Trop J Nat Prod Res, June 2024; 8(6):7388-7396 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Ethanol Leaf Extract of *Acrostichum aureum* Modifies Carbon Tetrachloride-induced Oxidative Stress and Hepato-renal Damage in Rats

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ARTICLE INFO

Article history:
Received 23 January 2023
Revised 18 May 2024
Accepted 22 May 2024
Published online 01 July 2024

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ABSTRACT

Liver and kidney diseases are public health concerns due to ineffectiveness and adverse effects of orthodox therapeutics. Consequently, medicinal plants are becoming attractive as plausible source of protective agents against hepatorenal toxicities. The protective effect of ethanol leaf extract of *Acrostichum aureum* (ELAA) was examined in a CCl_4 rat model of hepato-renal injury. Forty-eight adult male Sprague–Dawley rats were divided into eight treatment groups (n=6 each). Treatment lasted for 21 days and the groups included: a negative control that received olive oil, a positive control group that received quercetin (10 mg/kg/day), two groups that received ELAA (50 or 100 mg/kg/day) alone, a CCl_4 (1 ml/kg twice a week) treated-group and three CCl_4-cotreatment groups that received 50 mg/kg/day ELAA or 100 mg/kg/day ELAA or quercetin with CCl_4. On the 22nd day, blood was collected and used for evaluation of hepato-renal health markers including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, urea, total protein, albumin, Na^+, and Cl^-. Rats were sacrificed and malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels were determined in the liver and kidney after recording their weights. Compared to the negative control, CCl_4 caused significant ($p<0.05$) increases in organ weight, organo-somatic indices, ALT, AST, bilirubin, and creatinine, while Na^+ and Cl^- were significantly decreased. Marked elevation of MDA coupled with decreased SOD and GPx activities were also recorded following CCl_4 treatment. Supplementation with ELAA reversed the parameters toward control values similarly to quercetin. Suggesting that ethanol extract of *Acrostichum aureum* ameliorated CCl_4-induced hepato-renal injury by counteracting oxidative stress.

Keywords: Liver, Kidney, *Acrostichum aureum*, CCl_4, Oxidative stress, Histopathology

Introduction

Hepatic and renal diseases are major threats to public health in many parts of the world, especially in developing nations, where access to quality health delivery systems is limited. Liver diseases are responsible for the death of about 2 million people yearly throughout the world,[1] while about 5-10 million patients die from renal diseases on an annual basis.[2] The liver and kidneys are susceptible to the harmful effects of infectious agents including viruses. Both organs are also predisposed to the toxicities of drugs mainly because of their involvement in biotransformation and elimination of toxins from the body. In addition, environmental contaminants including carbon tetrachloride (CCl_4) add to the global burden of hepato-renal diseases. The CCl_4 is an industrial solvent that found application in many products including polish, rubber waxes, dry cleaning agents, fumigants, and insecticides.

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Citation: Akinwumi KA, Eleyowo, OO, Odesola KA. Adegboyega AM, Okon-ben VM, Onapelumi AT. Ethanol Leaf Extract of *Acrostichum aureum* Modifies Carbon Tetrachloride-induced Oxidative Stress and Hepato-renal Damage in Rats. Trop J Nat Prod Res. 2024; 8(6): 7388-7396. https://doi.org/10.26538/tjnpr/v8i6.8

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Paradoxically, it is a well-known environmental toxicant and biohazard that is released directly into to environment via these products and as a result of industrial activities.[3] Human exposure to CCl_4, therefore, occurs at workplaces and in polluted air, soil, and water through dermal inhalation, oral, and dermal routes. Inside the cell, CCl_4 is metabolically activated or converted into noxious free radical species such as trichloromethyl radical ($^{\bullet}CCl_3$), trichloromethyl peroxy radical ($\bullet CCl_3OO$) dichlorocarbene ($^{\bullet}CCl_2$) and chloride radical ($^{\bullet}Cl_2$) that can result in lipid peroxidation, oxidative stress, and cellular injury. The CCl_4 intoxication affects many tissues including the liver and kidneys.[4-5] In the liver, CCl_4 exposure results in hepatic necrosis, steatosis, fibrosis, and cirrhosis,[6-8] while its pathology in the kidney includes acute tubular necrosis and decreased glomerular mass.[9-10] In addition, CCl_4 exposure can result in cancers of the liver and other tissues in rodents, albeit with no sufficient evidence in humans. Therefore, regulatory bodies on cancers have classified it as a probable carcinogen (class IIB) in humans.[11] Apart from being an environmental toxicant and probable carcinogen, CCl_4 is a well-established model for studying oxidative stress, hepato-renal toxicity, and the potential beneficial effects of medicinal plants.[12] Conventional drugs used in the treatment of hepato-renal diseases are costly, limited, and can have serious adverse effects.[13] Relatively effective regimens and inexpensive drugs with little or no side effects are recently being sought from medicinal plants especially those with antioxidant properties since hepato-renal diseases are associated with oxidative stress.[3,14]

Acrostichum aureum Linn is a plant that is widely distributed in Mangrove forests around the world including Nigeria.[15-7] It belongs to

