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Research Article

Nephrotoxic and Hepatotoxic Effects of *Clerodendrum capitatum* (Willd) Schumach et. Thonn and *Phyllanthus fraternus Schum*. and Thonn. (Euphorbiaceae) extracts used as food grains protectant on Albino rats

Abstract

Background: *Clerodendrum capitatum* (Willd) Schumach et. Thonn. (Family: Verbenaceae) and *Phyllanthus fraternus* Schum. and Thonn. (Euphorbiaceae) are used as food grains protectants among resource poor farmers, nevertheless there is dearth of experimental data on the possible toxicity of such stored food grains if consumed. The toxic effects were considered by quantifying liver and kidney enzymes such as aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), total protein, creatinine and urea respectively.

Purpose of the study: This study evaluates the influence of *C. capitatum* hexane extract and *P. fraternus* ethyl acetate extract on likely alterations of renal and hepatic functions using some biochemical parameters.

Results: The results show that, there was no significant difference in the body weight of both treated and untreated animals at any of the doses administered throughout the experimental duration. No mortality or morbidity and behavioural changes was documented, also biochemical indices of AST, ALT, ALP, TP, urea and creatinine decreased significantly ($P \leq 0.05$) in the treated animals in comparison to the untreated ones as the concentrations of extracts increase. However, 500 and 1000mg/kg oral administration of *C. capitatum* and *P. fraternus* leaf extracts resulted in no noticeable changes in the liver biochemical indices of treated rats compared to untreated. While, there was progressive increase in AST, ALT and ALP activities in the serum of the animal administered with *C. capitatum* and *P. fraternus* extracts, which is directly proportional to increase in the dosage rates, the serum AST, ALT and ALP activities of the animal group administered with 1500 and 2000mg/kg of *C. capitatum* and *P. fraternus* extracts were significantly ($P \leq 0.05$) higher than those administered with 500, 1000mg/kg and untreated animals. The kidney serum activities of urea and creatinine in animals administered with both extracts exhibited dose-dependent response, as animal administered with 2000mg/kg of *C. capitatum* and *P. fraternus* extracts produced the highest serum activities of urea (61.50 and 64.50 mmol/l) and creatinine (116.0 and 118.0 mmol/l) respectively and was significantly higher ($p<0.05$) than the animals administered with other lower dosages and untreated.

Main findings: Oral administration of both plant extracts does not cause significant alteration in the kidney and liver function indicators in the experimental rats, suggesting that the plants were neither nephrotoxic nor hepatotoxic.

Conclusions: *C. capitatum* hexane extract and *P. fraternus* ethyl acetate extract possessed high safety index and their constant usage in suppressing insect pest infestation in stored food grains is supported among resource poor farmers as a component of integrated pest management. Further investigation is required to unravel the mechanism responsible for it's the nephroprotective and hepatoprotective actions.

Introduction

The prevalence of insect resistant, health and environmental hazard and residue in food grains occasioned by the continuous and indiscriminate usage of synthetic insecticides and fumigants in ensuring insect pest free stored produce has continued to threaten the efficacy and continue utilization of many existing synthetic insecticides and fumigants, leading to

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extensive investigation of medicinal and aromatic plants for its potential insecticidal activity in recent years. The insecticidal property of botanicals lies in their bioactive phytochemical constituents that produce definite physiological action leading to insect mortality and suppression of adult emergence [1,2].

Clerodendrum capitatum (Willd) Schumach et. Thonn. (Family: Verbenaceae) and *Phyllanthus fraternus* Schum. and Thonn. (Euphorbiaceae), are indigenous widespread tropical herbal plants used for various ethnomedicinal purposes [3-6]. In spite of the reported efficacy of these plants as phyto-insecticide in the management of stored product insect pest infestation and malaria vector [7-12], limited information is available on their toxicity and safety. Investigation of the acute oral toxicity is the first step in the toxicological investigation of the unknown substance [13]. Liver function tests conducted through serum assays give information about the state of the liver, describing its functionality (albumin), cellular integrity (transaminases) and its link with the biliary tract (alkaline phosphatase) [14]. Nephrotoxicity induced is exhibited functionally by decreased urine concentrating capacity, tubular proteinuria, lysosomal enzymuria, mild glucosuria, decreased ammonium excretion and lowering of glomerular filtration rate [15].

