x 10 ⁻²)
Control	61.35 ± 4.11	2.00 ± 0.03
200 mg/kg bwt	49.09 ± 4.83 ^a	3.50 ± 0.15
500 mg/kg bwt	47.39 ± 3.09 ^a	3.00 ± 0.05
1000 mg/kg bwt	42.38 ± 2.61 ^a	3.00 ± 0.08
2000 mg/kg bwt	37.28 ± 3.94 ^a	3.00 ± 0.05
3500 mg/kg bwt	31.65 ± 2.83 ^b	3.00 ± 0.04

Data are percentage weight increase and relative heart weight, and are expressed as mean ± SEM (n = 3). ^ap < 0.05, when compared with control group; ^bp < 0.05, when compared with the other treatment groups.

Cardiac Function in Extract-Treated Rats

Treatment with aqueous extract of *D. guineense* stem bark did not elicit any significant differences in the activities of LDH among the groups (p > 0.05). Activities of CK in groups II and III and

AST of groups II, III, and IV were not significantly different from those of control group (p > 0.05), but they were significantly increased in the other high dose groups (p < 0.05). In all instances, the basal activities of the measured indices of cardiac function were not significantly different from the values after treatment (p > 0.05). There were no significant increases in the concentrations of MDA in the heart of extract-treated rats (p > 0.05). These results are shown in Tables 2 and 3.

Table 2: Effect of Aqueous Extract of *D. guineense* Stem Bark on Cardiac Function

Groups		LDH (U/L)	CK (U/L)	AST (U/L)
Control		20.64 ± 0.00	40.45 ± 2.15	27.50 ± 0.89
200 mg/kg bwt	B	36.95 ± 15.05	38.61 ± 0.82	29.35 ± 4.90
	T	41.27 ± 20.64	40.06 ± 2.48	27.30 ± 1.90
500 mg/kg bwt	B	28.03 ± 2.47	55.72 ± 2.49	25.85 ± 4.00
	T	34.39 ± 6.88	59.79 ± 5.10	33.35 ± 5.80
1000 mg/kg bwt	B	33.41 ± 4.01	83.53 ± 5.18	40.15 ± 5.10
	T	40.01 ± 11.91	86.00 ± 7.25*	38.80 ± 3.15
2000 mg/kg bwt	B	50.83 ± 12.11	90.00 ± 4.91	38.85 ± 6.10
	T	61.91 ± 23.83	91.09 ± 5.52*	42.00 ± 2.85*
3500 mg/kg bwt	B	49.19 ± 1.10	101.52 ± 8.19	35.65 ± 5.65
	T	55.03 ± 6.88	103.34 ± 7.31*	41.00 ± 2.35*
5000 mg/kg bwt	B	29.01 ± 0.55	108.93 ± 5.13	40.80 ± 9.91
	T	35.90 ± 5.37	105.41 ± 1.00*	47.85 ± 6.50*

Data are indices of cardiac function and are expressed as mean ± SEM (n = 5). B = basal means;

and T = test means; *p < 0.05, when compared with control group.

Table 3: Concentrations of MDA in the Homogenates of Rat Heart

Groups	MDA Concentration (mole/mg tissue) x 10 ⁻⁴
Control	3.80 ± 0.24
200 mg/kg bwt	5.99 ± 2.81
500 mg/kg bwt	4.85 ± 0.27
1000 mg/kg bwt	5.12 ± 1.75
2000 mg/kg bwt	4.99 ± 1.19
3500 mg/kg bwt	5.16 ± 1.09
5000 mg/kg bwt	7.24 ± 0.80

Data are concentrations of cardiac MDA and are expressed as mean ± SEM (n = 5).

