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ROLE OF EITHER *PETROSELINUM CRISPUM* OR *ERUCA SATIVA* EXTRACTS AGAINST DIOXIN INDUCED REPRODUCTIVE TOXICITY IN MALE RATS

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ABSTRACT

Dioxin is a very toxic environmental pollutant that affect on human health. Its effects include carcinogenicity, hepatotoxicity, endocrine and metabolic changes. The effect of phytochemical extract, Petroselinum crispum (Pc) (2g/ kg B.wt) or Eruca sativa (Es) (500 mg/kg B.wt) for five weeks on 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induced reproductive system abnormalities was assessed in male albino rats.

The administration of dioxin at a dose 100 ng/kg B.wt for five weeks significantly increase testicular lipid peroxidation products (MDA), protein carbonyl (PC) content and nitric oxide (NO) level in concomitantly with decreases in superoxide dismutase (SOD) and catalase (CAT) activities as well as decline in reduced glutathione (GSH) level, DNA and RNA contents. Also, TCDD increased the frequency of transforming growth factor β1 (TGF?1) and Fas receptor known as cluster of differentiation 95 (CD95) percent relative to control rat. Pc or Es alcoholic extract has the possibility to suppress the adverse effects of TCDD due to their antioxidant constituents and the role of their fiber in preventing dioxin absorption.

Es alcoholic extract is better and more effective than Pc under the condition of this experiment.

Keywords: *TCDD, Testis, Lipid peroxidation, Protein Carbonyl, Nitric Oxide, Eruca sativa, Petroselinum crispum, CD95, TGFβ1.*

INTRODUCTION

The imbalance between the formation and inactivation of reactive oxygen species (ROS) leads to deleterious effects causing cellular, physiological and pathological abnormalities (Halliwell, 1996) through oxidation of DNA, lipids, proteins, and lipoproteins (Farber, 1994) and hence leads to increased testis apoptosis (Sönmez *et al.,* 2011).

TCDD, a persistent endocrine-disrupting environmental contaminant, due to its lipophilic properties, slow metabolism and excretion, it readily accumulates in the body (Enan

et al., 1998). Free radicals can bind polyunsaturated fatty acids of sperm membrane to generate lipid peroxides that are highly reactive, change enzyme activity inducing injury (Ogeturk *et al.,* 2005). Male reproductive tissues have been found to be very sensitive targets of this dioxin (Gray *et al.,* 2001). TCDD-treated rats showed decrease in the testicular enzyme activity that protect against oxidative damage (Ciftci *et al.* 2011).

There is increasing evidence of the protective role of dietary polyphenols particularly from vegetables (Pc, Es), fruits and some herbs against oxidative stress, and degenerative diseases (Han *et al.,* 2007).

Es is one of the nutritious green-leafy vegetable. It belongs to the Brassicaceae family. It has a high content in vitamin C, vitamin A, carotenoids, and polyphenols (Martinez-Sanchez *et al.,* 2008). It possesses free radical scavenging and antioxidant activity (Mradu *et al.,* 2012). It has antihyperlipidemic, antihyperglycemic, antiephrolethiatic hepatoprotective activity (Bukhashi *et al.,* 2007), and antiproliferative activity (Yahuda *et al.,* 2009). Homady *et al.,* (2000), showed that, ethanolic extract of Es has stimulating steroidogenic effect increasing mice spermatogenesis.

Pc, a leafy vegetale belongs to the family *Umbelliferae* is known as a rich source of ascorbic acid, carotenoids, flavonoids, coumarins, apiole, various terpenoic compounds, phenyl propanoids, phthalides, furano coumarins, and tocopherol (Tunali *et al.,* 1999). Pc scavenges hydroxyl radical and prevents membrane oxidation (Fejes *et al.,* 2000). Pc has been used as an aphrodisiac, improved reproductive performance in broiler, antimicrobial, (Lopez *et al.,* 1999), antianemic, hemorrhagic, anticoagulant, antihyperlipidemic, antihepatotoxic and laxative (Kreydiyyeh *et al.,* 2001).

Consequently, the aim of the present study was to investigate the possible use of ethanolic extract of either Pc or Es on blocking TCDD-induced testicular oxidative stress and apoptosis in male albino rats.

