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Atherogenic and Haematologic Indices of Paracetamol- Overdosed Albino Rats Treated With Aqueous Leaf Extracts of *Euphorbia Heterophylla* and *Jatropha Curcas*

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Abstract

Objective: The protective effect of aqueous leaf extracts of *Euphorbia heterophylla* and *Jatropha curcas* against paracetamol-induced acute changes in lipid, atherogenic and haematologic parameters of albino rats were studied.

Methodology: Twenty-five adult male albino rats weighing 180 to 200 g were randomly assigned into 5 experimental groups (I-V) of five animals each. Group I animals were administered 10 ml of distilled water, while group II rats were given 1000 mg/kg paracetamol. Groups III-V were pretreated with vitamin C (500 mg/kg), *E. heterophylla* (200 mg/kg) and *J. curcas* (1000 mg/kg) respectively, 1 h before administration of 1000 mg/kg paracetamol. The animals were orally administered the extracts/drugs daily for 14 days.

Result: Paracetamol administration reduced significantly ($p<0.05$) the total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and total non HDL-c concentrations as well as white blood cell (WBC) count of the animals when compared with the control. Pre-treatment of the animals with vitamin C non-significantly ($p>0.05$) countered the observed effects of paracetamol overdose more than the extracts of *E. heterophylla* and *J. curcas*. Acute paracetamol overdose did not significantly ($p>0.05$) affect most of the atherogenic risk predictor indices and haematological parameters studied.

Conclusion: The results indicate that atherogenic and haematologic indices were less responsive than lipid parameters to paracetamol-induced toxicity. Furthermore, aqueous leaf extracts of *E. heterophylla* and *J. curcas* had less protective effect than vitamin C against serum lipidaemic changes induced by paracetamol.

Keywords: Acetaminophen; Drug overdose; Lipid profile; Medicinal plants; Vitamin C; Atherogenic indices

Introduction

Many medicinal plant species contain both important nutrients and phytochemicals that could be pharmacologically essential [1]. The ethnopharmacological importance and application of plants in the treatment of diseases and illments in traditional setting have been an age-long practice [2]. Currently, herbal products are preferred by many people because of less testing time, higher safety, efficacy, cultural acceptability and assumed 'lesser' side effects. Furthermore, the phytochemicals present in plant-based products are thought be compatibility with the human body because they form part of the daily chemicals, humans ingested with food [3]. *Euphorbia heterophylla* and *Jatropha curcas* are among such traditional plants that have been reported to be useful for various purposes.

E. heterophylla plants are commonly available in temperate and tropical regions of the world. They occur in nature as herbs, shrubs or trees [1,4]. The plant is commonly called Mexican fire plant, milk weed and Spurge weed [5]. *E. heterophylla* belongs to the family Euphorbiaceae and to the subgenus *Poinsettia*, a group with stipules modified into glands [6]. It has a milky sap that is poisonous. Notwithstanding the poisonous nature of the plant's sap, it has been widely use in the treatment of various tropical diseases such as malaria, asthma, eczema and gonorrhea, as well as wart and respiratory tract infection [5]. In southeastern Nigeria, Igbo traditional doctors use the aqueous leaf extract of *E. heterophylla* for treatment of bacterial and parasitic infections of the blood and skin, and as a purgative [7]. Many pharmacologically important phytochemicals such as 4-hydroxylbenzoic acid, quercetin, beta-amyrin, and stigmasterol were isolated from the leaves. Similarly, essential and non essential amnio acids including, but not limited to, alanine, aspartic acid, cysteine, serine, proline, methionine and glutamic acid were also found to be present in the plant's leaf extract [8]. It was also observed that oral administration of aqueous leaf extract of the plant significantly reduced plasma glucose concentration of experimental induced diabetes in rats [9]. Aqueous leaf extract of *E. heterophylla* has also been reported to have good anticoagulant and preservative effect on human whole blood [10].

Like *E. heterophylla*, *J. curcas* L. is a widely grown flowering plant. It is a perennial plant that belongs to the Euphorbiaceae family [11]. The plant grows into a large shrub or small tree of up to 5 m in height. In the tropics, *J. curcas* is commonly grown as a living fence in fields and settlements [12]. All parts of the plant are very poisonous. The seed of *J. curcas* was reported to contain a purgative, phytotoxic oil called curcin, which causes dehydration and cardiovascular collapse as a result of haemorrhagic gastro-enteritis, and central nervous system

depression [13]. However, it is gaining a lot of economic significance because of its several potentials in industrial application and medicinal values. The leaves of *J. curcas* are traditionally used in different forms in West Africa for the treatment of various ailments like fever, guinea worm sores, joint rheumatism, mouth infections and jaundice [3].