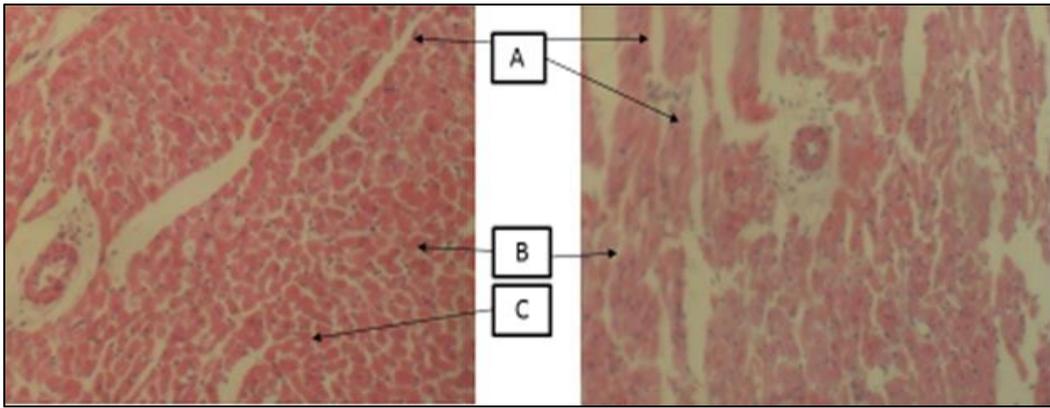


Plate 1 (Control): Rat heart composed of A (bundles of myocardial fibres); B (coronary artery); and C (interstitial space) (H & E x 100)

Plate 2: Rat heart treated with 200 mg/kg bwt extract showing A (normal myocardial fibres); and B (mild interstitial oedema) (H & E x 100)

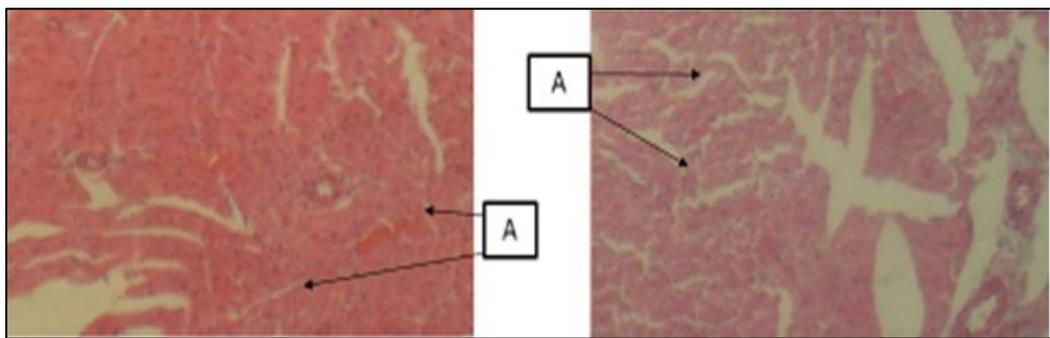


Plate 3: Rat heart treated with 500 mg/kg bwt extract showing A (normal myocardial architecture) (H & E x 100)

Plate 4: Rat heart treated with 1000 mg/kg bwt extract showing A (normal myocardial architecture) (H & E x 100)

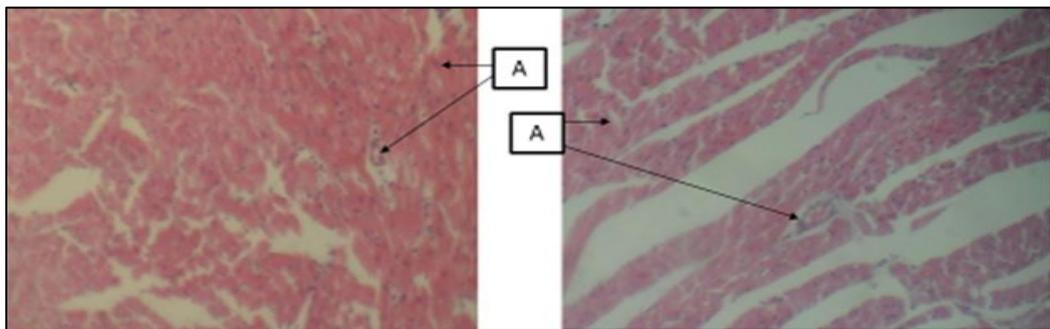


Plate 5: Rat heart treated with 2000 mg/kg bwt extract showing A (normal myocardial architecture) (H & E x 100)

