

THE PROTECTIVE EFFECTS OF LYCOPENE ON THE LOSS OF BODY WEIGHT AND HISTOPATHOLOGICAL LESIONS IN LIVER, KIDNEY, HEART, AND BRAIN TISSUE OF RATS EXPOSED TO SUBCHRONICALLY DIFFERENTIAL DOSES OF 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN

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Abstract

The aim of this study was to investigate the possible protective role of lycopene (LYC) on body weight changes, and histopathological lesions on liver, kidney, heart, and brain tissue in male rats exposed to subchronically differential doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a highly toxic xenobiotic.

Forty-eight rats were divided into six groups. The first group received 0.5 mL corn oil as control; the second group was treated with 10 mg/kg bw/day LYC. Groups 3 and 4 were treated with 50 and 500 ng/kg bw/day of TCDD, respectively. Groups 5 and 6 were subjected to 50 and 500 ng/kg bw/day of TCDD along with 10 mg/kg bw/day of LYC, simultaneously. The period of the experiment was 13 weeks. In TCDD-treated groups, a dose-related depression of mean body weight was observed when compared to control. Simultaneously LYC administration reduced the loss of body weight and partially or totally recovered the formed histopathological lesions in liver, kidney, and heart tissue of rats exposed to TCDD.

As a result, it is suggested that LYC has a protective effect against the loss of body weight and toxicity caused by TCDD.

Rezumat

Scopul acestui studiu a fost investigarea posibilului rol protector al licopenului (LYC) asupra modificării greutatei corporale și a leziunilor histopatologice induse la nivelul ficatului, rinichiului, inimii și creierului șobolanilor masculi, după expunere la doze diferențiate subcronice de 2,3,7,8-tetraclorodibenzo-*p*-dioxină (TCDD un xenobiotic extrem de toxic). 48 șobolani au fost împărțiți în 6 grupuri. Primul grup a primit 0,5 mL ulei de grâu ca martor; al doilea grup a fost tratat cu 10 mg/kgc/zi LYC. Grupurile 3 și 4 au fost tratate cu 50 și respectiv 500 ng/kgc/zi de TCDD. Grupele 5 și 6 au fost supuse la 50 și 500 ng/kgc/zi de TCDD împreună cu 10 mg/kgc/zi de LYC, simultan. Perioada de derulare a experimentului a fost de 13 săptămâni. În grupurile tratate cu TCDD a fost observată o scădere a greutății medii a corpului comparativ cu grupul control. În același timp

administrarea LYC a redus pierderea în greutate și recuperarea parțială sau totală a leziunilor histopatologice formate la nivelul ficatului, rinichilor, inimii șobolanilor expuși la TCDD.

Rezultatele sugerează că LYC are un efect protector asupra scăderii masei corporale și a toxicității provocate de TCDD.

Keywords: dioxin; toxicity; histopathology; lycopene

Introduction

TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is the most toxic congener among the polychlorinated dibenzo-*p*-dioxins, which are widespread, persistent and highly toxic environmental pollutants, and it has been widely investigated as a model compound of this class of chemicals [1, 2]. It is a lipophilic, bioaccumulative pollutant in the environment [3]. Animal data following oral exposure indicated that TCDD is one of the most toxic compounds known and that it produces a wide spectrum of toxic effects [4]. Prolonged exposure to TCDD may result in a wide variety of adverse health effects in experimental animals and in humans, including Wasting syndrome, dermal toxicity, reproductive toxicity, immunotoxicity, neurotoxicity, hepatotoxicity, teratogenesis, and carcinogenesis [5, 6]. Although many studies have been conducted for the toxicity of TCDD, the mechanism is not fully elucidated.

Lycopene (LYC), as a dietary source of a carotenoid antioxidant, has attracted considerable interest in recent years as an important phytochemical with a beneficial role in human health [7]. Among the carotenoids, lycopene is a major component found in the serum [8, 9]. It is also found in various tissues throughout the body such as the liver and kidney [9]. Several recent studies have indicated the effect of dietary lycopene in reducing the risk of chronic diseases such as cancer and cardiovascular diseases [8]. The biological activity of lycopene is thought to be primarily due to its antioxidant properties [7]. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidence is accumulating to suggest other mechanisms such as gap junction communication, cell growth regulation, modulating gene expression, immune response and modulators of Phase I and II drug metabolizing enzymes [7, 8].

