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Nephrotoxic Potential of Ethanol Root and Stem Extracts of Dennettia Tripetala on Wistar Rats Administered Thermoxidized Palm Oil

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Abstract

This study aimed at assessing the effect of ethanol root and stem extracts of Dennettia tripetala on kidney function indices in rats administered thermoxidized palm oil. Thirty apparently healthy wistar rats weighing between 150 g to 180 g were divided into six equal groups of 5 rats each and used for the study. Group 1 served as the positive control while Group 2 animals which received 1 ml of thermoxidized palm oil daily served as the negative control. Group 3 received 1 ml of thermoxidized palm oil + 50 mg/kg of the root extract daily. Group 4 received 1 ml of thermoxidized palm oil + 50 mg/kg of the stem extract daily. Group 5 was given 1 ml of thermoxidized palm oil + 100 mg/kg of the root extract daily while group 6 received 1 ml of thermoxidized palm oil + 100 mg/kg of the stem extract. The treatment of the rats were done by oral intubation and lasted for 21 days. Standard analytical methods were used to determine renal function indices including serum urea, creatinine and electrolyte (Na^+, K^+, Cl^- and $H_2CO_3^-$) levels. Treatment of the animals with 50 mg/kg of both root and stem extracts of D. tripetala led to a significant decrease ($p<0.05$) in the levels of urea (48.89 ± 1.78; 52.27 ± 1.51) and creatinine (0.94 ± 0.05; 0.89 ± 0.04) when compared with the negative control (74.42 ± 2.34 and 2.08 ± 0.08 respectively). There was, however, no significant change ($p>0.05$) in the levels of urea and creatinine in animals treated with 100 mg/kg of both stem and root extracts when compared with group 2 animals. Results showed a statistically significant change in the levels of Na^+, K^+, HCO_3^- and Cl^- in experimental rats that received 100 mg/kg of root and stem extracts of D. tripetala when compared with group 2 animals. In all the parameters measured (urea, creatinine, Na^+, K^+, HCO_3^- and Cl^-), group 2 animals (negative control) showed a significant change (74.42 ± 2.34; 2.08 ± 0.08; 136.16 ± 1.67; 2.50 ± 0.27; 36.20 ± 0.89; 110.40 ± 0.83) when compared with group 1 animals (37.20 ± 2.04; 0.82 ± 0.09; 152.60 ± 1.14; 4.46 ± 0.08; 25.40 ± 0.83; 95.20 ± 1.34). In conclusion, root and stem extracts of D. tripetala have those dependent negative effects on kidney function indices, may induce glomerular and tubular dysfunction of the nephron and contribute to renal failure. Herbal preparations of D tripetala should therefore be taken with proper medical advice and monitoring.

Keywords: Dennettia tripetala; Thermoxidized palm oil; Wistar rat; kidney function indices; Electrolytes

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Introduction

Popularity of use and acceptance of roots and herbs for wellbeing and medicinal purposes have been on the increase over the years. Use of plants as sources of remedies for the treatment of diseases date back to prehistoric times and people of all continents are used to this old tradition [1]. Plants are one of the richest sources of bioactive compounds and have been the basis of many traditional medicines throughout the world for thousands of years [2]. Despite the remarkable progress in synthetic organic chemistry of the twentieth century, over 25% of prescribed medicines in industrialized countries are derived directly or indirectly from plants [3]. Approximately, 60% of the world's population depends on traditional medicine and 80% of the population in developing countries depends almost entirely on traditional medicines for their primary health care needs [4-6]. The reasons for dependence on traditional medicines, especially in developing nations, includes ease of assessing herbal remedies, unavailability of orthodox medicine as well as cost of procuring

prescribed medications [7].

