Original article

Therapeutic influences of almond oil on male rats exposed to a sublethal concentration of lead

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A R T I C L E   I N F O

A B S T R A C T

Globally, human exposure to heavy metals has risen dramatically. Lead (Pb) is one of the most toxic heavy metals to human and other living organisms. Pb affects certain biochemical and physiological activities of the body. Many scientific investigations have documented the therapeutic and antioxidant properties of natural products which isolated from plant sources. The present study was therefore undertaken to evaluate the therapeutic influence of almond oil against Pb toxicity in male rats. The experimental rats were distributed into four groups. The first group was served as control. The second group was treated with 100 mg/kg body weight of Pb. The third group was subjected to almond oil (800 mg/kg body weight) and Pb. The fourth group was supplemented with almond oil. After six weeks, blood serum specimens were analyzed. In the second group, Pb produced a marked increase of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, glucose, triglycerides, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), creatine kinase (CK), lactate dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN), uric acid and malondialdehyde (MDA) levels, while the levels of total protein, albumin, high density lipoprotein cholesterol (HDL-C), glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) were significantly decreased. In contrast, the treatment with almond oil notably improved the biochemical changes and showed antioxidative effect. The present study disclosed the therapeutic influence of almond oil on the basis of its antioxidant effect against Pb toxicity. Moreover, these new findings indicated that the constituents of almond oil have a promising significant potential in biomedical and pharmacological studies.

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1. Introduction

Humans are exposed to various types of environmental contaminants at different stages of their life span, majority of them are harmful (Hamadouche et al., 2013). Exposure to heavy metals is mostly occupational. In biological systems, heavy metals have been reported to affect cellular organelles and components such as cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair (Wang and Shi, 2001). Lead (Pb) is a heavy metal environmental pollutant and is naturally occurring bluish grey metal found in small amount in earth crust and has continued to pose health hazards in animals and humans in many parts of the world (Navarro-Moreno et al., 2009; Tchounwou et al., 2012). Exposure to Pb occurs mainly via inhalation of Pb-contaminated dust particles or aerosols, and ingestion of lead-contaminated food, water, and paints (ATSDR, 1992, 1999). Adults absorb 35–50% of Pb through drinking water and the absorption rate for children may be greater than 50%. Pb absorption is influenced by factors such as age and physiological status. In the human body, the greatest percentage of Pb is taken into the kidney, followed by the liver and the other soft tissues such as heart and brain, however, Pb in the skeleton represents the major body fraction (Flora et al., 2006). The nervous system is the most vulnerable target of Pb poisoning. Headache, poor attention spam, irritability, loss of memory and dullness are the early symptoms of the effects of Pb exposure on the central nervous system (ATSDR, 1999; CDC, 2002). Health risks due to Pb toxicity are one of the world's current problems.

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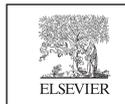
Pb has been found to induce a wide range of behavioral, histological, biochemical and physiological effects (Jackie et al., 2011; Zargar et al., 2016; Okesola et al., 2018; Gargouri et al., 2019; Saritha et al., 2019).

In recent years, interest has increased in using natural products for pharmacological purposes, as a form of complementary or replacement therapy. Herbal medicines have received great attention as alternative medicines in recent years. Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical disease (Gupta et al., 2004). Nowadays, a lot of research has been conducted on the use of herbal products as natural antioxidants because of their fewer side effects, easy and cheap availability (Riaz et al., 2011). Almonds, *Prunus dulcis* (Mill.) D.A.Webb syn. *P. amygdalus* (L.) Batsch, are among the most popular tree nuts on a worldwide basis and rank first in tree nut production. They belong to the family Rosaceae, which also includes apples, pears, prunes, and raspberries (Sang et al., 2002; Wijeratne et al., 2006; Jahanban Sfahlan et al., 2009). Almond is pale yellow in color and it is extracted from almond kernels. Almond oil contains proteins (amandine) and certain minerals such as calcium and magnesium, vitamin E and D and has high amounts of unsaturated fats, low amounts of saturated fats, and free of cholesterol (Chen et al., 2006; Atsu Barku et al., 2012). Almond oil has long been used in complementary medicine circles for its numerous health benefits, including anti-inflammatory, immunity-boosting and anti-hepatotoxicity effects (Ahmad, 2010). Therefore, the current study tends to ascertain whether almond oil could have a protective effect on rats exposed to a sublethal concentration of Pb.

