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Homeostatic changes of trace elements in diazinon toxicity in rat model: The beneficial role of resveratrol

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ABSTRACT

Background and objectives: Diazinon (DZN) is a cholinesterase inhibitor widely used to relieve agricultural pests and upgrade the productivity of crops. Resveratrol (Res), as a phenolic plant compound, has a protective role against free radicals. This study intended to evaluate the impacts of Res on homeostatic disturbances induced by DZN in rats.

Method: Twenty-four Wistar rats (4 weeks) were randomly distributed into four groups of six animals each. The first group (control group) received corn oil. The second group (Res group) received orally Res (20 mg/kg. The third group (DZN group) received the oral DZN (70 mg/kg); the fourth group (Res plus DZN group) was treated simultaneously with DZN (70 mg/kg) and Res (20 mg/kg); for a period of 5 weeks. The serum, liver, kidney, and heart levels of the Copper (Cu), zinc (Zn), iron (Fe), selenium (Se), and magnesium (Mg) as main trace elements are measured.

Results: DZN treatment decreased significantly serum, liver, kidney, and heart levels of Cu, Zn, Fe, Se, and Mg in comparison with the control group. Res administration enhanced serum, liver, kidney, and content of heart elements compared to the DZN group.

Conclusions: These results suggested that Res could ameliorate the homeostatic imbalance induced by DZN. Res had a protective effect against DZN-provoking heart, renal, and hepatic toxicity in animal models.

1. Introduction

Organophosphate pesticides (OPs) are the most successful common herbicides widely used in cultivation, domestics, veterinary medicine, and industries [24]. Many of these compounds are fat-soluble and easily absorbed by skin, oral mucosa, digestive, and respiratory tracts [22]. DZN, as prominent Ops, is extensively used worldwide for controlling plant pests. Also, DZN is a notable cause of health hazards in different countries [14]. The main mechanism of toxicity induced by DZN is the inhibition of acetylcholinesterase and the accumulation of acetylcholine in the cholinergic synapses which lead to cholinergic syndrome [27]. The evidence of many studies showed that oxidative stress is another mechanism for sub-chronic and chronic toxicity of DZN [37]. In addition to excessive production of reactive oxygen species, DZN can alter antioxidant and scavenger systems. Antioxidant administration may relieve DZN-induced toxicity. Res, a phytoalexin, is naturally found in grapes, peanuts, and etcetera. This polyphenolic compound has beneficial effects in antioxidant systems, anti-inflammatory systems, and trace elements balancing. Interestingly, previous studies confirmed the protective effect of Res in oxidative stress caused by DZN [27]. Antioxidant enzymes protect body cells from excessive free radicals, especially oxygen free radicals[32]. Trace elements are significant in the function and structures of these antioxidant enzymes [49]. Cu, Zn, Fe, Mg, and Se act as antioxidant enzyme cofactors and have a role in free radical trapping [28]. In vitro studies indicated hemostatic disturbances induced by pesticides [20,39]. Considering the importance of trace elements in the antioxidant system, we conducted this research to evaluate the possibility of protective impacts of Res against change in levels of Zn, Cu, Fe, Se, and Mg induced by DZN in animal models.

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2. Material and methods

2.1. Chemicals

We purchased The DZN (Merck Co., 99 % purity, Code: 075801) from the Agricultural Research, Education and Development Organization (AREDO) (Tehran, Iran). Besides, Res was provided from Sigma (St. Louis, MO, USA, Code: 339132). It is utilized high-quality analytical-grade chemicals and Elisa's kits from Kiazist (Tehran- Iran).

2.2. Animal and research protocol

We provided twenty-four healthy 4-year-old Male Wistar rats (200–250 gr) from the Animal Care Center, Hamadan University of Medical Sciences. Also, we directed the administration schedule according to the instruction published by the Review Board of Hamadan University of Medical Sciences with the code number (IR.UMSHA.REC.1401.170). Our research group maintained rats at a temperature of 21–23°C, humidity of 50±10 %and a 12 h light/12 h dark cycle. All rats were fed with a standard diet and water ad libitum. Ethical concerns handled all the procedures. The control group were treated with a vehicle based on our former research. The selective DZN dose was 70 mg/kg (equal to 1/5 of its LD50 (350 mg/kg) [36]. DZN (70 mg/kg) and Res (20 mg/kg)[48] were solvated in the corn oil and H_2O, respectively. These compounds were administrated every day via gavage for four weeks. We divided all rats randomly into four groups (six animals in each group). The control group received corn oil. The DZN group received DZN (70 mg/kg). The Res group received Resveratrol (20 mg/kg), DZN plus Res group simultaneously received DZN and Res at defined doses (70 mg/kg and 20 mg/kg, respectively). After 24 hours following the last dose, animals were sacrificed under anesthesia by ketamine (87 mg/kg) and xylazine (13 mg/kg) injection[46]. After blood sampling, serum separated and froze at −80 until biomarkers evaluation. It is removed Heart, liver, and kidney tissues and washed in cold saline. Next, the tissues rapidly sored in liquid nitrogen and froze at −70 °C until measuring.

