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ARTICLE

Hepatoprotective effect of the methanol extract of *Luffa cylindrica* fruit on carbon-tetrachloride induced chronic liver injury

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ABSTRACT *Luffa cylindrica* (Linn) commonly called sponge gourds has both medicinal and nutritional properties. It is used traditionally for the management of liver diseases. Herein, we investigated the hepatoprotective effect of the crude methanol extract of *L. cylindrica* fruit in rats chronically exposed to carbon tetrachloride (CCl_4). Male rats were exposed to CCl_4 twice a week for six weeks and the extract was administered five times a week for six weeks. Markers of liver toxicity, antioxidant enzymes and liver peroxidation were evaluated and histological analysis of the liver was carried out. Significant reduction in serum markers (ALT, AST and ALP), increase in antioxidant enzyme and reduction in lipid peroxidation compared to CCl_4 were observed in rats exposed to both CCl_4 and the extract. CCl_4-induced liver lesions were ameliorated by the extract. These show the protective effect of the methanol extract of *L. cylindrica* on CCl_4-induced chronic liver injury in rats.
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Introduction

The liver is a vital organ involved in the detoxification of drugs and toxins, which can also induce liver injury (Liu et al. 2021). Prolonged liver injury leads to hepatic steatosis and fibrosis, further degenerating into life-threatening conditions such as liver cirrhosis, portal hypertension and liver failure (Dhar et al. 2020) which are associated with high morbidity and mortality. Chronic liver injury further drives the neoplastic transformation of the liver (Matsuda and Sek 2020). It is also associated with other chronic pathologies such as decreased kidney function (Targher et al. 2010) and diabetes (Mantovani et al. 2021).

The global prevalence of liver diseases remains high due to the prevalence of viral diseases, and drug and alcohol-induced liver injury. Liver diseases account for about two million death worldwide every year (Asrani et al. 2019). Despite the high burden of liver disorders, no effective therapy for liver diseases exists as the conventional therapies are of limited efficacy (Niu et al. 2021). Hence the need to search for alternatives that are efficient with little or no toxicity. Phytomedicines have shown good potential in this regard, due to their low toxicity and good therapeutic performance.

Luffa cylindrica (Linn) Roem. (syn *Luffa aegyptiaca* Mill) commonly called sponge gourds, is a subtropical vegetable (Cao et al. 2021) with both medicinal and nutritional properties. Its fruits are used in traditional medicine for the management of several diseases including; fever, cough, rheumatism, breast cancer and skin disease (Xinrong et al. 2003, Ismail et al. 2010; Abdel-Salam et al. 2019). The anti-inflammatory (Kao et al. 2012), antioxidant (Hlel et al. 2017), antiproliferative (Hlel et al. 2017; Abdel-Salam et al. 2019), anti-obesity (Zhang et al. 2019) and antigenotoxic (Oyeyemi and Bakare 2013; Atoyebi et al. 2015) effect of the fruits have been reported. It also inhibited atopic dermatitis-like skin lesions (Ha et al. 2015) and SARS-CoV-2 protease (Cao et al. 2021).

Carbon tetrachloride (CCl_4) is a xenobiotic that induces liver injury in humans and animals (Rudnicki et al. 2007), with similar pathology. Exposure to CCl_4 induces liver injury via the production of free radicals which induce lipid peroxidation. The products of lipid peroxidation damage the organelles' membranes, induce inflammation and ultimately damage the liver (Abdelghffar et al. 2022). It is thus an important model to elucidate the mechanisms of action of hepatotoxic agents (Peng et al. 2009) and to screen anti-hepatotoxic and/or hepatoprotective activities

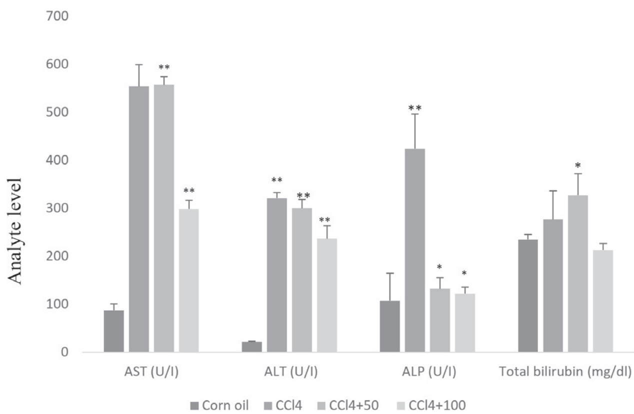

Figure 1. Effect of the methanol extract of *Luffa cylindrica* on serum markers of hepatic injury in rats chronically exposed to carbon tetrachloride. *p < 0.05, significantly different from control (corn oil), **p < 0.01, significantly different from control.

