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Ameliorative Effect of *Phyllanthus amarus* (Gale of Wind) on Cardiac, Renal and Hepatic Functions of Paracetamol Intoxicated Wistar Rat

[1]*Eni-Yimini Solomon Agoro* and [2]*Oviemova Nathan Agoro*

[1]*Department of Chemical Pathology and Molecular Diagnosis, Faculty of Medical Laboratory Science, Federal University Otuoke, Bayelsa State, Nigeria*

[2]*Department of Public Health, Faculty of Health Sciences, Bayelsa Medical University, Bayelsa State, Nigeria*

ABSTRACT

Background and Objective: Paracetamol overdose can cause severe liver, heart and kidney damage due to oxidative stress and glutathione depletion. *Phyllanthus amarus*, known for its hepatoprotective properties, may offer therapeutic benefits in mitigating such toxicity. This study evaluates the antioxidative effects of *Phyllanthus amarus* on biochemical markers in paracetamol-induced organ damage, exploring its potential as a natural remedy. **Materials and Methods:** The study comprised six groups of seven rats each. The first and second groups were composed of negative and positive controls, respectively. Excluding the first groups, all were given intraperitoneally 100-300 mg/kg/day of paracetamol for 30 days to induce acute hepatic, cardiac and renal injuries. Subsequently, 300 mg of *Phyllanthus amarus* extract was administered to all the groups excluding the controls for another 30 days. This was followed by the sample collection and laboratory analysis using WHO-approved methods. The evaluated biochemical analysis included lipid profile, renal and hepatic function parameters. The data analysis was performed on SPSS version 19-20 using One-way ANOVA (*post hoc*-LSD) as the choice statistical tool. **Results:** The phytochemical analysis revealed the presence of alkaloids, tannins and flavonoids in the leaves and seeds of *Phyllanthus amarus*. Similarly, the lipid profile and some of the renal and hepatic markers of the paracetamol-intoxicated rats treated with the extract decreased significantly compared to those not treated with the extract. Thus, the aqueous extract of *Phyllanthus amarus* has an ameliorative capacity for hepatic and renal toxicity, coupled with an anti-hyperlipidaemic capacity. **Conclusion:** The results suggest the aqueous extract of *Phyllanthus amarus* could be of use for the prevention of hepatic and renal compromise, coupled with disorders associated with lipid lipogenesis such as obesity.

KEYWORDS

Phyllanthus amarus, lipid profile, renal markers, hepatic marker, ameliorative effects

INTRODUCTION

Medicinal plants are plants in which one or more of its organs (leaves, fruits, seeds, stem and roots) are used for therapeutic purposes, or can be used as precursors for synthesizing useful drugs. An estimate

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from the World Health Organization has shown that about 80% of people across the globe rely almost exclusively on traditional medicine for their healthcare needs and preventive measures[1]. These medicinal plants abound with therapeutic potential for treating and managing diseases[2,3].

The genus Phyllanthus has a long history of use in treating liver, kidney and bladder problems, diabetes and intestinal, parasites. *Phyllanthus amarus*, *Phyllanthus niruri* L. and *Phyllanthus urinaria* L. are used to treat kidney/gallstones, other kidney-related problems, appendix, inflammation and prostate problems[4].

The kidney, liver and heart play crucial roles in maintaining the antemortem status of all humans and other animals. A disorder or compromise of any has a colossal effect on the entire metabolic process leading to either morbidity or mortality. Kidney, liver and cardiac disorders account for a majority of deaths recorded worldwide. The causes of these disorders remained obscure and complex due to the multiple associated and idiopathic causes.

Paracetamol, also known as acetaminophen, is an analgesic-antipyretic drug therapeutically used to treat fever and pain. The toxicity of paracetamol results from N-acetyl-p-benzoquinoneimine (NAPQI) produced during the drug metabolic process by the cytochrome P450 enzyme system[5,6]. Paracetamol overdosage could cause acute hepatic necrosis and could process to renal failure if its action not halted[5-8].

Paracetamol is an over-the-counter drug vulnerable to abuse and heavily used singly or synergistically with other drugs in Nigeria without prescription from the clinician or pharmacist. This makes the drug a major contributory factor to organ failures and another ancillary metabolic compromise. Handful Studies have established the ameliorative capacity of *Phyllanthus amarus* leaf extract of various intoxications associated with several organs of the body[9,10]. The present study is therefore designed to evaluate the ameliorative capacity of *Phyllanthus amarus* on paracetamol-induced injuries on some vital organs using respective indicative biochemical parameters.

