Protective Effects of α-Lipoic Acid on Hepatic and Renal Biomarkers and Histological Changes Induced by α−Cypermethrin in Treated Male Rats

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ABSTRACT

α-Cypermethrin is a synthetic type II pyrethroid insecticide. Earlier works have revealed the argumentative influence of α-cypermethrin on liver and kidney. This work aimed to estimate the potential character of α-lipoic acid in the induced toxicity of α-cypermethrin in the kidney and liver of male albino rats. Examined rats were alienated into four groups as following; α-cypermethrin/α- lipoic acid, α-lipoic acid, α-cypermethin as well as control. The results of this study showed that administration of α- cypermethrin caused a significant increase in the activity of ALT (Alanine Transaminase), AST (Aspartate Transaminase), ALP (Alkaline Phosphatase), the level of bilirubin, urea, uric acid, and creatinine, as well as decreased levels of total protein and albumin. Moreover, the presence of α- lipoic acid alleviates the harmfulness of α-cypermethrin by moderately regularizing these biochemical factors. The biochemical markers were maintained by the histological investigation. Our outcomes proposed that α- lipoic acid might play a defensive role in the induced toxicity of α- cypermethrin in the kidney and liver of treated rats.

Key Words: α-Cypermethrin, α- Lipoic acid, Biomarkers, Histology, Liver and kidney, Toxicity.

INTRODUCTION

Pyrethroids are potent insect repellents like α-cypermethrin (α-CYP) which is a synthetic type II pyrethroid insecticide used to kill insects (Timothy *et al*. 2005 and Sayim *et al*. 2005). Its side effects were demonstrated experimentally on variety of animals (Khan *et al*. 2009). Both of ion channels and ATPase have been identified as the molecular target of α-CYP damage of muscle and liver (Prashanth and David 2010). In liver, α-CYP causes an increase in liver marker enzymes and a decrease in total protein, albumin, and globulin (Ahmad *et al*., 2011). It also induces histological lesions involving necrosis of hepatocytes and dilatation in hepatic blood sinusoids (Omonona *et al*., 2015). In the kidney, it was found that α-CYP resulted in an increase in urea, uric acid, and creatinine levels (Ulaiwi 2011). Renal damage appeared histologically in the form of different lesions involving destruction of few renal glomeruli and deposition of eosinophilic materials in the renal tubules with dilatation of the tubules. The renal glomeruli were completely atrophied and destructed (Grewal *et al*., 2010). Moreover, α-CYP induces oxidative stress and increases lipid peroxidation in liver and kidney (Giray *et al*., 2001 and Gabbianelli *et al*., 2002). Alpha lipoic acid (ALA) is a component produced in the body in very small quantities and is present in many foods such as spinach, broccoli, and meats (Femiano *et al*., 2000). Alpha lipoic acid is synthesized in human and animal in mitochondria from its direct precursors; octanoic acid and cysteine. It may be a good antioxidant agent for its broad scavenger properties (Saxena and Saxena 2010). It catalyzes the oxidative decarboxylation of keto-acids (Maczurek *et al*., 2008). Alpha lipoic acid participates in the creation of the extra cellular antioxidant, for instance vitamin E, vitamin C, and the decrease of glutathione level in a reusable form by regenerating them (Saxena and Saxena 2010). Many studies suggested the useful effect of antioxidants in ameliorating the xenobiotic toxicity. Considering the relevant antioxidant properties of ALA, the goal of this work was to estimate the potential protecting influences of ALA alongside the toxicity produced by α-CYP in the liver and kidney of rats using biochemical parameters and histopathological assessment.

MATERIALS AND METHODS

1. Chemicals

α-Cypermethrin (Cat. No. 45806) and α-lipoic acid (Cat. No. 1368201) were obtained from Sigma Aldrich, Germany. Reagent kits for assay of Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), creatinine, urea, and total protein were purchased from BIOMED diagnostic, Germany. The kits of reagent for bilirubin assay was purchased from Diamond Diagnostics, Germany. The kits of reagent for albumin and uric acid assay were purchased from SPECTRUM, Egypt.

