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L-arginine Attenuates Cadmium Chloride-Induced Hepatoxicity in Rats: Histopathological and Biochemical Mechanisms

Onyilo Peace Omewomano [1], Ebeye Oladunni Abimbola [2], Osagie Mercy Awele [3], Majekodunmi Olamide Favour [3]

[1] Department of Anatomy, School of Basic Medical Sciences, University of Benin, Nigeria.
[2] Department of Health and Social Care, Global banking school, United Kingdom.
[3] Department of Anatomy, Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria.
*Correspondence:
peaceewoma@gmail.com

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ABSTRACT

Objective: Cadmium chloride is an environmental pollutant, known for inducing cytotoxicity via oxidative stress, DNA damage and apoptotic activities. This study evaluated the hepatoprotective potentials of L-arginine against cadmium-chloride induced toxicity in adult Wistar rats.

Methods: Twenty-five (25) adult Wistar rats were randomized into five groups (n=5): a control group given standard rat chow and water *ad libitum*; a toxicant group administered cadmium chloride orally at 5 mg/kg body weight/day; and two treatment groups receiving cadmium chloride (5 mg/kg) co-administered orally with L-arginine at 100, and 200 mg/kg body weight/day, respectively and a positive control group administered 200 mg/kg L-arginine only, for twenty-eight days. Hepatotoxicity was assessed via histopathological examination of liver tissue, evaluation of hepatic functional parameters notably serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities, Also, antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase were assessed alongside hepatic malondialdehyde levels.

Results: Co-administration of L-arginine attenuated inflammatory changes and preserved hepatic architecture, with the high dose showing near-complete tissue recovery, significantly reduced serum alanine aminotransferase and aspartate aminotransferase levels, decreasing malondialdehyde concentrations, and restored antioxidant enzyme activities.

Conclusion: These findings demonstrate that oral L-arginine at high dose significantly ameliorates cadmium chloride-induced hepatotoxicity by restoring antioxidant defense and suppressing oxidative damage, supporting its potential as a possible therapeutic agent in heavy metal-induced hepatoxicity.

Keywords: L-arginine, Cadmium chloride; Hepatotoxicity; Wistar rats

Introduction

Cadmium (Cd) is an environmental and industrial pollutant with multi-systemic toxicological effects. Human exposure to cadmium could be through contaminated food, water, cigarette smoke, and occupational hazard, leading to bioaccumulation[1,2]. Cadmium-induced hepatotoxicity is often characterized by oxidative stress, cellular disruption, mitochondrial dysfunction, and inflammatory responses, resulting in hepatocellular injury and necrosis[3] . The liver is highly susceptible to assaults and heavy metal induced oxidative damage due to its core role in detoxification and high metabolic activities. Oxidative stress is widely recognized mechanism underlying cadmium-induced liver injury. Cadmium indirectly generates reactive oxygen species (ROS) by depleting endogenous antioxidants such as glutathione and inhibiting antioxidant enzymes including superoxide dismutase and catalase[4]. This imbalance promotes lipid peroxidation, protein oxidation, and DNA damage, thereby impairing hepatic function. Given the limitations of endogenous defense systems under toxic insult, there has been growing interest in identifying therapeutic agents capable of mitigating toxicity, among these, naturally occurring amino acids and their derivatives have attracted attention due to their antioxidant, anti-inflammatory, and cytoprotective properties.

L-arginine, a semi-essential amino acid, plays vital role in numerous physiological and biochemical processes, beyond its classical function in protein synthesis. It is a key substrate for nitric oxide synthase (NOS), involved in the production of nitric oxide (NO), a signaling molecule effective in vasodilation, immune modulation, neurotransmission, and cellular homeostasis[5,6]. In the liver, NO has been shown to regulate hepatic blood flow, inhibit platelet aggregation, and modulate inflammatory responses, thereby contributing to the maintenance of hepatic integrity under stress conditions. Furthermore, L-arginine participates in the urea cycle, facilitating ammonia detoxification, and serves as a precursor for the synthesis of polyamines and proline, which are essential for cell proliferation, collagen synthesis, and tissue repair.

