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Lipid profile and atherogenic predictor indices of albino rabbits administered coconut water as antidote to paracetamol overdose

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ABSTRACT

Objective: To investigate the effects of coconut water intake on lipid profile and atherogenic predictor indices of albino rabbits overdosed with paracetamol using standard methods.
Methods: Thirty-five albino rabbits weighing between 800–1 200 g and aged between 2 and 3 months, were divided into 7 groups (I–VII) of 5 animals each. Groups I, II and III were orally administered distilled water (20 mL/kg body weight), coconut water (20 mL/kg body weight) and paracetamol (1 000 mg/kg body weight) respectively, for 7 days. Groups IV and V were administered coconut water (20 mL/kg body weight) and silymarin (35 mg/kg body weight), respectively, for 6 days, then paracetamol (1 000 mg/kg body weight) on the 7th day. Groups VI and VII were administered distilled water for 6 days, paracetamol on the 7th day, then coconut water and silymarin, respectively, after 3 h.
Results: The results showed that paracetamol overdose significantly reduced ($P < 0.05$) the mean body weight of the animals, increased the concentrations of serum total cholesterol, triacylglycerol, very low density lipoprotein cholesterol, low density lipoprotein cholesterol and the atherogenic predictor indices but reduced the serum high density lipoprotein cholesterol concentration of the animals relative to the control. The observed changes in the lipid profile and atherogenic predictor indices were countered more by post- than pre-treatment with coconut water and silymarin.
Conclusions: The results indicated that coconut water acted as an effective antidote to paracetamol overdose-induced lipid abnormality in animals.

1. Introduction

Disorders associated with lipid metabolism are varied. However, they are diagnosed and the treatment monitored with the aid of a set of biochemical assays termed lipid profile test[1]. Generally, hyper- or hypo-lipidaemia is elevation or reduction in the concentration of one or more of the plasma lipids which includes cholesterol, cholesteryl esters, triacylglycerols and phospholipids[2]. On the other hand, lipoproteinaemias are disorders associated with changes in the levels and distributions of the blood lipid-transport biomolecules called lipoproteins. Thus, initial protocols in the diagnosis of lipidaemias and/or lipoproteinaemias involve ascertaining the levels and patterns of the lipids and lipoproteins in blood via lipid profile tests[1]. Many research studies have strongly correlated changes in the concentrations of blood lipids and lipoproteins, as well as changes in atherogenic risk predictor indices with the occurrence and extent of liver disorders, atherosclerosis and coronary artery diseases[3]. These relationships with liver disorders may stem from the role of the liver in the biosynthesis, catabolism and secretion of lipids and lipoproteins into blood. Hence, dysfunctions of the organ, such as in acute liver damage, might interfere with the metabolism of lipids and may lead to changes in plasma lipid and

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All experimental procedures in the present study involving animals were conducted in accordance to the standard principles of Laboratory Animal Care of the United States National Institutes of Health and approved by the Ethical Committee of Department of Biochemistry, Federal University of Technology, Owerri, Nigeria (Ethics Approval Number: ODVC/REN/1051/15).

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lipoprotein patterns[4].

Paracetamol, also called acetaminophen, is a common non-narcotic drug that is widely recommended by physicians as an analgesic and antipyretic agent[5]. When used at recommended doses, it has minimal side effects and rarely interacts with other drugs. However, overdose or protracted intake of paracetamol produce acute liver damage along with other system associated disorders[6]. Paracetamol overdose due to prescription is not a common occurrence. Its availability over-the-counter, especially in developing countries, has indirectly encouraged its use in self-medication, with the attendant damage to hepatocellular metabolic functions[7]. Metabolism of paracetamol takes places mainly in the liver where it forms easily excreted sulphate and glucuronide conjugates. During prolonged intake or overdose of paracetamol, toxic intermediary metabolites such as N-acetyl-p-benzoquinoneimine (NAPBQI) are produced. NAPBQI, which is formed during the catabolic activation of paracetamol by cytochrome P-450 of liver origin, is an extremely reactive cytotoxic electrophile that binds to cellular proteins[8,9]. Hepatocytes detoxify NAPBQI by conjugating it with reduced glutathione to form mercapturic acid[4]. However, in the presence of paracetamol overdose, there will be excessive production of NAPBQI with concomitant depletion of reduced glutathione and subsequent drop in NAPBQI detoxification. This creates room for NAPBQI to oxidize macromolecules such as DNA, lipids and proteins of body cells and tissues. It also alters calcium homeostasis of cells. Such damage could be prevented or ameliorated by drugs. Methionine oral preparation and N-acetylcysteine oral and intravenous formulations are two antidotes that are used to treat paracetamol toxicity in many hospitals[10]. Similarly, many approved and not-yet-approved herbal extracts and formulations are currently being marketed as potential hepatoprotective agents. Among these is silymarin which is labeled and sold as a herbal drug for hepatoprotection against xenobiotic damage[7].