The optimal effectiveness of a medicinal and aromatic plants might not be due to one main active constituent, but may be due to the combined action of different compounds originally in the plant [16-17]. Since plants contain secondary metabolites that could induce toxic effects to invading organisms, there is the need for phytochemical analysis and standardisation of this plant through acute, sub-acute and chronic toxicity analysis with a view to ascertain its safety. Hence, this study aims to investigate the biochemical alterations accompanying oral toxicity of *C. capitatum* hexane and *P. fraternus* ethyl acetate extracts on liver and kidney of albino rats.

Materials and Methods

Collection of plant materials and preparation of extracts

The leaves of *C. capitatum* and *P. fraternus* were collected from different locations within Owo metropolis, Ondo State, Nigeria. Identification of the plant materials was done at the Forestry and Wood Technology Department, Rufus Giwa Polytechnic, Owo, Ondo State, Nigeria (Latitude 7° 11' N and Longitude 5° 35' E). The leaves were shade dried for a week, thereafter milled to powder using hammer mill and package in a polythene bag till use.

Two hundred (200g) grams of the plant powder was sequentially extracted with a series of solvents of increasing polarity viz., petroleum ether, hexane, ethyl acetate, acetone, chloroform and methanol, in a soxhlet apparatus. The solvent from the extract was evaporated and concentrated in rotary evaporator under low pressure, below 60°C to make it solvent free and the residue dissolved in a known volume of methanol. The solution was then assayed for insecticidal activity by the fumigant toxicity. Active extract which showed maximum activity, was selected for the toxicological activity.

Experimental animals and oral toxicity study

Twenty-seven (27) adult albino rats of both sex weighing between 150 and 170kg were housed in a cage and acclimatized for 2 weeks under strict hygienic ambient conditions with free access to feed and water *ad libitum* and randomized into experimental and control groups.

Group I – control rats

Group II - rats treated with 500 mg/kg *C. capitatum* hexane extract

Group III – rats treated with 1000 mg/kg *C. capitatum* hexane extract

Group IV – rats treated with 1500 mg/kg *C. capitatum* hexane extract

Group V – rats treated with 2000 mg/kg *C. capitatum* hexane extract

Group VI – rats treated with 500 mg/kg *P. fraternus* ethyl acetate extract

Group VII – rats treated with 1000 mg/kg *P. fraternus* ethyl acetate extract

Group VIII – rats treated with 1500 mg/kg *P. fraternus* ethyl acetate extract and

Group IX – rats treated with 2000 mg/kg *P. fraternus* ethyl acetate extract.

The extract doses were administered using special stomach tube with a smooth tip to protect the oral mucosa and oesophagus from injury. All the experimental animals were individually observed daily for mortality or morbidity and general behavioural changes throughout the duration of the experiment [5].

The use of the animals was approved by the appropriate Ethics Committee and all experiments were performed according to National Health Guide for the Care and Use of Laboratory Animals [18].

Collection and preparation of tissue homogenate

At the end of the experimental period, the rats were deprived of food but had free access to water for 24 hrs before being sacrificed by cervical decapitation. The blood samples were collected through heart puncture by means of a 5ml hypodermic syringe and needle into lithium heparin bottle. The liver and kidneys of the rats were also excised and used for biochemical analysis. Ten percent (10%) homogenates of the organs were prepared by homogenizing in ice-cold normal saline. The homogenates were centrifuged at 2000 rpm for 15 minutes and the supernatant obtained were used for biochemical analysis [6].

Biochemical analysis

The plasma and the homogenates of kidney and liver of each rat was used in the determination of biochemical

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parameters (aspartate amino transferase (AST), alanine amino transferase (ALT) and Alkaline phosphatase (ALP)) using Randox Laboratories, UK reagent. Plasma was separated by centrifugation of blood samples at 3000 rpm for 5 minutes [19]. The activity of aspartate amino transferase (AST) and alanine amino transferase (ALT) were determined colorimetrically at 546 nm using a standard method [20]. Alkaline phosphatase (ALP) was measured using colometric method described by Gesellschaft [21]. Total protein (TP) and urea were measured colorimetrically at 546 nm using the biuret method [22] and urease cleavage Berthelot's reaction method [23] respectively, while creatinine level was determined by the method of Bonsnes and Taussky [24].

Statistical analysis

Data collected were analysed using one-way analysis of variance (ANOVA) and group means were compared using the Tukey Multiple Comparison Test to evaluate significant differences between groups using Statistical package for social science (SPSS software version 17). The results are expressed as mean ± standard error of the mean (SEM) and were considered to be significant at $p < 0.05$.