2. Material and methods

2.1. Animals

Forty male albino rats of the Wistar strain (*Rattus norvegicus*), weighing 135–158 g were taken for the present experiment. The principles of laboratory animal care were followed throughout the duration of experiment and instruction given by King Abdulaziz University ethical committee was followed regarding experimental treatments. The experimentations were conducted at the Experimental Animal Unit, Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia during March and April 2019. The rats were housed in standard cages at an ambient temperature of 20 ± 1 °C with 12 h light: 12 h dark cycle. The experimental rats had free access to standard diet and water.

2.2. Experimental protocol

The rats were distributed into four experimental groups (ten rats per group) and treated as follows:

1. Rats of group 1 were untreated and served as controls.
2. Rats of group 2 were orally administrated with 100 mg/kg body weight of Pb, daily for 6 weeks.
3. Rats of group 3 were orally supplemented with almond oil at a dose of 800 mg/kg body weight and after 4 h exposed to Pb at the same dose given to group 2, daily for 6 weeks.
4. Rats of group 4 were orally supplemented with almond oil at the same dose given to group 3, daily for 6 weeks.

2.3. Body weight changes

The body weights of rats were estimated at the start of the experimental period and after six weeks using a digital balance.

Moreover, the experimental animals were observed for signs of abnormalities throughout the period of study.

2.4. Blood serum analyses

After six weeks, the experimental animals were fasted for 8 h, water was not restricted, and then anaesthetized with diethyl ether. Blood specimens were collected from orbital venous plexus in non-heparinized tubes. Blood specimens were centrifuged at 2500 rpm for 15 min, and the clear samples of blood serum were separated and stored at −80 °C. Dimension Vista® 1500 System (USA) was used to evaluate the levels of selected biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, total protein, albumin, glucose, triglycerides, cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), creatine kinase (CK), lactate dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN), uric acid. Moreover, the methods of Beutler et al. (1963), Nishikimi et al. (1972), Ohkawa et al. (1979) and Aebi (1984) were used to measure the levels of glutathione (GSH), superoxide dismutase (SOD), malondialdehyde (MDA) and catalase (CAT) respectively.

2.5. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows version 22.0 software. Each value is expressed as mean ± standard deviation (SD). The values were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test. Statistical probability of $P \leq 0.05$ was considered to be significant.

3. Results

Fig. 1 shows the changes of body weights after six weeks in all experimental groups. Significant increases of body weight gain were noted in rats of control group (+68.3%) and rats treated with almond oil plus Pb (+59.6%), and almond oil (+70.7%). The minimum increase of body weight gain was observed in rats exposed to only Pb (+41.9%).

The levels of serum ALT, AST, ALP, GGT, total bilirubin, total protein and albumin in control, Pb, almond oil plus Pb and almond oil treated rats are represented in Table 1. Serum ALT levels were markedly increased in rats exposed to Pb ($P \leq 0.000$) and almond oil plus Pb ($P \leq 0.01$) compared with control rats. Significant increases in the level of serum AST were observed in rats treated with Pb ($P \leq 0.000$) and almond oil plus Pb ($P \leq 0.005$). In comparison with control rats, the level of serum ALP was significantly elevated in rats treated with Pb ($P \leq 0.000$). Serum GGT level was statistically enhanced in rats exposed to Pb ($P \leq 0.000$) and almond oil plus Pb ($P \leq 0.03$). In comparison with control rats, the level of serum total protein ($P \leq 0.001$) and albumin ($P \leq 0.01$) were markedly decreased in Pb treated rats. In comparison with control rats, there were no significant alterations in the levels of serum ALP, total bilirubin, total protein and albumin in rats treated with almond oil plus Pb. Moreover, the levels of all of these parameters were statistically unchanged in rats treated with only almond oil.

