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Hepatoprotective and Antioxidant Effects of *Juniperus procera* Leaves Extract on Lead Induced Liver Injury in Male Rats

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Abstract: Environmental pollution is a major global problem to living organisms. The exposure to heavy metals is considered to be a major public health problem. Lead (Pb) is a heavy metal and is a common industrial and environmental risk pollutant. Recently, the utility of medicinal plants and their natural products as therapeutic factors is in vogue in different parts of the world. Kingdom of Saudi Arabia has a lot of medicinal plants whose therapeutic influences have not been sufficiently investigated. The present study was aimed to investigate the effects of *Juniperus procera* leaves extract (JPLE) in male rats intoxicated with Pb. Rats were randomly divided into four experimental groups. The first group was served as control. The second group was administrated with 100 mg/kg body weight of Pb, daily for six weeks. The third group was supplemented with JPLE at a dose of 400 mg/ kg body weight and exposed to Pb. The fourth group was treated with JPLE at a dose of 400 mg/ kg body weight. After six weeks, significant increases in the levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin, while the levels of serum glutathione (GSH) and superoxide dismutase (SOD) were significantly decreased in experimental rats exposed to only Pb. The results indicated that the treatment with JPLE led to attenuation effect against Pb induced hepatotoxicity. Moreover, these new results suggest that the effects of JPLE were attributed to antioxidant properties of its chemical constituents.

Key words: *Juniperus procera* · Lead Toxicity · Liver · Antioxidant · Rats

INTRODUCTION

Recently, the growing attention of the scientific community has been focused on the threat to health created by environmental pollutants. Environmental pollution has many facets and the resultant health risks include diseases in almost all organ systems [1-3]. The environmental impacts on our health have become a large concern of our societies worldwide [4]. Toxicity due to heavy metal is one of the major environmental problems and remains a serious health concern today [5]. Globally, human exposure to heavy metals has risen dramatically [6]. Lead (Pb) could be an extremely toxic heavy metal and thought of as an accumulative poisonous impact on all biological system through water, soil and air. However, it is still used extensively in several parts of the globe and cause environmental pollution additionally as serious health issues [7-9]. Moreover, Pb has been found to induce a wide range of behavioral, histological, biochemical and physiological effects [6, 10-12].

Medicinal plants have been known to be effective following their roles in the treatment of various diseases. Recent interest has shifted to the role played by medicinal plants and natural products in mitigating and ameliorating the toxicity of different toxicants because of their safety profiles, associated with minimal transient side effects, as well as their antioxidant and powerful bioactive compounds [13-15]. *Juniperus* is one of the major genera of *Cupressaceae* family. *Juniperus* species are a rich and variety source of phytochemical components that have

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desirable health advantages. They are traditionally famous to be helpful for preventing and curing many chronic ailments. Different parts (leaves, berries, bark) of *J. procera* is used in the traditional medicine for remedy of liver diseases, hyperglycemia, jaundice, tuberculosis, pneumonia, bronchitis, diarrheal, intestinal worms, bladder infections and urinary tract. Additionally, *J. procera* fruits have some medicinal uses for curing skin diseases and headaches [16-18]. In the current literature, there is no data concerning the effect of *J. procera* on Pb toxicity in experimental animals. Therefore, an attempt was made to evaluate the possible protective effect of *J. procera* leaves extract on Pb induced liver injury in male rats.

MATERIALS AND METHODS

Animals: Male albino rats of the Wistar strain (*Rattus norvegicus*), weighing 91-132 g were used in the present study. The experimental animals were housed in standard plastic cages and maintained under controlled room conditions of humidity (65%), temperature (20±1°C) and 12:12 h light: dark cycle. Rats were fed *ad libitum* on normal commercial chow and had free access to water. The experimental treatments were conducted in accordance with ethical guidelines of the Animal Care and Use Committee of King Abdulaziz University.