Dennettia tripetala is a medicinal plant found in the rain forest zone of Africa, widely domesticated in the Southern, Eastern and Western parts of Nigeria and consumed by inhabitants of Western Cameroons, Ivory Coast, Southern and Eastern Nigeria [8]. It is a spicy indigenous fruit tree which belongs to the family *Annonaceae* [9]. Dennettia tripetala grows to a height of 12 m to 15 m and has a girth of 0.6 m [10]. It has a bark that possesses a very strong characteristic scent, a wood that is white and soft, fruits which are edible with spicy taste and green in color when developing but turns red with ripening and leaves which are elliptical in shape with sizes of 3 inches to 6 inches long and 1.5 inches to 2.5 inches broad [11]. Dennettia tripetala is popularly known as pepper fruit. In Nigerian local languages, it is called "Mmimi" in Ibo, "Nkarika" in Efik and "Ata Igbere" in Yoruba [12].

Like other medicinal plants, use of Dennettia tripetala for health-care purposes largely depends on the presence of phytochemicals. Sparg [13] revealed the presence of tannins, alkaloids, steroids, flavonoids, cardiac glycosides, saponins and terpenoids following a phytochemical screening of ethanol extract of D. tripetala. There is also presence of proteins, fiber, ash, lipids and moisture which increases with ripening [8]. Also found in D. tripetala are antioxidants such as lycopene, ascorbic acid, p-coumaryl alcohol, ethoxyquin and capsaicinoids [14] and essential oils like carvacrol, carvone, caryophyllene, limonene and thymol [15,16].

Documentations of medicinal and health benefits of Dennettia tripetala abound in literatures. It has been reported to have antibiotic [17-19], antioxidant [8,20-24] antinociceptive and anti-inflammatory potentials [12,14,25-27]. Other benefits of D. tripetala include anticancer activity [14,28-31]; antiviral activity [32] also serve as an appetite stimulant, mouth wash and anti-pyretic [33,34].

The kidney is one of the vital organs of the body intimately involved with maintenance of body homeostasis through its regulation of body fluid and compositions. It plays a pivotal role in excretion of drugs, chemicals and waste products of metabolism [35]. Toxic substances can inflict injury on the kidney and in turn limit it from performing notable excretory functions that may lead to renal failure [36]. Estimates of plasma or serum levels of creatinine, urea and certain electrolytes are employed as a marker for kidney functions [37,38]. This is understood considering the fact that creatinine and urea are non-protein nitrogenous metabolites that are cleared from the body by the kidneys during the processes of urine formation.

Thermal oxidation of edible oils has become widespread in most homes in Nigeria regardless of the fact that this practice according to Ames et al. [39] and Halliwell [40] produces free radicals which lead to tissue damage and cell death and which have been implicated in the pathogenesis of various chronic and degenerative disorders with attendant consequence of impaired renal function. It is now a common tendency for people to repeatedly reuse thermally heated oil in frying and cooking with little or no knowledge of its adverse effects on health and general well-being. The medicinal value of different parts of Dennettia tripetala tree has gained acceptability in communities in South-Eastern Nigeria where alternative medicine is prevalent because of high level of poverty, poor education and lack of access to quality health care [41]. However, as much as several works have been done to substantiate the enormous health benefits of Dennettia tripetala, there is still paucity of information regarding its effects on renal functions. In view of this therefore, this study aimed at assessing the effect of ethanol root and stem extract of Dennettia tripetala on kidney function indices in rats administered thermoxidized palm oil.

Materials and Methods

Identification and collection of plant materials

Root and fresh stem of Dennettia tripetala were obtained from different local farmlands in Ulakwo, Egbelu and Ngwoma in Owerri-North L.G.A of Imo State Nigeria. They were identified and authenticated in the department of plant science and biotechnology, Imo State University, Owerri. Both the root and stem were cut to pieces with knife (to facilitate drying), thoroughly washed to remove unwanted debris and air-dried at room temperature for 14 days until constant weight was obtained. After drying, they were pulverized to fine powder with the aid of a mechanical grinder and kept in labeled airtight containers under dry conditions until required for use.

