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The Rhizome of *Curculigo pilosa* Exerts Hepatoprotective and Nephroprotective Effects in Rats Exposed to Acetaminophen Toxicity

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Authors' contributions

This work was carried out in collaboration among all authors. Author OOO designed the study, performed the statistical analysis, wrote the protocol. Author HAP, GOA, DOM and CAM managed the analyses of the study. Author OAO managed the analysis of data. Author OOO, OKA and OAO managed the literature searches and wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The exposition of drug-induced hepatotoxicity and nephron injury is highly uneven; some range from asymptomatic but elevated liver and kidney parameters to meteoric liver and kidney damage. The medicinal plants have been exploited for fighting toxicity, but their mechanisms remain unexplored. The purpose of this study was to see how an aqueous extracts of *Curculigo pilosa* (*C. pilosa*) rhizome affected the hepato- and nephro-toxicity caused by 750 mg/kg and 1000 mg/kg body weight doses of acetaminophen (APAP) in rats.

Methodology: Thirty (30) female rats used for this study were divided into six groups (n = 5). Group A served as control. *C. pilosa* (300 mg/kg body weight) was given to Group B. Group C was administered a 750 mg/kg body weight dose of APAP. Group D was administered a 750 mg/kg body weight APAP dose plus 300 mg/kg body weight of an aqueous extracts of *C. pilosa*. A 1000 mg/kg body weight APAP dose was given to Group E. Group F was administered APAP (dose 1000 mg/kg body weight) plus an aqueous extracts of *C. pilosa* (300 mg/kg body weight). The

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serum concentrations of urea, creatinine, chloride, potassium, sodium, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were analyzed using standard methods.

Results: The APAP-induced toxicity caused a significant ($P=0.05$) increase in the levels of ALT, AST, ALP, creatinine, urea, potassium, sodium, and chloride, but treatment with an aqueous extracts of *C. pilosa* rhizome significantly ($P=0.05$) decreased the levels of these markers compared to the control.

Conclusion: The aqueous extracts of *C. pilosa* rhizome has hepatoprotective and nephroprotective effects against APAP-induced toxicity.

Keywords: Hepatoprotective; nephrotoxicity; acetaminophen; *Curculigo pilosa*.

1. INTRODUCTION

The naturally occurring phytoconstituents compounds (alkaloids, phenols, saponins, carbohydrates, terpenoids, steroids, flavonoids, and tannins, among others) in plants are derived from different plant parts and are primarily responsible for the treatment of different illnesses and diseases brought on by toxicity [1]. Acetaminophen (APAP) causes hepatotoxicity and nephrotoxicity. APAP is commonly used as an analgesic and antipyretic drug to relieve mild and chronic pain and reduce fever when taken in a normal, prescribed dose. Its metabolism happens within liver microsomes, where it forms water by conjugating with glucuronate and sulfate to be eliminated from the liver and blood through the bile and urine [2-4]. At prescribed doses, APAP is oxidized to the electrophile N-acetyl-p-benzoquinone imine (NAPQI), a toxic compound, by microsomal cytochrome P450. The detoxification of NAPQI is done with reduced glutathione (GSH) by conjugation to form the acetaminophen-glutathione conjugate (APAP-SG). The prolonged use of APAP causes APAP-SG, which, collectively with GSH depletion, stirs up a series of damaging reactions leading to acute liver damage (ALD) and cell death [2,4]. In addition to ALD, the long-term use of APAP is metabolized in the kidney to produce NAPQI that is deacetylated to produce a nephrotoxic product, 4-aminophenol (PAP), resulting in nephrotoxicity such as acute kidney injury (AKI). The APAP-induced toxicity results in oxidative stress, inflammation, lipid peroxidation, protein oxidation, modification and inhibition of enzyme activity, mitochondrial dysfunction, and endoplasmic reticulum stress [2,3,5-7].

The search for a drug with hepato-nephro-protective and/or hepato-nephro-regenerative functions that is reliable, without side effects, and readily available is difficult [8,9]. *Curculigo pilosa* (*C. pilosa*) is a tuberous rhizome herb belonging

to the Amaryllidaceae family, widely distributed in the tropical West Africa, and, known as “epakun” in the Yoruba traditional medicine of southwestern Nigeria. It is used in the treatment of hernia, infertility, genital infections, sexually transmitted infections, etc. [10,11]. In addition it is used in the production of baby food and sorghum beer in West Africa [12]. The mechanism of action in carrying out these treatments remains enigmatic. The present study is designed to investigate the hepatoprotective and nephroprotective properties of APAP in toxicity-induced rats.