Extraction of *J. procera* Leaves: The fine quality of *J. procera* leaves were directly collected from the outskirts of Albaha region of Saudi Arabia. The leaves were scientifically defined by the herbarium of Biological Sciences Department, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia. The collected leaves were completely washed, air dried at room temperature and stored in dry plastic container until use for extraction processes. The method of Al-Attar and Abu Zeid [19] was used to prepare the extract with some modifications. The aqueous extract of leaves was prepared every two weeks. The dried *J. procera* leaves (200 g) were powdered and added to 8 L of hot water. After 3 h, the mixture was slowly boiled for 30 min. After boiling period, the mixture was cooled at room temperature and it was gently subjected to an electric mixer for 20 min. Thereafter, the solutions of *J. procera* leaves were filtered. Finally, the filtrates were evaporated in an oven at 40°C to produce dried residues (active principles). With references to the powdered samples, the yield means of leaves extract were 18.7%. Additionally, the extract was stored in a refrigerator for subsequent experiments.

Experimental Design: A total of forty rats were randomly divided into four experimental groups, ten of rats each. The experimental groups were treated as follows:

- Rats of the first group were untreated and served as controls.
- Rats of the second group were orally administrated with 100 mg/kg body weight of Pb, daily for six weeks.
- Rats of the third group were orally supplemented with *J. procera* leaves extract (JPLE) at a dose of 400 mg/ kg body weight and after 4 h exposed to Pb at the same dose given to the second group, daily for six weeks.
- Rats of the fourth group were orally supplemented with JPLE at a dose of 400 mg/ kg body weight/ day for six weeks.

Blood Serum Analyses: After six weeks, the experimental animals were fasted for 8 hours, water was not restricted and then anaesthetized with diethyl ether. Blood samples were collected from orbital venous plexus in non-heparinized tubes, centrifuged at 2500 rpm for 15 minutes and blood sera were then collected and stored at -80°C. The levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using the method of Reitman and Frankel [20]. The methods of MacComb and Bowers [21] and Doumas *et al*. [22] were used to evaluate the levels of serum alkaline phosphatase (ALP) and total bilirubin respectively. The level of serum glutathione (GSH) was estimated according to the method of Beutler *et al*. [23]. The method of Nishikimi *et al*. [24] was used to measure the level of serum superoxide dismutase (SOD).

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.

RESULTS

Figure 1 showed the levels of serum ALT in control, Pb, JPLE plus Pb and JPLE treated rats. Statistically increases in the level of serum ALT were observed in rats exposed to Pb (+68.8%, $P \leq 0.000$) and JPLE plus Pb (+35.1%, $P \leq 0.01$) compared with control rats, while this

