# Biochemical, Histological, and Immunohistochemical Changes Associated with $Alcl_3$- Induced Hepatic Injury in Rats: Protective Effects of L-carnitine

**Original Article**

*Basant Mahmoud Mohamed[1], Nagui Hassan Fares[1], Neveen Asem Ashaat[2] and Faten Sabra Abo-Zeid[1]*

[1]*Department of Zoology, Faculty of Science, Ain Shams University, Cairo, Egypt.*

[2]*Departments of Science and Education, Faculty of Women for Arts, Ain Shams University, Cairo, Egypt*

## ABSTRACT

**Background:** There has been a great interest in the toxicity of Aluminum (Al) due to its environmental wide distribution and every day usage. The key mechanisms of Al -induced toxicity in the liver are recognized as reactive oxygen species (ROS), development of free radicals, oxidative stress, and lipid peroxidation. L-carnitine is a conditionally important amino-acid (4-N-trimethylammonium-3-hydroxybutyric acid). By L-carnitine, long-chain fatty acids are taken into the mitochondria contributing to the metabolism of cellular energy. Also, it can enhance the antioxidant status by accelerating the free radicals removal from cells.

**Objective:** The purpose of this report was to determine the possible detrimental impact of $Alcl_3$ and to evaluate for the first time the possible potential hepato-protective effect of exogenous L-carnitine supplementation in ameliorating these possible deteriorations.

**Materials and Methods:** Thirty two rats were subdivided into equal four groups, Group I: Control rats, Group II: Rats treated with L-carnitine at a dose of 200 mg/kg. b.wt., Group III: Rats treated with $Alcl_3$ at a dose of 100 mg/kg. b.wt., and Group IV: Rats treated with L-carnitine and $Alcl_3$ (200 and 100 mg/kg. b.wt., respectively). All procedures of given materials to animals were orally once daily for one month.

**Results:** The current investigation showed that $Alcl_3$ ingestion caused an obvious hepatic deterioration evidenced by increased liver enzymes level and imbalance in oxidant/antioxidant status. This was accompanied by histological changes and increased caspase-3 immunoreactivity. These effects were significantly improved by L-carnitine supplementation.

**Conclusion:** These findings suggested that L-carnitine may have a protective effect against hepatic damage sustained by $Alcl_3$ through its antioxidative property and its inhibitory effect on apoptosis.

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**Key Words:** $Alcl_3$, biochemistry, histology and immunohistochemistry, L-carnitine.

**Corresponding Author:** Faten Sabra Abo-Zeid , PhD, Department of Zoology, Faculty of Science, Ain Shams University, Cairo, Egypt, **Tel.**: +20 10601 22605, **E-mail:** faten.sabra@yahoo.com

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## INTRODUCTION

Aluminum (Al) is known to be of the furthermost common metals in the crust of earth[1]. Recently, sensitivity to Al has been growing. The principle route for Al to reach the human body is the ingestion of processed food and water filtered with additives containing Al[2]. It has the potential to cause toxicity for the human beings and animals in multiple tissues, such as the liver, kidney, brain, and heart. Al accumulation occurs causing hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, and Alzheimer's disease[3].

Al salts such as Al Chloride ($Alcl_3$) are broadly used as flocculants in the treatment of drinking water for purification purposes which permitted its easy access into the body via gastrointestinal tract and lung tissue[4]. Antioxidant defense and reactive oxygen species (ROS) imbalance refers to oxidative stress[5] that participate in free radicals formation[6]. Free radicals affect essential elements of the cell, such as lipids, proteins, and DNA[2,7]. In addition, ROS is occupied in lipid peroxidation (LPO), which also boosts the permeability of mitochondria and changes their role[8]. Ingestion of $Alcl_3$ interferes with the oxidative/antioxidative equilibrium inducing LPO, and reducing the antioxidant enzyme activities causing oxidative damage, cell death and toxicity[9,10]. A possible therapeutic strategy for $Alcl_3$-induced hepatotoxicity is therefore known to be attenuation of oxidative stress with antioxidant supplementation.

L-carnitine (4-N-trimethylammonium-3-hydroxybutyric acid) is a provisionally important amino acid. Its primary source in human is exogenous from animal diet and the smaller quantity in the brain, kidney, and liver is endogenous from methionine or lysine[11]. It is responsible

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for long-chain fatty acids transport into mitochondria; thus it is a significant provider to cellular energy metabolism[12]. Several experimental researches have indicated that L-carnitine can boost the antioxidant status by accelerating the free radicals and LPO elimination[13]. Furthermore, many studies have stated that L-carnitine has possible hepatoprotective effects through several mechanisms against hepatotoxicity of various drugs[14-16], and anti-inflammatory, and anti-apoptotic properties[17].