MATERIALS AND METHODS

Chemicals :

TCDD (Cas No. 1746-01-6) was purchased from Sigma-Aldrich (Saint Louis, Missouri, USA). Ethanol was purchased from (Al-Gomohria Company for chemicals, Abou-Zabal, Egypt). The corn oil was purchased from local store. All other chemicals were of analytical grade

Animals :

Male Albino rats weighing about (160-180g) was performed in this study. They were housed in stainless steel cages in an artificially illuminated and thermally controlled room (22- 25℃ and 12 h light / dark cycle). They were fed on standard diet and given water *ad libitum* for one week of acclimation prior to the experimental work. All animals received human care in compliance with the guidelines of the Animal Care and Use Committee of Mansoura University, Egypt.

Preparation of plant extracts :

Petroselinum crispum and *Eruca sativa* were purchased from a local market in Mansoura, Egypt. Fresh leaves were separated,

washed, rinsed with distilled water and dried in shade, then crushed, powdered, soaked in 96% ethanol for 72hr and evaporated under vacuum to obtain extract, where the extract was suspended in distilled water before administration (Vora *et al.,* 2009).

Experimental protocol :

Forty two male rats were allocated to one of seven groups of 6 rats each. Normal control (G1) group was fed on standard diet without any supplementation. Corn oil (G2) group treated orally with corn oil as vehicle at dose of (0.2 ml/ kg/b.wt.). Animals of the Pc (G3) group were treated orally with Pc alcoholic extract at a dose (2g/kg/b.wt.) (Al-Howiriny *et al.,* 2003a). Animals of the Es (G4) group were treated orally with Es alcoholic extract at a dose (500 mg/kg/b.wt.) (Alqasoumi, 2010). Animals of the TCDD (G5) group received 100/ng/kg/day (Latchoumycandane and Mathur, 2002) diluted in 0.2 ml corn oil. Animals of the Pc +TCDD (G6) group were treated orally with 2g/kg/b.wt Pc and 100 ng/kg/day TCDD. Animals of the Es+TCDD (G7) group were treated orally with 500mg/kg/b.wt Es and 100ng/kg/day TCDD.

Sample collection and preparation of testis homogenate:

At the end of the experimental period (5 weeks), all rats were fasted for 12 hrs, weighed and then sacrificed under ether anesthesia. Rats were dissected, and the two testes from each rat were removed, then a portion of the right testis was weighed and homogenized by tephlon homogenizer in a 10 fold volume of ice-cold distilled water, centrifuged at 860 Xg for 20 min at 4℃ and the resultant supernatants were frozen at -20℃ for for measuring SOD, CAT, GSH, MDA and PC analysis. Another portion from right testis was weighed and homogenized with phosphate buffer solution (pH 7.4) and centrifuged at 10.000 Xg for 20 minutes and supernatant was separated for NO analysis (Montgomery and Dymock, 1961). The remaining portion of the testis was homogenized in cold phosphate buffer saline (PBS) using tephlon homogenizer, centrifuged at 860 Xg for 5 min at 4℃ and the resultant supernatants were frozen at -20℃ for flow cytometric analysis.

Biochemical assays:

The level of malondialdehyde (MDA) in testis was estimated according to the modified method of Ohkawa, *et al.* (1982).

Protein carbonyl (PC) content in testis was measured according to Smith *et al.* (1991).

Nitric oxide (NO) level in testis was measured according to Montgomery *et al.,* (1961) by the determination of total nitrate and nitrite concentrations using (Bio-Diagnostic kit Co. Dokki, Giza, Egypt).

Superoxide dismutase (SOD) activity in testis was measured by the method of Nishikimi *et al.* (1972).

Catalase activity in testis was determined by the method of Bock *et al.* (1980).

Reduced glutathione (GSH) level in testis was estimated according to the method of Prins and Losse (1969).

Determination of nucleic acid in testis:

The extraction of nucleic acids was carried out according to the method reported by Melmed *et al.,* (1976).

DNA content was estimated in testis homogenate using the method reported by Dische and Schwarz (1977).

RNA content was determined by using the method of Thoresen *et al.* (1983) depending on the determination of nucleic acids by the reaction of its ribose component with orcinol reagent.