2. Rats

Twenty adult male rats weighing about 180-200 g were obtained from the household animal of College of Science- King Faisal University. Five rats were placed in plastic crates and kept at the same laboratory conditions at temperature (25°C), humidity (60%) and lighting (12 h light, 12 h dark) for one week for adaptation before start the experimentation. The rats were allowed to contact for food and water. They were fed normal profitable rat food. Institutional Animal Care and Use Committee (IACUC) at the King Faisal University approved the investigational procedure of this study.

3. Investigational Groups

The tested rats were arbitrarily classified into four collections and each one collection contain five rats. Tested collections were intended as follows: The first collection was the control in which the rates were established with oral dose of saline followed by corn oil through gavaging. Second collection was the α-CYP collection in which the rats were established with every day oral dose of α-CYP (14.5 mg/kg body weight (bw)) dissolved in corn oil by gavage; third collection was ALA collection in which the rats were established with day-to-day oral dose of ALA (20 mg/kg bw) dissolved in saline by gavage. Fourth collection was an α-CYP/ALA collection in which the rats were established with everyday oral dose of α-CYP (14.5 mg/kg bw) dissolved in corn oil and followed by oral dose α-lipoic acid (20 mg/kg bw) dissolved in saline by gavage. The experiment duration was four weeks and the administration method and drug dose was selected from the prior works (Elsawy *et al*., 2017).

4. Biochemical Investigation

The hepatic function was evaluated through the estimation the enzymatic activities of AST, ALT, and ALP and determination of Bilirubin and albumin concentration. Serum samples were obtained by centrifuging blood samples from each animal at 6000 rpm for 10 min. The activities of the marker enzymes and bilirubin and albumin concentration were determined using the assay kits according to the instructions of the supplier. The values of the hepatic marker enzymes were expressed as U/L whereas the results of bilirubin and albumin were reported as g/dl. The concentration of the protein was determined using the method of Bradford (Bradford 1976) and crystalline bovine serum albumin was used as standard protein. The evaluation of the renal function was carried out through determination of creatinine, uric acid, and urea in serum using their relevant commercial kits following the manufactures' protocol.

5. Histopathological Examination

Liver and kidney specimens were collected from the different animal groups and were fixed in 10% formalin, processed and embedded in paraffin wax, sectioned at five μm and stained with haematoxylin and eosin stain (H and E) according to Bancroft and Gamble (2002). Then stained sections were investigated by light microscope (Olympus Microscope BX-51 connected with Cool-Snap Prodigital camera and Image-Pro Plus image with analysis Software Version 6.0).

6. Statistical Analysis

Analysis of Variance (ANOVA) followed by Least Significant Difference (LSD) many

variety investigation was used to compare all the features using one-way analysis. Changes at $P<0.05$ were reflected major. Statistical tests were achieved using SAS statistical software (SAS v.9.2, SAS institute, inc).

RESULTS

1. Biochemical Indicators of Hepatic Function

Our results showed that the mean serum ALT, ALP and AST activities, and bilirubin level were significantly higher in α-CYP group in comparison to that achieved from the control group. On the other hand, the values of these factors were considerably less in α-CYP/ ALA group than that recorded in α-CYP group (Table 1). In addition, exposure to α-CYP was considerably decreases the total protein and albumin concentrations compared to the control group. Total protein and albumin concentrations were significantly increase in α-CYP/ALA group compared to α-CYP group. No important difference was detected in the parameters studied amongst ALA group when matched with the control group (Table 1).

Table 1: Effect of α-lipoic acid on some Hepatic Biochemical Markers in Male Rats treated with α-cypermethrin