The aim of the present study was to investigate subchronic lethality, body weight change and macroscopic effects on liver, kidney, heart and brain in male rats exposed to differential doses of subchronically TCDD, and to determine the possible protective role of LYC against the toxicity induced by TCDD.

Materials and Methods

Chemicals

TCDD was purchased from AccuStandard (New Haven, CT, USA). LYC 10% FS (RedivivoTM, Code 7803) was obtained from DSM Nutritional Products (İstanbul, TURKEY) and other reagents were supplied from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA) or Merck (Darmstadt, GERMANY).

Animals and experimental design

The protocol for animal use was approved by the Institutional Review Board of the National Institute of Health and the Local Committee on Animal Research. The animals were obtained from Firat University, Experimental Research Centre (Elazığ, Turkey) and were housed under standard laboratory conditions (temperature $24 \pm 3^\circ\text{C}$, humidity 40–60%, a 12-h light: 12-h dark cycle). A commercial pellet diet (Elazığ Food Company, Elazığ, Turkey) and fresh drinking water were given *ad libitum*. Forty-eight healthy adult male Sprague-Dawley rats (6–8 weeks old, weighing 190–250g) were used. The rats were divided into six groups containing eight rats each. All administrations were applied by gavage as emulsion in 0.5 mL corn oil. The experiment lasted 13 weeks.

Experimental groups were as follows:

Group 1 (Control): The group was given 0.5 mL corn oil.

Group 2: The group was given a dose of 10 mg/kg bw/day LYC.

Group 3: The group was given a dose of 50 ng/kg bw/day TCDD.

Group 4: The group was given a dose of 500 ng/kg bw/day TCDD.

Group 5: The group was given doses of 50 ng/kg bw/day TCDD plus 10 mg/kg bw/day LYC.

Group 6: The group was given doses of 500 ng/kg bw/day TCDD plus 10 mg/kg bw/day LYC.

Histopathological examinations

All tissues were fixed in 10% neutral-formaline solution, embedded in paraffin wax, sectioned at 5 μm , and stained with haematoxyline and eosin [10].

Statistical analysis

All values were presented as mean $\pm$ S.E.M. Differences were considered to be significant at $p < 0.05$. One-way analysis of variance (ANOVA) and *post hoc* Tukey-HSD test were used to determine differences between groups. The SPSS/PC program (Version 10.0; SPSS, Chicago, IL) was used for the statistical analysis.

Results and Discussion

During the experiment, no animal deaths were recorded in groups 1, 2, 3 or 5. Four rats died in group 4 (on day 62, 71, 85, and 86, respectively) and in group 6 (on day 70, 75, 77, and 83, respectively). This situation can be related to a decrease in food intake and deterioration of nutrient absorption. The fact that half of the animals to which a 500 ng/kg bw/day dose of TCDD was applied died, can be related to Wasting syndrome, which is one of the most evident symptoms of dioxin poisoning [11].

Mean body weights of animals are given in Table I. Body weight decreased depending on TCDD doses, while LYC treatment tended to restore this decrease in the body weight.

Table I
Mean $\pm$ S.E.M. values of body weight (g) according to weeks of treatment in all groups along the study and alteration (%) of body weight between initial and at the end of the study.

