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The Effect of *Melissa officinalis* Hydro Alcoholic Extract on Liver Enzymes, Markers of Kidney Function and Testosterone in Lead Poisoned Rats

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Abstract

Background: Lead, one of the most important environmental pollutants, can induce a broad range of physiological dysfunction. The aim of this study was to investigate the protective effect of the *Melissa officinalis* plant extract on biomarkers of liver and kidney function as well as serum testosterone concentration in lead-exposed male rats.

Methods: We used 40 Wistar rats and divided them into 5 groups. The control group received saline (1 mL/kg) by gastric gavage and 30 minutes later received saline (1 mL/kg) through i.p injection. The lead group received saline (1 mL/kg) by gastric gavage and 30 minutes later received i.p injection of lead acetate (20 mg/kg). The treatment groups received different doses of *M. officinalis* alcoholic extract (20, 100, and 500 mg/kg, respectively) by gastric gavage and 30 min later received i.p injection of lead acetate (20 mg/kg). The rats were treated for 5 days and then twenty -four hours after the last injection, blood samples were collected for the measurement of urea, creatinine, uric acid, alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST) and testosterone. Data analysis was performed through SPSS (version 16).

Results: *Melissa extract* (100 mg/kg) significantly reduced liver enzymes and kidney function markers when compared to the lead group. Treatment with Melissa extract (100 mg/kg and 500 mg/kg) significantly increased serum testosterone concentration compared to the lead group.

Conclusion: The biochemical results of this study showed that *M. officinalis* may be beneficial in lead-induced liver and kidney dysfunction.

Keywords: *Melissa officinalis*, Lead toxicity, Biochemical markers, Testosterone, Rat

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Introduction

Lead, one of the most important environmental pollutants, is widely used in the chemical industry and it has been a major problem for human health (1). Lead exposure may be a widespread problem in many countries. The sources of human exposure to the present metal include many foods, beverages, and mud (2). Lead exposure can induce a broad range of physiological dysfunction including, the central nervous system, hematopoietic system, reproductive system, liver, and kidneys, depending upon the level and duration of exposure (1,3). Lead can cause oxidative stress by accumulating in tissues and reducing the activity of the antioxidant system, and on the other hand, increasing the production of reactive oxygen species. In addition, this heavy metal can lead to apoptosis by reducing energy production in cells and damaging mitochondria and DNA (4).

Glomerular Sclerosis, proximal tubular nephropathy, and interstitial fibrosis are characteristics of lead poisoning. Human insufficiencies related to excessive lead exposure include enzymuria, low- and high relative molecular mass proteinuria, impaired transport of organic anions, and glucose and depressed glomerular filtration rate (5).

Exposure to lead can disrupt spermatogenesis and produce poor semen quality, decreasing sperm count, seminiferous tubule diameter, sperm adhesion ability, and sperm viability. These disorders resulted in reduced male fertility that is reversible (6,7). Some previous studies showed direct effects of lead on testes, while others reported a central action on the hypothalamic-pituitary axis involving changes in LH, FSH and testosterone levels (6). Human sperm has unsaturated fatty acids that generate ROS (such as superoxide anion and hydrogen

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peroxide) that are vulnerable to peroxidative lesions (7).

Human and animal studies have shown that lead causes histological and histochemical changes in liver. In rats, lead acts on hepatocytes and causes hydropic degeneration, cytoplasmic swelling, necrosis, and a decrease in glycogen levels (8). In humans, lead increases the risk of non-alcoholic fatty liver disease (9). There is a correlation between blood lead concentration and liver enzyme levels (10). In a previous study, the prevalence of lead poisoning in occupationally exposed people was 57%. In these subjects, the levels of liver enzymes (such as alanine transaminase [ALT], alkaline phosphatase [ALP] and aspartate transaminase [AST]) were significantly higher than controls (11).

