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Curculigo pilosa rhizome Supplementation Reverses P-Hydroxyacetanilide-Induced Oxidative Stress and Lipid Profile Dysfunction in Rats

Ogunrinola O. Olabisi [a*], Ogunrinola A. Oluwaseyi [a,b], Nwaemeke D. Iweunor [a], Lawal N. Adetutu [a], Salako O. Taiwo [a] and Dosunmu A. Oluwatosin [a]

[a] Department of Biochemistry, Faculty of Science, Lagos State University, Ojo, Lagos State, Nigeria.
[b] School of Nutrition Sciences, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario K1H 8M5, Canada.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Exposure to drug toxicity results in stress and dysfunction of metabolizing enzymes that cause illnesses and diseases. Consumption of medicinal plant rhizomes is a regime for managing the complications. On the activities of some oxidative stress marker enzymes (catalase, glutathione, and superoxide dismutase), as well as the concentration of lipid profiles (cholesterol, triglycerides,

**Corresponding author: E-mail: oogunrinola@yahoo.com; , olabisi.ogunrinola@lasu.edu.ng;*

and phospholipids) of p-hydroxyacetanilide (pPHA)-induced toxicity in rats, the effects of an aqueous extract of *Curculigo pilosa* (*C. pilosa*) rhizome were assessed. Forty rats were randomly grouped into eight groups (n = 5). The control group; aqueous extract of *C. pilosa* rhizome group; 750 mg/kg and 1000 mg/kg per body weight of pPHA group; the preventive groups (aqueous extract of *C. pilosa* rhizome and 750 mg/kg per body weight of pPHA; aqueous extract of *C. pilosa* rhizomes and 1000 mg/kg per body weight of pPHA); and the curative groups (750 mg/kg per body weight of pPHA and aqueous extract of *C. pilosa* rhizome; 1000 mg/kg body weight of pPHA and aqueous extract of *C. pilosa* rhizome). The oxidative stress marker enzymes and lipid profiles were analyzed spectrophotometrically in the serum, kidney, brain, and liver of the animals on the seventh and fourteenth days after the administrations. The results show that pPHA decreases the oxidative stress marker activities and the lipid profile concentrations in all the compartments, but the pre- and post-treatment with an aqueous extract of *C. pilosa* rhizome improved the activities of the stress marker enzymes and the lipid profiles dysfunction. The result suggests that an aqueous extract of *C. pilosa* rhizome has preventive and curative therapeutic potential for pPHA-induced toxicity.

Keywords: Preventive; curative; p-hydroxyacetanilide; spectrophotometrically; aqueous.

1. INTRODUCTION

Analgesics are among the most popular drugs that are being abused, which brings about drug toxicity. The p-hydroxyacetanilide (pPHA) compound, also called acetaminophen, paracetamol, or Tylenol, is an analgesic drug that was derived by oxidizing two analgesics, phenacetin and acetanilide, and is widely used as a therapeutic drug for pain [1]. However, high doses (abuse) of pPHA are toxic, which is harmful to the body and influences organs (liver, kidney, ocular, etc.), damage, blood, and central nervous system dysfunction [2]. Stress and malfunction of the metabolizing enzymes necessary for normal body function can occur due to drug toxicity, which causes illnesses and diseases [1-3]. The metabolism of a drug may generate a reactive intermediate that can reduce molecular oxygen directly to generate reactive oxygen species, which are a byproduct of normal metabolism and have roles in cell signalling and homeostasis. When the cellular antioxidant capacity (such as ascorbic acid, vitamin E, and glutathione) and antioxidant enzymes (such as thioredoxins, reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase, etc.) that regulate cellular levels exceed that of reactive oxygen species, oxidative stress can result [4]. Oxidative stress causes damage that comes from the significant modification of intracellular targets such as deoxyribose nucleic acid, proteins, and lipids, which modulate survival signalling cascades. These lead to a wide range of diseases, including cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, cataracts, and cancer, to mention a few [4-7]. Also, oxidative stress resulted in damage to cellular biomembranes caused by radical-mediated lipid peroxidation, which converts unsaturated lipids into polar lipid hydroperoxides. Any small changes in the abundance, composition, or location of lipids (cholesterol, triglycerides, phospholipids, and free fatty acids) can have profound effects on cellular viability and functions. Therefore, hydroxyl radical attack on the fatty acyl chains of phospholipids and triglycerides caused lipid peroxidation, which affects cellular function, and the disorder in homeostasis of these lipids resulted in dysfunction [7-10]. Lipid dysfunction has been considered a global public health challenge and a contributor to complications in the endocrine, central nervous, hepatic, and renal systems [8,11,12].

