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Protection of Resveratrol Against Nephrotoxicity in Rats Produced by 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin

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ABSTRACT

WE CONDUCTED A STUDY to examine the impact of Resveratrol (RES) on the renal tissues of Wistar rats that were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and developed kidney damage. Applied on albino male rats (102), the age range (8-9) weeks and the weight range (80 -90) gms, (32) rats were used for acute stage of toxicity, while others (70) rats were involved as a chronic toxicity; the experiment design consists of 7 groups ; G1 (control –ve), G2 vehicle (acetone + corn oil), G3 TCDD (4 µg/kg b. w.), G4 TCDD (2 µg/kg b. w.), G5 (RES), G6 (TCDD (4 µg/kg b. w.)+ RES),G (TCDD(4 µg/kg b. w.) + RES). We found that malondialdehyde (MDA), urea and creatinine levels in the groups treated with TCDD showed significant increases compared to the other groups, despite a decrease in the levels of reduced glutathione (GSH) and catalase (CAT) in the TCDD groups. Comparing to the other groups, we observed a rise in GSH and CAT levels, as well as a decrease in MDA, urea, and creatinine levels in the RES treated group. The administration of RES improved the oxidative stress markers and histological alterations caused by TCDD.

Key words: TCDD Resveratrol kidney nephrotoxicity.

Introduction

Dioxins are extremely harmful substances that are released into the environment as byproducts of industrial processes such burning plastic and medical waste, bleaching paper with chlorine, and producing certain pesticides, herbicides, and fungicides [1,2], additionally, these contaminants are found in trace concentrations in areas where geological processes and spontaneous combustion occur [3].

Due to these compounds' lipophilicity and resistance to biological and environmental degradation, dioxins bioaccumulate and become more amplified in the food chain, making them persistent in the environment [4]. Thus, the main method that humans are exposed is through the consumption of contaminated high-fat foods including cheese, milk, meat, fish, and breast milk [5,6].

The most hazardous of the dioxins is 2, 3, 7, 8, Tetrachlorodibenzo-p-dioxin (TCDD), when acting as a xenobiotic agent, it can induce toxicity and carcinogenesis [7]. The mechanism of action involves the high-affinity binding of the substance to a specific cellular protein known as the aryl hydrocarbon receptor (AhR) [8-10]. Exposure to TCDD can lead to various harmful effects, including digestive, liver, and cancers of the breast, problems with development, liver damage, birth imperfections like cleft palate and kidney malformation, immunotoxicity, neurological damage, heart disease, vomiting, breathing problems, disorders of reproduction, hypertension, and asthmatic symptoms. Dioxins have detrimental impacts such as causing DNA mutations, generating free radicals, and promoting lipid oxidation. [11,12]. Oxidative stress occurs when there is an increase in the creation of free radicals or a decrease in the ability to remove them. Oxidative stress refers to a notable imbalance between the production of free radicals and the body's ability to counteract their harmful effects through antioxidant mechanisms of defense [13-15].

Resveratrol (RES; 3,5,4-trihydroxystilbene), Resveratrol, a type of polyphenolic phytoalexin present in grapes and other seed-bearing plants, has been identified as a competitive antagonist of the AhR receptor in various types of cells.[16] Display beneficial traits such as the ability to inhibit the growth of cancer cells and tumors (17), The substance exhibits hepatoprotective [18], antibacterial[19], nephroprotective[20], anti-inflammatory [21], antidepressant and antioxidant properties [22-24]and effects of immunity enhancers

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[25]. RES has been observed to exert protective effects on the kidneys against metabolic syndrome [26], chronic neuropathic pain, ischemia-reperfusion induced kidney and muscular destruction, and seizures of epilepsy [27,28]. We conducted a study to examine the impact of Resveratrol on the renal tissue of rats that were exposed to TCDD.

Material and methods

Animals

We acquired a total of 102 male Wistar albino rats from the Animal House located at the Faculty of Veterinary Medicine in Tikrit University. The rats were of age 8-9 weeks and had a weight ranging from 80-90 grams. We have obtained approval from the experimental animal ethics committee (687/P.G./2024). The rats were housed in a regulated environment maintained at a temperature of 25 °C and a humidity level ranging from 55% to 60%. They were subjected to a 12-hour light and 12-hour dark cycle. The rats were given a standard pellet diet and had unlimited access to water. The animals' water supply was supplied on a daily basis, and the cage was cleaned every other day.

Chemical preparation

The 2,3,7,8-TCDD (purity>99%) was sourced from Accustandart, Inc. (New Haven, Connecticut, USA). The TCDD dose was prepared by dissolving 1mg of TCDD in acetone, followed by mixing it with corn oil. Resveratrol was obtained from ark pharm USA. Resveratrol was prepared by dissolving in distal water with shaking**.** The study involved 102 male albino rats,

Acute toxicity (Dixon method, 1980s):

The determination of TCDD LD_{50} utilized the up-and-down method [29], employing a dose range of 20-80 µg/kg of TCDD as outlined by Pohjanvirta and Tuomisto [30]. Thirty-two rats were allocated LD50 for this investigation, with four assigned to each dose level. Doses were adjusted by either increasing or decreasing by 100% of the initial dose based on the survival or mortality of the dosed rat after 21 days. The median lethal dose was computed based on the mortality of 50% of the animals.