2.3. The trace element concentrations' assessment of heart, kidney, and liver tissue

It was submerged all containers in nitric oxide, then rinsed in ultrapure water. Finally dried in an oven. Microwave digestion system (Topex, Preekem Scientific Instruments Co., Ltd., Shanghai, China) was used for degrading of the heart, the liver, and kidney tissues. Following sample mineralization, the trace element levels were assessed. 0.1 g of tissue put in high-pressure Teflon vessels and concentrated HNO_3 (3 ml), H_2O_2 (1 ml), and HClO4 (0.5 ml, ultrapure, Merck, Germany) were added. After sealing the vessels with a Teflon lid, they were put into the steel bombs (sealed with the same momentum). Microwave oven was used to heat mixture according to the following temperatures: 90°C/13 min, 120°C/13 min, 130°C/60 min, and 140°C/60 min. The solution was cooled at room temperature and quantitatively transferred to a flask of ultra-water (10 ml, Millipore Direct Q UV, Japan). Trace element levels evaluated by inductively coupled plasma-optical emission spectroscopy (ICP-OES); Spectro Genesis, Germany)[17]. The data of the ICP-OES condition are available in Table 1.

2.4. Statistical analysis

Our research group partners statistically analyzed the results of all groups with the SPSS-20 software. Data were compared with a one-way analysis of variance (ANOVA) and Tukey posttest. The differences were statistically regarded as significant when the P-value was less than 0.05. The results were represented as mean ± standard error. A P-value less than 0.05 was regarded as statistically significant.

Table 1
ICP-OES apparatus specifications and analytical conditions for the determination of elements.

Instrument	Spector genesis
Nebulizer	Cross flow
Plasma power	1380 W
Coolnat flow	13.00 L/min
Auxiliary flow	1.00 L/min
Nebulizer flow	1.03 L/min
Optic flush	Normal
Measure strategy Best	SNR
Reply	2
Measure time	80 s
Flush time	30 s

3. Results

3.1. Serum trace element levels

It was provided the measurement of Serum trace element concentrations in all groups. In the control group, serum levels of Cu, Fe, Zn, Mg, and Se were significantly higher than those in the DZN group (p less than 0.01). Also, Res treatment significantly could increase Cu and Se levels compared to the control group (p less than 0.05). The co-treatment of DZN and Res could increase serum levels of Cu, Fe, Se, and Zn in contrast with the DZN groups (p-value less than 0.05 and 0.01, respectively). Although serum Mg concentration was higher in the co-treatment of DZN and Res compared to the DZN groups, this difference was not statistically significant (Table 2).

3.2. Heart level of Trace element levels

As indicated in the (Table 3) control group, the heart levels of Cu, Mg, Zn, Mg, Fe, and Se were higher than those of the DZN group (Cu and Mg; p value less than 0.01 and Zn, Fe, Se; p value less than 0.001). The heart tissue levels of Fe and Zn in the DZN plus Res group were significantly higher than those in the DZN group (Fe and Zn; p value less than 0.05 and Se; p value less than 0.01). The heart Mg and Cu concentrations were not indicate statistical significant differences.

3.3. Liver level of trace element levels

According to Table 4, the mean levels of Cu (P value less than 0.001), Zn (P value less than 0.05), Mg (P value less than 0.01), and Se (P value less than 0.01)) in the control group were significantly higher than those of the DZN group. In the liver of the DZN group, the iron level was higher than that of the control group. The Res treatment could increase Cu (P value less than 0.001), Fe (P value less than 0.01), Zn, Mg, and Se (P value less than 0.001) in comparison with the DZN group. Also, DZN plus Res treatment could increase Cu, Zu, Mg (P value less than 0.01),

Table 2
The effects of RES on serum Cu, Fe, Zn, Mg, Se level of Rats treatment with Diazinon (70 mg/kg).

