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Original Article

Deltamethrin-Induced Hepatotoxicity and Virgin Olive Oil Consumption: An Experimental Study

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What's Known

- Deltamethrin is an insecticide used worldwide as a major class of insecticides in agriculture. Deltamethrin can elicit pathophysiological effects through oxidative stress in non-targeted organisms such as mammals.
- It is essential that antioxidant supplements be used to reduce the side effects. There is accumulating evidence that virgin olive oil, a rich source of polyphenolic components, has antioxidant properties.

What's New

- Dietary virgin olive oil can significantly attenuate the indicators of the deltamethrin-induced toxicity. Thus, it can be recommended as a dietary supplement to reduce the side effects of synthetic pyrethroid insecticides.

Abstract

Background: Deltamethrin (DM) is a synthetic pyrethroid insecticide which can lead to pathological effects in mammals through oxidative stress. On the other hand, virgin olive oil (VOO) is a rich source of phenolic compounds with antioxidants. The aim of the present study was to determine the protective effects of VOO against DM-induced hepatotoxicity.

Methods: Thirty-six mice were randomly separated into 4 groups: vehicle group, VOO group, DM group, and DM plus VOO group. Immunohistochemistry of PARP, COX-2, and caspase-3 with the biochemical analysis of malondialdehyde and total antioxidant capacity levels were performed in the liver samples 5 weeks after gavaging. Statistical analysis was performed using SPSS, version 15. The data were compared between the groups using the Tukey multiple comparison tests and the analysis of the variance. A P value <0.05 was considered significant.

Results: The malondialdehyde level in the liver was increased in the DM group (71.18±0.01), whereas it was significantly (P=0.001) decreased after VOO administration in the DM plus VOO group (39.59±2.43). While the total antioxidant capacity level in the liver was decreased in the DM group (3.05±0.05), it was significantly increased (P=0.03) after VOO administration in the DM plus VOO group (3.95±0.04). A greater expression of caspase-3 (P=0.008), COX-2 (P =0.004), and PARP (P 0.006) could be detected in the DM group, while it was significantly (P=0.009) attenuated in the DM plus VOO group. Also, the degeneration of hepatocytes, which was detected in the DM group, was attenuated after VOO consumption.

Conclusions: VOO exerted protective effects against DM-induced hepatotoxicity, which might be associated with its anti-apoptotic, anti-inflammatory, and antioxidative properties.

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Keywords ● Decamethrin ● Olive oil ● Antioxidants ● Inflammation ● Apoptosis ● Hepatotoxicity

Introduction

Relatively safe pyrethroid insecticides have been classified as type I and type II according to their chemical structure.[1] Deltamethrin (DM), a type II synthetic pyrethroid insecticide with relatively low mammalian toxicity, is used worldwide in agriculture.[2] It is well documented that DM is readily absorbed through contaminated food and water[2] with high bioavailability in urine and feces.[3] In this regard, research has documented that

long-term exposure to DM among mammals has many side effects such as neurotoxicity,[4] genotoxicity,[5] hemolysis,[6] reproductive damage,[7] pulmonary disorders,[8] and nephrotoxicity.[9] Recently, it was also reported that exposure to DM could elicit histopathological changes in the liver.[10-12] Several mechanisms account for DM toxicity such as the production of free radicals, induction of lipid peroxidation, disturbance of the total body's antioxidant capacity, inflammation, and apoptosis.[13,14] Therefore, it seems that the use of antioxidant supplements is essential to subside the side effects. Within the previous decades, a rapidly growing number of natural polyphenols, secondary metabolites of plants, with antioxidant and anti-apoptotic effects have been described. One of the main sources of these molecules is olive oil. Olive oil is a rich source of polyphenolic components, which have many beneficial health effects in humans.[15] There is accumulating evidence attributing the beneficial effects of olive oil to a variety of biological activities such as free radical scavenging action, which is mediated by the chelation of metal ions and provision of the hydroxyl group for the quenching and neutralization of free radicals,[16,17] anti-inflammatory potency, which is mediated by the attenuation of anti-inflammatory mediators, and anti-apoptotic property, which is mediated by the inhibition of the proapoptotic and induction of anti-apoptotic proteins.[18,19] Meanwhile, total plasma antioxidant capacity increases after olive oil consumption.[20]

Accordingly, in the present study, we investigated the protective effects of virgin olive oil (VOO) consumption against DM-induced hepatotoxicity.