Chronic toxicity:

1- First group (C -ve): Control group including (10) rats were fed on ordinary rat pellets and water *ad libitum.*

2- Second group (C +ve): (10 rats) were administered orally by gavage 1 ml from vehicle (aceton + corn oil) solution once /week/100 days.

3- Third group (10%): (10 rats) were administered orally by gavage 1/10 from LD_{50} of the TCDD dissolved by aceton + corn oil solution weekly for 100 days.

4- Fourth group (5%): (10 rats) were administered orally by gavage 1/20 from LD50 TCDD dissolved by aceton + corn oil solution weekly for 100 days.

5- Fifth group (Resveratrol): (10 rats) were administered orally by gavage 50 microgram Resveratrol dissolved by Distal water weekly for 100 days.

6- Sixth group (10% from LD_{50} of TCDD + Resveratrol): (10 rats) were administered orally by gavage 10% from LD50 TCDD dissolved by aceton + corn oil solution+ 50 microgram Resveratrol dissolved by Distal water weekly for 100 days.

7- Seventh group (5% from LD_{50} of TCDD + Resveratrol): (10 rats) were administered orally by gavage 5% from LD50 TCDD dissolved by aceton + corn oil solution + 50 microgram Resveratrol dissolved by distal water weekly for 100 days.

TCDD was orally administered at a dosage of LD_{50} in acute toxicity experiments. For chronic toxicity studies, TCDD was orally administered at dosages of 1/10 and 1/20 of the LD50 dose µg/kg/week [31]

Blood collection: Blood were collected at day 100 of the experiment according to the collection protocol [16], for biochemical assay (urea and creatinine), enzymic assay (CAT and MDA), and non enzymic assay(GSH): Were measured by rat ELISA kit Clone- Corp USA [32].

Histopathological changes: At the end of experiment (100 days) all animal were scarified under slight ether anesthesia and kidney swiftly extracted and dissected to note any abnormalities in size, color, consistency, or adherence. Subsequently embedded in paraffin and stained using a standard stain (hematoxylin and eosin) after being fixed in 10% formalin, thrown in ascending grades of ethanol (70, 80, 90, 100%), and then in xylene[33, 34].

Statistical analysis

Data analysis by using computer statistical program SPSS and sigma stat program. Tow way analysis variance was used $p \leq 0.05$ [2].

Results

Median lethal dose of TCDD

The results revealed that the LD_{50} of the TCDD was 40 µg/kg, B.W. that killed half of the animals in single dose orally. The findings are consistent with Simanainen *et al.,* [35].

Biochemistry

MDA was increased significantly and GSH and CAT levels were decreased significantly in the TCDD treated group compared to all other groups.

GSH and CAT levels were increased significantly, while MDA levels was decreased significantly in the RES treated group compared to all other groups. In the TCDD + RES group, MDA was increased levels were decreased and GSH and CAT levels were increased significantly in control group levels compared to the TCDD group (Table 1). Urea and creatinine levels were increased significantly in the TCDD group compared to all other groups. Urea and creatinine levels were decreased significantly in the RES group compared to all other groups. Increased Urea and creatinine levels in the TCDD group were decreased significantly in the TCDD + Urea and group compared to all other groups (Table 1).

Kidney Lesions

The G –ve showed normal Malpighian (renal) corpuscle consists of glomeruli (Bowman's space Bowman's capsule)) which invaginated to the tuft (Capillaries) with present of proximal convoluted. tubular lined by atypical columnar epithelium figure (6).

The G3 (10 % LD_{50} TCDD) showed sever interstitial hemorrhage & blood vessels congestion with acute cellular swelling (cloudy swelling) Bowman's space was dilated with mononuclear cells, infiltration (lymphocytes or macrophages) (Fig.7) Sever interstitial edema with interstitial hemorrhage, mononuclear cells infiltration with necrosis and apoptosis of cell epithelium (Figs. 8 and 9)

The G4 in (Fig.10) showed sever Interstitial hemorrhage with acute cellular swelling necrotic apoptotic cells, multiple areas in the cortex with congested blood vessels (veins). The interstitial hemorrhage (acute cellular swelling & lymphocytic infiltration (Figs 11;12), moreover, atherosclerotic (Fig.13). In Kidney medulla showed distal tubules with interstitial hemorrhage (figure, 14).

The G6 (10 % LD50 of the TCDD + Res) showed congestion and mild edema (Fig.15), with mild acute cellular swelling (Fig.16). While the G7 (5 % LD50 TCDD + Res) (Fig.17) showed swelling, with mild edema.