2. METHODOLOGY

2.1 Plant Collection and Extraction

C. pilosa rhizomes were purchased from a Lusada market, Ado-odo/ota L.G.A., Ogun State, in South Western part of Nigeria, and identified by the Department of Botany, Lagos State University, Ojo, Lagos State, Nigeria. The rhizomes were thoroughly washed under clean running water and grounded with high speed blender (Kenwood BLK - 828), and 200 g were boiled in 1000 ml of clean water for 30 minutes. The solution was filtered using Whatman’s No.1 filter paper, and the filtrate was concentrated using a rotary evaporator. The extract was kept in the refrigerator prior to analysis (4°C). The dried mass yielded 62.5 g.

2.2 Experimental Animals

Thirty (30) healthy female Wistar rats weighing 85–100 g were kept in the animal house of the Department of Biochemistry, Lagos State University, Ojo, Lagos, Nigeria, between April 2018 and July 2018. The animals were acclimatized for two (2) weeks, fed *ad libitum* daily with commercial rat feed (product of Animal care, Lagos, Nigeria), and clean water, and kept under a constant 12-hour light and dark cycle. A

single dose of acetaminophen suspension was administered by the oral route, at a dose of 750 mg/kg b.wt (groups C - D) and 1000 mg/kg b.wt (groups E - F). Preliminary pilot studies showed that aqueous *C. pilosa* extracts was not toxic up to 300mg/kg body weight, according to the method of Karigidi and Olaiya [13]. The experimental protocols were conducted in accordance with the international guiding principles of laboratory animal care [14] and were approved by the Animal Ethical Committee of the Department of Biochemistry, Lagos State University; Ojo, Nigeria.

2.3 Experimental Design

The rats were randomly divided into six (6) groups of five rats each as shown below:

Group A = Control

Group B = Rats treated with 300 mg/kg body weight of *C. pilosa* aqueous extracts

Group C = Rats treated with 750 mg/kg body weight acetaminophen

Group D = Rats treated with 750 mg/kg body weight acetaminophen plus 300 mg/ kg body weight of *C. pilosa* aqueous extracts

Group E = Rats treated with 1000 mg/kg body weight acetaminophen

Group F = Rats treated with 1000 mg/kg body weight acetaminophen plus 300 mg/ kg body weight of *C. pilosa* aqueous extracts

The extracts were administered orally for 14 days using intragastric tube. After 14 days, the rats were fasted overnight and euthanized under light anesthesia. The blood was collected without anticoagulant sample bottles for serum.

2.4 Blood Sample Collection and Biochemical Analysis

Blood samples for biochemical analysis were collected from all the rats under light ether anaesthesia by cardiac puncture with a syringe into plain tubes and allowed to clot. Serum was separated with a high speed macro-centrifuge at 3,500 rpm for 10 minutes and stored for further analysis. The activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were examined with commercial diagnostic kits (Randox Laboratories

Ltd. UK) according to the description by Ogunrinola et al. [15] and Afolabi et al. [16]. The concentrations of urea, and creatinine were analysed in the serum using commercial kits (Agappe Diagnostics, Switzerland), as reported by Afolabi et al. [16], while the electrolytes (sodium, potassium, and chloride) were determined in the serum using commercial kits (Agappe Diagnostics, Switzerland), as previously reported by Obetan et al. [17]. All these analyses were performed using a colorimetric instrument from Surgienfield Instrument, Zhejiang, China, Mainland.

2.5 Statistical Analysis

Data were expressed as mean \pm SEM, and analyzed by one-way analysis of variance (ANOVA) using Statistical Package for Social Sciences version 17.0 (SPSS, Chicago, Illinois). Values that gave a $p < 0.05$ were taken to be statistically significant.

3. RESULTS AND DISCUSSION

The variables that were assessed in the current investigation, including creatinine, urea, chloride, potassium, sodium, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) concentrations, provided an indirect evaluation of hepatic and renal function. In the liver, ammonia, a waste product and highly toxic substance, is detoxified through conversion to urea, which is nontoxic and water-soluble and excreted through urine by the kidneys, but a high concentration of urea is also toxic, hence it is considered a marker of hepatic or renal functional status [18,19]. Likewise, creatinine is an excretion product of muscle activity, and its elimination is entirely by the kidneys, where it is freely filtered in renal glomeruli, by the tubular component, which is a good indicator of renal-glomerular function [19]. The kidney's capacity to control blood volume and chemical composition in accordance with the body's shifting needs calls for a very sophisticated functional system. Renal functions are coordinated with those of the cardiovascular and pulmonary systems to maintain homeostasis to a significant extent [17]. Both urea and creatinine are end products of body metabolism and essentially reflect the glomerular filtration rate (GFR) [18,20]. APAP-induced hepatotoxicity and nephron injury are usually characterized by elevated serum levels of urea and creatinine, which are significant biomarkers of renal dysfunction [20,21]. In the present study, urea and creatinine