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the family and genius, *Pteridaceae* and *Acrostichum* respectively. It is found in mangrove swamps, salt marshes, and canal margins.[18] It is commonly known as mangrove fern, golden leather fern, tiger fern, and swamp fern. The plant is locally used in Nigeria for the treatment of stomachache, internal heat, skin diseases, and migraines.[19] It is also used in other countries for the treatment of fever, skin infections, boils, ulcers, wounds, diabetes, pharyngitis, hemorrhoids, dysentery, hernia, chest pain, constipation, and snake bites.[19-23] Other documented traditional medicinal uses of the plants are in the treatment of asthma, sore throat, elephantiasis, asthma, worm infection, hypotension, and digestive problems.[16,24] Moreover, the young fronds of the plant are consumed as vegetables in some Asian countries.[25] The plant is rich in beneficial secondary metabolites and valuable phytochemicals including quercetin and its glycosides, isotachioside, kaempferol, lupeol, campesterol, stigmasterol, β and γ- sisosterol, pterosin P and C, tetracosane, patriscabratine and α-amyrin.[16,26-30]

The plant has been reported to have anti-tumor,[16,29] antiulcer,[31] anthelmintic,[32] antibacterial,[33] anti-diarrheal,[18] analgesic,[22] antiviral,[34] and tyrosinase inhibitory[35] properties. The *in vitro* antioxidant activity and the reducing power of different extracts of the plant have also been demonstrated.[21] Recently Wu et al[31] showed that a polar extract of the plant protected against ethanol-induced ulcers in rats by reducing oxidative stress and inflammation. However, there is a paucity of information on the effect of the plant on hepatic and renal damage. Consequently, the CCl_4 rat model of hepato-renal toxicity was used to evaluate the protective effect of ethanol extract of *Acrostichum aureum* in the liver and kidney.

Materials and Methods

Chemicals
The CCl_4, 2-thiobarbituric acid, 1-chloro-2,4-dinitrobenzene, and reduced glutathione (GSH) were sourced from Sigma-Aldrich Co, St Louis, USA. The biochemical assay kits were obtained from Cobas Diagnostics (Mannheim, Germany). Other reagents used were of analytical grade and produced by standard Biotech companies.

Collection of plant materials and extract preparation
Fresh leaves of *Acrosticum aureum* were collected in February 2021 from the wild at Lagoon Waterfront, University of Lagos, Lagos State. The plant was authenticated by Dr. G.I. Nodza, an experienced Taxonomist at the herbarium of the Department of Botany, University of Lagos. A voucher specimen (no. 112796) was deposited at the herbarium. The leaves were thoroughly cleaned with water and air-dried in a shady room for 4 weeks. Dried leaves were milled into a powdered form using a laboratory blender and extracted as previously described.[36]

Animal Husbandry and Experiment Protocol
The study was conducted with forty-eight, 12-weeks-old healthy male Sprague Dawley rats with an average weight of about 140 g. They were purchased after physical and behavioral veterinary examination at the Department of Physiology, University of Ibadan, Ibadan, Nigeria. The rats were housed under standard conditions prescribed in the guidelines for the use of laboratory animals for experiments[37] at the institutional Animal Holding Facility and ethical permission was obtained before the commencement of the studies (FMCA/470/HREC/02/2022/18). The ARRIVE guideline was adopted for reporting the study.[38] The rats were fed with commercially available rat chow (Top Feeds Nigeria Limited) and clean water ad libitum. A week after acclimatization; the rats were separated into eight groups of six rats each and treated with corn oil, 10 mg/kg body weight quercetin, 50 mg/kg body weight of Ethanol leaf extract of *A.aureum* (ELAA), 100mg/kg body weight of ELAA, 1 ml/kg body weight of carbon tetrachloride (CCl_4) , 10 mg/kg body weight quercetin + 1 ml/kg body weight CCl_4, 50 mg/kg body weight of ELAA + 1 ml/kg body weight CCl_4, 100 mg/kg body weight of ELAA + 1 ml/kg body weight CCl_4

The CCl_4 was given intraperitoneally twice every week, while ELAA was fed orally once daily for three weeks. The rats were placed on an overnight fast after the last treatment and euthanized by cervical dislocation. Before euthanasia, the final weights of the rats were taken and blood was collected from the retro-orbital plexus of each rat anesthetized with 45 mg/kg ketamine and 5 mg/kg xylazine into tubes containing heparin. The tubes were spun for 15 minutes at 3000 X g to separate the plasma supernatant that was used for the evaluation of liver and kidney health biochemical parameters. In addition, the liver and kidney were harvested from all the sacrificed rats, washed in saline, and blotted with filter paper. Both organs were weighed and organ-somatic indices were determined. Subsequently, a portion of the liver and right kidney were processed for the evaluation of oxidative stress markers, while the remaining portion of the liver and left kidney were saved for pathological examination.

Determination of plasma biochemistry parameters
The biochemical indices were determined using assay kits from Cobas Diagnostics (Mannheim, Germany) following the manufacturer's instruction on a Roche/Hitachi C311 chemistry analyzer (Mannheim, Germany). The markers determined assayed were alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, urea, total protein, albumin, sodium ion (Na^+) and chloride (Cl^-).