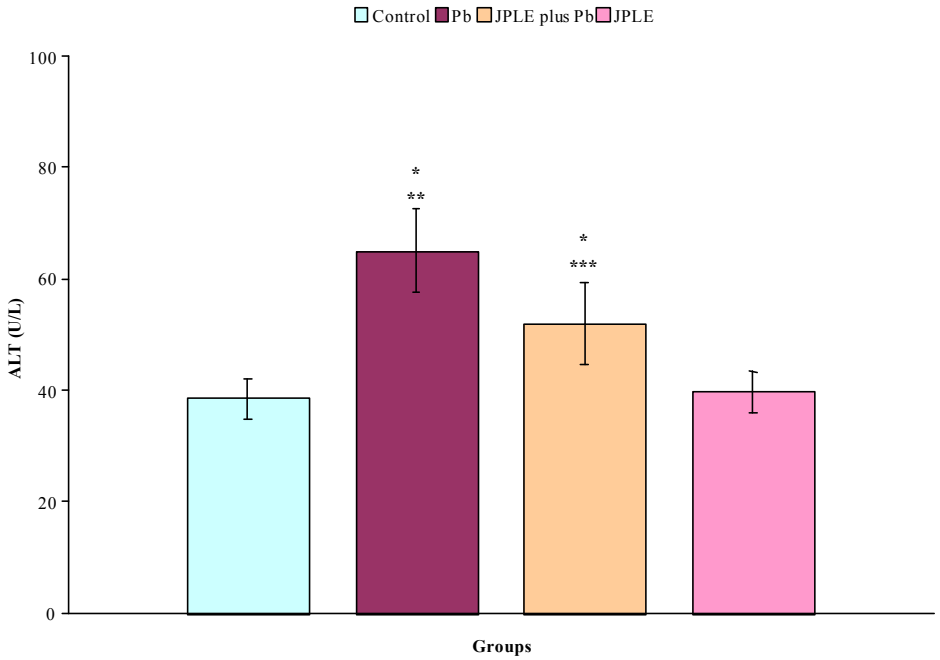

Fig. 1: Level of serum ALT in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks
* indicates a significant difference between control and treated groups
** indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract
*** indicates a significant difference between rats treated with JPLE plus Pb and JPLE

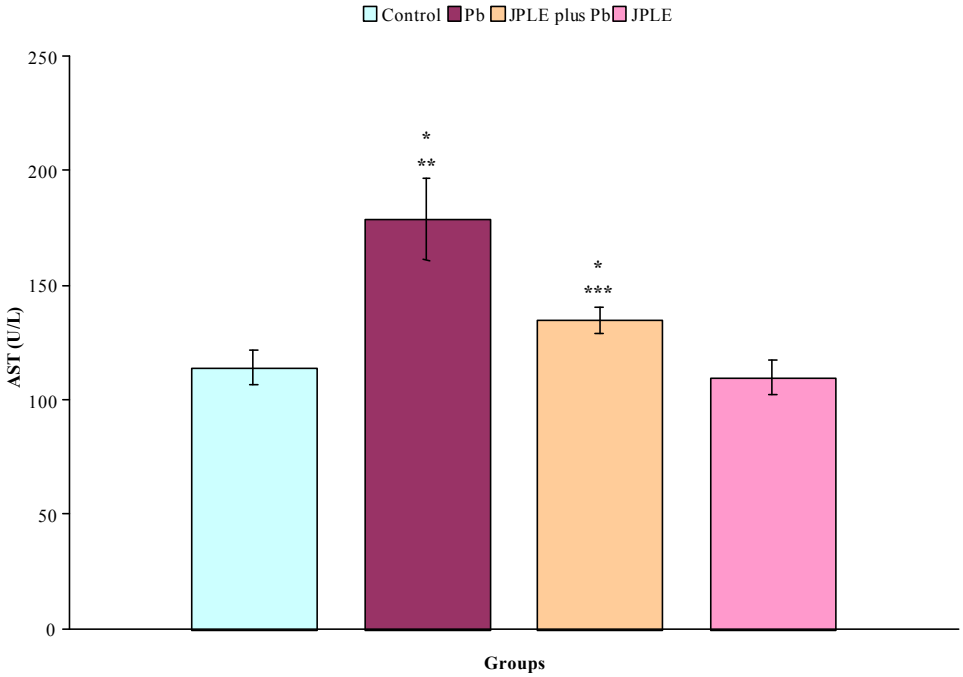

Fig. 2: Level of serum AST in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks
* indicates a significant difference between control and treated groups
** indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract
*** indicates a significant difference between rats treated with JPLE plus Pb and JPLE