Paracetamol, also known as acetaminophen, is a widely used over-the-counter non-steriodal anti-inflammartory drug (NSAID) for treatment of pains and fever [14]. It is not a very strong analgesic, but can be used in conjuction with opioid analgesics in the management of more severe pains such as post-surgical and cancer pains [15]. It is generally safe when used at recommended doses even when taken for a long time. However, when taken in overdose paracetamol can be very toxic and fatal [16]. Paracetamol toxicity has been ascribed to the formation of Nacetylpbenzoquinoneimine (NAPQI), a toxic metabolite by hepatic cytochrome P450 [17]. NAPQI oxidizes the lipids and proteins of tissues, depletes glutathione and alters calcium homeostasis [18]. The oxidation of lipids and damage to liver hepatocytes could lead to derangements in lipid profile. The role of derangement in lipid profile in the progression of cardiovascular diseases (CVD) has been well established, with primary interest in CVD therapy focused on deranged low density lipoprotein cholesterol (LDL-c) levels [19]. High plasma triglyceride and cholesterol levels are both independent and synergistic risk factors for cardiovascular diseases and are often correlated with hypertension, obesity and diabetes mellitus [20]. Significant elevations in plasma low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol concentrations are known risk factors for cardiovascular disease and are also often seen in hypertension and obesity [21]. Meanwhile, different combinations or ratios of these lipid profile parameters have been reported to be better indices for identification of high risk individuals to CVDs than direct use of the lipid parameters themselves [19]. Atherogenic index of plasma (AIP), atherogenic coefficient (AC) and Castelli's risk indices (CRIs) are the ratios of such lipid profile parameters that have been studied as markers of lipid atherogenic risk [22]. They are calculated lipid fraction ratios which are suggestively gaining attention in clinical setting for assessing the risk of CVD, over and above the routinely used lipid profile parameters [23]. In this study, we investigated the protective effect of the aqueous leaf extracts of *J. curcas* and *E. heterophylla* against paracetamol-induced changes in atherogenic and haematologic indices of albino rats.

Materials and Methods

Plants collection and extract preparation

The leaves of *Jatropha curcas* and *Euphorbia hetrophylla* were collected from bushes around Eziobodo in Owerri West Local Government Area of Imo State. They were authenticated by a botanist, Mr Francis Nwanze of the Department of Forestry and Wildlife, Federal University of Technology Owerri, Nigeria.

Apparently healthy leaves of the two plants were separately air-dried for 2 weeks and then oven-dried at a temperature of 50˚C for 8 h to a constant weight. Using pestle and mortar, the dried leaves were ground into powder form. The powders were separately stored in labeled air-tight containers. Five hundred grams (500 g) of each leaf powder was soaked in 1,000 ml of distilled water for 48 h and filtered with whatman filter paper No. 1. The filtrate was evaporated to dryness. Then the dried powder was suspended in 100 ml of 0.5% tween 80 solvent in a 500 ml beaker, allowed to stand for 1 hr and filtered. The filtrate was evaporated in an electric oven at 50˚C to obtain the stock solutions. Then, respective doses of 200 mg/kg and 1000 mg/kg for *E. heterophylla* and *J. curcas* were prepared from the stocks. Each concentrate was transferred into labeled glassware and refrigerated at 4˚C until needed.

Drugs used

The paracetamol and vitamin C tablets used were products of Emzor Pharmaceuticals Ltd, Nigeria. They were sourced from Orchad Pharmacy in Owerri, Nigeria. Each tablet containing 1000 mg of paracetamol was dissolved in 10 ml of distilled water, while each tablet of vitamin C containing 100 mg of ascorbic acid was dissolved in 1 ml of distilled water. They were reconstituted and administered as 1000 mg/kg and 500 mg/kg body weight of the animals respectively.

Laboratory animals

Laboratory animals used were made up of 25 adult male albino rats (*Rattus novergicus*) weighing between 180 g and 200 g, obtained from the Department of Vertinary Medicine, University of Nigeria, Nsukka. The animals were kept in stainless steel cages under good laboratory conditions of humidity (60 ± 0.2 %), temperature (30 ± 1˚C) and a 12 h light/dark cycle. They were kept for 14 days to acclimatize to laboratory conditions in the Animal House Unit of Department of Biochemistry, Federal University of Technology Owerri. During the acclimatization period, they were provided with clean water and standard feed (Growers marsh, Vital Feeds Ltd.) *adlibitum*. Ethical approval was obtained for the study protocol from the University ethical committee. Principles of Laboratory Animal Care (NIH Publication, 1985-1993) were fully adopted in all the experimental procedures involving the use and handling of the laboratory animals.