Discussion

LD_{50} of the TCDD was 40 µg/kg B.W. that killed half of the animals in single oral dose [35].Tissues continuously generate reactive oxygen species (ROS) and antioxidants. The body's endogenous defensive mechanisms, including GSH (glutathione), GPO (glutathione peroxidase), GRx (glutaredoxin), GST (glutathione S-transferase), SOD (superoxide dismutase), CAT (catalase), and vitamins A, C, and E, counteract excessive reactive oxygen species (ROS) [2, 36]. Oxidative stress occurs when there is an imbalance between the antioxidant concentration and the oxidants, leading to harm to tissues [37,38]. Oxidative tissue damage occurs as a result of chemical interactions between oxidant particles and lipids, carbohydrates, proteins, nucleic acids, and enzymes [39-41]. ROS, or reactive oxygen species, react with cell membrane lipids to generate malondialdehyde (MDA) [42]. Oxidative stress contributes to the prolonged toxicity of TCDD [43]. The specific mechanism via which TCDD triggers oxidative stress is now unidentified. TCDD has been discovered to boost lipid oxidation, diminish GSH content, elevate the levels of 8-hydroxy 2-deoxyguanosine (8-OHdG), lower hepatic membrane fluidity, increase DNA damage, encourage superoxide generation, and decrease nonprotein sulfhydryl content [44]. Created a nephrotoxicity model by giving rats a weekly dose of 2 µg/kg of TCDD. The rat kidneys were evaluated after a period of 60 days. The TCDD treatment resulted in a decrease in the levels of SOD, CAT, and GSH, while causing an increase in MDA levels. The renal tissues treated with TCDD exhibited a high incidence of glomerulosclerosis [45]. A liver damage model was established to investigate the chronic consequences of TCDD poisoning. The subjects were administered a dosage of 200 nanograms of TCDD for periods of 30, 60, 90, and 120 days. After these specific time intervals, the liver showed evident indications of cellular damage, necrosis, and the infiltration of inflammatory cells. The administration of TCDD lasted for 4 days, and by the conclusion of day 9, there was a noticeable elevation in the concentrations of urea and creatinine [46]. A kidney damage model was created by delivering TCDD daily for a period of 30 days. It was observed that the levels of MDA and TOS increased, while the levels of GSH, SOD, CAT, and TAS dropped in the group treated with TCDD [44]. RES enhances the body's ability to neutralize harmful free radicals and counteracts the damaging effects of oxidative stress [47-49] Resveratrol possesses the capacity to efficiently eliminate reactive oxygen species, inhibit oxidative harm induced by As_2O_3, and decrease the accumulation of arsenic in kidney tissues by facilitating the metabolism of As_2O_3. The data suggest that using resveratrol as a post-remission treatment for acute promyelocytic leukaemia, as well as a supplementary therapy for patients exposed to arsenic, may mitigate the detrimental impact of arsenic on the kidneys [50]. The results of our biochemical analysis, which included measurements of oxidant-antioxidant indicators, kidney-specific enzymes, inflammatory factors, and histology, were in line with previous studies [51].

Conclusion

Our research revealed that TCDD caused oxidative stress in the liver, while RES had a potent antioxidant action that effectively inhibited the development of TCDD-induced liver damage. In this study, we established a model of nephrotoxicity generated by TCDD and utilized RES as a protective agent. TCDD induced renal damage that was

comparable to its hepatotoxicity. RES demonstrated antioxidant activity and caused a shift in the equilibrium between antioxidants and oxidants towards antioxidants. RES has demonstrated the ability to provide protection against nephrotoxicity generated by TCDD.

Acknowledgments

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Competing Interest

The authors declares that there is no conflict interest.

Author contribution

Ahmed A. Sultan: Research article, funding the acquisition and preparing materials, Statistical analysis, review and editing. Bushra. I. al. Kaisi: Explain the finding, Experiment design.

Ethical approval

was granted through the local committee of the animal care and use at the College of Veterinary Medicine/University of Baghdad (Number 687/P.G. at 27/3/2024).

TABLE 1. Effect of TCDD on MDA, CAT, GSH, Urea, Creatinine(Mean ±SE.)

Groups	MDA Mean ±SE.	Catalase Mean ±SE.	Glutathione Mean ±SE.	Urea Mean ±SE.	Creatinine Mean ±SE.
Control –ve	2.22±0.39^{f}	309.23±1.85^{b}	7.36±0.24^{b}	22.28±1.03^{d}	0.22±0.01^{g}
Control +ve	3.01±0.04^{e}	293.84±6.50^{c}	6.19±0.22^{c}	32.09±0.45^{c}	0.33±0.03^{e}
t10%	6.10±0.03^{a}	157.50±0.96^{g}	2.78±0.05^{g}	44.09±0.71^{a}	1.26±0.02^{a}
t5%	5.57±0.06^{b}	188.62±2.49^{f}	3.00±0.03^{f}	39.54±1.89^{b}	0.98±0.02^{b}
Res	1.43±0.09^{g}	349.96±9.96^{a}	10.30±0.21^{a}	32.70±0.16^{c}	0.25±0.33^{f}
t10% +Res	4.22±0.38^{c}	219.90±3.56^{e}	4.37±0.15^{e}	34.55±0.12^{c}	0.90±0.02^{c}
t5%+RES	3.35±0.02^{d}	247.545±2.27^{d}	5.22±0.04^{d}	34.03±0.11^{c}	0.73±0.04^{d}
p-value	0.000*	0.000*	0.000*	0.000*	0.000*
LSD	0.15	14.26	0.46	2.55	0.08

*Significant differences at probability value (p≤0.05).
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The same latters indicated non-significant differences among the groups.

