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Hepatoprotective Effect of Aqueous Extract of *Solanum macrocarpon* Leaves against Carbon tetrachloride-Induced Liver Damage in Rats

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ABSTRACT

Liver damage is a growing concern of today's modern society. The increasing incidence of exposure to toxic agents has contributed to liver diseases. There is therefore need for hepatoprotective agents. This study was aimed at investigating the protective effect of aqueous extract of the leaves of *Solanum macrocarpon* against CCl_4-induced liver damage in rats. Six groups of four animals each were used for the investigation. Group 1 served as control, groups 2, 3 and 4 animals were pre-treated with leaf extract of *Solanum macrocarpon* at 250mg/kg, 500mg/kg and 750mg/kg body weight respectively for 14 days prior to a single intraperitoneal administration of CCl_4. Animals in groups 5 and 6 received only the extract at a dose of 750mg/kg body weight and CCl_4 respectively. All animals were sacrificed 24 h after the administration of CCl_4. The liver functions tests were performed in addition to their histopathological evaluation. Results obtained showed significant adverse changes in the levels of all measured parameters in CCl_4 treated rats. However, pre-treatment with aqueous extract of *S. macrocarpon* prevented the adverse changes. Our findings suggest that *S. macrocarpon* protects the liver against CCl_4-induced damage. This could be attributed to the presence of phytochemical compounds in the plant.

INTRODUCTION

Exposure to carbon tetrachloride (CCl_4), a well-known hepatotoxin, is known to induce oxidative stress and causes liver injury by the formation of free radicals. Free radical-induced lipid peroxidation is one of the major causes of cell membrane damage which leads to a number of pathological conditions (Slater, 1984; Oberley, 1988; Halliwell, 1993). Therefore, there is a great need for the development of agents with potent antioxidant effect against the $CC1_4$ – induced tissue pathology. Studies showed that various plant extracts could has the potential to protect organs against CCl_4 - induced oxidative stress by altering the levels of increased lipid peroxidation as well as enhancing the decreased activities of antioxidant enzymes (Rajesh and Latha, 2004). *Solanum macrocarpon* is an important medicinal plant with rich source of nutritional and medicinal constituents. It is widely cultivated in West Africa where it serves as an important fruit and leaf vegetable. The leaves are considered very nutritious and are used in preparing soups and stews. The leaves were known to be rich in protein, fat, crude fiber, calcium and zinc (Oboh *et al*., 2005). Bukenya-Ziraba and Bonsu reported that the leaves have a variety of medicinal uses such as in Sierra Leone for the treatment of throat problems; in Kenya, for the treatment of stomach problems (Bukenya-Ziraba and Bonsu, 2004). The fruit or the leafy part of the plant was reported to be used for the treatment of constipation, ulcers, tooth ache and the leaves as snake bite remedy (Oladiran, 1989). The leafy part of *Solanum macrocarpon* was effective for treatment of skin disease, infections and sores when applied to the infected areas (Edijala *et al*., 2005). Generally, the plant has been used as indigenous medicine for the treatment of several ailments such as asthma, allergic rhinitis, nasal catarrh, skin infections, rheumatic disease and swollen joint pains, gastro-esophageal reflux disease, constipation, dyspepsia and also in weight reduction (Dalziel, 1937). The aqueous fruit extract of the plant was reported to exhibit lipid lowering activities as well as renal and hepatoproptective effects in diet-induced hypercholesterolemic rats (Sodipo *et al*., 2009a,b; Sodipo *et al*., 2009c, 2011b).

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The plant was also shown to improve hematological parameters in hypercholesterolemic and triton-induced hyperlipidemic rats (Sodipo *et al*., 2011b). The leaves of *S. macrocarpon* have also been revealed to contain high phenolic and flavonoid content, thus possessing a potent antioxidant activity which can offer good protection against oxidative damage to some body tissues (Adewale *et al*., 2014). The aim of this study was to evaluate the protective potential of aqueous extract of the leaves of *Solanum macrocarpon* against CCl_4-induced liver damage in rats. To the best of our knowledge, this study provides first line of information that aqueous extract of the leaves of *S. macrocarpon* at different doses could be effective in preventing hepatic insufficiency occasioned by CCl_4-intoxication. This is particularly important since traditional consumption of *Solanum macrocarpon* is usually by aqueous medium.