Weeks	Body weight (g)					
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
1.	209.8 $\pm$ 14.8 ^c	214.2 $\pm$ 8.4 ^f	221.1 $\pm$ 10.1 ^{cd}	196.5 $\pm$ 10.3	207.5 $\pm$ 13.9 ^c	190.7 $\pm$ 10.5
2.	232.7 $\pm$ 15.5 ^{bc}	232.8 $\pm$ 7.8 ^e	214.6 $\pm$ 09.9 ^d	211.5 $\pm$ 10.2	219.2 $\pm$ 11.7 ^{bc}	201.1 $\pm$ 15.0
3.	241.2 $\pm$ 16.2 ^{abc}	234.6 $\pm$ 7.2 ^e	215.3 $\pm$ 14.5 ^d	213.3 $\pm$ 10.4	221.0 $\pm$ 11.3 ^{bc}	216.6 $\pm$ 07.8
4.	253.0 $\pm$ 16.2 ^{abc}	246.2 $\pm$ 6.4 ^{de}	233.7 $\pm$ 06.6 ^{cd}	222.1 $\pm$ 10.1	221.6 $\pm$ 09.2 ^{bc}	216.1 $\pm$ 07.9
5.	236.3 $\pm$ 13.8 ^{abc}	234.7 $\pm$ 6.2 ^e	222.8 $\pm$ 04.8 ^{cd}	207.1 $\pm$ 07.2	215.7 $\pm$ 05.9 ^{bc}	210.0 $\pm$ 07.2
6.	257.5 $\pm$ 15.5 ^{abc}	251.0 $\pm$ 5.8 ^{cde}	246.3 $\pm$ 06.3 ^{bc}	215.2 $\pm$ 09.8	227.6 $\pm$ 07.9 ^{bc}	215.5 $\pm$ 08.2
7.	254.3 $\pm$ 14.8 ^{abc}	251.2 $\pm$ 6.6 ^{cde}	248.3 $\pm$ 05.7 ^{bc}	208.7 $\pm$ 12.1	220.8 $\pm$ 08.4 ^{bc}	209.2 $\pm$ 09.7
8.	283.5 $\pm$ 16.4 ^{ab}	269.3 $\pm$ 6.2 ^{abc}	271.5 $\pm$ 04.6 ^{ab}	212.7 $\pm$ 13.2	244.0 $\pm$ 07.9 ^{ab}	215.5 $\pm$ 10.2
9.	281.1 $\pm$ 16.3 ^{ab}	258.1 $\pm$ 3.5 ^{bcd}	264.8 $\pm$ 07.0 ^{ab}	213.5 $\pm$ 13.2	243.1 $\pm$ 07.6 ^{ab}	209.8 $\pm$ 12.2
10.	277.1 $\pm$ 15.4 ^{ab}	284.1 $\pm$ 5.6 ^a	280.5 $\pm$ 07.8 ^a	214.6 $\pm$ 17.9	255.8 $\pm$ 06.7 ^a	200.8 $\pm$ 19.6
11.	286.2 $\pm$ 16.3 ^a	285.5 $\pm$ 6.1 ^a	289.1 $\pm$ 08.3 ^a	210.0 $\pm$ 22.1	262.0 $\pm$ 08.0 ^a	222.6 $\pm$ 18.0
12.	267.0 $\pm$ 14.3 ^{ab}	271.2 $\pm$ 5.7 ^{ab}	283.2 $\pm$ 11.6 ^a	211.0 $\pm$ 32.3	241.5 $\pm$ 07.2 ^{ab}	235.2 $\pm$ 11.2
13.	282.0 $\pm$ 15.3 ^{ab}	285.3 $\pm$ 6.4 ^a	273.5 $\pm$ 12.6 ^{ab}	211.7 $\pm$ 35.1	257.5 $\pm$ 07.5 ^a	229.7 $\pm$ 06.2
<i>Significance</i>	*	***	***	NS	***	NS
% alteration	+34.3	+33.2	+23.7	+7.7	+24.1	+20.4

NS: Non significant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ^{a, b, c, d, e, f}: Different letters within same column showed significant differences

The most significant symptoms in animals exposed to long-term, low doses of TCDD are: decrease in food intake, lack of appetite, and consequent fatal loss of weight [12, 13]. However, it has been pointed out

that not merely decline in food and water intake, but also deterioration of nutrient absorption through digestive tract and other several factors can be shown as causes of death as well [11].

The histopathological changes observed in liver tissue are summarized in Table II. Degenerative changes characterized by cloudy swelling or lipid deposition along with hepatocellular necrosis and apoptosis were prominent changes in liver tissue of groups 3 and 4 (figure 1A).

Table II
Histopathological changes in the liver, kidney and heart tissues.