Medicinal plant products and their derivatives have been considered the origin of therapeutic elements since ancient times. The use of medicinal plants as herbal remedies has also been widely embraced in many developed countries, with complementary and alternative medicines now becoming mainstream globally [13-15]. The *Curculigo pilosa* (*C. pilosa*) Schum and Thom plant belongs to the family Hypoxidaceae. The rhizomes of the *C. pilosa* plant possess medicinal properties (bioactive constituents) that are used as food for adults and infants, as well as in the management and treatment of several diseases [16-21], but the mechanism of action is yet to be understood. Therefore, this study aims to investigate the effect of an aqueous extract of *C. pilosa* rhizome on the activities of some oxidative stress marker enzymes (catalase, reduced glutathione, and superoxide dismutase), as well as the serum concentration of lipid profiles (cholesterol, triglycerides, and phospholipid) of para-hydroxy acetanilide (pPHA)-induced toxicity in rats.

2. METHODOLOGY

2.1 Collection of Plant Material and Processing

The plant material, *C. pilosa* rhizome, was purchased from Lusada market, Ado-Odo/Ota L.G.A., Ogun State, in the south-western part of Nigeria. The plant was identified, authenticated, and stored in the herbarium. The rhizome extract was performed according to previous method [16].

2.2 Experimental Animals and Study Design

Forty (40) healthy female albino rats (6 weeks old) of an average weight of 100 - 150 g were housed in plastic cages and allowed to feed (product of Animal Care Feeds, Nigeria) and water freely to acclimatize with the environment for two weeks under standard environmental conditions (25 ± 21°C; 12/12 h light/dark cycle). After which, they were divided into eight groups (n = 5) as described in Table 1.

At the end of the administration, the animals were fasted overnight and sacrificed under intraperitoneal injection of ketamine anaesthesia (Ketarays; 50 mg/kg). Blood was collected by cardiac puncture into heparinized tubes, allowed to clot, centrifuged at 3,000 rpm for 10 minutes, and serum was collected and stored at -20^{0}C. The organs (brain, liver, and kidneys) were excised, washed with ice-cold saline and homogenized (10%), and supernatant stored at -20^{0}C for further analysis [24].

2.3 Biochemical Analysis

Catalase, superoxide dismutase, and reduced glutathione activities were measured following the methods of [25,26]. Phospholipid was extracted with a chloroform-methanol mixture (2:1, v/v), and then 100 µl of the extract as well as 100 µl of chloroform were evaporated to dryness over a hot water bath at 60^{o}C and allowed to cool. The serum concentrations of the cooled phosphoplipids, cholesterol, and triglycerides were determined using Randox commercial kits, and the absorbance was read at 488 nm, 550 nm, and 500 nm, respectively, against a blank using a UV/visible spectrophotometer (Model SM 755s), a product of Surgien Field Instrument, Zhejiang, China (Mainland).

2.4 Statistical Analysis

The statistical analysis was performed using SPSS version 20.0. The results were expressed as mean ± SEM. A one-way analysis of variance (ANOVA) was carried out at $P < 0.05$ among the groups.