MATERIALS AND METHODS

Plant collection, Identification and Extraction

The leaves of *Solanum macrocarpon* were obtained from Bisi market in Ado-Ekiti, Ekiti State, and were authenticated at the Department of Plant Science, Ekiti State University, Ado-Ekiti, Nigeria. The voucher specimen of the plant is available and a sample of the plant leaf was deposited at the Departmental Herbarium for future reference. The leaves were air-dried, blended and soaked in distilled water for 24 h. It was then filtered using Whatman filter paper no. 1 and the filtrate was concentrated at 50ºC using the rotary evaporator, following which it was dried by means of a freeze dryer. The extract was administered orally using gavage according to the required doses of 250, 500 and 750 mg/kg body weight for 14 days.

Chemicals

All chemicals and reagents used were of analytical grade while the water was glass distilled.

Experimental animals

Twenty-four female albino rats of Wistar strain weighing between 120 - 180 g purchased from the central animal house of Afe Babalola University, Ado-Ekiti were used for the study. The animals were housed in cages under laboratory conditions in the departmental animal house and were acclimatized for 14 days before starting experiments. They were provided with standard pelleted feed and water *ad libitum*. After acclimatization period, the animals were divided into groups. All animal procedures were in strict accordance with the Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press, Washington, DC, USA, 2011). All animal experiments were approved by the animal care committee of Afe Babalola Research Center, Ado-Ekiti.

Grouping of animals

Six groups of four rats each were studied; Group 1 served as normal control; Groups 2, 3 and 4 were pretreated with aqueous extract of *Solanum macrocarpon* at doses of 250mg/kg, 500mg/kg and 750 mg/kg body weight for 14 days respectively prior to CCl_4 administration. Groups 5 and 6 received only 750mg/kg extract and CCl_4 respectively.

Administration of CCl_4 was done after 14 days of *Solanum macrocarpon* treatment and following an overnight fast. Animals were sacrificed 24hours after CCl_4 administration. The extract was administered orally using gavage according to the required doses.

Administration of CCl_4

Where necessary, each animal received 3 ml/kg body weight of a 1:1 preparation of CCl_4 and groundnut oil (in the ratio 1:1). Administration of CCl_4 was by a single intraperitoneal injection. Administration was done after 14 days day treatment with *S. macrocarpon*, and following an overnight fast.

Preparation of plasma and liver homogenate

The rats were sacrificed 24 h after CCl_4 administration by cervical dislocation and then dissected. Blood samples were collected from the heart using the heart puncture technique. Blood was collected in heparinized bottles. The blood samples were subsequently centrifuged at 3000 x *g* for 10 min using a bench centrifuge to obtain plasma. The plasma obtained was separated, and transferred into fresh plain sample bottles and used for the subsequent biochemical analyses. The liver of each animal was excised immediately after sacrifice. They were rinsed in ice-cold 1.15% potassium chloride, blotted with filter paper and weighed. Weighed portions were minced with scissors in 4ml of ice-cold 0.1M phosphate buffer, pH 7.4 and homogenized in a Potter-Elvehjem homogenizer.

The homogenates were later centrifuged using refrigerated centrifuge at 12,000 x *g* for 15 min at 4^{o}C to obtain clear supernatant, which was used for subsequent biochemical analyses.

Biochemical analyses

Biochemical analyses carried out includes measurement of the activities of plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT or GGT) and alkaline phosphatase (ALP); plasma total protein and albumin concentrations. The determination of the concentrations of these biochemical parameters was done using commercially available test kits, products of Randox Laboratories (Crumlin, United Kingdom).

Antioxidant assays

Lipid peroxidation was assessed by measuring the formation of thiobarbituric (TBA) reactive substances according to the method described by Varshney and Kale, (1990). Catalase (CAT) activity was determined according to the method of Sinha, (1972). Superoxide dismutase (SOD) activity was measured as described by Misra and Fridovich, (1972).

Histopathological assessment

Liver sections from rats of different groups were fixed in 10% neutral formalin solution, dehydrated in graded alcohol, and embedded in paraffin. Fine sections obtained were mounted on glass slides and counter-stained with hematoxylin-eosin for light microscopic analyses.

To eliminate bias the slides which were coded, examined and photographed by a qualified histopathologist who had no knowledge of the treatment groups.

Statistical analysis

Statistical analysis was done by one-way analysis of variance (ANOVA) using SPSS 16 for windows software package. Post hoc testing was performed for inter-group comparisons using the Least Significant Difference (LSD) test according to the method described by Zar, (1984). In all instances p values < 0.05 were considered statistically significant.