Ethanol stem extraction of Dennettia tripetala

Ethanol root and stem extraction of Dennettia tripetala was done using the modified method of Abdulrahman et al. [42]. Six hundred and fifty grams (650 g) of powdered root and stem of Dennettia tripetala was each macerated in 2 liters of 95% absolute ethanol for 24 h. It was filtered with sterile filter paper and evaporated afterwards to dryness at 40°C in a vacuum using a rotary evaporator RE52. Approximate concentrations of the extract were constituted to the required doses for the treatment of the animals using normal saline.

Animals and experimental design

Thirty albino wistar rats weighing between 150 g to 180 g were used for the study. The animals were randomly divided into six groups of 5 rats each and were acclimatized for 7 days under standard environment at a temperature of 22°C to 25°C, 12 h light and 12 h dark cycle before commencement of administration. While being acclimatized and treated, the rats were fed normal rat chow (Product of Vital Feed Nig. Ltd) and water ad libitum. D. tripetala extracts were orally administered to the rats using oral gastric tube inserted through their mouth. The extracts were administered for 21 days.

Group 1: rats were not treated (positive control).

Group 2: received normal rat chow with 1 ml of thermoxidized palm oil daily (negative control).

Group 3: received 1 ml of thermoxidized palm oil + 50 mg/kg of root extract of D. tripetala daily.

Group 4: received thermoxidized palm oil + 50 mg/kg of stem extract of D. tripetala daily.

Group 5: received 1 ml of thermoxidized palm oil + 100 mg/kg of root extract of D. tripetala daily.

Group 6: received 1 ml of thermoxidized palm oil + 100 mg/kg of stem extract of D. tripetala daily.

Analytical procedure

Twenty-four hours (24 h) after the last day of administration, the rats were sacrificed under chloroform anesthesia and with sharp scissors; their cavities were cut open to expose the heart. Blood samples of the rats were collected by cardiac puncture into a plain sterile test tube using a sterile syringe and allowed to clot for 10 min. Serum was obtained by centrifuging at 1000 rpm for 5 min using a Whisperfuge

Table 1: Effects of ethanol stem and root extracts of Dennettia tripetala on serum Urea and Creatinine.

Group	1	2	3	4	5	6
Treatment	Rat chow + water (+ve control)	Rat chow + water + 1 ml of oil (-ve control)	Oil + 50 mg/kg of root extract	Oil + 50 mg/kg of stem extract	Oil + 100 mg/kg of root extract	Oil + 100 mg/kg of stem extract
Urea (mg/dl)	37.20 ± 2.04	74.42 ± 2.34[a]	48.49 ± 1.78[ab]	52.27 ± 1.51[ab]	63.56 ± 1.38[a]	68. 14 ± 1.45[a]
Creatinine (mg/dl)	0.82 ± 0.09	2.08 ± 0.08[a]	0.94 ± 0.05[b]	0.89 ± 0.04[b]	1.42 ± 0.06[ab]	1.95 ± 0.05[a]

The values are triplicates of three determinations and are given as mean ± standard deviation.
a = significantly different from group 1 (+ve control)
b = significantly different from group 2 (-ve control)
n=5, p<0.05

centrifuge (model 1384), collected with a Pasteur pipette into clean labeled sample bottle and was later used for biochemical analysis.

Biochemical analysis

Kidney function indices were analyzed from the sample. Determination of urea concentration was done by diacetylmonoxime method using assay kit from Randox laboratories UK while creatinine concentration was determined by the alkaline picrate method [43]. Determination of serum sodium and potassium concentrations was done using reagent kit [43]. Serum bicarbonate concentration was determined trimetrically while determination of chloride concentration was done using the mercuric nitrate method as modified by Teco diagnostics 1268N Lakeview Avenue Anahein; CA 92807, USA [44].

Statistical analysis

Data generated in this study were entered, cleaned and coded in excel sheets and were presented as mean ± SD of three determinations. Statistical analysis was done using the Statistical Package for Social Science (SPSS)/IBM version 21 software. Statistical differences between the experimental and control groups were determined using ANOVA and students t-test. Values were considered significant at $p<0.05$.

