Original Research Article

Unripe plantain *Musa paradisiaca* extract ameliorates deranged biochemical parameters in rat model of hepatotoxicity and nephrotoxicity

ABSTRACT

Aim: Hepatoprotective and nephroprotective potentials of unripe plantain*Musa paradisiaca*on CCl_4-induced oxidative damage in albino rat was studied. This was with the aim of providing a locally available and potent therapeutic alternative to the conventional drugs used in the management of liver and kidney diseases.

Place and Duration of study: The study was conducted at the Department of Medical Biochemistry, College of Medicine, Ekiti State University, Ado Ekiti between July 2018 and January, 2019.

Methodology: Twenty-five adult male albino rats were placed into seven groups of 5 animals each. Group I animals received distilled water throughout the duration of the experiment, while group II were exposed to CCl_4 only. Groups III, IV, V and VI received 3 ml/kg b.w of CCl_4 intraperitoneally but were post treated with 50 mg/kg and 100 mg/kg of unripe plantain extractrespectively while group seven were post-treated with silymarin by oral gavage. Animals were sacrificed for the excision of the liver and kidney. Activities of creatinine kinase (CK),aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), as well as levels of urea, uric acid,bilirubin and lipid profile were assessed. Tissue antioxidant level of reduced glutathione (GSH) and activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) were also determined.

Results: Exposure to CCl_4 caused a derangement in lipid profile as well as marked (P=0.05)increase in the serum level of CK, AST, ALP, ALT, bilirubin, urea and uric acid relative to the control.Administration of the *Musa paradisiaca*caused a significant restoration of all biochemical parameters measured. Histopathogical observation of the tissues also gave credence to biochemical results.

Conclusion: These findings showed that*Musa paradisiaca*extract exhibited positive modulatory effects on the injured liver, kidney and hence, its potential usefulness in the management diseases associated with these organs.

Keywords: biomarkers, carbon tetrachloride, unripe plantain,liver, kidney.

1.0 INTRODUCTION

The liver and kidneyare critical to severalbiochemical processes including metabolism of drugs, hormones,toxins as well as maintenance of cellular homeostasis (Thuawaini*et al*., 2019).The liver is the main metabolic organ in the body and is considered a viable defense system against both environmental and metabolic toxicants (Manfo*et al*., 2014). Conversely, the kidneys are mainly involved in urinary excretion of metabolites and osmoregulation. The biological roles of these organs make them vulnerable to oxidative attacks by xenobiotics (Brzóska*et al*., 2003). Several synthetic drugs have been used in the management of liver and kidney diseases. Although, their potency cannot be overemphasized, they are often very expensive, hence they are not affordable by a large percentage of people in developing nations. Moreover, these therapies have been suggested to partially compensate for metabolic derangements seen in diseases, they do not necessarily correct the fundamental biochemical lesions (Chatila and West 1996). Considering these limitations, the need for plant-basedmedicines as alternative therapies becomes critical. Plants are natural and are biologically friendly. They synthesize certain compounds that are primarily designed toprotect them against invasion by both micro and

macro-predators. Co-incidentally, these compounds such as polyphenolic substances, melatonin, carotenoids, quercetin, resveratrol, vitamin E, vitamin C, L-carnitine, and coenzyme Q10 (Wang *et al*., 2013; Ibrahim *et al*., 2014; El-Boshy*et al*., 2015; El-Sayed *et al*., 2016) have been found to possess medicinal properties that can be exploited by man in the management of diseases. These phytochemicals, which act as antioxidants protect critical organs and macromolecules from oxidative attack of endogenous and exogenous free radicals (Lakshmi *et al*., 2014; Baiomy and Mansour, 2016; El-Sayed *et al*., 2016).

Plantain (*Musa paradisiaca*) is cultivated in several tropical countries of the world. It is rich in fiber, iron, serotonin, minerals and vitamins (Chatila, 1999; Iweala*et al*., 2011; Jimmy andOkon2012). According to an estimate by WHO, about 80% of the population in developing nations of the world recognized the use of plantain for enhancing wound healing(Asuquo and Udobi 2016), (Amuthaand Selvakumari 2016; Krishnan et al. 2014; Pereira and Maraschin 2015; Shodehinde and Oboh 2013). In fact, unripe plantain pulp has been used as poultice (Agyare et al. 2009; Pereira and Maraschin 2015) in the management of skin inflammation due to its ability to stimulate angiogenesis by virtue of collagen fibres synthesis and remodeling (Joshi et al. 2013; Murthy et al. 2013; Patil et al. 2012). Recently, Ajiboye et al. (2018) and Oluwajuyitan and Ijarotimi (2019) recommended plantain meal as dietary approach for the management of diabetes and other diseases related to dysfunctional lipid profile.Besides, reports had identified the anticancer potential of plantain as well as its anti-inflammatory activities in cell lines and animal models respectivelyCorrea et al. 2016; Krishnan et al. 2014; Pereira and Maraschin2015).Plantain new 2.Besides, folkloric reports have shown that unripe plantain is helpful in the management of hepatic and renal disorders including anemia (Iweala*et al*., 2011; Jimmy and Okon, 2012). Considering the vast medicinal relevance of plantain in traditional parlance, coupled with an ever increasing burden of liver and kidney diseases, there is a dire