		Histopathological changes						
Lesions		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	p
Liver	Karyomegaly	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	2.14 ± 0.26 ^a	1.14 ± 0.34 ^b	0.86 ± 0.26 ^b	2.29 ± 0.18 ^a	0.001
	Double nucleus hepatocytes	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	2.00 ± 0.00 ^a	1.00 ± 0.20 ^b	1.57 ± 0.20 ^b	1.43 ± 0.00 ^b	0.001
	Lipid degeneration	0.00 ± 0.00 ^d	0.00 ± 0.00 ^d	1.86 ± 0.14 ^a	2.00 ± 0.00 ^a	1.57 ± 0.20 ^b	1.86 ± 0.14 ^a	0.001
	Cloudy swelling	0.00 ± 0.00 ^c	0.14 ± 0.14 ^c	1.00 ± 0.00 ^b	1.86 ± 0.00 ^a	0.86 ± 0.14 ^b	1.71 ± 0.18 ^a	0.001
	Necrosis	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	1.29 ± 0.29 ^b	2.00 ± 0.22 ^a	1.00 ± 0.18 ^b	1.53 ± 0.14 ^b	0.001
	Biliar duct proliferation	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	1.57 ± 0.20 ^{ab}	1.86 ± 0.14 ^a	1.43 ± 0.20 ^{ab}	1.72 ± 0.18 ^a	0.001
	Disorganisation	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	2.00 ± 0.00 ^a	2.00 ± 0.00 ^a	1.29 ± 0.18 ^b	1.53 ± 0.22 ^{ab}	0.001
	Periportal cell infiltration	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	0.71 ± 0.18 ^b	1.29 ± 0.18 ^a	0.54 ± 0.22 ^c	1.00 ± 0.00 ^a	0.001
	Periportal fibrosis	0.00 ± 0.00 ^b	0.00 ± 0.00 ^b	1.14 ± 0.22 ^{ab}	1.86 ± 0.29 ^a	0.71 ± 0.14 ^b	1.53 ± 0.14 ^a	0.001
	Sinusoidal congestion	0.00 ± 0.00 ^b	0.00 ± 0.00 ^b	0.22 ± 0.13 ^{ab}	0.53 ± 0.43 ^{ab}	0.00 ± 0.00 ^b	0.27 ± 0.22 ^{ab}	0.001
Kidney	Karyomegaly in proximal tubules	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	0.87 ± 0.20 ^{ab}	0.43 ± 0.30 ^{bc}	0.71 ± 0.29 ^{ab}	1.29 ± 0.18 ^a	0.001
	Necrosis in proximal tubules	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	1.00 ± 0.22 ^{ab}	1.86 ± 0.26 ^a	0.71 ± 0.18 ^b	1.17 ± 0.20 ^{ab}	0.001
	Degeneration in proximal tubules	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	2.00 ± 0.14 ^a	2.14 ± 0.20 ^a	1.29 ± 0.18 ^b	1.71 ± 0.14 ^b	0.001
	Intraluminal hyaline formations	0.00 ± 0.00 ^d	0.00 ± 0.00 ^d	2.00 ± 0.29 ^a	2.29 ± 0.18 ^a	1.00 ± 0.14 ^c	1.14 ± 0.14 ^{bc}	0.001
	Interstitial nephritis	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	0.57 ± 0.30 ^{ab}	0.71 ± 0.18 ^a	0.00 ± 0.00 ^c	0.43 ± 0.18 ^b	0.001
Heart	Interstitial oedema	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	0.86 ± 0.26 ^b	2.37 ± 0.30 ^a	0.23 ± 0.14 ^c	1.29 ± 0.18 ^{ab}	0.001
	Myofibriller necrosis	0.00 ± 0.00 ^c	0.00 ± 0.00 ^c	0.57 ± 0.20 ^b	1.43 ± 0.30 ^a	0.00 ± 0.00 ^c	0.86 ± 0.14 ^b	0.001
	Myofibriller degeneration	0.00 ± 0.00 ^d	0.00 ± 0.00 ^d	1.20 ± 0.22 ^b	1.86 ± 0.34 ^a	0.71 ± 0.18 ^c	1.14 ± 0.14 ^b	0.001

a, b, c, d. Different letters within same line showed significant differences.

The intensity and distribution of these lesions in liver tissues were prominent in group 4 compared with that of group 3. Karyomegaly in hepatocytes, disorganization in hepatic cord, mononuclear cell infiltrations, and fibrosis in periportal areas along with sinusoidal congestion were other observed changes. Periportal fibrosis, hyperplasia in biliar duct and oval-cell proliferations were present in both groups 3 and 4. Hepatocellular karyomegaly was more prominent in group 4 than in group 3. Hepatocytes with double nuclei in periportal areas were observed. Hepatocytes in group 4 had structures similar to asinus (figure 1B). Degenerative and necrotic changes decreased in group 5 compared to those in group 3, but this decrease did not present statistical significance (figure 1C). However, LYC

administration to TCDD-treated (50 ng/kg bw/day) rats significantly decreased the fibrotic changes in periportal areas and sinusoidal congestion. Although necrotic changes were present in moderate intensity in group 6 more than in group 4, these lesions were more prominent in these two groups compared with groups 3 and 5. It was observed that karyomegaly was more intense in group 6 than in the other experimental groups (figure 1D). Hepatocellular regeneration and asinus formation were more prominent in group 6 than in group 4. Although the histological structure of liver in the control group was normal (figure 1E). Slight cloudy swelling was observed in the LYC group (figure 1F).