Grouping of animals

After acclimatization period, the albino rats were randomly allotted into 5 groups of 5 rats each. Group I served as the negative control and were orally administered daily dose of 10 ml/kg body weight of distilled water only. Group II served as the positive control and were orally administered daily dose of 1000 mg/kg of paracetamol. Group III animals (the standard group) were pretreated with oral dose of 500 mg/kg of vitamin C solution one hour before the oral administration of 1000 mg/kg of paracetamol. Group IV animals were pretreated with single oral dose of 200 mg/kg of *Euphorbia heterophylla* leaf extract one hour before administration of 1000 mg/kg of paracetamol. This served as test group 1. Group V animals were pretreated with daily oral dose of 1000 mg/kg of *Jatropha curcas* leaf extract 1 h before administration of 1000 mg/kg of paracetamol. This served as test group 2. The chosen dose ranges for the paracetamol and aqueous plant extracts used were based on result of earlier toxicity studies [1,24,25]. The oral administration of the drugs and plant extracts were for a period of fourteen days.

Sample collection

At the end of the 14 days of treatment, the animals were fasted overnight, anaesthetized with diethyl ether and sacrified. Then, 5 mL of whole blood was collected by cardiac puncture. About 3 mL of each blood sample was gently dispensed into a well labeled 10 ml capacity plain sample bottle, while the rest was dispensed into ethylene diamine tetra acetic acid (EDTA) bottle. The blood samples in the plain bottles were allowed to clot and centrifuged at 2000 rpm for 15 minutes to separate sera from the clot. The sera were carefully separated into fresh

labeled sample bottles and were used for lipid profile analysis, while the EDTA containing whole blood was used for haematological parameters.

Lipid profile analyses

Serum triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-c) concentrations were determined using enzymatic colorimetric method [26], phosphotungstate precipitation and enzymatic endpoint methods [27] with the aid of commercial reagent kits (Randox Laboratories Ltd, UK). Calculation of the concentration of low density lipoprotein cholesterol (LDL-c) in the serum was as previously described [28].

Calculations of the atherogenic indices

Serum total non-HDL cholesterol (TnHDL-c) concentration was calculated as TC – HDL-c [29], while Castelli's Risk Index I (CRI-I) and Castelli's Risk Index II (CRI-II) were determined as TC / HDL-c and LDL-c / HDL-c respectively [22,30]. Atherogenic index of plasma (AIP) and atherogenic coefficient (AC) levels were calculated as log (TG / HDL-c) and (TC - HDL-c) / HDL-c respectively [31,32].

Haematological analyses

Haemoglobin concentration of the anticoagulated blood was determined using Cyan-methaemoglobin method. Heamatocrit method was used in the determination of Packed Cell Volume (PCV), while Romanowsky stains/May-Grunwald-Giemsa Stain Technique was used in the determination of white and red blood cell counts [33,34].

Statistical analysis

Data obtained from the analyses were presented as mean ± standard deviation. The data generated were statistically analysed using one way Analysis of Variance (ANOVA) and Tukey Post HOC test with the aid of GraphPad Prism Version 5.3 (GraphPad, USA). Values that gave $p \leq 0.05$ were taken to be statistically significant.

Results

Table 1 shows the lipid profile and atherogenic predictor indices of the paracetamol overdosed animals. Paracetamol treatment reduced significantly ($p<0.05$) the TG, TC, and HDL-c concentrations, but increased the LDL-c and total non-HDL cholesterol concentrations of the animals in comparism to the control animals. Treatment of the paracetamol overdosed animals with vitamin C and extracts of *E. heterophylla* and *J. curcas* increased non-significantly ($p>0.05$) the concentrations of the lipid and lipoproteins of the treated groups. Paracetamol overdose did not change significantly ($p>0.05$) the Castelli's Risk Index I (TC/HDL-c ratio), Castelli's Risk Index II (LDL-c/HDL-c ratio), atherogenic coefficient [(TC - HDL-c)/HDL-c ratio] and atherogenic index of plasma (Log [TG/HDL-c]) of the animals when compared with the control, vitamin C, *E. heterophylla* and *J. curcas* groups.