RESULTS

Administration of CCl_4 produced significant toxic effects on the liver, as shown by the data obtained from the parameters investigated (Figures 1 to 3).

Marker enzymes

Figure 1 showed the effect of aqueous extract of the leaves of *Solanum macrocarpon* on CCl_4 - induced changes in some marker enzymes. When compared with the control, CCl_4 treatment gave rise to significant increase ($p < 0.05$) in the marker enzymes such as alanine tansaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). However, pretreatment of rats with aqueous extract of *S. macrocarpon* (AESM) at 250 mg/kg, 500 mg/kg and 750 mg/kg body weight produced a significant decrease in the activities of these enzymes when compared with CCl_4 group. As regards the different pretreatment doses of the extract, there was a significant difference in the activities of ALT, GGT and ALP when compared with 250 mg/kg b.w. dose as shown in figure 1. Treatment with AESM at 750 mg/kg b.w. produced a comparable result with that of the control.

Liver function parameters

Figure 2 showed the effect of aqueous extract of the leaves of *Solanum macrocarpon* on CCl_4 - induced changes in plasma total protein and albumin levels. A significant decrease ($p<0.05$) in the levels of these parameters was observed following a single intraperitoneal administration of CCl_4 when compared with the control group. Pretreatment of rats with aqueous extract of *C. rubens* leaves at 250 mg/kg, 500 mg/kg and 750 mg/kg body weight produced a significant increase ($p<0.05$) in the levels of total protein and albumin when compared with CCl_4 group. There was a significant difference in the level of albumin in the pretreatment group at 250 mg/kg b.w. when compared with both 500 mg/kg and 750 mg/kg b.w. as shown in figure 2.

Antioxidant enzymes and lipid peroxidation

As shown in figure 3, intraperitonal administration of CCl_4 resulted in marked hepatic injury as revealed by significant decrease ($p<0.05$) in the activities of antioxidant enzymes (SOD and catalase) and significant increase ($p<0.05$) in the level of MDA respectively when compared with the control group. Pre-treatment with the leaves extract of *S. macrocarpon* at all the three dose levels (250 mg/kg, 500 mg/kg and 750 mg/kg b.w.) resulted in a significant increase ($p<0.05$) in the activities of these enzymes and prevented the observed peroxidation when compared with the toxicant group. A significant difference was observed in these parameters during the pretreatment with the lower dose when compared with the higher doses as shown in figure 3. Treatment of rats with 750 mg/kg b.w. extract produced a non significant difference in these parameters as compared with the control group.

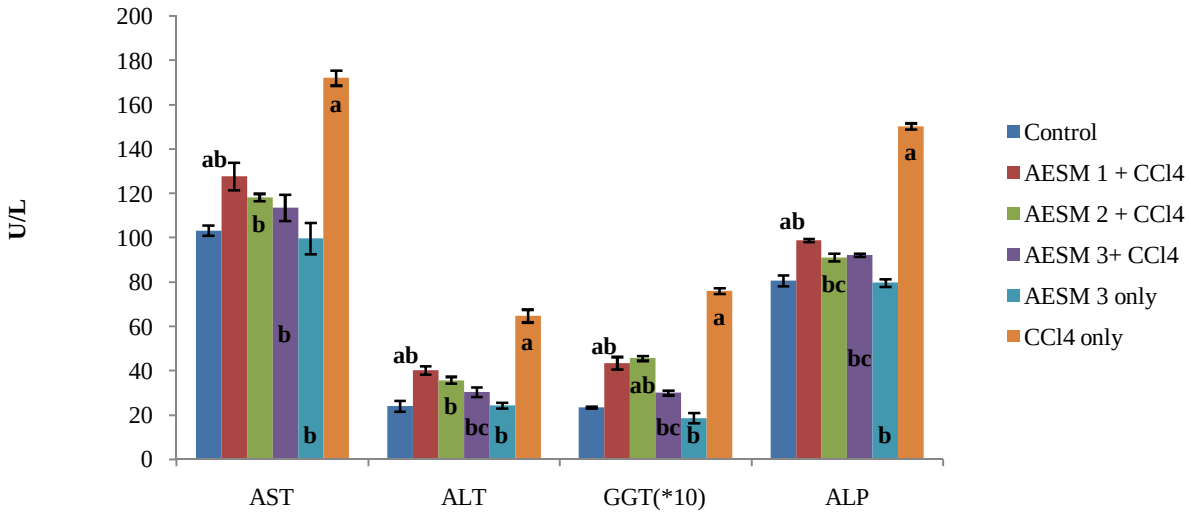

Fig. 1: Effect of aqueous extract of *Solanum macrocarpon* on CCl_4-induced changes in the plasma in ALT, AST, GGT and ALP. AESM 1, AESM 2 and AESM 3 are the pretreatment doses of aqueous extract of *Solanum macrocarpon* at 250mg/kg, 500mg/kg and 1000mg/kg body weight respectively. Values are expressed as Mean ± SEM (n=4) [a]p< 0.05 when compared with Control group; [b]p<0.05 when compared with CCl_4 group; [c]p< 0.05 comparison among the pretreatment groups.