Table 2 demonstrates the levels of serum glucose, triglycerides, cholesterol, HDL-C, LDL-C and VLDL-C, in all experimental groups. Significant elevations in the levels of serum glucose ($P \leq 0.002$), triglycerides ($P \leq 0.000$), cholesterol ($P \leq 0.000$), LDL-C ($P \leq 0.04$) and VLDL-C ($P \leq 0.000$) were noted in rats exposed to Pb, while the level of serum HDL-C was statistically decreased ($P \leq 0.01$) compared with control rats. In rats treated with almond
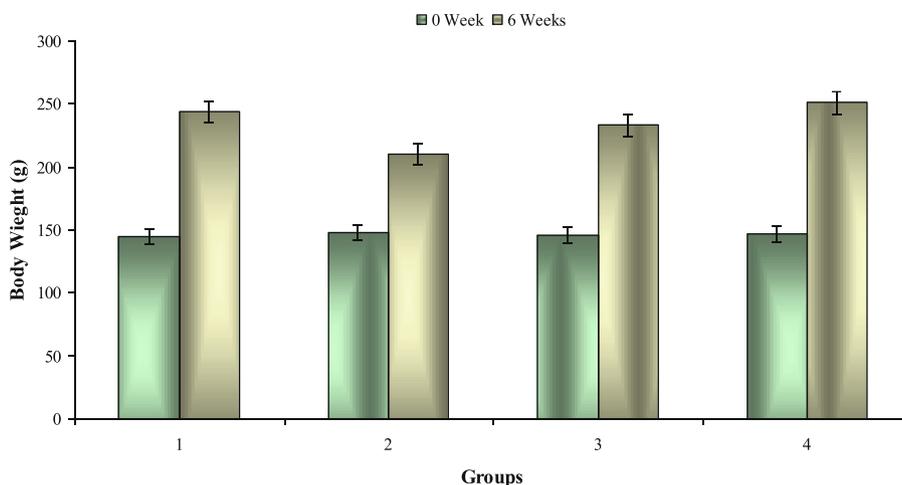
Fig. 1. Changes of body weight after six weeks in control (group 1), Pb (group 2), almond oil plus Pb (group 3) and almond oil (group 4) treated rats.

Table 1
Levels of serum ALT, AST, ALP, GGT, total bilirubin, total protein and albumin in control (group 1), Pb (group 2), almond oil plus Pb (group 3) and almond oil (group 4) treated rats after six weeks.

Parameters	Groups			
	Group 1	Group 2	Group 3	Group 4
ALT (U/L)	57.57 ± 6.85	90.66 ± 7.25[ab]	70.55 ± 6.73[ac]	57.71 ± 7.11
AST (U/L)	114.00 ± 3.42	178.43 ± 17.83[ab]	134.86 ± 11.47[ac]	117.71 ± 4.96
ALP (U/L)	185.29 ± 19.56	276.29 ± 14.40[ab]	165.43 ± 23.30	180.14 ± 18.28
GGT (U/L)	1.74 ± 0.28	3.37 ± 0.57[ab]	2.46 ± 0.60[ac]	1.72 ± 0.17
Total bilirubin (μmol/L)	2.86 ± 0.69	6.00 ± 1.29[ab]	3.57 ± 1.13	2.84 ± 0.66
Total protein (g/L)	61.86 ± 2.73	53.71 ± 3.35[ab]	59.00 ± 1.63	60.14 ± 1.95
Albumin (g/L)	11.86 ± 1.35	8.57 ± 1.51[ab]	11.77 ± 1.40	11.71 ± 1.11

Data represent the means ± SD of 7 animals per group.
[a] Indicates a significant difference between group 1 and treated groups (2, 3 and 4).
[b] Indicates a significant difference between group 2, and groups 3 and 4.
[c] Indicates a significant difference between groups 3 and 4.

Table 2
Levels of serum glucose, triglycerides, cholesterol, HDL-C, LDL-C and VLDL-C in control (group 1), Pb (group 2), almond oil plus Pb (group 3) and almond oil (group 4) treated rats after six weeks.