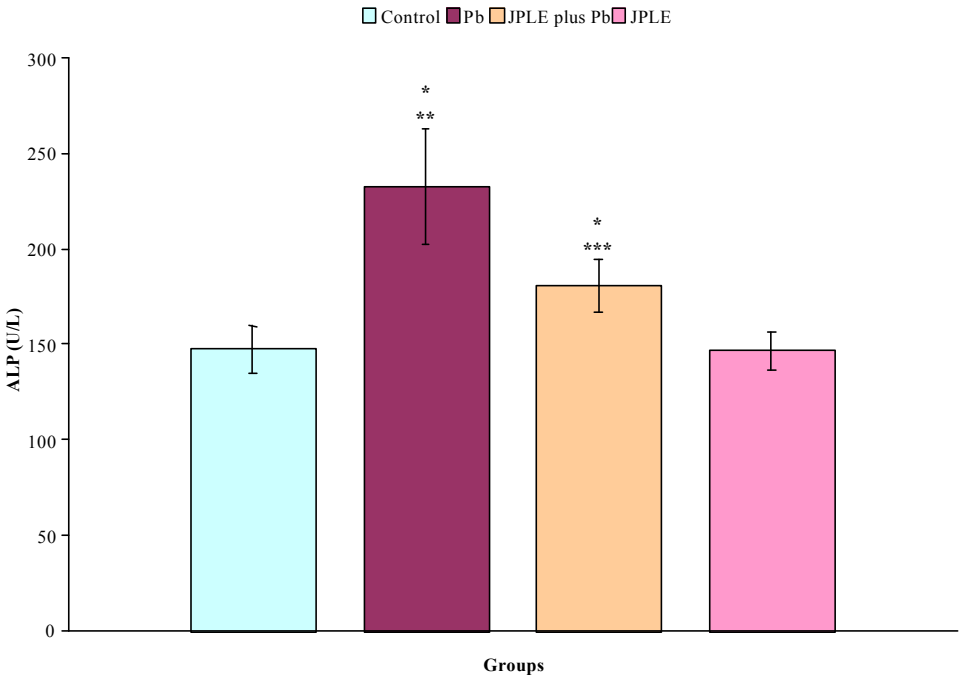

Fig. 3: Level of serum ALP in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks
* indicates a significant difference between control and treated groups
** indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract
*** indicates a significant difference between rats treated with JPLE plus Pb and JPLE

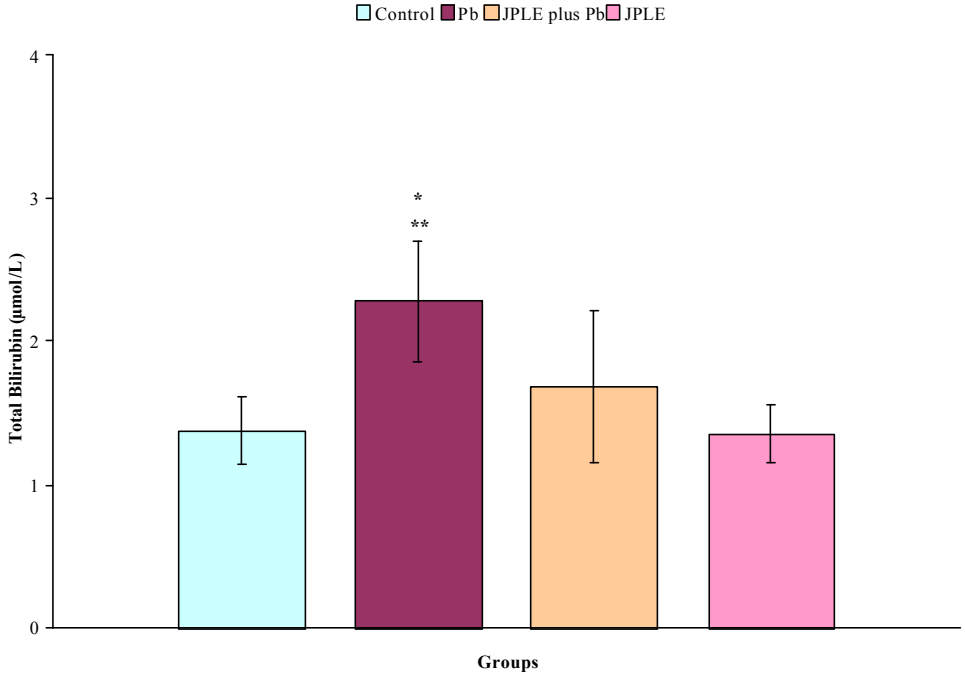

Fig. 4: Level of serum total bilirubinin in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks.
*indicates a significant difference between control and treated groups.
**indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract.