MATERIALS AND METHODS

Study location: The study's animal breeding and intoxication components were carried out at the Biochemistry Laboratory of the Federal University Otuoke, Ogbia Local Government Area, Bayelsa State, Nigeria. Fresh leaves of *Phyllanthus amarus* were collected in January 2022 at Okolobiri Town, Yenagoa Local Government Area of Bayelsa State. The plant was identified and authenticated by Dr. Ihinmikaiye Samuel of the Botany Department of Federal University Otuoke. Three hundred milligrams (300 mg) of paracetamol was purchased at Otuoke Pharmacy in Otuoke Town, Ogbia, Bayelsa State. The laboratory analysis component of the study was performed at the Eni-Yimini Laboratory Ltd., Yenzue-gene, Epie, Yenagoa, Bayelsa State, Nigeria.

Research design/study population: The research design used for the study was derived from that of Adias *et al.*[11]. Mead's resource equation was utilized to calculate the sample size[12].

The study comprised six groups (T = 6), with 7 animals per group, making 42 animals total (N = 42), without any further stratification (B = 0), then E would equal 36, which is above the cutoff of 20, indicating that sample size is very suitable for the research.

Wistar rats of weights ranging between 100-150 g were used for this experiment. The rats were kept for two weeks to be acclimatized. The rats were randomly distributed into 6 treatment groups of 7 each while the experiment lasted 12 weeks. The groups were housed separately in different cages. Groups 2-6 were given different grams of the paracetamol injection intraperitoneally for 4 weeks. For the rest of the experiment period, groups 3, 4, 5 and 6 received doses of 300 mg/kg body weight aqueous extract of *Phyllanthus amarus*, respectively for another 8 weeks.

Table 1: A table showing the dosages of Paracetamol and *Phyllanthus amarus* administered

Groups	Paracetamol (mg/kg)	*Phyllanthus amarus* (mg/kg)
1 (Negative control)	-	-
2 (Positive control) (paracetamol toxicity)	100	-
3 (paracetamol toxicity+*Phyllanthus amarus*)	150	300
4 (paracetamol toxicity+*Phyllanthus amarus*)	200	300
5 (paracetamol toxicity+*Phyllanthus amarus*)	250	300
6 (paracetamol toxicity+*Phyllanthus amarus*)	300	300

Ethical approval/ selection criteria: The ethical clearance and experimental protocol were approved by the Directorate of Research and Quality Assurance (DR&QA) and the Department of Biochemistry all of the Federal University Otuoke. The Animal Welfare Act of 1985 of the United States of America for Research and Institutional Animal Care and Use Committee (IACUC) protocols were stringently followed[13].

The rats used were healthy and active as confirmed and approved by the university veterinary doctor. Diseased or ill rats were excluded from the study.

***Phyllanthus amarus* preparations/administration:** The harvested fresh leaves were washed to remove dirt and debris, sun-dried for about 3 days and ground into a fine powder. The dried material (200 g) was infused in 2 L of distilled water for 72 hrs. The extract was sieved using Whatman No 1 filter paper and refrigerated for preservation.

The rats in the treatment groups (3-6) received 300 mg/kg body weight of aqueous extract of *Phyllanthus amarus* orally through an orogastric tube daily. The negative control group received an equal volume of distilled water without the extract of *Phyllanthus amarus* added for the experimental period (Table 1).

Sample collection: Blood samples of the animals were collected via cardiac puncture under mild chloroform anaesthesia. The plasma was separated after centrifugation at 2000 rpm for 5 min. The supernatants were separated into a plain container and sent to the laboratory for the required biochemical analysis using standard WHO-approved procedures.

Laboratory analysis

Phytochemical analysis: Tannins, alkaloids, saponins and flavonoids were estimated using the methods advanced by Harborne[14].