Quantification the frequency of transforming growth factor β1 (TGFβ1) cells (%) and CD95 cells (%) by flow cytometry

The frequency of TGFβ1 cells (%) was determined according to the manufacturer's instructions (ab31013, Abcam biochemicals®, UK). The frequency of CD95 cells (%) was determined by (Cifone *et al.,* 1994) in testis tissue in the different groups were quantified using the G1 peak staining with iodide (Riccardi and Nicoletti, 2006) using Becton FACSC flow cytometry (Becton Dickinson Corporation, USA).

Statistical analysis:

All values are presented as mean ±SE. Differences were considered to be significant at $p<0.05$. One-way analysis of variance (ANOVA) and post-hoc test were used to determine differences between groups. The SPSS/PC program (version 17; SPSS, Chicago, Illiniois, USA) was used for statistical analysis (Snedecor and Cochran, 1980).

RESULTS

As shown in figure (1) TCDD intoxication showed significant increase in testicular MDA, PC, and NO level (192%, 206%, 271%, respectively) as compared with the control. On the other hand, testicular SOD, CAT, GSH, DNA and RNA were significantly decreased in TCDD treated rats as compared to control (65%, 34% and 55%, 68% and 65%, respectively).

Concerning Pc+ TCDD group, a significant decrease in testicular MDA, PC and NO level (66%, 70% and 59/%, respectively) were observed, while SOD, CAT, GSH, DNA and RNA were significantly increased (138%, 208%, 158%, 128% and 129%, respectively) compared to TCDD treated rats.

Regarding to Es+ TCDD group, testis MDA, PC and NO were significantly decreased as compared to TCDD treated rats (63%, 67% and 49%, respectively), while SOD, CAT and GSH were significantly increased as compared to TCDD treated rats (142%, 227%, 170%, 134% and 140%, respectively).

As shown in figure (2) there was significant increase in the frequency of TGF-β1 and CD95 cells in the testis of TCDD treated rats as compared with control. In Pc+ TCDD group there was significant decrease in testis TGF β1 and CD95 (54% and 63%, respectively) as compared with TCDD treated rats. In Es+ TCDD group there was significant decrease in testis TGF β1 and CD95 (65% and 76%, respectively) as compared to TCDD treated rats.