Effects of *C. capitatum* and *P. fraternus* extracts on percentage body weight of albino rats

Data in table 1 shows the response of the rats to administration of *C. capitatum* and *P. fraternus* extracts to percentage body weight during the experimental duration. The results show that, there was no significant difference in the body weight of both treated and untreated animals. However, all the animals responded well to the extracts administration by gaining weight at the end of the experiment.

Effects of *C. capitatum* hexane Extract and *P. fraternus* ethyl acetate extract on some liver biochemical indices of albino rats

Results presented in tables 2 and 3 show the effects of *C. capitatum* and *P. fraternus* extracts on liver and serum biochemical indices of Albino rats correspondingly. No lethality or behavioural changes were recorded in both untreated and treated groups at any of the doses administered throughout the experimental duration. In sub-chronic toxicity study, 500 and 1000mg/kg oral administration of *C. capitatum* and *P. fraternus* leaf extracts resulted in no noticeable changes in the liver biochemical indices of treated rats compared to untreated. Aspartate aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) and Total Proteins (TP) of the animals administered with 500 and 1000mg/kg of both extracts were not significantly different ($p<0.05$) from each other compared with untreated animals, while significant difference ($p<0.05$) exist in animals administered with 1500 and 2000mg/kg of both extracts in comparison with 500 and 1000mg/kg and untreated animals. However, there was significant decrease in AST, ALT, ALP and TP activities of all the treated animals in relation to the untreated ones. Total protein contents were significantly ($P \leq 0.05$) reduced as the concentrations of extracts increased (Table 2).

There was progressive increase in AST, ALT and ALP activities in the serum of the animals administered with *C. capitatum* and *P. fraternus* extracts; which is directly proportional to the increase in the dosage rates. (Table 3). An increase in the serum enzyme activity signifies damages to the liver membrane. The increase recorded was not significantly different in the animals administered with 500 and 1000mg/kg of *C. capitatum* and *P. fraternus* extracts respectively compared to untreated animals. However, there was a slight significantly difference ($P \leq 0.05$) between the untreated animals and those administered with 500 and 1000mg/kg for ALT and ALP activities. The serum AST, ALT and ALP activities of the animal group administered with 1500 and 2000mg/kg of *C. capitatum* and *P. fraternus* extracts were significantly ($P \leq 0.05$) higher than those administered with 500, 1000mg/kg and untreated animals (Table 2). Largely, the activities of these enzymes in the animals administered with 500 and 1000mg/kg of *C. capitatum* and *P. fraternus* extracts compared favourably with untreated animals (Tables 2,3).

Table 1: Effects of *C. capitatum* hexane extract and *P. fraternus* ethyl acetate extract on body weight of albino rats

Treatment Group	Initial weight (g)	Final weight (g)	% Weight gain
I	166.43	173.04	3.97[a]
II	157.67	165.15	4.74[a]
III	172.53	179.37	3.97[a]
IV	157.12	160.42	2.10[a]
V	164.55	168.30	2.27[a]
VI	160.08	164.11	2.52[a]
VII	175.28	179.52	2.42[a]
VIII	155.54	159.43	2.50[a]
IX	171.76	175.21	2.01[a]

Each value is a mean of three replicates.

Table 2: Toxicity of *C. capitatum* and *P. fraternus* Extracts on some Liver Biochemical Indices of Albino Rats.

Plant Extracts/ Conc. (ml)	Aspartate aminotransferase (AST) IU/g	Alanine aminotransferase (ALT) IU/g	Alkaline phosphatase (ALP) IU/g	Total protein min (x 10-1)
500mg/kg				
C. capitatum	167.00±4.21[b]	120.25±2.20[b]	24.25±2.20[b]	1.60±0.04[b]
P. fraternus	169.50±4.10[b]	119.25±2.20[b]	25.00±1.21[b]	1.58±0.02[b]
1000mg/kg				
C. capitatum	162.50±4.10[b]	116.00±2.21[b]	24.25±1.20[b]	1.57±0.03[b]
P. fraternus	163.00±4.21[b]	115.75±2.28[b]	25.00±1.21[b]	1.54±0.03[b]
1500mg/kg				
C. capitatum	146.00±4.21[a]	100.25±2.20[a]	10.50±1.10[a]	0.70±0.04[a]
P. fraternus	144.25±4.20[a]	107.50±2.20[a]	9.50±1.10[a]	0.85±0.03[a]
2000mg/kg				
C. capitatum	140.00 ±4.21[a]	108.00±2.21[a]	9.00±1.11[a]	0.75±0.02[a]
P. fraternus	138.00 ±4.21[a]	101.50±2.10[a]	8.50±1.10[a]	0.70±0.02[a]
Untreated	172.75 ±2.17[b]	125.25±2.20[ab]	28.50±1.11[b]	1.64±0.01[b]

Each value is a mean ± standard error of three replicates. Mean in the same column with the similar superscripts are not significantly different at ($p<0.05$) using Tukey Multiple Comparison Test.