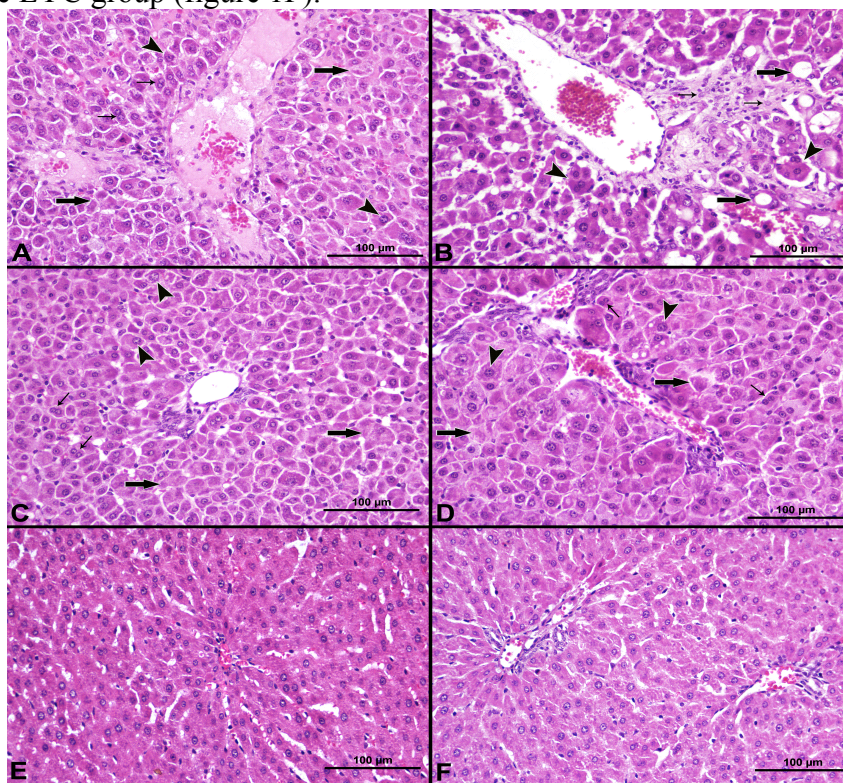


Figure 1

- A- Necrosis and degenerative changes in periportal area (big arrows), karyomegaly in hepatocytes (arrowheads) and appearance of regenerated hepatocytes (small arrows) in group 3, H-E.
- B- Periportal fibrosis and mononuclear cell infiltrations and oval cell proliferations (small arrows), asinus formation in hepatocytes (arrowheads) and macrovesicular lipid degeneration (big arrows) in group 4, H-E.
- C- Cloudy swelling in hepatocytes of periportal area, moderate necrotic changes (big arrows), karyomegaly in hepatocytes (arrowheads) and regenerated hepatocytes (small arrows) in group 5, H-E.
- D- Hepatocellular necrosis (big arrows) and karyomegaly in hepatocytes with (arrowheads) and regenerative changes (small arrows) in group 6, H-E.
- E- Histological appearance of liver in control group, H-E.
- F- Histological appearance of liver in group 2, H-E.

The liver is a target organ for dioxin toxicity. Hepatotoxicity is a primary effect of dioxin [14]. TCDD-induced hepatotoxicity and carcinogenesis have been studied extensively in experimental animals. Our findings were similar with the findings of Chang et al. [15], and Kociba et al. [16] who reported many histopathological lesions in liver of rats exposed TCDD.