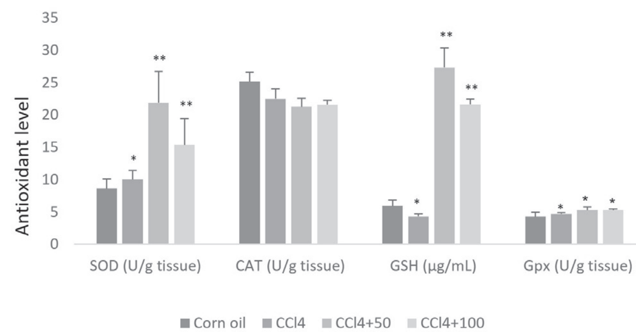

Figure 2. Effect of the methanol extract of *Luffa cylindrica* on hepatic antioxidant enzymes activities in rats chronically exposed to carbon tetrachloride. *p < 0.05, significantly different from control (corn oil), **p <c0.01, significantly different from control.

of drugs (Ranawat et al. 2010).

There have been reports of the hepatoprotective effect of *L. cylindrica* on acute liver toxicity/injury (Sharma et al. 2014). However, there is a limited report on its effect on chronic liver injury. This study is therefore aimed at investigating the hepatoprotective effect of the fruit of *L. cylindrica* in rats exposed to carbon tetrachloride for six weeks.

Materials and methods

Plant collection and extraction

Fruits of *L. cylindrica* were collected from the University of Ibadan premises, Ibadan, Nigeria. The plant was identified and authenticated as earlier reported (Oyeyemi et al. 2015). The fruits were rinsed, sliced, air-dried, and ground to coarse particles. Coarse fruit particles were extracted by maceration in methanol for seven days. The resultant mixture was filtered and the solvent was evaporated using a rotatory evaporator (Rotavapor® R-300, USA) at 40 °C. The residue was kept at 4 °C until use.

Experimental animals

Five to six weeks old healthy Wistar male (121 ± 12) albino rats were obtained from Animal House of the Department of Veterinary Anatomy, University of Ibadan, Nigeria. The animals were maintained as earlier reported (Oyeyemi et al. 2017). All experiments were conducted following the Guidelines for the Care and Use of Laboratory Animals, and the Research Ethics Committee of the University of Ibadan Animal Care and Use approved the study (UI-ACUREC/App/2015/019).

Experimental design

Thirty rats were randomly divided into six groups of five rats each. Group I served as control and was administered corn oil (0.3 mL), group II was administered CCl_4 (1 : 3, CCl_4 : corn oil) alone (Sigma Aldrich, USA, 1 mL/kg), group III received CCl_4 (1 mL/kg) and extract (50 mg/kg) and group IV received CCl_4 (1 mL/kg) and extract (100 mg/kg). CCl_4 was administered intraperitoneally twice a week, whereas corn oil or extract was administered by gavage five times a week for 6 weeks (Oyeyemi et al. 2017). The extract was reconstituted in corn oil and doses were prepared based on body weight.

Preparation of serum and liver homogenates

The rats were fasted overnight after the last dose of extract. Twenty-four hours after the last exposure, rats were weighed, bled by retro-orbital bleeding, sacrificed and liver was collected. Blood was allowed to clot for 30 mins, and centrifuged at 3000 g for 10 min to obtain serum. The liver was quickly excised and washed in ice-cold 1.15% potassium chloride solution to remove blood residues, and was dried, and weighed. A section of the liver (3 g) was homogenized in phosphate buffer at pH 7.4 and centrifuged at 10 000 g to obtain postmitochondrial fraction (PMF) which was used for antioxidant profiling.

Biochemical assays

The activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT). alkaline phosphatase (ALP), and level of total bilirubin (TB) in the serum were determined using Randox diagnostic kits (Randox Laboratory Limited, UK) according to the manufacturer's guidelines. The activity of antioxidant enzymes namely; superoxide dismutase (SOD) (Misra and Fridovich 1972), catalase (CAT) (Clairborne 1985), glutathione peroxidase (GPx) (Rotruck et al. 1973), and concentration of reduced glutathione (GSH) (Beutler et al. 1963), were assayed using previously described procedures. Total protein (Gornall et al. 1949) and thiobarbituric acid reactive substances (TBARS) (Rice-Evans et al. 1986) were also estimated using standard procedures.