Results

Table 1 show the effect of ethanol root and stem extracts of Dennettia tripetala on serum urea and creatinine. The result showed a statistically significant increase ($p<0.05$) in serum levels of urea and creatinine in experimental animals that received only thermoxidized palm oil (group 2) when compared with group 1 animals which served as the positive control. The levels of both urea and creatinine were significantly elevated on administration of 50 mg/kg and 100 mg/kg of both root and stem extracts of D. tripetala when compared with group 1 animals. However, administration of 100 mg/kg of root and stem extracts showed no significant decrease ($p>0.05$) in the levels of both urea and creatinine when compared with rats that were administered thermoxidized palm oil only. Effects of ethanol stem and root extracts of D tripetala on serum electrolytes are shown on Table 2. From the result, animals that received 1 ml of thermoxidized palm oil for 21 days showed a statistically significant decrease ($p<0.05$) in the levels of Na^+, K^+, HCO_3^- and Cl^- when compared with group 1 animals. Also, treatment with 100 mg/kg of both root and stem extracts produced a significant change in the levels of Na^+, K^+, and significant increase in HCO_3^- and Cl^- when compared with the negative control (group 2 animals). While the results of animals that received 50 mg/kg of root and stem extracts of Dennettia tripetala showed a significant increase in the levels of K^+ and Cl^- when compared with group 2 animals, such animals did not show any significant change in the levels on Na^+ and HCO_3^- when compared with the negative control.

Discussion

The kidney is primarily responsible for maintenance of homeostasis of fluid and electrolytes in the body. Its functions include urine formation, regulation of acid-base balance, excretion of waste products of metabolism and toxic substances, protein conservation, secretory functions and recovery of useful metabolites which filter through them [45]. The physiologic roles of the kidneys as the major excretory organs of the body make them paramount to the normal functioning of the body. Their pivotal role in maintaining the body homeostasis, excretion of drugs, chemicals and waste products of metabolism are vital to maintenance of health [35]. Assessment of kidney function indices such as serum urea, creatinine and electrolytes (Na^+, K^+, Cl^-, HCO_3^-) which are vital and sensitive biochemical markers is usually employed in the diagnosis of renal damage and failure [36,37,46]. Creatinine and urea are non-protein nitrogenous metabolites that are cleared by the body following glomerular filtration. They are among the waste products of metabolism excreted by the kidneys while needful electrolytes are reabsorbed in maintenance of homeostasis [47,48,49].

Heating of palm oil during domestic use is known to cause oxidative changes which brings about the formation of ketones, aldehydes, peroxides, ozonides and other free radicals from the polyunsaturated palm oil components of the oil [1,50]. These by-products of oil thermoxidation are known to be toxic to cells, tissues and organs [51,52]. Administration of thermoxidized palm oil in experimental rats led to a significant increase in the major kidney biomarkers thus: urea, creatinine, sodium and potassium. Ani et al.

Table 2: Effects of ethanol stem and root extracts of Dennetia tripetala on serum electrolytes.

Group	1	2	3	4	5	6
Treatment	Rat chow + water (+ve control)	Rat chow + water + 1ml of oil (-ve control)	Oil + 50 mg/kg of root extract	Oil + 50 mg/kg of stem extract	Oil + 100 mg/kg of root extract	Oil + 100 mg/kg of stem extract
Na^+ (mmol/L)	152.60 ± 1.14	136.16 ± 1.67[a]	142.43 ± 0.70[a]	140.18 ± 0.71[a]	148.26 ± 1.14[b]	150.54 ± 1.16[b]
K^+ (mmol/L)	4.46 ± 0.08	2.50 ± 0.27[a]	3.50 ± 0.07[b]	3.84 ± 0.07[b]	3.96 ± 0.12[b]	4.01 ± 0.20[b]
HCO_3^- (mmol/L)	25.40 ± 0.83	36.20 ± 0.89[a]	32.73 ± 1.58[a]	30.48 ± 1.59[a]	23.82 ± 2.26[b]	24.52 ± 1.87[b]
Cl^- (mmol/L)	95.20 ± 1.34	110.40 ± 0.83[a]	98.24 ± 0.70[b]	97.17 ± 0.71[b]	96.66 ± 0.83[b]	94.21 ± 0.45[b]