Biochemical parameter analysis: Plasma total cholesterol, triacylglycerol, High-Density Lipoprotein (HDL) and uric acids concentrations were estimated enzymatically by using the Agappe kit as specified by Agappe Diagnostics (Switzerland) (Agappe Kit Leaflet). Plasma low-density lipoprotein (LDL) and very low-density lipoproteins (VLDL) concentrations were derived mathematically by the formula enunciated by Oliveira *et al.*[15] and Friedewald *et al.*[16], respectively. Below are the formulas:

$$LDL = \text{Total cholesterol} - (TG/2 + HDL)$$

$$VLDL = \text{Total cholesterol} - (HDL + LDL)$$

The methods of choice for the estimations of creatinine and urea were that of Jaffe and diacetyl monoxime, respectively. Ion-Selective Electrodes (ISE) was the choice method for the estimation of the serum electrolytes (Na, K, Cl and H_2CO_3). Randox kits (UK) were used for the estimations of serum total proteins and albumin using biuret and bromocresol green (BCG) methods respectively. In a similar vein, Randox kits (UK) were used for the estimation of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) using end-point and kinetic methods, respectively.

Statistical analysis: Data were analyzed with a Statistical Package for Social Sciences (SPSS) program (SPSS Inc., Chicago, Illinois, USA; Version 18-21) and Microsoft Excel. One-way ANOVA (*post hoc*) was used in comparing the means of the various biochemical parameters of the various groups of the study. The level of significance was pegged at a 95% confidence interval.

RESULTS

Table 2 shows the phytochemical analysis carried out which revealed the presence of alkaloids, tannins and flavonoids in the leaves and seeds of *Phyllanthus amarus*. The results in Table 3 revealed that the mean serum TC, TG, HDL and LDL concentration was reduced in the animals with paracetamol intoxication after treatment with aqueous extract of *Phyllanthus amarus* when compared with the positive control animals. The study compared the lipid profiles across six groups, revealing notable trends. Cholesterol and triglyceride levels varied, with Group 2 showing higher triglycerides compared to others (3.021±3.350 mmol/L), though differences were not statistically significant ($p>0.05$). HDL levels were highest in Group 2 (1.806±0.806 mmol/L) but did not show significant variation. LDL levels were relatively consistent across groups, with no statistically significant differences observed.

In a similar vein Table 4 revealed that the mean serum creatinine, urea, uric acid and electrolyte concentration was significantly reduced ($p<0.05$) in the animals with the paracetamol intoxication after treatment with aqueous extract of *Phyllanthus amarus* when compared with the positive control animals. The study revealed significant inter-group variations in certain renal function parameters. Creatinine and uric acid levels showed notable differences, with p-values of 0.037 and 0.005, respectively. Sodium and bicarbonate levels also exhibited marked disparities, with p-values of 0.002, while chloride, potassium and calcium showed no statistically significant variation ($p>0.05$). These findings suggest specific renal function parameters are influenced under the studied conditions.

Table 5 shows that there was no significant difference in the concentration of AST and ALT, after treatment with aqueous extract of *Phyllanthus amarus*. There was a decrease in the concentrations of total proteins, albumin and globulin. The study found significant differences in hepatic function parameters among the groups, particularly in AST levels ($p = 0.03$), with Group 2 showing the highest value (89±19 U/L) compared to others. ALT, TP, ALB and GLO showed no significant variations ($p>0.05$). Notable trends included slightly lower ALT in Group 6 (8±08 U/L) and varied protein concentrations across groups. Overall, AST levels highlighted group differences, while other markers remained consistent.

DISCUSSION

This study involved the exposure of Wistar rats to grades of paracetamol intoxication and the consequent measuring of the effect upon the administration of *Phyllanthus amarus* extracts (Table 1). The phytochemical analysis of the leaves and seeds of the *Phyllanthus amarus* revealed the presence of some active compounds which include alkaloids, flavonoids, tannins and saponins (Table 2). These compounds are what give plants their therapeutic and ameliorative properties and reveal that it is a valuable plant for nutraceuticals. *Phyllanthus amarus* is made of arrays of compounds that aid in the amelioration of a lot of organ injuries and compromises[17].

The study revealed a decrease in concentrations of plasma total cholesterol, triacylglycerol, HDL and LDL in the groups treated with *Phyllanthus amarus* when compared to the paracetamol-intoxicated group (Table 3). This depicts that the extract can reverse lipid distortions resulting from paracetamol intoxication.