Histopathological analysis

A small section of each liver was cut and preserved in 10% formalin for histopathological analysis as earlier reported (Oyinleye et al. 2021).

Statistical analysis

Data were analyzed using SPSS® 20.0 (SPSS Inc., Chicago, IL) and expressed as mean ± SD. Statistical comparisons were performed by one-way analysis of variance (ANOVA) followed by the post hoc Duncan multiple range test at the 0.05 probability level.

Results

Markers of hepatic injury

Administration of CCl_4 alone significantly ($p < 0.05$) increased the activities of AST, ALT and ALP in the serum (Fig. 1). An increase in total bilirubin was also observed ($p > 0.05$). This trend was reversed when the extract was administered. The group that received extract at the dose of 100 mg/kg had AST, ALT and ALP values that were significantly lower than those in the CCl_4 group ($p < 0.05$). The level of total bilirubin was significantly increased ($p < 0.05$) in rats that received only CCl_4 and CCl_4 + 50 mg/kg of extract. The extract at 100 mg/kg however reduced the level of TB to a level comparable to the negative control group.

Antioxidant assays

The estimation of the antioxidant compounds showed that the levels of CAT ($p > 0.05$) and GSH were decreased

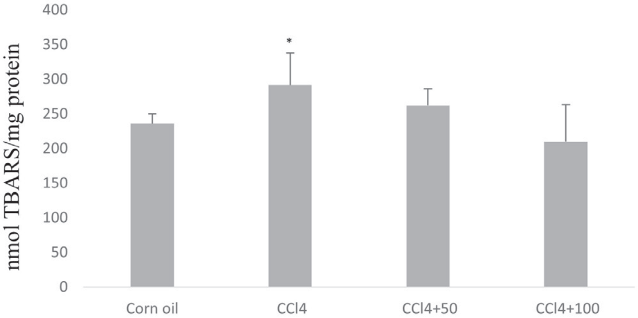

Figure 3. Effects of the methanol extract of *Luffa cylindrica* on lipid peroxidation in rats chronically exposed to carbon tetrachloride (CCl_4). *p < 0.05, significantly different from the control (corn oil).

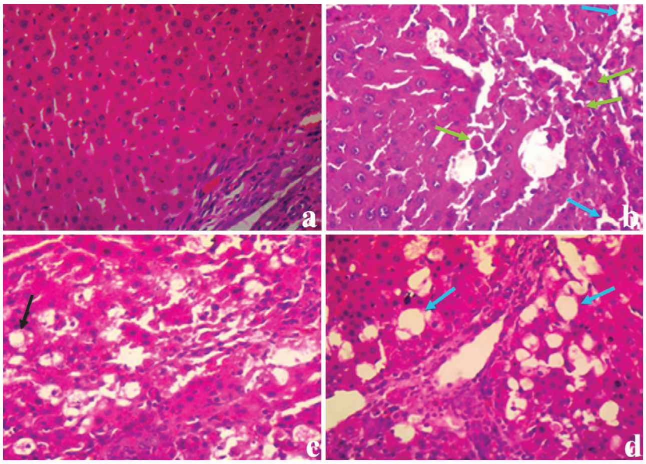

Figure 4. Effects of methanol extract of *Luffa cylindrica* (MLC) on hepatic morphology and architecture of rats exposed to CCl_4. Representative H&E-stained liver sections show: (a) no visible lesion in the negative control group; (b) bile ductular hyperplasia, moderate vacuolar change of peri-portal hepatocytes (blue arrows) and few foci of mild coagulative necrosis of hepatocytes (green arrows) in CCl_4 group; (c) severe vacuolar change of peri-portal hepatocytes and moderately congested portal blood vessels (black arrow) in CCl_4 + 50; (d) Mild vacuolar change of peri-portal hepatocytes (blue arrow) in CCl_4 + 100 (400 magnification).

($p<0.05$) in rats exposed to CCl_4 for six weeks while SOD and GPx were significantly ($p<0.05$) increased relative to the control. Co-exposure of CCl_4 and extract, however, led to a significant increase in the level of SOD, GSH and Gpx ($p < 0.05$) (Fig. 2), thus completely attenuating CCl_4-induced depletion of the rats' antioxidant status.

Lipid peroxidation

Analysis of lipid peroxidation shows that CCl_4 induced a significant increase ($p < 0.05$) in liver lipid peroxidation products measured as TBARS when compared with the control (Fig. 3). Co-administration of extract and CCl_4 resulted in a significant reduction ($p < 0.05$) in the levels of liver TBARS relative to the CCl_4 group.

