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# Effects of aqueous leaf extract of avocado (*Persea americana*) on total cholesterol, triacylglycerols, protein and haematological parameters in CCl<sub>4</sub>-intoxicated rats

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## Abstract

**Background:** Avocado (*Persea americana*) is one of the plants widely used in ethnomedicine in Nigeria. The present study was aimed at investigating effects of aqueous Avocado (*Persea americana*) leaf extract on total cholesterol, triacylglycerols, protein and haematological parameters in carbon tetrachloride (CCl<sub>4</sub>)-intoxicated rats.

**Methods:** We evaluated the possible effects of pre-treatment with aqueous extract of *Persea americana* (AEPA) on protein, total cholesterol (T-CHOL), triacylglycerols (TAGs) and haematological parameters in Wistar male albino rats intoxicated with CCl<sub>4</sub>. Group 1 was the healthy control; group 2 rats were pre-treated with Reducdyn® (100 mg/kg/day) as a standard drug, groups 4 and 5 rats were pre-treated with AEPA at a dose of 100 mg/kg and 200 mg/kg per day respectively, the treatments were administered orally for 7 days. On the seventh day, rats in the treatment groups were injected with a fresh mixture of CCl<sub>4</sub> and olive oil (3 ml/kg, 1:1; sc).

**Results:** Pre-treatment of rats with AEPA resulted in marked increase ( $p < 0.05$ ) in total protein and reduction in T-CHOL (19–34%) compared to CCl<sub>4</sub> alone. Also, there was significant decrease ( $p < 0.05$ ) in serum TAG concentration when rats were pre-treated with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA. Similarly, AEPA provoked ( $p < 0.05$ ) a lowering of T-CHOL and TAG levels and an increase in liver protein concentration in the rats. Administration of AEPA at both concentrations restored ( $p < 0.05$ ) WBC count and ameliorated neutropenia and lymphocytosis caused by CCl<sub>4</sub> intoxication.

**Conclusion:** These results suggest that AEPA could be protective against the development of fatty liver and might also be exhibiting the potential to prevent alterations in haematological parameters caused by CCl<sub>4</sub> intoxication in rats.

**Keywords:** *Persea americana*, Total cholesterol, Triacylglycerols, Haematological parameters, Carbon tetrachloride (CCl<sub>4</sub>)

## Introduction

The liver plays a pivotal role in drug and xenobiotic metabolism and is thus susceptible to attacks by these agents leading to liver injuries or damage. Injury to the liver results in several disorders including elevation in hepatic enzymes, steatosis (accumulation of triacylglycerols

in the liver), reduced  $\beta$ -oxidation of fatty acids, and necrosis [7].

Fatty degeneration of the liver (steatosis) resulting from CCl<sub>4</sub> intoxication is attributed to an imbalance between lipid biosynthesis and degradation. It could also result from the failure of triacylglycerols to be transferred as VLDL from liver to the circulation [7, 38].

In the rats, a major metabolic defect induced by CCl<sub>4</sub> intoxication appears to be inhibition of triacylglycerols release from the liver. This inhibition of outward transport would allow the accumulation of triacylglycerols

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within the liver and the development of fatty liver associated with  $\text{CCl}_4$  poisoning [16].

Plant-derived drugs and herbal formulations are obtained from natural sources and their use have been on the increase in many countries around the world. This is because they are usually viewed to be less toxic and free from serious side effects than the conventional synthetic drugs [4, 6, 24].

Avocado (*Persea americana*) is one of the plants that have been widely used in ethno-medicine. In Nigeria, the leaf has various local names such as *Ewé pia* (Yoruba), *Akwukwo Ube oyibo* (Igbo), and *Ganyen piya* (Hausa).

Avocado leaves extracts have been reported to possess anti-inflammatory, antihypertensive/hypotensive, and hypoglycemic activities as well as vasorelaxant action and anticonvulsant effect [2, 3, 5, 14, 15, 26, 28]. Also, the leaf extracts of *P. americana* have been shown to be protective against cholesterol-induced hyperlipidemia in rats [9, 19].

The most abundant bioactive phytoconstituents of Avocado include phenolics, phytosterols, minerals, vitamins, and carotenoids [12, 27, 33]. These bioactive compounds have been shown to possess lipid-lowering, antidiabetic, cardioprotective, antiatherosclerotic activity [35].

Thus, the possible effects of aqueous AEPA on protein, total cholesterol (T-CHOL), triacylglycerols (TAGs) and haematological parameters in Wistar male albino rats intoxicated with carbon  $\text{CCl}_4$  were evaluated.

