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Research Article
Ethanol Extract of *Curcuma longa* L. Protects Against Carbon Tetrachloride-Induced Oxidative Damage in Renal and Hepatic Tissues of Rats

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Abstract

Background and Objective: The rapid increase rate in the progression of several pathological disorders such as organ failure, diabetes mellitus, cancer and cardiovascular diseases has been related to the upsurge in toxic xenobiotics exposures and release into the biosystem. This study elucidated the protective roles of the ethanolic extract of *Curcuma longa* (EECL) in an experimental model of renal and hepatic damage mediated by Carbon Tetrachloride (CCl_4). **Materials and Methods:** Twenty-four Wistar albino rats were randomized into four groups of six animals each. Group I (control) received distilled water orally while groups II, III and IV were exposed to 0.5 mL kg^{-1} b.wt., of CCl_4 intraperitoneally for 14 days to induce tissue damage. However, groups III and IV were administered 100 mg kg^{-1} and 200 mg kg^{-1} b.wt., of EECL, respectively for 2 weeks. **Results:** The result showed that CCl_4 significantly ($p<0.05$) caused elevation in serum renal (urea and creatinine) and hepatic (serum acid phosphatase, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and gamma-glutamyl transferase) damage indices and a concomitant decrease in tissue GSH levels as well as elevated MDA content in the organs. Histological examination of hepatic tissue revealed distorted tissue architecture with severe portal congestion and diffuse hepatic necrosis while glomerular lesion damaged bowman's capsule, degenerated and vacuolated renal tubules, severe interstitial haemorrhage with diffuse tubular necrosis were evident following exposure to CCl_4. Nevertheless, EECL significantly ($p<0.05$) reversed alterations to biochemical indices and restored normal tissue architecture in groups treated with the extract. **Conclusion:** The EECL possesses therapeutic potential in the management/treatment of renal and hepatic-related disorders.

Key words: Carbon tetrachloride, *Curcuma longa*, renal damage, hepatic dysfunction, oxidative stress, phytomedicine, anticoagulant activities

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Human and animal toxicity of Carbon Tetrachloride (CCl_4) cannot be overemphasized especially in the liver where the varying degree of symptoms ensues, such as centrilobular necrosis, cirrhosis and fatty infiltration[1,2] resulting in leaking of liver-specific enzymes[3] due to the effects of hazardous active metabolites produced. High reactivity associated with Carbon Tetrachloride (CCl_4) metabolism has been reported to generate a tremendous amount of free radicals before the induction of liver injury[4,5]. However, the detrimental effects of this cytotoxin are not restricted to the liver, as other target organs such as the brain, lungs, hearts, testes and kidneys have also been reported[6,7]. The major propagating mechanism of CCl_4 toxicity involves its enzymatic activation by the cytochrome P450 enzyme system present in the liver microsome, resulting in the generation of trichloromethyl radicals (CCl_3) which spontaneously react with molecular oxygen to produce toxic peroxyl radicals (CCl_3O_2) which cause membrane lipid peroxidation of phospholipids unsaturated fatty acid components in cells within the liver[8,9].

Cellular antioxidant and anti-inflammatory systems are however energised by numerous dietary antioxidant sources[10] such as fruits, vegetables and spices and are documented to play a critical role in mitigating these toxic effects via a plethora of mechanisms which involve neutralizing lipid peroxides and scavenging of free radicals[11] among others. Recent advances in phytomedicine and plant research have illuminated the world of plant secondary metabolites such as flavonoids and phenol compounds, especially in the advent of their implicated usage during the treatment and management of various deleterious illnesses due to their ubiquitous plant sources and substantial biological activities[12].

Curcumin (diferuloylmethane) is a crystalline, yellow-pigmented lipophilic polyphenol compound with chain-breaking antioxidant properties[13,14], which constitutes about 4 % rhizome composition of *Curcuma longa* Linn (turmeric) a member of the ginger family used as spice, colouring and flavouring agent as well as in ancient health care traditional medicine in the treatment of inflammatory diseases[15,16]. The active curcuminoid found in *Curcuma longa* is a phenolic compound constituting approximately 90 % of total rhizome curcuminoid, followed by demethoxycurcumin and bisdemethoxycurcumin[17]. Biological activities of curcumin include, hypolipidemic[18], anti-amoeboid[19], antibacterial[20], anti-HIV[21], anticoagulant activities[22], anti-carcinogenic[23], immunomodulatory activities[24] regulation of gene expression[24] and DNA-protecting properties[25] among others.