concentrations, as indicated in Table 1, were elevated in APAP-treated rats (750 and 1000 mg/kg b.wt), respectively, suggesting kidney damage compared to the control (0.56±0.15 mg/ml (creatinine); 25.74±2.64 mg/ml (urea)) and *C. pilosa* extracts (0.47±0.11 mg/ml (creatinine); 23.71±1.41 mg/ml (urea)) groups. This is in accordance with the administration of acrylamide [19], and lipopolysaccharide [6], respectively. The treatment with an aqueous extracts of *C. pilosa* rhizome the APAP-induced toxicity significantly ($P= .05$). This indicates that the aqueous extracts of *C. pilosa* ameliorate renal damage. It may be due to the phytoconstituents present in the *C. pilosa* aqueous extracts that inhibit the accumulation of urea and creatinine, respectively. This is in agreement with the research of Imo and Uhegbu [22], and Karigidi and Olaiya [13].

Overdose of APAP causes similar tubular effects to non-steroidal anti-inflammatory drugs via inhibition of prostaglandin synthesis, vasoconstriction, and activation of the renin-angiotensin-aldosterone system, causing electrolyte changes and/or disturbances [23]. The stability of the blood's sodium, potassium, and chloride contents is a reliable sign of how well the kidneys and heart are working. An increase in electrolytes (potassium, sodium, and chloride) is the hallmark of APAP-induced toxicity. The serum electrolytes, potassium (K^+), sodium (Na^+), and chloride (Cl^-), are presented in Table 2. It was observed that, in the APAP-induced groups, there is a significant ($P= .05$) increase in the concentration of K^+ , Na^+ , and Cl^- compared to the control (3.69±0.25 mEq/L (K^+); 133.17±2.66mEq/L (Na^+), 73.13±6.98 mEq/L (Cl^-)) and *C. pilosa* extracts (3.24±0.26 mEq/L (K^+); 130.10±3.94 mEq/L (Na^+), 72.79±7.15 mEq/L (Cl^-)) groups. The intoxication of APAP leads to the breakdown of endogenous tissue and as a result, the derangement of serum electrolytes that occurs [24]. Toxic and overdose of APAP induces nephron damage, forms serum osmolality of the electrolytes (K^+ , Na^+ , and Cl^-), and significantly ($P= .05$) elevates these parameters, which may be due to renal hemodynamic compromise and tubular dysfunction [25,26]. The administration of an aqueous rhizome extracts of *C. pilosa* significantly decreased the electrolytes, thereby protecting any of the alterations. This is in accordance with the research of Imo and Uhegbu [22]. A decrease in sodium lowers blood

pressure in hypertensive individuals because there is linked between sodium and blood pressure. Likewise, potassium in the intracellular fluid, has been reported to be among the protective electrolytes against hypertension. The decrease effect of aqueous rhizome extracts of *C. pilosa*, is an indication that membrane structure may possibly be protected or stabilized, as observed with *Gongronema latifolium* Benth leaf extracts by Imo and Uhegbu [22].

The liver is the vital organ that is highly sensitive to toxic agents, and its functions include detoxification of deleterious materials, regulation of numerous metabolic processes, and maintenance of body homeostasis [27,28]. The elevation of serum hepatic biomarker enzymes (ALT, AST, and ALP) is an indication of hepatocellular damage, which reveals liver enzyme leakage into the blood stream and loss of functional integrity of cell membrane in liver [8,29-31]. ALP level in the serum is a mark of liver function or bone metabolism due to its involvement in the transport of metabolites across the cell membranes, glycogen metabolism, secretory activities, and protein synthesis [15]. The increase in serum ALP level is caused by increased synthesis in the presence of increasing biliary pressure because serum ALP is connected to hepatic cell function [28]. Being a sensitive sign of liver disease, AST is in charge of transaminating aspartate in the body's metabolism, whereas ALT, which is found in hepatocytes, is released into the blood during the cell damage [15]. The results in Table 3 showed a significant ($P= .05$) increase in ALT, AST, and ALP liver enzymes in the APAP-induced groups compared to the control (29.64±2.59 U/L (ALT); 37.00±1.09 U/L (AST), 23.88±0.26 U/L (ALP)) and *C. pilosa* extracts (25.75±0.71 U/L (ALT); 30.56±0.98 U/L U/L (AST), 21.981±0.68 U/L (ALP)) groups. This causes liver damage as a result of the leakage of these hepatic enzymes into the circulation. These liver enzyme concentrations were significantly ($p<0.05$) lower in the *C. pilosa* aqueous extracts-treated groups. The report confirms previous findings by Ogunrinola et al. [15], and Lakshmi et al. [24]. The reversal of these enzymes with *C. pilosa* aqueous extracts is evidence of the protection of cellular membrane integrity and tissue damage against APAP-induced damage, which may be due to the presence of the phytoconstituents by preventing oxidation [15,32-34].