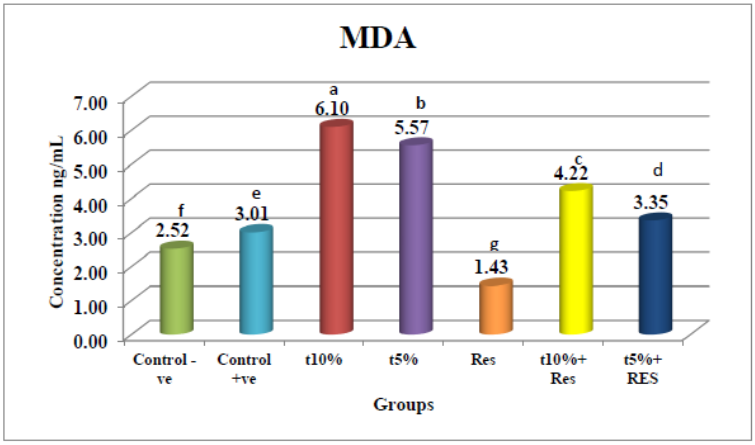

Fig.1. Effect of TCDD on Malon –Di – Aldehyde MDA (ng/mL) in serum of albino male rats.
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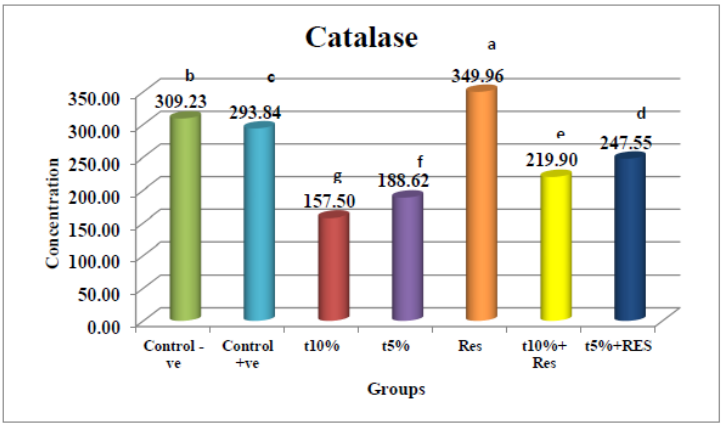

Fig.2. Effect of TCDD on Catalase (ng/mL) in serum of albino male rats.
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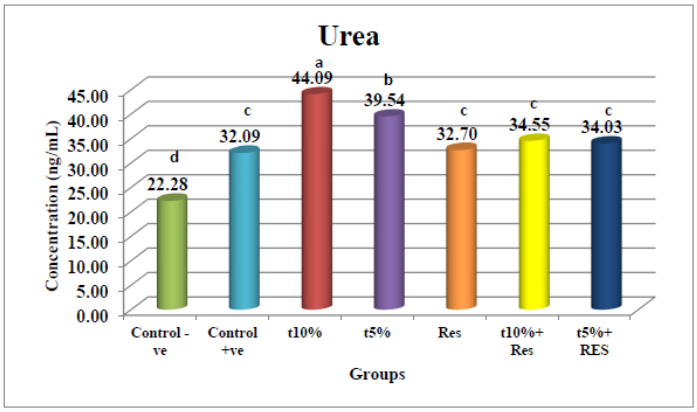

Fig.3. Effect of TCDD on Urea (ng/mL) in serum of albino male rats
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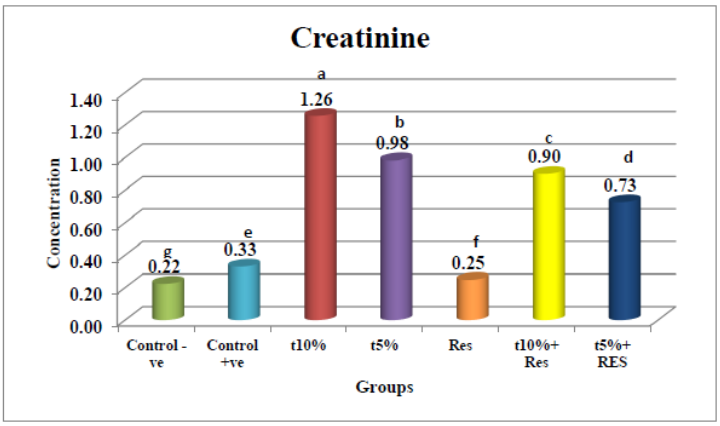