Studies have shown that CCl_4 exerts its deleterious effects on tissues via the generation of free radicals with attendant depletion of the cellular antioxidant capacity[26]. Phytochemicals with strong antioxidant properties have been shown to mitigate the damaging roles of CCl_4 on the hepatic cells[26]. Nevertheless, despite the popularity of *Curcuma longa* rhizome and its health benefits as well as its protective effect against CCl_4-induced hepatotoxicity, there is still a dearth of information on its effect on CCl_4 exposure on renal tissue. Therefore, this study was designed to examine the protective roles of the ethanolic extract of *Curcuma longa* on Carbon Tetrachloride (CCl_4)-mediated hepatic and renal damage in rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Chemical Sciences, Kings University, Ode-Omu, Nigeria from January, 2019 to June, 2019.

Chemicals and reagents

Methods: Urea kit, creatinine, Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Gamma Glutamyl Transferase (GGT), acid phosphatase (ACP) and Alanine Aminotransferase (ALT) were obtained from Randox Laboratories Limited, United Kingdom. Ethanol, petroleum ether and all other reagents are of analytical grade obtained both from Sigma and Analar BDH Limited.

Plant materials and extract preparation: Rhizomes of *Curcuma longa* L. were obtained from a garden in Gbongan, Osun State, Nigeria. A voucher specimen was placed at the Biology Department of the Federal University of Technology in Akure, Nigeria, where the samples' authentication was done. These rhizomes were oven dried at 45 °C to a consistent weight before being ground into powder. The sample was then defatted in petroleum ether with the use of a soxhlet extractor device. The defatted *Curcuma longa* was extracted for 72 hrs in 90% ethanol to obtain the extract which was subsequently used in the study.

Experimental rats: For this investigation, twenty-four albino Wistar strain rats weighing 150-160 g raised at the breeding colony of the Department of Chemical Sciences at Kings University, Ode-Omu, Osun State, Nigeria, were used. The rats were housed in stainless steel cages under ambient standard conditions and metabolic wastes were cleaned twice daily.

The rats were fed commercially available rat pellets and given unlimited access to water for fourteen days to acclimate to these conditions. The NIH guide for the use and care of laboratory animals was followed in this investigation.

Experimental design: The rats were divided at random into four groups of six rats each. While groups II, III and IV were given 0.5 mL kg^{-1} b.wt., of Carbon Tetrachloride (CCl_4) intraperitoneally for 14 days to cause renal and hepatic damage, group I (the control) was given distilled water orally. Additionally, for two weeks, groups III and IV received oral doses of 100 and 200 mg kg^{-1} b.wt., respectively, of the ethanolic extract of *Curcuma longa* (EECL).

Blood collection and preparation of serum: The rats have sacrificed 24 hrs after the last dose has been administered by cervical dislocation. The blood samples were collected via direct heart puncture into a sterile dry centrifuge tube. These blood samples were allowed to be cloth at room temperature for 10 min and then pinned at 4,000 rpm in an MSC (Essex, UK) bench centrifuge. The clear supernatant (serum) was transferred into clean dry sample bottles aspirated Pasteur pipette and then stored at -4°C for further analyses.

Tissues homogenates preparation: The kidney and liver samples were immediately removed from the rats and blotted to remove blood stains. These tissues were then cleansed in 1.15% KCl to remove haemoglobin, weighed and homogenized in ice-cold 10 mM potassium phosphate buffer, (pH 7.4) using the teflon homogenizer. The homogenates were centrifuged at 12,500 g for 20 min at 4°C to obtain clear post-mitochondrial fractions which were stored until required for analysis.

Measurement of biochemical parameters: Creatinine and urea were measured in the serum using the method reported by Cheesbrough[27]. Serum acid phosphatase (ACP), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST) and Gamma-Glutamyl Transferase (GGT) activities were analysed according to the procedure given by the Kit manufacturer (Randox diagnostic) based on the principle documented by Reitman and Frankel[28]. Protein content was determined using a method reported by Lowry *et al.*[29]. The Ellman's reagent-dependent method of Jollow *et al.*[30] was used to evaluate the reduced glutathione concentration. Oxidative damage was assessed following the protocol reported by Varshney and Kale[31], by measuring the level of malondialdehyde which is a lipid peroxidative product, after forming a pink-coloured chromogen upon reacting with 2-thiobarbituric acid.