Table 1. The grouping and animal treatments

Groups	Treatment dose
I	Control given water (7 days)
II	Oral administration of 300 mg/kg body weight of an aqueous extract of *C. pilosa* rhizome (7 days) [22]
V	Oral administration of 750 mg/kg of p-hydroxyacetanilide (pPHA) per body weight (7 days) [23]
VI	Oral administration of 1000 mg/kg of p-hydroxyacetanilide (pPHA) per body weight (7 days) [23]
Preventive group	
III	Oral administration of 300 mg/kg body weight of an aqueous extract of *C. pilosa* rhizome (7 days) and 750 mg/kg p-hydroxyacetanilide (pPHA) per body weight (7 days)
IV	Oral administration of 300 mg/kg body weight of an aqueous extract of *C. pilosa* rhizome (7 days) and 1000 mg/kg of p-hydroxyacetanilide (pPHA) per body weight (7 days)
Curative group	
VII	Oral administration of 750 mg/kg of p-hydroxyacetanilide (pPHA) per body weight (7 days) and 300 mg/kg body weight of an aqueous extract of *C. pilosa* rhizome (7 days)
VIII	Oral administration of 1000 mg/kg of p-hydroxyacetanilide (pPHA) per body weight (7 days) and 300 mg/kg body weight of an aqueous extract of *C. pilosa* rhizome (7 days)

3. RESULTS AND DISCUSSION

The present study was conducted to investigate the effect of analgesic pPHA-induced toxicity on some oxidative stress markers and lipid metabolizing enzymes in the serum, kidney, brain, and liver of a female rat treated with an aqueous extract of *Curculigo pilosa* rhizome. The study reveals that the hallmark of pPHA-induced toxicity in rats is a significant ($P < 0.05$) reduction in the activities of oxidative stress marker enzymes (catalase (Table 2), superoxide dismutase (Table 3), and reduced glutathione (Table 4) in all the compartments.

These enzyme reductions occur when pPHA is activated by cytochrome P450, amidases, and peroxidases to form the toxic reactive metabolite N-acetyl-p-benzoquinoneimine. At toxic doses of pPHA, there is excessive production of N-acetyl-p-benzoquinoneimine, causing a reduction in glutathione activity (Table 4), which leads to hepatotoxicity, as observed in previous research [16,27]. However, due to the inadequate glutathione activity, the production of reactive oxygen species like superoxide, hydrogen peroxide, and hydroxyl radicals has been increased by N-acetyl-p-benzoquinoneimine, which leads to a reduction in the enzymatic defense systems: catalase (Table 2) and superoxide dismutase (Table 3) activities, respectively. Therefore, these enzyme reductions caused an imbalance in the formation and removal of free radicals (oxidative stress). But, in a condition with severe oxidative stress, the generated oxidant compounds will react with cell components such as lipid, protein, deoxyribose nucleic acid, and cell membrane and lead to pathological complications and oxidative damage, including atherosclerosis, vascular diseases, diabetes, and cancers, to mention a few [1,7,16,28-33].