Plants and plant derived products have been long found and used in the management and control of human diseases and disorders. Similarly, plant based secondary metabolites such as alkaloids, flavonoids, tannins, terpenoids and steroids have attracted so much attention because of their positive effect against many human ailments. They have been reported to have many physiological effects and pharmacological potentials like antihyperlipidaemic and hepatoprotective properties[11,12].

Coconut (*Cocosnucifera* L.) is a large palm tree that belongs to the family Arecaceae and genus *Cocos*. It is a perennial tree, which grows to approximately 30 m in height. Its pinnate leaves and pinnae are 4 to 6 m and 60 to 90 m long, respectively. The coconut fruit has coconut flesh, water and oil which form part of the human diet. These can be eaten as a delicacy, taken as a refreshing drink or used as part of the traditional ingredient for cooking certain foods such as coconut rice. Coconut water contains many macro and micronutrients. Furthermore, it contains growth promoting factors which contribute significantly to its use in *in vitro* cell and tissue culture techniques[13]. Traditionally, coconut water is recommended as a refreshing drink to patients suffering from cholera and diarrhea to replace the fluid lost from the gastrointestinal tract. It is also prescribed for the management and elimination of kidney and urethral stones, elimination of mineral poisons and enhancement of drug absorption. The electrolytes in coconut water interact synergistically to enhance and ensure peak concentration of drugs in the blood[12].

Coconut water is traditionally used in Nigeria as antidote for poisonous agents and drug overdose. Thus, this study was designed to investigate such claims by assessing the changes in the lipid profile and atherogenic predictor indices of paracetamol overdosed albino rabbits pre- and post-treated with coconut water.

2. Materials and methods

2.1. Drugs

Paracetamol (product of Emzor Phramaceuticals Ltd., Lagos, Nigeria) and silymarin (product of Panacea Biotech Ltd., Tamil Nadu, India) tablets were purchased from a registered pharmaceutical shop in Owerri Municipal Council, Imo State, Nigeria.

2.2. Coconut water

A total of 14 apparently healthy mature green coconuts, 7 to 8 months of age, were harvested from a coconut plantation at Umuagwo, Imo State, Nigeria. Two coconuts were randomly picked and dehusked, and their coconut water extracted under aseptic conditions for use per day.

2.3. Experimental animals

All experimental procedures in the present study involving animals were conducted in accordance to the standard principles of Laboratory Animal Care of the United States National Institutes of Health[14] and approved by the Ethical Committee of Department of Biochemistry, Federal University of Technology, Owerri, Nigeria (Ethics Approval Number: ODVC/REN/1051/15).

Thirty-five apparently healthy albino rabbits weighing between 800–1200 g and aged 2 to 3 months, were used for the study. The animals were purchased from an Animal House at Owerri-Ebeiri, Orlu, Imo State, Nigeria and kept in the Animal House of the

Department of Biochemistry, Federal University of Technology, Owerri, Nigeria, under a 12 h light/dark cycle. The animals were acclimatized for 2 weeks by maintaining them on standard chow diets and water, *ad libitum*, after which they were randomly divided into 7 groups of 5 animals each.

2.4. Preparation and oral administration of drugs

Two tablets of paracetamol (1 000 mg) and silymarin (70 mg) were dissolved in 2 mL of distilled water, respectively. The drugs were administered to the albino rabbits on the basis of their body weight.