Histological studies: The liver and kidney sections were fixed in 10 % formalin and embedded in paraffin wax. Thin sections (7-9 mm thickness) of the liver and kidney tissues were cut and dewaxed in xylene, hydrated in decreasing percentage of alcohol and stained with haematoxylin and eosin (H&E). They were differentiated in 90% alcohol and cleared in xylene. These stained sections were observed under the microscope for histopathological analysis.

Statistical analysis: Results obtained were expressed as mean ± standard error of the mean (mean ± SD) and analysed using One-way Analysis of Variance (ANOVA) with the aid of SPSS 22.0 computer software package (SPSS Inc, Chicago, USA) to compare the experimental groups followed by Bonferroni's *post-hoc* test. Values at $p<0.05$ were considered significant.

RESULTS

Effect of EECL on organs weights and body weight gain of rats treated with CCl_4: The effect of EECL on body and organ weights in CCl_4 treated rats were presented in Table 1. Intraperitoneal administration of CCl_4 caused a significant decrease in body weight gain as well as in liver and kidney weights. However, compared with the rats exposed to CCl_4 alone, treatment with EECL significantly attenuated the adverse effects of CCl_4 by restoring the body weight as well as the liver and kidney weights to near control rats in a dose-dependent manner.

Effect of EECL and CCl_4 on serum urea and creatinine concentrations of experimental rats: The rats treated with 0.5 mL kg^{-1} b.wt., of CCl_4 alone (group II) showed a significant increase ($p<0.05$) in serum concentration levels of urea and creatinine as compared to the control group I (Fig. 1). These altered values were reversed significantly ($p<0.05$) toward normal in a dose-dependent manner in rats treated with 100 and 200 mg kg^{-1} b.wt., of EECL (group III and IV, respectively).

Effects of EECL and CCl_4 on serum ALT and AST activities of experimental rats: Figure 2 and 3 showed that rats exposed to 0.5 mL kg^{-1} b.wt., of CCl_4 alone (group II) showed a significant increase ($p<0.05$) in serum concentration levels of ALT, AST, ACP, GGT and ALP as compared to the control (group I). These altered valves were reverted significantly ($p<0.05$) toward normal in a dose-dependent manner in rats treated with 100 and 200 mg kg^{-1} b.wt., of EECL (group III and IV, respectively).

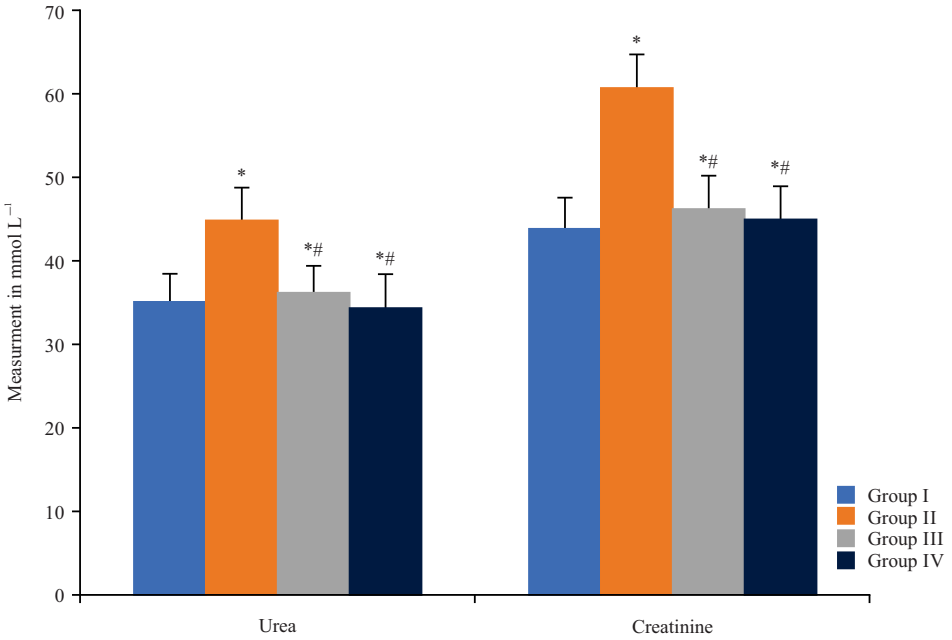

Fig. 1: Effects of EECL and CCl_4 on serum urea and creatinine concentrations of experimental animal

