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Research Article
Ameliorative Effect of Lipoic Acid on Cadmium Induced Hepatotoxicity and Nephrotoxicity in Rats

Eman T. Mohammed and Khalid S. Hashem

Department of Biochemistry, Faculty of Veterinary Medicine, Beni-Suef University, 62511 Beni-Suef, Egypt

Abstract

Background and Objective: Environmental pollution with cadmium is one of the most deleterious agents to the biological life. Industries such as cement plants, batteries and smoke offered additional hazards to the environment surrounding man and animals. The present study aimed to assess the protective effects of high dose of lipoic acid on cadmium-induced toxicity in rats. **Materials and Methods:** The experiment was carried out on 30 male albino rats, these rats were divided randomly into 3 groups (n = 10 rats): Control group (0.5 mL phosphate-buffered physiological saline orally), Cd group (5 mg kg^{-1} b.wt., cadmium chloride ($CdCl_2$) orally). LA+Cd group (5 mg kg^{-1} b.wt.,/day $CdCl_2$+100 mg kg^{-1}/day Lipoic acid orally). All treatments were administered daily for 30 days. **Results:** The study revealed that the administration of cadmium chloride induced a significant increase in serum alanine transaminase (ALT), aspartate transaminase (AST), creatinine and urea. In addition, cadmium significantly decreased the serum total protein, albumin concentrations and acetyl cholinesterase activity. It also induced a significant increase in catalase (CAT), superoxide dismutase (SOD), Malondialdehyde (MDA) and DNA fragmentation (%) in liver and kidney tissues of rats. In addition, reduced glutathione (GSH) content of liver and kidney tissue homogenates significantly decreased. The biochemical results were confirmed by histological findings where many lesions were noticed in liver and kidneys treated with cadmium. Administration of lipoic acid with cadmium chloride showed a significant improvement in the above parameters and histopathological pictures. **Conclusion:** The present study concluded that the supplementation with 100 mg kg^{-1} b.wt., of lipoic acid is effective against cadmium toxicity. It is advisable to give it to workers in cement factories.

Key words: Oxidative stress, cadmium, lipoic acid, liver, kidney, rat

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Corresponding Author: Eman T. Mohammed, Department of Biochemistry, Faculty of Veterinary Medicine, Beni-Suef University, 62511 Beni-Suef, Egypt Tel/Fax: +20 822327982

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cadmium is an environmental pollutant with an extremely long biological half lifetime of 15-20 years in human[1]. Mining, agricultural and industrial activities of humans are the main reasons for increasing cadmium concentration in the environment. The divalent Cadmium is not biodegradable and persists in the environment. Despite efforts by many countries and international agencies to reduce the usage of Cadmium, it continues to be a major public health problem, especially in emerging industrial nations where environmental controls are still being developed [2]. Humans typically exposed to Cadmium either in the workplace or through the ingestion of Cadmium-contaminated food or water[3]. Among the sources of cadmium is Tobacco smoking[4] and cement industry[5]. Cement dust spread along a large area through wind, rain and then Cadmium accumulated in plants, animals and soil and can affect human health badly[5].

Cadmium exposure induces numerous pathological effects, including liver and kidney dysfunction, disturbed calcium metabolism and lung cancer after inhalation[1].

Acute Cadmium toxicity causes liver and testes damage, pulmonary edema, while chronic toxicity leads to immuno-toxicity, nephrotoxicity andosteotoxicity[6]. Cadmium is categorized by the International Agency for Research on Cancer (IARC) as a human carcinogen causing lung and prostate tumors[7].

Oxidative stress is a major mechanism of acute Cadmiumtoxicity[8]. The liver is the main storage organ for cadmium in the body but the highest concentration eventually reached in the kidneys[9]. Cadmium is efficiently retained in the kidney (half-time 10-30 years) causing kidney tubular damage. Bone damage is caused either by a direct effect of Cadmium on bone tissue or indirectly because of kidney dysfunction. After prolonged exposure to Cadmium, the tubular injury may progress to glomerular damage with decreased glomerular filtration rate and eventually to renal failure[10].