Groups I, II and III were administered distilled water (20 mL/kg body weight), coconut water (20 mL/kg body weight), and paracetamol (1 000 mg/kg body weight) for 7 days, respectively. Groups IV and V were administered coconut water (20 mL/kg body weight) and silymarin (35 mg/kg body weight), respectively, for 6 days before administering paracetamol (1 000 mg/kg body weight) on the 7th day. Groups VI and VII were administered distilled water (20 mL/kg body weight) for 6 days, paracetamol (1 000 mg/kg body weight) on the 7th day, then coconut water (20 mL/kg body weight) and silymarin (35 mg/kg body weight), respectively, after 3 h. Group III served as the paracetamol administered but coconut water untreated or paracetamol administered but silymarin untreated group. Groups IV and VI were the paracetamol administered but coconut water treated groups, whereas Groups V and VII were the paracetamol administered but silymarin treated groups.

All the groups were given feed and water *ad libitum*, and weighed daily throughout the experimental period of 7 days.

2.5. Sera collection

After the 7 days of treatment, the animals were fasted overnight, anaesthetized with dichloromethane vapour and whole blood was quickly collected by cardiac puncture. The blood samples were gently dispensed into labeled dry test tubes, allowed to clot and centrifuged at 3 000 r/min for 5 min. Sera samples were aspirated from the clotted blood with sterile Pasteur pipette and stored in labeled sample bottles.

2.6. Analysis of biochemical parameters

Enzymatic method[15] was used to measure total cholesterol (TC) with the aid of Randox cholesterol kit (Randox Laboratories, Antrim, UK). High density lipoprotein cholesterol (HDL-c) concentration was determined by HDL-c precipitant method[16], while triacylglycerol (TG) concentration was estimated using the method of Buccolo and David[17]. Low density lipoprotein cholesterol (LDL-c) was estimated using the Friedewald formula[18], while very LDL-c (VLDL-c) was calculated as TG/2.2[19].

The atherogenic predictor indices were estimated using the following formulae: atherogenic index of plasma = log TG/HDL-c; Castelli's risk index I = TC/HDL-c; Castelli's risk index II = LDL-c/HDL-c; and atherogenic coefficient = (TC – HDL-c)/HDL-c. The concentration of total non-HDL-cholesterol was calculated by subtracting the concentration of HDL-c from TC[20], while percentage of protection was calculated using the formula[21]:

$$\text{Protection (\%)} = \frac{\text{AC of PABCWUT group} - \text{AC of PABCWT/PABST group}}{\text{AC of PABCWUT group}} \times 100$$

where AC is atherogenic coefficient, PABCWUT is paracetamol administered but coconut water untreated, PABCWT is the paracetamol administered but coconut water treated and PABST is paracetamol administered but silymarin treated.

2.7. Statistical analysis

The data generated were expressed as mean ± SD and subjected to One-way ANOVA using computer-based GraphPad Prism 5.3 (GraphPad Inc., USA). Significant differences between group means were detected at $P \leqslant 0.05$ using Tukey *post-hoc* test.

3. Results

The animals treated with only coconut water significantly ($P < 0.05$) gained more weight [(0.09 ± 0.001) g] than the control [(0.07 ± 0.003) g] and the other animal groups. Similarly, the animal groups that were pre- and post-treated with either coconut water or silymarin significantly ($P < 0.05$) gained weight relative to the animals that received paracetamol only. Animals that were not treated with coconut water or silymarin lost weight [(–0.01 ± 0.001) g].

Administration of paracetamol overdose significantly ($P < 0.05$) increased the serum concentrations of TC [(5.15 ± 0.60) mmol/L], TG [(2.72 ± 0.07) mmol/L], LDL-cholesterol [(2.36 ± 0.01) mmol/L] and VLDL-cholesterol [(1.28 ± 0.04) mmol/L] concentrations, but reduced the HDL-cholesterol [(0.56 ± 0.02) mmol/L] concentration of the animals that received only paracetamol relative to the untreated control group and the other treatment groups (Table 1). Post-treatment of paracetamol overdosed animals with coconut water significantly reduced ($P < 0.05$) the concentrations of TC, TG, LDL-c and VLDL-c than pre-treatment with coconut water. Similarly, post-treatment with coconut water significantly

Table 1
Lipid profile of albino rabbits on paracetamol overdose and percentage protection by coconut water and silymarin.