Parameters (mg/l)	Control	DZN	Res	DZN+ Res (20 mg)
Cu	2.46±0.03**	2.11±0.04	2.55±0.09***	2.29±0.07*
Fe	10.89±1.17***	6.4±0.66	10.66±0.56***	8.86±0.58*
Zn	16.04±1.61***	8.59±1.3	16.95±1.22***	13.52±0.58**
Mg	67.4±2.12**	53.92±3.54	62.15±2.63*	56.79±2.06
Se	7.21±0.02**	6.68±0.08	7.51±0.19***	7.12±0.24*

Data are indicated as the mean ±standard error of 6 separate animals in each group. copper (Cu); zinc (Zn); iron (Fe); selenium (Se); magnesium (Mg); DZN: the group administrated Diazinon (70 mg/kg); Res: the group administrated Resveratrol (20 mg/kg); DZN+Res: the group administrated 70 mg/kg of Diazinon, after an hour 20 mg/kg of Res *p<0.05 (compared to DZN group); **p<0.01 (compared to DZN group); *** p<0.001 (compared to DZN group).

Table 3
The effects of RES on heart Cu, Fe, Zn, Mg, Se level of Rats treatment with Diazinon (70 mg/kg).

Parameters (mg/l)	Control	DZN	Res	DZN+Res (20 mg)
Cu	4.49±0.18**	3.54±0.35	4.25±0.09*	4.11±0.14
Fe	44.57 ±1.53***	33.53±0.98	42.9±2.54**	38.42±1*
Zn	9.75 ±0.45 ***	6.71±0.12	0.13±0.02***	8.14±0.76*
Mg	177.48±2.1**	153.92 ±3.54	164.25 ±0.98**	152.51 ±2.09
Se	10.58 ±0.41***	8.11±0.2	9.68±0.1***	9.17±0.11**

Data are indicated as the mean ±standard error of 6 separate animals in each group. Data are indicated as the mean ±standard error of 6 separate animals in each group. copper (Cu); zinc (Zn); iron (Fe); selenium (Se); magnesium (Mg); DZN: the group administrated Diazinon (70 mg/kg); Res: the group administrated Resveratrol(20 mg/kg); DZN+Res: the group administrated 70 mg/kg of Diazinon, after an hour 20 mg/kg of Res *p<0.05 (compared to DZN group); **p<0.01 (compared to DZN group); *** p<0.001 (compared to DZN group).

Table 4
The effects of RES (20 mg/kg) on liver Cu, Fe, Zn, Mg, Se level of Rats treatment with Diazinon (70 mg/kg).

Parameters (mg/l)	Control	DZN	Res	DZN+Res (20 mg)
Cu	3.98±0.09***	2.67 ±0.11	4.21 ±0.18***	3.14±0.1**
Fe	98.09±0.24*	109.77 ±5.15	92.15±3.73**	114.63±0.51
Zn	20.25±1.01*	18.13± 0.26	23.15±1.01***	21.3 ±0.33**
Mg	176.43 ±3.02**	150.92 ±3.06	184.58 ±3.76***	163.18 ±4.01**
Se	11.75±0.49**	9.04±0.17	12.56±0.45***	10.66±0.44*

Data are indicated as the mean ±standard error of 6 separate animals in each group. Data are indicated as the mean ±standard error of 6 separate animals in each group. Copper (Cu); zinc (Zn); iron (Fe); selenium (Se); magnesium (Mg); DZN: the group administrated Diazinon (70 mg/kg); Res: the group administrated Resveratrol (20 mg/kg); DZN+Res: the group administrated 70 mg/kg of Diazinon, after an hour 20 mg/kg of Res *p<0.05 (compared to DZN group); **p<0.01 (compared to DZN group); *** p<0.001 (compared to DZN group).

and Se (P value less than 0.05) compared to the DZN group. Liver Fe level was not significantly different between DZN and DZN plus Res groups.

Table 5
The effects of RES on kidney Cu, Fe, Zn, Mg, Se level of Rats treatment with Diazinon (70 mg/kg).