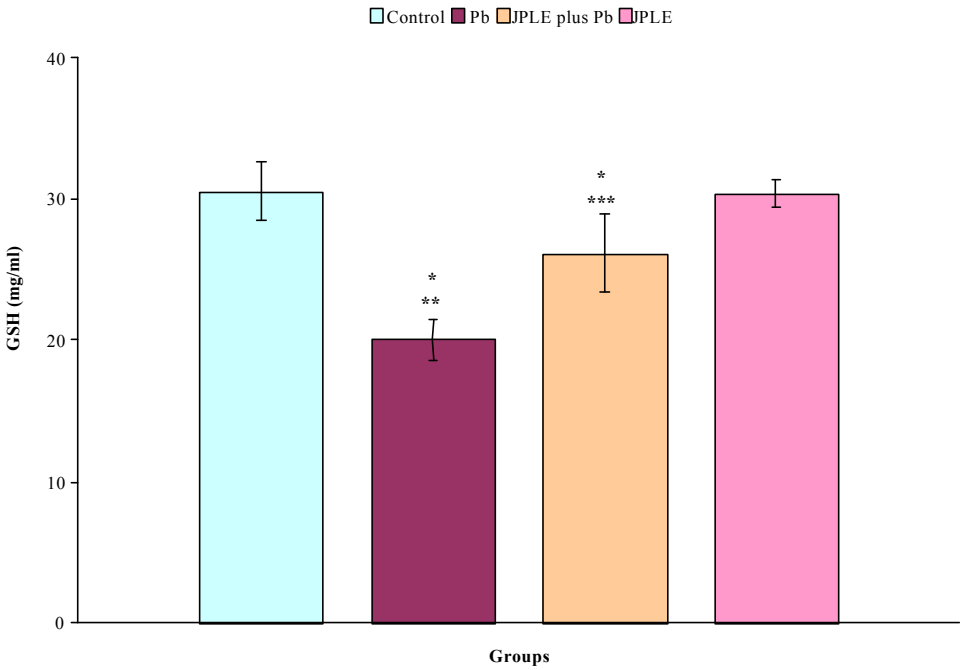

Fig. 5: Level of serum GSH in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks
* indicates a significant difference between control and treated groups
** indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract
*** indicates a significant difference between rats treated with JPLE plus Pb and JPLE

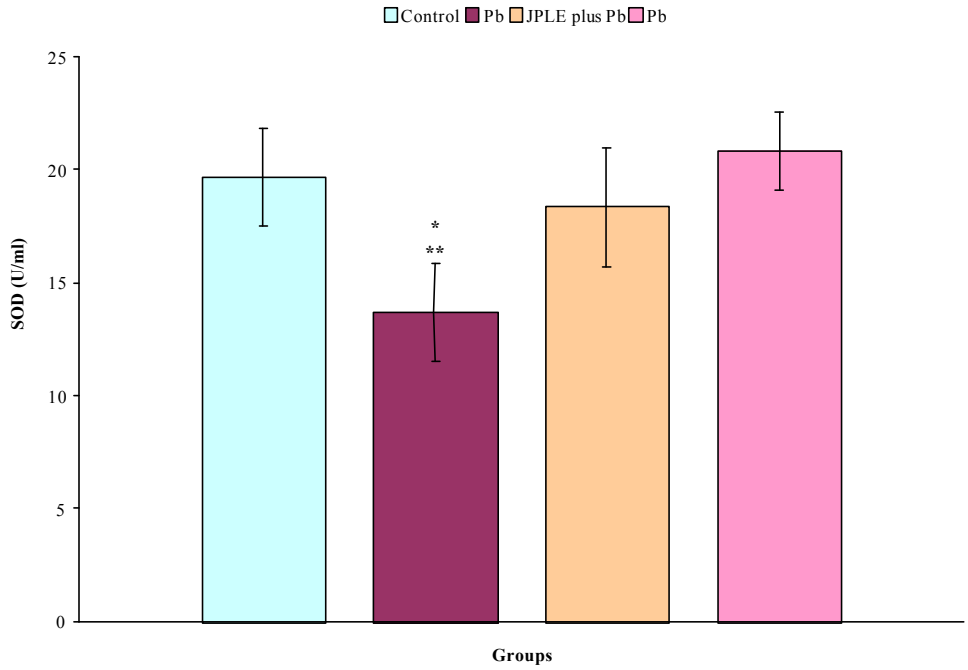

Fig. 6: Level of serum SOD in control, Pb, JPLE plus Pb and JPLE treated rats after six weeks
* indicates a significant difference between control and treated groups
** indicates a significant difference between rats treated with Pb and JPLE plus Pb and JPLE extract

