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Hepatoprotective Effects of *Tetrapleura tetraptera* (Schmach & Thonn) Taub, and Vitamin C on Plasma Enzyme Activities and Histopathological Alterations in Cadmium-Induced Wistar Rats

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Abstract

Cadmium (Cd) is a highly toxic heavy metal associated with oxidative stress, hepatocellular injury, and disruption of enzymatic antioxidant defense. This study investigated the hepatoprotective effects of vitamin C and *Tetrapleura tetraptera* (TT) extract on plasma enzyme activities and liver histopathology in Cd-intoxicated Wistar rats. Thirty-five male albino rats were divided into five groups and administered the test substances orally for 28 days. The results showed that Cd exposure significantly elevated plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, indicating hepatic injury. Histopathological analysis revealed hepatocellular degeneration, sinusoidal congestion, and portal inflammation in the Cd-treated rats. Co-treatment with vitamin C markedly reduced ALT and AST activities and ameliorated histological damage, demonstrating partial hepatoprotection in the study animals. TT at 100 mg/kg offered moderate protection, whereas TT at 200 mg/kg produced significant improvements comparable to vitamin C, with near-normal hepatic architecture and reduced inflammatory infiltrates. These findings support the therapeutic potential of TT as a natural hepatoprotective agent against heavy metal-induced toxicity and suggest its possible application as a complementary or alternative strategy to synthetic antioxidants.

Keywords: Cadmium toxicity, Vitamin C, *Tetrapleura tetraptera*, Hepatoprotection, Plasma Enzymes

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Introduction

Metallic elements are natural components of the environment that are difficult to eliminate, and their extensive use in industries and daily activities has led to severe metal pollution with major environmental and health consequences (Tchounwou *et al*., 2012; Briffa *et al*., 2020). The widespread presence of heavy metals in the environment, resulting from industrial, agricultural, residential, and technological uses, has heightened public health and ecological concerns, especially as human exposure increases through air, water, food, and consumer products (Tchounwou *et al*., 2012). Heavy metals enter living organisms via absorption, ingestion, or respiration and tend to bioaccumulate, causing significant toxicity in various organs in both humans and animals (Rana *et al*., 2018; Das and Al-Naemi 2019). Among these metals, cadmium (Cd) stands out as one of the most toxic, It is used industrially in pigments, stabilisers, alloys, and electrical products like nickel-cadmium batteries, which have contributed to its growing environmental burden (Bull, 2010). Cadmium, which occurs naturally in the environment, becomes hazardous when combined with food, water, and cigarette smoke. However, the precise cellular and molecular mechanisms of its toxicity remain unclear (Bull, 2010). Cd-induced toxicity has been associated with increased reactive oxygen species (ROS) production, leading to oxidative stress and tissue damage via lipid peroxidation (Genchi *et al*., 2020; Jacopo *et al*., 2020). Cells are normally equipped with enzymatic and non-enzymatic antioxidants to mitigate oxidative damage; however, Cd disrupts these defenses by impairing antioxidant enzyme activities and modifying gene expression pathways (Milena *et al*., 2019). Disrupted redox balance due to Cd exposure results in severe tissue damage and reduced organ function (Bull, 2010). Consequently, numerous studies have focused on understanding how endogenous antioxidants maintain redox homeostasis and counteract Cd-induced oxidative stress (Brzoska *et al*., 2016; Genchi *et al*., 2020).