Fig.4. Effect of TCDD on Creatinine (ng/mL) in serum of albino male rats The different letters indicated that the present of significant differences among groups.
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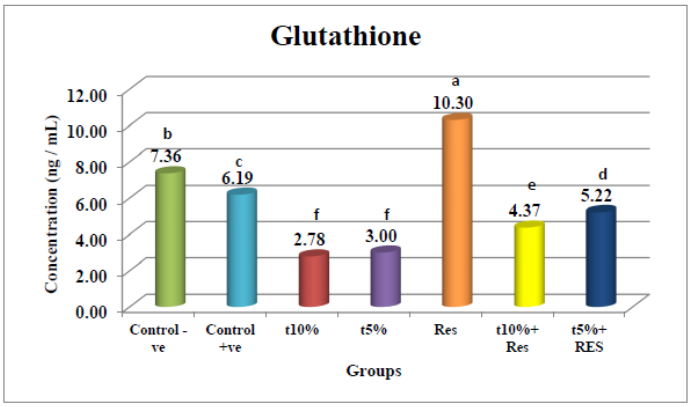

Fig.5. Effect of TCDD on reduced glutathione (ng/mL) in serum of albino male rats
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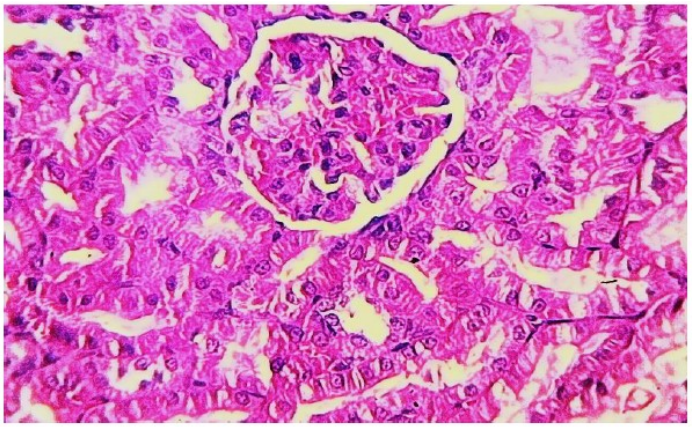

Fig.6. A micrograph of part of the kidney cortex of G1 rat showed a-Malpighian (renal) corpuscle consist of glomeruli (Bowman's space & Bowman's Capsule) to the tuft (capillaries); b-proximal convoluted tubules lined by atypical columnar epithelium. X400 H&E stain.

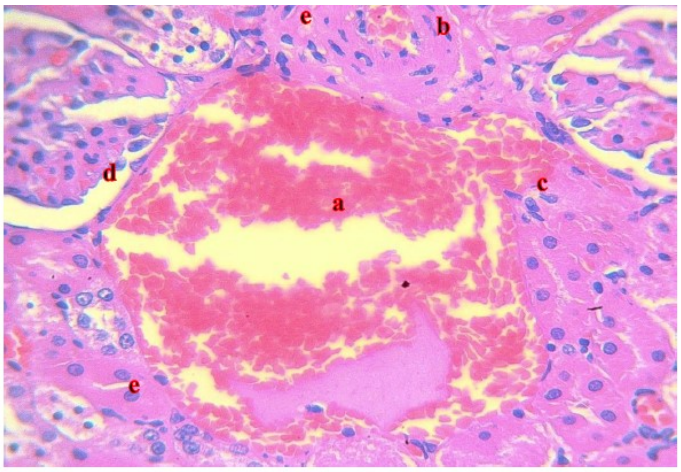

Fig.7. A micrograph of part of the Kidney cortex of G3 (10 % LD50 TCDD) showed a) Sever interstitial hemorrhage of blood vessels congestion b) Congested blood vessels interstitial layer c) Acute cellular swelling.(cloudy swelling) d) dilated Bowman's space e) Mononuclear cells (lymphocytes & macrophages) infiltrated X400 H&E stain.

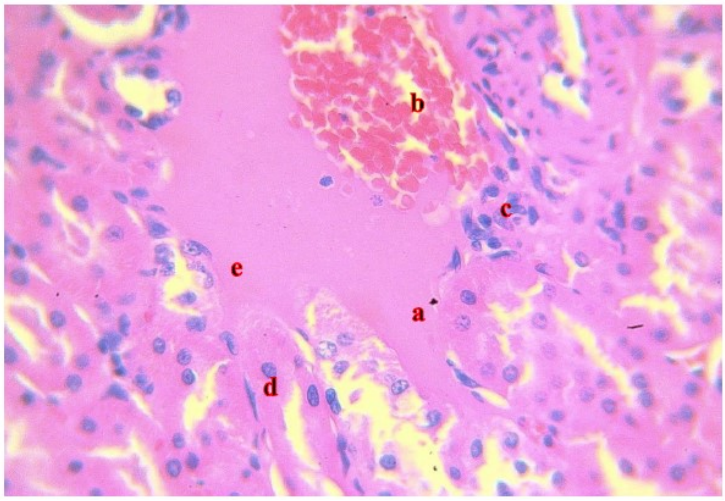

Fig.8. A micrograph of part of the Kidney cortex of G3 (10 % LD_{50} TCDD) showed a) Sever interstitial edema b) Congestive interstitial hemorrhage. c) mononuclear cells infiltration mostly lymphocytes & macrophages d) Acute cellular swelling d) epithelia cells necrosis and apoptosis. X400 H&E stain.