Effective therapeutic plan is often required to minimize the emergence and spread of diseases, therefore the present work was directed to study for the first time the possible hepatoprotective outcome of exogenous L-carnitine in ameliorating liver injury induced by $Alcl_3$. Therefore, activities of serum liver enzymes, oxidative stress, antioxidant biomarkers, and liver histological and immunohistochemical assessments were conducted.

## MATERIALS AND METHODS

### *Chemicals and drugs*

Aluminum chloride ($Alcl_3$) powder was actually bought from Alpha Chemika (India). L-carnitine capsules were obtained from Pharmaceuticals & Medicinal plants Arab Company, Enshas El Rami, Sharkeya, Egypt. Each capsule is made from active 350 mg L-carnitine powder. The chemicals were produced from El-Nasr pharmaceutical chemicals co. (Cairo, Egypt). Prior to use, all chemicals and solutions were prepared instantaneously.

### *Experimental animals*

Animal handling trial was in concurrence with the ethical standards of Ain Shams University Research Ethics Committee and the Helsinki Declaration of 1975 as revised in 1983. Healthy thirty-two male albino rats weighing 120–140 g, were collected from the Medical Research Center at the Faculty of Medicine, Ain Shams University (Cairo, Egypt). The animals were taken to the animal house unit at the Zoology Department, Faculty of Science, Ain Shams University. All the animals were allowed 2 weeks to adapt before the start of any experimental procedures. The animals were maintained in plastic cages at 25 °C and 12 h light/dark cycle. Access to water and standard diet ad libitum was provided to the animals and monitored daily for health status. All attempts have been made to reduce animal suffering and to use only the number of animals required for generating accurate scientific data.

### *Experimental protocol*

Rats were split into four groups of eight rats each, as the following: Group I: Control rats, given the vehicle (0.9% saline). Group II: Rats treated with L-carnitine at a dose of 200 mg/kg. b.wt. Group III: Rats treated with $Alcl_3$ at a dose of 100 mg/kg. b.wt. Group IV: Rats treated with L-carnitine and $Alcl_3$ (200 and 100 mg/kg/b.wt, respectively).

The animals were administered 100 mg/kg.b.wt. of $Alcl_3$ as previously reported by[18]. LD50 of $Alcl_3$ was recorded to be 400 mg/kg b.wt[19]. L-carnitine was administered at a dose of 200 mg/kg.b.wt. as mentioned before and as reported by Heo *et al*.[20]. All treated groups received the drugs once daily for 1 month. Rats were administrated L-carnitine followed by $Alcl_3$. Control group received the vehicle in a similar way.

### *Sample collection*

After 24 hours from the last treatment of all studied drugs, rats were anaesthetized, decapitated, and blood samples were gathered and centrifuged at 3000 rpm for 20 min to obtain sera. The obtained sera were divided into 200 µl aliquots and put in−80◦C until being used for measuring liver enzymes, and oxidant/antioxidant levels. After necropsy, the livers were excised, blotted to eliminate excess blood, weighed, measured and photographed. The estimation of liver index (relative liver weight) was constructed on the formula: (liver weight/bodyweight) × 100.

### *Biochemical analysis*

Biochemical analysis was conducted to identify the alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) serum levels via the manufacturer's protocol of Biodiagnostics Reactivos GPL kits and assessed by electro-chemiluminescence immunoassay on a cobas® e601 immunoassay analyzer (Roche-Hitachi Diagnostics, Mannheim, Germany).

### *Estimation of serum MDA*

Serum lipid peroxidation (LPO) such as malondialdehyde (MDA) was analyzed by colorimetric method, after the reaction with thiobarbituric acid in acidic medium at 95 °C for 30 min. forming thiobarbituric acid reactive product. The resulting substance absorbance was estimated at 534 nm according to Ohkawa *et al*.[21] by usage of commercially accessible diagnostic kits (BIO DIAGNOSTIC, CAT. No. MD 2529 Tahreer St., Dokki, Giza, Egypt).

### *Super oxidase dismutase (SOD)*

According to Nishikimi *et al*.[22], serum SOD was analyzed using the colorimetric approach. The method based on SOD catalyzes the superoxide anion breakdown into molecular hydrogen peroxide and oxygen, thereby becoming a central component of the cellular antioxidant defense mechanism. The resulting absorbance of the product was calculated at 560 nm using commercially diagnostic kits (BIO DIAGNOSTIC, CAT. NO. SD 2521, Giza, Egypt).

### *Glutathione peroxidase (GSH-px)*

Using UV technique, serum levels of GSH-px were assessed according to the procedure defined by Paglia and Valentine[23]. The technique established on the GSH-px enzymes catalyze the hydrogen peroxide conversion to organic peroxide and water to the opposite stable alcohols via the use of glutathione (GSH) as a source of reducing

equivalents. The resulting pink substance absorbance was assessed commercially available diagnostic kits at 340 nm (BIO DIAGNOSTIC, CAT. No. GP 2524, Giza, Egypt).