This study also observed a reduction in the cholesterol, triglycerides, and phospholipid concentrations caused by pPHA-induced toxicity (Table 5), which is similar to the result from other research [34]. The reduction might be due to high activation of enzymes like cytochrome P450, lipoxygenases, and cyclooxygenases in oxidized lipids, and high levels of two free radicals, or reactive oxygen species, namely, hydroxyl radical and hydroperoxyl, that can inflict direct damage to lipids. The hydroxyl radical is produced from oxygen in cell metabolism and under a variety of stress conditions and causes oxidative damage to cells because it unspecifically attacks biomolecules. It is assumed that hydroxyl radicals in biological systems are formed through redox cycling by the Fenton reaction, where free iron reacts with hydrogen peroxide, and the Haber-Weiss reaction, which results in the production of free iron when superoxide reacts with ferric iron. In addition to the iron redox cycling transition-metals, including copper, nickel, cobalt, etc., can also be responsible for hydroxyl radical formation in living cells. The hydroperoxyl radical is a protonated form of superoxide that yields hydrogen peroxide, which can react with redox-cycling active metals to further generate hydroxyl radicals through Fenton or Haber-Weiss reactions. It is a much stronger oxidant than superoxide anion-radical and could initiate lipid peroxidation through the chain oxidation of polyunsaturated phospholipids, thereby leading to impairment of membrane function. Phospholipids and cholesterol are targets of damaging and potentially lethal peroxidative modification [31,35]. Lipid peroxidation occurs in a process in which oxidants such as free radical species attack lipids containing carbon-carbon double bond(s) that involve hydrogen abstraction from a carbon with oxygen insertion, resulting in lipid peroxyl radicals and hydroperoxides, by enzymes such as selenium-dependent glutathione peroxidases and selenoprotein, which catalyze the reduction of hydrogen peroxide or organic hydroperoxides to water or the corresponding alcohols, respectively, using glutathione as a reductant. At the catalytic site of glutathione peroxidases, the presence of selenocysteine (catalytic moiety) makes for fast reactions with hydroperoxide and reducibility by glutathione. And selenoprotein reduced phospholipid hydroperoxide using glutathione or thioredoxin as co-substrate [31,36-38]. This process continues to attack the lipids and cause damage until there is an alleviation of the stress response. A standard therapeutic for pPHA overdose is N-acetyl cysteine, a scavenger of reactive oxygen species. However, due to the strait therapeutic opening, rapid disease progression, and severe adverse effects, the therapeutic effectiveness of N-acetyl cysteine is still scanty. Therefore, new treatments that are better than N-acetyl cysteine as regards therapeutic efficacy and safety are required [39-41]. Recently, components of medicinal plants were found to be promising therapeutics as herbal medicines. In this present study, the pre- and post-treatment of *C. pilosa* rhizome aqueous extract has a significant ($P < 0.05$) therapeutic potential (curative and preventive) effect on the

induced oxidative stress damage in the tissues, where there is an up-regulation of the activities of catalase (Table 2), superoxide dismutase (Table 3), and glutathione (Table 4), respectively, which are similar to the results of previous research [13,27,42], and lipid concentrations (Table 5).

The presence of bioactive constituents (phenolics, flavonoids, tannins, and cardiac glycosides) found in the aqueous extract of *C. pilosa* rhizome [31,43,44] is responsible for protective effects mechanisms against pPHA-induced oxidative stress. These compounds are attributed to the extract's free radical scavenging activity, suppression of reactive oxygen species synthesis, and improvement of antioxidative defense enzyme systems to suppress radical damage [45-48]. The scavenging of free radicals is effected by the bioactive components in the aqueous extract of the *C. pilosa* rhizome by reducing the activity of cytochrome P450. This decreases the toxic metabolite N-acetyl-p-benzoquinoneimine and improves the cellular state of glutathione, which then eliminates free radical species like hydrogen peroxide and superoxide radicals and boosts the activities of catalase and superoxide dismutase. As well as the bioactives, reducing the activities of enzymes responsible for the production of hydroperoxides and improving the lipid concentration. This has justified the use of an aqueous extract of *C. pilosa* rhizome in traditional medicine for the treatment of various clinical conditions, such as inflammation, in the management of health issues.

Table 2. The effect of *C. pilosa* rhizome extract on catalase activity in pPHA-induced toxicity rats

Treatment dose	Catalase activity			
	Serum (U/ml)	Brain (U/g wet tissue)	Liver (U/g wet tissue)	Kidneys (U/g wet tissue)
Control	96.53±43.67^{a}	157.89±1.71^{a}	138.86±7.99^{a}	134.41±1.24^{a}
C pilosa	367.99±92.29^{b}	177.81±4.86^{b}	171.17±1.72^{b}	139.01±1.15^{b}
Cp + 750 mg/kg	132.94±66.05^{b*}	164.61±1.19^{b*}	158.03±0.97^{b*}	123.81±0.67^{b*}
Cp + 1000 mg/kg	71.96±13.66^{b**}	158.91±3.18^{b**}	135.83±2.07^{b**}	134.58±2.65^{b**}
750 mg/kg	109.57±19.14^{c}	129.63±1.29^{c}	61.97±2.27^{c}	114.58±1.01^{c}
750 mg/kg + Cp	152.71±33.74^{c*}	135.63±1.46^{c*}	86.35±1.85^{c*}	124.58±1.01^{c*}
1000 mg/kg	108.69±7.76^{d}	90.10±0.96^{d}	46.03±0.51^{d}	100.58±3.24^{d}
1000 mg/kg + Cp	142.79±20.17^{d*}	105.90±2.16^{d*}	67.99±1.06^{d*}	128.58±0.58^{d*}