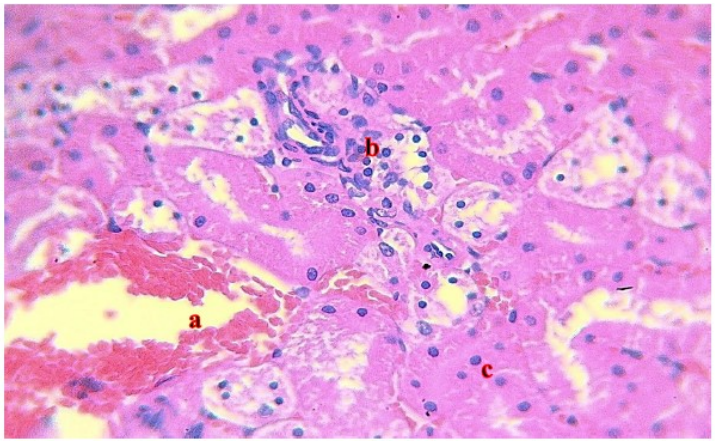

Fig.9. A micrograph of part of the rat Kidney cortex of G3 (10 % LD_{50} TCDD) showed a) Sever interstitial hemorrhage b) mononuclear cells infiltration mostly lymphocytes & macrophages c) Acute cellular swelling. X400 H&E stain

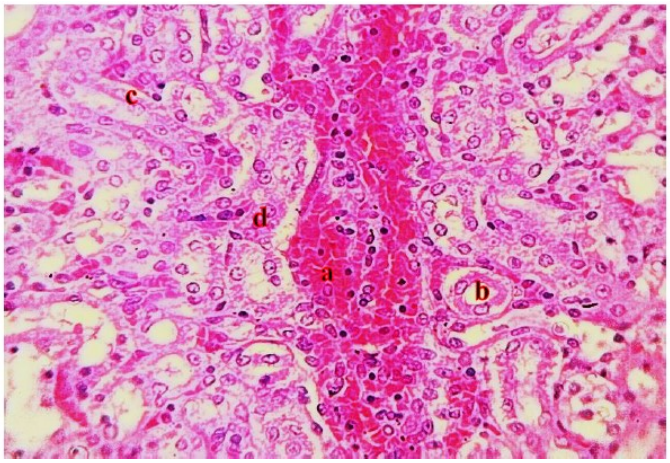

Fig.10. A micrograph of part of the rat Kidney cortex of G4 (5 % LD50 TCDD) showed a) Sever interstitial hemorrhage b) acute cellular swelling c) cell necrosis d) apoptosis in Cell necrosis X400 H&E stain

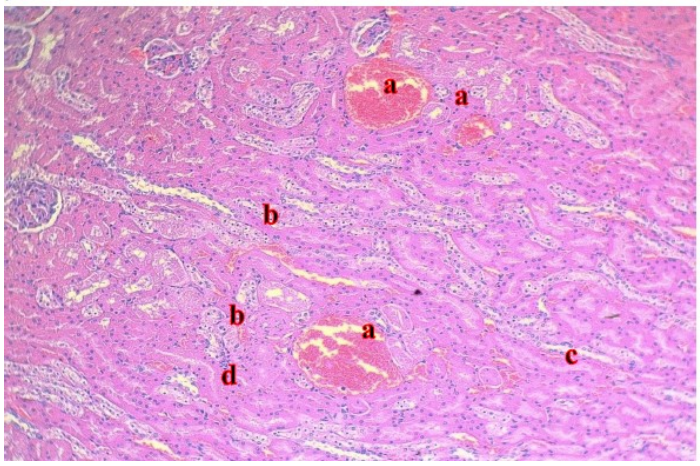

Fig.11. A micrograph of part of the rat Kidney cortex of G4 (5 % LD50 TCDD) showed a) congested blood vessels b) Interstitial hemorrhage; c) Acute cellular swelling d) lymphocytic infiltration X400 H&E stain