### *Histological assessment*

After weighing the liver tissue, the left lobe was fixed for 24 hours in 10 percent neutral buffered formalin solution, dehydrated in ascending series of ethanol, cleared in terpineol, embedded in paraffin, then cut at 5 µm. Paraffin sections were deparaffinized in xylene, and hydrated to water through descending sequence of ethanol. Staining was performed using Harris's haematoxylin, and counterstained with 1% aqueous eosin for histological investigation and Masson trichrome technique for fibers detection[24]. Photomicrographs were taken at the Mycology and Biotechnology Regional Center, El-Azhar University, by a camera connected to a Leica DM LS2 microscope (Leica Microsystems, Wetzlar, Germany).

### *Immunohistochemical assessment*

The immunohistochemical assay was done on liver sections (5 µm-thick) for the apoptotic marker (caspase-3). In brief, deparaffinized liver sections were boiled in Declere to show antigen sites, then incubated at 4 °C with a 1:200 dilution overnight of anti-caspase-3 antibodie in phosphate-buffered saline (PBS). The slides were incubated with a 1:500 dilution of biotinylated secondary antibody following the removal of the primary antibodies and repetitive rinsing with PBS. With the avidin-biotin-peroxidase complex, bound antibodies were observed. Three PBS washes were applied between applications. Then, using of 3, 3-diaminobenzidine as a chromogen for visualizing antibody binding. In order to counter stain the slides, hematoxylin was used. Under the same condition and the same time, all sections were incubated with the same antibodies concentration, then the slides were checked under a light microscope. The positive response (i.e., binding of the antigen to the primary antibody) is detected by cellular brownish color appearance.

The caspase-3 expression was assessed as scoring analysis (H-score) as described by Mahamed *et al*.[25]. The authors applied a scoring system constructed on stained cell incidence and reaction intensity. Immunopositivity was determined at 400X amplification by the semi-quantitative method. The stained cells percentages were ranked as the following: 0% (rank 0), (from 1 to 25%) (rank 1), (from 26 to 50%) (rank 2), (from 51 to 75%) (rank 3), and (from 76 to 100%) (rank 4) of the cells in a particular field. The immunoreactions intensity was recorded as: Negative, 0; mild, 1; moderate, 2; or intense, 3. Liver sections without staining were considered to be negative. The total index was achieved by the following equation: Total index = immunopositive cells percentage x immunopositivity intensity. The outcomes are displayed as ranks from 0 to 12.

### *Statistical procedures*

Numerical data collected in the present work were presented as Mean ± Standard Error (SEM). One-way analysis of variance (ANOVA), followed by Tukey's Multiple Comparison Test, was applied to test the significance interrelation of data of the different groups, using GraphPad Prism version 5 for Windows, GraphPad software, San Diego, CA, USA. Means were considered significant when $p<0.05$.

## RESULTS

### *Mortality rate*

During the experiment, there was two rats died in the $Alcl_3$-treated group with mortality rate of 20%. In the other groups, no further deaths were registered.

### *Body weight change*

At the end of the experiment, there was a weight gain in all groups as shown in (Table 1). Rats administered $Alcl_3$ exhibited a significant diminution ($p < 0.001$) in the weight gain in comparison with the control ones. The administration of $Alcl_3$-treated rats with L-carnitine revealed a significant surge ($p < 0.05$) in their body weights gain compared to those of rats intoxicated with $Alcl_3$ as shown in (Table 1).

### *Liver gross morphology and relative weight*

Livers of control and L-carnitine groups had normal texture and color (Figures 1a,1b). Whereas, livers of $Alcl_3$-treated rats displayed yellowish color in comparison with those of control groups (Figure 1c). The yellowish coloration decreased with the administration of L-carnitine (Figure 1d). A significant rise ($p < 0.05$) in the relative liver weight of $Alcl_3$-intoxicated rats was observed in comparison with that of control rats (Table 1). Treatment of model group with L-carnitine significantly restored such increment to its normal values as shown in Table 1.

### *Serum liver enzymes ALT, AST, and ALP level*

The results of biochemical serum parameters in the control and experimental groups are described in Table 2. Administration of $Alcl_3$ in rats initiated liver damage, as revealed by appreciable surge in activity of ALT, AST, and ALP enzymes as compared with control rats. $Alcl_3$-intoxicated rats treated with L-carnitine revealed an obvious improvement in the ALT, AST, and ALP levels as shown in (Table 2).

### *Serum MDA, GSH-px, and SOD activity*

$Alcl_3$ caused a significant rise ($P < 0.01$) in the serum MDA level when compared to the control rats. Whereas, MDA level of L-carnitine+$Alcl_3$ was significantly decreased ($P < 0.05$) in comparison with the $Alcl_3$ treated group (Table 2). Rats administered $Alcl_3$ displayed a significant decline ($P < 0.01$ and $P < 0.001$) in GSH-Px and SOD levels, respectively, in comparison with the control group values. Co-treatment with $Alcl_3$ and L-carnitine

exhibited a significant increase ($P < 0.01$ and $P < 0.001$) in the serum levels of GSH-px and SOD when compared to the $AlCl_3$ group as shown in Table 2.