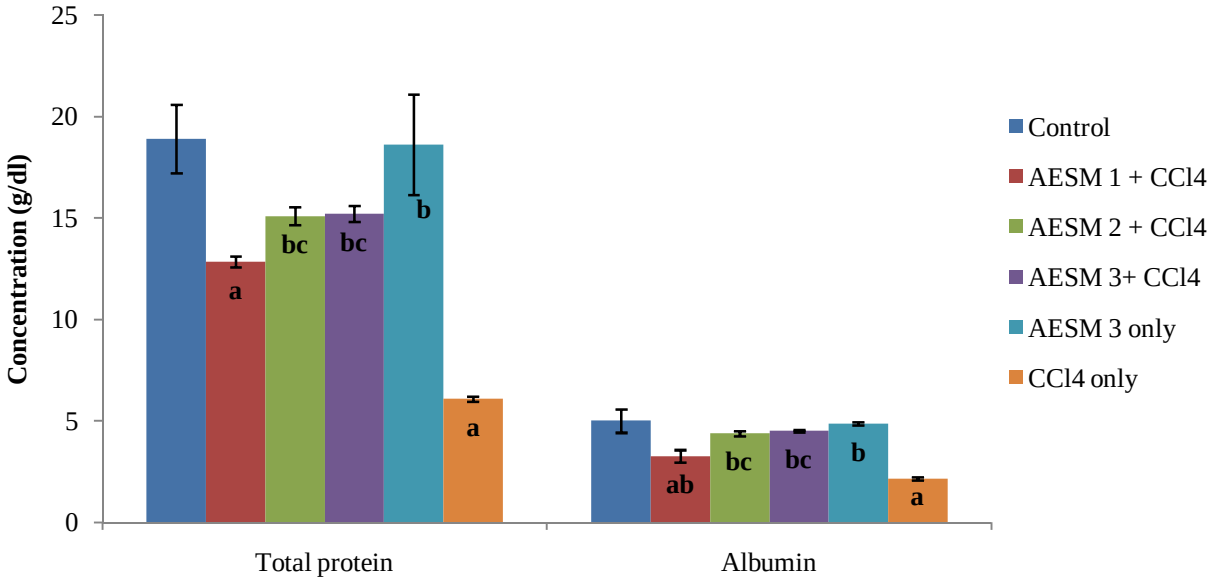

Fig. 2: Effect of aqueous extract of the fruits of *Solanum macrocarpon* on CCl_4 - induced changes in plasma total protein and albumin levels. AESM 1, AESM 2 and AESM 3 are the pretreatment doses of aqueous extract of *Solanum macrocarpon* at 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight., Values are expressed as Mean ± SEM (n=4)., $^{a}p< 0.05$ when compared with Control group; $^{b}p<0.05$ when compared with CCl_4 group; $^{c}p< 0.05$ comparison among the pretreatment groups