Parameters (mg/l)	Control	DZN	Res	DZN+Res (20 mg)
Cu	5.55±0.48**	4.09±0.13	5.13±0.21*	4.91±0.11*
Fe	58.14±1***	48.23±1.01	52.20±1.54*	50.11±0.55
Zn	9.42±0.22**	8.36±0.11	10.21± 0.08***	9.37±0.2**
Mg	157.81 ±2.53*	145.92 ±3.04	166.25±5.54**	151.72 ±1.48
Se	14.89±0.58*	12.81±1.03	17.31±0.59***	13.66±0.54

Data are indicated as the mean ±standard error of 6 separate animals in each group. Data are indicated as the mean ±standard error of 6 separate animals in each group. Data are indicated as the mean ±standard error of 6 separate animals in each group. Copper (Cu); zinc (Zn); iron (Fe); selenium (Se); magnesium (Mg); DZN: the group administrated Diazinon (70 mg/kg); Res: the group administrated Resveratrol(20 mg/kg); DZN+Res: the group administrated 70 mg/kg of Diazinon, after an hour 20 mg/kg of Res *p<0.05 (compared to DZN group); **p<0.01 (compared to DZN group); *** p<0.001 (compared to DZN group).

3.4. Renal trace element levels

The result of kidney trace element levels is indicated in Table 5**.** The renal Mg and Se levels in the DZN group were significantly lower than those in the control group (p-value less than 0.05). Also, Cu, Zn, and Fe concentrations were reduced in the group treated with DZN compared with the control group (p value less than 0.01, p value less than 0.001, respectively). On the other hand, Res treatment increased Cu, Mg, Zn, Mg, Fe, and Se concentrations compared with the control group (p value less than 0.05). Additionally, in the DZN co-treatment with the Res group, the concentration of Cu and Zn were considerably higher than those in the DZN group (p value less than 0.05 and p value less than 0.01, respectively). Although Fe, Se, and Mg levels decreased in the DZN group, these differences were not statistically significant.

4. Discussion

In previous studies, we assessed the advantageous impact of Res on DZN-induced oxidative stress and inflammation in rat models [15,27]. It is proved diverse health benefical impacts of Res on pathological condition including neurological disease and cognitive performance, diabetes, cancer, cardiovascular disease. Importantly, oxidative stress and inflammation have major function in these disturbances[38].Several studies reported the protective impact of Res on trace element content [32,42]. DZN has multiorgan toxicity by means of oxidative stress induction in crucial tissues including brain, cardio vascular system, hepatic tissue, renal tissue and spleen [34]. As we know, there is no data on the impact of Res on tissue content of trace elements in DZN toxicity. Various studies have indicated that Ops toxicity could alter tissue trace element levels and ameliorate these changes [10]. In vivo and in vitro research confirmed the importance of oxidative stress in the pathophysiology of DZN-induced tissue injuries [12,32]. Oxidative stress induced by DZN toxicity has impacts on various bio systems such as kidney, liver, heart or even hemopoietic organs and hemathological systems(decrease in hemoglobin level, the count of RBC and WBC [3]. It is noted that oxidative stress can stimulate RBC apoptosis or eryptosis. Also WBC and platelets can perceive oxidative stress mediators and aggressive oxidative stress status by ROS generation [9]. Some Trace elements have a prominent role in metabolic hemostasis regulation and antioxidant balance [43]. Zn is an essential component in various enzymes and transcription factors. This element has a significant function in glutathione peroxidase (GPX) regulation and metallothionein expression. Also it has a role in super oxide dismutase (SOD) structure. Zn affects glutamate-cystein ligase expression which is involved in glutathione synthesis [23]. Metal transcription factor 1 (MTF-1) as a Zn-dependent transcription factor modulates the expression of genes involved in anti-oxidative pathways [18]. The studies proved that Zn supplementation in chlorpyrifos-treated animals could moderate free radical production and lipid peroxidation. This was mediated by antioxidant improvement, including Glutathione (GSH) and glutathione S-transferase (GST). Human studies concluded that Zn deficiency has a function in delayed polyneuropathy induced by Ops [1]. Cu has various roles in biological and antioxidant systems, including SOD, ceruloplasmin (a ferroxidase that act as an antioxidant), and lysyl oxidase (necessary for extracellular matrixes stabilization)[41]. SOD is a noteworthy antioxidant enzyme which can eliminate toxic superoxide anions. The activity of this enzyme is dependent on active metal ions, including Cu and Zn [29]. DZN treatment can diminish SOD activity which is attributed to mitochondrial superoxide radical generation [13]. In this study, our findings statistically marked differences in Cu and Zn content in different tissues among the DZN administrated group and the control group. Se is a key component in antioxidant defense particularly TAC (total antioxidant capacity) which can evaluate the content of total antioxidants [8].Our former studies showed the reducing effect of DZN on TAC [15]. GPx is an antioxidant enzyme that can protect membrane lipids and macromolecules against ROS-induced oxidative damage. It is