Determination of liver and kidney oxidative stress indices
A portion of the liver and right kidney obtained from each rat were weighed and homogenized in 5 times the volume of their weight in cold 50 mM Tris-HCl buffer (pH 7.4) using a Potter Elvejhem homogenizer equipped with a Teflon pestle. The homogenates were centrifuged for 15 minutes at 12000 X g in a Himac CR21G cold centrifuge (Hitachi Co Ltd, Japan). The supernatant was decanted and used for the spectrophotometric determination of oxidative stress markers. A Uniscope SM7504 UV (Surgified Medicals, England) was employed for the assessment of oxidative stress parameters. Lipid peroxidation was measured as malondialdehyde (MDA) was determined following the method of Esterbauer and Cheeseman.[39] The method of Sun and Zigma[40] was employed to measure SOD activity. The GST activity was evaluated based on the method previously described by Habig *et al*[41], while the activity of GPx was assessed according to Rotruck *et al.*[42]

Histopathology Examination
The remaining portion of the liver and left kidney saved for pathological examination were kept in ten percent neutral buffered formaldehyde. Both organs were dehydrated in graded ethanol and embedded in paraffin blocks as previously described.[43] The blocks were cut into 3-4 µm thick sections and stained with hematoxylin and eosin (H/E). A light microscope was used to examine pathological changes in the sections.

Statistical Analysis
Data were displayed as averages and standard errors of the average. They were analyzed by one-way analysis of variance (ANOVA) using the 17th version of SPSS. For each parameter, the variation between the average of the control and test groups was assessed using the Duncan Multiple Range Test. The level of significance was set at $p < 0.05$.

Results and Discussion

The liver and kidney are targets of CCl_4 toxicity, primarily due to their involvement in its metabolism and elimination from the body. The CCl_4 toxicity in both organs is associated with oxidative stress and damage to cellular components.[7,10-11] In the current study, the CCl_4-induced model of hepato-renal injury was used to assess the anti-oxidative and protection offered by ELAA in rats. *Acrostichum aureum* is one of the local medicinal plants that have been used as remedies for various human diseases including gastrointestinal diseases.[44] The results showed that ELAA has potential *in vivo* antioxidant and protective effects against CCl_4-induced injury in the

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liver and kidney as evidenced by the reduction of organo-somatic indices, oxidative stress, and amelioration or inhibition of hepato-renal lesions in treated rats.

The effect of the different treatments on hepato-renal weight and relative weight is presented in Figure 1. Injection of CCl_4 significantly increased LWT ($p< 0.01$) and RLW ($p< 0.001$) when compared to the control. The values obtained for both parameters were reduced by the co-treatment with either of the two doses of ELAA or quercetin. The KWT values were similar across groups, while RKW was significantly ($p < 0.01$) increased in the CCl_4-treated group. The RKW values were dose-dependently reduced in the ELAA co-treatment groups. In addition, quercetin also reduced the RKW to a similar degree as 100 mg/kg ELAA. The RKW of the groups that were administered quercetin or the two doses of the ELAA were similar to the control. The increase in relative organ weight observed in the CCl_4-treated group is suggestive of hepato-renal injury and inflammation. Following CCl_4-induced hepatic injury, inflammatory cells are recruited into the liver,[45] and this may be responsible in part for the increase in LWT, RLW, and RKW in the CCl_4-treated. This study's increase in LWT and RLW study is similar to that of a recent report in a mice model of CCl_4-hepato-renal toxicity.[46] The protective effect of ELAA was, however clearly demonstrated by the dose dependently-reduction in absolute and relative hepato-renal weights.