need to investigate its curative potential in animal models of hepatotoxicity and nephrotoxicity. Hence, this study.

2.0 MATERIALS AND METHODS

2.1 Collection, preparation and extraction of unripe plantain

Unripe plantain fruit were obtained from a local farmin Ado Ekiti and authenticated at the Department ofPlant Science, Ekiti State University, Ado Ekiti, Nigeria.

2.2 Reagents and chemicals

All experimental parameters were determined using diagnostic kits from Rando Chemicals Ltd, England.

2.3 Preparation of extract

Fresh unripe plantains (300 g) were washed with distilled water, weighed, chopped into pieces without peeling and extracted in 80% ethanol for 72 hours to allow for extraction.The supernatant was filtered using Whatman filter paper. The filtrate was then freeze dried, labelled as crude extract and kept in an airtight container in the refrigerator.

2.4 Experimental animals

Twenty-five (25) male wistar rats of average weight 200g were purchased from the animal house of the College ofMedicine, Ekiti State University, Ado-Ekiti. All experimental animals were acclimatized for one week and housed in neat metallic cages at standard temperature, relative humidity as well as 12/12-h light and dark cycle. The animals were granted unrestricted access to food and water ad libitum on a daily basis. Rat bedding were routinely changed and replaced for the period of the experiment. The 25 rats were randomly placed into five groups and treated as follows:

2.5 List 1: Animal Treatment

Group	Treatment

I	Animal feed and distilled water only
II	3 ml/kg bw CCl_4 only
III	3 ml/kg b.w CCl_4 + 50 mg/kg bw. *M. paradisiaca*
IV	3 ml/kg b.w CCl_4 + 100 mg/kg bw. *M. paradisiaca*
V	3 ml/kg b.w CCl_4 + 100 mg/kg bw. silymarin

Animals were fasted 24 h before sacrifice on the 15th day of commencement of the work.

2.6 Preparation of organs homogenate

Animals were decapitated under very mild, cold-ether anesthesiaand quickly dissected to excise the liver, kidney as well as serum. Ten percent (10%) homogenateeach of the liver and kidney were prepared separately in 6.8mM potassiumphosphate buffer, (pH 7.4) using chilled pestle and mortar. The resulting homogenate was centrifuged at 10,000 rpm for 10 min at 4 °C to obtain a supernatant which was stored in a refrigerator and used for the determination of biochemical parameters.

2.7 Preparation of serum

Heart of experimental animals were punctured immediately after decapitation while the animals were still breathing. Blood was collected into plain sample bottles and allow to stand for coagulation. Whole blood (coagulated) was then centrifuged at 3000 rpm for 15 min to obtain the serum which was gently decanted and kept in the refrigerator.

2.8 Determination of biochemical parameters

Creatine kinase was measured following the method of Mattenheimer(1981). Aspartate aminotransferase(AST) and alanine amino transferase (ALT) activity wereassayed as described by Reitman and Frankel (1969), while and alkaline phosphatase (ALP)wasdetermined according to Englehardt*et al*. (1970). Lipid profile: triglycerides, total cholesterol, LDL and HDL were assayed according to the method of Trinder,(1969), Tietz(1995), Grove (1979) and Friedewald*et al.*(1972) respectively. Catalase (CAT) and superoxide dismutase (SOD) were assayed following

the methods of Sinha (1972) and Misra(1972) respectively. Reduced glutathione (GSH) level was determined by the method of Beutler*et al.*(1963) while the modified Biuret method of Weichselbaum(1995) was followed for the determination of total protein.

2.9 Statistical analysis

All values are expressed as mean ± SD. Statistical evaluation was done using One Way Analysis of Variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT) by using SPSS 11.09 for windows. The significance level was set at $p < 0.05$.