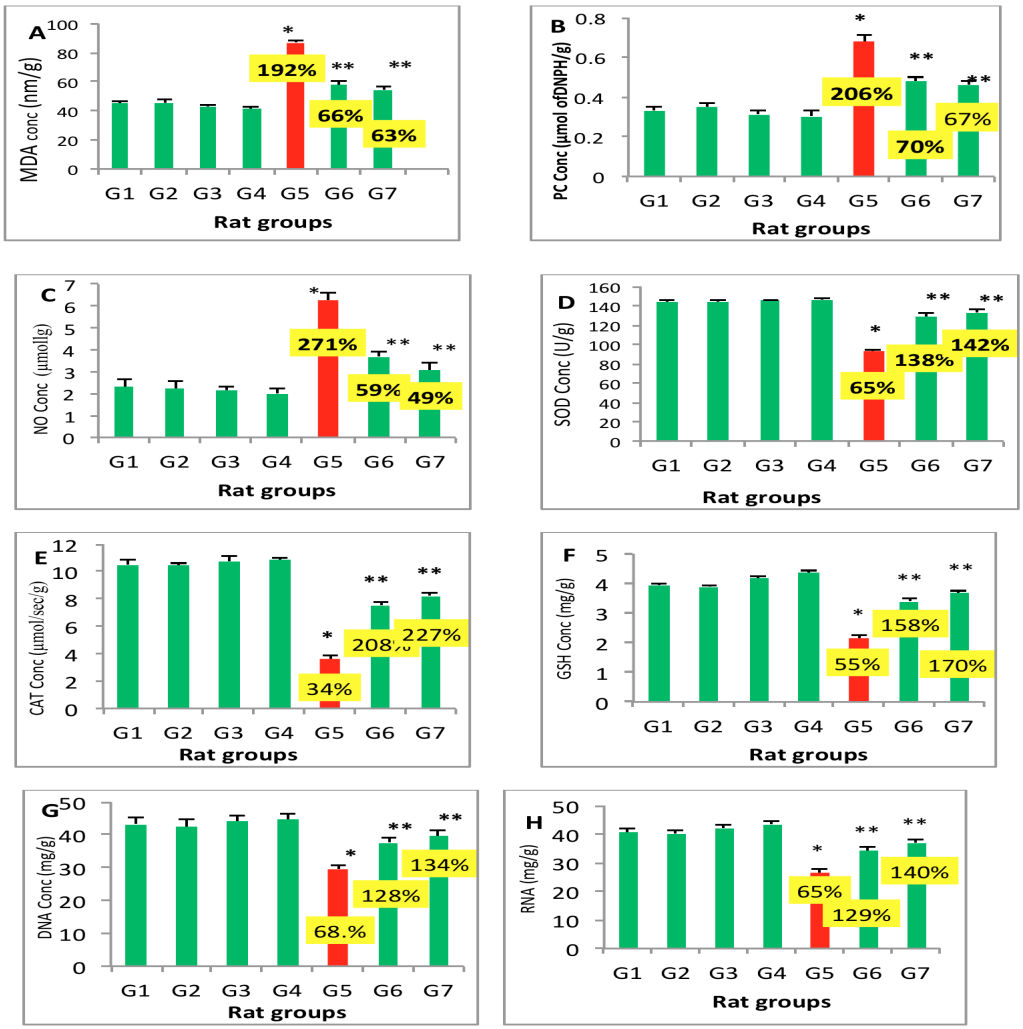

Fig. (1) : MDA, PC, NO, SOD, CAT, GSH, DNA, and RNA in testes of the different groups. *Denotes P<0.001 significantly different compared with control.**Denotes P<0.001, significantly different compared with TCDD treated rats.

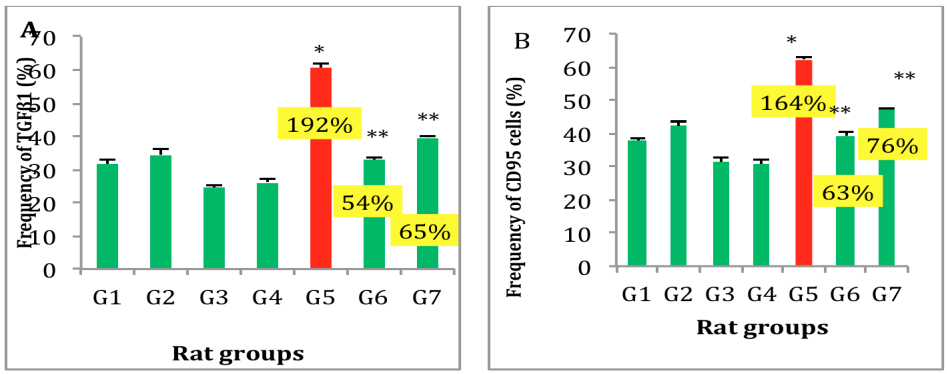

Fig. (2) : Frequency of TGFβ1 and CD95 (%) in testes of the different groups. Values are presented means ± SE. *Denotes P<0.001 significantly different compared with control. **Denotes P<0.001, significantly different compared with TCDD treated rats.