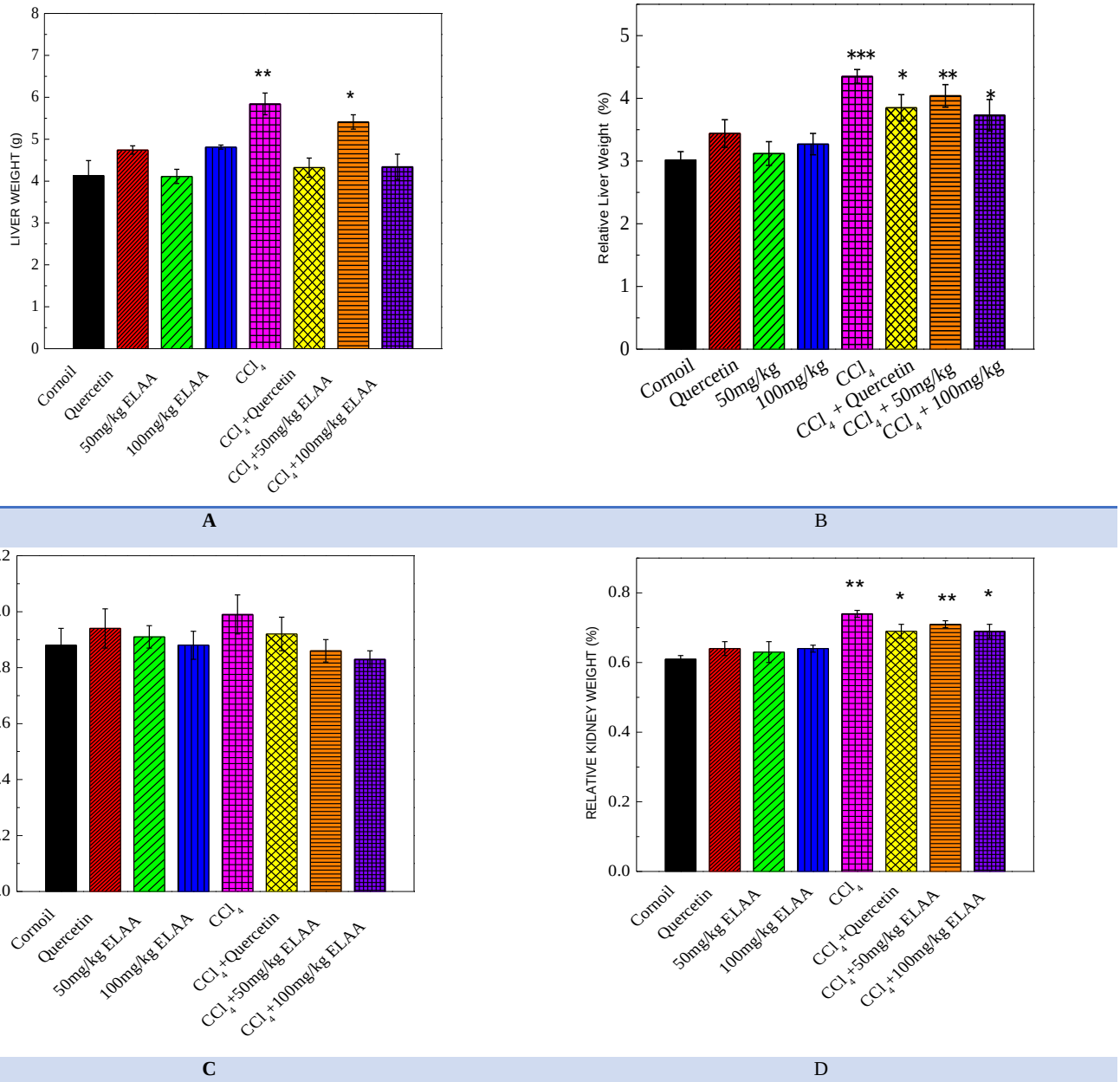

Figure 1: The effects of ELAA on organ weight indices in rats exposed to CCl_4 and ethanol leaf extract of *Acrostichum aureum* (A) Liver weight (B) Relative Liver (C) Kidney Weight (D) Relative Kidney Weight.
*Significantly different from control at $p < 0.05$,*Significantly different from control at $p < 0.01$. ***Significantly different from control at $p < 0.001$

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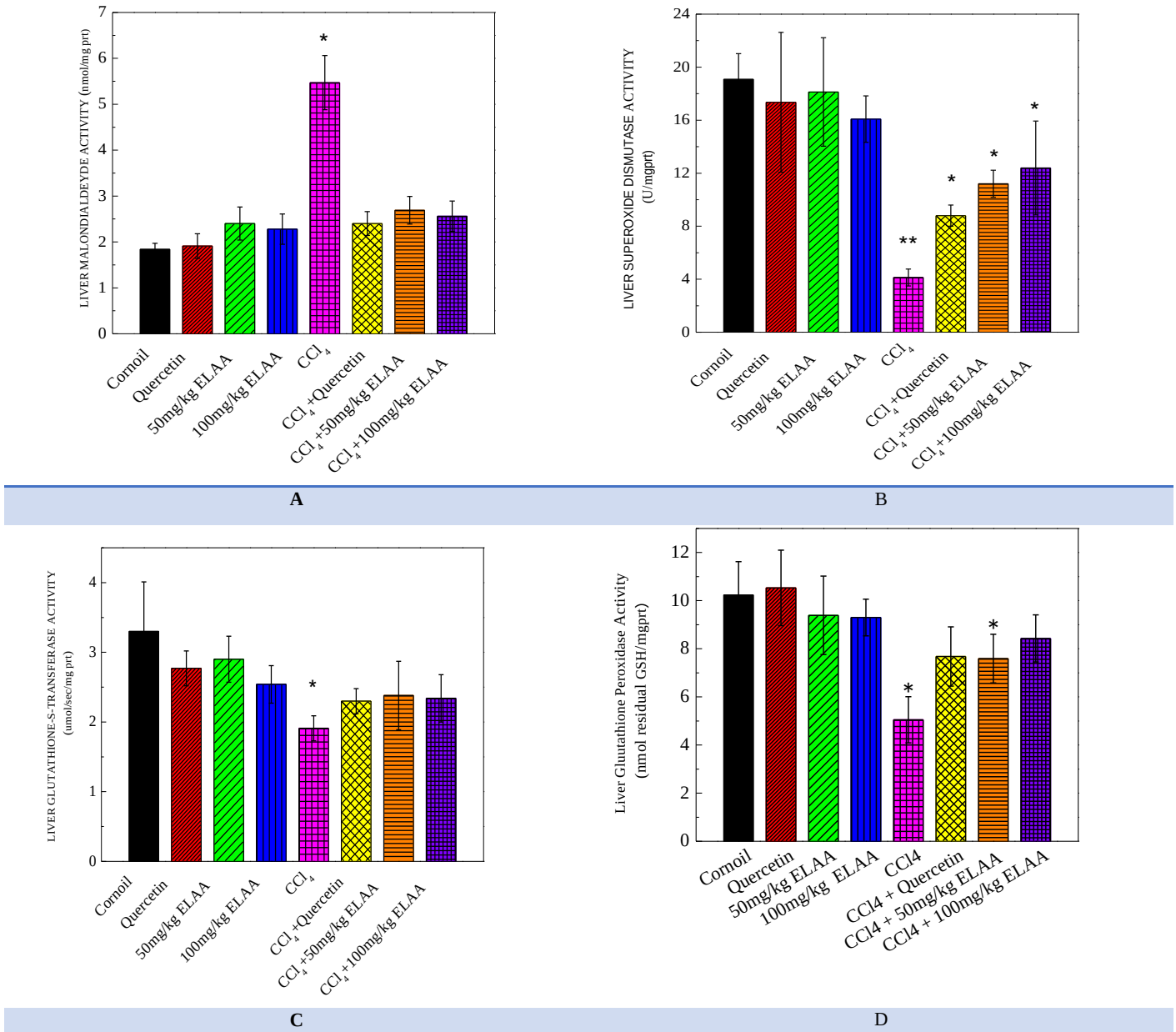