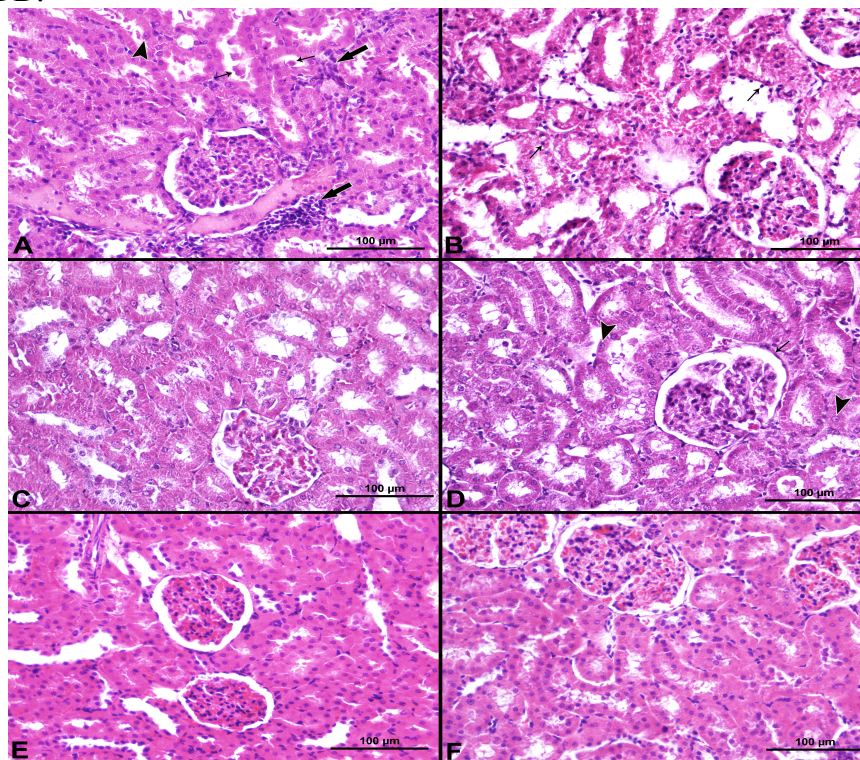


Figure 2

- A- Cloudy swelling and mononuclear cell infiltrations in proximal tubules (big arrows), karyomegaly in epithelium of proximal tubules (arrowheads) and intraluminal hyaline rollers (small arrows) in group 3, H-E.
- B- Severe congestion and karyopycnosis in proximal tubules (small arrows) in group 4, H-E.
- C- Cloudy swelling and glomerular congestion in proximal tubules in group 5, H-E.
- D- Cloudy swelling and karyomegaly in proximal tubules (arrowheads) and thickening of glomerular basal membrane (arrow) in group 6, H-E.
- E- Histological appearance of kidney in control group, H-E.
- F- Histological appearance of kidney in group 2, H-E.

The histological changes observed in kidney tissue are given in Table II. Cloudy swelling and desquamation in proximal tubules were prominent lesions in group 3 (figure 2A). In group 4, necrotic changes characterized by karyopycnosis in proximal tubules were more prominent

(figure 2B). Focal interstitial nephritis characterized with mononuclear cell infiltrations, intraluminal hyaline formation, thickening of glomerular basal membrane, and cloudy swelling and glomerular congestion in proximal tubules were observed in both groups 3 and 4 (figure 2C). Cloudy swelling and karyomegaly in epithelium of proximal tubules were more severe in group 4 (figure 2D). Severe congestion and free erythrocytes in lumen of tubules were observed in group 4. Necrotic and degenerative changes had a moderate intensity in group 5 compared to group 3. Mononuclear cell infiltrations were absent in group 5. Decreases in necrotic, degenerative, and infiltrative changes, as well as in intraluminal hyaline formation, but an increase in karyomegaly, were observed in group 6 compared with group 4. No thickening in glomerular basal membrane was observed in either groups 5 or 6. The histological structure of kidneys in both the control and LYC alone groups was normal (figure 2E, F).