Exogenous antioxidants from the diet, including vitamins A, D, E, and C, carotenoids, and other phytochemicals, are increasingly recognized for their role in sustaining antioxidant defense systems in biological tissues (*Amel et al*., 2020). Vitamin C is a potent water-soluble antioxidant that scavenges superoxide and hydrogen peroxide radicals and restores oxidized vitamin E, thereby enhancing antioxidant status (Elias and Deo, 2013; Carr and Maggini, 2017). It donates electrons to neutralise ROS and plays a critical role in immune function, collagen synthesis, wound healing, and iron absorption enhancement, thus protecting against anaemia commonly induced by cadmium toxicity (Iqbal *et al*., 2019). Studies have shown that Vitamin C reduces Cd toxicity through various mechanisms, including ROS scavenging, enhancement of antioxidant enzyme activity, reduction in lipid peroxidation, and restoration of glutathione (GSH) levels (El-Nekeety *et al*., 2014). Furthermore, it may chelate Cd ions, thereby lowering their bioavailability and organ accumulation, particularly in the liver and kidneys (Kumar, 2014). Vitamin C also affects pro-inflammatory pathways, such as NF-κB, by reducing cytokine production and promoting cell survival under oxidative stress conditions (Ding *et al*., 2019). Common parameters used to indicate hepatocellular damage are aspartate transaminase **(**AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) activities (El Hailaly *et al*., 2004). AST is an enzyme found in the cytoplasm and mitochondria of tissues such as the heart, skeletal muscles, liver, kidney, and erythrocytes (Aniagu *et al*., 2004). The concomitant increase of AST and ALT could be an indication of liver injury (Onyema *et al*., 2006; Egbuonu *et al*.,2009; Abbas and Abbas 2016).

The liver is a crucial organ that detoxifies metabolic waste products, medicines, and poisons. It also destroys worn-out red blood cells and reclaims their constituents, achieving homeostasis through drug detoxification using metabolizing enzymes (Upadhyay *et al.*, 2007; Upadhyay *et al*., 2008; Pandit *et al*., 2012). When the liver is exposed to the effects of inducing oxidative stress, certain cells, such as parenchymal cells, kupffer cells, and hepatic stellate cells, as well as certain organelles such as the mitochondria, microsomes, and peroxisomes, become affected, which may lead to an increase in the production of apoptosis and inflammation (Sakaguchi *et al*., 2011; Sanchez *et al*., 2012; Cochozlach and Michalak 2014). Studies have reported the traditional use of vegetables, fruits, herbs, and plant extracts in treating liver diseases. Therefore, dietary incorporation is regarded as a critical factor in supporting liver function, particularly in the detoxification of harmful compounds (Zhang *et al*., 2013).

Tetrapleura tetraptera, a medicinal plant from the Leguminosae family native to West Africa and known as "Aidan fruit," "Prekese," or "Aridan," is being studied for its potential therapeutic properties (Uyoh *et al*., 2013; Adusei *et al.,* 2019). It is rich in nutrients such as ash, fiber, protein, carbohydrates, lipids, and vitamins, and exhibits regional variability in its nutritional composition across different parts of the fruit (Uyoh *et al*., 2013; Adadi and Kanwugu, 2020). More importantly, it contains various bioactive compounds such as alkaloids, flavonoids, tannins, triterpenoids, steroids, and phytates that have been linked to pharmacological effects (Akin-Idowu *et al*., 2011; *Adusei et al.,* 2019). These bioactive compounds contribute to its reported antibacterial, hypoglycemic, anti-inflammatory, neuromuscular, anti-ulcerative, molluscicidal, and trypanocidal properties (Ojewole and Adewunmi 2004; Aladesanmi, 2007; Kuate *et al*., 2015), especially in the prevention and management of hepatic injuries (Obidike *et al.*, 2022). *The protective effect of Tetrapleura tetraptera extracts* against Cd-induced toxicity remains inadequately studied, whereas vitamin C is widely accepted as a conventional antioxidant. Therefore, this study aimed to evaluate the hepatoprotective effects of Vitamin C and *Tetrapleura tetraptera* on plasma enzyme activities and

histopathological alterations in cadmium-induced Wistar Rats.

Methodology

Collection and preparation of Plant

Fresh fruits of *Tetrapleura tetraptera* were harvested from the campus of Cross River State University of Technology, Calabar, Nigeria, and identified at the Department of Botany, University of Calabar, Nigeria. The fruits were cleaned with tap water, sliced into tiny pieces, and oven-dried at 45^0C for nine hours. The dried plant sample (5 kg) was subsequently ground into a powder using a mechanical food mixer (corona).