Figure 2: Liver oxidative stress parameters in test and control rats. (A) Malondialdehyde (B) Superoxide peroxidase (C) Glutathione –S-transferase (D) Glutathione Peroxidase
*Significantly different from control at p <0.05,*Significantly different from control at p <0.01

The effects of the administration of ELAA or quercetin on the hepato-renal lipid peroxidation and oxidative stress maker enzymes following treatment with CCl_4 are presented in Figures 2 and 3. According to the results, CCl_4 significantly ($p< 0.05$) increased MDA levels in both the liver and kidney when compared to the control. In contrast, co-administration with 50 and 100 mg/kg ELAA dose-dependently reduced MDA. A similar reduction of MDA level was observed for quercetin co-treatment. The SOD, GPx, and GST activities in both the liver and kidney were however significantly reduced following CCl_4 treatment as compared to the control. Supplementation with the two doses of ELAA or quercetin enhanced the activities of the enzymes and returned them toward control value. Meanwhile, the values obtained for lipid peroxidation and antioxidant parameters in the groups that were exposed alone to each of the two doses of ELAA or quercetin were comparable to the control. In the liver and kidney, CCl_4 is metabolically biotransformed primarily by CYP2E1 into trichloromethyl radical ·chloromethane, dichlorocarbene, and trichloromethyl peroxyl radicals.[3-5] These radicals can either bind directly to tissues or initiate a cascade of free radical-mediated reactions leading to lipid peroxidation. Therefore, the elevation MDA observed in the CCl_4-treated group is a manifestation of CCl_4-induced lipid peroxidation. Similar results are well documented in recent reports.[7,45-6] During lipid peroxidation, cellular antioxidant and detoxification systems including SOD, GPX, and GST are intrinsically activated to counter lipid peroxidation. However, CCl_3 and CCl_2 radicals are capable of binding and inhibiting these antioxidants. Therefore, the decrease in antioxidant enzymes, SOD, GPX, and GST in the CCl_4-treated groups could be due to the overwhelming effects of oxidants and their inhibitory actions on antioxidant defense in both tissues during CCl_4 intoxication. The observed decrease in the antioxidant enzymes is in accord with previous studies.[47-8] However, ELAA retarded lipid peroxidation and augmented antioxidant enzymes against CCl_4 intoxication as displayed by the reduction of MDA together with enhancement of SOD, GPX, and GST activities in both the liver and kidney in a similar fashion to quercetin that was

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used as the standard drug in this study. A prior study showed that water extract of *Acrostichum aureum* exerted an antioxidant effect against ethanol-induced gastric ulcers in rats[31] and our current findings are consistent with it. Thus demonstrating that the decline in MDA and up-regulation of SOD, GPX, and GST in the groups treated with ELAA and CCl_4 could be attributed to the antioxidant potential of ELAA.