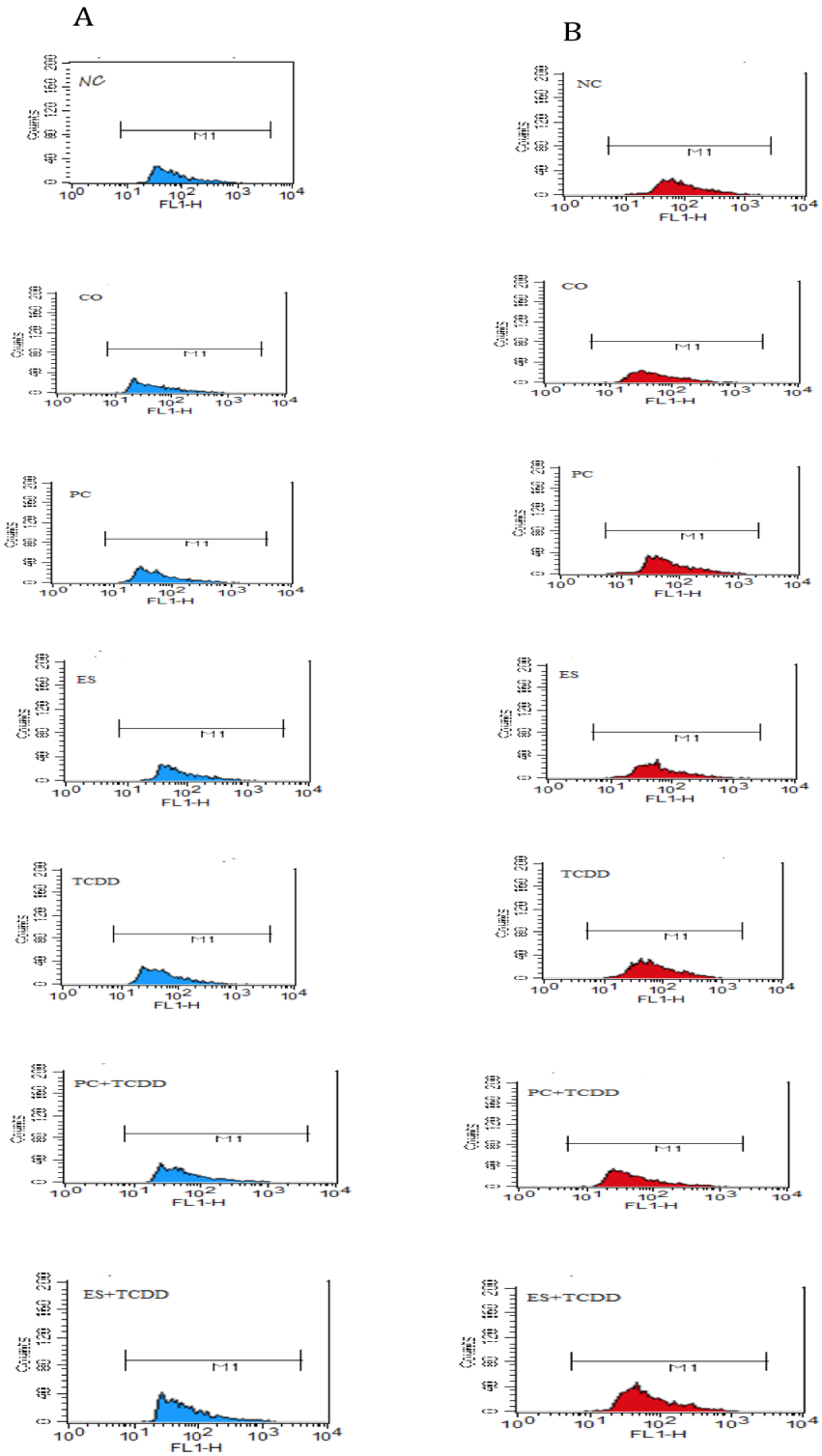

Fig. (3) : Flow cytometric histograms of (A) tumor growth factor β1 and (B) CD95 for different groups showing a variation of cells as a positive for staining for both markers the flourochrome for TFGβ1 and CD95 was FITC (fluorescence isothiocyanate).

DISCUSSION

The testis has been reported to be among the most sensitive organs to TCDD exposure (Schultz *et al.,* 2003) since the balance between pro-oxidants and antioxidants is vital for normal testis functions and sperm fertilization ability (Mathur *et al.,* 2008).

The resulted testicular damage by TCDD may be due to oxidative stress produced by free radicals (Oguz *et al.,* 2013). The increase in lipid peroxidation (LPO) agree with Dhanabalan *et al.* (2013), these effects may be due to testicular membrane rich in fatty acids, which are prone to undergo peroxidative decomposition and increase in testicular LPO due to excess ROS (Kalaiselvan *et al.,* 2014).

The present results showed significant increase in testicular protein peroxidation level of rats treated with TCDD. These results are in agreement with Aly *et al.* (2013), who found that, the significant increase in carbonyl content and uridine 5'-diphosphoglucuronyl transferase (UDPGT) and cytochrome P450 (CYP) activities in TCDD treated rats. Causing protein damage through oxidative stress and decreasing the antioxidant system (Davies, 1988).