### *The histological results*

Histological examination of control and L-carnitine treated rats liver tissue showed normal histological structure as shown in (Figures 2a,2b), respectively. While liver sections of intoxicated rats with $AlCl_3$ revealed hydropic vacuolar and ballooning degeneration, blood sinusoids and portal vein congestion, microvesicular steatosis, focal necrosis, and inflammatory cellular infiltration (Figure 2c). Co-treatment of $AlCl_3$ treated rats with L-carnitine alleviated the liver lesions induced by $AlCl_3$ as in (Figure 2d). Briefly, the blood congestion, microvesicular steatosis, and inflammation disappeared, but some areas still having vacuolar degeneration. In Masson's trichrome-stained liver sections, collagen fibers looked blue in color. In control and L-carnitine treated groups, minimal collagen fibers seemed around the central vein and between the hepatic strands (Figures 3a,3b). In $AlCl_3$-intoxicated group, the collagen fibers were intense around the portal triad and inbetween the hepatic strands (Figure 3c). Obvious decrease in collagen fibers was noticed around the portal vein (Figure 3d) in the co-administered group with L-carnitine and $AlCl_3$ compared to group treated with $AlCl_3$ alone.

### *The immunohistochemical results*

Immunohistochemical examination for caspase-3 revealed a mild immunoreactivity in control and L-carnitine groups (Table 3, Figures 4a,4b, respectively). But, $AlCl_3$ supplementation produced an intense caspase-3 immunoexpression compared to control rats (Table 3, Figure 4c). Treatment of $AlCl_3$-treated rats with L-carnitine showed a significant reduction in the caspase-3 immunoreactivity compared to $AlCl_3$-intoxicated rats (Table 3, Figure 4d).

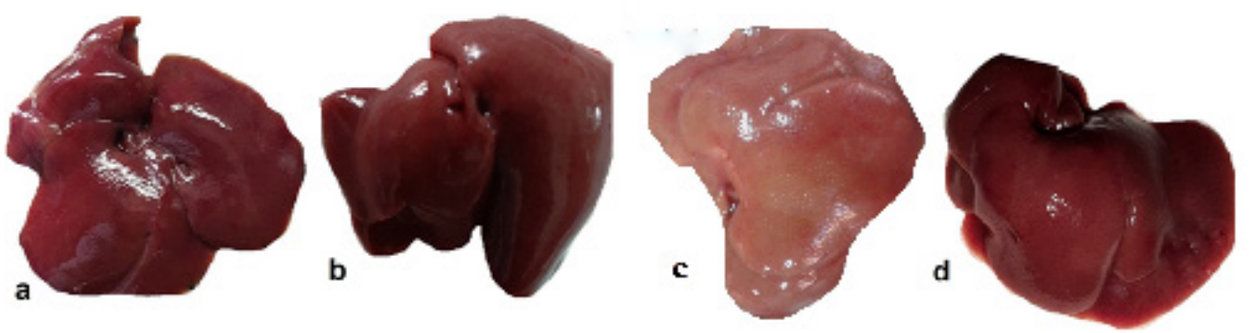


**Fig. 1:** The influence of L-carnitine on the liver gross morphology of $AlCl_3$-treated rats. (a) Liver of control group. (b) Liver of L-carnitine group. (c) Liver of $AlCl_3$ group. (d) Liver of $AlCl_3$+L-carnitine group. Note that liver of $AlCl_3$-treated rats is faint and yellowish in color compared to the control groups. The yellowish coloration decreases with the administration of L-carnitine.