Parameters (mmol/L)	Groups (% protection)						
	Control	CWG	PARA	PRE-CWG	PRE-SIL	POST-CWG	POST-SIL
TC	2.27 ± 0.26^{a}	3.24 ± 0.34^{ac}	5.15 ± 0.60^{b}	4.11 ± 0.12^{c} (20.19%)	3.83 ± 0.76^{c} (25.63%)	3.35 ± 0.20^{ac} (34.95%)	3.14 ± 0.41^{ac} (39.03%)
TG	1.79 ± 0.06^{a}	1.14 ± 0.07^{b}	2.72 ± 0.07^{c}	2.13 ± 0.03^{e} (21.69%)	1.57 ± 0.08^{d} (42.28%)	1.48 ± 0.05^{d} (83.78%)	1.47 ± 0.09^{d} (45.96%)
HDL-c	0.96 ± 0.04^{a}	0.92 ± 0.08^{a}	0.56 ± 0.02^{b}	1.07 ± 0.03^{ac} (91.07%)	1.13 ± 0.04^{c} (101.79%)	1.16 ± 0.05^{c} (107.14%)	1.51 ± 0.03^{d} (169.64%)
LDL-c	0.50 ± 0.05^{a}	0.80 ± 0.07^{b}	2.36 ± 0.01^{c}	1.22 ± 0.06^{d} (48.31%)	1.66 ± 0.03^{e} (29.66%)	0.82 ± 0.04^{b} (65.25%)	1.29 ± 0.07^{d} (45.34%)
VLDL-c	0.81 ± 0.02^{ad}	0.52 ± 0.12^{b}	1.28 ± 0.04^{c}	0.96 ± 0.05^{d} (25.00%)	0.72 ± 0.08^{a} (43.75%)	0.68 ± 0.08^{ab} (46.88%)	0.66 ± 0.04^{ab} (48.44%)

CWG: Coconut water group; PARA: Paracetamol group; PRE-CWG: Pre-coconut water group; PRE-SIL: Pre-silymarin group; POST-CWG: Post-coconut water group; POST-SIL: Post-silymarin group. Values were expressed as mean ± SD. Values with different superscript letter per row are significantly different ($P < 0.05$).

Table 2
Atherogenic predictor indices of albino rabbits on paracetamol overdose and percentage protection by coconut water and silymarin.

Parameters (mmol/L)	Groups (% protection)						
	Control	CWG	PARA	PRE-CWG	PRE-SIL	POST-CWG	POST-SIL
TC/HDL-c	2.42 ± 0.37^{a}	3.41 ± 0.85^{ac}	9.18 ± 0.75^{b}	4.06 ± 0.14^{c} (55.77%)	3.06 ± 0.14^{ac} (66.67%)	3.11 ± 0.08^{ac} (66.12%)	2.69 ± 0.13^{a} (70.70%)
LDL-c/HDL-c	0.54 ± 0.03^{a}	1.81 ± 0.09^{b}	4.07 ± 0.16^{c}	2.37 ± 0.13^{d} (41.77%)	1.42 ± 0.12^{e} (65.11%)	1.21 ± 0.06^{e} (70.27%)	1.22 ± 0.14^{e} (70.02%)
Total non-HDL-c	1.31 ± 0.14^{a}	2.31 ± 0.17^{b}	4.59 ± 0.18^{c}	3.04 ± 0.15^{d} (33.77%)	2.01 ± 0.13^{b} (56.21%)	2.18 ± 0.16^{b} (52.51%)	2.32 ± 0.15^{b} (49.46%)
(TC-HDL-c)/HDL-c	1.42 ± 0.17^{a}	2.41 ± 0.15^{bd}	8.18 ± 0.75^{c}	3.06 ± 0.14^{b} (62.59%)	2.06 ± 0.14^{ad} (74.82%)	2.11 ± 0.08^{ad} (74.21%)	1.69 ± 0.13^{ad} (79.34%)
Log TG/HDL-c	0.27 ± 0.05^{a}	0.05 ± 0.01^{b}	0.78 ± 0.04^{c}	0.30 ± 0.02^{a} (61.54%)	0.09 ± 0.02^{b} (88.46%)	0.18 ± 0.02^{d} (76.92%)	0.12 ± 0.03^{bd} (84.62%)