Recently, more attention has been paid to the protective effects of natural antioxidants against chemicals-induced toxicities especially whenever free radical generations are involved. Among these natural antioxidants is α-Lipoic acid (LA). Alpha-lipoic acid (also known as thioctic acid) is an endogenous, sulfur-containing, free radical scavenger[11]. Chemically, LA with the five-member ring with a smaller CS-CS torsional angle makes the S-S bond more easily reduced and oxidized than open-chain analogs[12]. The LA is a potent antioxidant and it acts as an efficient chelator of numerous metals. α-Lipoic acid can be used as a vitamin-like substance because it acts as an important coenzyme for enzymes essential for metabolism inside the mitochondria[13], such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase[14]. Since LA is produced in small amounts in human bodies, many people turn to increase their intake as supplements. There is inadequate data about the potential side effects of taking higher doses and the previous reports use small doses. Therefore, the current study aimed to evaluate the possible protective effects of lipoic acid supplementation with a high dose (100 mg kg^{-1} b.wt.,) on cadmium-induced toxicity in liver and kidney of rats beside the histopathological changes of hepatic and renal tissues.

MATERIALS AND METHODS

Experimental animals: A total number of 30 adult male Wister rats of an average body weight 130-150 g were used in this experiment. The rats were obtained from Helwan farm of laboratory animals, Cairo, Egypt. After 2 weeks acclimatization, rats were distributed into 3 groups (n = 10). Rats were kept at a humidity (60%) and an optimum temperature (25±2°C) under 12:12 h light-dark cycle. Rats were fed a basal diet and water ad libitum. All experimental methods were performed according to the recommendations for the care and use of laboratory animals and approved by the Institutional Animal Care and Use Committee at Beni-Suef University.

Chemicals: Cadmium chloride (Cd Cl2)(99.0% purity) was purchased from Lobachemie Company (India). Alpha-lipoic acid (ALA-also known as thioctic acid) is marketed as (Thiotacid®) by EVA pharma for Pharmaceuticals and Medical Appliances, Egypt. It is available as tablets of 300 and 600 mg concentrations. The diagnostic kits used for testing of the acetyl cholinesterase activity, alanine transaminase (ALT), aspartate transaminase (AST), total proteins, albumin, creatinine and urea were purchased from Spinreact., Spain. Reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and malondialdehyde (MDA) kits were obtained from Bio-diagnostic Company, Egypt. All chemical reagents were purchased from Sigma Aldrich Co., USA.

Methods

Experimental design and animal grouping: About 30 male albino rats weighing 130-150 g were used. The animals were divided into 3 groups (10 each) and were treated as follows: control group: Orally received saline daily for 4 weeks. The Cd group: Received an oral dose of 5 mg kg^{-1} b.wt.,t\day $CdCl_2$

dissolved in distilled water[15]. The LA+Cd group: Received an oral dose of 5mg kg^{-1} b.wt., $CdCl_2$ followed by 100 mg kg^{-1} b.wt., lipoic acid[16]. The lipoic acid tablets were crushed, suspended in distilled water and then given orally daily for 4 successive weeks.

Sampling and tissue preparation: Blood samples were collected at the end of the experiment from each rat at a fasting state. Blood samples were collected and left to coagulate at room temperature and then centrifuged at 1000 Xg for 10 min. The clear supernatant sera were stored at -20°C until used for biochemical investigation of ALT, AST, acetyl cholinesterase, total proteins, albumin, urea and creatinine. After dissection of the animals, liver and kidneys were quickly excised and divided into two parts. The first one was homogenized in ice-cold phosphate buffered saline PH: 7 and the homogenate was kept in deep freezer at-20°C for estimation of Redox biomarkers including CAT, SOD, GSH, MDA and DNA fragmentation (%). The second one was kept in 10% formalin for histopathological investigation.

Biochemical assays: Kits for serum ALT, AST[17], total proteins[18], albumin[19], urea[20], creatinine[21] and serum acetyl cholinesterase activity[22] were assayed spectrophotometrically. The estimation of GSH, MDA concentrations, SOD, CAT activities and DNA fragmentation (%) were determined in tissues of liver and kidney using the methods of Beutler *et al.*[23], Albro *et al.*[24], Nishikimi *et al.*[25], Aebi[26] and Burton[27], respectively.