Materials and Methods

Animals

The present experimental study used 36 adult male mice (25±5.0 g) (Laboratory Animal Research Center, Sari, Iran). The mice were kept under constant conditions of temperature (23±1 ºC) and light/dark cycle (12 h/12 h) in the process of investigation. All the procedures were done according to the guidelines of the university's animal care codes to minimize the animals' suffering. The animals were fed a standard mouse chow and drinking water *ad libitum* throughout the study period. DM was purchased from Sigma-Aldrich (Germany) and VOO from Giah Essence Phytopharm Co. (Tehran, Iran).

The mice were randomly allocated to 4 equal groups, each containing 9 mice: I) the DM-treated group, which received 5 mg/kg/d of DM, diluted in dimethyl sulfoxide, for a period of 5 weeks by gavage;[21] II) the DM plus VOO-treated group, which received VOO (0.4 mL) for 5 weeks after 2 hours of DM gavage;[22] III) the VOO-treated group, which received VOO (0.4 mL) for 5 weeks by gavage; and IV) the vehicle group, which received dimethyl sulfoxide for 5 weeks by gavage. At the end of the 5th week, the animals' livers were removed for immunohistochemical, biochemical, and histopathological assessments. The doses and treatment schedules were based on previous studies[21,22] and pilot experiments in our laboratory.

Biochemistry

The obtained samples (sections of the right lobe of the liver) were thoroughly cleaned of blood and were then immediately frozen and stored in a -80 °C freezer for assays of tissue malondialdehyde (MDA) levels as a product of lipid peroxidation[23] and total antioxidant capacity (TAC).[24] The absorbance of the supernatant was measured by spectrophotometry. The data regarding MDA and TAC levels are expressed as micromoles per milligram of protein (µmol/mg-protein) and nanomoles Trolox equivalent per milligram of protein (nmol Trolox equivalent/mg-protein), respectively.

Histopathology

The obtained samples (3-mm thick sections of the left lobe of the liver)[25] were collected, thoroughly cleaned of blood, and then were immediately fixed in 10% (w/v) PBS-buffered formaldehyde and embedded in paraffin. Five-micrometer serial sections were prepared from the paraffin-embedded blocks using a microtome. Some tissue sections were deparaffinized with xylene, stained with hematoxylin and eosin (H&E), and studied by light microscopy (DME; Leica Microsystems Inc., Buffalo, NY, USA) to assess the histopathological changes. All the histological studies were performed in a blinded fashion.

Immunohistochemistry

For immunohistochemistry, some sections were incubated in goat normal serum (in order to block the nonspecific site), and subsequently with anti-caspase 3 rabbit polyclonal antibody (1:100 in PBS, v/v, Abcam, Cambridge, USA), anti-COX 2 rabbit polyclonal antibody (1:100 in PBS, v/v, Abcam, Cambridge, USA), and anti-PARP rabbit polyclonal antibody (1:100 in PBS, v/v, Abcam, Cambridge, USA) overnight at 4 °C. The sections were washed with PBS and then incubated with secondary antibody conjugated with horseradish peroxidase (goat

anti-rabbit IgG, Abcam, Cambridge, USA) for 2 hours and detected by diaminobenzidine tetrahydrochloride for 5 minutes. Afterward, they were dehydrated and mounted. For negative controls, primary antibodies were omitted. For quantitative analysis, immunohistochemical photographs (n=5 photos from each sample were collected from all the mice in each experimental group) were assessed by densitometry using MacBiophotonics ImageJ 1.41a software on an ASUS personal computer. The data are expressed as a percentage of the total tissue area.

Statistical Analysis

The statistical analyses were carried out in SPSS, version 15 (Chicago, IL, USA). The results are presented as means±SDs. The Kolmogorov–Smirnov test was used in order to evaluate the normality of the data. Also, the Tukey multiple comparison tests and the analysis of the variance were used to compare each 2 groups and the data between the groups, respectively. A $P<0.05$ was considered significant.

Results

Biochemical Analysis

The MDA levels for all groups at the end of the experiment are shown in table 1. The administration of DM in the DM group produced a significant elevation (P=0.003) in the lipid peroxidation level compared to the other groups. The MDA level in the DM plus VOO group was significantly (P=0.001) lower than that in the DM group, while the differences between the DM plus VOO group, vehicle group, and VOO group were not significant (P=0.31) (figure 1).