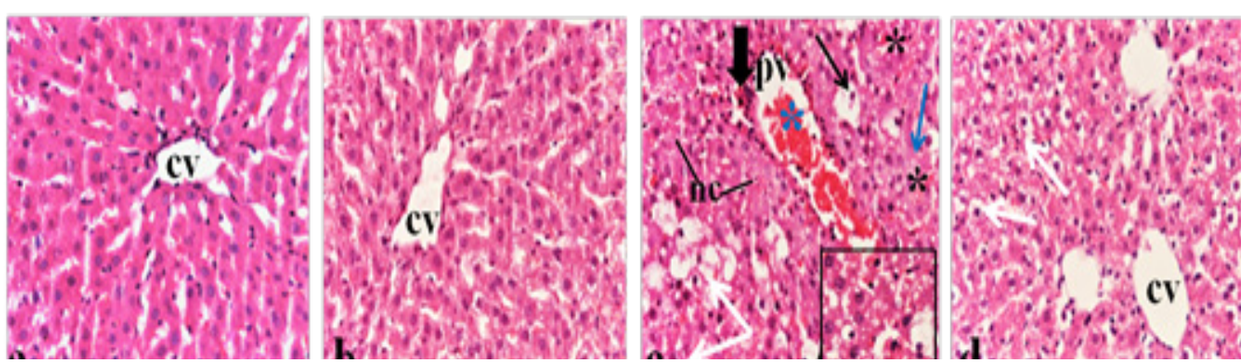


**Fig. 2:** Representative photomicrographs of liver sections from control (a), L-carnitine (b), $AlCl_3$ (c), and $AlCl_3$ + L-carnitine (d) groups. In $AlCl_3$ group, note the vacuolar degeneration (white arrow), ballooning degeneration (black thin arrow), blood sinusoids congestion (black asterisk) and portal vein congestion (blue asterisk), microvesicular steatosis (blue arrow), focal necrosis (nc), and inflammatory cells infiltration (black thick arrow). In $AlCl_3$ + L-carnitine group, note the moderate improvement in histological architecture. The blood congestion, ballooning degeneration, and microvesicular steatosis disappeared except the vacuolar degeneration (white arrow). (H&E stain, 400 X, Bar= 50µ).

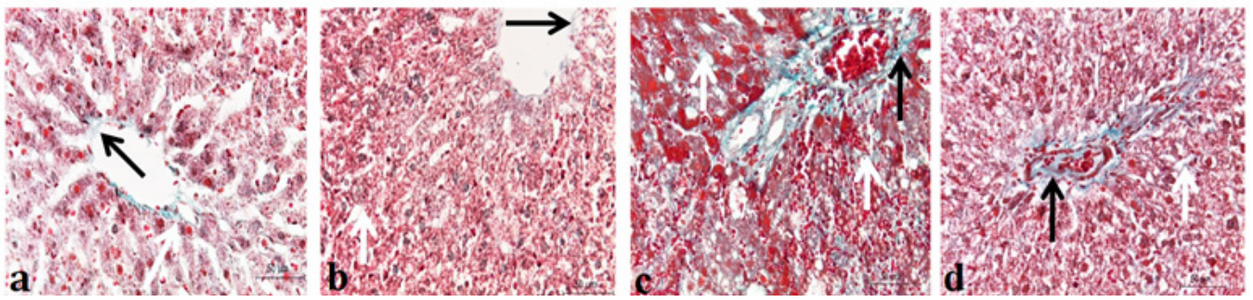


**Fig. 3:** Representative photomicrographs of liver sections from control (a), L-carnitine (b), $Alcl_3$ (c), and $Alcl_3$ + L-carnitine (d) groups. Notice that collagen fibers appear as blue color in central and portal veins lining (black arrows) and in-between hepatic strands (white arrows). The collagen content was increased around portal tract and between sinusoids in $Alcl_3$ group. This content is decreased in $Alcl_3$+ L-carnitine group. (Masson s trichrome stain, 400 X, Bar=50µ).

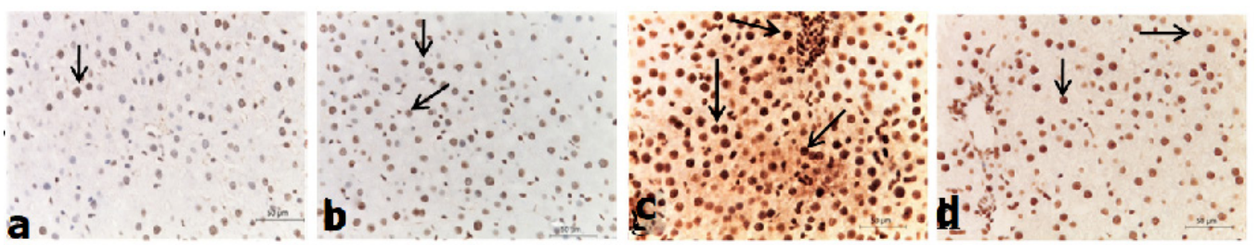


**Fig. 4:** Representative photomicrographs of liver sections illustrating the immunohistochemical staining of caspase-3; where (a) Control, (b) L-carnitine, (c) $Alcl_3$, and (d) $Alcl_3$+L-carnitine groups (a) Showing mild expression of caspase-3 immunopositivity. (b) Showing mild positive expression of caspase-3. (c) Showing intense immunoexpression of caspase-3. (d) Showing moderate immunoexpression of caspase-3. (Immunohistochemical staining for caspase-3, 400 X, Bar=50µ).

