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Nephrotoxic evaluation of ethanol stem bark extract of *Dialium guineense* in normal wistar rats

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Abstract

The present study was undertaken to investigate the nephrotoxic effect of ethanol extract of *Dialium guineense* stem bark in normal Wistar albino rats. Thirty-five male rats were assigned to seven (7) groups (5 rats per group). One group served as control, while graded doses of the extract (200 - 5000 mg/kg body weight, bwt) were administered to the test rats daily for twenty-eight days. The control rats received distilled water. Thereafter plasma concentrations of creatinine, urea, electrolytes and urease activity were measured. There were no significant differences in the concentrations of the measured renal parameters before and after treatment, among the groups ($p > 0.05$). These results indicate that ethanol extract of the medicinal plant stem bark may be relatively safe. However, further studies spanning several months may be necessary.

Keywords: *Dialium guineense*, electrolytes, medicinal plant, nephrotoxicity, renal function

Introduction

As an organ that participates in whole-body homeostasis, the kidney regulates acid-base balance, electrolyte concentrations, extracellular fluid volume and blood pressure. The kidney accomplishes these homeostatic functions both independently and in concert with other organs, particularly those of the endocrine system [1]. Different endocrine hormones coordinate these endocrine functions. Many of the kidney's functions are accomplished by relatively simple mechanisms of filtration, reabsorption, and secretion, which take place in the nephron [2, 3]. The kidneys are responsible for elimination of unmodified drugs and metabolites. Kidney dysfunction is often found in severe liver disease and once liver function falls below a certain threshold, sodium retention occurs followed by ascites [4, 5]. Nephrotoxicity refers to injury to the kidneys or impairment of kidney function caused by exposure to xenobiotics such as drugs, food additives, alcohol, chlorinated solvents, per oxidized fatty acids, fungal toxins, radioactive isotopes, environmental toxicants, and even some medicinal plants [6]. Nephrotoxicity is one of the main toxicities of herbal medicines [7]. Plants are at the center of Traditional Medicine. Their use in disease management is as old as man [8, 9]. Medicinal plants serve as cheap alternative to orthodox medicine since they are readily available [10-12]. *Dialium guineense* is a medicinal plant that is used in parts of Africa for the treatment of various ailments [13]. In Nigeria, it is known by different names: *Icheku* (Igbo), *Awin* (Yoruba), *Tsamiyarkurm* (Hausa) and *Amughen* (Benin) [14]. The plant contains bioactive substances such as alkaloids, tannins, saponins and phenolics [15, 16]. Some of these bioactive compounds may have adverse effects on the kidney. Till date, not much is known about the subchronic toxicity of extracts of *Dialium guineense* stem bark. This study was undertaken to investigate the nephrotoxic effect of ethanol extract of *D. Guineense* stem bark in normal Wistar rats.

Materials and Methods

Chemicals and Kits

Reagents used in this study were of analytical grade. Kidney function tests kits were obtained from Randox Laboratories Limited (UK). All other chemicals were bought from British Drug House (BDH) (England), Merck (Germany) and Sigma-Aldrich Ltd. (USA). Fresh stem barks of *D. Guineense* were obtained from Auchi, Edo State, Nigeria and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria (No. UBHp330).

Plant Extraction

Extraction of the pulverized plant material was by maceration over a 72 h period [17]. A portion (500 g) of the powdered stem bark was soaked in 5000 mL of absolute ethanol. The resultant extract was filtered with a muslin cloth and freeze dried using a lyophilizer.

Experimental Rats

A total of 35 adult male wistar rats, which weighed between 160 and 180 g (mean weight = 170 ± 10 g) were procured from the Department of Anatomy, University of Benin, Benin City, Nigeria. The rats were housed in metal cages under standard laboratory conditions: room temperature, 55 – 65 % humidity and 12-h light/12-h dark cycle. They were allowed free access to pelletized growers mash and clean drinking water. Prior to commencement of the study, the rats were acclimatized to the laboratory environment for seven days. Standard experimental protocol was followed for this study.

Experimental Design

The rats were assigned to 7 groups (5 rats per group). One group served as control, while graded doses of the extract (200 - 5000 mg/kg body weight, bwt) were administered to the test rats daily for twenty-eight days. Blood samples were collected before treatment (basal samples) and at the end of the 28th day. Blood sample collected in plain or heparin containers was centrifuged at 3000 rpm for 10 min to obtain plasma which was used for kidney function tests.