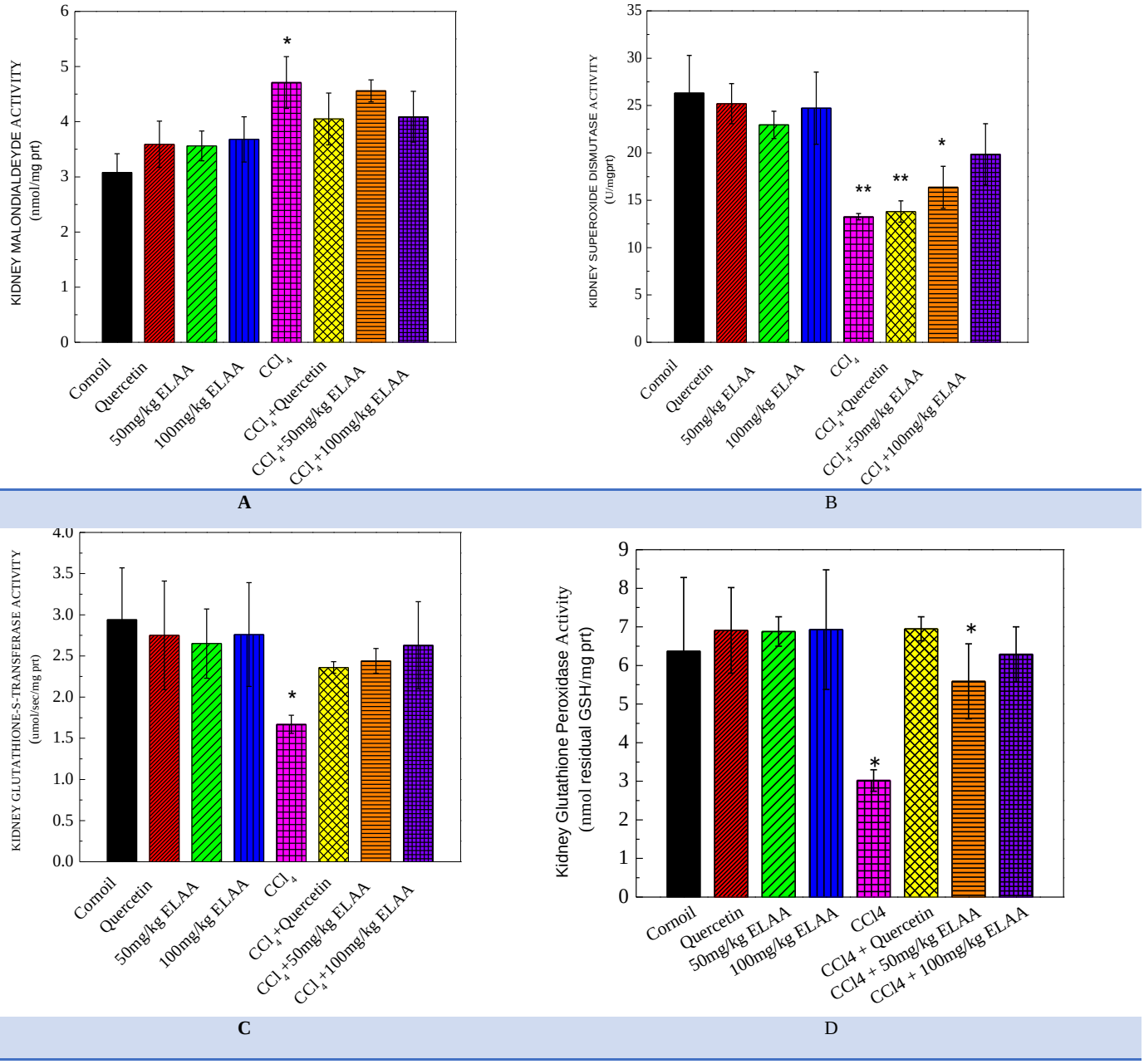

Figure 3: Kidney oxidative stress parameters in test and control rats. (A) Malondialdehyde (B) Superoxide peroxidase (C) Glutathione –S-transferase (D) Glutathione Peroxidase.
*Significantly different from control at p <0.05, *Significantly different from control at p <0.01,

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The results of the hepato-renal function/health biomarkers presented in Figure 4 showed that CCl_4-administration resulted in significant increases in serum ALT (51.53%), AST (41.03%), bilirubin (47.00%) and creatinine (81.4%) as compared to the control. Co-treatment with 50 and 100 mg/kg ELAA dose-dependently reduced ALT activity to 48.59 and 7.9% respectively, while quercetin reduced ALT to 1.67% when compared to the control. Similarly, AST was decreased to 5.68, 9.37, and 4.53% in the groups supplemented with quercetin, 50 and 100 mg/kg ELAA respectively as compared to the control. In addition, bilirubin level was reduced to 37.30% and 32.12% respectively in the 50 and 100 mg/kg ELAA co-treatment groups, while quercetin reduced it to 38.86%. Creatinine values were reduced to 42.67% and 33.90 % by 50 and 100 mg/kg ELAA co-administration respectively, whereas it was reduced to 33.33% by quercetin co-administration. The Na^+ and Cl^- were significantly reduced by 5.79 and 7.05% respectively in the CCl_4-administered group. In contrast, serum Na^+ was improved slightly to 3.68% and 2.98% in the 50 and 100 mg/kg ELAA co-administration groups. Enhancement of lipid peroxidation and inhibition of enzymes, otherwise known as oxidative stress could lead to alteration of membrane permeability, loss of membrane integrity, and cellular damage in both the liver and kidney. Consequently, hepato-cellular contents including liver health and function markers are leached into the bloodstream. The rise in blood AST and ALT may therefore be indicative of CCl_4-induced damage and impairment of hepatic function. Similarly, the high blood bilirubin in the CCl_4-treated rats is suggestive of impairment of bilirubin conjugation and excretion.