well-known that the GPX activity is dependent on selenium, an element incorporated in GPx [25].Our former studies indicated that DZN exposure caused a significant decrease in GPx activity [27]. In this study, we observed that Se concentrations decreased in the heart, liver, kidney, and serum of rats administered DZN. In line with this study, Cemeka et al., and Nisar Ahmad et al., reported that fenthion and chlorpyriphos (as OPs) diminish GPx levels in some tissues such as the heart, kidney, and liver [11,35]. In vitro studies indicated that DZN exposure caused reproductive toxicity and DNA damage [47]. It is documented that Se can protect against DNA damage induced by DZN [21]. Also, animal studies presented protective effects of Se against hepatotoxicities associated with DZN exposure [31]. Iron is an important cofactor for catalase (CAT), proline, and lysyl hydroxylases, which have functions in collagen cross-linking. CAT as an important antioxidant enzyme, contains a prosthetic group of heme (ferric protoporphyrin IX) which is involved in reaction with H_{2O2}. This enzyme is found in the peroxisomes [11,33]. It is documented that DZN hurts CAT activity [26]. Consistent with our previous studies [27]. Ju-Hai et al. [39] and Baltaci et al., [7] found that DZN treatment meaningfully decreased Fe content compared with the control group. Mg, as the most important divalent intercellular cation, has an antioxidant impact via enzymatic mechanisms. This element can intensify the expression and activity of antioxidant enzymes such as SOD, CAT [16] and glutathione peroxidase [30]. Also, Mg functions as a cofactor of various enzymes which involved in cell membrane steadiness. It is indicated that hypomagnesemia has an association with further stages of oxidative stress; low level of tissue Mg content involves more hydrogen peroxide and superoxide production. Gorelick et al. reported supplementation with Mg reduced lipid peroxidation in animal models of Mg deficiency [6]. In the serum and other studied organs of the group of rats which received resveratrol the imbalance of studied trace elements changed to normalize, showing the beneficial role of resveratrol. Several studies investigated the protective effect of some supplements with ant oxidative characteristics in Ops toxicities [11,35]. Res, as a natural phenolic compound, has attracted high attention because of hindering free radical reactions, including neutralizing free radicals [44]. Also, Res can enhance cellular defense via an increase in activity and gene expression of antioxidant enzymes [5,19,32]. Our previous study represented that Res treatment could improve hepatic and renal oxidative stress induced by DZN through enhancement of TAC, SOD, and CAT activities (CAT) [24]. Several studies confirmed the beneficial function of Res on homeostatic changes of trace elements [32]. In the current study, Res could restore some trace elements, including Zn, Se, Mg and in the kidney, liver, and tissue of rats exposed to DZN. Muselin et al. showed the protecting impact of Res on Cu, Zn, Fe, Mn, and Mg levels against toxicity induced by Aluminum [32]. Also, Abolaji et al. proved the beneficial effect of Res on Sodium Fluoride toxicity [2]. Cerebral ischemia caused oxidative stress via ROS overproduction. Ju-Hai Ro indicated that Res administration had a neuroprotective effect on oxidative stress status induced by cerebral ischemia. These effects were mediated via the modulation of trace elements with antioxidant properties, including Mg, Zn, and Se [40].Valko M [45] and He Y [20] indicated that Res treatment had a protection impact on cardiac cells against endoplasmic reticulum via elevation of intercellular Zn level. In vitro studies revealed that these effects are mediated via The transient potential receptor melastatin-2 (TRPM2) channel modulating [4]. Zhang e, al showed that Res administration increased renal se levels in arsenic exposure [50]. Ro, Ju-Hai pointed out that Res increased antioxidant activity (SOD and CAT) and Se levels in the brain tissue of rat animals [39]. It is suggested that Res can preserve Se level [39].

5. Conclusion

Some trace elements, including Zn, Cu, Se, Mg, and Fe, are prominent in antioxidant enzymes' function or even structure. So it is critical to maintain trace element balances. As noted above, Res protects against DZN-induced oxidative stress via antioxidant activity enhancement and diminishing oxidative markers. It is concluded that Res can alter trace element levels, these effect show the other protective effects of this natural polyphenol against DZN toxicity. However, the exact mechanisms remain to be more clarified.

Compliance with ethical standards

Informed consent forms were signed by all the participants. Approval from the Institutional Research Board has been taken to conduct the study.

CRediT authorship contribution statement

Maryam Esfahani: Writing – review & editing. **Fereshteh Mehri:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Author contributions

FM designed the study and interpreted the data. M.S. conducted the in vitro experiments. FM drafted the article, and MS revised it critically and finally approved the version to be submitted.

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