3.0 RESULTS

Exposure to CCl_4 resulted in marked (P=0.05) derangement in lipid profile in all tissues of experimental animals analyzed (Table 1). Treatment with *M. paradisiaca* extract caused a dose-dependent restoration of deranged lipid profile in a manner comparable to animals treated with silymarin(Table 1).Serum activities of liver enzyme biomarkers such as alkaline phosphatase (ALP), alanine aminotransferase(ALT) and aspartate aminotransferase (AST) weresignificantly elevated following exposure to CCl_4(Table 2) relativeto the negative control animals. Post administration of *M. paradisiaca* extract, however, reversed the toxic trend at a level comparable to animals treated with standard drug (Table 2).Serum and tissue levels of kidney biomarkers such as urea, uric acid and bilirubin were significantly (P=0.05) elevated after administering CCl_4, while oral administration of *M. paradisiaca* extract to exposed rats brought about a marked reversal of the toxic trend in a dose-dependent manner (Table 2). Activities of antioxidant enzymes such as superoxide dismutase and catalase as well as creatine kinase weremarkedly (P=0.05)depleted in animals exposed to CCl_4 toxicity (Table 3), while treatment with *M. paradisiaca* extract caused a dose-dependent restoration of activities in a manner comparable

with animals treated with standard drug. On the other hand,serum level of GSH and total protein (Table 3) respectivelywas significantly decreased following exposure toCCl_4(Table 3)but restored following treatment with unripe plantain extract.

Table 1. Effect of unripe plantain extract on lipid profile of animals exposed to CCl_4 toxicity

Parameters (mg/dL)	Negative control	Positivecontrol CCl_4(3ml/kg bw) only **SERUM**	CCl_4 + Unripe Plantain (50 ml/kgbw)	CCl_4 + Unripe Plantain (100 ml/kgbw)	CCl_4 + Silymarin (100mg/kgbw)
CHOL	73.28±1.84 [a]	140.21±0.00[b]	105.24±0.56[a]	88.43±1.25 [a]	77.76±0.96 [a]
TRIG	23.05±1.30 [a]	46.22±1.18[b]	39.87±0.61	31.46±0.75 [a]	25.35±0.81 [a]
HDL	15.91±0.68 [a]	10.10±0.04[b]	11.33±0.59	12.88±0.43 [a]	13.35±0.28 [a]
LDL	54.10±0.53 [a]	120.87±0.46[b]	102.15±1.53[a]	71.38±1.31 [a]	59.34±1.22 [a]
		KIDNEY			
CHOL	23.96±1.80 [a]	38.49±0.65[b]	35.22±0.59 [b]	27.83±0.43 [a]	24.16±5.89 [a]
TRIG	7.75±0.65 [a]	11.6±0.50[b]	10.42±0.51 [b]	9.63±0.89 [a]	9.51±0.74 [a]
HDL	6.40±0.07 [a]	3.57±0.11[b]	4.32±0.42 [a]	4.14±0.61 [a]	5.61±0.25 [a]
LDL	16.01±1.71 [a]	32.6±0.68[b]	28.56±0.10 [b]	21.12±0.04 [a]	16.64±0.16 [a]
		LIVER			
CHOL	72.96±1.01 [a]	119.75±1.52[b]	103.31±1.23 [a]	97.39±1.20 [a]	65.36±1.19 [a]
TRIG	64.40±0.16 [a]	96.58±0.27[b]	85.63±0.47 [a]	71.06±0.36 [a]	74.11±0.25 [a]
HDL	53.62±0.11 [a]	34.19±0.10[b]	40.05±0.83 [a]	49.73±0.43 [a]	54.15±0.19 [a]
LDL	6.53±1.06 [a]	67.44±3.41[b]	54.64±2.15[b]	37.62±2.23 [a]	13.10±1.77 [a]

Data represents mean $\pm$ SEM values animal experiments performed in triplicate ‘a’ indicates significant difference ($p<0.05$) from the control, (n= 5).

Table 2. Effect of unripe plantain extract on selected biomarkers of liver and kidney injury