Preparation of Ethanol Extracts

Following the method of extraction by Sasidharan *et al.,* (2011) with modification, a hundred grams (100 g) powder sample was soaked in 2ml 90% ethanol for 48 hours before being filtered. The homogenate was filtered through cheesecloth and Whatman No1 filter paper. The filtrate was then heated to 45°C in a water bath to produce a semi-solid extract, which was then refrigerated at 4°C.

Experimental design

Following a 14-day period of acclimatization, the animals were divided into five experimental groups, (A, B, C, D, and E), with a minimum of seven animals in each group. The groups were identified as follows: A: Normal control; B, $CdCl_2$ + distilled water; C, $CdCl_2$ + $VitC_{100}$; D, $CdCl_2$ + TT_{100}; and E, $CdCl_2$ + TT_{200}. The animals were treated daily for 28 days (Table 1).

Table 1. Experimental Protocol

Groups	Numbers of Rats	Treatments (28days)
A	7	Distilled water (Normal Control)
B	7	$CdCl_2$ (5mg/kg/day) + Distilled water
C	7	$CdCl_2$ (5mg/kg/day) + Vit C (100mg/kg/day)
D	7	$CdCl_2$ (5mg/kg/day) + TT (100mg/kg/day)
E	7	$CdCl_2$ (5mg//day) + TT (200mg/kg/day)

Tetrapleura tetraptera (TT), cadmium chloride ($CdCl_2$)

Experimental animal and protocol

Thirty-five male albino Wistar rats (all male) aged 8-10 weeks (170–246 g) were obtained from the Department of Biochemistry Animal House, Cross River University of Technology, Nigeria. The rats were kept in standard, well-ventilated cages at room temperature with a 12-hour light/dark cycle. The rats were given free access to food and water. Their body weights were monitored at 7 days interval and recorded throughout the study period. The animals were kept in accordance with the guidelines for Animal Care as contained in the Animal Ethics Handbook of the Faculty of Basic Medical Sciences and Ethical Committee University of Calabar on the experimental use of animals for research purposes.

Blood Collection

After 28 days, the animals were fasted for Twelve hours (12 hr) and anesthetized with chloroform. Whole blood samples were collected through cardiac puncture using a 2 mL syringe into sterile plain sample bottles and allowed for 2 hours to clot before being centrifuged at 4000 g for 10 minutes to obtain a clear portion that was used for biochemical analysis (Nna *et al*., 2017).

Liver collection for normal histological procedure

The abdomen of chloroform-anesthetized animals was dissected to access the liver for standard histology procedures.

Liver function markers

The activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined using kinetic spectrophotometry-based Assay kit and Protocol described for enzymatic activity quantification. The method involves measuring the pyruvate produced from the transamination reactions at a wavelength of 546 nm.

Statistical analysis

Statistical analysis was conducted using Analysis of Variance (ANOVA) to compare the biochemical parameters across the five experimental groups. Data are presented as mean ± standard deviation (SD), and the significance of differences between groups was determined using p-values. Statistical significance was set at 0.05 ($P < 0.05$) was considered statistically significant.

Results

Effects of Vitamin C and Tetrapleura tetraptera extract on liver function markers

Cadmium chloride ($CdCl_2$) exposure significantly ($P < 0.05$) increased ALT (47.75 IU/L) and AST (112.50 IU/L) levels compared to the control group (ALT: 31.75 IU/L, AST: 74.75 IU/L). Co-administration of Vitamin C (100 mg/kg) with $CdCl_2$ significantly reduced ALT (36.25 IU/L) and AST (93.50 IU/L) levels compared to the $CdCl_2$-only group. However, the enzyme levels in Group C remained slightly elevated compared to the control, suggesting partial

protection rather than complete prevention of hepatic damage. In Group D, after administration with TT 100 mg/kg, ALT and AST levels were 43.50 IU/L and 105.75 IU/L, respectively. Although the values were lower than those of the $CdCl_2$-only group (Group B), this reduction was not as pronounced as that observed with Vitamin C. Finally, in Group E (TT 200 mg/kg), ALT and AST levels decreased further (36.50 IU/L and 93.50 IU/L, respectively), comparable to the Vitamin C-treated group (Table 2).