Kidney Function Tests

Kidney function tests (KFTs) such as urea, creatinine, sodium ion, potassium ion, chloride ion and bicarbonate ion were performed in plasma [18-20]. Urease activity was determined as shown below:

$$\text{Urease activity (U/L)} = \frac{\Delta [\text{urea}]/\text{time}}$$

Statistical Analysis

Data are expressed as mean ± SEM (n = 5). The 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

Effect of Graded Doses of Ethanol Extract of *D. guineense* Stem Bark on Weight Parameters

Percentage increases in body weights of rats treated with ethanol extract of *D. Guineense* stem bark were significantly reduced, when compared with control group (p < 0.05), but there were no significant differences in the corresponding relative organ weights among the groups (p > 0.05; Table 1).

Data are percentage weight increase and relative kidney weight, and are expressed as mean ± SEM (n = 3). ^ap < 0.05, when compared with control group; ^b p < 0.05, when compared with the 200 mg/kg bwt group.

Table 1: Percentage body weight increase and relative kidney weight of rats treated with ethanol extract of *D. Guineense* stem bark

Groups	% Increase in weight	Relative kidney weight (x 10 ⁻³)
Control	61.35 ± 4.11	3.34 ± 0.03
200 mg/kg bwt	52.60 ± 2.92 ^a	3.60 ± 0.08
500 mg/kg bwt	22.63 ± 1.56 ^{ab}	3.87 ± 0.31
1000 mg/kg bwt	21.00 ± 1.00 ^{ab}	3.30 ± 0.15
2000 mg/kg bwt	18.30 ± 1.06 ^{ab}	3.47 ± 0.11
3500 mg/kg bwt	17.73 ± 0.92 ^{ab}	3.84 ± 0.21
5000 mg/kg bwt	16.80 ± 1.10 ^{ab}	3.50 ± 0.20

Indices of Kidney Function

There were no significant differences in the plasma concentrations of creatinine, urea, electrolytes and urea/creatinine in rats treated with ethanol extract, when compared with the control group (p > 0.05). These results are shown in Tables 2 and 3.

Table 2: Concentrations of creatinine and urea in rats treated with ethanol extract of *D. Guineense* stem bark

Groups		Creatinine (mg/dL)	Urea (mg/dL)	Urea / Creatinine
Control		1.70±0.03	17.52±6.50	10.31±2.91
200 mg/kg bwt	B	1.59±0.00	15.34±1.29	9.65±0.00
	T	1.73±0.03	16.94±1.69	9.79±1.03
500 mg/kg bwt	B	1.73±0.05	15.56±0.32	8.99±0.73
	T	2.02±0.20	18.35±4.13	9.79±0.84
1000 mg/kg bwt	B	1.50±0.03	17.78±1.94	11.85±0.47
	T	1.75±0.30	22.88±7.31	9.79±0.91
2000 mg/kg bwt	B	1.51±0.00	16.25±0.00	10.76±0.07
	T	1.70±0.20	13.50±2.75	7.94±0.53
3500 mg/kg bwt	B	1.02±0.34	23.92±0.16	23.45±5.02
	T	1.70±0.20	22.58±1.34	13.28±2.03
5000 mg/kg bwt	B	2.70±0.02	17.85±0.64	6.61±0.03
	T	3.05±0.85	19.27±0.74	6.32±0.16

Data are indices of kidney function and are expressed as mean ± SEM (n = 5). B = Basal means; and T = Test means.

Table 3: Concentrations of plasma electrolytes in rats treated with ethanol extract of *D. Guineense* stem bark

Groups	Na ⁺ (mmol/L)	K ⁺ (mmol/L)	HCO ₃ ⁻ (mmol/L)	Cl ⁻ (mmol/L)
Control	138.50±5.50	7.90±0.20	18.00±0.40	105.50±6.50
200 mg/kg bwt	136.50±1.50	6.55±0.15	17.00±2.00	105.50±3.50
500 mg/kg bwt	132.50±8.50	5.65±1.25	15.50±1.50	101.50±5.00
1000 mg/kg bwt	143.50±0.50	8.85±0.85	16.00±1.00	108.00±0.00
2000 mg/kg bwt	143.50±0.50	5.95±0.05	19.00±2.00	109.50±0.50
3500 mg/kg bwt	141.00±1.00	6.15±1.95	17.00±1.00	106.50±0.50
5000 mg/kg bwt	140.00±2.00	7.90±0.60	20.50±3.50	109.00±1.00

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

Effect of Graded Doses of Ethanol Extract of *D. Guineense* Stem Bark on Urease Activity

There were no significant differences in urease activity before and after treatment, among the groups (p > 0.05; Figure 1).