Group	Mean value of Serum					
	ALT (U/L)	AST (U/L)	ALP (U/L)	Bilirubin (g/dl)	Protein (g/dl)	Albumin (g/dl)
Control	$38.6^{a} \pm 1.03$	$69.8^{a} \pm 3.5$	$47.8^{a} \pm 1.2$	$0.4^{a} \pm 0.01$	$7.4^{a} \pm 0.2$	$4.4^{a} \pm 0.1$
α-CYP	$85^{c} \pm 1.6$	$126^{c} \pm 1.1$	$105.8^{c} \pm 1.2$	$1.3^{c} \pm 0.1$	$4.5^{c} \pm 0.2$	$2.8^{b} \pm 0.1$
ALA	$39.2^{a} \pm 0.7$	$72.4^{a} \pm 0.9$	$47.4^{a} \pm 0.8$	$0.4^{a} \pm 0.01$	$7.2^{a} \pm 0.1$	$4.28^{a} \pm 0.1$
α-CYP/ ALA	$55.6^{b} \pm 1.6$	$82.6^{b} \pm 0.9$	$64.2^{b} \pm 1.3$	$0.7^{b} \pm 0.01$	$6.5^{b} \pm 0.1$	$4.1^{a} \pm 0.1$
F (p)	288.276^{*} ($<0.001^{*}$)	182.478^{*} ($<0.001^{*}$)	550.881^{*} ($<0.001^{*}$)	97.784^{*} ($<0.001^{*}$)	105.541^{*} ($<0.001^{*}$)	43.679^{*} ($<0.001^{*}$)

Each group consists of five experimental animals. Means ± SE followed by same superscript letter in the same column are not significantly different according to Post Hoc Test (LSD) for comparison between groups.
*: Statistically significant at $P \leq 0.05$

2. Biochemical Indicators of Renal Function

Our results showed that the values of uric acid, urea, and creatinine levels were significantly increase with exposure to α-CYP relative to the control collection. However, α-CYP/ ALA group showed significantly lower values compared to α-CYP collection. No significant difference was observed in the level of creatinine, urea and uric acid between ALA collections when compared with the control collection (Table 2).

Table 2: Effect of α-lipoic acid on some Renal Biochemical Markers in Male Rats treated with α-cypermethrin

Group	Serum		
	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)
Control	$26.4^{a} \pm 0.9$	$0.5^{a} \pm 0.01$	$1.6^{a} \pm 0.1$
α-CYP	$65^{c} \pm 1.2$	$1.3^{c} \pm 0.1$	$3.6^{c} \pm 0.1$
ALA	$26.4^{a} \pm 1.1$	$0.5^{a} \pm 0.01$	$1.6^{a} \pm 0.04$
α-CYP/ ALA	$42.4^{b} \pm 0.9$	$0.8^{b} \pm 0.01$	$1.9^{b} \pm 0.1$
F (p)	311.735^{*} ($<0.001^{*}$)	164.997^{*} ($<0.001^{*}$)	200.197^{*} ($<0.001^{*}$)

Each group consists of five experimental animals. Means ± SE followed by same superscript letter in the same column are not significantly different according to Post Hoc Test (LSD) for comparison between groups.
*: Statistically significant at $P \leq 0.05$

3. Histopathological results

1.1. *Liver Histopathology*

Typical microscopic architecture of the liver was shown in the normal group in which the hepatic cords originate from the central vein towards the periphery (Figure 1a). The central vein is lined with endothelial cells and the sinusoids contain Kupffer cells (Figure 1b). Hepatic tissue of α-CYP group showed damage of architecture of liver cells along with disarrangement of hepatic cords, dilated portal vein, inflammatory cell infiltration and bile duct hyperplasia (Figure 1c). There were also proliferation of binucleated cells and monocytes infiltration (Figure 1d). On the other hand, the hepatic tissue of ALA group showed a normal hepatic cord in between blood sinusoid that is originated from the central vein (Figure 1e) and hepatocytes with normal nucleus arranged in cords in between sinusoid(s) and contain active Kupffer cells (Figure 1f). Hepatic tissue of α-CYP/ALA group showed reset in hepatic parenchyma nearly normal with presence of normal central vein (Figure 1g) and sinusoids (S) and central vein are more or less normal (Figure 1h).