Melissa officinalis or Lemon balm belonging to the *Lamiaceae* family, being a perennial herb, is a medicinal plant native to the East Mediterranean region and West Asia and Possesses a high amount of antioxidant activity (12,13). The phytochemical study demonstrates the existence of different components in *M. officinalis* such as poly acids (rosmarinic acid, caffeic acid, and protocatechuic acid), aldehydes monoterpenoid oil, terpenes, flavonoids, and tanan (7).

In traditional medicine, this plant is used to treat asthma, bronchitis, amenorrhea, and wound healing. In addition, this plant is effective in the treatment of headaches, indigestion, colic, nausea, nervousness, anemia, vertigo, syncope, malaise, insomnia, epilepsy, depression, psychosis, and hysteria (14). The researchers reported that *Melisa* extract has antioxidant and anti-inflammatory properties, lowers the level of liver enzymes and renal markers, and prevents tissue changes caused by toxic agents in testicular tissue. Therefore, it has a protective role against harmful factors and can be effective in improving kidney and liver function and the reproductive system (15-18).

The aim of this study was to investigate the protective effect of Melissa plant extract on liver, kidney and testicular tissue in lead-exposed male rats.

Materials and Methods

Preparation of Melissa officinalis extracts

Melissa officinalis leaves were obtained from the faculty of pharmacology, Medical University of Tehran and genus and species were approved by experts. Voucher specimens (n = 83 454) have been deposited in the Herbarium of the Medical University of Tehran. Extract preparation was, according to the procedure of Khodsooz et al. Briefly, 150 g of dried and milled leaves of *M. officinalis* were mixed with 600 mL of 96% v/v ethanol. After 24 hours, the mixture was filtered through a filter paper and residuum was re-extracted with ethanol 70% for 24 hours. The filtrates were mixed together and concentrated to one-third by means of a rotary evaporator at 50°c and 70 rpm. Melisa extract was dried in the oven at 45°C. The extract was powdered and then dissolved in distilled water and was administered to the animals through gavage (19).

Experimental protocol

Rats were divided into 5 groups (8 rats in each group) and treated for 5 consecutive days: the first group or the control group received saline (1 mL/kg) through gastric gavage and 30 minutes later received i.p injection of saline (1 mL/kg).The second group or lead group received saline (1 mL/kg) through gastric gavage and 30 minutes later received i.p injection of lead acetate (20 mg/kg).The third, fourth and fifth groups or treatment groups received different doses of MO alcoholic extract (20, 100 and 500 mg/kg, respectively) by gastric gavage and 30 min later received i.p injection of 20 mg/kg lead acetate (19,20).

Blood sampling

Twenty-four hours after the last injection, rats were sacrificed by inhalation of ether, and blood samples were obtained by direct cardiac puncture and centrifuged at 3000 rpm for 20 min. Serum was aliquoted and frozen to -20°C until different assays were performed.

Animals

Forty male Wistar rats (weight 180-200 g) were purchased from Tehran University and housed in the animal laboratory of Tehran University (Iran). The rats were kept under controlled environmental conditions (23°C and a 12-hour light/dark cycle) with water and food *ad libitum*.

Biochemical analyses

Urea, creatinine, uric acid, ALT, ALP and AST (Pars Azmoun, Karaj, Iran) and testosterone of the blood serum samples were determined by commercial kits according to the manufacturer's instruction (Padtan Gostar, Tehran, Iran).

Statistical analysis

The obtained data were expressed as mean ± SD in each group. The SPSS software package (version 16) was used to perform statistical analyses**.** Statistical analysis of the biochemical assays was done using one-way analysis of variance test. Then, we used post hoc Tukey's test and $P < 0.05$ was considered to be significant.

Results

The effect of Melissa extract on liver enzymes

Intraperitoneal injection of lead acetate (20 mg/kg) resulted in a significant increase in serum ALP, AST and ALT enzymes ($P < 0.001$, Figure 1). Treatment with *Melissa* extract (100 mg/kg) significantly reduced liver enzymes ($P < 0.001$, Figure 1A, B, C) when compared with the lead group. But consumption of *Melissa* (500 mg/kg), exerted such a significant effect only on the AST enzyme ($P < 0.05$, Figure 1C).