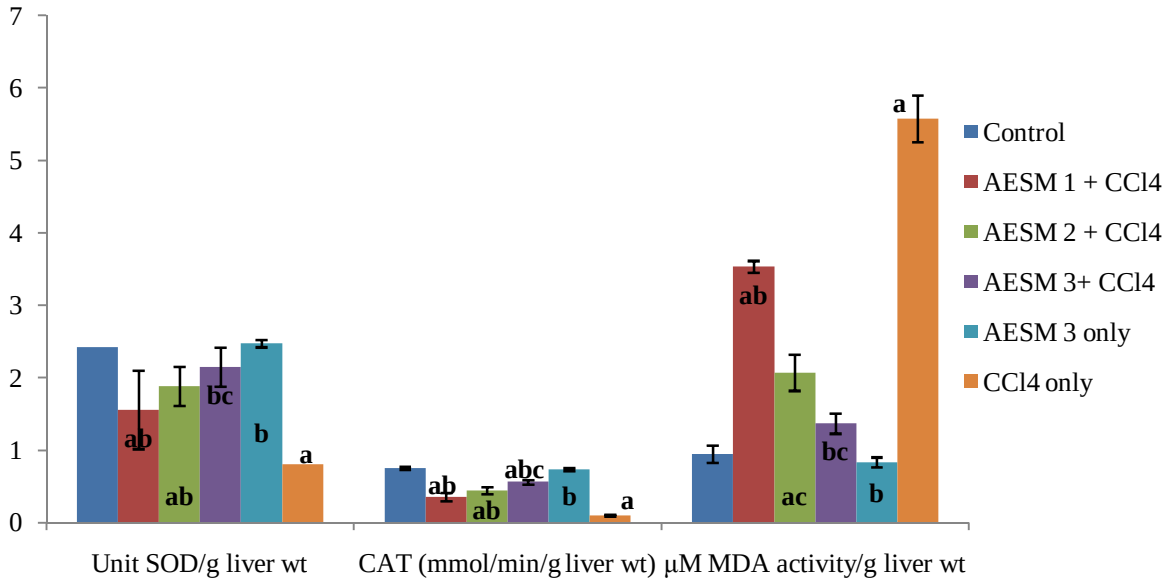

Fig. 3: Effect of aqueous extract of *Solanum macrocarpon* on carbon tetrachloride (CCl_4) induced changes in liver superoxide dismutase (SOD) activity, catalase (CAT) activity and malondialdehyde (MDA) level. AESM 1, AESM 2 and AESM 3 are the pretreatment doses of aqueous extract of *Solanum macrocarpon* at 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight Values are expressed as Mean ± SEM (n=4) $^{a}p< 0.05$ when compared with Control group; $^{b}p<0.05$ when compared with CCl_4 group; $^{c}p< 0.05$ comparison among the pretreatment groups.

Histopathology of the Liver

Histopathological examinations as presented in plate 1 revealed that liver section from normal rats showed mild lymphocytic infiltration and no significant lesions (plate 1 (a)). The liver of rats pretreated with 250mg/kg AESM (aqueous extract of *Solanaum macrocarpon*) showed periportal congestion, mild lymphocytic parenchyma infiltration and fragmentation of the hepatocytes with progressive occlusion of the sinusoid (plate 1 (b)). Rats pretreated with 500 mg/kg (plate 1 (c)) and 750 mg/kg (plate 1 (d)) AESM, lymphocytic infiltration with the degeneration of the hepatocytes were observed respectively. However, rats treated with 750 mg/kg dose of the extract showed mild lymphocytic infiltration and no significant lesions (plate 1 (e)). However, evidence of cellular degeneration in the hepatocytes and multiple foci of hepatocellular were seen on sections of rats treated with CCl_4 only (plate 1 (f)).