Data presented as Mean±SD of 6 animals each per group, *significantly different from normal control group at p< 0.05 and #significantly different from group II at p< 0.05

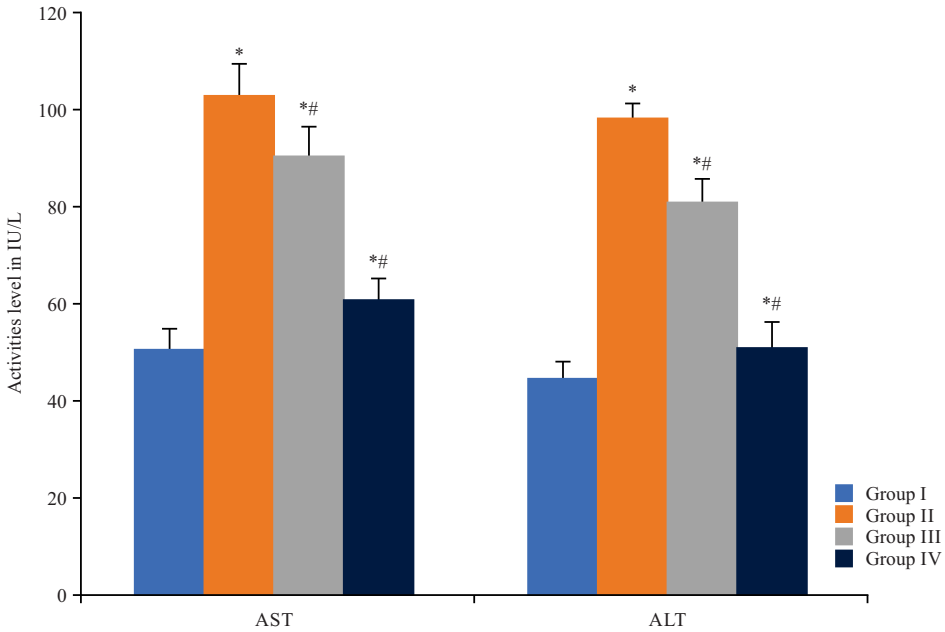

Fig. 2: Effects of EECL and CCl_4 on serum ALT and AST activities of experimental animals

Data presented as Mean±SD of 5 animals each per group, *significantly different from normal control group at p<0.05, #significantly different from group II at p<0.05, ALT: Alanine Aminotransferase and AST: Aspartate Aminotransferase

Effects of EECL and CCl_4 on GSH content in kidney and liver of experimental rats: The effect of curcumin and CCl_4 on the antioxidant status of the experimental rats was shown in Fig. 4. Renal and hepatic GSH concentrations were significantly reduced (p<0.05) as compared to the control, as well as significantly increased (p<0.05) in lipid peroxidation

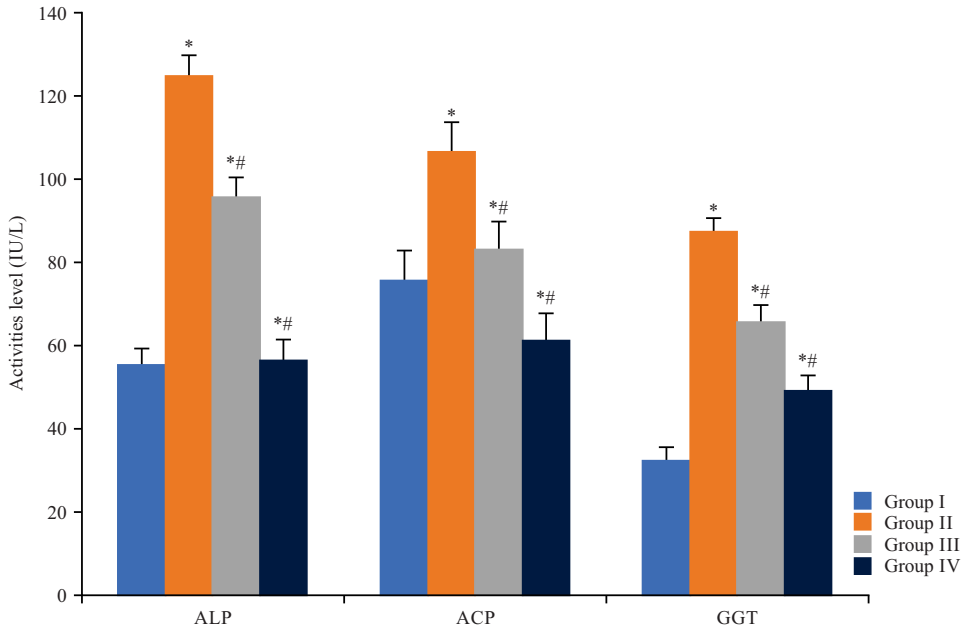

Fig. 3: Effects of EECL and CCl_4 on serum ALP, ACP and GGT activities of experimental animals