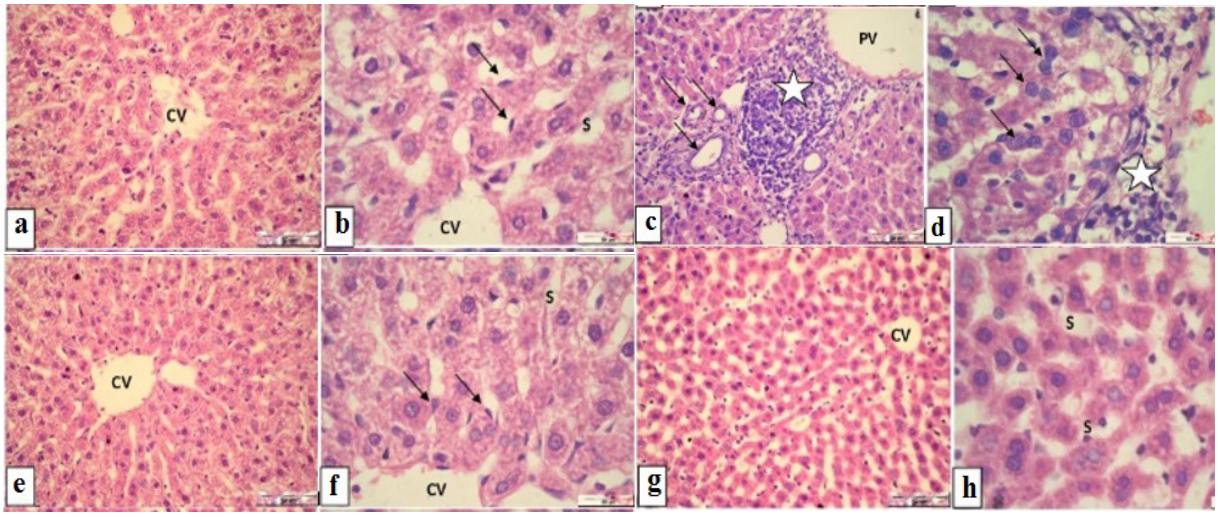

Figure 1: Light micrographs of liver sections stained with H and E. (a): Control group of hepatic tissue showing typical architecture in which the hepatic cords originate from the central vein (CV) to the periphery (x10). (b) Enlarged part from figure (a) showing the central vein (CV) lined with endothelial cell, sinusoids (S) lined with Kupffer cells (arrows) (x40). (c) Hepatic tissue of α-CYP group showing damage of architecture of liver cells along with disarrangement of hepatic cords, dilated portal vein (PV), inflammatory cell infiltration (star), bile duct hyperplasia (arrows) (x10). (d) Enlarged part from figure (c) showing proliferation of binucleated cells (arrows) (x10), monocytes infiltration (star) (x40). (e) Hepatic tissue of ALA group showing normal hepatic cord in between blood sinusoid and originate from central vein (CV) (x10). (f) Enlarged part from figure (e) where hepatocyte with normal nucleus arranged in cords in between sinusoid (s) and contain active Kupffer cells (arrows) (x40). (g) Hepatic tissue of α-CYP/ALA group showing restore in hepatic parenchyma nearly normal with presence of normal central vein (CV) (x10). (h) Enlarged part from figure (g) where sinusoids (S) and central vein (CV) more or less normal (x40).

1.2. *Kidney Histopathology*

Light micrographs of kidney sections stained with H and E of cortical tissue of the control group showed normal glomerular tuft, proximal convoluted tubule and distal convoluted tubule (Figure 2a). Glomerular tuft was surrounded by urinary space and enclosed by glomerular capsule, the proximal convoluted tubule was lined with high cuboidal epithelium and the distal convoluted tubules was lined with low cuboidal epithelium. (Figure 2b). Cortical tissue of α-CYP group showed interstitial blood congestion, renal corpuscle with focally segmented glomerulus and atrophied glomerulus (Figure 2c). Some glomeruli appeared with wide urinary space and degenerative changes in tubules as necrosis

of tubular cells with pyknotic nuclei were observed (Figure 2d). While, the cortical tissue of ALA group showed normal appearance (Figure 2e) where cortical tissue contain well-organized renal corpuscles, proximal tubule and distal tubule (Figure 2f). Cortical tissue of α-CYP/ALA group showed prominent restore in structure of both renal corpuscles and renal tubules (Figure 2g). However, there were still affected few proximal tubules among healthy renal corpuscles and distal tubules (Figure 2h).