Parameters	Groups			
	Group 1	Group 2	Group 3	Group 4
Glucose (mmol/L)	4.600 ± 0.58	6.76 ± 0.72[ab]	5.19 ± 0.69	4.67 ± 0.54
Triglycerides (mmol/L)	0.55 ± 0.07	0.93 ± 0.15[ab]	0.71 ± 0.07[ac]	0.50 ± 0.08
Cholesterol (mmol/L)	1.26 ± 0.14	1.94 ± 0.15[ab]	1.59 ± 0.11[ac]	1.19 ± 0.09
HDL-C (mmol/L)	1.22 ± 0.11	1.00 ± 0.12[ab]	1.20 ± 0.10	1.23 ± 0.10
LDL-C (mmol/L)	0.49 ± 0.09	0.62 ± 0.12[ab]	0.54 ± 0.07	0.48 ± 0.06
VLDL-C (mmol/L)	0.25 ± 0.06	0.43 ± 0.07[ab]	0.33 ± 0.03[ac]	0.23 ± 0.04

Data represent the means ± SD of 7 animals per group.
[a] Indicates a significant difference between group 1 and treated groups (2, 3 and 4).
[b] Indicates a significant difference between group 2, and groups 3 and 4.
[c] Indicates a significant difference between groups 3 and 4.

oil plus Pb, notable increases in the levels of serum triglycerides ($P \leq 0.001$), cholesterol ($P \leq 0.005$) and VLDL-C ($P \leq 0.005$) were observed, while the levels of serum glucose, HDL-C and LDL-C were statistically unchanged. Additionally, insignificant changes in the levels of serum glucose, triglycerides, cholesterol, HDL-C, LDL-C and VLDL-C were noted in rats exposed to only almond oil compared with control rats.

The levels of serum CK, LDH, creatinine, BUN and uric acid are shown in Table 3. Statistically increases in the levels of serum CK ($P \leq 0.000$) and LDH ($P \leq 0.000$), creatinine ($P \leq 0.001$), BUN ($P \leq 0.01$), uric acid ($P \leq 0.004$) were noted in rats exposed to

Pb. Insignificant change was found in the levels of serum CK, LDH, creatinine, BUN and uric acid in rats with almond oil plus Pb (group 3) and almond oil (group 4).

Fig. 2A–D represents the levels of serum GSH, SOD, MDA and CAT. In comparison with control rats of group 1, the levels of serum GSH ($P \leq 0.001$), SOD ($P \leq 0.001$) and CAT ($P \leq 0.001$) were statistically decreased, while the level of MDA was significantly increased ($P \leq 0.001$) in rats exposed to Pb. Noticeably decreases of serum GSH ($P \leq 0.01$) and SOD ($P \leq 0.004$) were observed in rats treated with almond oil plus Pb. Furthermore, insignificant change was found in the levels of serum MDA and CAT in rats subjected to

Table 3
Levels of serum CK, LDH, creatinine, BUN and uric acid in control (group 1), Pb (group 2), almond oil plus Pb (group 3) and almond oil (group 4) treated rats after six weeks.

Parameters	Groups			
	Group 1	Group 2	Group 3	Group 4
CK (U/L)	544.14 ± 40.01	811.13 ± 33.55[ab]	591.43 ± 98.05	529.86 ± 34.80
LDH (U/L)	712.86 ± 59.92	958.57 ± 80.55[ab]	771.14 ± 68.82	706.71 ± 48.63
Creatinine (μmol/L)	37.86 ± 2.12	61.43 ± 11.00[ab]	42.29 ± 4.89	36.76 ± 3.39
BUN (mmol/L)	7.67 ± 0.78	10.96 ± 2.40[ab]	8.57 ± 1.51	7.59 ± 0.43
Uric acid (μmol/L)	72.86 ± 4.88	97.00 ± 11.73[ab]	72.00 ± 7.05	72.14 ± 4.98