Data presented as Mean±SD of 5 animals each per group, *significantly different from normal control group at p<0.05, #significantly different from group II at p<0.05, ALP: Alkaline phosphatase, ACP: Acid phosphatase and GGT: Gamma-Glutamyl Transferase

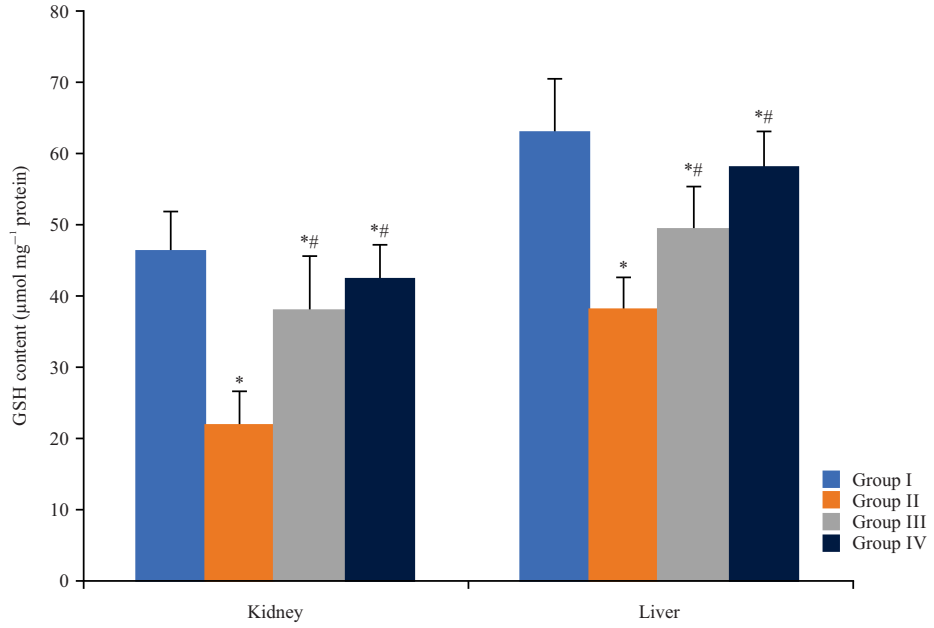

Fig. 4: Effects of EECL and CCl_4 on GSH content in the kidney and liver of experimental rats

Data presented as Mean±SD of 5 animals each per group, *significantly different from normal control group at p< 0.05 and #significantly different from group II at p< 0.05

Table 1: Effects of EECL on organs weights and body weight gain of animals treated with CCl_4

Group	Liver (g)	Kidney (g)	Total body weight gain (g)
Group I	7.42±1.22	1.20±0.12	11.04±0.66
Group II	5.68±0.77*	0.89±0.26*	3.80±0.51*
Group III	7.18±0.92#	1.06±0.09#	7.50±0.42#
Group IV	7.36±1.06#	1.13±0.17#	9.65±0.87#

Data presented as Mean±SD of 6 animals each per group, *Significantly different from normal control group at p<0.05 and #significantly different from group II at p<0.05