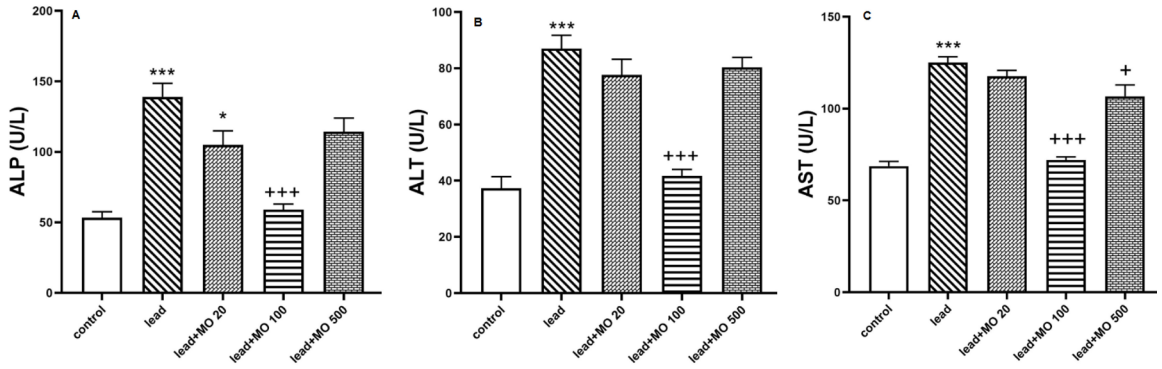

Figure 1. The Effect of lead acetate (20 mg/kg) and *Melissa* extract (20 mg/kg, 100 mg/kg, 500 g/kg) on liver enzymes in rats. Data are reported as mean ± SEM; the number of animals in each group was 8; **P* value < 0.01 and ****P* value < 0.001 compared to the control group; ^{+}P value < 0.05 and ^{+++}P value < 0.001 compared to the lead group.

The effect of Melissa extract on kidney function markers

Intraperitoneal injection of lead acetate (20 mg/kg) resulted in a significant increase in serum concentration of uric acid ($P < 0.001$), Urea ($P < 0.001$) and creatinine ($P < 0.01$, Figure 2). Treatment with *Melissa* extract (100 mg/kg) significantly ($P < 0.001$ and $P < 0.05$) reduced kidney function markers compared to the lead group (Figure 2).

The effect of Melissa extract on testis function

In order to assess testis function, the blood testosterone level was measured.

As shown in Figure 3, lead injection significantly reduced serum testosterone level compared with the control group ($P < 0.001$). Treatment with *Melissa* extract (100 mg/kg and 500 mg/kg) significantly increased serum testosterone concentration compared to the lead group ($P < 0.05$).

Discussion

The goal of the present survey was to study the effect of *Melissa* hydro alcoholic extract on liver enzymes, kidney function markers and serum testosterone concentration in rats exposed to lead. *Melissa* extract (100 mg/kg) significantly reduced liver enzymes and kidney function markers when compared to the lead group. Treatment with *Melissa* extract (100 mg/kg and 500 mg/kg) significantly increased serum testosterone concentration compared to the lead group.

In accordance with former studies (10,11,21), the data of our study showed that intraperitoneal injection of lead acetate, 20 mg/kg, for 5 consecutive days resulted in an elevation of liver enzymes (ALP, AST and ALT) and markers of renal function (urea, uric acid and creatinine).

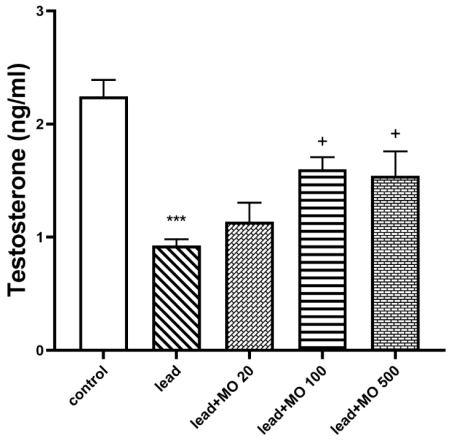

Figure 3. The effect of lead acetate (20 mg/kg) and *Melissa* extract (20 mg/kg, 100 mg/kg, 500 mg/kg) on serum testosterone level in rat. Data are reported as mean ± SEM; the number of animals in each group was 8; *** *P* value < 0.001 compared to the control group. ^{+}P value < 0.5 compared to the lead group.