Histopathology

The hepatotoxicity of CCl_4 and protective effects of *L. cylindrica* extract was also supported by histological observations (Fig. 4). The liver tissue of rats in the normal control group showed normal architecture of hepatic cells but liver sections of CCl_4-intoxicated rats showed excessive necrosis and cellular infiltration of cells. Slides from rats coadministered extract and CCl_4 showed mild hepatic lesions.

Discussion

Carbon tetrachloride-induced liver injury in animals is a commonly used model for the study of hepatic injury and screening of hepatoprotective agents due to the similarity in its pathological lesions and human liver diseases (Lin et al. 2014). Serum activities such as ALT and AST are very sensitive markers employed in the diagnosis of liver diseases (Owojuyigbe et al. 2022). ALT is highly precise for monitoring hepatocellular status, while AST is a sensitive indicator of mitochondrial problems (Chiu et al. 2018). The activities of ALT, AST and ALP were significantly increased after administering CCl_4 in this study. This implies CCl_4 induced hepatic damage in the exposed rats, which resulted in increased permeability of the plasma membrane leading to leakage of the enzymes into the bloodstream (Bashandy et al. 2020). Co-exposure of extract and CCl_4, especially at 100mg/kg significantly mitigated CCl_4-induced changes in AST, ALT and ALP activity. The extract possibly stabilized the plasma membrane, thus repairing CCl_4-induced liver damage (Wang et al. 2015).

Oxidative stress is central to liver damage. In this study, CCl_4 mediated oxidative stress in rats exposed to it. This was made evident by the significant decrease in glutathione level and increase in lipid peroxidation. Excess free radicals produced during oxidative stress damage organelles, DNA and other macromolecules, ultimately inducing liver damage (Abdelghffar et al. 2022). These free radicals are kept at optimal levels by raising the levels of endogenous free radical scavengers such as SOD, CAT, GSH, Gpx (Mirończuk-Chodakowska et al. 2018). SOD reduces the concentration of highly reactive superoxide radicals by converting them to hydrogen peroxide (H_2O_2) whereas CAT and GSH-Px decompose H_2O_2 and protect the tissues from highly reactive hydroxyl radicals (Jia et al. 2007). GSH scavenges free radicals, removes H_2O_2 and suppresses lipid peroxidation (Blair 2006). In this study, a significant increase in SOD, GSH and GPx was observed in rats which received the extract and CCl_4, which implies the inhibitory effect of the extract on CCl_4-induced oxidative stress.

Lipid peroxidation leads to a cascade of reactions which destroys the membrane lipids and also generates endogenous toxicants that can readily react with adjacent molecules like membrane proteins or diffuse to more distant molecules like DNA, which may lead to more hepatic complications and functional anomalies (Singh et al. 2008). Thus, lipid peroxidation is a critical factor in the pathogenesis of CCl_4-induced hepatic injuries (Ai et al. 2013). In this study, the extract inihibited lipid peroxidation as evidenced by low level of TBARS. This implies the ability of the extract to perturb the cascade of reactions involved in CCl_4-induced hepatotoxicity. The hepatoprotective effect of the methanol extract of *L. cylindrica* was further confirmed by histopathology. The necrosis and ductular hyperplasia induced by CCl_4 were ameliorated by the extract. Necrosis is related to oxidative stress-induced mitochondrial damage (Yang et al. 2022) while ductular hyperplasia is associated with fibrotic liver damage (Sato et al. 2019). The ability of the extract to mitigate necrosis and ductular hyperplasia thus confirms its potential to mitigate CCl_4-induced oxidative liver damage.

This study confirmed the hepatoprotective effect of the fruits of *L. cylindrica* with 100mg/kg being the effective dose in this study. Plant crude extracts are composed of complex mixtures of phytochemicals which have different forms of interaction with one another (Oyeyemi and Bakare 2013). In this study, the interaction produced the optimal result at 100 mg/kg. Hence, the need to determine the effective dosage for medicinal plants and herbal products.

Conclusion

This study shows the hepatoprotective effect of the methanol extract of *Luffa cylindrica* in CCl_4-intoxicated rats. This was shown by improvements in liver function, inhibition of oxidative stress, and amelioration of hepatic lesions. Inhibition of oxidative stress is the likely underlying mechanism for the hepatoprotective effect observed.

Acknowledgement

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