Beyond its metabolic activities, L-arginine exhibits significant antioxidant and cytoprotective properties. It enhances endogenous antioxidant defense systems by upregulating enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, while also reducing lipid peroxidation. It has been reported to modulate key molecular pathways involved in oxidative stress and inflammation, including the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway and the inhibition of nuclear factor-kappa B (NF-κB) signaling, thereby attenuating pro-inflammatory cytokine production. Its ability to improve endothelial function and mitochondrial integrity further supports its therapeutic potential in conditions associated with oxidative damage[7,8]. More so, emerging evidence suggests that L-arginine may alter heavy metal toxicity by acting as a chelating agent enhancing nitric oxide bioavailability, and restoring redox balance, although the precise molecular mechanisms has not been fully elucidated.

Previous experimental studies have explored the protective effects of L-arginine against different hepatotoxic agents. L-arginine ameliorated carbon tetrachloride-induced liver damage in mice by restoring antioxidant enzyme activities and reducing lipid peroxidation[9]. Similarly, L-arginine was reported to ameliorate and reverse alterations in cyclosporine-induced hepatotoxicity in rat[10], aid hepatic regeneration in rat model[11] and mitigates amiodarone-induced hepatotoxicity[12] . In the context of heavy metal toxicity, some evidence suggests that L-arginine may counteract cadmium-induced oxidative stress by enhancing nitric oxide bioavailability and improving antioxidant status; however, these findings remain limited and somewhat inconsistent, particularly regarding dose-dependent effects and mechanistic pathways.

Despite the availability of literature on both cadmium-induced hepatotoxicity and the therapeutic potential of L-arginine, there remains a paucity of comprehensive studies specifically investigating the mechanistic interplay between L-arginine supplementation and cadmium chloride-induced liver injury. Existing studies often focus on general antioxidant effects without detailed evaluation of biochemical, histopathological, and molecular endpoints in a unified experimental framework. Therefore, this study aims to investigate the protective effects of L-arginine against cadmium chloride-induced hepatotoxicity in rats. Specifically, evaluating liver function biomarkers (ALT, AST, ALP), assessing the oxidative stress parameters including lipid peroxidation and antioxidant enzyme activities; and examining the histopathological alterations in hepatic tissues. This work seeks to provide insights into the therapeutic potential of L-arginine as a modulator of heavy metal-induced liver toxicity, thereby contributing to the development of effective intervention strategies.

Methods

ANIMAL CARE AND MANAGEMENT

Twenty-five (25) adult male Wistar rats (150–180 g) were obtained from the animal facility of the Faculty of Basic Medical Sciences, Delta State University, Abraka. Animals were housed under standard laboratory conditions (temperature: 25°C; relative humidity: 50%; 12-hour light/dark cycle) in well-ventilated cages and were provided standard growers' mash and water *ad libitum*. All animals were acclimatized for 14 days prior to the experiment. Experimental procedures were conducted in accordance with institutional guidelines and approved by the Institutional Animal Ethics Committee (IAEC) of Delta State University, Abraka with ethical approval number RBC/FBMC/25/1060.

EXPERIMENTAL DESIGN

Twenty five (25) adult Wistar rat weighing between 150-180g were randomly divided into five groups (n = 5 per group):

Group A (Control): Feed and water only
Group B: 5 mg/kg Cadmium chloride only
Group C: Cadmium chloride (5 mg/kg) + low-dose arginine 100 mg/kg)
Group D: Cadmium chloride (5 mg/kg) + high-dose arginine (200 mg/kg)
Group E: High-dose arginine (200 mg/kg) only

Sample Collection and Tissue Preparation

At the end of the experimental period, animals were euthanized via cervical dislocation. Blood samples were collected from the inferior vena cava for liver function analysis. The liver was excised, and portions were fixed in 10% formal saline for histological studies. The remaining tissue was homogenized in appropriate buffer, centrifuged, and the supernatant collected for biochemical assays.

BIOCHEMICAL ANALYSIS

Antioxidant enzyme activities and lipid peroxidation were determined using standard methods: superoxide dismutase was assayed by established method of Misra and Fridovich (1972)[13], catalase adopted method of Aebi (1984)[14], glutathione peroxidase was assessed by method of Rotruck *et al.,* (1973)[15], and malondialdehyde Ohkawa *et al.,* (1979)[16]. The liver enzymes were assessed following standard methods adopted by Schumann *et al.,* (2002)[17].