Another pathway involved in the testicular damage by TCDD is the inflammatory process as mentioned by Bruner-Tran *et al.* (2014). NO plays crucial roles in testicular inflammation and injury (O'Bryan and Hedger, 2008). It is produced in large quantities by various xenobiotics including TCDD. In the present study, there was a marked elevation in NO production of testes in TCDD treated rats. This increase in NO level agrees with Liao *et al.,* (2014), and may be a result of activation of iNOS genes via oxidative stress resulting in excessive NO generation (Kleniert *et al.,* 2004). The resulted peroxynitrite from reaction of NO with ROS is cytotoxic agent which causes cellular damage (Davis *et al.,* 2001).

TCDD exposure disrupts the redox balance of tissues, suggesting that biochemical and physiological disturbances result from oxidative stress (Bentli *et al.,* 2013).

The obtained results show a decrease in testicular SOD activity in dioxin intoxicated group, a result which agrees with those of Palaniswamy *et al.* (2014) and this effect may be due to increased H_2O_2 production and ROS generation which in turn induces oxidative stress (Banudevi *et al.,* 2005).

The decreased CAT activity in dioxin intoxicated group is in accordance with the study of Ilavarasi *et al.* (2014) and may be due to accumulation of superoxide radicals (Kono and Fridovich, 1982).

The observed decrease in testicular GSH level, in the present study, may be due to increased utilization of GSH for metabolism of lipid hydroperoxides by GPx or interaction of GSH with free radicals as mentioned by Ciftci *et al.* (2011). Depletion of GSH may be due to increased generation of superoxide radicals (Reed *et al.* 1990).

TCDD impairs protein biosynthesis by forming adducts with DNA, RNA and protein, inhibits RNA synthesis (Schreck *et al.,* 2009). The oxidative DNA damage and LPO in the testis of TCDD treated rats are in accordance

with Dhanabalan *et al.* (2011), these effects may be due to increased generation of NO and other reactive oxides (Moncada and Higgs, 1993).

TGF β1 is fibrosis cytokine marker which can regulate Sertoli, Leydig and germ cell growth, differentiation functions and apoptosis (Sánchez-Capelo, 2005). In the present study, TCDD induces significant increase in the levels of TGF-β1 cytokine. This elevation is accompanied by increased MDA, DNA, RNA and NO levels, together with low level of SOD, CAT and GSH, indicating the interplay between oxidative stress and TGF β1. Liu and Gaston Pravia *et al.* (2010) have demonstrated that TGF β1 stimulates the production of ROS and mediate many of the fibrogenetic effects.

Fas is a death receptor on the surface of cells that leads to programmed cell death (apoptosis). In the present study, TCDD has been found to significantly raise the testicular level of CD95 (Fas). This result is in consistent with that of Dhanabalan *et al.* (2013), and may be attributed to oxidative stress which increased the expression of apoptosis related surface molecule CD95 and that it induced apoptosis via CD95 mediated pathways (Denning *et al.,* 2002).

Flavonoids are potent molecules that donate a hydrogen atom from an aromatic hydroxyl group to a free radical, yielding a stable phenolic radical (Bandy and Bechara, 2001). *Pc* or *Es* indeed showed superior antioxidant activity evidenced by increased activities of SOD, CAT and elevated GSH levels above control group. In the current study, the co- administration of either alcoholic extract of *Es* or *Pc* concomitantly with TCDD reduced the LPO, and PC as well as NO level in testis associated with the elevations of SOD and CAT activity and GSH levels. The protective effect of *Es* or *Pc* against TCDD-induced oxidative stress in this study could be either direct by inhibiting LPO and scavenging free radicals or indirect through the enhancement of the activity SOD and CAT leading to elimination of H_2O_2. These properties could be due to their excess antioxidants levels (phenolic compounds, flavonoids, glucosinolate) as well as degradation products (isothiocyanates, sulforaphane, carotenoids, coumarins, β–carotene, vitamins and minerals) (Hanafi e*t al.,* 2010, Kuzma *et al.,* 2014).