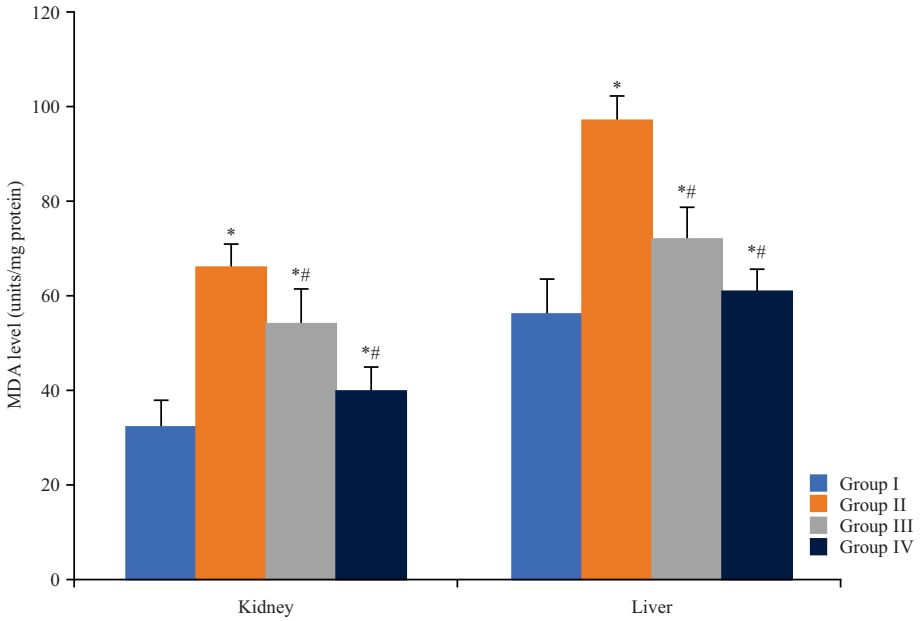

Fig. 5: Effects of EECL and CCl_4 on lipid peroxidation (MDA level) in the kidney and liver of experimental rats
Data presented as Mean±SD of 5 animals each per group, *significantly different from normal control group at $p< 0.05$ and #significantly different from group II at $p<0.05$

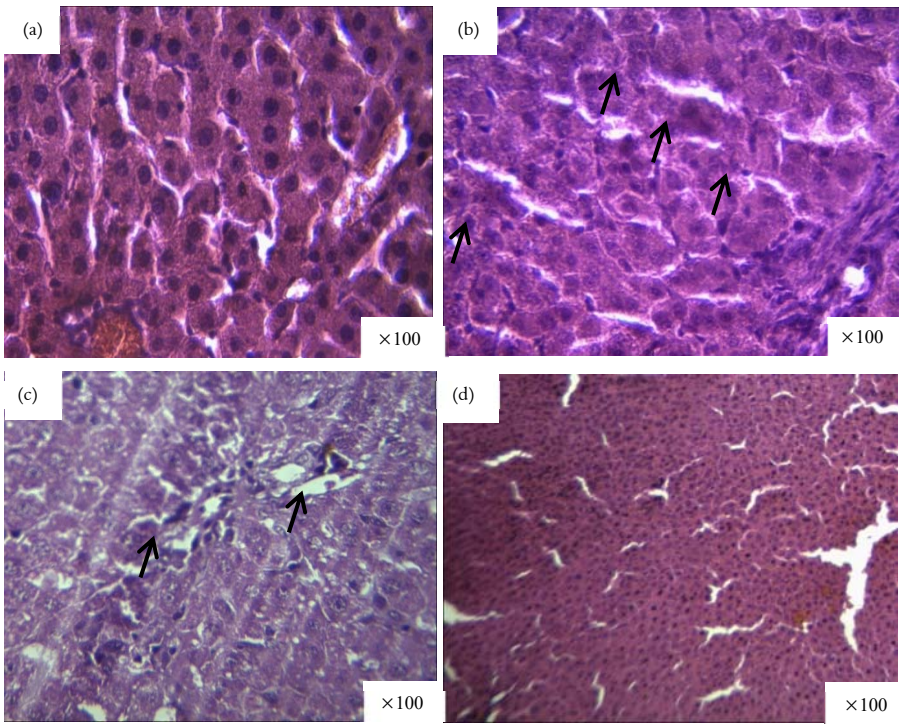

Fig. 6(a-d): Photomicrographs of a longitudinal section of hepatic tissues of rats administered CCl_4 and EECL, (a) Control rats showing normal hepatic morphology with no visible lesions seen, (b) Rats intoxicated with CCl_4 showing abnormal hepatic morphology with distorted histoarchitecture characterized by severe portal congestion and diffuse hepatic necrosis, (c) Rats administered CCl_4+100 mg kg^{-1} b.wt., of EECL showed normal hepatic morphology with mild visible lesions and (d) Rats administered CCl_4+200 mg kg^{-1} b.wt., of EECL showed normal hepatic morphology with no visible lesions seen