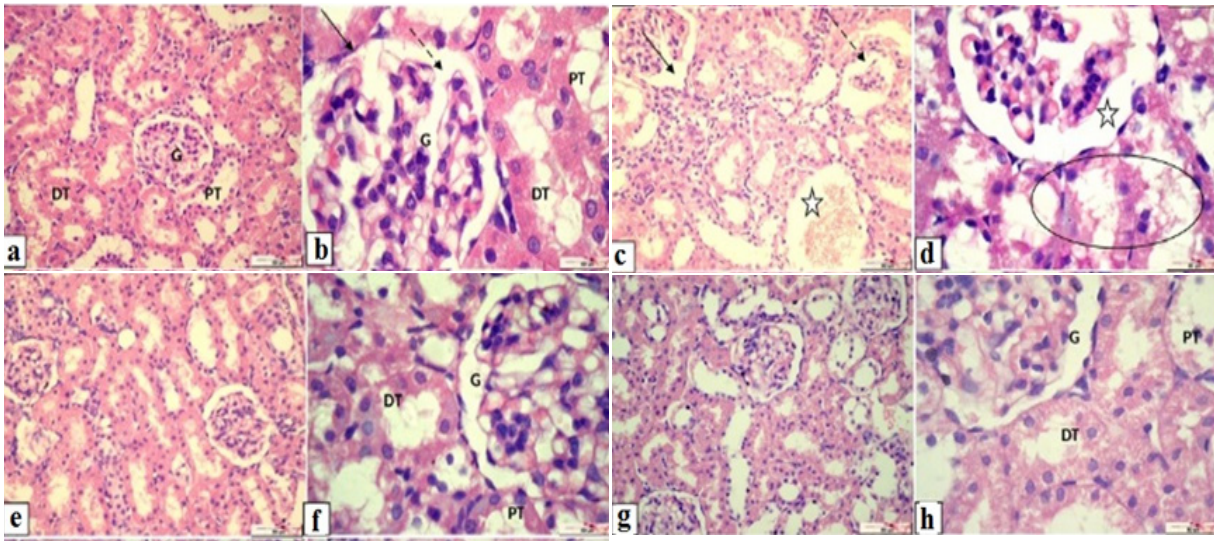

Figure 2: Light micrographs of kidney sections stained with H and E. (a): Control group of cortical tissue with normal glomerular tuft (G), proximal tubule (PT) and distal tubule (DT) (x40). (b) Enlarged part from figure (a) where glomerular tuft (G) surrounded by urinary space (dashed-arrow) and enclosed by glomerular capsule (arrow), proximal tubule (PT) lined by cuboidal cells and distal tubule (DT) lined by high cubical cell (x100). (c) Cortical tissue of α-CYP group showing interstitial blood congestion (star), renal corpuscle with focally segmented glomerulus (arrow) and atrophied glomerulus (dashed-arrows) (x40). (d) Enlarged part from figure (c) where glomerulus with wide urinary space (star), degenerative changes in tubules (circle) as necrosis of tubular cells with pyknotic nuclei (x100). (e) Cortical tissue of ALA group showing normal appearance (x40). (f) Enlarged part from figure (e) where cortical tissue contain well-organized renal corpuscles (G), proximal tubule (PT) and distal tubule (DT) (x100). (g) Cortical tissue of α-CYP/ALA group showing prominent recovery in both renal corpuscles and renal tubules (x40). (h) Enlarged part from figure (g) showing still affected few proximal tubule (PT), healthy renal corpuscles (G) and distal tubule (DT) (x100).