Values in columns are mean ± S.E.M for 5 rats in each group. Values having different superscripts within a column differ significantly from each other (P < 0.05). Cp = aqueous extract of C. pilosa rhizome

Table 3. The effect of *C. pilosa* rhizome extract on superoxide dismutase activity in pPHA-induced toxicity rats

Treatment dose	Superoxide dismutase activity			
	Serum (U/ml) x 10^2	Brain (U/g wet tissue) x 10^2	Liver (U/g wet tissue) x 10^3	Kidneys (U/g wet tissue) x 10^3
Control	0.19±0.04^{a}	0.32±0.04^{a}	0.38±0.07^{a}	0.30±0.01^{a}
C pilosa	0.25±0.03^{b}	0.61±0.03^{b}	0.78±0.25^{b}	0.70±0.09^{b}
Cp + 750mg/kg	0.10±0.05^{b*}	0.47±0.19^{b*}	0.48±0.14^{b*}	0.50±0.03^{b*}
Cp + 1000mg/kg	0.21±0.02^{b**}	0.08±0.06^{b**}	0.40±0.06^{b**}	0.36±0.06^{b**}
750mg/kg	0.23±0.03^{c}	0.14±0.01^{c}	0.43±0.08^{c}	0.22±0.02^{c}
750mg/kg + Cp	0.54±0.06^{c**}	0.25±0.06^{c**}	0.51±0.09^{c**}	0.27±0.05^{c**}
1000mg/kg	0.23±0.02^{d}	0.13±0.06^{d}	0.41±0.06^{d}	0.19±0.01^{d}
1000mg/kg + Cp	0.33±0.03^{d**}	0.36±0.07^{d**}	0.58±0.02^{d**}	0.28±0.03^{d**}

Values in columns are mean ± S.E.M for 5 rats in each group. Values having different superscripts within a column differ significantly from each other (P < 0.05). Cp = aqueous extract of C. pilosa rhizome

Table 4. The effect of *C. pilosa* rhizome extract on glutathione activity in pPHA-induced toxicity rats

Treatment dose	Glutathione activity			
	Serum (mmol/L)	Brain (mmol/g tissue)	Liver (mmol/g tissue)	Kidney (mmol/g tissue)
Control	3.52±0.49^{a}	14.67±1.04^{a}	23.69±0.39^{a}	9.33±0.38^{a}
C pilosa	3.38±0.36^{b}	15.67±1.05^{b}	24.70±0.46^{b}	14.47±0.93^{b}
Cp + 750mg/kg	4.00±0.51^{b*}	13.61±0.27^{b*}	22.80±0.31^{b*}	13.14±0.34^{b*}
Cp + 1000mg/kg	5.86±0.34^{b**}	13.55±0.67^{b**}	17.90±0.57^{b**}	11.87±0.38^{b**}
750mg/kg	6.85±0.43^{c}	12.13±0.67^{c}	20.89±0.24^{c}	15.30±1.19^{c}
750mg/kg + Cp	4.87±0.58^{c**}	13.19±0.53^{c**}	22.90±0.17^{c**}	14.05±0.62^{c**}
1000mg/kg	8.27±0.47^{d}	11.33±0.46^{d}	18.29±0.40^{d}	12.50±0.51^{d}
1000mg/kg + Cp	6.64±0.42^{d**}	13.15±0.45^{d**}	21.59±0.24^{d**}	11.70±0.48^{d**}

Values in columns are mean ± S.E.M for 5 rats in each group. Values having different superscripts within a column differ significantly from each other (P < 0.05). Cp = aqueous extract of C. pilosa rhizome