Parameters	Negative Control	Positive Control (Paracetamol)	Standard Group (Vitamin C)	Test Group 1 (*E.heterophylla*)	Test Group 2 (*J. curcas*)
TG (mg/dl)	150.74 ± 6.90^{a}	137.64 ± 7.5^{b}	145.09 ± 6.30^{ab}	140.80 ± 4.70^{ab}	143.37 ± 4.90^{ab}
TC (mg/dl)	198.51 ± 4.60^{a}	182.30 ± 5.50^{b}	189.79 ± 6.80^{ab}	186.80 ± 4.60^{b}	187.56 ± 7.30^{ab}
HDL-c (mg/dl)	40.34 ± 0.26^{a}	36.94 ± 0.16^{b}	38.72 ± 0.26^{c}	37.97 ± 0.16^{d}	37.84 ± 0.13^{d}
LDL-c (mg/dl)	82.66 ± 0.39^{a}	89.80 ± 0.42^{b}	85.12 ± 0.70^{c}	84.83 ± 0.48^{c}	84.55 ± 0.83^{c}
CRI-I	4.92 ± 0.64^{a}	4.94 ± 0.70^{a}	4.90 ± 0.61^{a}	4.92 ± 0.40^{a}	4.96 ± 0.41^{a}
CRI-II	2.22 ± 0.09^{a}	2.24 ± 0.06^{a}	2.20 ± 0.02^{a}	2.23 ± 0.01^{a}	2.23 ± 0.03^{a}
TnHDL-c(mg/dl)	158.18 ± 4.80^{a}	165.36 ± 5.20^{b}	151.07 ± 6.60^{ab}	148.83 ± 4.80^{ab}	149.72 ± 7.00^{ab}
AC	3.92 ± 0.03^{a}	3.94 ± 0.08^{a}	3.90 ± 0.04^{a}	3.92 ± 0.09^{a}	3.96 ± 0.05^{a}
AIP	0.57 ± 0.02^{a}	0.57 ± 0.01^{a}	0.57 ± 0.02^{a}	0.57 ± 0.01^{a}	0.58 ± 0.01^{a}

Table 1: Lipid Profile and Atherogenic Index Parameters of Paracetamol-overdosed Albino Rats Treated with *E. heterophylla* and *J. curcas*. Values are mean ± standard deviation. Values with different alphabet letters per row are statistically significant ($p<0.05$). TC: Total Cholesterol; TG: Triglyceride; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; TnHDL-c: Total Non-HDL-c; CRI-I: Castelli's Risk Index I; CRI-II: Castelli's Risk Index II; AC: Atherogenic Coefficient; AIP: Atherogenic Index of Plasma.

Table 2 shows the haematologic indices of the paracetamol overdosed animals. Paracetamol treatment did not change significantly ($p>0.05$) the blood haemoglobin (Hb) concentration, packed cell volume (PCV) values and red blood cell (RBC) counts of the animals in comparism with the control and those of the vitamin C, *J. curcas* and *E. heterophylla* treated groups. However, there was a significant ($p<0.05$) reduction in the white blood cell (WBC) count of the animals after treatment with paracetamol overdose in comparism with the control. This was significantly ($p<0.05$) attenuated after treatment of the paracetamol overdosed animals with vitamin C, *E. heterophylla* and *J. curcas*.

Parameters	Negative Control	Positive Control (Paracetamol)	Standard Group (Vitamin C)	Test Group 1 (*E. heterophylla*)	Test Group 2 (*J. curcas*)
HB (g/dl)	11.30 ± 1.59^{a}	11.87 ± 1.60^{a}	12.65 ± 1.11^{a}	11.95 ± 1.00^{a}	12.07 ± 0.90^{a}
PCV (%)	33.93 ± 4.71^{a}	35.60 ± 4.81^{a}	37.95 ± 3.34^{a}	35.85 ± 3.00^{a}	36.07 ± 2.90^{a}
WBC (x1012/L)	5.45 ± 0.10^{a}	4.20 ± 0.17^{b}	6.68 ± 0.23^{c}	6.45 ± 0.30^{c}	4.77 ± 0.25^{d}
RBC (x1012/L)	35.65 ± 4.37^{a}	37.70 ± 4.86^{a}	40.05 ± 3.41^{a}	37.80 ± 2.93^{a}	38.10 ± 3.05^{a}

Table 2: Haematological Parameters of Paracetamol-overdosed Albino Rats Treated with *E. heterophylla* and *J. curcas*. Values are mean ± standard deviation. Values with different alphabet letters are statistically significant ($p<0.05$). HB: Haemoglobin; PCV: Packed cell volume; WBC: white blood cell count; RBC: Red blood cell count.