DISCUSSION

Effect of ALA on Biochemical Indicators of Hepatic Function in rats treated with α-CYP

Liver is the major detoxifying organ in the body; it targets various drugs and chemicals (Armagan *et al*., 2015). Damage of cellular components may lead to the death of liver cells (Teppema *et al*., 2002). The present study demonstrated that α-cypermethrin (α-CYP) induced many biochemical and histological alterations in liver of treated rats. Several studies reported the above-mentioned alterations caused by α-CYP in liver (Abdul-Hamid *et al*., 2017, Bhushan *et al*., 2013a and b, and Ulaiwi 2011). Alanine Transaminase (AST), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP) activities, and bilirubin level were significantly higher while albumin level was lower in α-CYP group relative to the control group. In this respect, liver function enzymes involve ALT, AST, and ALP (Thrall *et al*., 2012). ALP is a marker enzyme for plasma and endoplasmic reticulum membranes and is employed to assess the integrity of these membranes (Shahjahan *et al*., 2004). It has a crucial role in the metabolism and biosynthesis of energy macromolecules for different cell functions in the liver, as it catalyzes the splitting of phosphoric esters (Arshad *et al*., 2007). The increase in ALP activity threats to the life of cells that are

dependent on phosphate esters for their vital process (Sangai and Verma 2012). The activity of ALT is a measure of the degree of cell membrane damage (Campos-Pereira *et al*., 2002). It is thought to be more specific for hepatic injury because it is present mainly in the cytosol of the liver and in low concentrations elsewhere (Fowler *et al*., 2012) whereas the AST is a mitochondrial enzyme found in the heart, liver, skeletal muscle, and kidney and is normally present in plasma (Gao *et al*., 2004). Activities of ALT, AST and ALP are correlated with hepatic necrosis and indicate alteration in hepatic functions (Thrall *et al*., 2012) and liver damage, which is accompanied by the release of such enzymes from the hepatocytes into the blood stream (Parimoo *et al*., 2014). The increase in ALT, AST and ALP activities acts as indicator to liver toxicity (Bhushan *et al*., 2013a and b, and Soliman *et al*., 2015). In addition, a decrease in serum level of albumin and an increase in bilirubin are sensitive indicators for liver damage (Shukla and Bhatia 2010). The higher value of bilirubin observed in the present study may be attributed to defense mechanisms against free radical induced oxidative damage including a reduction of free radicals by increasing electron donors, such as bilirubin (Sies 1999). Reduced serum albumin level may be due to decreased formation of protein in the liver and impaired ability of the liver to form albumin sequel to liver injury (Yousef *et al*., 2006). It may be also due to loss from renal insufficiency (Ulaiwi 2011). The present study showed that ALA treatment of rats intoxicated with α-CYP has protective hepatic potential where it showed a significant improvement in all tested serum biochemical parameters. Some studies emphasized similar protective effect of ALA in liver injured by various chemicals such as malathion and methotrexate (Sehirli *et al*., 2008 and Teppema *et al*., 2002).

Effect of ALA on Biochemical Indicators of renal Function in rats treated with α-CYP

Creatinine and urea are major catabolic products of protein metabolism. Exposure to α-CYP produced substantial increase in the values of uric acid, urea, and creatinine levels comparative to the control collection. However, there was a significant decrease in their levels in α-CYP/ALA group compared with α-CYP group. Other authors (Giray *et al*., 2001 and Ulaiwi 2011) observed these changes. According to (Yousef *et al*., 2006), the increment in plasma creatinine and urea level was due to their low clearance values due to diminished ability of kidneys to filter them from blood and excrete them in the urine. Increases in serum urea levels might be an indicative of impaired kidney function. Other researchers reported that renal failure leads to retention of creatinine and other non-protein nitrogenous constituents of the blood (Afolayan *et al*., 2009 and Karakilcik *et al*., 2004). The increase in creatinine level could be attributed to tubular necrosis with a subsequent decrease in the number of functioning nephrons and decline in glomerular filtration rate (Abdulazeez *et al*., 2010). Oxidative stress can promote the formation of a variety of vasoactive mediators that can affect renal function directly by initiating renal vasoconstriction or decreasing the glomerular capillary ultrafiltration coefficient; and thus reducing glomerular filtration rate (Garcia-Cohen *et al*., 2000). These changes may be either directly caused by α-CYP, or developed upon the degradation and conversion of the free radicals generated by α-CYP into less harmful metabolites (Grewal *et al*., 2010). The mode of action of α-CYP can be expected to have two ways: it may generate reactive oxygen species that induce oxidative stress or it may accumulate in cell membrane and disturb membrane structure due to its hydrophobic nature (Saxena and Saxena 2010). Oxidative stress contributes to initiation and propagation of liver injury, so it is considered a main pathological mechanism (Arany and Safirstein 2003). α-CYP has been demonstrated to cause significant decrease in the activities