Also, *Es* or *Pc* stimulates the excretion of TCDD through production of the phase-II metabolizing enzymes system that catalyzes the conjugation of activated TCDD with reduced glutathione (Inui *et al.,* 2014).

Since $Fe3^+$ is a Fenton catalyst accelerating ROS formation, the inhibition of $Fe3^+$-ascorbate induced damage to lipids and proteins by Pc or Es with its potent free radical scavenging ability may block TCDD damaging effect (Rajabbeigi *et al.,* 2013).

Alcoholic extracts of either Pc or Es caused decreased levels of NO through inhibition of iNOS and COX-2 expression by its anti-inflammatory property, thereby protecting the testis (Byun *et al.,* 2013; Cho *et al.,* 2013).

Administration of either *Pc* or *Es* extract with TCDD treated rats decreased TGF β1 and CD95, these effects may be related to its relation with phenolic composition where phenol-

ic composition mostly caffeic, ferulic acid, and p-coumaric acid in addition to ascorbic acid that found in either Pc or Es are responsible for free radical scavenging and activity of these antioxidants (Tiveron e*t al.,* 2012), or may be due to binding of caffeic acid to the AhR receptor, being an inhibitor of its action, thus decreasing the transcription and activity of CYP1A1 (Kampa *et al.,* 2004).

On the other hand, one human study found that the higher-fat meal produced a higher absorption rate of TCDD (Schlummer *et al.,* 1998), in addition, various vegetable fibers have been shown to increase fecal excretion of dioxin in animals, the presence of fibers in the alcoholic extract used in this experiment leading to decreased intestinal fat absorption, which consequently reduce the absorption of dioxin (Aozasa *et al.,* 2003).

In conclusion, TCDD induced oxidative stress and apoptosis in rat testis. The alcoholic extract of either Pc or Es has blocking effect on TCDD-induced testicular oxidative damage.

Conflict of interest:

The authors declare no financial or commercial conflict of interest.

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الملخص العربى

دور مستخلص كل من البقدونس أو الجرجير
ضد تسمم الأجهزة التناسلية بالديوكسين فى ذكور الجرذان

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الديوكسين من الملوثات البيئية السامة التى تؤثر على صحة الأنسان، حيث يسبب العديد من الأمراض نظرا لأنه مسبب للسرطان وتسمم الكبد ويؤثر على الغدد الصماء بالإضافة إلى التغيرات الأيضية. تم دراسة تأثير المستخلص النباتى لأى من البقدونس بجرعة (٢جم / كجم من وزن الجسم) أو الجرجير بجرعة (٥٠٠ مجم / كجم من وزن الجسم) لمدة خمسة أسابيع على الخلل الناجم عن التعرض للديوكسين فى الأجهزة التناسلية لذكور الجرذان.

أظهرت الدراسة أن التعرض للديوكسين بجرعة (١٠٠ نانو جم / كجم من وزن الجسم) مذابا فى زيت الذرة لمدة خمسة أسابيع يسبب زيادة محتوى الدهون الفوقية (MDA) للخصية وأكسدة البروتين (PC) وكذلك مستوى أوكسيد النيتريك (NO) مع انخفاض نشاط إنزيم السوبرأوكسيد ديسميوتيز (SOD) والكاتاليز (CAT) متزامنا مع نقص مستوى الجلوتاثيون (GSH) وكذلك محتوى DNA , RNA. وأظهرت الدراسة أن الديوكسين يسبب زيادة نسبة TGFβ1 و CD95 بالمقارنة إلى المجموعة الضابطة. يبدو أن استخدام المستخلص الكحولى للبقدونس أو الجرجير قادر على الحد من التأثير السيئ للديوكسين نتيجة احتوائهما على مضادات الأكسدة وكذا دور الألياف الموجودة بهما فى تقليل معدل امتصاص الديوكسين.

بالإضافة إلى أن مستخلص الجرجير قد أظهر تحسنا أفضل من مستخلص البقدونس.

JOESE 5

ROLE OF EITHER *PETROSELINUM CRISPUM* OR *ERUCA SATIVA* EXTRACTS AGAINST DIOXIN INDUCED REPRODUCTIVE TOXICITY IN MALE RATS

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