Table 2. Comparative Effects of Vitamin C and *Tetrapleura tetraptera* Extract on ALT and AST Activities Following Cadmium-Induced Hepatic Injury

Group	ALT (IU/L)	AST (IU/L)
A (control)	31.7±2.50	74.7± 10.40
B ($CdCl_2$)	47.7±5.56	111.5± 13.18
C ($CdCl_2$ +Vit C)	36.3 ±2.50	93.5± 3.70
D ($CdCl_2$ + TT 100 mg/kg)	43.5± 3.51	105.7 ± 3.50
E ($CdCl_2$ + TT 200 mg/kg)	36.5± 2.65	93.5± 4.20

*Values are presented as mean ± standard deviation. Statistical differences between groups were analyzed using one-way analysis of variance (ANOVA). Statistical significance was set at $P < 0.05$.

Histological Observation of the Liver

The hepatocytes were normal and organized around the central veins, with moderate enlargement and coarse chromatin patterns. The sinusoidal spaces were mildly congested and contained scant infiltrates, whereas the portal area displayed moderate inflammation. Photomicrograph shows normal histological features, which were evidenced by the presence of the central vein of the liver (CV), liver sinusoids (SS), hepatocytes (HA), and portal triad (PT). There were plates of hepatocytes (HP) radiating outward from the congested central veins (CV). Moderately enlarged hepatocytes with prominent nuclei and coarse chromatin patterns were observed. The intervening sinusoidal spaces (SS) were congested, dilated, and contained scant sinusoidal infiltrates. The portal triad (PA) was enlarged with intact limiting plate hepatocytes but contained moderate amounts of inflammatory infiltrate, mainly mononuclear cells. This finding is consistent with portal hepatitis due to cellular injury (Figure 1A).

Hepatocyte enlargement, sinusoidal congestion, and portal inflammation with mild interface hepatitis were observed in the $CdCl_2$ + Distilled Water group. Patchy damage to the limiting plates indicated Cd-induced cellular injury. The liver architecture showed marked damage, confirming cadmium hepatotoxicity. The photomicrograph shows an enlarged central vein (CV), narrow sinusoids (SS), hepatocytes (HA), and portal triad (PT). The plates of hepatocytes (HP) radiated outward from the congested central veins (CV) with moderately enlarged hepatocytes (HA), enlarged with prominent nuclei having coarse chromatin patterns. The intervening sinusoidal spaces (SS) were congested, dilated, and contained scant sinusoidal infiltrates. The portal triad is enlarged with intact limiting plate hepatocytes but contains moderate amounts of inflammatory infiltrate, mainly mononuclear cells. A patchy bridge of limiting plates with an interface of hepatitis was observed (Figure 1B).

Photomicrographs of the livers of Vitamin C treated rats (Figure 1C) and *Tetrapleura tetraptera* (100 mg/kg) group (Figure 1D) showed normal histological features, as witnessed in the normal size of the central vein (CV), sinusoids (SS), congestion of veins around the portal area (PT), and hepatocytes (HP). Hepatocytes (HP) were moderately enlarged, with prominent nuclei with coarse chromatin patterns. The intervening sinusoidal spaces (SS) were congested, dilated, and contained mild sinusoidal infiltrates. The portal area was enlarged with intact limiting plate hepatocytes but contained severe amounts of inflammatory infiltrate, mainly mononuclear cells.