**Table 1:** The influence of L-carnitine on body weight gain, absolute and relative liver weights in $Alcl_3$-intoxicated rats

| Groups | Body weight gain (gm) | Absolute liver weight (gm) | Relative liver weight (%) |
|---|---|---|---|
| Control group | 97.2±2.42 | 5.9±1.03 | 3.52±0.16 |
| L-carnitine group | 90.4±14.20 | 6.62±0.62 | 3.32±0.33 |
| $Alcl_3$ group | 25.8±3.8*** | 5.06±0.61 | 4.08±0.12* |
| $Alcl_3$+L-carnitine group | 71.8±6.73# | 6.72±0.69 | 3.02±0.25## |

Data are represented as mean ± SEM (n=8/group).
* Symbol shows significance compared with control group, where *: $P < 0.05$, ***: $P < 0.001$.
# Symbol shows significance compared with $Alcl_3$ group, where #: $P < 0.05$, ##: $P < 0.01$.

**Table 2:** The influence of L-carnitine on serum liver enzymes and oxidant/antioxidant levels in $Alcl_3$-intoxicated rats

| Groups | ALT (U/L) | AST (U/L) | ALP (U/L) | MDA (nmol/ml) | GSH-px (mU/mL) | SOD (U/ml) |
|---|---|---|---|---|---|---|
| Control Group | 53.6±4.8 | 102.4±7.4 | 178.8±12.2 | 4.81±0.5 | 45.8±6.4 | 133.8±1.7 |
| L-carnitine group | 54.2±4.1 | 107.6±4.3 | 182.6±20.5 | 5.10±0.7 | 34.2±1.9 | 126.0±3.6 |
| $Alcl_3$ Group | 195.0±13.8*** | 366.2±35.3*** | 277.8±23.9** | 10.56±1.3** | 12.6±2.6** | 82.66±6.1*** |
| $Alcl_3$+L-carnitine group | 58.8±3.9### | 111.8±4.1### | 160.6±8.1## | 5.57±0.7# | 65.0±9.8## | 144.0±6.7### |

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, MDA: malondialdehyde, GSH-px: glutathione peroxidase, and SOD: super oxidase dismutase.
Data are represented as mean ± SEM (n=8/group).
* Symbol shows significance compared with control group, where **: $P < 0.01$, ***: $P < 0.001$.
# Symbol shows significance compared with $Alcl_3$ group, where #: $P < 0.05$, ##: $P < 0.01$, ###: $P < 0.001$.

**Table 3:** The influence of L-carnitine on caspase-3 immunoexpression in $Alcl_3$-intoxicated rats

| Groups | Caspase-3 (H score) |
|---|---|
| Control group | 0.33±0.21 |
| L-carnitine group | 0.5±0.22 |
| $Alcl_3$ group | 10.67±0.84*** |
| $Alcl_3$+L-carnitine group | 6.0±0.89## |

Data are represented as mean ± SEM (n=8/group).

* Symbol shows significance compared with control group, where ***: $P < 0.001$.

# Symbol shows significance compared with $Alcl_3$ group, where ##: $P < 0.01$.

## DISCUSSION

There has been great interest in the toxicity of Aluminum (Al) due to its environmental wide distribution and every day usage[26]. Numerous clinical conditions have been reported to be caused by Al toxicity, such as hepatotoxicity, neurotoxicity, gastrointestinal toxicity, and bone disease[27-29].

At the cessation of the current trial, there was body weight gain in all groups. $Alcl_3$ supplementation induced an obvious reduction in the body weight gain and a significant elevation in the relative liver weight in comparison with those of control rats. $Alcl_3$ administration had a negative influence on rats body weight, which is in consistent with previous reports[30,31]. Treatment of Al-intoxicated rats with L-carnitine improved the decreased body weight gain, which was reported in methotrexate-induced toxicity[32] that may be connected to its fat burning ability[33]. The increasing influence of $Alcl_3$ on the relative liver weight goes in line with the result of Mahmoud and Elsoadaa[30]. This effect confirms hepatic lesions linked to its toxic effects. These lesions may be due to the microvesicular steatosis presence and collagen deposition as proved here in in the liver microscopical examination. The harmful effect of $Alcl_3$ on the relative liver weight has been markedly remediated with applying L-carnitine plus $Alcl_3$. This means that L-carnitine might play a protective influence on Al toxicity in rats.