Preparation of histological sections: Specimens of the liver and kidney were fixed in 10% formalin for 24 hand processed according to Drury and Wallington[28]. The specimens were embedded in paraffin and sectioned at a thickness of 5 microns. The sections were stained with hematoxylin and eosin stain and examined under the light electric microscope.

Statistical analysis: All values are presented as Mean±SE Statistical significance was evaluated by one-way analysis of variance (ANOVA) test followed by Tukey-Kramer multiple comparisons post-test. Significance was measured using Graph Pad In stat software (Version 3, ISS, Rome, Italy). The difference between groups was considered significant when $p<0.05$.

RESULTS

Biochemical changes in different groups: The results in a Table 1 showed a significant increase ($p<0.05$) in serum liver enzymes ALT and AST and a significant decrease in both total proteins and albumin concentrations and acetyl cholinesterase activity in Cd group compared to control group. Administration of LA with Cadmium reversed the values in a significant manner ($p<0.05$) compared to those of the (Cd group). The obtained results in a Table 2 showed a marked significant increase ($p<0.05$) in serum urea and creatinine concentrations in the Cd group compared to control group. Lipoic acid nearly returned the values towards the normal. Regarding redox status, Table 3 and 4 showed a significant decrease ($p<0.05$) in GSH concentration and a significant increase ($p<0.05$) in MDA concentration, CAT and SOD activities in both liver and kidney in the Cd group compared to control group. The results also showed a marked significant ($p<0.05$) increase in DNA fragmentation (%) in the Cd group compared to the control. Lipoic acid treatment nearly returned these values toward the normal.

Histopathological changes in liver and kidney in different groups: Light micrographs of liver sections (Fig. 1: b1, 2) in Cd group showed pyknotic hepatocytes with enlarged hepatic sinusoids and severely congested blood vessels as well as the presence of inflammatory cells infiltration in hepatic sinusoids. Light micrographs of liver sections (Fig. 1c) in Cd+LA group showed a little congestion of blood vessels as compared with that of the Cd group, no inflammatory cells infiltration. The liver cells begin to return to normal. Light micrographs of kidney sections (Fig. 2b) in Cd group showed a marked dilatation of Bauman's capsule and damage of the glomerular epithelium with severe congestion of the renal blood vessels

Table 1: Changes in serum ALT, AST, acetyl cholinesterase activities (U L^{-1}), total proteins and albumin concentrations (g dL^{-1}) in different rat groups

Animal groups	ALT (U L^{-1})	AST (U L^{-1})	Acetyl cholinesterase (U L^{-1})	Total proteins (g dL^{-1})	Albumin (g dL^{-1})
Control group	16.35±1.6^a	36.42±2.8^a	23.19±0.91^a	6.4±0.21^a	4.8±0.16^a
Cd group	96.50±5.3^b	97.70±4.5^b	5.67±0.62^b	3.7±0.30^b	2.6±0.17^b
LA+Cd group	30.50±2.0^c	32.80±2.2^c	12.46±0.8^c	5.0±0.22^c	3.7±0.14^c

Cd: Cadmium, LA: Lipoic acid. Values are represented as Mean±Standard error. The different superscript letters mean a significant difference at $p>0.05$