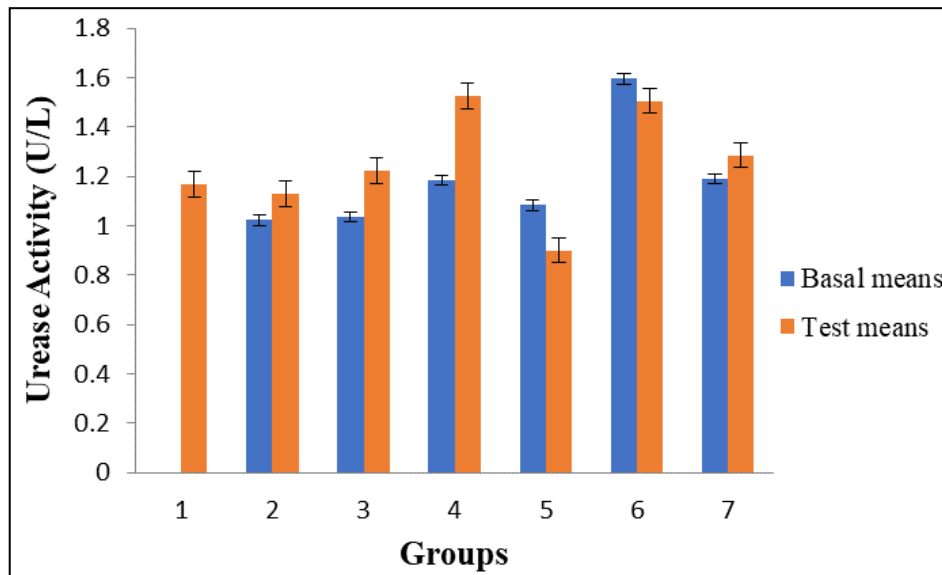


Fig 1: Urease activity in the different groups

Discussion

Bioactive agents from natural sources have gained wide acceptability in modern medicine, as they are known to reduce the risk of diseases by either scavenging free radicals or halting their formation [21]. Most of the pharmacologically important drugs are derived from plants. Plant derivatives used as drugs play crucial role in health-care systems around the globe. They are not only used for the management of disease conditions but also for maintenance of proper health [22]. As good as medicinal plants are, they can be toxic at certain doses and prolonged exposure. In the 1960s, some scholars first reported cases of acute renal failure caused by the administration of *Aristolochia manshuriensis* Kom in China, after which relevant reports also appeared abroad [23]. Nephrotoxicity is one of the main toxicities of herbal medicines [7]. In 1993, Belgian scholars reported that nine European women suffered from renal failure after taking weight-loss capsules containing Chinese herbal medicine *A. Obliqua* S.M. Hwang; this condition is called “Chinese herb nephropathy (CHN)” [7]. Besides aristolochic acid, many other herbal medicine components cause renal toxicity. Severe renal tubular lesions have been found in renal puncture examinations of patients with kidney disease caused by *Tripterygium regelii* Sprague ET. Takeda. The lesions are accompanied by obvious inflammatory cell infiltration, degeneration, and necrosis of renal tubular epithelial cells [24, 25]. The administration of a large amount of *Glycyrrhiza uralensis* Fisch. Caused rhabdomyolysis and acute renal injury. Reports on the beneficial effects of *D. guineense* stem bark abound, but little or nothing is known about its nephrotoxic effect. This study investigated the nephrotoxic effect of ethanol extract of *D. guineense* stem bark in normal Wistar rats. The results showed that graded doses of ethanol extract of *D. guineense* stem bark did not significantly alter the levels of electrolytes, urea and creatinine, an indication that it may not be toxic at the subchronic level. The safety of the plant extracts had been reported in previous studies [26-31].

Conclusion

The results obtained in this study indicate that ethanol extract of *D. Guineense* stem bark is not nephrotoxic and may be used in traditional system of medicine at doses not

exceeding 5000 mg/kg bwt. However, further studies spanning several months may be necessary.

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Author's Contribution

Not available

Conflict of Interest

Not available

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