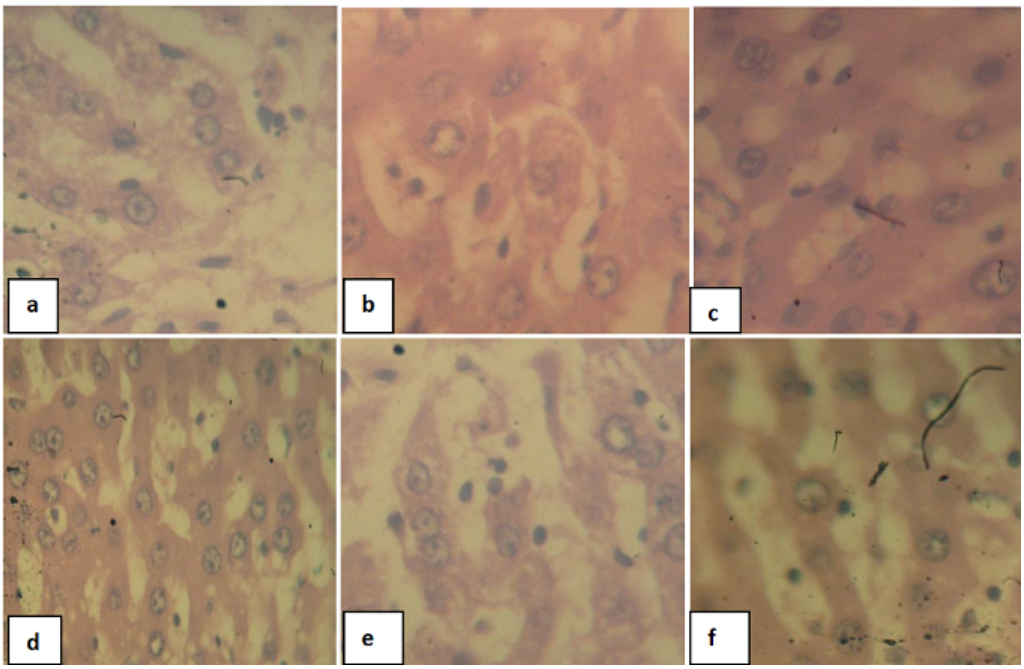

Plate 1: Photomicrograph of rat liver sections (Mag. x 400): (a). Normal control; (b). 250 mg/kg AESM + CCl_4; (c). 500 mg/kg AESM + CCl_4; (d). 750 mg/kg AESM + CCL_4; (e). 750 mg/kg AESM only; (f). CCl_4 only.

DISCUSSION

Hepatotoxicity, an injury to the liver is associated with impaired liver function caused by free radicals derived from oxygen on exposure to drugs, chemical and non-infectious agents (Navarro and Senior, 2006). Various report confirmed that CCl_4 induces hepatic injury by producing free radicals (Tirkey *et al.*, 2005; Yang *et al*., 2008; Lavanya *et al*., 2009). Also, the onset and progression of CCl_4-induced toxicity is tightly linked to the generation of reactive oxygen species (Rechnagel *et al*., 1989). Carbon tetrachloride is now known to be metabolized to a highly reactive intermediate, trichloromethyl radical (CCl_3^*) (Fadhel and Amran, 2002). Trichloromethyl radical and trichloromethylperoxyl radical derived from CCl_4 are known to be involved in a number of deleterious interactions with biological molecules, which includes proteins, lipids and DNA (Packer *et al*., 1978). This is believed to be part of the critical chemical process in the aetiology of CCl_4-induced tissue damage. Increase in the levels of the liver marker enzymes (AST, ALT and GGT) following CCl_4 administration may have resulted from the leakage of these enzymes into the circulation, which may be attributed to the damaged structural integrity of the liver, because these enzymes are located in the cytoplasm (Bilgin *et al*., 2011). Plasma levels of ALT and AST have been shown to be important parameters in the diagnosis of liver damage (Williamson *et al*., 1996; Renugadevi and Prabu, 2010). Liver cells are particularly rich in the transaminases (ALT and AST), as well as alkaline phosphatase and γ-glutamyltransferase. Increased activities of plasma ALP may be due to its increased synthesis in the presence of increasing biliary pressure. Plasma alkaline phosphatase is known to increase as a result of biliary obstruction as seen in cholestatic disease of the liver. GGT is a membrane-bound enzyme and increased plasma level is an indicator of tissue damage (Vasudha *et al.,* 2006). Carbon tetrachloride negatively interferes with protein metabolism probably by inhibiting the synthesis of proteins such as albumin (Iniaghe *et al.*, 2008) which may be attributed to the decreased levels of total protein and albumin observed in this study. The susceptibility of the liver cell to oxidative insult occasioned by CCl_4 can be linked to the failure of the antioxidant mechanism to prevent free radical damage thereby leading to lipid peroxidation and ultimately tissue damage (Morakinyo *et al*., 2012). Lipid peroxidation is a marker of oxidative stress. Evaluation of hepatic antioxidant status in the present study revealed a significantly elevated MDA levels, and a concomitant decrease in the activities of the antioxidant enzymes (SOD and catalase). Thus CCl_4-mediated damage to the liver was secondary to the establishment of oxidative stress.

The ability of the aqueous extract of *S. macrocarpon* leaves to significantly prevent all the observed biochemical lesions is worthy of note. We therefore speculate that the action of the plant extract may revolve around the possibility that the extract effectively down-regulate the amount of CCl_4 or its toxic metabolites reaching the liver.

It may also be possible that *S. macrocarpon* may actually act as a free radical scavenger or quencher, thus preventing the oxidative damage to the cell. Based on the findings from this study, it can be suggested that aqueous extract of the leaves of *S. macrocarpon* in a dose dependent manner holds great hope in preventing liver damage occasioned by CCl_4 toxicity.

CONCLUSION

It is confirmed based on the results of this experiment that free radicals are important in the pathogenesis if CCl_4-induced hepatotoxicity. Therefore, doses up to 750 mg/kg body weight of aqueous extract of the leaves of *Solanum macrocarpon* have been able to prevent the injuries associated with the adverse effect of CCl_4.

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