of superoxide dismutase, catalase and glutathione peroxidase antioxidant enzymes in treated rats (Li *et al*., 2015). It has been shown that α-CYP caused free radical mediated tissue damage in kidney and liver (Gomaa *et al*., 2011). By causing several negative changes within the cell and in the cell membrane, oxidative stress reduces the ability of the cells to maintain their normal functions (Tao *et al*., 2008). The biochemical changes observed in the present study were supported by histological observations.

The pathological changes induced by α-CYP in the kidney and liver of treated rats are in agreement with those observed by previous researchers (Bhatti *et al*., 2014, Garcia-Cohen *et al*., 2000, Mossa *et al*., 2015, Mostafalou and Abdollahi 2013, and Sakr and Albarakai 2014). The ability of hepatoprotective agent to reduce the injurious effect caused by hepatotoxin, is an index of its protective effect (Pradeep *et al*., 2009). The present study showed that ALA treatment of rats intoxicated with α-CYP has protective renal potential where it showed a significant improvement in all tested serum biochemical parameters. Similar protective effect of ALA in kidney was reported in case of other chemicals such as malathion and methotrexate (Armagan *et al*., 2015 and Al-Atar 2010). Sehirli *et al*. (2008) suggested that among mechanisms of ALA protection of kidney tissues is balancing the oxidant/anti-oxidant status, and inhibiting neutrophil infiltration.

CONCLUSION

In conclusion, this study confirmed that α-cypermethrin exposure damaged the kidney and liver as revealed by changes in the studied of biochemical parameters and histological alterations observed in the liver and kidney. These adverse effects were attenuated by α-lipoic acid in the treated experimental group. α-lipoic acid might manifest a protective effect against α-cypermethrin-induced toxicity in the liver and kidney.

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التأثيرات الوقائية لحمض ألفا ليبويك على المؤشرات الحيوية الكبدية والكلوية والتغيرات الهستولوجية المستحثة بألفا سيبرمثرين في ذكور الجرذان المعالجة

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الملخص

ألفا سيبرمثرين هو مبيد حشري من البيريثرويد المصنفة من النوع الثاني، وأظهرت الدراسات السابقة التأثير الضار للألفا سيبرمثرين على الكبد والكلى، ولقد خططت هذه الدراسة لتقييم الدور المحتمل لحمض ألفا ليبويك في السمية المستحثة بألفا سيبرمثرين في كبد وكلى الجرذان البيضاء، وقد قسمت الفئران إلى أربع مجموعات: المجموعة الضابطة، ومجموعة ألفا سيبرمثرين، ومجموعة حمض ألفا ليبويك ومجموعة ألفا سيبرمثرين مع حمض ألفا ليبويك.

أظهرت نتائج هذه الدراسة أن تناول ألفا سيبرمثرين يسبب زيادة في مستوى إنزيمات الآنين ترانس أمينيز، أسبرتات ترانس أمينييز والترانس أمينييز القلوي، البيلوروبين، يوريا، حمض اليوريك والكرياتينين، كما يسبب نقص في مستويات البروتين الكلي والزلال، كما أظهرت الدراسة أيضا أن تناول حمض ألفا ليبويك يقلل من السمية المسحثة بألفا سيربرمثرين عن طريق الاستعادة الجزئية للقيم الطبيعية لهذه المؤشرات الكيموحيوية، وقد تم تدعيم النتائج بالفحص النسيجي، وتبين من النتائج أن حمض ألفا ليبويك يمكن أن يكون له دور وقائي ضد السمية المستحثة بألفا سيبرمثرين في كبد وكلى الجرذان المعالجة.

الكلمات المفتاحية: ألفا سيبرمثرين، حمض ألفا ليبويك، المؤشرات الحيوية الكبدية والكلوية، الهستولوجية الكبدية والكلوية.