## Materials and methods

### Plant material

Fresh avocado leaves were collected from a cultivated plant in Ilupeju, Lagos. The leaves were authenticated at the Department of Botany, University of Lagos, and a voucher specimen (LUH 4199), was deposited at the herbarium of the department.

### Preparation of plant extract

The leaves were air-dried, pulverized and the aqueous extract was prepared by loading the powdered leaves into a Soxhlet apparatus. The extraction lasted for 12 h, and the extract solution was evaporated to dryness in a rotary evaporator at  $40^\circ\text{C}$  to obtain a residue labeled AEPA which was stored in clean vials until required.

### Experimental animals

Thirty male Wistar strain albino rats (130–160 g), were purchased from the Animal House of Nigerian Institute of Medical Research (NIMR), Lagos. The rats were acclimatized for 1 week, and maintained under standard conditions of temperature ( $23 \pm 2^\circ\text{C}$ ) and 12 h light/dark cycle. The rats were treated with humane care, fed with a standard diet and water ad libitum.

### Experimental design

Hepatotoxicity was induced in the rats by subcutaneous injection of carbon tetrachloride as described by Wang et al. [37].

The albino rats were randomly divided into five treatment groups of six rats per group. Group 1 served as healthy control. Groups 2, 3, 4, and 5 served as treatment groups. Group 2 rats received distilled water (3 ml/kg), Group 3 rats were pre-treated with Reducdyn® (100 mg/kg/day). Groups 4 and 5 rats were pre-treated with AEPA at a dose of 100 mg/kg and 200 mg/kg per day respectively. All the treatments were administered orally for 7 days. On the seventh day, rats in the treatment groups were subcutaneously injected with a fresh mixture of  $\text{CCl}_4$  and olive oil (3 ml/kg, 1:1), 30 minutes after the administration of the last dose of the pre-treatment drug (Group 3), or extract Groups 4 and 5), or distilled water (Group 2). Rats in Group 1 were administered olive oil (3 ml/kg, sc). After 24 h, the rats were sacrificed by cervical dislocation and blood samples collected by cardiac puncture into plain sterile tubes, allowed to coagulate and then centrifuged at 3000 rpm for 10 min., at  $4^\circ\text{C}$ . The serum obtained was stored at  $-80^\circ\text{C}$  pending analysis. Some of the blood samples were also dispensed into clean ethylene diamine tetra acetic acid (EDTA)-containing bottles for haematological investigation. Rat livers were quickly excised and perfused with chilled 1.15% (w/v) potassium chloride (KCl) solution to remove all traces of haemoglobin. The livers were blotted dry, weighed and used to prepare liver homogenates.

### Biochemical analysis

Protein concentration was determined using the Bradford method which is based on the absorbance maximum of Coomassie Brilliant Blue G-250 at 595 nm.

Total cholesterol (T-CHOL) and triacylglycerols (TAG), were measured using kits purchased from RANDOX Laboratories Ltd. (Crumlin, UK).

### Haematological parameters

Haematological parameters including packed cell volume, hemoglobin concentration, white blood cell count, red blood cell count, eosinophils, lymphocyte and neutrophils counts, were measured using standard methods as described by Dacie and Lewis [10].

### Statistical analysis

Results were expressed as mean  $\pm$  standard error of the mean (S.E.M). Differences between the groups were determined using one-way analysis of variance (ANOVA). Statistical significance of the difference of means was determined and indicated by  $p$ -values  $\leq 0.05$ .

## Results

### Effect of pre-treatment with aqueous leaf extract of *P. americana* on serum total protein, total cholesterol and triacylglycerols in CCl<sub>4</sub>-induced hepatotoxicity in rats

Serum total cholesterol, triacylglycerols and protein concentrations in rats pre-treated with AEPA and challenged with CCl<sub>4</sub> are as presented in Table 1. Serum T-CHOL level was slightly raised (12%) in CCl<sub>4</sub>-intoxicated rats compared to normal control rats. Pre-treatment with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA resulted in the lowering of T-CHOL by 19% and 34% respectively while pre-treatment with 100 mg kg<sup>-1</sup> b. wt. Reducdyn® caused 52% decrease in T-CHOL. Serum TAG concentration was markedly raised ( $p < 0.05$ ; 113%) in CCl<sub>4</sub>-treated rats compared with healthy control. A significant reduction ( $p < 0.05$ ; 65% and 64% of CCl<sub>4</sub> control) in TAG concentration was observed when rats were pre-treated with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA, respectively. Serum total protein concentration was significantly reduced ( $p < 0.05$ ; 54%) in CCl<sub>4</sub>-treated rats. Pre-treatment with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA caused a significant increase ( $p < 0.05$ ; 119% and 129%, respectively) in serum protein compared to CCl<sub>4</sub> control animals. However, the levels of T-CHOL, TAGs and protein in rats pre-treated with AEPA were not significantly different from the normal control.