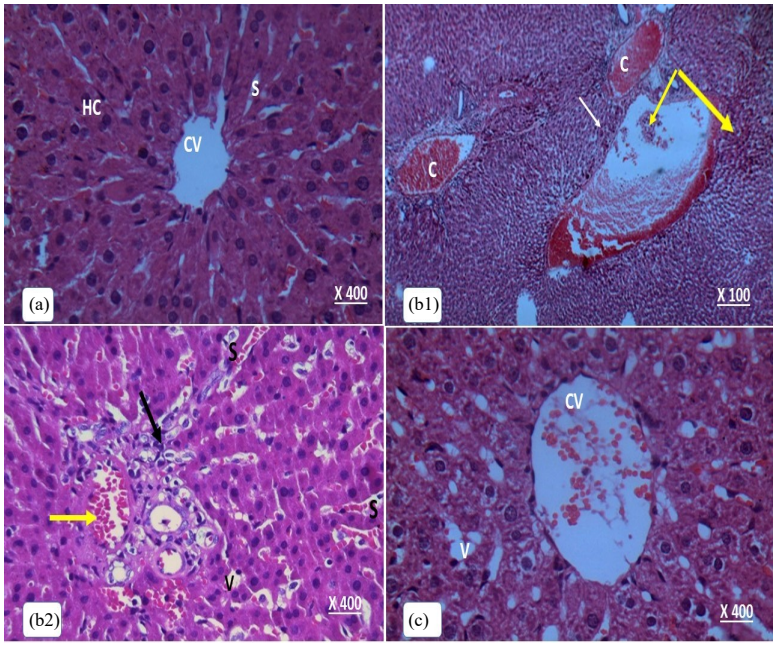

Fig. 1: (a) Photomicrograph of rat liver tissues of control group. It showed normal hepatic lobule, centrally located central vein radiating from it hepatic cords with normal hepatic sinusoids (s) and hepatocytes (H) (H and E stain-X 400). (b1-2): Photomicrographs of rat liver tissues of Cd group, it showed a pyknotic hepatocytes (black arrow) with enlarged hepatic sinusoids (s) and severe congested blood vessels, (c) presence of inflammatory cells infiltration (yellow arrow) in hepatic sinusoids (H and E stain X100), (c) Photomicrograph of rat liver tissues of LA+Cd group. It showed a little congestion of blood vessels (c) as compared with that of the Cd group, no inflammatory cells infiltration. The liver cells begin to return to normal and the nucleoli began to appear again (H and E stain X 400)

Table 2: Changes in blood urea and serum creatinine concentrations (mg dL^{-1}) in different rat groups

Animal groups	Urea (mg dL^{-1})	Creatinine (mg dL^{-1})
Control group	33.5±1.6^{a}	0.9±0.06^{a}
Cd group	69.8±2.7^{b}	2.6±0.11^{b}
LA+Cd group	46.3±1.4^{c}	1.3±0.09^{c}

Cd: Cadmium, LA: Lipoic acid. Values are represented as Mean±Standard error. The different superscript letters mean a significant difference at p>0.05

Table 3: Changes in liver and kidney GSH and MDA concentrations in different rat groups

	Parameters			
	GSH (mmol g^{-1} tissue)		MDA (nmol g^{-1} tissue)	
Groups/tissue	Liver	Kidney	Liver	Kidney
Control group	46.60±2.3^{a}	42.76±1.6^{a}	31.9±1.6^{a}	35.27±1.4^{a}
Cd group	12.50±0.7^{b}	9.17±0.7^{b}	85.6±3.6^{b}	88.47±2.4^{b}
LA+Cd group	33.35±2.7^{c}	26.05±2.03^{c}	54.4±1.5^{c}	55.70±1.6^{c}

Cd: Cadmium, LA: Lipoic acid. Values are represented as Mean±Standard error. The different superscript letters mean a significant difference at p>0.05

Table 4: Changes in liver and kidney catalase and SOD activities and DNA fragmentation % in different rat groups

	Parameters					
	CAT (U g^{-1} tissue)		SOD (U g^{-1} tissue)		DNA fragmentation (%)	
Groups/tissue	Liver	Kidney	Liver	Kidney	Liver	Kidney
Control group	1.80±0.17^{a}	2.45±0.15^{a}	71.2±3.2^{a}	57.45±2.0^{a}	28.08±2.1^{a}	27.10±1.5^{a}
Cd group	8.04±0.61^{b}	7.34±0.33^{b}	143.4±12.1^{b}	143.70±10.1^{b}	64.50±3.8^{b}	73.17±1.11^{b}
LA+Cd group	5.95±0.42^{c}	5.16±0.42^{c}	96.8±1.5^{c}	86.60±3.2^{c}	52.60±3.24^{c}	53.76±2.6^{c}

Cd: Cadmium, LA: Lipoic acid. Values are represented as Mean±Standard error. The different superscript letters mean a significant difference at p>0.05