The intracellular enzymes (AST, ALT, and ALP) are biomarkers of toxic injury to the liver[34]. In the present work, it was observed that $Alcl_3$ administration caused a significant surge in these enzyme levels when compared to the control group. This elevation is in a consonance with the previous reports of increased serum enzymes activity in $Alcl_3$-treated rats[35,30,36,37]. Exposure to elevated Al levels can result in its aggregation in liver, followed by liver deterioration, as cell necrosis[38], and consequent liberation of membrane bound enzymes into the bloodstream[39-41]. Lipid peroxidation (LPO), as demonstrated here, can mediate the abnormal liver function detected in the present report, causing cell membranes and hepatic cells damage[41,42], and the enzymes release from the liver cells. Also, Martinez *et al*.[43] stated that the elevated enzymes in $Alcl_3$ intoxicated rats may be due to its ability to raise vascular dysfunction. In our results, there was an obvious improvement in serum liver enzymes in rats co-administrated with L-carnitine plus $Alcl_3$ compared to those of model group. The mechanism responsible for the depressing influence of L-carnitine administration on liver enzymes is indistinct, it may be mediated by the free fatty acids (FRAs) β-oxidation, and so declines the FFAs-induced lipotoxic metabolites aggregation. The later may have led to mitochondrial dysfunction[44,45] that is considered a marker for liver diseases that raise liver enzymes level[44,46]. Furthermore, anti-inflammatory properties of L-carnitine might improve liver function and decrease liver enzyme levels[47,48]. Moreover, several previous studies declared in patients with chronic hepatic disease that supplementation with L-carnitine contributed to normalization of the levels of liver enzymes[49,50].

The liver is the primary metabolism site, comprising detoxification and activation of several substances as drugs[51]. The increase in toxic metabolite metabolism resulting in the increase in ROS and oxidative stress production in the hepatocytes[52,53]. The outcomes of the current report displayed that $Alcl_3$ treatment induced a prominent augmented level of MDA (as an indicator for LPO). This finding is consistent with other researchers[41,2,35]. The administration of L-carnitine to $Alcl_3$-intoxicated animals diminished the MDA levels as previously stated by Özkaya *et al*.[1] and Chowdury *et al*.[54] by improving metabolic function[56]. It has been shown that L-carnitine has a powerful scavenging impact on free radicals and oxidative damage[56,13,57].

In the current study, $Alcl_3$ also induced antioxidant defense mechanisms depletion represented by GSH-px and SOD reduction that play critical role in the free radicals destruction and in the oxidative damage inhibition[58]. The lessening in these enzyme levels in $Alcl_3$ group may be a result of the decrease in mRNA expression of endogenous antioxidants[55]. Our data illustrated that L-carnitine restored the oxidant/antioxidant balance found in $Alcl_3$-treated rats as evidenced by the serum MDA level decline and enhancement of the serum antioxidants GSH-px, and SOD levels. These outcomes are in consistence with other experimental researches[59,56,60,57], in which L-carnitine preserves and improves the antioxidant activity in brain, liver, kidney, and heart injury triggered by some toxic substances. This effect may be related to the stimulation of glutathione production[57,60]. Thus, L-carnitine might have quenched free radicals and prevented peroxidation of lipids, and gradually reduced the antioxidants burden.

In the present report, the histological findings of the liver were in consistence with the measured biochemical findings. The histological changes, such as hepatocellular degeneration, inflammatory cellular infiltration, microvesicular steatosis, apoptosis, and blood congestion in the liver of $Alcl_3$ group most likely indicates the

hepatotoxicity of $Alcl_3$. Similar reports on $Alcl_3$ toxicity on rats liver have been reported by other authors[61-63]. In addition, liver sections inspection of these rats stained with Masson's trichrome showed a significant elevation in collagen fibers deposition around the portal tract and in between the hepatic strands. The rise in collagen amount in Al-intoxicated rats is supported by previous reports[64-66]. Senoo *et al*.[67] stated that hepatocytes damage initiate hepatic fibrosis, leading to Kupffer cells activation and subsequent release of cytokines release and growth factors. These factors play a crucial role in activating hepatic stellate cells (HSCs) that proliferate and transform into myofibroblast, which in turn proliferate, probably migrate and synthesize collagen[68]. On the other hand, ROS-induced lipid peroxidation products can lead to the collagen synthesis augmentation by hepatic Ito cells, resulting in fibrosis[69] and hepatocyte death[70].

The present findings revealed that treatment with L-carnitine ameliorates these histological abnormalities induced by $Alcl_3$. Our findings are confirmed by many authors, who have demonstrated that L-carnitine improved the hepatic histopathological alterations caused by various drugs[59,13]. Moreover, Kart *et al*.[71] reported that L-carnitine improved the renal histolopathology induced by gentamicin. This may be due to the fact that L-carnitine preserves cell integrity by regulating the intra-mitochondrial percentage of acyl-CoA/CoA, suppressing toxic compounds, preserving the mitochondrial membrane's permeability integrity, and facilitating the free radicals expulsion[72,73]. Oxidative stress is also extremely detrimental to mitochondria and impaired mitochondrial β-oxidation[7] resulting in hepatocytes accumulation of fatty acids and production of hepatic injury such as hepatic steatosis. Treating of intoxicated rats with L-carnitine might have a reversible action on the steatosis appearance due to its function in β-oxidation of fatty acid and converting of fats into energy in the mitochondria[74]. This may explain the protective potential influence of L-carnitine against the toxic effect of $Alcl_3$.