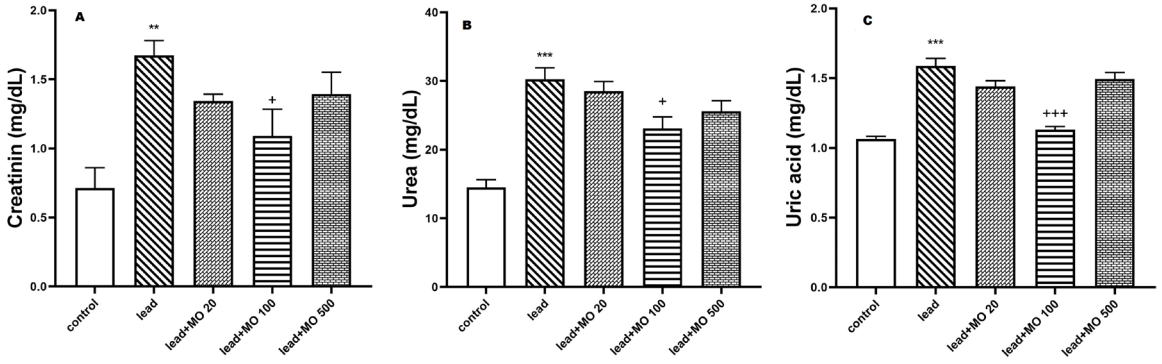

Figure 2. The effect of lead acetate (20 mg/kg) and *Melissa* extract (20 mg/kg, 100 mg/kg, 500 mg/kg) on kidney function markers in rat. Data are reported as mean ± SEM; the number of animals in each group was 8; ** *P* value < 0.01 and *** *P* value < 0.001 compared to the control group. ^{+}P value < 0.5 and ^{+++}P value < 0.001 compared to the lead group.

In addition, serum testosterone level decreased significantly following i.p injection of lead.

The effect of lead on liver enzyme levels and markers of renal function may be due to its toxicity on the tissues of these two organs. Jarrar and Taib reported that subtoxic concentration of lead acetate causes changes in the portal triads, hepatocytes and the sinusoids (8). Also, the use of lead carbonate (50 mg/kg) for 5 weeks in dogs caused desensitization changes in the proximal tubules of the inner cortex of the kidney (22). It has been shown that lead acetate inhibits steroidogenesis in Leydig cells by reducing the expression of StAR protein and P450scc activity and 3β-hydroxysteroid dehydrogenase enzymes (23).

It is likely that some toxic effects of lead in body tissues are due to the release of free radicals and oxidative stress (24). Offor et al reported that treatment of rats with lead acetate (60 mg/kg) caused a significant increase in the serum concentration of urea and a significant decrease in the antioxidant enzymes (glutathione peroxidase, superoxide dismutase) when compared with the control group. Also, the lipid peroxidation biomarker, malondialdehyde, was significantly higher in the lead-treated group versus the control group (21). Free radicals destroy cell membranes, including hepatocytes, by damaging the membrane and enzymes normally found in the cell's cytosol go into the bloodstream (17). Consequently, elevated levels of these enzymes in the serum indicate liver damage.

Furthermore, lead via lipid peroxidation triggers the signaling cascades of the inflammatory process. Inflammation is thought to act as a mediator of the adverse health effects caused by lead exposure (16).