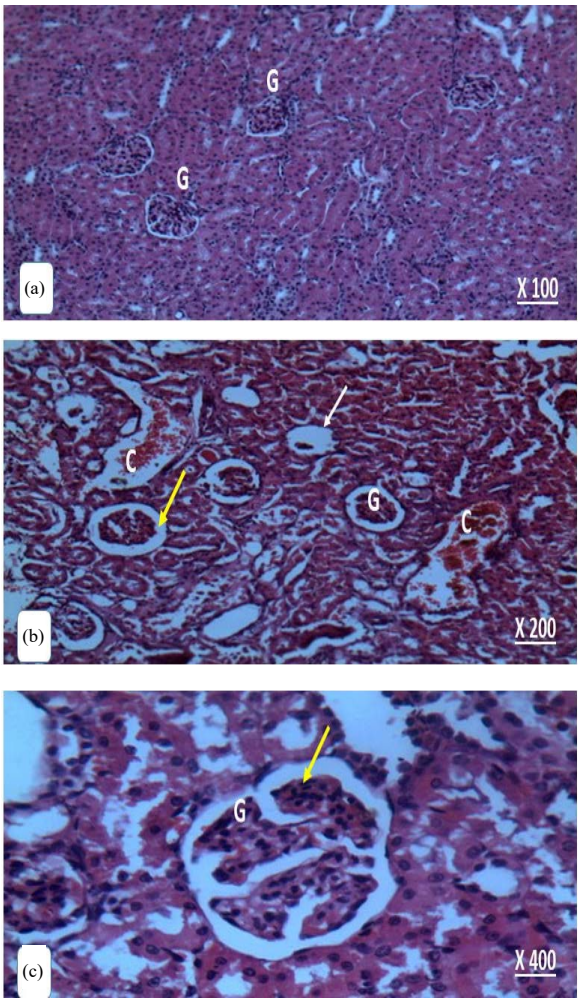

Fig. 2(a-c): (a) Photomicrograph of rat kidney tissues of control group. It showed normal glomeruli (G) with no inflammatory reaction and no congestion of blood vessels (H and E stain X100), (b) Photomicrographs of rat kidney tissues of Cd group, it showed a severe damage of glomeruli (yellow arrow) and severe congestion of the renal blood vessels (c). Marked dilatation of Bauman's capsule and damage of glomerular epithelium (white arrow) were obvious (H and E stain X200) and (c) Photomicrograph of rat kidney tissues of LA+Cd group. It showed little inflammatory reactions (yellow arrow), less hemorrhage as compared to that of Cd group (H and E stain X400)

after cadmium exposure. Lipoic acid supplementation prevents cadmium-induced degenerative changes in kidney tissues (Fig. 2c).

DISCUSSION

The mechanism of cadmium-induced damage includes the generation of reactive oxygen species (ROS) that alters the mitochondrial viability and genetic information[29]. Therefore, the antioxidants are valuable and effective agents against cadmium toxicity[15]. Therefore, lipoic acid was chosen to evaluate its possible protective effect against cadmium-induced hepatotoxicity and nephrotoxicity. The liver is a major target of Cadmium toxicity following acute exposure[6] and ROS have been implicated in Cadmium hepatotoxicity. Cadmium has been shown to generate (Phenyl tertbutylnitrone) radical adducts and alpha-(4-pyridyl-1-oxide)-N-t-butylnitrone (POBN)-radical products[8].