Caspase-3 plays a vital function in the execution-cell apoptosis phase[75,76]. $Alcl_3$ intoxication in the current study caused a severe augment in the caspase-3 immunoexpression. This result is in harmony with other studies[76,77,63], which stated that Al intoxication resulted in increase in caspase-3 expression in various tissues. Furthermore, confirming to our findings, Brenner *et al*.[78] reported that Al treatment extensively declines anti-apoptotic (Bcl-2) protein expression which prevents the resultant caspase cascade initiation and apoptotic cell death. The dysregulation effect of $Alcl_3$ on apoptosis occurred via the pro-oxidant properties stimulation of copper and iron causing mitochondrial dysfunction that ends with degradation of macromolecules and releasing of mitochondrial cytochrome-c[79,10]. Additionally, as shown in our biochemical observations, the apoptotic appearance in the liver tissue may be attributable to the antioxidant enzyme loss and oxidative stress resulting from Al ingestion[80]. Co-administration of L-carnitine with $Alcl_3$ diminished the caspase-3 immunoexpression relative to $Alcl_3$ alone-treated group, proving that L-carnitine has anti-apoptotic action.

## CONCLUSION

The present study provides an evidence of the ameliorative effect of L-carnitine against the hepatic injury induced by $Alcl_3$, probably via its antioxidative property and its inhibitory effect on apoptosis.

## CONFLICTS OF INTERESTS

There are no conflicts of interest.

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**الملخص العربى**

# التغيرات الكيميائية الحيوية والنسيجية والمناعية الكيميائية المصاحبة للإصابات الكبدية الناجمة عن كلوريد الألومنيوم فى الفئران: التأثيرات الوقائية لـ الـكارنتين

**بسنت محمود محمد[١]، ناجى حسن فارس[١]، نيفين عاصم أشعت[٢]، فاتن صبرة أبوزيد[١]**

**[١]قسم علم الحيوان، كلية العلوم، جامعة عين شمس، القاهرة، مصر**

**[٢]كلية البنات للآداب و العلوم و التربية، جامعة عين شمس، القاهرة، مصر**

**الخلفية:** يوجد اهتمام كبير بسمية الألومنيوم (Al) بسبب إنتشاره الواسع فى البيئة واستخداماته اليومية. يتسبب الالومنيوم فى إنتاج الشوارد الحرة والإجهاد التأكسدي و فوق أكسدة الدهون نتيجة لإنتاج أنواع الأكسجين التفاعلية (ROS) فى الكبد، ويعتبر الـ -كارنيتين من الاحماض الأمينية الهامة فى الجسم حيث ينقل سلسلة الأحماض الدهنية الطويلة إلى الميتوكوندريا لكى يتم التمثيل الغذائي للطاقة الخلوية. أيضا يعزز حالة مضادات الأكسدة من خلال تسريع إزالة الشوارد الحرة من الخلايا.

**الهدف:** تحديد التأثير الضار المحتمل لكلوريد الألومنيوم، ولأول مرة تقييم التأثير المحتمل للإمداد الخارجى ب مكملات الـ -كارنتين لحماية الكبد فى تخفيف هذه التدهورات المحتملة.

**المواد والطرق:** تم تقسيم اثنان وثلاثون من الفئران إلى أربع مجموعات متساوية، المجموعة الأولى: مجموعة الفئران الضابطة، المجموعة الثانية: مجموعة الفئران المعالجة بـ الـ -كارنتين بجرعة ٢٠٠ ملجم/كجم، المجموعة الثالثة: مجموعة الفئران المعالجة بكلوريد الألومنيوم بجرعة ١٠٠ ملجم/كجم، والمجموعة الرابعة: مجموعة الفئران المعالجة ب الـ -كارنتين وكلوريد الألومنيوم (٢٠٠ ملجم/كجم، ١٠٠ملجم/كجم) على التوالي. أعطت جميع الأدوية عن طريق الفم مرة واحدة يوميا لمدة شهر واحد.

**النتائج:** أوضحت الدراسة الحالية أن الإمداد الفموى للفئران بكلوريد الألومنيوم سبب تدهور واضح للكبد ويتضح ذلك من ارتفاع مستوى إنزيمات الكبد واختلال التوازن بين حالة المؤكسد ومضادات الأكسدة . وصاحب ذلك تغيرات في النسيج وزيادة فى التفاعلات المناعية لكلا من Ki-٦٧ وcaspase-٣. وقد لوحظ تحسن فى هذه الآثار بشكل كبير بإعطاء مكملات الـ -كارنيتين.

**الخلاصة:** أشارت هذه النتائج إلى أن الـ -كارنتين قد يكون له تأثير وقائي محتمل ضد الضرر الكبدي الناتج من كلوريد الألومنيوم من خلال خصائصة المضادة للأكسدة وتأثيره المثبط على زيادة عدد الخلايا والموت المبرمج للخلايا.