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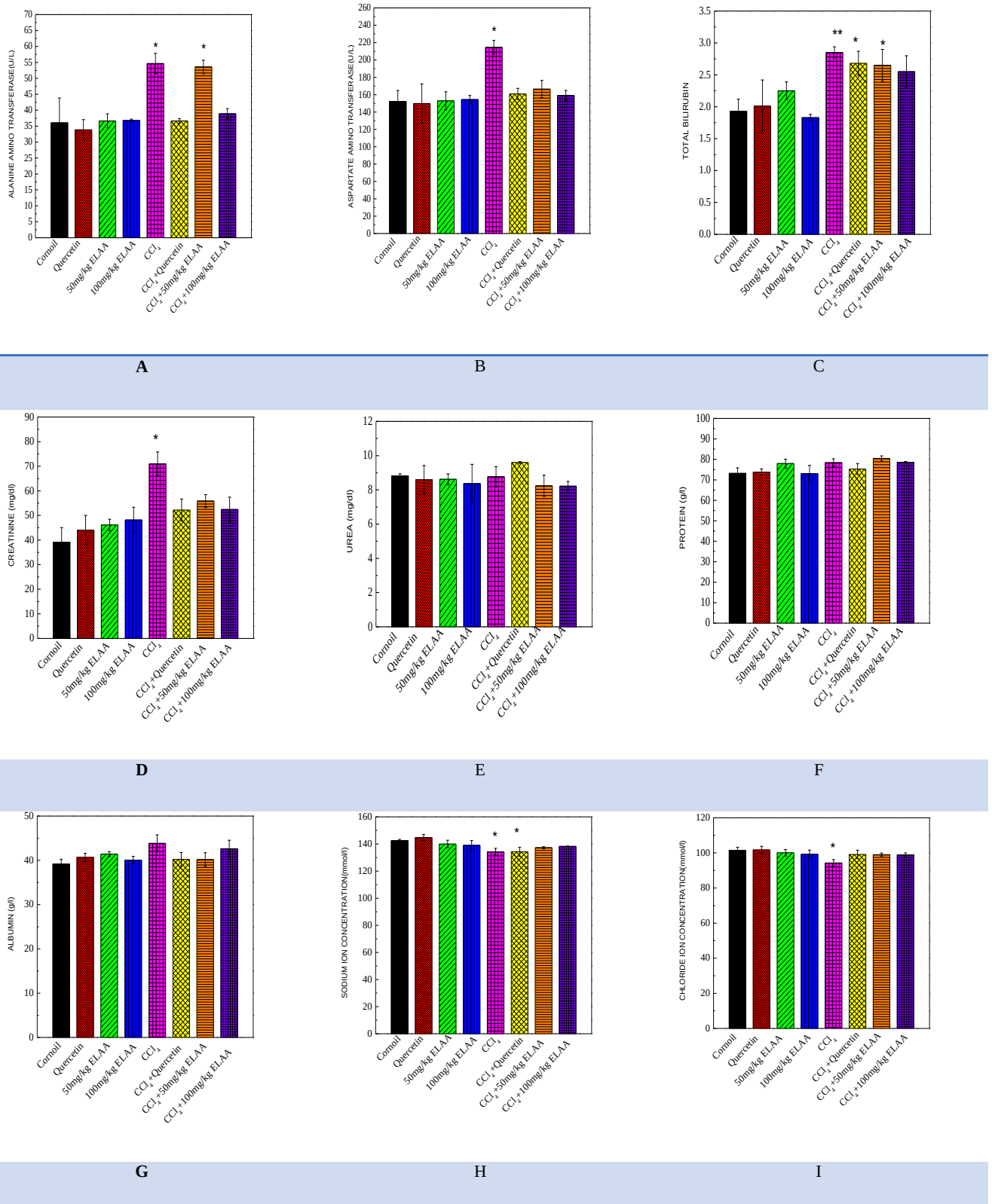

Figure 4: Effect of ethanol leaf extract of *Acrostichum aureum* on CCl_4-induced alteration of liver and kidney health parameters. (A) Alanine aminotransferase (B) Aspartate aminotransferase (C) Bilirubin (D) Creatinine (E) Urea(F) Total protein (G) Albumin (H) Sodium ion (I) Chloride ion.
*Significantly different from control at $p < 0.05$,*Significantly different from control at $p < 0.01$

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The surge in markers of hepatic injury and function in the current study is supported by recent reports.[48-9] The rise in creatinine and reduction of Na^+ and Cl^- may be indicative of CCl_4–induced toxicity in the kidney.

Related findings have been documented by Ujowundu *et al*[50] and Wang *et al*[51]. However, ELAA seems to modify liver health and function as demonstrated by the reduction of ALT, AST, and bilirubin concentration in groups co-administered CCl_4 and ELAA. Similarly, the reversal of creatinine, Na^+, and Cl^- towards the control levels by the co-treatment with ELAA may be indicative of the protective effect of ELAA in the kidney. The protection offered by ELAA against CCl_4-induced alteration of renal and hepatic health markers in this study suggests that extract possesses membrane stabilizing and/ or repairing properties.

The effect of ELAA on the pathological changes caused by CCl_4 intoxication in the liver is displayed in Figure 5. No apparent pathological lesions were observed in the hepatic histo- architecture of the rats that received corn oil, quercetin, and each of the two doses of ELAA alone (A-D). However, the group administered CCl_4 only had severe bridging hepatocellular swelling (arrowhead), necrosis (black arrows), kupffer cell hyperplasia (blue arrows), and inflammation (red arrows) (E) Quercetin ameliorated the effect of CCl_4 as treated rats showed attenuated hepatocellular swelling (arrowhead), necrosis (black arrow) and inflammation (red arrows) (F). Similarly, ELAA dose-dependently reduced the degree of CCl_4-induced hepatic lesion as evidenced by random hepatocellular necrosis with kupffer cell hyperlasia (blue arrow) in the 50 mg/kg ELAA co-treatment group (G) and moderate portal inflammation (red arrow) in the 100 mg/kg ELAA co-treatment group (H).