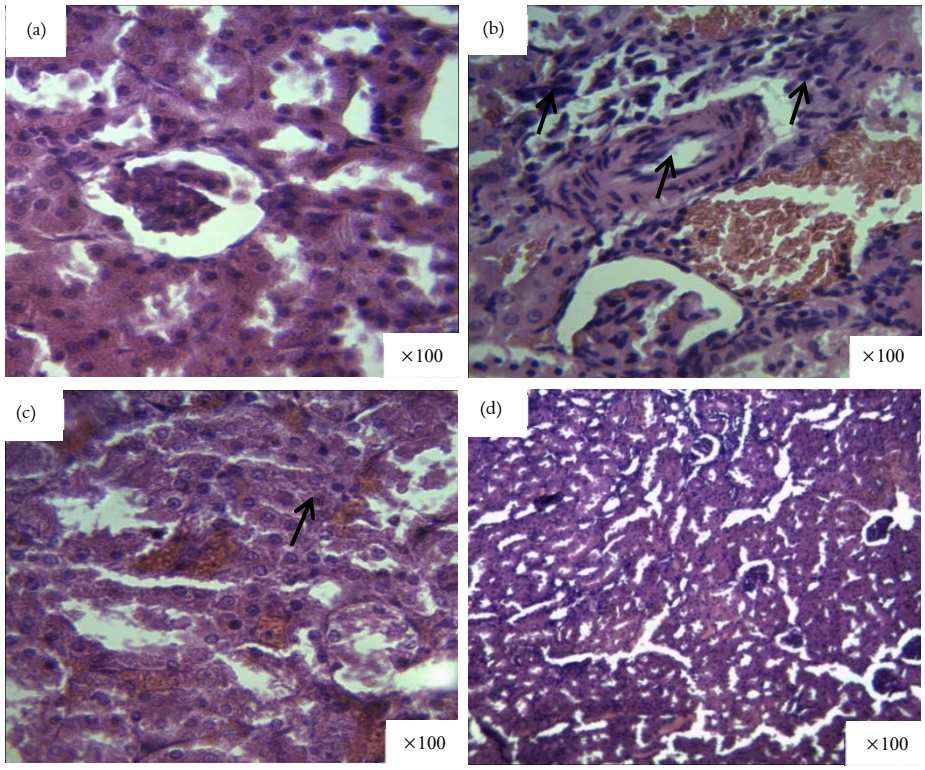

Fig. 7(a-d): Photomicrographs of the longitudinal section of renal tissues of rats administered CCl_4 and EECL, (a) Control rats showing normal renal morphology with no visible lesions seen, (b) Rats intoxicated with CCl_4 showing abnormal renal morphology with distorted histoarchitecture characterized by lesion of the glomerulus, damaged Bowman's capsule, degenerated and vacuolated renal tubules, severe interstitial haemorrhage, with diffuse tubular degeneration and necrosis, (c) Rats administered CCl_4+100 mg kg^{-1} b.wt., of EECL showed normal renal morphology with diffuse tubular degeneration and necrosis and (d) Rats administered CCl_4+200 mg kg^{-1} b.wt., of EECL showed normal renal morphology with mild visible lesions

(MDA) in rats treated with CCl_4 (group II). Administration of EECL significantly ($p<0.05$) attenuates these anomalies in a dose-dependent manner.

Effects of EECL and CCl_4 on lipid peroxidation in the kidney and liver of experimental rats: The effect of curcumin and CCl_4 on the antioxidant status of the experimental rats was shown in Fig. 5. Renal and hepatic GSH concentrations were significantly reduced ($p<0.05$) as compared to the control, as well as significantly increased ($p<0.05$) in lipid peroxidation (MDA) in rats treated with CCl_4 alone (group II). Administration of EECL significantly ($p<0.05$) attenuates these anomalies in a dose-dependent manner.

Histological evaluation of the effects of EECL and CCl_4 on the kidney and liver of experimental rats: The toxicity effects of CCl_4 in the hepatic tissue of animals were shown by abnormal hepatic morphology with distorted histoarchitecture characterized by severe portal congestion and diffuse hepatic necrosis (Fig. 6). Also, kidneys of rats administered CCl_4 alone shows abnormal renal morphology with distorted histoarchitecture characterized by lesion of the glomerulus, damaged Bowman's capsule, degenerated and vacuolated renal tubules, severe interstitial haemorrhage, with diffuse tubular degeneration and neurosis (Fig. 7). Administration of the chosen doses of EECL in this study reverse the histological modifications in a dose-dependent manner. These biochemical results were further validated by the histological findings.