Table 5. The effect of *C. pilosa* rhizome extract on serum lipid profile concentrations of pPHA-induced toxicity rats

Treatment dose	Serum		
	Cholesterol concentration (mg/dl)	Triglyceride Concentration (mg/dl)	Phospholipids Concentration (mg/dl)
Control	88.54±1.73^{a}	71.11±8.49^{a}	285.92±2.25^{a}
C. pilosa	94.41±2.27^{b}	52.22±2.42^{b}	248.46±1.40^{b}
Cp + 750mg/kg	86.48±8.44^{b*}	55.96±4.11^{b*}	270.30±4.40^{b*}
Cp + 1000mg/kg	84.99±5.19^{b**}	58.19±4.24^{b**}	286.30±6.08^{b**}
750mg/kg	69.90±4.75^{c}	66.58±2.57^{c}	297.81±3.43^{c}
750mg/kg + Cp	74.42±4.04^{c**}	47.14±4.51^{c**}	290.09±2.98^{c**}
1000mg/kg	54.99±8.05^{d}	87.05±5.51^{d}	319.78±8.88^{d}
1000mg/kg + Cp	59.30±5.70^{d**}	49.81±3.90^{d**}	289.03±4.58^{d**}

Values in columns are mean ± S.E.M for 5 rats in each group. Values having different superscripts within a column differ significantly from each other (P < 0.05). Cp = aqueous extract of C. pilosa rhizome

Table 6. The effect of *C. pilosa* rhizome extract on glutathione activity in pPHA-induced toxicity rats

Treatment dose	Glutathione activity			
	Serum (mmol/L)	Brain (mmol/g tissue)	Liver (mmol/g tissue)	Kidney (mmol/g tissue)
Control	3.52±0.49^{a}	14.67±1.04^{a}	23.69±0.39^{a}	9.33±0.38^{a}
C pilosa	3.38±0.36^{b}	15.67±1.05^{b}	24.70±0.46^{b}	14.47±0.93^{b}
Cp + 750mg/kg	4.00±0.51^{b*}	13.61±0.27^{b*}	22.80±0.31^{b*}	13.14±0.34^{b*}
Cp + 1000mg/kg	5.86±0.34^{b**}	13.55±0.67^{b**}	17.90±0.57^{b**}	11.87±0.38^{b**}
750mg/kg	6.85±0.43^{c}	12.13±0.67^{c}	20.89±0.24^{c}	15.30±1.19^{c}
750mg/kg + Cp	4.87±0.58^{c**}	13.19±0.53^{c**}	22.90±0.17^{c**}	14.05±0.62^{c**}
1000mg/kg	8.27±0.47^{d}	11.33±0.46^{d}	18.29±0.40^{d}	12.50±0.51^{d}
1000mg/kg + Cp	6.64±0.42^{d**}	13.15±0.45^{d**}	21.59±0.24^{d**}	11.70±0.48^{d**}

Values in columns are mean ± S.E.M for 5 rats in each group. Values having different superscripts within a column differ significantly from each other (P < 0.05). Cp = aqueous extract of C. pilosa rhizome

4. CONCLUSION

The generation of reactive oxygen species that cause oxidative stress and lipid dysfunction during high doses or abuse of pPHA is known to be detrimental to health. This study observed that it causes a reduction in the activities of catalase, superoxide dismutase, and glutathione, as well as cholesterol, triglycerides, and phospholipid concentrations.

An aqueous extract of *C. pilosa* rhizome has many bioactive constituents (antioxidants) that have contributed to the positive effects on the serum, brain, liver, and kidney catalase, superoxide dismutase, and glutathione activities, as well as the cholesterol, triglycerides, and phospholipid concentrations. This can be attributed to its function during pre- and post-treatment in preventing, managing, or treating health issues that occur during the toxicity of induced oxidative stress.

ETHICAL APPROVAL

All authors hereby declare that the Guide for the Care and Use of Laboratory Animals and Principles of Laboratory Animal Care were followed. All experiments have been examined and approved by the appropriate ethics committee of the university.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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