### Effect of pre-treatment with aqueous leaf extract of *P. americana* on liver total protein, total cholesterol and triacylglycerols in CCl<sub>4</sub>-induced hepatotoxicity in rats

Liver protein, total cholesterol and triacylglycerol concentrations in CCl<sub>4</sub>-intoxicated rats and AEPA pre-treated rats are depicted in Table 2. Total cholesterol increased significantly ( $p < 0.05$ ; 206%) in CCl<sub>4</sub> control rats compared with healthy control. Pre-treatment with AEPA (100 mg and 200 mg kg<sup>-1</sup> b. wt.) significantly reduced ( $p < 0.05$ ; 57% and 58% respectively) T-CHOL concentration compared to CCl<sub>4</sub> control. Liver TAG concentration was profoundly elevated ( $p < 0.05$ ; 351%) by CCl<sub>4</sub> administration compared to healthy control. Pre-treatment with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA provoked a reduction in liver TAG (50% and 51% respectively) compared to

CCl<sub>4</sub>. Total protein concentration was lowered by 18% following CCl<sub>4</sub> intoxication and this was improved by pre-treatment with AEPA and Reducdyn® up to 14% and 18% respectively. There was no significant difference ( $p > 0.05$ ) in the observed protection by AEPA and Reducdyn®.

### Effect of pre-treatment with aqueous leaf extract of *P. americana* on peripheral blood smears in CCl<sub>4</sub>-intoxicated rats

Table 3 shows the levels of some haematological parameters observed in the experimental rats pre-treated with AEPA and intoxicated with CCl<sub>4</sub>. There was a non-significant decrease ( $p > 0.05$ ) in the packed cell volume (7%) and haemoglobin concentration (7%) of CCl<sub>4</sub>-treated rats, respectively compared to healthy control. Also, total white blood cells (WBC) counts and neutrophils were significantly reduced ( $p < 0.05$ ) while lymphocytes were increased by CCl<sub>4</sub> administration compared to healthy control. Pre-treatment with 100 mg and 200 mg kg<sup>-1</sup> b. wt. AEPA restored WBC counts while pre-treatment with 100 mg kg<sup>-1</sup> b. wt. AEPA only increased neutrophils and lowered lymphocytes counts. Similarly, AEPA at 200 mg kg<sup>-1</sup> b. wt reduced packed cell volume and haemoglobin concentration by 12.5 and 19%, respectively.

## Discussion

Administration of CCl<sub>4</sub> caused inhibition of protein synthesis manifested as decrease in both serum and liver total proteins compared with healthy control. This finding is similar to earlier reports by other workers [1, 22, 23, 36]. Inhibition of protein synthesis in the liver is primarily considered to bring about lowering of lipoprotein synthesis and accumulation of fat in the liver, resulting in the development of fatty liver [30]. It is also suggested that a decline in total protein content is a useful index of the severity of cellular dysfunction in chronic liver diseases [36]. Pre-treatment with AEPA restored serum and liver total protein to near the levels in healthy controls. The restoration of total protein content in serum and liver of rats treated with AEPA is indicative of stimulation of protein synthesis. This could accelerate the regeneration process and the

**Table 1** Effect of pre-treatment with aqueous leaf extract of *P. americana* on serum total protein, total cholesterol and triacylglycerols in CCl<sub>4</sub>-induced hepatotoxicity in rats

Treatment (Dose, mg/kg)	T-CHOL (mg/dl)	TAG (mg/dl)	Total Protein (mg/g tissue)
<b>Control</b>	63.05 ± 4.76	59.65 ± 3.96	84.88 ± 2.33
<b>CCl<sub>4</sub> + AEPA (100)</b>	57.25 ± 2.66 <sup>b</sup>	44.68 ± 3.95 <sup>a</sup>	85.07 ± 1.39 <sup>a</sup>
<b>CCl<sub>4</sub> + AEPA (200)</b>	46.57 ± 7.10 <sup>b</sup>	46.28 ± 6.67 <sup>a</sup>	89.11 ± 1.85 <sup>a</sup>
<b>CCl<sub>4</sub> + Reducdyn</b>	33.89 ± 0.33 <sup>a</sup>	58.42 ± 3.96 <sup>a</sup>	82.62 ± 3.60 <sup>a</sup>
<b>CCl<sub>4</sub></b>	70.79 ± 8.95 <sup>b</sup>	126.94 ± 11.63 <sup>b</sup>	38.79 ± 4.91 <sup>b</sup>