HISTOLOGICAL EXAMINATION

Liver tissues were processed and stained with hematoxylin and eosin (H&E) using standard procedures as described by Drury and Wallington (1980)[18], Fixed liver tissues were processed, embedded in paraffin, sectioned using a rotary microtome, and stained with hematoxylin and eosin (H&E). Histological observations were performed using a digital microscope (SCOPETEK DCM 500, 5.0 megapixels).

STATISTICAL ANALYSIS

Statistical analysis was carried out using GraphPad Prism, Data were expressed as mean ± standard error of mean (SEM).. Differences between groups were analyzed using one-way analysis of variance (ANOVA), followed by post hoc multiple comparison tests. $p < 0.05$ was considered statistically significant.

Results

HISTOLOGICAL ASSESSMENT OF L-ARGININE ON CADMIUM-CHLORIDE INDUCED HEPATOXICITY

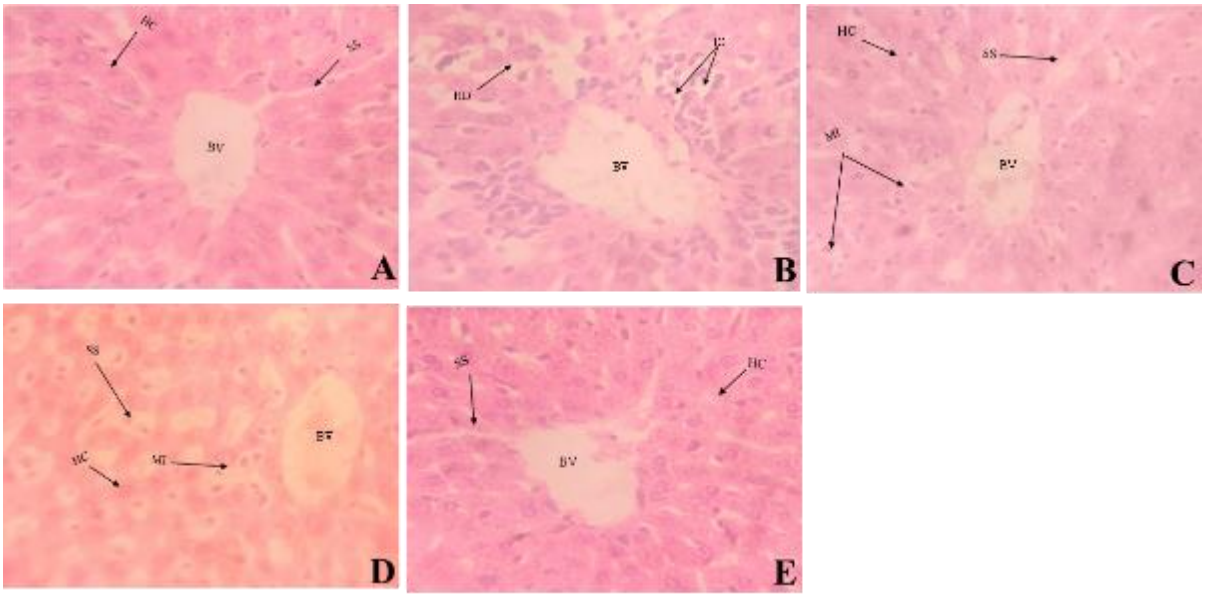
Histological examination of liver sections from the control group (Group A) showed normal hepatic architecture. Hepatocytes were well arranged with uniform, round nuclei and prominent nucleoli. The cytoplasm appeared intact with no evidence of degeneration or necrosis. Sinusoids were clearly defined and lined by endothelial cells, while blood vessels were intact without congestion or signs of inflammation (Plate 1).

In the cadmium chloride-treated group (Group B), there was marked disruption of hepatic architecture. Hepatocytes appeared disorganized with evidence of cellular degeneration, including cytoplasmic vacuolation and nuclear alterations. Sinusoids were irregular and distorted, accompanied by significant inflammatory cell infiltration. These findings indicate severe hepatocellular injury and inflammation induced by cadmium toxicity (Plate 2).

Liver sections from the low-dose L-arginine co-treatment group (Group C) demonstrated partial restoration of hepatic structure. Hepatocyte cords were moderately aligned, and sinusoids appeared more regular compared to the cadmium-only group. Blood vessels showed improved integrity with reduced inflammatory infiltration. However, mild inflammatory changes and slight hepatocellular degeneration were still observed (Plate 3).