Parameters (IU/L)	Positive Control	Negative control CCl_4 (3ml/kg bw)	CCl_4 + Unripe Plantain (50 ml/kg bw)	CCl_4 + Unripe Plantain (100 ml/kg bw)	CCl_4 + Silymarin (100 mg/kg bw)
		SERUM			
ALP	85.37±0.00[a]	145.96±0.00[b]	121.78±4.03	98.83±2.45 [a]	96.39±0.00 [a]
ALT	66.09±0.88[a]	106.69±1.7 [b]	76.92±0.34 [a]	64.36±0.34 [a]	66.92±0.46 [a]
AST	75.19±1.06[a]	113.01±1.08[b]	83.30±1.46 [a]	78.84±0.98 [a]	73.36±0.49 [a]
		KIDNEY			
ALP	80.17±0.00[a]	125.96±0.00[b]	120.37±4.32[a]	80.63±2.43 [a]	96.39±0.00 [a]
ALT	56.14±0.94[a]	158.71±7.56[b]	73.50±0.39 [a]	63.88±0.56 [a]	64.06±0.97 [a]
AST	69.58±1.28 [a]	99.74±1.08[b]	74.90±0.64 [a]	68.90±1.24 [a]	75.27±1.47 [a]
UREA	52.69±0.67 [a]	93.08±0.00[b]	57.38±2.18 [a]	54.65±0.63 [a]	58.85±0.00 [a]
URIC	24.36±0.29 [a]	50.48±0.33[b]	47.00±3.59[b]	33.45±3.58 [a]	25.55±0.55 [a]
		LIVER			
ALP	55.08±0.00 [a]	112.91±0.00[b]	94.88±5.01 [a]	69.56±2.86 [a]	65.41±1.38 [a]
ALT	44.99±3.23 [a]	116.55±3.18[b]	84.53±0.36 [a]	73.08±0.45 [a]	66.03±0.96 [a]
AST	69.07±1.55 [a]	104.59±4.32[b]	84.34±1.05[a]	73.50±1.44 [a]	68.64±1.74 [a]
T. BIL	24.85±1.28 [a]	46.48±0.18 [b]	41.03±0.47[b]	32.11±1.04 [a]	26.65±1.15 [a]

Data represents mean ± SEM values animal experiments performed in triplicate 'a' indicates significant difference ($p<0.05$) from the control, (n= 5).

Table 3. Effect of unripe plantain extract on selected antioxidant enzymes

Parameters (IU/L)	Positive Control	Negative control CCl_4 (3ml/kg bw)	CCl_4 + Unripe Plantain (50 mg/kg bw)	CCl_4 + Unripe Plantain (100 mg/kg bw)	CCl_4 + Silymarin (100 mg/kg bw)
		SERUM			
SOD	8.47±0.49 [a]	5.02±0.35[b]	5.73±0.53 [b]	6.91±0.88 [a]	7.80±1.04 [a]
CAT	4.36±0.18 [a]	1.84±0.05[b]	2.16±0.72[a]	2.99±0.81 [a]	3.77±0.60 [a]
GSH	6.81±1.10 [a]	4.53±1.22 [b]	5.03±0.95[b]	6.17±0.66 [a]	6.04±0.87 [a]
TP	3.75±0.20 [a]	1.67±0.60 [b]	2.14±0.57[a]	2.79±0.27 [a]	2.59±0.18 [a]
		KIDNEY			
SOD	5.26±0.02 [a]	2.28±0.12 [b]	3.63±0.27 [a]	3.84±0.36 [a]	3.62±0.21 [a]
CAT	1.36±0.11 [a]	0.64±0.07 [b]	0.95±0.04[a]	1.39±0.14 [a]	1.47±0.60 [a]
GSH	2.52±0.17 [a]	0.93±0.02 [b]	1.64±0.08 [a]	2.27±0.28 [a]	1.95±0.04 [a]
TP	2.97±0.02 [a]	2.14±0.01 [b]	2.48±0.12 [a]	2.93±0.16 [a]	2.74±0.11 [a]
		LIVER			
SOD	2.04±0.10 [a]	1.42±0.42 [b]	1.83±0.32 [a]	1.97±0.19 [a]	2.11±0.32 [a]
CAT	1.14±0.13 [a]	0.26±0.21 [b]	0.74±0.16 [a]	1.04±0.43 [a]	0.97±0.22 [a]
GSH	1.93±0.03 [a]	0.39±0.01 [b]	0.65±0.08 [a]	1.41±0.12 [a]	1.79±0.03 [a]
TP	1.88±0.13 [a]	1.07±0.09 [b]	1.39±0.05 [a]	1.69±0.45 [a]	1.58±0.43 [a]

Data represents mean ± SEM values animal experiments performed in triplicate 'a' indicates significant difference ($p<0.05$) from the control, (n= 5).