Table 1. Effects of *C. pilosa* aqueous extracts on kidney functions of acetaminophen-induced toxicity

Treatment dose	Creatinine Conc. (mg/ml)	Urea Conc. (mg/ml)
Control	0.56±0.15 ^a	25.74±2.64 ^a
<i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	0.47±0.11 ^b	23.71±1.41 ^b
750 mg/kg b. wt APAP	2.86±0.05 ^c	60.97±7.07 ^c
750 mg/kg b.wt APAP + <i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	1.29±0.22 ^d	33.92±4.28 ^d
1000 mg/kg b.wt APAP	3.02±0.29 ^e	65.10±2.31 ^e
1000 mg/kg b.wt APAP+ <i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	1.42±0.31 ^f	37.14±4.86 ^f

Values are represented as Mean values ± Standard error of means, n=5. Rows of the same compartment carrying different letters of the alphabet are significantly different from each other (P= .05). APAP = acetaminophen (paracetamol), b. wt = body weight, aq. extr. = aqueous extracts, Conc.= concentration

Table 2. Effects of *C. pilosa* aqueous extracts on serum electrolytes of acetaminophen-induced toxicity

Treatment dose	Potassium Conc. (mEq/L)	Sodium Conc. (mEq/L)	Chloride Conc. (mEq/L)
Control	3.69±0.25 ^a	133.17±2.66 ^a	073.13±6.98 ^a
<i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	3.24±0.26 ^b	130.10±3.94 ^b	072.79±7.15 ^b
750 mg/kg b.wt APAP	6.61±0.71 ^c	150.96±2.39 ^c	117.61±2.73 ^c
750 mg/kg b.wt APAP + <i>C.pilosa</i> (300 ml/kg b. wt) aq. extr.	5.47±0.35 ^d	143.89±4.93 ^d	083.67±6.14 ^d
1000 mg/kg b.wt APAP	7.74±0.25 ^e	157.29±1.94 ^e	140.12±3.65 ^e
1000 mg/kg b.wt APAP + <i>C.pilosa</i> (300 ml/kg b. wt) aq. extr.	6.32±0.49 ^f	138.15±0.59 ^f	129.72±2.14 ^f

Values are represented as Mean values ± Standard error of means, n=5. Rows of the same compartment carrying different letters of the alphabet are significantly different from each other (P= .05). APAP = acetaminophen (paracetamol), b. wt = body weight, aq. extr. = aqueous extracts, Conc.= concentration

Table 3. Effects of *C. pilosa* aqueous extracts on liver function test biomarkers of acetaminophen-induced toxicity

Treatment dose	Alanine transaminase Conc. (U/L)	Aspartate transaminase Conc. (U/L)	Alkaline phosphatase Conc. (U/L)
Control	29.64±2.59 ^a	37.00±1.09 ^a	23.88±0.26 ^a
<i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	25.75±0.71 ^b	30.56±0.98 ^b	21.981±0.68 ^b
750mg/kg b.wt APAP	59.45±2.51 ^c	49.04±1.21 ^c	21.50±0.47 ^c
750mg/kg b.wt APAP + <i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	50.59±2.49 ^d	25.44±1.87 ^d	18.39±0.39 ^d
1000mg/kg b.wt APAP	82.42±2.35 ^e	74.50±1.79 ^e	25.68±0.42 ^e
1000mg/kg b.wt APAP + <i>C. pilosa</i> (300 ml/kg b. wt) aq. extr.	64.04±3.46 ^f	62.18±2.17 ^f	23.91±0.22 ^f

Values are represented as Mean values ± Standard error of means, n=5. Rows of the same compartment carrying different letters of the alphabet are significantly different from each other (P= .05). APAP = acetaminophen (paracetamol), b. wt = body weight, aq. extr. = aqueous extracts, Conc.= concentration

4. CONCLUSION

According to this study, the oral administration of *C. pilosa* aqueous extracts recovered the liver from hepatotoxicity and the kidney from nephrotoxicity. The protective effect of the extract may be due to the presence of bioactive compounds that lead to hepatoregenerative and nephroprotective capacities. Further studies are needed to investigate the molecular targets

involved in the hepatoregenerative and nephroprotective effects. The current study only looked at the effect of *C. pilosa* aqueous extracts on the APAP hepato-and nephro-toxicity maker parameters; however, more research into the mechanism of action of APAP on membrane integrity and stress on other body organs, as well as the effects of *C. pilosa* aqueous extracts is needed.

ETHICAL APPROVAL

All authors hereby declare that the Guide for the Care and Use of Laboratory Animals, "NIH Publication No. 85–23," Revised 1985, was followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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