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Effects of plant extracts on kidney function of albino rats

The effects of *C. capitatum* and *P. fraternus* extracts on kidney and serum biochemical parameters of albino rats were presented in tables 4 and 5. Increase in the extract doses significantly resulted in decrease in urea and creatinine values of treated animals compared to the untreated in kidney biochemical parameters (Table 5). The decrease is more pronounced in those animals treated with 1500 and 2000mg/kg.

The kidney serum activities of urea and creatinine in animals administered with both extracts exhibited dose-dependent response (Table 5), as animal administered with 2000mg/kg of *C. capitatum* and *P. fraternus* extracts produced the highest serum activities of urea (61.50 and 64.50 mmol/l) and creatinine (116.0 and 118.0 mmol/l) respectively and was significantly higher ($p<0.05$) than the animals administered with lowers dosages and untreated (Table 5). An increase in the serum enzyme activity signifies damages to the kidney membrane.

Table 3: Toxicity of *C. capitatum* and *P. fraternus* Extracts on some Serum Biochemical Parameters of Albino Rats.

Plant Extracts/ Conc. (ml)	Aspartate aminotransferase (AST) IU/g	Alanine aminotransferase (ALT) IU/g	Alkaline phosphatase (ALP) IU/g
500mg/kg			
C. capitatum	47.25±2.20^{a}	42.00±2.10^{a}	26.50±2.10^{a}
P. fraternus	47.00±2.10^{a}	44.50±2.10^{a}	28.25±1.20^{a}
1000mg/kg			
C. capitatum	54.00±2.10^{a}	46.50±2.10^{a}	28.00±1.10^{a}
P. fraternus	55.50±2.10^{a}	47.50±2.10^{a}	29.50±1.10^{a}
1500mg/kg			
C. capitatum	70.50±2.15^{b}	63.00±2.10^{b}	43.00±2.10^{b}
P. fraternus	73.00±2.10^{b}	70.00±2.20^{b}	42.50±2.15^{b}
2000mg/kg			
C. capitatum	87.25 ±2.20^{c}	82.50±2.15^{c}	58.00±2.10^{c}
P. fraternus	90.50 ±2.15^{c}	86.00±2.10^{c}	58.50±2.15^{c}
Untreated	45.00 ±2.21^{a}	38.50±2.10^{ab}	19.00±1.11^{b}

Each value is a mean ± standard error of three replicates. Mean in the same column with the similar superscripts are not significantly different at ($p<0.05$) using Tukey Multiple Comparison Test.

Table 4: Toxicity of *C. capitatum*, and *P. fraternus* Extracts on some Kidney Biochemical Parameters of Albino Rats.

Plant Extracts/ Conc. (ml)	Urea (mmol/l)	Creatinine (mmol/l)
500mg/kg		
C. capitatum	30.50±2.15^{b}	160.50±3.15^{b}
P. fraternus	28.00±2.10^{b}	159.00±3.10^{b}
1000mg/kg		
C. capitatum	23.00±2.10^{b}	154.25±3.20^{b}
P. fraternus	22.50±2.15^{b}	153.50±3.15^{b}
1500mg/kg		
C. capitatum	19.25±2.20^{a}	131.00±3.10^{a}
P. fraternus	18.00±2.10^{a}	128.00±3.10^{a}
2000mg/kg		
C. capitatum	16.00±2.20^{a}	125.50±3.15^{a}
P. fraternus	18.00±2.10^{a}	122.50±3.15^{a}
Untreated	33.50±2.15^{b}	166.25±3.20^{b}

Each value is a mean ± standard error of three replicates. Mean in the same column with the similar superscripts are not significantly different at ($p<0.05$) using Tukey Multiple Comparison Test.

Table 5: Toxicity of *C. capitatum*, and *P. fraternus* Extracts on some Serum Biochemical Parameters of Albino Rats.