Table 2: A qualitative phytochemical presentation of *Phyllanthus amarus*

Phytochemicals	Occurrence
Alkaloids	0
Flavonoids	0
Tannins	0
Saponins	0

Table 3: A comparison of the mean lipid profile concentrations of the various studied groups

Parameter	Group 1 (Negative control)	Group 2 (Positive control)	Group 3	Group 4	Group 5	Group 6	F-value	p-value
Cholesterol (mmol/L)	3.777±1.066	4.430±1.845	3.309±0.477	3.380±0.767	3.690±0.517	3.871±0.473	0.986	0.443
Triglyceride (mmol/L)	1.787±0.835	3.021±3.350[a]	1.866±0.522[b]	0.959±0.120[b]	1.093±0.298[b]	1.296±0.367[b]	1.820	0.139
HDL (mmol/L)	0.934±0.810	1.806±0.806[a]	1.212±0.256[b]	1.190±0.440[b]	1.299±0.372[b]	1.385±0.195[b]	1.444	0.238
LDL (mmol/L)	2.165±1.002	1.252±0.899[a]	1.250±0.434[a]	1.755±0.976[a,b]	1.895±0.732[a,b]	1.898±0.674[a,b]	1.224	0.322

HDL: High-density lipoprotein, LDL: Low density lipoprotein, p<0.05: Significant, p>0.05: Non-significant, Group 1 vs 2,3,4,5 and 6 = a, Group 2 vs 3,4,5 and 6 = b, Group 3 vs 4,5 and 6 = c, Group 4 vs 5 and 6 = d, Group 5 vs 6 = e

Table 4: A comparison of the mean renal function parameter concentrations of the various studied groups

Parameter	Group 1 (Negative control)	Group 2 (Positive control)	Group 3	Group 4	Group 5	Group 6	F-value	p-value
Creatinine (mol/L)	67.638±33.968[a]	81.620±26.216[a]	67.382±8.236[b]	55.232±22.942[b]	52.898±16.530[a,b]	40.653±14.875[a,b]	2.717	0.037
Urea (mmol/L)	3.113±1.349	8.615±0.895[a]	5.976±3.024[a,b]	6.351±2.063[a,b]	6.865±3.071[a,b]	5.485±2.931[a,b]	2.199	0.093
Uric acid (mg/dL)	113.000±43.209	150.750±82.987[a]	170.857±65.824[a]	71.571±31.485[a,b,c]	87.429±50.523[a,b,c]	72.571±25.948[a,b,c]	4.296	0.005
Chloride (mmol/L)	78.828±12.531	101.806±24.513[a]	76.092±24.493[b]	84.659±8.701[b]	84.718±20.295[b]	86.484±15.308[b]	1.226	0.321
Potassium (mmol/L)	6.129±1.415	6.513±1.780	5.137±1.942	4.425±0.966	5.022±1.556	4.684±0.978[b]	1.701	0.165
Sodium (mmol/L)	122.767±12.516	165.266±44.764[a]	189.129±25.759[a]	200.208±57.937[a]	271.248±103.601[a,b,c,d]	328.256±137.555[a,b,c,d,e]	4.986	0.002
Calcium (mmol/L)	0.619±0.197	1.568±0.728[a]	1.403±1.557[a]	0.844±0.626[a,b,c]	0.710±0.446[a,b,c]	1.092±0.616[a,b]	1.201	0.331
Bicarbonate (mmol/L)	7.008±2.696	18.869±6.384[a]	10.571±6.843[a,b]	5.900±1.371[a,b,c]	7.545±4.183[a,b]	8.172±4.827[a,b]	4.905	0.002

P<0.05: Significant, p>0.05: Non-significant, Group 1 vs 2,3,4,5 and 6 = a, Group 2 vs 3,4,5 and 6 = b, Group 3 vs 4,5 and 6 = c, Group 4 vs 5 and 6 = d and Group 5 vs 6 = e

Table 5: A comparison of the hepatic function activities/concentrations of the various studied groups

Parameter	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	F-value	p-value
AST (U/L)	27±03	89±19[a]	47±36[b]	31±07[b]	41±07[b]	25±05[b]	2.903	0.030
ALT (U/L)	25±12	25±17	21±17	12±4	25±29	8±08[a,b]	0.956	0.460
TP (g/L)	20.41±8.98	38.16±8.99	25.60±13.87	32.39±13.03	31.58±12.27	32.21±11.39	1.863	0.127
ALB (g/L)	20.41±8.98	38.16±8.98	25.60±13.87	32.39±13.03	31.58±12.27	32.21±11.39	1.836	0.127
GLO (g/L)	43.02±12.63	53.84±8.93	44.40±6.34	46.96±5.35	52.46±17.62	47.43±9.68	1.023	0.420