The TAC levels for all the groups at the end of the experiment are shown in table 1. The administration of DM in the DM group produced a significant (P=0.02) decrease in the TAC level compared to the other groups. We found a significantly (P=0.01) increased level of TAC in the DM plus VOO group compared to the DM group, while the differences between the DM plus VOO group, vehicle group, and VOO group were not significant (P=0.45) (figure 2).

Histopathologic Changes

The results of the histopathological examination are depicted in figure 3. Cytoplasmic hypereosinophilia, extensive nuclear pyknosis, and loss of intercellular borders in some of the hepatocytes were detected in the sections of the liver obtained from the DM group (figure 3A).

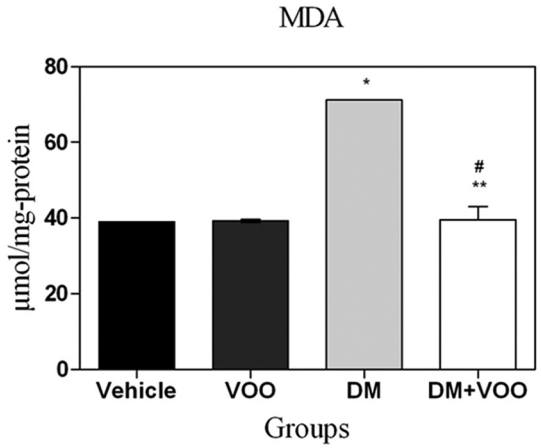

Figure 1: Histogram shows the levels of malondialdehyde (MDA) at the end of the experiment. Values are expressed as micromole per milligram protein. *P=0.001 versus the vehicle and VOO groups; **P=0.002 versus the DM group; #P=0.36 versus the vehicle and VOO groups.

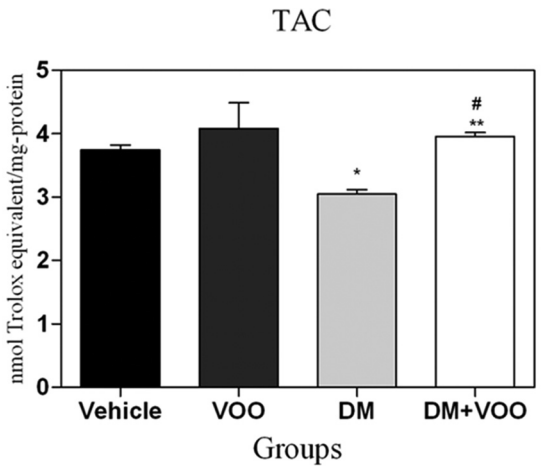

Figure 2: Histogram shows the levels of total antioxidant capacity (TAC) at the end of the experiment. Values are expressed as nanomoles Trolox equivalent per milligram protein. *P=0.003 versus the vehicle and VOO groups; **P=0.001 versus the DM group;#P=0.09 versus the vehicle and VOO groups.

Table 1: Effect of virgin olive oil on the biochemical markers of the liver affected by deltamethrin-induced hepatotoxicity

Experimental groups	MDA	P value µmol/mg-protein	TAC nmol Trolox equivalent/mg-protein	P value
Vehicle	38.94±0.01		3.74±0.05	
VOO	39.24±0.26		4.08±0.28	
DM	71.18±0.01	0.003	3.05±0.05	0.02
DM+VOO	39.59±2.43	0.001	3.95±0.04	0.01

DM: Deltamethrin; VOO: Virgin olive oil

Treatment with VOO reduced the changes, so that only focal nuclear pyknosis and cytoplasmic vacuolation were detected in the DM plus VOO group (figure 3B). No detectable injury was shown in the vehicle and VOO groups.

Immunohistochemical Assessment

Figures 4, 5, and 6 show the immunohistochemical staining of caspase-3, COX-2, and PARP, respectively. The administration of DM in the DM group increased the expression of caspase-3 (figure 4A), COX-2 (figure 5A), and PARP (figure 6A), while VOO treatment in the DM plus VOO group reduced the degree of positive staining for caspase-3 (figure 4B), COX-2 (figure 5B), and PARP (figure 6B) compared to the DM group. The histograms of the quantitative analysis of caspase-3, COX-2, and PARP positive staining in the experimental groups are shown in figures 4C, 5C, and 6C, respectively.