In the high-dose L-arginine co-treatment group (Group D), there was a marked improvement in liver histology. Hepatocytes exhibited near-normal morphology with preserved nuclei and cytoplasm. Sinusoids and blood vessels appeared well organized, with minimal inflammatory infiltration. These findings suggest a dose-dependent protective effect of L-arginine against cadmium-induced hepatic damage (Plate 4).

The group treated with L-arginine only (Group E) showed normal liver architecture comparable to the control group. Hepatocytes, sinusoids, and blood vessels were well preserved, with no evidence of inflammation, degeneration, or structural abnormalities (Plate 5).



Micrograph of Rat Liver control group (A); shows: HC-Hepatocyte; SS- sinusoid; BV-blood vessel. group (B) treated with Cadmium only: HC-Hepatocyte; SS- sinusoid; BV-blood vessel; HD- hepatocyte degeneration. Group (C) co-treatment of l-

arginine 100mg/kg and Cdcl2 shows: HC-Hepatocyte; SS- sinusoid; BV-blood vessel; MI- Mild infiltrates of inflammatory cells; group (D) treated with l-arginine 200 mg/kg and Cdcl2 shows: HC-Hepatocyte; SS- sinusoid; BV-blood vessel; MI-Mild infiltrates of inflammatory cells; group (E) treated with l-arginine 200 mg/kg only: HC-Hepatocyte; SS- sinusoid; BV-blood vessel; (H&E x 400).

EFFECT OF L-ARGININE ON OXIDATIVE STRESS INDICES IN THE LIVER OF RATS TREATED WITH CADMIUM CHLORIDE

Superoxide dismutase (SOD) activity showed a significant difference ($p<0.05$) across all groups. The cadmium chloride ($CdCl_2$)-treated group exhibited a significant decrease ($p<0.05$) in SOD activity compared to the control and arginine-only groups. However, co-treatment with L-arginine ($CdCl_2$ + Arg) resulted in a significant increase ($p<0.05$) in SOD activity compared to the $CdCl_2$-treated group (Figure 1).

Catalase (CAT) activity was significantly increased ($p<0.05$) in the arginine-only group compared to the control. In contrast, the $CdCl_2$-treated group showed a significant reduction ($p<0.05$) in CAT activity compared to both control and arginine groups. Co-treatment with arginine significantly increased ($p<0.05$) CAT activity relative to the $CdCl_2$ group, although no significant difference ($p>0.05$) was observed when compared with the arginine-only group.

Glutathione peroxidase (GPx) activity showed a statistically significant difference ($p<0.05$) across all experimental groups (Figure 1).

Lipid peroxidation, assessed by malondialdehyde (MDA) levels, was significantly increased ($p<0.05$) in the $CdCl_2$-treated group compared to control and arginine-only groups. However, co-treatment with arginine ($CdCl_2$ + Arg) significantly reduced ($p<0.05$) MDA levels compared to the $CdCl_2$ group. This reduction was dose-dependent, with higher arginine doses showing greater decreases in MDA levels (Figure 2).