5.0 DISCUSSION

The therapeuticpotential of unripe plantain pulp in the management of hepatic and renal diseases was investigated. Established liver and kidney markers have been used routinely in monitoring the health status of both organs. Specifically, aspartate aminotransferase (AST),alanine aminotransaminase (ALT) and alkaline phosphatase are reliable markers of hepatic disorders (Bi *et al*., 2008; Ayepola*et al*., 2013;Mossa*et al*., 2013; Kim and Wyckoff, 1991). Exposure of experimental rats to carbon tetrachloride toxicity resulted in significant elevation in the serum level of these biomarkers relative to animals that were not exposed. Notably, the surge in serum level of these biomarkers implies free-radical induced oxidative injury to the hepatocytes.Increased ALT level indicates hepatocellular damage followed by cardiac tissue damage and is usually accompanied by a rise in AST activity. ALP is a marker of biliary function and cholestasis. However, functional alterations of liver can lead to different pathologies in other organs. Serum level of these enzymes become elevated in cases of liver diseases or damage because they are normally contained inside hepatocyte. They only leak into the blood stream when the liver cells are damaged. The spill-over of the enzyme into the blood is routinely measured as a marker of abnormal cell damage; hence, a markedly raised serum activity indicates severe liver disease(Champe*et al*., 1994). These biochemical parameters were on the increase as a result of tetrachloromethane (CCl_4)-induced oxidative attack on the liver cells.This might be due to deterioration and necrosis of the liver cells by the oxidative attack of trichloromethyl radicals resulting in the release of transaminases into the blood stream (Airaodion*et al*., 2019a; Airaodion*et al*., 2019b). This observation is in line with the earlier reports of Shahzad *et al*. (2016), Araoud*et al*. (2012), Khan *et al.* (2008) and Jamal *et al.* (2016) where liver biomarkers of experimental animals were increased following exposure to pesticides. Treatment of exposed animals with unripe plantain extract caused a significant, dose- dependent

restoration of AST, ALT and ALPactivities in the serum and tissue homogenates relative to exposed animals that were not treated with the extract. This suggests the hepatoprotective potentials of unripe plantain extract which can be exploited in the management of liver diseases.

Lipid profile (low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triacylglycerol (TG) could provide useful information on the predisposition of the heart to atherosclerosis and its associated coronary heart disease (Yakubu*et al*., 2008). The significant reduction in triacylglycerolof exposed but untreated animals may be associated with impaired lipolysis while reduction in HDL-C at all doses investigated may not be clinically beneficial to the animals since the rate at which plasma cholesterol are carried to the liver were also decreased. Furthermore, the enhanced level of cholesterol and LDL-C may suggest cardiovascular risk in the animals. This is supported in the present study by the increase in the computed atherogenic index, a useful indicator of cardiovascular diseases (Panagiotakos*et al*., 2003). The unripe plantain extract was able to restore the level of triacylglycerol and carp up the level of HDL-C compared the control (Table1). This observation suggests the potential usefulness of plantain in the management of cardiovascular diseases.

Superoxide dismutase (SOD) and catalase (CAT) are the two major radical scavenging enzymes. Superoxide dismutase is the main enzymatic defense against the superoxide anion. It detoxifies the superoxide anion, thus converting it into hydrogen peroxide and water. Although SOD is an antioxidant enzyme, some studies have suggested that it's over expression is actually harmful to cells (Gardner *et al*., 2002). The toxic effect of reactive oxygen species observed in many cells with over expressed SOD has been linked to elevated levels of hydrogen peroxide (H_2O_2) and accompanying oxidative damage following hydroxyl radical formation (De Haan*et al*., 1996).

Catalase is a heme protein that catalyzes the reduction of hydrogen peroxides and protects tissues from hydroxyl radicals (Searle and Wilson, 1980). Consequently, the decrease in activities of SOD and CAT as well as GSH level in both liver and kidney during disease condition may be due to over-production of reactive oxygen species in animals (Kaleem *et al.,* 2006). The overproduction of free radicals in turn, causes oxidative damages to membrane's lipid and protein, and ultimately leads to a decrease in the content of GSH and activity of its dependent enzyme.However, treatment of exposed animals with unripe plantain extract ameliorated the activities of these antioxidant enzymes as well as GSH (Table 3). This is in agreement with Ji *et al*. (1992).

In the present study, integrity of the kidney was assessed through serum urea and uric acid levels. All animals exposed to CCl_4showed significantly increased level of serum urea and uric acid relative to unexposed animals. This suggests the nephrotoxic potential of CCl_4 (Table 2). However, administration of unripe plantain extract restored the serum urea and uric acid levels to values comparable with unexposed animals. This is an indication that unripe plantain is a potential nephroprotective agent that can be exploited in the management of kidney diseases.

Unripe plantain restored deranged lipid profile, remedied disturbed liver and kidney biomarkers as well as restored the activities of antioxidant enzymes. Hence, it is a potential plant with hepatoprotective and nephroprotective properties that can be exploited in the management of liver and kidney diseases.

Ethical Approval

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee"

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of

knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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