DISCUSSION

This present study elucidates the beneficial effects of EECL against CCl_4 mediated renal and hepatic damage. Results obtained demonstrated that there was a significant ($p<0.05$) decrease in the growth rate of rats exposed to CCl_4 only when

compared with the control but treatment with EECL enhanced the growth rate as shown in the total body weight gained in Table 1. This tandem with previous results documented by Oyewole and Oladele[32] who reported that plant extract can enhance growth in rats by increasing feeding efficiency and appetite, enhancing nutrient biotransformation and utilization. The observed increase in growth rate as shown by the body weight gained may also be suggested that the extract aided intestinal absorption of food and prevent gastrointestinal irritation which interfere with the rate of food absorption[33].

Figure 1 confirmed the nephrotoxic effect of carbon tetrachloride as the rats that were treated with carbon tetrachloride alone showed a marked increase in levels of renal metabolites (urea and creatinine) in the serum. Previous experiments showed that increased levels of renal metabolites in serum are indicative of damage to renal functions[34,35]. Increased serum levels of these renal markers may probably be a result of their escape from their compartmentalized tissue into the circulatory system due to damage to their cellular membranes, however, this was ameliorated following the administration of 100 and 200 mg kg^{-1} b.wt., EECL in a dose-dependent pattern. This result indicated that EECL mitigated kidney damage by enhancing the structural integrity of the renal membrane and facilitating the healing process from oxidative damage.

Similarly, Fig. 2 and 3 revealed significant ($p<0.05$) elevation in serum levels of ALP, ACP, GGT, ALT and AST in rats administered carbon tetrachloride alone, an indication of its hepatotoxic effects. ALT and AST activities are clinical diagnostic parameters routinely used in the evaluation of hepatic damage and the health condition of the hepatocytes[36]. The ACP and ALP are membrane-bounded enzymes needed for the appropriate functioning of internal organs and plasma membranes. Treatment with EECL however significantly reversed the elevated ALP, ACP, GGT, AST and ALT levels in the serum, suggesting EECL could have the capability to prevent hepatic membrane damage.

Figure 4 and 5 showed a significant reduction ($p<0.05$) in reduced glutathione content of the kidney and liver of rats administered with CCl_4 alone which may be a result of the overwhelming protecting activities of antioxidant enzymes. Glutathione plays a major role in cellular antioxidant defence mechanisms against oxidative stress facilitated by reactive free radicals and other oxidant species. Oxidative stress occurs in cells as a result of an imbalance between antioxidants and reactive oxygen species (ROS) leading to destructive oxidative damage of macromolecules which is the major key player in the pathogenesis of many human diseases[37-41]. Lipid peroxidation has been documented as the route of oxidative degradation of membrane polyunsaturated fatty acids[42,43]. This was confirmed in the present study with a significant upsurge ($p<0.05$) in malondialdehyde (MDA) in the kidney and liver of rats administered with CCl_4 alone. However, treatment with EECL ameliorates these deleterious activities by elevating GSH content and reversing MDA levels in the tissues. This result suggested that EECL offer a protective role by preventing metabolic reactions that produce reactive species, improving the antioxidant enzyme activities and scavenging generated ROS and free radicals.

In this study, exposure of rats to CCl_4 caused hepatic and renal damage as evident in the microscopic examination of the liver and kidney respectively. This result agreed with the previous findings of Rahmat *et al.*[44] who reported cellular infiltration, multifocal centrilobular hepatic necrosis and massive fatty degeneration in the liver of rats exposed to CCl_4. Hepatic damage caused by CCl_4 is a very common paradigm for the screening of potential hepatoprotective drugs. The cause of CCL_4's acute hepatotoxicity is its biotransformation to the free radical trichloromethyl Trichloroperoxyl radical generated by the cytochrome P450 with mixed functions. The endoplasmic reticulum's (CYP) oxygenase system This results in oxidative stress and damaged membrane[45].

CONCLUSION

Taken together, the administration of EECL elicits renal protection and hepatoprotective functions through its ability to enhance the structural integrity of tissue membranes, influence the cellular antioxidant defense mechanism and improve antioxidant status, lowering and reversing serum renal and hepatic metabolites. Thus, EECL poses a therapeutic potential in the management/treatment of renal and hepatic-related disorders.

SIGNIFICANCE STATEMENT

This research reported the therapeutic potential of the ethanolic extract of *Curcuma longa* in the management/treatment of renal and hepatic-related disorders. This could be beneficial in mitigating pathological conditions mediated via exposure to toxic substances which are the major environmental factors responsible for the pathogenesis of many human diseases.

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