Effect of l-arginine on antioxidant enzyme activities

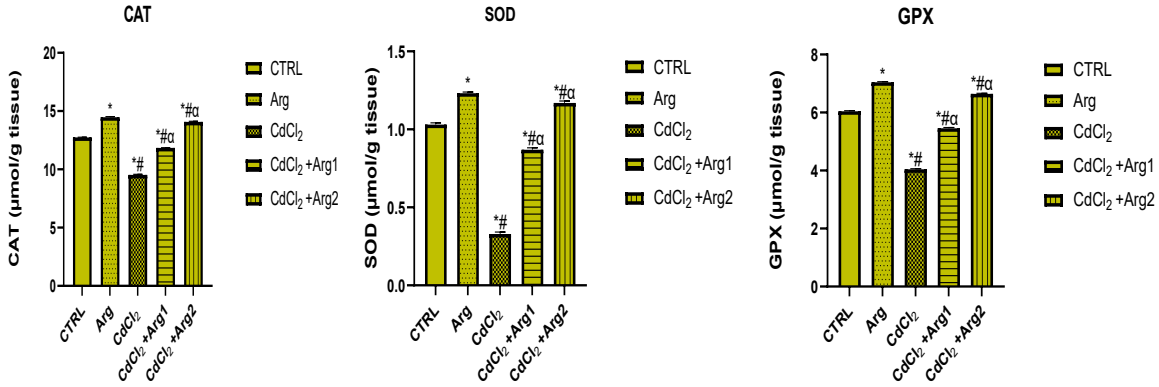


Figure 1: *shows the effect of l-arginine supplementation on serum level of catalase, superoxide dismutase and glutathione peroxidase in lead induced hepatoxicity. Key:* ***CTR****: Control;* ***Arg****: 200 mg/kg arginine only;* ***Cdcl₂****: received 5 mg/kg;* ***Cdcl₂+Arg 1;*** *received 5 mg/kg Cdcl₂ with 100 mg/kg Arg.* ***Cdcl₂+Arg 2;*** *received 5 mg/kg Cdcl₂ with 200 mg/kg Arg side by side for 28 days. *p<0.05 compared to CTR; #p<0.05 compared to Arg; α p<0.05 compared to Cdcl₂.*

Effect of l-arginine on Malondialdehyde (MDA) level

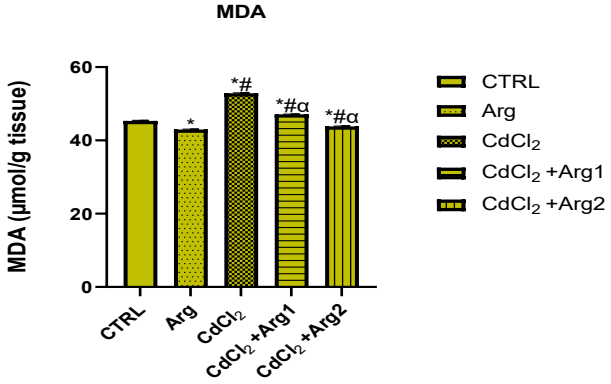


Figure 2: *shows the effect of l-arginine on malondialdehyde level (lipid peroxidation). Key:* ***CTR****: Control;* ***Arg****: 200 mg/kg arginine only;* ***Cdcl₂****: received 5 mg/kg;* ***Cdcl₂+Arg 1;*** *received 5 mg/kg Cdcl₂ with 100 mg/kg Arg.* ***Cdcl₂+Arg 2;*** *received 5 mg/kg Cdcl₂ with 200 mg/kg Arg side by side for 28 days. *p<0.05 compared to CTR; #p<0.05 compared to Arg; α p<0.05 compared to Cdcl₂.*

EFFECT OF L-ARGININE ON LIVER FUNCTION PARAMETERS

Alanine aminotransferase (ALT) levels were significantly elevated ($p<0.05$) in the $CdCl_2$-treated group compared to control. Arginine co-treatment significantly reduced ($p<0.05$) ALT levels compared to the $CdCl_2$ group. Aspartate aminotransferase (AST) levels followed a similar pattern, showing a significant increase ($p<0.05$) in the $CdCl_2$-treated group compared to control. Co-treatment with arginine significantly decreased ($p<0.05$) AST levels relative to the $CdCl_2$ group (Figure 3). Alkaline phosphatase (ALP) levels were significantly increased ($p<0.05$) in both the arginine-only and $CdCl_2$-treated groups compared to control, with a more pronounced increase observed in the $CdCl_2$ group. Arginine co-treatment significantly reduced ($p<0.05$) ALP levels compared to the $CdCl_2$ group. Total bilirubin (TB) levels were significantly elevated ($p<0.05$) in the $CdCl_2$-treated group compared to both control and arginine-only groups. However, arginine co-treatment significantly reduced ($p<0.05$) bilirubin levels compared to the $CdCl_2$-treated group (Figure 4).