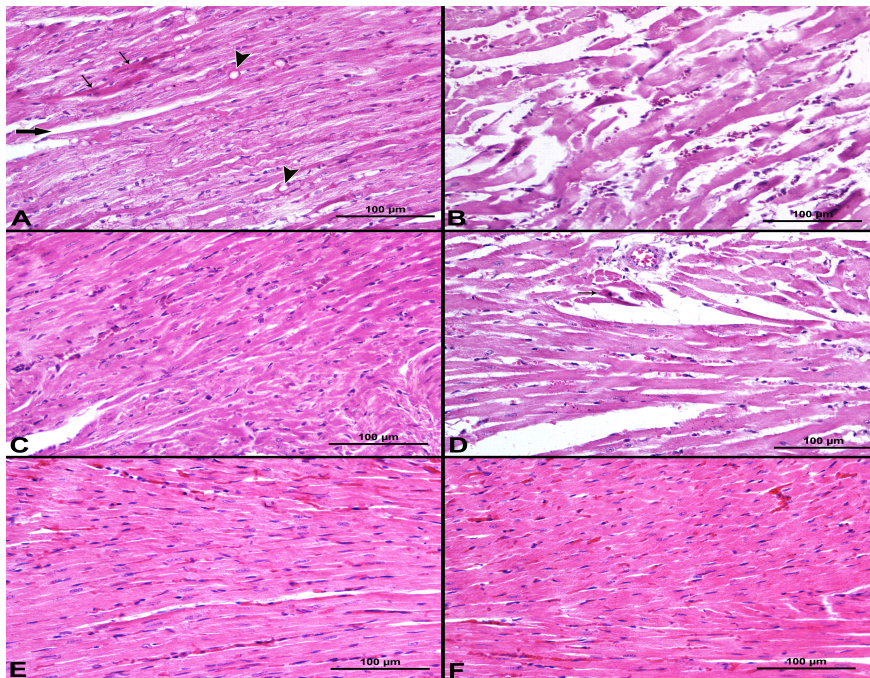


Figure 3

- A- Myofibrillar degeneration and necrotic changes (small arrows), anointment (arrowheads) and interstitial oedema (big arrow) in group 3, H-E.
- B- Severe necrosis, degeneration, oedema and congestion and myofibrillar destruction in group 4, H-E.
- C- Moderate myofibrillar degeneration in group 5, H-E.
- D- Clear myofibrillar degeneration and oedema and myofibrillar necrosis (arrow), H-E.
- E- Histological appearance of heart in control group, H-E.
- F- Histological appearance of heart in group 2, H-E.

The histopathological changes observed in heart tissue are summarized in Table II. Myofibrillar degeneration was the most prominent lesion in group 3. Vesicular fat deposition in cytoplasm of some myofibrillar areas was observed in group 3. Eosinophilic cytoplasm and pycnotic nucleus in some myofibrilles, slight interstitial oedema, and congestion were observed in group 3 (figure 3A). Destriation in myofibrilles was the most prominent lesion in group 4. Myofibrillar degeneration, necrosis, and interstitial edema were more severe in group 4 than in group 3 (figure 3B). Although no myofibrillar necrosis was observed in group 5, a slight degeneration existed (figure 3C). Lesions mentioned in group 4 were in moderate intensity in group 6 (figure 3D). The histological structure of the heart in the control and LYC alone groups was normal (figure 3E, F).

Riecke et al. [17] reported that TCDD treatment increased myocardial fibrosis in marmosets within 2–4 weeks of treatment, Dalton et al., [18] also reported that TCDD increased on set and severity of atherosclerotic lesions in hyperlipidemic mice exposed to 150 ng TCDD/kg bw, three times weekly, for 7 or 26 weeks. In addition, a 2-year chronic study of female rats exposed to TCDD at doses of 10–100 ng/kg bw/day demonstrated an increased incidence of cardiomyopathy and arteritis [19]. Similarly, fibrotic lesions in the hearts and vessels of rats were seen after 2 years treatment with daily doses of 10ng TCDD/kg bw [19]. Our findings regarding the histopathological findings are in agreement with previous reports [17-19].

Pathological changes in brain tissue were not observed microscopically.

In the current study, simultaneously LYC administration (10 mg/kg bw/day) partially or totally recovered the histopathological lesions in liver, kidney, and heart tissues of rats exposed to TCDD. The improvements after LYC administration may be explained by the potent antioxidant effect of LYC.

Conclusions

In this study it was observed that both low and high doses of TCDD increased the loss of body weight, and caused significant histopathological lesions in liver, kidney, and heart tissues of rats. However, concomitant administration of LYC with TCDD provided marked improvements in the loss of body weight and TCDD-induced lesions in tissues. In conclusion, considering all of the positive effects as a whole, LYC, a powerful antioxidant, can be used in the treatment of several chronic diseases, such as

cancer and cardiovascular diseases caused by environmental pollutants like TCDD.

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