Discussion

Induction of lipid peroxidation via the action of N-acetyl-parabenzoquinonimine (NAPQI), a highly reactive intermediate of paracetamol, is the principal route of paracetamol elicited toxicity. This intermediary metabolite covalently binds to cell's intracellular and membrane macromolecules leading to cell death and consequent liberation of intracellular contents including the cytosolic enzymes [35]. The release and induction of cytochrome based enzymes such as CYP2E1, CYP1A2 and CYP3A4, as well as depletion of intracellular glutathione (GSH) and induction of oxidative stress have been reported to be the most important mechanisms involved in the pathogenesis of paracetamol-induced cell injury [18,36]. Interestingly, such damages have been reportedly prevented or ameliorated by herbal preparations.

Results of our study showed that oral administration of overdose of paracetamol decreased serum triglyceride, total cholesterol, and HDL-c concentrations but increased LDL-c concentration. Paracetamol overdose has been reported to cause impairment in lipid and lipoprotein metabolism [37]. This could be as a result of hepatotoxicity that has been associated with excessive intake of paracetamol. The liver is the major organ for metabolism of lipids especially cholesterol and lipoproteins, and a significant site for re-generation of GSH required for control of lipid peroxidation processes in the body. Meanwhile, administration of vitamin C and extracts of *E. heterophylla* and *J. curcas* non-significantly ($p>0.05$) attenuated the TC concentrations. Serum low density lipoprotein cholesterol (LDL-c) and TG concentrations were equally attenuated in the extracts-treated groups. The concentrations of TC and LDL-c in blood have been reported to be direct related with mortality and morbidity from coronary artery diseases. Isolated rise in blood triglyceride above normal is not an independent risk factor for coronary disease. However, hypertriglyceridaemia becomes a risk factor for coronary disease when associated with high LDL-c and low HDL-c levels in blood. Impaired catabolism of chylomicron remnant, intermediate density lipoprotein (IDL), and LDL gives rise to increase in serum cholesterol [38]. The attenuation in serum TC concentration observed in the extracts-treated rats may be attributed to increase in the serum HDL-c concentration. HDL-c mobilizes cholesterol into the cells thereby decreasing or reducing the formation of atherosclerotic plaque. Relative or absolute decrease in the cholesterol carried in the HDL-fraction of plasma is seen in atherosclerotic patients [39].

Atherogenic indices are strong indicators of the risk of heart disease. The higher their values, the higher the risk of developing cardiovascular problems and vice versa [21,31]. There was no significant difference ($p>0.05$) observed in the Castelli's index I and II, atherogenic coefficient and atherogenic index of plasma of the paracetamol-overdosed animals in comparism with those of the groups treated with vitamin C, *E. heterophylla* and *J. curcas*. These indicate no potential risk of cardiovascular disease among the treatment groups. However, total non-HDL cholesterol (TnHDL-c) was significantly ($p<0.05$) increased in the paracetamol-overdosed group in comparism to the control. Administration of vitamin C, *E. heterophylla* and *J. curcas* to the paracetamol-challenged animals significantly ($p<0.05$) lowered the TnHDL-c values of the treatment groups.

There were no observed significant ($p>0.05$) changes in the blood parameters (Hb, PCV and RBC) of both the paracetamol-overdosed and the extracts-treated groups in comparism with the control animals. The absence of significant changes in these haematologic parameters suggest that paracetamol overdose and treatment with the extracts did not elicit anaemia-related conditions in the rats. Decreased haemoglobin and haematocrit levels, indicative of anaemia, are associated with intravascular haemolysis [24]. These observations may be due to the understanding that paracetamol metabolism and toxicity occur mainly in the liver. However, there was observed reduction in white blood cell (WBC) count of the paracetamol-overdosed rats while administration of vitamin C, *E. heterophylla* and *J. curcas* extracts led to a significant ($p<0.05$) increase in the WBC count of the rats, an observation which corroborates previous report that WBC counts are significantly decreased by paracetamol administration [40].

Conclusion

In the light of the results obtained in this study, it may be concluded that atherogenic and haematologic indices were less responsive than lipid parameters to paracetamol-induced toxicity. Furthermore, aqueous leaf extracts of *E. heterophylla* and *J. curcas* have protective effect, although less than vitamin C, against serum lipidaemic changes induced by paracetamol toxicity. The observations reported herein may explain the widespread use of the extracts of these plants in ethnotraditional medicine practice.

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