Plant Extracts/ Conc. (ml)	Urea (mmol/l)	Creatinine (mmol/l)
500mg/kg		
C. capitatum	18.50±1.15^{a}	52.25±2.20^{a}
P. fraternus	17.00±1.10^{a}	54.25±2.20^{a}
1000mg/kg		
C. capitatum	21.00±2.10^{a}	55.00±2.10^{a}
P. fraternus	23.50±2.15^{a}	56.00±2.10^{a}
1500mg/kg		
C. capitatum	46.50±2.15^{b}	90.25±2.20^{b}
P. fraternus	47.25±2.20^{b}	92.50±2.20^{b}
2000mg/kg		
C. capitatum	61.50±2.15^{c}	116.00±3.10^{c}
P. fraternus	64.50±2.15^{c}	118.00±3.10^{c}
Untreated	13.25±1.20^{a}	45.00±2.10^{a}

Each value is a mean ± standard error of three replicates. Mean in the same column with the similar superscripts are not significantly different at ($p<0.05$) using Tukey Multiple Comparison Test.

Discussion

The insecticidal activities of *C. capitatum* and *P. fraternus* against *Dermestes maculatus* (Coleoptera: Dermestidae), *C. maculatus* (Coleoptera: Chrysomelidae) and *Sitophilus zeamais* (Coleoptera: Curculionidae) had been documented [8-10]. The insecticidal efficacy of *P. fraternus* and *C. capitatum* is due to the presence of 4-Methoxy-1,3-butanediol, 2,4,6-trimethyloctane, 2,6-diisopropylnaphthalene, 2-pentadecanone, 6,10,14-trimethyl, methyl palmitate and stearic acid [25] and 2-Heptanone, 3-methyl- Hexahydrofarnesyl acetone, 3-Dodecen-1-al and 8-Methyl-1-undecene accordingly.

The oral acute administration of 2000mg/kg body weight of the extracts of *C. capitatum* and *P. fraternus* did not result in any death or clinical signs of toxicity; thus indicating high protection and safety index of these plant extracts. This suggests that the LD50 is greater than 2000mg/kg and can be classified as practically non-toxic using the Hamburger's [26] classification of range of LD50. World Health Organization (WHO) [27] and Organization for Economic and Cultural Development (OECD) [28] recommended that LD50 greater than 5g/kg body weight is considered safe. Therefore, it can be suggested that acute toxicity of the leaf extract of *C. capitatum* and *P. fraternus* is devoid of acute oral toxicity. This correlates with the findings of Mirtes et al. [29] and Caroline et al. [30].

Alanine amino transferase (ALT) and aspartate amino transferase (AST) are the two most vital transaminases which predominate the muscles, liver and myocardium in high concentrations. ALT is more predominant in the liver compared to AST which is most predominant in the myocardium [31]. Enzymatic activities of ALT and AST are of clinical and toxicological importance as alterations in their activities are suggestive of liver impairment by toxicants or in diseased conditions [32]. Generally, damage to the liver cells will result in an elevated level of these enzymes [33]. In this study, oral administration of both extracts caused decrease in the levels of ALT, AST and ALP. This suggests that the extracts may not be toxic to the liver but could have hepatoprotective effects. Thus

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confirming the results of Arun and Balasubramanian [34] and Kokou et al. [5].

The biochemical parameters which reflect the functioning of kidney are level of urea and creatinine [35]. In the present investigation, it was recorded that the serum urea level in treated animals decreased significantly ($P \geq 0.05$) compared to untreated animals. The decrease in serum urea concentration in the treated rats suggest that functioning of the kidney is normal. This confirms the findings of Vidya et al. [36], who observed that *Phyllanthus acidus* leaves significantly lowered the serum level of creatinine, urea when compared with the control.

Serum urea level varies directly with protein intake and inversely with the rate of excretion. Creatinine is the waste product formed in muscle by creatinine metabolism and it is synthesized in liver, passes into circulation and taken up almost entirely by skeletal muscles [37]. The markers of kidney function in this study were grossly seen to be within the normal limits in the treated animals, thus signifying nephroprotective effect. In the treated animal, biochemical markers of kidney function were found to be significantly lower than in the untreated animal, thus extracted treated animal produced a significant level of nephroprotection based on the biochemical markers of kidney function. This support the findings of Tanuja et al. [38].

Conclusion

The results from this study suggest that the plants were neither nephrotoxic nor hepatotoxic as it does not cause significant alteration in the kidney and liver function indicators in rats. Thus, these plant leaf extracts possess high index of safety and their continual usage in the management of insect pests of stored food grains are advocated among resource poor farmers. However, further investigation is necessary to reveal the precise mechanism responsible for the nephroprotective and hepatoprotective action of the P. *fraternus* and *C. capitatum.*

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