Values are expressed as means ± SEM (n = 6)

T-CHOL Total cholesterol, TAG Triacylglycerol, CCl<sub>4</sub> carbon tetrachloride, AEPA Aqueous extract of *Persia americana*

Values not sharing a common superscript differ significantly at  $p < 0.05$

**Table 2** Effect of pre-treatment with aqueous leaf extract of *P. americana* on liver total protein, total cholesterol and triacylglycerols in CCl<sub>4</sub>-induced hepatotoxicity in rats

Treatment (Dose, mg/kg)	T-CHOL (mg/dl)	TAG (mg/dl)	Total Protein (mg/g tissue)
<b>Control</b>	36.95 ± 8.93	176.42 ± 13.93	44.96 ± 0.73
<b>CCl<sub>4</sub> + AEPA (100)</b>	49.04 ± 3.8 <sup>b</sup>	395.56 ± 53.55 <sup>a</sup>	42.02 ± 0.44
<b>CCl<sub>4</sub> + AEPA (200)</b>	47.73 ± 7.98 <sup>b</sup>	388.11 ± 31.05 <sup>a</sup>	40.80 ± 0.72
<b>CCl<sub>4</sub> + Reducdyn</b>	53.87 ± 9.07 <sup>b</sup>	371.53 ± 20.51 <sup>a</sup>	43.49 ± 0.35
<b>CCl<sub>4</sub></b>	113.13 ± 8.50 <sup>a</sup>	795.50 ± 41.2 <sup>b</sup>	36.77 ± 0.54

Values are expressed as means ± SEM (n = 6)

T-CHOL Total cholesterol, TAG Triacylglycerol, CCl<sub>4</sub> carbon tetrachloride, AEPA Aqueous extract of *Persia americana*

Values not sharing a common superscript differ significantly at  $p < 0.05$

production of liver cells as well as further elucidate its hepatoprotective activity.

Increases in the levels of cholesterol and TAGs were observed in serum and hepatic tissues. This confirms previous reports that CCl<sub>4</sub> treatment provokes increase in cholesterol and TAGs levels in rat liver [18, 34, 36]. CCl<sub>4</sub> increases the synthesis of fatty acids and TAGs from acetate. This could be due to the transport of acetate into the liver cell, resulting in increased substrate availability.

Also, it is postulated that the major metabolic defect induced by CCl<sub>4</sub> intoxication to rats is inhibition of hepatic TAGs release. This inhibition of outward transport allows the accumulation of TAGs within the liver and the occurrence of fatty liver associated with CCl<sub>4</sub> poisoning [16]. Intoxication with CCl<sub>4</sub> has also been shown to increase the synthesis of cholesterol [7].

On the other hand, CCl<sub>4</sub> reduces the hydrolysis of TAGs and  $\beta$ -oxidation of fatty acids thus, making more fatty acids available for esterification [20]. Disruption of  $\beta$ -oxidation of fatty acids in the mitochondrial causes microvesicular steatosis, typified by accumulation of tiny lipid vesicles in the cytoplasm of hepatocytes [13]. Owing to reduced mitochondrial oxidation, non-esterified fatty acids (NEFAs) build up in the liver and become esterified into TAG. Also, it has been shown that during CCl<sub>4</sub> toxicity, fat from the peripheral adipose tissue is translocated to the liver and kidney leading to its accumulation [11]. It is suggested that an essential step in the outward transport of hepatic TAGs is the synthesis of lipoproteins at the

endoplasmic reticulum by the utilization of TAG previously synthesized at another site. Damage to the endoplasmic reticulum during CCl<sub>4</sub> intoxication inhibits lipoprotein synthesis. This may effectively decrease outward TAGs transport and results in the development of a fatty liver [16, 17, 29, 32]. These factors could possibly explain the significant increase in hepatic TAGs observed in CCl<sub>4</sub>-intoxicated rats in this study. However, pre-treatment with AEPA produced a substantial reduction in the elevated hepatic cholesterol and TAGs levels. This suggests that the extract prevented CCl<sub>4</sub>-induced hyperlipidaemia probably due to its hepatoprotective activity [8] in a mechanism that involves increase outward translocation of TAGs. *P. americana* has previously been shown to protect rats against cholesterol-induced hyperlipidemia by lowering total cholesterol, triglycerides and LDL, and increasing HDL levels [9, 19]. Various mechanisms have been postulated for the antihypertriglyceridemic activity of medicinal plants including: inhibition of sterol regulatory element-binding transcription factor 1 (SREBP-1), antioxidant and anti-inflammatory activities, inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, inhibition of lipogenesis, inhibition of leptin secretion among others [25, 31].