Data represent the means ± SD of 7 animals per group.
[a] Indicates a significant difference between group 1 and treated groups (2, 3 and 4).
[b] Indicates a significant difference between group 2, and groups 3 and 4.
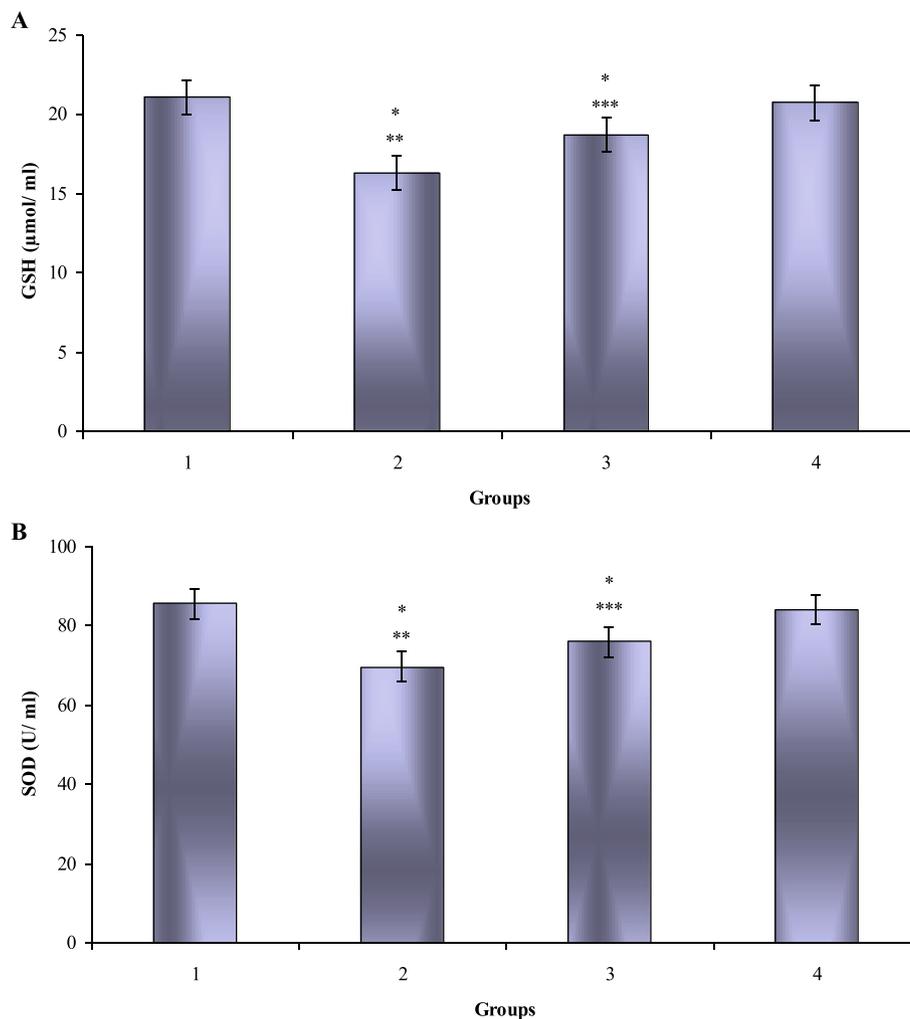
Fig. 2. (A–D) The levels of serum GSH (A), SOD (B), MDA (C) and CAT (D) in control (group 1), Pb (group 2), almond oil plus Pb (group 3) and almond oil (group 4) treated rats after six weeks.* Indicates a significant difference between group 1 and treated groups (2, 3 and 4). ** Indicates a significant difference between group 2, and groups 3 and 4. *** Indicates a significant difference between group 3 and group 4.

with almond oil plus Pb compared with control rats. Finally, the levels of serum GSH, SOD, MDA and CAT were statistically unchanged in rats treated with only almond oil as compared with control rats.

4. Discussion

Heavy metal toxicity has proven to be a major threat and there are several health risks associated with it. The toxic effects of these metals, even though they do not have any biological role, remain present in some or the other form harmful for the human body and its proper functioning (Jaishankar et al., 2014). It has been recognized that environmental pollution can affect the quality of health of the human population. Heavy metals are among the group of highly emitted contaminants and their adverse effect of living organisms has been widely studied in recent decades. Lifestyle and quality of the ambient environment are among these factors which can mainly contribute to the heavy metals exposure in humans (Rzymski et al., 2015). Pb exposure has been a widely rec-