The hepatocytes of *Tetrapleura tetraptera* (200 mg/kg) group showed minimal enlargement, and sinusoidal congestion was mild in this group. The portal areas were intact, with no hepatotoxicity. Photomicrographs revealed an enlarged central vein (CV) of the liver, normal sinusoids (SS), hepatocytes (HP), and portal area (PT). Hepatocytes (HP) radiated outward from the congested central veins (CV) and were moderate, with prominent nuclei with coarse chromatin patterns and distinct nucleoli. The intervening sinusoidal spaces (SS) were congested and mildly dilated. The portal area displayed intact limiting plate hepatocytes and contained the bile duct, hepatic artery, and portal vein. (Figure 1E).

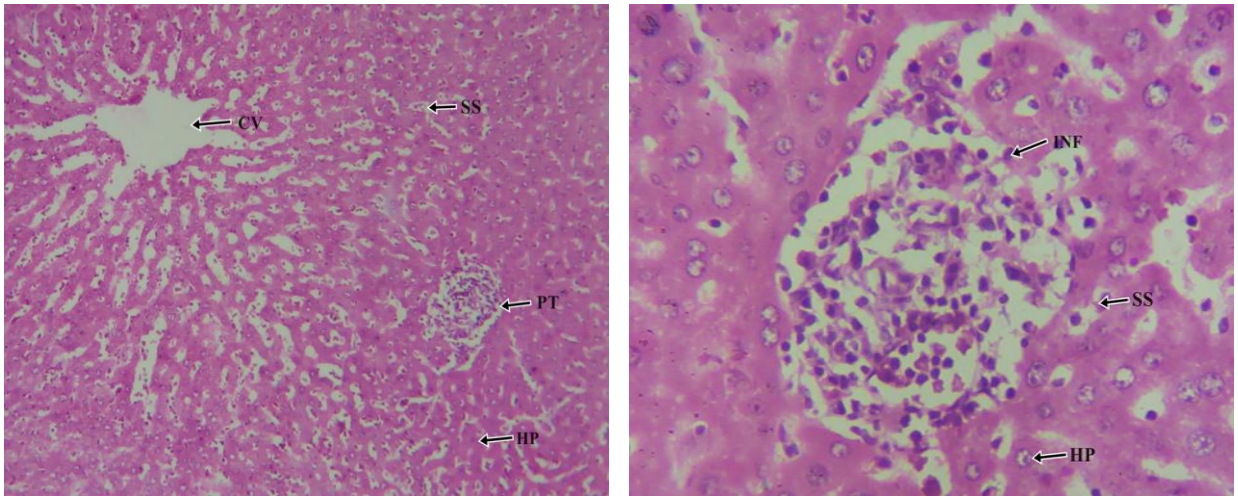