Administration of CCl<sub>4</sub> alone caused leucopenia, neutropenia and lymphocytosis in the rats similar to the findings of Mandal et al. [21]. The administration of AEPA at a concentration of 100 mg and 200 mg kg<sup>-1</sup> b. wt restored WBC count level by 99% and 85% respectively compared to CCl<sub>4</sub> control rats. This finding therefore suggests that

**Table 3** Effect of pre-treatment with aqueous leaf extract of *P. americana* on peripheral blood smears in CCl<sub>4</sub>-intoxicated rats

Treatment (Dose, mg/kg)	WBC	PCV	Hb	N	L	M	E	B
<b>Control</b>	8666.67 ± 785.99	36.08 ± 1.54	12.03 ± 0.51	45.60 ± 8.15	55.80 ± 8.50	0.20 ± 0.20	0 ± 0	0 ± 0
<b>CCl<sub>4</sub> + AEPA (100)</b>	8700.00 ± 687.75	38.67 ± 3.25	12.89 ± 1.08	33.50 ± 6.48	66.17 ± 6.33	0.33 ± 0.21	0 ± 0	0 ± 0
<b>CCl<sub>4</sub> + AEPA (200)</b>	9683.33 ± 656.97	27.08 ± 3.10	9.77 ± 0.88	20.00 ± 2.97	77.60 ± 1.12	0.20 ± 0.20	0.40 ± 0.40	0 ± 0
<b>CCl<sub>4</sub> + Reducdyn</b>	10,066.67 ± 635.96	34.33 ± 1.45	11.61 ± 0.64	39.60 ± 6.42	60.20 ± 6.37	0.20 ± 0.20	0 ± 0	0 ± 0
<b>CCl<sub>4</sub></b>	4833.33 ± 811.04	33.50 ± 1.70	11.17 ± 0.57	22.60 ± 2.66	76.00 ± 2.68	0.60 ± 0.40	0.20 ± 0.20	0 ± 0

All the values are presented as mean ± S.E.M

WBC white blood cells (10<sup>3</sup>/μL, PCV packed cell volume (%), Hb haemoglobin (g/dl), N neutrophils (%), L lymphocytes (%), M monocytes (%), E eosinophils (%), B basophils (%), CCl<sub>4</sub> carbon tetrachloride, AEPA Aqueous extract of *Persia americana*



AEPA has the potential to restore CCl<sub>4</sub>-induced alterations of haematological parameters in rats.

## Conclusion

The increases in cholesterol and triacylglycerol provoked by CCl<sub>4</sub> administration were considerably reduced by pre-treatment with AEPA. This suggests that AEPA could prevent CCl<sub>4</sub>-induced hyperlipidaemia and inhibit the development of fatty liver in the rats. Furthermore, AEPA exhibited the potential to prevent CCl<sub>4</sub>-induced leucopenia, lymphocytosis and other hematological related alterations in rats.

## Abbreviations

AEPA: Aqueous extract of *Persia americana*; B: Basophils (%); CCl<sub>4</sub>: Carbon tetrachloride; E: Eosinophils (%); Hb: Haemoglobin (g/dl); L: Lymphocytes (%); M: Monocytes (%); N: Neutrophils (%); PCV: Packed cell volume (%); TAG: Triacylglycerol; T-CHOL: Total cholesterol; WBC: White blood cells (10<sup>3</sup>/μL)

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None.

## Authors' contributions

BBIC conceived, designed and carried out the laboratory experiments, wrote the manuscript; ARA read and improved the manuscript; FJA read and prepared the manuscript for publication; OAA designed and supervised the work.

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## Availability of data and materials

Research data and materials can be provided on request.

## Ethics approval

Animals were handled and used in accordance with the National Institute of Health guide for the care and use of laboratory animals (Washington (DC): National Academies Press (US); 2011).

## Consent for publication

All authors totally agreed to the publication of the research.

## Competing interests

The authors declare that they have no competing interest.

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