CWG: Coconut water group; PARA: Paracetamol group; PRE-CWG: Pre-coconut water group; PRE-SIL: Pre-silymarin group; POST-CWG: Post-coconut water group; POST-SIL: Post-silymarin group. Values were expressed as mean ± SD. Values with different superscript letter per row are significantly different ($P < 0.05$).

increased ($P < 0.05$) the HDL-c concentration of the paracetamol-overdosed animals more than the pre-treatment group. Pre- and post-treatments with silymarin had comparatively similar effects as coconut water on serum TC, TG, LDL-c and VLDL-c as well as HDL-c concentrations of paracetamol overdosed animals.

Table 2 presents the atherogenic risk predictor indices of the albino rabbits administered paracetamol overdose and the pre- or post-treated animals with silymarin or coconut water. Paracetamol overdose significantly ($P < 0.05$) increased the Castelli risk indices I and II as well as the concentrations of total non-HDL-c and atherogenic index of plasma in comparison with those of the control group and animals administered coconut water only. Pre- and post-treatment of paracetamol overdosed animals with silymarin significantly reduced ($P < 0.05$) the atherogenic indices more than pre- and post-treatment with coconut water, respectively. Generally, post-treatment with either silymarin or coconut water significantly reduced ($P < 0.05$) the atherogenic indices than pre-treatments.

4. Discussion

Coconut water is the clear juice inside fruits of coconut tree. The sweet, sterile liquid is composed of about 200 to 1 000 mL of water, sugars, vitamins, minerals, electrolytes, enzymes, amino acids, cytokines and phyto-hormones. It is one of nature's most refreshing drinks and was consumed worldwide for its nutritious and health benefiting properties[13]. In Africa, coconut water is traditionally used as an antidote to drug overdose. Thus, the present study was aimed at evaluating this widely held view of coconut water. This effect was evaluated against overdose with paracetamol, a commonly available over-the-count drug that is prone to uncontrolled intake.

Our results indicated that paracetamol overdose may have induced physiological distress in the animals preventing them from feeding normally or effectively digesting, absorbing and utilizing the nutrients present in their feed, which may have elicited the observed reduction in body weight. The gain in body weight of the pre- and post-treated animal groups in comparison with those of the animals in the paracetamol administered but untreated group indicated the ameliorative effect of coconut water and silymarin on paracetamol overdose. The effect of coconut water as a nutritive drink was obvious with the body weight gain of the animal group placed on coconut water only, which was higher than those of the control animals. This was in consonance with various reported findings in literature elucidating the numerous potential applications of coconut water in the prevention, management and treatment of human ailments[13,22].

The results of the present study showed that the serum TC, TG, LDL-c and VLDL-concentrations were higher, while that of HDL-c was reduced in the animals administered paracetamol overdose only in comparison with the untreated control group and the other treatment groups. The increases in the serum concentrations of TC and TG of the paracetamol overdosed animals was in agreement with previous findings[4,23] that reported hypercholesterolemia and