Figure 1A

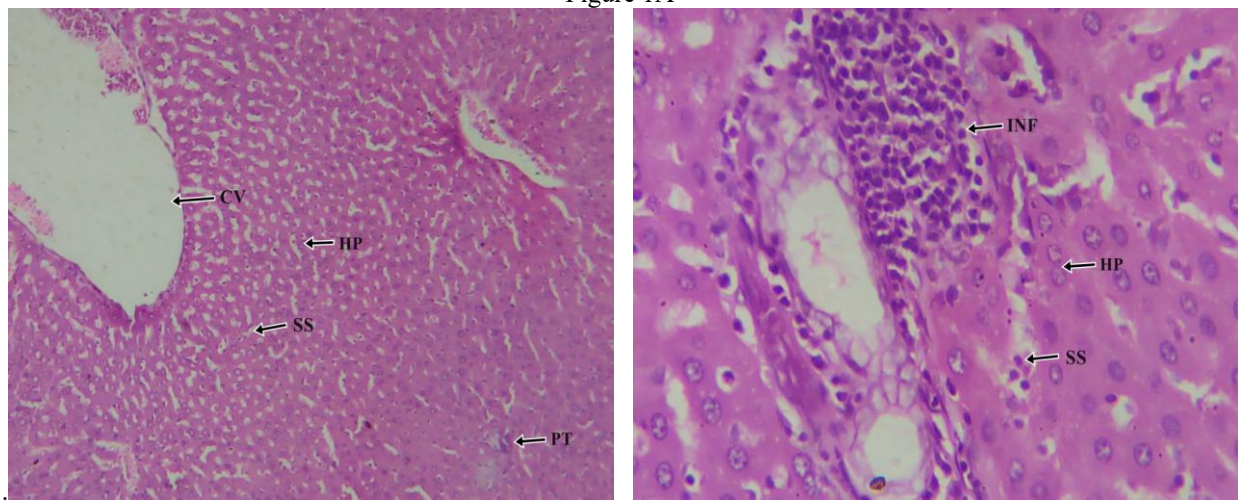

Figure 1B

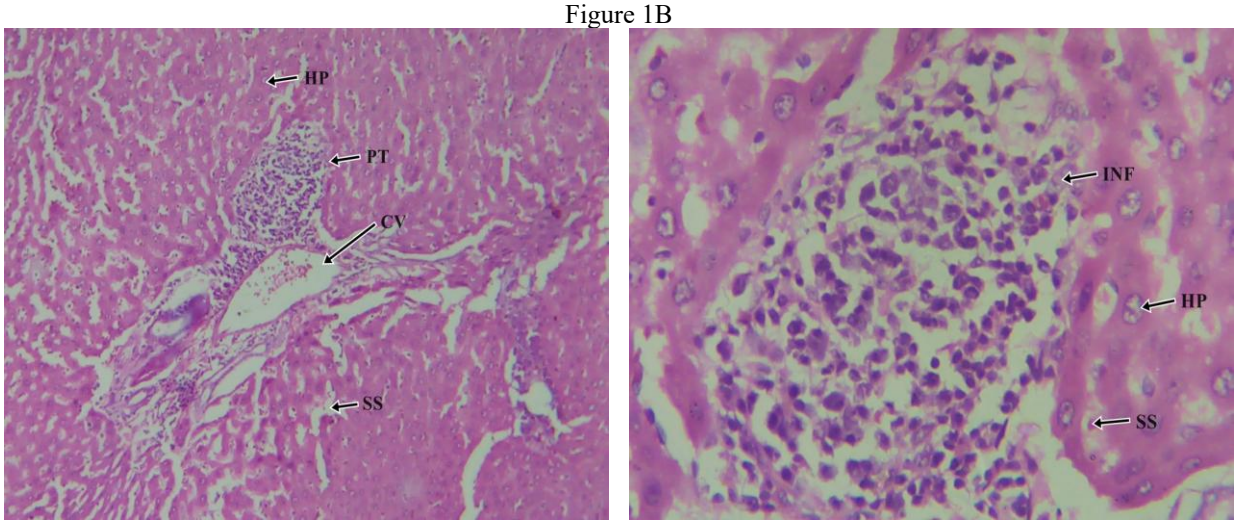

Figure 1C

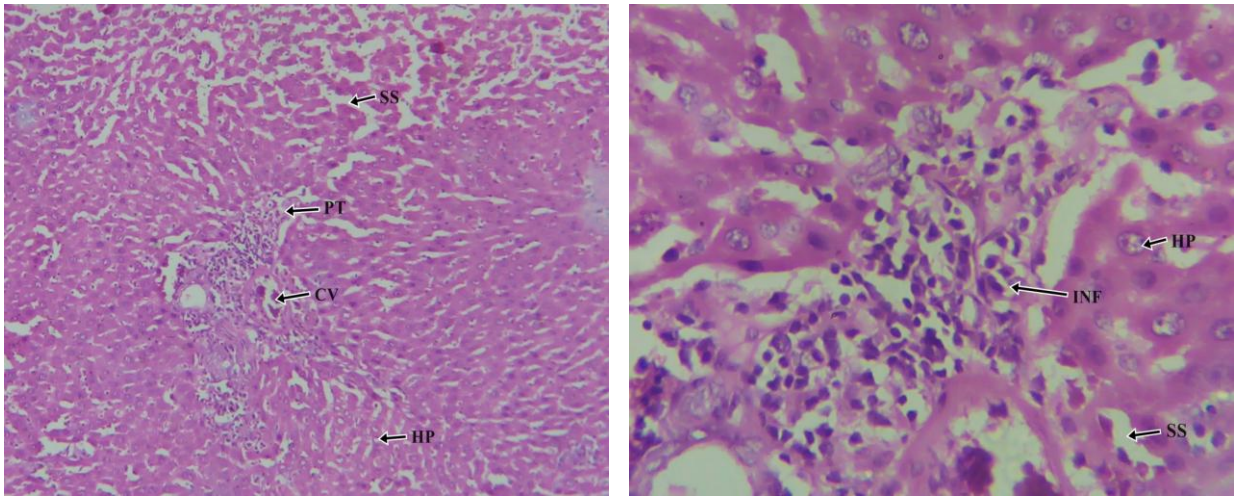

Figure 1D

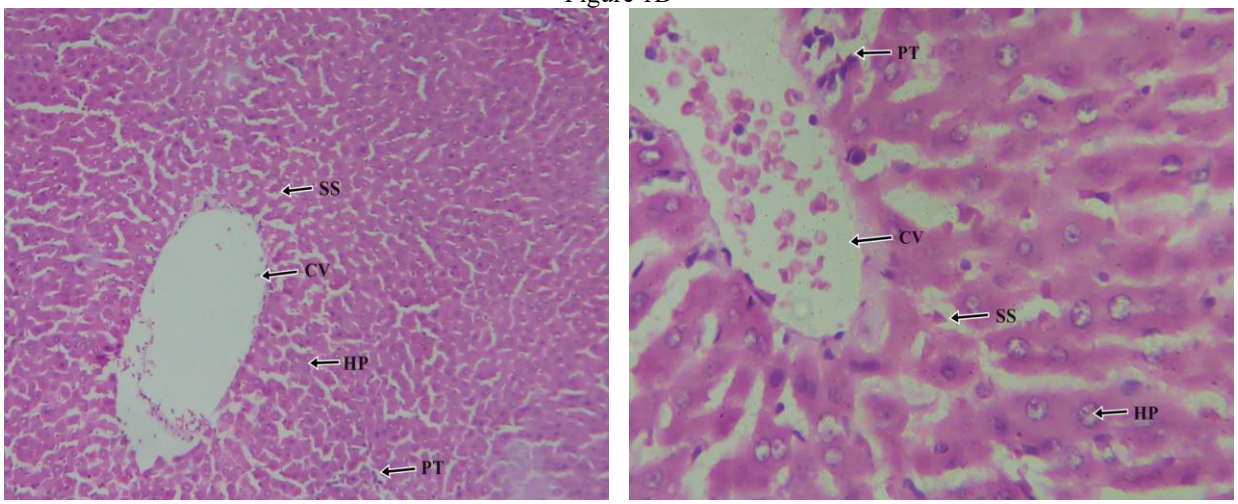

Figure 1E

Figure 1 (A-E): Photomicrographs of Liver Sections from Control and Treated Wistar Rats. Left x100; Right x400 Magnification