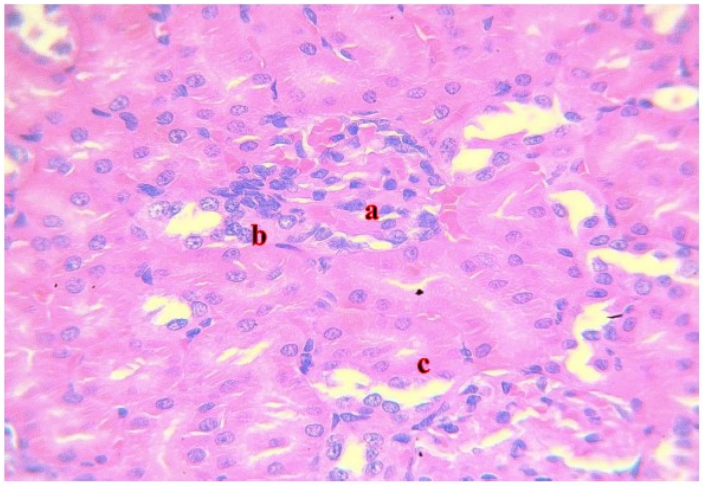

Fig.12. A micrograph of part of the rat Kidney cortex of G4 (5 % LD_{50} TCDD) showed a) Congested glomerular tuft b) mononuclear cells infiltration mostly lymphocytes c)Acute cellular swelling X400 H&E stain

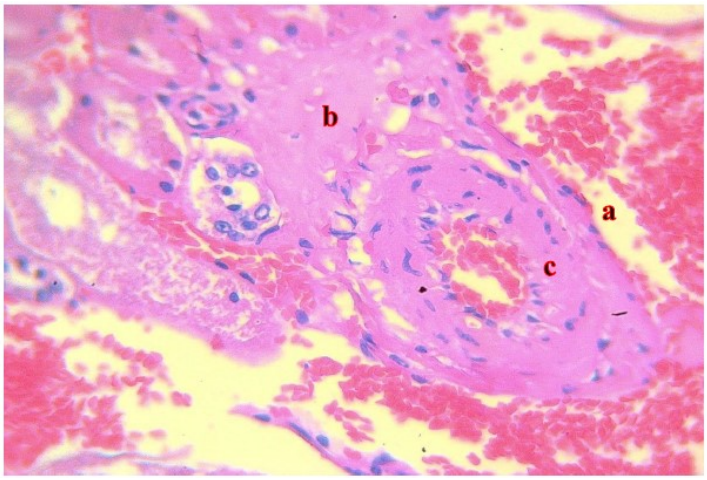

Fig.13. A micrograph of part of the rat Kidney cortex of G4 (5 % LD_{50} TCDD) showed a) Interstitial hemorrhage b) edema c) atherosclerotic artery with atherosclerotic plaques X400 H&E stain.

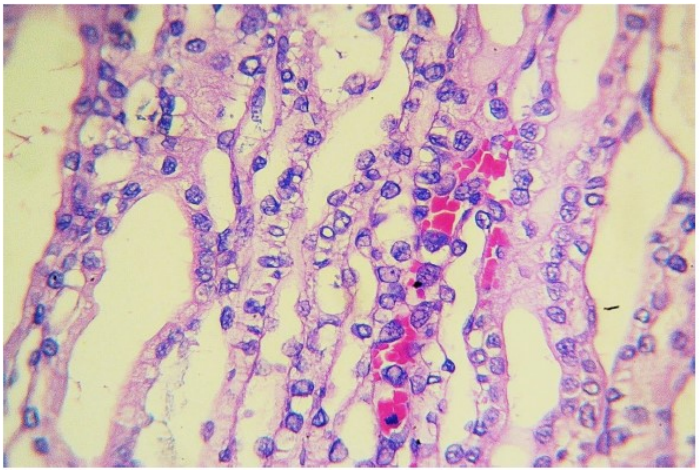

Fig.14. A micrograph of part of the rat Kidney medulla of G4 (5 % LD50 TCDD) showed distal tubules with Interstitial haemorrhage X400 H&E stain

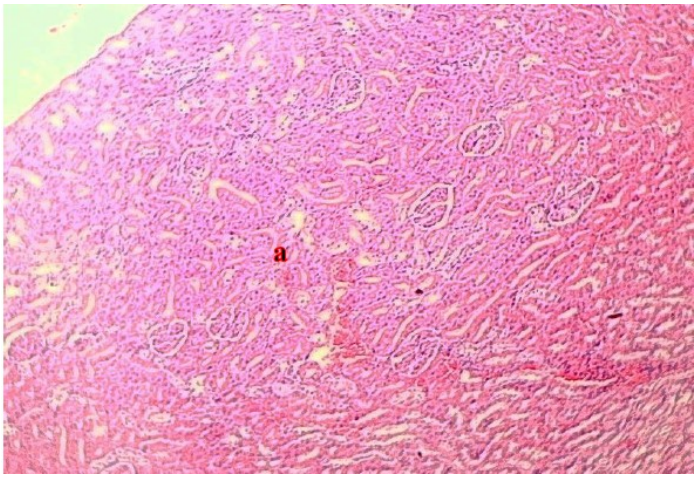

Fig.15. A micrograph of part of the rat Kidney cortex of G5 (Resveratrol) showed a)slight odema only X400 H&E stain