In this study, liver enzymes ALT and AST in the Cd group were significantly elevated compared with the control group as shown in the Table 1, agreed with Renugadevi and Prabu[30] and Obioha *et al.*[31] denoting the presence of liver dysfunction[32]. The increase in plasma AST and ALT activities indicated an active transamination of amino acids and operation of keto acids, which are probably fed into tricarboxylic acid cycle (TCA) for oxidation[33]. The increase in the activities of AST and ALT in serum is mainly due to the leakage of these enzymes from the liver cells into the blood stream[34], which gives an indication of the hepatotoxic effect of $CdCl_2$. In this investigation, it was also found a significant diminution in serum total proteins and albumin in the Cd group compared with the control group as shown in the Table 1. The decrease in serum total proteins and albumin of Cd-treated rats might be due to changes in protein synthesis and/or metabolism[35]. This result is in agreement with other findings reported by Yousuf[36]. Cadmium is one of the heavy metals that induce membrane damage[37], so the decrease in serum proteins and albumin formation may indicate some liver dysfunction. The decrease in plasma proteins due to exposure to Cadmium may be due to increased excretion of high molecular weight protein (proteinuria)[38]. Serum acetyl cholinesterase activity was significantly decreased (Table 1). The result was agreed with El-Demerdash *et al.*[39] *in vitro*, El-Demerdash and Elagamy[40] in fish. The mechanism of the inhibition of acetyl cholinesterase by metals is not clear. It has been generally accepted that metals deactivate cholinesterase by binding to their anionic site[41], thus preventing acetylcholine from binding to cholinesterase and degradation suggesting that different metals can inhibit acetyl cholinesterase distinctly because of their unique properties, such as ionic size, the capacity of forming a complex, electro-negativity and reduction potential[42].

With the chronic, low-level patterns of Cadmium exposure that are commonly seen in human populations, the primary target organ of Cadmium toxicity is the kidney, where Cadmium causes a generalized dysfunction of the proximal tubule characterized by polyuria and increases the urinary excretion of glucose, amino acids, electrolytes (particularly Na^+, K^+ and Ca^{2+}) and low molecular weight proteins[43,44]. The present results showed a significant elevation of the serum levels of creatinine and urea after cadmium treatment in Cd group compared to the control group (Table 2) indicated kidney dysfunctions, which were in agreement with Novelli *et al.*[45]. Urea is the first acute renal marker, which increases in response to any kind of kidney injuries. Creatinine is the most accurate renal bio-marker that increases after a complete loss of renal function[46]. The increased levels of serum urea and creatinine noted in the current study concluded the severely injured effect of cadmium on the kidney.

Oxidative stress is a major mechanism of acute Cadmium toxicity[8]. The ROS induce lipid per-oxidation, protein oxidation and alter DNA, RNA thereby interfering with normal cell growth and differentiation[47]. Currently, lipid per-oxidation was indicated by the significant elevation of MDA in liver and kidney tissues of rats treated with cadmium (Table 3), thus suggesting increased oxidative stress. These results were supported by Manca *et al.*[48], Hassoun and Stohs[49], Jurezuk *et al.*[50] and Kawamoto *et al.*[51], who reported that lipid per-oxidation is the first consequence of cadmium toxicity. The GSH concentration was significantly decreased in the liver and kidney of Cd group compared to the control group (Table 3). The decrement in GSH contents may be due to its consumption in the detoxification of heavy metals[52] and prevention of the lipid peroxidation[53]. In contrast, Kamiyama *et al.*[54] found that cadmium could increase the GSH concentrations in liver and kidney as a response mechanism against oxidative stress.

This study showed that the administration of cadmium could significantly increase SOD and CAT activities in liver and kidney (Table 4), which agreed with the findings of Maritim *et al.*[55]. The SOD and CAT establish a defense mechanism against ROS. The SOD is a metalloprotein that catalyzes the dismutation of superoxide anion (O^{-2}) to hydrogen peroxide[56] H_2O_2. Catalase is a hemeprotein that catalyzes the reduction of H_2O_2 to water and oxygen and thus protects the cell from oxidative damage[57] by H_2O_2 and OH^-. The increase in these enzyme activities suggested a response toward increased ROS generation[58,59]. The principal mechanism of Cadmium genotoxicity, mutagenicity and carcinogenicity is the generation of ROS[60], which leads to inhibition of DNA repair[61] and depletion of glutathione[62]. The results of the current study confirmed such changes in DNA where a significant increase in the percentage DNA damage was observed in the liver and kidney of rats treated with Cadmium when compared with control group (Table 4). Malondialdehyde, 4-hydroxy-2-nonenol and several reactive mutagenic and genotoxic lipid per-oxidation products bind to DNA causing strand breakage and distortion[63], which is in line with the present findings. This may explain the reason for increased DNA damage after cadmium exposure.