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TP: Total protein, ALB: Albumin, GLO: Globulin, p<0.05: Significant, p>0.05: Non-significant, Group 1 vs 2,3,4,5 and 6 = a, Group 2 vs 3,4,5 and 6 = b, Group 3 vs 4,5 and 6 = c, Group 4 vs 5 and 6 = d and Group 5 vs 6 = e

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From another perspective, it may be indicative that the extract of *Phyllanthus amarus* has the potential to reduce the risk of the development of cardiovascular diseases as lipid concentration in the bloodstream is an indispensable indicator[18]. The mechanism orchestrated by the extract could be that of halting lipid peroxidation resulting from the paracetamol intoxication. Studies have shown that saponins are known antinutritional factors that reduce the uptake of certain nutrients including glucose and lipids[19]. Hence, saponins have been reported to have a hypocholesterolaemia effect and this may explain the antilipidemic effect observed in this study. The findings of the study are in line with a handful of authors[9,20,21].

However, the study also revealed a significant decrease in serum concentrations of creatinine, urea, uric acid, calcium, potassium and bicarbonate in the *Phyllanthus amarus* treatment groups when compared to the group without *Phyllanthus amarus* treatment) (positive controls) (Table 4). This is suggestive of the ameliorating effect of *Phyllanthus amarus* on dysfunctional kidneys at the various doses administered. Furthermore, the decrease in the concentrations of creatinine, urea and uric acid points to the nutraceutical roles of *Phyllanthus amarus* in the amelioration of compromised kidneys and an extent arthritis. In a similar vein, the serum electrolyte presentations resulting from the extract administrations could aid in correcting electrolyte imbalances to the exclusion of sodium that was elevated. The findings of this study as per the creatinine and urea presentation are in line with that of Pramyothin *et al*.[22]. Thus, these findings suggest that the aqueous extract of *Phyllanthus amarus* is nephroprotective and is capable of restoring deranged kidney parameters after paracetamol intoxication.

On the contrary, sodium concentration increased (Table 4). The increase in serum sodium concentration points to the non-suitability of the extract for hypertensive patients as it could further shoot up the concentration. The increase in sodium concentration aligns with the reports of Peters *et al*.[23] and Onyesom *et al*.[24] on the use of the extract of *Phyllanthus amarus* on cisplatin-induced nephrotoxicity in Wistar rats and that of malaria studies respectively. However, the finding is in contrast to a study carried out by Yakubu *et al*.[25]. In the study, they averred a significant decrease in sodium ion concentration between groups administered doses of *Phyllanthus amarus* extract compared to the control. However, the basis of the leap in sodium concentration remained unknown.

Moreover, the presentation of the concentrations of total protein, albumin and protein exhibited a decrease in the groups of rats administered with the aqueous extract of *Phyllanthus amarus* when compared to the paracetamol-intoxicated group (Table 5). However, the liver enzymes such as AST and ALT were not affected in the study. The findings of the study implicate hepato-protective tendencies of the extract as it contains alkaloids, flavonoids, tannins and saponins which are beneficial for the treatment of hepatic diseases. The posture of the study is in line with that of Ogunmoyole *et al*.[9] which detailed that *Phyllanthus amarus* extract restored deranged biochemical parameters in rat models of hepatotoxicity and nephrotoxicity.

First, this study was animal based and there is a need to be replicated in humans. Second, the paucity of funds hampered the expansion of the study to the use of more sophisticated equipment and the application of advanced and recent biochemical parameters.

CONCLUSION

The results of the study, therefore, indicate that an aqueous extract of *Phyllanthus amarus* has a therapeutic and ameliorating effect on the kidney and the liver and is also anti-hyperlipidaemic. This inferred that the extract could be an effective nephroprotective and hepatoprotective agent against paracetamol-mediated nephrotoxicity and hepatotoxicity. In addition to inhibiting lipid peroxidation and possibly obesity. Further studies on *Phyllanthus amarus* should focus on confirming its efficacy in treating liver and kidney toxicity and its anti-hyperlipidaemic effects in humans. Additionally, research should identify and quantify the active compounds responsible for these therapeutic benefits to encourage safe, science-backed herbal medicine use.

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