The values are triplicates of three determinations and are given as mean ± standard deviation
a = significantly different from group 1 (+ve control)
b = significantly different from group 2 (-ve control)
n=5, P<0.05

[53] reported a similar change in the levels of serum electrolytes, urea and creatinine in rabbits fed with thermoxidized palm oil and hence a compromised renal status in such rabbits. Also Osims et al. [54] reported nephritic damage and tubular atrophy in rats administered thermoxidized palm oil. High level of oxygen free radicals and hydroxyl esters present in thermoxidized palm oil which are cytotoxic may be responsible for the observed kidney damage [55-57].

High serum levels of urea and creatinine are indicative of kidney damage. While creatinine is produced endogenously in the muscle by a non-enzymatic action on creatine phosphate, urea is the primary non-protein catabolite of protein metabolism. The results showed that the administration of the extract (50 mg/kg) significantly reduced the levels of urea and creatinine when compared with rats that received thermoxidized palm oil only. However, increase in the dosage of the extract tends to return serum urea and creatinine to the toxic levels seen in animals that received only thermoxidized palm oil. These changes are more pronounced in animals that received stem extract. Nwankpa et al. [58] reported similar dose-dependent increase in creatinine level in animals fed with 100 mg/kg, 200 mg/kg and 300 mg/kg stem extract of Dennettia tripetala. While this study did not delve into understanding the exact mechanism that brought about such elevation of serum creatinine, inflammatory changes in the glomerular cells and interstitial nephritis may have played a role. Our findings on high serum levels of urea at 100 mg/kg of extract is in agreement with that of Salawu et al. [59] who reported a significant and dose dependent increase in the levels of urea in experimental rats fed with ripe D. tripetala fruit extract. This elevation may be explained by the glomerular and tubular damage that may have resulted from the administration of D. tripetala extracts [60]. Such elevations of both serum urea and creatinine are indicative of renal damage [58,59].

The kidneys serve as the major site for the regulation of fluid and electrolyte balance. While K^+ is predominant in the ICF compartment and plays a role in neuromuscular activities, contraction of cardiac muscles and H^+ regulation, Na^+ is the major ECF compartment electrolyte and helps in the maintenance of blood pressure, nerve impulses and muscle function [60,61]. The significant increase in Na^+ and K^+ in groups 5 and 6 rats when compared with the negative control observed in this study agrees with the findings of [58,62,63]. Okaka and Okaka [63] reported a high concentration of potassium (2.48%), calcium (1.80%) and sodium (0.72%) in fruit extracts of D tripetala. The exact mechanism for the effect of the extracts on serum electrolytes in this study is unclear. Na^+ K^+ -ATPase which regulates efflux of Na^+ and influx of K^+ may not be primarily involved since there is increase in both serum N^+ and K^+ concentrations. Na^+/H^+ exchanger which can be controlled by membrane-bound aldosterone that regulates the reabsorption of Na^+ may be more appropriately linked to the observed hypernatremia [56,59]. Thus Na^+/K^+ pump may have been impaired on the administration of root and stem extracts of Dennettia tripetala. This is supported by the observed significant decrease ($P<0.05$) in chloride and bicarbonate concentrations, suggesting that the extract may have induced renal damage resulting to impairment on renal function. It may not be wrong therefore to suggest that root and stem extracts of Dennettia tripetala may have induced histopathological and biochemical derangements in renal tissues that may affect the Na^+/H^+ exchanger or Na^+/K^+ pump in some ways and possibly lead to oliguria, anuria and renal failure which are anomalies often associated with electrolyte alterations [64].

Conclusion

In conclusion, root and stem extracts of Dennettia tripetala have negative impact on kidney function indices, may induce glomerular and tubular dysfunction of the nephron and contribute to renal failure. We therefore recommend that herbal preparations of Dennettia tripetala should be taken with proper medical advice and monitoring.

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