In the current study, treatment with $CdCl_2$ caused liver damage demonstrated functionally by increasing the activity of ALT and AST and histological alterations. These alterations were in the form of dilatation and congestion of central veins and blood sinusoids. Presence of inflammatory cells infiltration (IR) in hepatic sinusoids and pyknotic hepatocytes as well (Fig. 1). These results coincide with the results of Borges *et al.*[46]. In the present study, the administration of cadmium induced a significant damage in function and structure of kidney indicated by the increased serum creatinine and urea concentrations and presence of a severe damage of glomeruli and severe congestion of the renal blood vessels. Marked dilatation of Bauman's capsule and damage of glomerular epithelium were also obvious (Fig. 2). Similar findings were observed by Damek-Proprawa and Sawicka-Kapusta[64].

Alpha-lipoic acid is an endogenous, sulfur-containing antioxidant[11]. The LA has a metal chelating capacity, ROS scavenging ability, regeneration of endogenous antioxidants as vitamin E, vitamin C, GSH and repairing of oxidative damage throughout the body[65]. Several studies on the distribution and metabolism of LA in human and rats have shown that LA is rapidly absorbed in the gut, taken up into various tissues where the highest amount was detected in the liver after 4 h of oral administration[66]. During the first 24 h, 45% of LA was excreted in the urine and only 3% is excreted in the faces[67].

The administration of LA in this study caused a significant improvement in liver function and structure, which appeared in restoring the enzymes ALT, AST, acetyl cholinesterase, total proteins and albumin in LA+Cd group (Table 1) to be approached to their normal levels in comparative with Cd group. In the present study, LA caused a significant improvement in kidney function that appeared in the decrease in the levels of blood urea and serum creatinine (Table 2), similar results were obtained in previous studies, Abdel-Zaher *et al.*[68] reported that LA was effective in normalizing the antioxidant levels as well as levels of creatinine and blood urea nitrogen in acetaminophen-

induced renal damage in rats. In another study, LA attenuated the elevation in creatinine and blood urea nitrogen induced by cisplatin in mice[69].

In the present study, administration of LA increased the level of GSH in liver and kidney tissues compared to the Cd group (table 3), a finding which is in agreement with that of Melhem *et al.*[70]. This may be explained on the bases that LA and their reduced form (dihydrolipoic acid) may act as extra- and intracellular redox couples and powerful lipophilic free radical scavenger[71]. This explanation is supported by the findings that stated that LA is a powerful free radical scavenger and capable of increasing concentration of GSH in tissues[72]. LA increase the de novo synthesis of cellular GSH by improving cystine utilization and enabling the enzyme gamma-glutamylcysteine synthetase, to work at optimum conditions[73]. In the present study, the beneficial effects of LA were manifested by a significant decrease in MDA levels in liver and kidney tissues (Table 3) and a decrease in antioxidant enzyme activities (CAT and SOD) (Table 4). A similar decrease was reported in rats treated with cisplatin[74,75]. The LA has a strong ability to chelate metals and to scavenge free radicals such as hydroxyl radical[74]. In addition, LA is easily absorbed and transported across cell membranes, thus, free radical protection occurs both inside and outside of cells[76]. Moreover, the present results showed that LA has the capacity to induce repair of DNA damage that is in agreement with what was reported with Suzuki *et al.*[77].

The histopathological findings of liver and kidney illustrated in Fig. 1, 2 confirmed the success of LA treatment in the prevention of the alterations caused by $CdCl_2$ toxicity and the amelioration of organ damage.

According to Jones and Cherian[78], an ideal heavy metal chelator should be able to enter the cell easily, chelate the heavy metal from its complex with metallothionein or other proteins and increase the metal excretion without its accumulation in other organs. There is evidence that LA is chemically able to trap circulating heavy metals, thus preventing cellular damage caused by metal toxicity[79]. Lipoic acid is lipophilic and is able to penetrate cell membranes and reach high intracellular concentrations within 30 seconds of its administration[80].

CONCLUSION

The present biochemical and histological results verified that lipoic acid with a high dose of (100 mg kg^{-1} b.wt.,) has the ability to protect the liver and kidney against oxidative damages and could be used as an effective antioxidant against cadmium-induced hepatotoxicity and nephrotoxicity without inducing any adverse effects. It is advisable to give it safely to workers in cement factories.

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