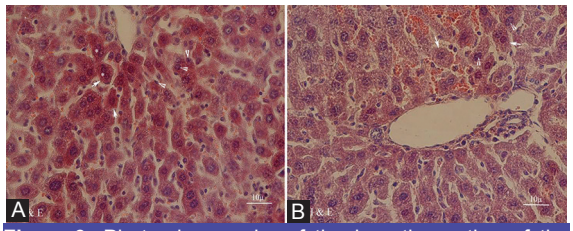

Figure 3: Photomicrographs of the hepatic section of the DM group (A) with cytoplasmic hypereosinophilia (arrows), extensive nuclear pyknosis (arrowheads), and loss of intercellular borders in some of the hepatocytes (asterisks), and the DM plus VOO group (B) with only focal nuclear pyknosis (arrowheads) and cytoplasmic vacuolation (arrows) (stained with hematoxylin and eosin, ×400).

Discussion

The main findings of the current study showed that the administration of VOO attenuated (I) histopathological changes, (II) apoptosis, (III) inflammation, and (IV) lipid peroxidation, while it (IV) improved TAC in the liver against DM-induced hepatotoxicity.

Despite its low mammalian toxicity and worldwide use in agriculture, chronic exposure to DM exerts some undesirable effects on different organs, including the liver. Studies have shown that DM administration significantly increases the liver MDA content, as an indicator of lipid peroxidation, in rats compared with the control group.[10,26,27] Lipid peroxidation is an important pathologic event, the breakdown of polyunsaturated fatty acids, which is induced by free radicals.[28] Our results showed that elevated MDA levels were attenuated significantly after the administration of VOO in the treatment group. Olive oil contains a large number of molecules such as several different combinations of phenolic antioxidants, which are free radical scavengers that neutralize toxic species and sometimes even prevent the early stages of their formation.[29,30] In this regard,

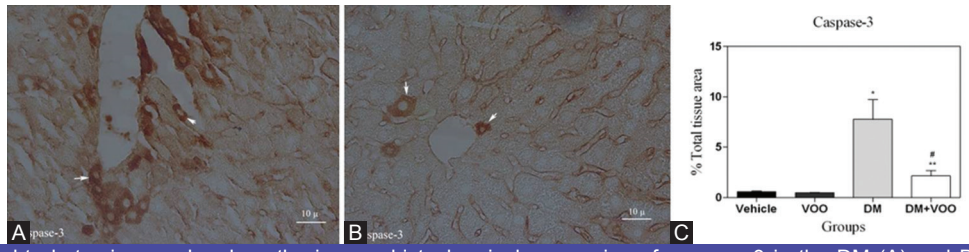

Figure 4: Light photomicrographs show the immunohistochemical expression of caspase-3 in the DM (A) and DM plus VOO (B) groups (magnification, ×400). The positive staining of caspase-3 is presented by a brown color of cytoplasm (arrows). Densitometry analysis of immunohistochemical photomicrographs for caspase-3 was conducted. Data are expressed as a percentage of the total tissue area (C). *P=0.01 versus the vehicle and VOO groups; **P=0.02 versus the DM group;#P=0.15 versus the vehicle and VOO groups.

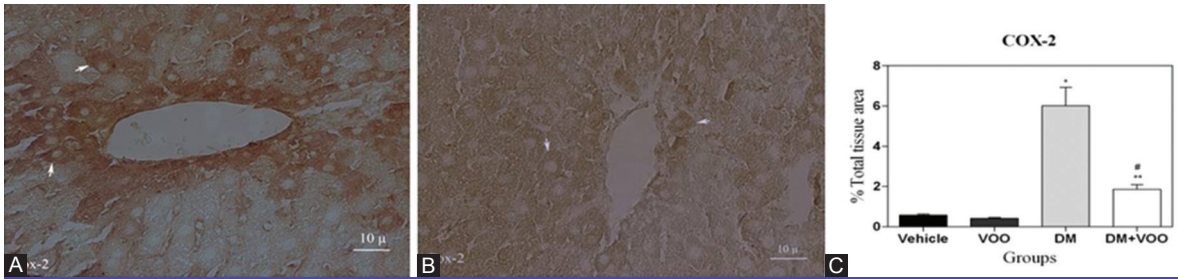

Figure 5: Light photomicrographs show the immunohistochemical expression of COX-2 in the DM (A) and DM plus VOO (B) groups (magnification, ×400). The positive staining of COX-2 is presented by a brown color of cytoplasm (arrows). Densitometry analysis of immunohistochemical photomicrographs for COX-2 was conducted. Data are expressed as a percentage of the total tissue area (C). *P=0.001 versus the vehicle and VOO groups; **P=0.004 versus the DM group;#P=0.09 versus the vehicle and VOO groups.