C

D
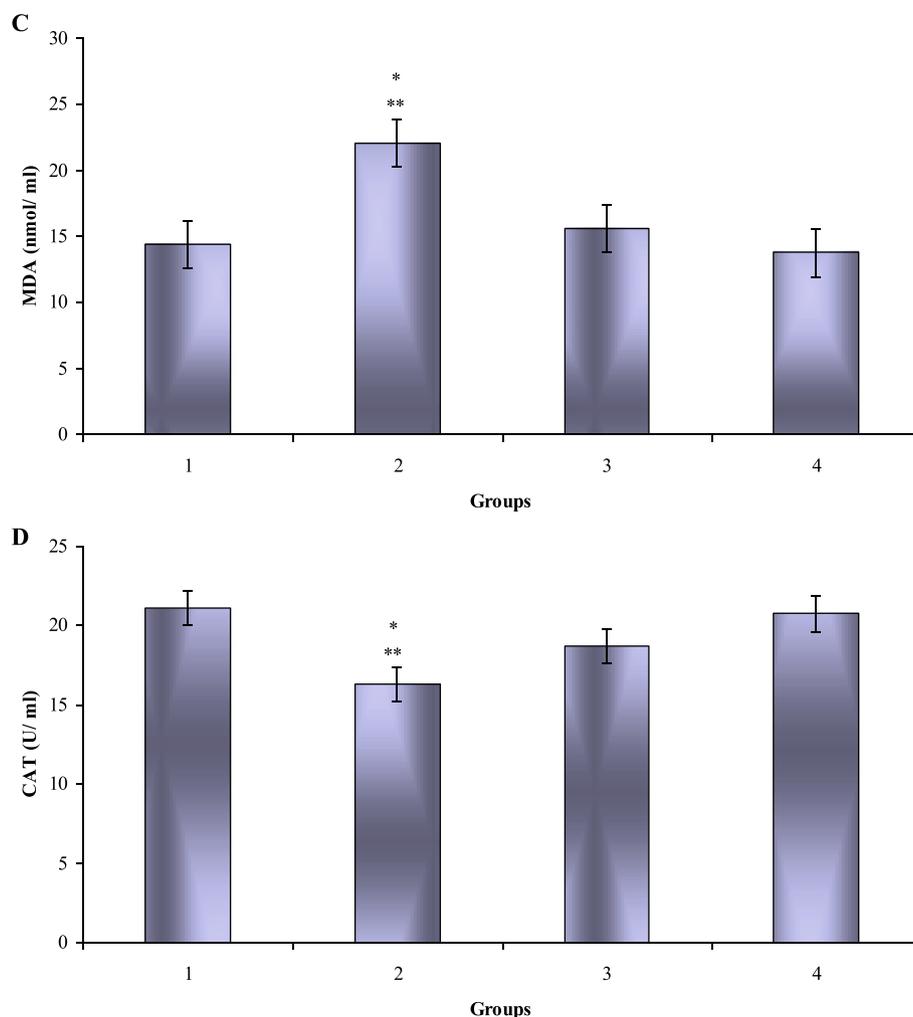
Fig. 2 (continued)

ognized as a significant public health problem over recent decades, and high levels of occupational lead contact are now strictly controlled due to their adverse health effects (Assi et al., 2016).

The present study revealed that the minimum increase of body weight gain was observed in rats exposed to only Pb. It was suggested that animals having a continuous exposure to heavy metals usually lose weight (Nwokocha et al., 2011). Exposure to Pb may reduce growth and food consumption through the contact of Pb with appetite-depressant receptors in the gastrointestinal tract. Chronic exposure to Pb leads to gradual loss of body weight. This might be due to nausea, vomiting and anorexia, which usually accompany any metal toxicity (Hammond et al., 1989; Rafique et al., 2008). Additionally, previous studies showed that the decrease of body weight associated with inhibition of feeding behavior in experimental animals exposed to Pb (Ibrahim et al., 2012; Mphele et al., 2013; de Figueiredo et al., 2014).

The present results indicate that oral administration of Pb to rats caused significant changes in hematobiochemical parameters. Statistically significant increases in the level of serum ALT, AST, ALP, GGT and total bilirubin were observed. These biochemical parameters are important biomarkers of liver function. Several experimental studies showed that the exposure to Pb caused statistically increases of these parameters with histological alterations of liver structure (Liu et al., 2012; Hasanein et al., 2016; Abd Allah and Badary, 2017; Azadbakht et al., 2017; Luo et al., 2019; Nakhaee et al., 2019).

The present significant decrease of blood total protein and albumin levels in rats exposed to Pb reflected a disturbance of protein metabolism. Total protein level is a rough measure of protein status. It also reflects major functional changes in liver and kidney functions[10]. Toxicity or damage to the liver in any form may result in decreased levels of total protein in blood (Kaneko et al., 2008). Deposition of Pb leads to the liver injury and consequent disturbances in protein metabolism. The reduction in blood total protein and albumin may be due to inhibition of protein and albumin biosynthesis through the specific enzymes in the cell processes, also may be due to decrease utilization of free amino acids for protein synthesis (Georing, 1993). Pb also binds to plasma proteins where it causes alterations in high number of enzymes and can also pertub protein synthesis in hepatocytes (Okediran et al., 2016). Reduced blood albumin levels in Pb intoxicated rats show poor liver function and resultant impaired albumin synthesis (Ibrahim et al., 2012).