Effect of l-arginine on Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)

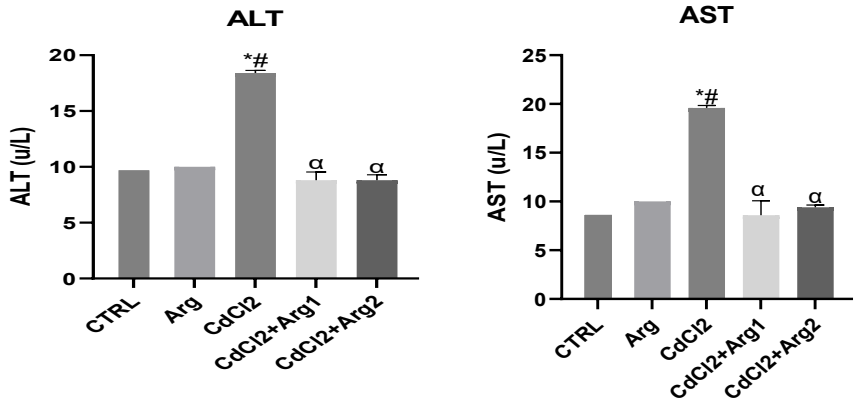


Figure 3: *shows the effect of l-arginine supplementation on serum level of ALT and AST. Key:* ***CTR****: Control;* ***Arg****: 200 mg/kg arginine only;* ***Cdcl₂****: received 5 mg/kg;* ***Cdcl₂+Arg 1;*** *received 5 mg/kg Cdcl₂ with 100 mg/kg Arg.* ***Cdcl₂+Arg 2;*** *received 5 mg/kg Cdcl₂ with 200 mg/kg Arg side by side for 28 days. *p<0.05 compared to CTR; #p<0.05 compared to Arg; α p<0.05 compared to Cdcl₂.*

Effect of l-arginine on Alkaline phosphatase (ALP) and Total bilirubin (TB).

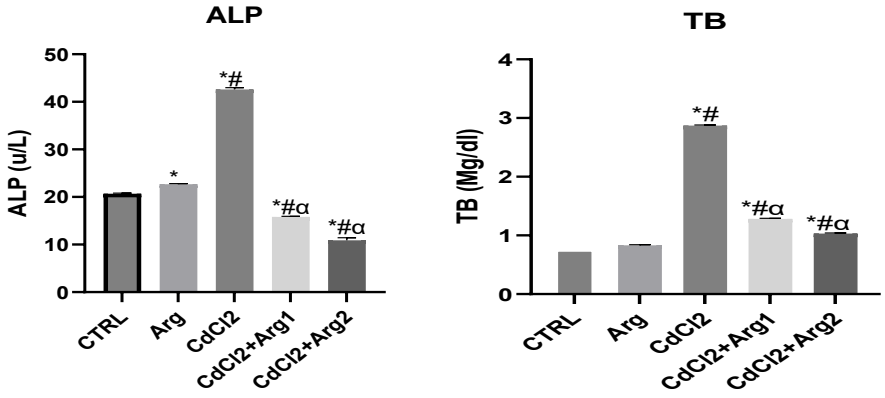


Figure 4: *shows the effect of l-arginine supplementation on serum level of ALT and AST. Key:* ***CTR****: Control;* ***Arg****: 200 mg/kg arginine only;* ***Cdcl₂****: received 5 mg/kg;* ***Cdcl₂+Arg 1;*** *received 5 mg/kg Cdcl₂ with 100 mg/kg Arg.* ***Cdcl₂+Arg 2;*** *received 5 mg/kg Cdcl₂ with 200 mg/kg Arg side by side for 28 days. *p<0.05 compared to CTR; #p<0.05 compared to Arg; α p<0.05 compared to Cdcl₂.*

Discussion

Cadmium chloride is a well-established toxicant as evidenced in the findings of this present study where it induced oxidative stress, inflammation, and hepatocellular injury with significant histopathological alterations in the liver, characterized by hepatocyte degeneration, sinusoidal distortion, and inflammatory infiltration. These findings are consistent with previous studies reporting that cadmium exposure disrupts liver architecture through oxidative stress-mediated mechanisms and inflammatory responses.[19, 20] The observed hepatocellular degeneration and inflammatory changes may be attributed to excessive generation of reactive oxygen species (ROS), leading to lipid peroxidation, which disrupt cellular integrity and impair antioxidant defense mechanisms.[20] Similar structural alterations, including vacuolation, necrosis, and sinusoidal dilatation, have been documented in experimental models of cadmium-induced hepatotoxicity.[20, 21]

Moreso, cadmium induced oxidative stress and hepatic dysfunction, have been reported in similar work demonstrating decreased enzyme activities, where it interferes with enzyme synthesis and function[22]. The

observed reduction in antioxidant enzymes in the cadmium treated group suggests depletion of the endogenous antioxidant defense system. These enzymes are sensitive biomarkers of liver injury, and their increase is indicative of cellular damage and necrosis[23]. Similar findings have been reported in experimental models, where cadmium exposure led to hepatocyte necrosis, sinusoidal dilatation, and inflammatory cell infiltration[23]. However, there are reports showing that co-treatment with a protective compound (naringenin) in a cadmium induced model of liver damage, significantly restored normal hepatic architecture, indicating that reversal of histological alterations is a hallmark of effective hepatoprotection[24].