Plate 6: Rat heart treated with 3500 mg/kg bwt extract showing A (normal myocardial architecture) (H & E x 100)

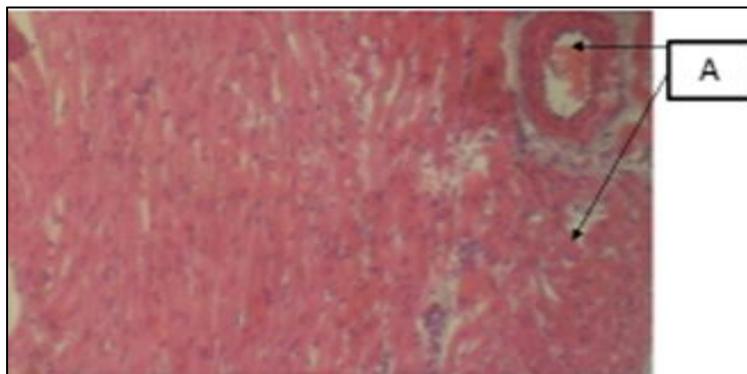


Plate 7: Rat heart treated with 5000 mg/kg bwt extract showing A (normal myocardial architecture) (H & E x 100)

Figure 1: Effect of Aqueous Extract of *D. guineense* Stem Bark on the Histology of Rat Heart

DISCUSSION

An important goal during the process of drug development is to assess whether drug candidates have toxic effects that would prevent their clinical use [1]. Cardiotoxicity is a particular concern.

Cardiac toxicity can be reversible or irreversible, with reversibility referring to recovery of cellular or organ function [26]. Myocardial changes such as myocardial cell loss (by necrosis or apoptosis), myofibrillar loss, and mitochondrial degradation are generally considered irreversible in the context of cellular or tissue injury. A functional definition of reversibility would mean the resolution of clinical signs and symptoms associated with cardiac dysfunction [27].

Cardiotoxicity has often been observed with the advent of pharmaceuticals for conditions such as cancer and characterized by abnormality of cardiac electrical activity and contractile dysfunction, ultimately leading to heart failure. The identification and understanding of the primary cause of cardiotoxicity would improve pharmaceutical development for effective treatment without cardiac side effects [28]. However, complexities of muscle structure and the heterogeneity of cell populations in the heart make *in vivo* and *in vitro* studies of the whole-heart preparations problematic to identify the primary cause and mechanisms underlying cardiotoxicity at the cellular level [29]. Thus, isolated cardiomyocytes have been powerful tools in the discovering of functional changes in individual cardiac myocytes, in response to stimuli. With careful design and control of cell growth, isolated cardiomyocytes can be maintained for a long time in culture and can provide stable model systems for both short-term and long-term studies of genetic physiology, evaluation of cardiotoxicity, and reparative medicine [29, 30]. Cultured cardiomyocytes constitute the best systems for physiological, pharmacological, and toxicological studies to evaluate direct effects and underlying mechanisms of xenobiotics on the heart at cellular, subcellular, and molecular levels [31]. This study investigated the cardiotoxic effect of aqueous extract of *D. guineense* stem bark in Wistar rats. The results showed that percentage increases in body weights of rats treated with aqueous extract of the medicinal plant stem bark were significantly reduced, relative to the control group, but there were no significant differences in the relative heart weights among the groups. Treatment with the extract did not elicit any significant differences in the activities of LDH and cardiac MDA level among the groups. In all instances, the basal activities of the measured indices of cardiac function were not significantly different from the values after treatment. These results are in agreement with those of previous reports [32 - 34].

CONCLUSION

The results obtained in this study indicate that aqueous extract of *D. guineense* stem bark is not toxic to the heart and could be included in herbal medicine for the treatment of diseases. However, further studies will be needed to ascertain the long-term effect of the extract on other systems in animals.

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