The current study showed that oral use of *Melissa* improved liver function in lead-poisoned rats. Many previous studies have reported that *Melissa* extract alone lowers the level of liver enzymes. Treatment of hypercholesterolemic rats with different doses of alcoholic extract of *M. officinalis* has significantly reduced hepatic ALP enzyme (25). In another similar study, oral use of *M. officinalis* L extract (2 g/kg) for 24 days in hyperlipidemic rats not only reduced blood lipid levels but also decreased liver enzymes (ALT, AST, and ALP) (15). In streptozotocin-induced diabetic rats, the alcoholic extract of *Melissa* (100 mg/kg) significantly reduced the ALP γ-glutamyltransferase (GGT) (17).

The results of the present study showed that *Melissa* reduces the serum concentration of biochemical markers of renal function in lead-poisoned rats. In this regard, some past studies have shown the nephroprotective effect of *Melissa* extract versus various toxic agents. Seif et al reported that the alcoholic extract of *Melissa* officinalis (200 mg/kg bw) alone did not cause significant changes in the concentrations of liver enzymes as well as serum concentrations of uric acid, creatinine and urea, but reduced these biochemical parameters in rats exposed to organophosphorus *Malathion* (27 mg/kg bw). In addition, in this study, *Melissa* treatment significantly decreased the concentration of malondialdehyde (MDA) and significantly increased antioxidant enzymes in the renal homogenate (26). In another study, intraperitoneal injection of acetaminophen (800 mg/kg) increased the concentration of GGT in 24-hour urine volume and pretreatment with the watery extract of *M. officinalis* (500 mg/kg) significantly declined the concentration of GGT (as a marker of renal tubular cell function) in urine (16). Also, In diabetic rats, gastric gavage hydroalcoholic extract of *M. officinalis* L. (100 and 200 mg/kg) caused a significant decrease in urea concentration (17).

The results of current research show that the dose of 100 mg/kg of *Melissa* extract is an effective dose and the effect of *Melissa* on renal and liver function is not dose-dependent. Some references have mentioned that the dose of 100 mg/kg *Melissa* on blood biomarkers is more effective than the higher doses of this plant extract (17,19).

It is unclear why a dose of 500 mg/kg of *M. officinalis* has no significant effect on liver and kidney performance indicators. To answer this question, it seems that the cellular mechanism of the components of the *Melissa* extract should be further investigated.

In our study, the group treated with *M. officinalis* L. extract plus lead showed a significant increase in plasma testosterone. Given that testosterone is a key hormone in regulating spermatogenesis, it can be said that *Melissa* extract also has a protective role against the toxicity of lead in rat testes. In similar research, oral administration of malathion (an OP pesticide) significantly reduced sperm count and serum concentrations of FSH, LH and testosterone. Oral administration of *M. officinalis* extract (200 mg/kg bw) protected sperm against malathion stress and improved gonadotropin and testosterone levels (18).

The antioxidant and anti-inflammatory properties of *Melissa* have been illustrated in many past studies. Sipos et al reported that the antioxidant properties of the aqueous extract of *Melissa* are 30% ascorbic acid (27). The antioxidant properties of this plant are due to its phenolic compounds and flavonoids (14). These compounds prevent oxidative damage to body tissues by trapping and removing free radicals (14,25). Due to the antioxidant properties of this plant, which prevents the oxidation of membrane fats, a decline in the level of liver enzymes and markers of kidney function can be expected in mice treated with the extract of this plant.

One of the limitations of this study is that the effect of *Melissa* extract on these biochemical factors and testosterone alone has not been investigated. Another limitation of this study is the absence of histopathology tests.

Conclusion

Biochemical findings of this study showed that *Melissa officinalis* can be beneficial in lead-induced hepatic and renal dysfunction.

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Author Contributions

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Supervision: Laya Ghahri.
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Visualization: Parvin Zareian.
Writing – original draft: Mehdi Eivani.
Writing – review & editing: Parvin Zareian, Laya Ghahari.

Conflict of Interests

The authors have no conflicts of interest to disclose.

Ethical Approval

The experimental protocol was approved by the Committee of Animal Care and Use, AJA University of Medical Sciences (IR.AJAUMS.REC.1398.122).

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