Discussion

The present study provides evidence that cadmium chloride ($CdCl_2$) induces profound hepatocellular injury through biochemical dysregulation and structural derangement of hepatic tissue. The significant elevation of ALT and AST levels observed in the $CdCl_2$-treated group relative to the controls reflects marked hepatocellular membrane disruption and leakage of cytosolic enzymes, a biochemical signature previously reported in Cd-induced hepatotoxicity models (Rehman *et al*., 2020). Histopathologically, $CdCl_2$ induced sinusoidal congestion, hepatocellular enlargement, portal inflammatory infiltrates, and partial bridging of the limiting plate, which collectively signify portal hepatitis and early interface activity. These lesions align closely with reports by Ubah et al. (2019) and Ekong *et al*. (2008), reinforcing cadmium ability to perturb hepatic microarchitecture by promoting cellular swelling, endothelial dysfunction, and hepatocyte chromatin condensation. The Cd hepatotoxic phenotype is largely attributed to its ability to catalyze reactive oxygen species (ROS) generation, deplete cellular glutathione pools, inhibit antioxidant enzymes, and activate pro-inflammatory transcription factors such as NF-κB (Rehman *et al*., 2020). The convergence of these pathways may explain the severe biochemical and histological perturbations detected in this study, confirming the successful establishment of a Cd hepatotoxicity model suitable for evaluating hepatoprotective interventions.

Vitamin C co-administration conferred measurable hepatoprotection, as demonstrated by the significant attenuation of ALT and AST concentrations and partial restoration of hepatic cytoarchitecture. Although hepatocyte enlargement and portal inflammatory infiltrates persisted, the reduction in sinusoidal congestion and mild inflammatory cell infiltration indicated notable but

incomplete protection. These outcomes align with earlier findings that vitamin C mitigates Cd toxicity primarily by scavenging ROS, restoring the activities of antioxidant enzymes such as SOD, catalase, and GPx, and suppressing lipid peroxidation (Bashandy and Alwasel, 2011; Poli *et al*., 2022). The persistence of histological alterations in the present study suggests that while vitamin C counteracts oxidative stress, it may be insufficient to fully neutralize the broader molecular pathways engaged by Cd, including mitochondrial permeability transition, calcium dyshomeostasis, and pro-inflammatory cytokine release. Comparatively, the degree of improvement achieved with vitamin C mirrors previous observations, where antioxidants reduced but did not fully reverse xenobiotic-induced hepatic injury (Poli *et al*., 2022). The hepatoprotective effects of *Tetrapleura tetraptera* (TT) were dose-dependent. Treatment with TT at 200 mg/kg significantly reduced ALT and AST levels, and histological examination revealed restoration of normal lobular architecture, with intact portal triads, reduced sinusoidal dilation, and minimal inflammatory infiltration. These improvements corroborate previous findings (Kusi *et al*. 2023), who demonstrated that TT stem bark extracts conferred up to 80% hepatoprotection against paracetamol and CCl_4-induced toxicity. Likewise, the dose-response improvement parallels the observation that TT ameliorated cyanide-induced hepatotoxicity by restoring serum enzyme levels, reducing lipid peroxidation, and enhancing antioxidant enzyme activity (Kadiri *et al*., 2020). The synthesis of the present findings with those from previous investigations strongly suggests that TT offers hepatoprotective efficacy. While Vitamin C predominantly acts via ROS scavenging, TT appears to engage additional cytoprotective pathways, including modulation of inflammatory responses, enhancement of glutathione metabolism, protection against membrane lipid peroxidation, and possible interaction with xenobiotic detoxification enzymes, as inferred from the multi-pathway responses (Kusi *et al*., 2023; Bonsou *et al*., 2022). Cadmium toxicity is characterized by simultaneous oxidative, inflammatory, and structural damage (Nuli *et al.,* 2024), and this multimodal activity may explain the superior histological restoration observed with the higher dose of TT (200 ng/kg).

Conclusion

These findings suggest that *Tetrapleura tetraptera* is a promising hepatoprotective medicinal product. *Tetrapleura tetraptera* exhibited a dose-dependent protective effect, producing hepatoprotective outcomes comparable to those of vitamin C. The normalization of plasma enzyme levels and preservation of hepatic architecture further affirm the therapeutic value of *Tetrapleura tetraptera*. These results not only provide experimental evidence for the traditional use of *Tetrapleura tetraptera* in managing liver-related disorders but also suggest that it could serve as a promising natural alternative or adjunct to conventional antioxidant therapy.

Conflicts of Interest

The authors declare no conflicts of interest

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