L-arginine supplementation increased antioxidant enzyme activities with reduction in MDA levels, thereby enhancing antioxidant defense system. This agrees with similar study where it has been shown to enhance endogenous antioxidant defense systems by increasing the activity of enzymes such as superoxide dismutase and catalase, thereby reducing oxidative damage [25]. This mechanism is consistent with the improved biochemical indices observed in the treated groups. Liver functional parameters were significantly attenuated indicating its hepatoprotective potential. This finding resonates with earlier studies demonstrating that L-arginine supplementation reduces oxidative stress and improves liver function parameters in toxicant-induced liver injury, highlighting its potential as a possible therapeutic agent in mitigating cadmium-induced hepatotoxicity[25]. Furthermore, L-arginine may modulate inflammatory responses and inhibit apoptosis, contributing to the preservation of hepatic architecture seen in histological examinations[11]. This finding is consistent with previous studies demonstrating the antioxidant and cytoprotective effects of L-arginine in toxicological conditions. These findings suggest that it promotes cellular recovery and structural integrity of the liver. The dose-dependent improvement observed in this study further supports the therapeutic potential of L-arginine in mitigating cadmium-induced hepatotoxicity. Also, earlier studies indicating that L-arginine exerts protective effects against toxicant-induced liver injury by enhancing antioxidant defense systems and reducing oxidative stress[25]. Similarly, there are reports consistent with the restoration observed in this study, involving co-administration of L-arginine and a hepatotoxic agent (cyclosporine A) which demonstrated marked reduction of histopathological lesions, including decreased hepatocellular necrosis and inflammatory changes compared to the toxicant-only group, indicating that L-arginine can reverse liver injury at the tissue level[10].This hepatoprotective effect may be linked to its role as a precursor of nitric oxide (NO), a signaling molecule involved in hepatic microcirculation, antioxidant regulation, and cellular homeostasis. Adequate NO production has been shown to improve sinusoidal blood flow, reduce oxidative stress by scavenging of free radicals, and stabilize hepatocyte membranes, thereby contributing to the preservation of normal liver morphology[7,12].

The absence of histological alterations in the L-arginine-only group demonstrate its non-toxic nature, there was maintenance of normal liver histoarchitecture in this present study suggesting that L-arginine did not elicit inflammatory infiltration, hepatocellular degeneration, or vascular congestion, thereby confirming its safety profile at therapeutic doses. This finding is in tandem with similar work where L-arginine treatment was shown to enhance hepatic antioxidant enzyme activities, increase nitric oxide bioavailability, and maintained normal histological appearance of liver tissues in experimental animals treated with L-arginine alone or preconditioned prior to hepatic injury[26]. Furthermore, arginine administration has been reported to improve hepatic antioxidant status through increased glutathione, superoxide dismutase, and nitric oxide levels while preventing oxidative damage and structural distortion of hepatocytes[27]. Their findings reinforce the concept that L-arginine also possesses cytoprotective properties. These observations collectively support the present findings and indicate that L-arginine administration alone may contribute to the maintenance of normal liver function.

Conclusion

This study findings reinforce the role of oxidative damage as a central mechanism in cadmium-induced liver injury demonstrating L-arginine supplementation effectiveness in attenuation of these adverse effects in a dose-dependent manner. Its administration restored antioxidant enzyme activities, reduced lipid peroxidation improved liver enzyme profiles and preserved hepatic histoarchitecture. The protective effects observed are likely mediated through its role as a nitric oxide precursor, enhancement of antioxidant defenses, and modulation of inflammatory responses. L-arginine possesses significant hepatoprotective potential against cadmium-induced toxicity and may serve as a therapeutic agent. However, further studies are highly recommended to elucidate its precise molecular mechanisms underlying its protective effects and possible clinical application in human populations.

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