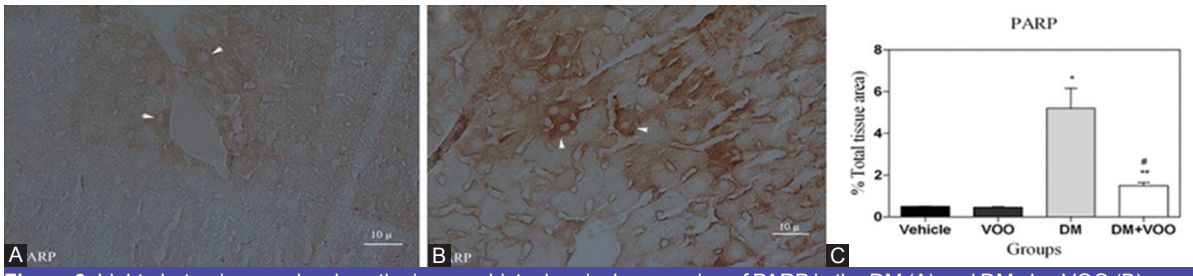

Figure 6: Light photomicrographs show the immunohistochemical expression of PARP in the DM (A) and DM plus VOO (B) groups (magnification, ×400). The positive staining of PARP is presented by a brown color of cytoplasm (arrows). Densitometry analysis of immunohistochemical photomicrographs for PARP was carried out. Data are expressed as a percentage of the total tissue area (C). *P=0.001 versus the vehicle and VOO groups; **P=0.008 versus the DM group; #P=0.08 versus the vehicle and VOO groups.

studies have documented the protection of the liver cell membrane lipid peroxidation with olive oil after partial hepatectomy[31] and in aging-related changes[32] compared to control groups. Endogenous antioxidants prevent cellular oxidative damage caused by free radicals. Studies have shown that TAC in the liver tissues is significantly decreased after DM administration compared to control groups,[26,27] meanwhile these studies have documented a significant decrease in the liver glutathione, catalase, and superoxide dismutase. Our results showed that the administration of DM decreased TAC levels in the liver, meanwhile the decrease was somewhat attenuated after the administration of VOO in the treatment group. It has been documented that olive oil and phenolics such as hydroxytyrosol and tyrosol can restore the antioxidant status in the liver after TCDD-induced hepatotoxicity[30] and partial hepatectomy.[31]

Apoptosis is a key mechanism of degenerative diseases and is triggered by some factors such as toxins. *In vivo* and *in vitro* studies have revealed that exposure to DM significantly affects cell survival and induces apoptosis in thymic cells,[14] neuronal cells,[32] renal tubular cells,[33] splenocytes,[34] PC12 cells,[35] and hepatocytes.[36] Our immunohistochemical assessments revealed that the gavaging of DM significantly increased the expression of caspase-3, PARP, and COX-2, which are involved in the production of inflammatory mediators. Also, VOO consumption significantly decreased these upregulations. It is well documented that VOO and its phenolics have inhibitory effects against apoptosis. In this regard, Pan et al.[37] documented that hydroxytyrosol, a main olive oil phenolic compound, exerted protective effects against hepatic ischemia/reperfusion injury through the attenuation of parenchymal apoptosis in mice. Another study demonstrated that the consumption of olive oil and its phenolics ameliorated apoptosis in TCDD-induced hepatotoxicity in rats.[30]

Conclusion

In sum, our results support the notion that dietary VOO, a good source of phytochemicals, can significantly attenuate the indicators of DM-induced hepatotoxicity. It can, therefore, be recommended as a dietary supplement to reduce the side effects of synthetic pyrethroid insecticides.

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Conflict of Interest: None declared.

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