The obtained results showed that the exposure to Pb caused statistical increases in the levels of serum glucose, triglycerides, cholesterol, LDL-C and VLDL-C, while the level of HDL-C was significantly declined. These results indicate that the exposure to Pb caused a severe disturbance of carbohydrates and lipids metabolism. Similar observations were reported by other studies (Ibrahim et al., 2012; Abdou et al., 2014; Zargar et al., 2016). This study also revealed that the exposure to Pb produced statistically significant increases of serum CK and LDH. Serum CK and LDH

levels were previously used as biomarkers to diagnose myocardial infarction (Maghamiour and Safaie, 2014; Callegari et al., 2017; Ouyang et al., 2019). However, the present increases of serum CK and LDH levels may be due to the damage and necrosis of cardiac muscle tissues. The present an elevation of blood creatinine, BUN and uric acid levels in rats exposed to Pb confirmed kidney dysfunction and considered as a functional evidence of Pb-induced nephrotoxicity. Kidney is particularly suceptible to Pb, causing proximal tubular malfunction or irreversible nephropathy depending on the exposure type (Conterato et al., 2007). Additionally, previous investigations showed that the exposure to Pb caused nephrotoxicity (Sudjarwo et al, 2017; Soussi et al., 2018; El-Boshy et al., 2019).

The present investigation showed that Pb induced oxidative stress as indicated by significant decrease of serum GSH, SOD and CAT levels, and an increase of MDA level. A balance between oxidants and antioxidant is known to exist under physiological conditions. However, even small changes in oxidant or/and antioxidant levels may disturb its balance and leads to oxidative stress (Bahrami et al., 2016). Pb-induced oxidative stress or disruption of prooxidant/antioxidant balance in blood and other soft tissues has been postulated to be the major mechanism of Pb associated tissue injury (Flora et al., 2003; Mohamed et al., 2016; Hou et al., 2019).

The present study shows a beneficial influence of almond oil against Pb toxicity, as it significantly attenuated the biochemical alterations. The therapeutic property of almond oil seems appropriate in improving the measured biochemical parameters. It can be summed that phytochemicals of almond oil possess various kinds and levels of antioxidant components and activities. However, the possible mechanism of almond oil attributed to its antioxidant activity which estimated by GSH, SOD, MDA and CAT levels. Natural antioxidants are the plants- and other living organism-derived compounds with a strong potential to inhibit oxidative stress by controlling the formation of free radicals, scavenging the free radicals, interrupting the free radical-mediated chain reactions, and preventing the lipid peroxidation process. Thus, natural antioxidants have potential to balance the irregulated oxidative stress and to restore the cellular homeostasis. Therefore, natural antioxidants can decrease the deleterious effects of various oxidative stress-induced pathological conditions (Ramana et al., 2018). Antioxidants are compounds or systems that delay autoxidation by inhibiting formation of free radicals or by interrupting propagation of the free radical by one (or more) of several mechanisms: (1) scavenging species that initiate peroxidation, (2) chelating metal ions such that they are unable to generate reactive species or decompose lipid peroxides, (3) quenching $\bullet O_2^-$ preventing formation of peroxides, (4) breaking the autoxidative chain reaction, and/or (5) reducing localized O_2 concentrations (Nawar, 1996). Almond oil contains antioxidant and antiradical activity, may be helpful in preventing or slowing the progress of various oxidative stress-related diseases (Hussein and Raheem, 2016). Additionally, the present study suggests that the almond oil can be considered as a promising therapeutic factor against Pb toxicity. Based on above mentioned data, this is the first experimental study indicate that the almond oil is beneficial therapeutic factor for counteracting the toxicity of Pb. Collectively, the present obtained results confirm that the therapeutic properties of almond oil attributed to the antioxidant activity of its chemical components. Finally, further pharmacological and biochemical investigations are required to explore the efficacy of different doses of almond oil as therapeutic factor against Pb toxicity and may be against other chemical pollutants and pathogenic factors.

Declaration of Competing Interest

The author has declared that there are no conflicts of interest.

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