The results of the pathological examination of the kidney presented in Figure 6 showed no observable lesson in the kidney of the groups treated alone with corn oil, quercetin, 50 mg/kg, and 100 mg/kg of ELAA (A-D). However, the group administered CCl_4 only presented with foci of tubular necrosis (black arrows) and glomerular tuft, hyperplasia (black arrows) (E). Co-treatment with quercetin prevented CCl_4-induced lesions in the kidney (F), while 50 mg/kg of ELAA co-treatment showed random tubular atrophy and necrosis (black arrows) (G). The renal histo-architecture of the group co-treated with 100 mg/kg of ELAA showed no observable lesion (H). Lesions observed in CCl_4-treated group confirmed the toxicity of CCl_4 to the liver and kidney. Many of the lesions are oxidative stress-related and are risk factors for many diseases including hepatocellular and renal cancers. The observed attenuation of hepatic and inhibition of renal lesions by ELAA similar to quercetin may not be unrelated to its ability to stem down lipid peroxidation and boost antioxidant enzyme defenses against CCl_4–induced toxicities.

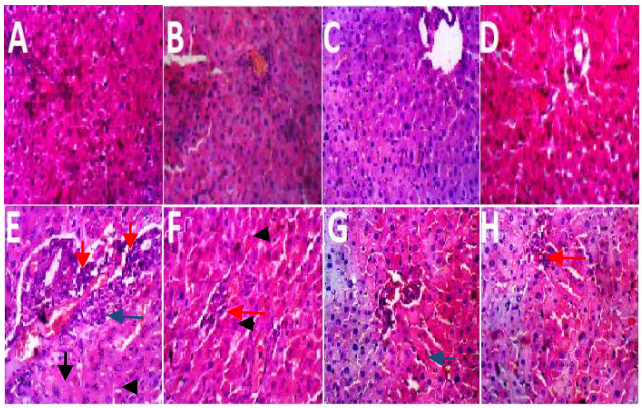

Figure 5: Amelioration of CCl_4-induced hepatic damage by ethanol leaf extract of *Acrostichum aureum* in rats (H&E). Liver sections in the groups treated with corn oil (A), quercetin (B), 50 mg/kg ELAA (C), 100 mg/kg ELAA (D) (E) CCl_4, CCl_4 + quercetin (F) CCl_4 + 50 mg/kg (G) CCl_4 + 100 mg/kg (H).

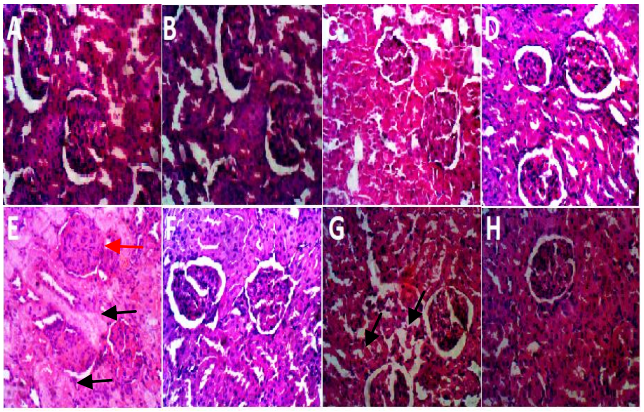

Figure 6: Prevention of CCl_4-induced renal damage by ethanol leaf extract of *Acrostichum aureum* in rats (H&E). Renal sections in the groups treated with corn oil (A), quercetin (B), 50 mg/kg ELAA (C), 100 mg/kg ELAA (D) (E) CCl_4, CCl_4 + quercetin (F) CCl_4 + 50 mg/kg (G) CCl_4 + 100 mg/kg (H).

The benefits of ELAA in protecting against CCl_4-induced oxidative stress and hepato-renal toxicity could be due to its rich content of phytochemicals including lignans, sterols, flavonoids, and phenolic compounds.[20,26,29] Some of these compounds suppress ROS production and boost antioxidant defense mechanisms *in vitro* and animal models. For example, kaempferol, quercetin, and quercetin-3-O-β-D-glucoside[30] which are present in the plant,[30] exert protective action against oxidative damage in the liver and kidney.[51-52] Moreover, pinoresinol-4-*O*-glucoside isolated from *A.aureum* by Minh et al[26] possesses antioxidant activity and was shown to reduce serum ALT and AST activity in a CCl_4 model of hepatoxicity.[53] In addition, β-sitosterol and lupeol identified in *Acrostichum aureum* by Basyuni et al[27] were recently shown to exert hepatoprotective effects in different models of hepatoxicity.[54-5]

Conclusion

Our findings suggest that ethanol extract of *Acrostichum aureum* protects against oxidative stress and hepato-renal injury caused by CCl_4 intoxication. *Acrostichum aureum* could therefore be a potential therapeutic agent for managing hepato-renal injury. However, further studies are required to isolate the active principles in the plant.

Conflict of Interests

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

Mr. W.A. Yusuf is appreciated for his effort in the management of the rats used in this study

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