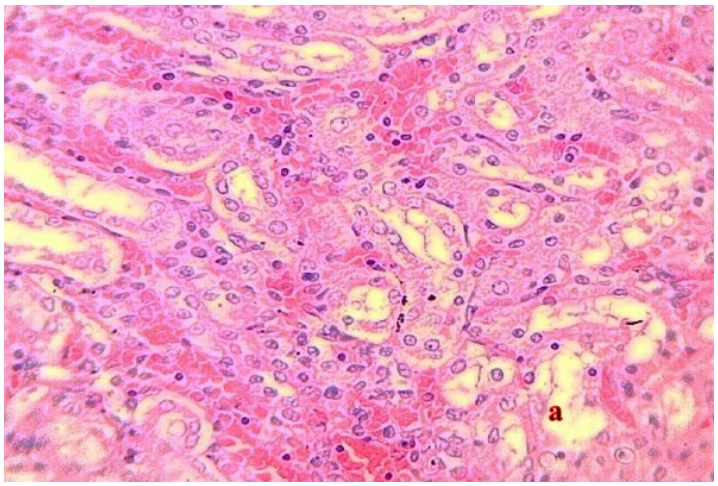

Fig.16. A micrograph of part of the rat Kidney cortex of G6 (10 % LD50 TCDD + Resveratrol) showed a) mild acute cellular swelling X400 H&E stain

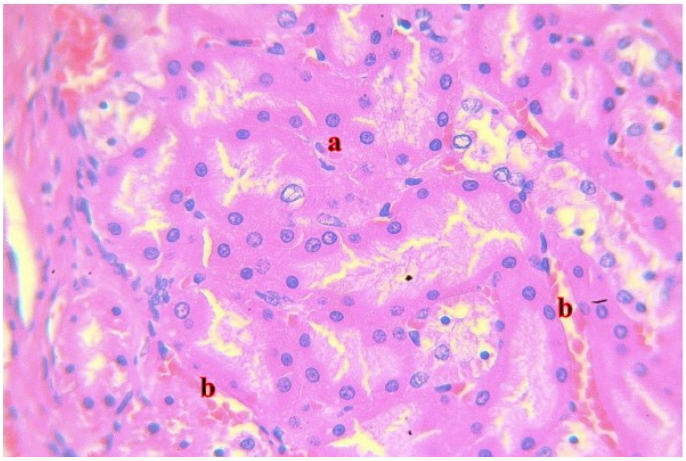

Fig.17. A micrograph of part of the rat Kidney cortex of G7 (5 % LD50 TCDD + Resveratrol) showed a) acute cellular swelling b)Slight haemorrhage X400 H&E stain

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حماية الريسفيراترول ضد السمية الكلوية في الجرذان المنتجة بواسطة 2، 3، 7، 8- رباعي كلورو ثنائي بنزو ب- ديوكسين

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المستخلص

أجرينا دراسة لفحص تأثير ريسفيراترول (RES) على أنسجة الكلى لدى فئران ويستار التي تعرضت لـ 2،3،7،8- رباعي كلورو ثنائي بنزو-ب-ديوكسين (TCDD) وتطورت إلى تلف الكلى. تم تطبيق ذلك على ذكور الجرذان البيضاء (102) والعمر (8-9) أسابيع والوزن (80 -90) جرام، واستخدم (32) فأراً للمرحلة الحادة من التسمم، في حين تم استخدام (70) فأراً أخرى كـ سمية مزمنة. يتكون تصميم التجربة من 7 مجموعات) G1 ; التحكم (ve– ، مركبة) G2 الأسيتون + زيت الذرة(، 4) G3 TCDD ميكروجرام/كجم من وزن الجسم(، 2) G4 TCDD ميكروجرام/كجم من وزن الجسم (،RES) G5 ، 4) G6 (TCDD ميكروجرام/كجم من وزن الجسم(،RES) G5 ، 4) G6 (TCDD ميكروجرام/كجم من وزن الجسم(RES +(.(، 4)TCDD) G ميكروغرام/كغ وزن الجسم .(RES + (لقد وجدنا أن مستويات المالونديالدهيد (MDA) واليوريا والكرياتينين في المجموعات التي عولجت بـ TCDD أظهرت زيادات كبيرة مقارنة بالمجموعات الأخرى، على الرغم من انخفاض مستويات الجلوتاثيون المنخفض (GSH) والكاتلاز (CAT) في مجموعات .TCDD بالمقارنة مع المجموعات الأخرى، لاحظنا ارتفاعًا في مستويات GSH وCAT، بالإضافة إلى انخفاض في مستويات MDA واليوريا والكرياتينين في المجموعة المعالجة بـ .RES أدت إدارة RES إلى تحسين علامات الإجهاد التأكسدي والتغيرات النسيجية الناجمة عن.TCDD

الكلمات الدالة: TCDD ، ريسفيراترول الكلى ، التسمم الكلوي.