hyperglyceridaemia after induction of liver injury with paracetamol. Acute hepatitis has been associated with increased TG, LDL-c and VLDL-c concentrations[4,24]. Lipids combine with various types of apolipoproteins to produce lipoproteins which transport lipids to lipolytic organs of the body for metabolism. Thus, abnormalities in blood lipid levels have strongly been correlated with changes in lipoprotein levels. Furthermore, high levels of serum TC, TG, VLDL-c, and LDL-c concentrations and reduced serum HDL-c level have been associated with the development and/or causation of hyperlipidaemias and cardiovascular diseases[25]. Elevated serum lipids and lipoproteins like TG, LDL and VLDL may contribute to the aetiology of cardiovascular diseases through different means. The reduction in concentrations of TC, TG, LDL-c and VLDL-c, with increase in HDL-c concentrations following pre- and post-treatment with coconut water and silymarin suggested possible hypolipidaemic effects of coconut water and silymarin. The percentage protection to changes in lipid levels of the paracetamol overdosed groups post-treated with coconut water and silymarin, respectively, were more than those pre-treated with coconut water and silymarin, respectively. These indicated that the effects of both coconut water and silymarin against paracetamol-induced toxicity were more of treatment or amelioration rather than protection. Of course, silymarin is a standard drug used for the treatment of hepatotoxicity through prevention of oxidative damage and necrosis of liver cells[11], which are the hallmark of NAPBQI activity. Coconut water contains many minerals, vitamins and phytohormones such as cytokinins, which have been reported to have antioxidant activities and possible hepatoprotective effects[22]. Furthermore, cytokinins such as kinetin and transzeatin in coconut water have been reported to have anti-thrombotic, anti-carcinogenic, and anti-ageing effects, and inhibit oxidative damage to cellular proteins, unsaturated fatty acids and DNA[22,26].

Pro-atherogenic lipoproteins are biomolecules that carry cholesterol and other lipids in the bloodstream. They are distinguishable from anti-atherogenic HDL-c because of their tendency to accumulate in blood vessels and block circulation, thereby causing cardiovascular disease. Determination of the relative amounts of cholesterol in the pro- and anti-atherogenic lipoproteins has been reported to be more important in cardiovascular disease risk assessment than measurement and use of the actual individual or collective values of serum TC, TG, LDL-c, HDL-c or VLDL-c[27]. These have been collectively described as atherogenic risk predictor indices[28-31]. These indices have been applied in assessing the risk of cardiovascular disease in humans. However, their application has been limited to monitoring experimentally induced diseases or laboratory conditions associated with cardiovascular disease. Our results showed that the atherogenic risk predictor indices were elevated in the paracetamol overdosed animal group in comparison with the animals of the control group and those administered only coconut water. Pre- and post-treatment of the paracetamol overdosed animals with coconut water and silymarin reduced the atherogenic ratios, with the post-treated groups having lower atherogenic values. A study of the percentage protection potentials of the treatments with coconut water and silymarin using the atherogenic indices showed that atherogenic index of plasma consistently gave higher percentages than the other atherogenic indicators calculated. This indicated that atherogenic index of plasma may be a better atherogenic predictor index than the other indices. As stated earlier, the calculation of atherogenic index of plasma involves the ratio of the logarithmic values of TG to HDL-c. The atherogenic connection between elevated TG and HDL-c concentrations is attributable to the increased concentration of VLDL (naturally rich in TG) in plasma that generates LDL-c during further release of TGs by lipoprotein lipase from VLDL remnants. The core of the mature, spherical HDL particle is formed when lecithin-cholesterol acyl transferase on the surface of nascent HDL particles converts the cholesterol and phosphatidylcholine of VLDL remnants and chylomicron to cholesteryl esters[32]. Atherogenic index of plasma which was earlier proposed as a ratio of TG to HDL-c[28] has been reported to be better and stronger than Castelli's risk index-I and Castelli's risk index-II in the prediction of myocardial infarction in human subjects. Furthermore, it has been proposed that the TG/HDL-c ratio can serve as a non-invasive technique that can approximately predict the degree and incidence of coronary artery disease[33].

Acute paracetamol overdose causes increase in plasma concentrations of TC, TG, LDL-cholesterol and VLDL-cholesterol but reduced HDL-cholesterol concentration suggesting possible induction of dyslipidaemia in overdosed subjects. Post-treatment of paracetamol overdosed animals with coconut water and silymarin countered the effects of the paracetamol overdose more than pre-treatment with coconut water. The results indicated that coconut water is an effective antidote to paracetamol overdose-induced lipid abnormality and other possible atherogenic complications thereof in animals. The above observations confirm the ethnopharmacological use of coconut water as an antidote to drug overdose.

Conflict of interest statement

We declare that we have no conflict of interest.

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