parameter was notably unchanged in rats supplemented with JPLE. In comparison with control rats, the levels of serum AST were markedly increased in rats exposed to Pb (+ 57.1%, $P \leq 0.001$) and JPLE plus Pb (+ 18.3%, $P \leq 0.002$). Insignificant change was noted in the level of serum ALT in rats supplemented with JPLE (Fig. 2).

Figure 3 showed the level of serum ALP in all experimental groups. Pb administration to normal rats significantly increased the level of serum ALP (+ 58.0%, $P \leq 0.001$) compared with control rats. Statistically increase in the level of serum ALP was observed in JPLE plus Pb treated rats (+ 22.9%, $P \leq 0.01$) compared with rats of group 1. On the other hand, no statistically significant difference was observed in the level of serum ALP in JPLE treated rats compared with control rats. Serum total bilirubin level was statistically enhanced in rats exposed to Pb (+ 64.5%, $P \leq 0.002$) compared with control rats. Rats supplemented with JPLE plus Pb and JPLE showed insignificant change in the level of serum total bilirubin (Fig. 4).

Figure 5 showed the level of serum GSH in control, Pb, JPLE plus Pb and JPLE treated rats. Significant decreases in the level of serum GSH were observed in rats treated with Pb (-34.3%, $P \leq 0.001$) and JPLE plus Pb (- 14.2%, $P \leq 0.01$) compared with control rats. Moreover, no statistically significant difference was noted in the level of serum GSH in rats supplemented with JPLE compared with control rats. Relative to the control rats, the experimental rats treated with Pb exhibited significantly decline in the level of serum SOD (- 30.4%, $P \leq 0.000$). In addition, no statistically significant differences were noted in the level of serum SOD in JPLE plus Pb and JPLE treated rats compared with control rats (Fig. 6).

DISCUSSION

The present study is the first experimental investigation designed to evaluate whether supplementation of JPLE would have hepatoprotective effect on Pb induced liver injury. The present study showed that the administration of Pb for six weeks induced an elevation in the levels of serum ALT, AST, ALP and total bilirubin in rats, since necrosis or membrane damage releases these parameters into circulation, which agrees with the previously reported results [25]. These biochemical parameters are important biomarkers of liver function. The observed increase in the levels of ALT, AST, ALP and total bilirubin are the major diagnostic symptoms of hepatic damage and diseases [26-30]. Moreover, serum or plasma enzyme levels have been used as markers for monitoring chemically induced tissue damages [31-33]. Damage of hepatocytes is reflected by an elevation in the levels of hepatic specific enzymes (ALT, AST and ALP), these are cytoplasmic in lection and are released in to circulation after cellular damage [34]. The increase in serum total bilirubin may be owing to blockage of bile ductules as the inflammation and fibrosis in the portal triads and/ or due to regurgitation of conjugated bilirubin from the necrotic hepatocytes to sinusoids [35]. Additionally, ALT, AST, ALP and total bilirubin will leak into the serum resulting in elevating their serum concentrations. Serum levels of these parameters are very sensitive markers employees in diagnosis of liver diseases [36]. Previous experimental studies showed that the exposure to Pb caused statistically increases of these parameters with histological alterations of liver structure. [6, 37-42].

The present study showed that Pb induced oxidative stress which confirmed by the decrease of serum GSH and SOD levels. These findings clearly showed that Pb induced oxidative stress in male rats. Oxidative stress has been shown to be involved in the pathophysiology of many diseases. Moreover, the results obtained in present study are in agreement with previous studies which indicated that the levels of GSH, SOD and other oxidative markers were changed in rats exposed to Pb [6, 43, 44].

In the present study, JPLE treatment significantly attenuated the alteration levels of ALT, AST, ALP, total bilirubin, GSH and SOD. This indicated the effectiveness of JPLE in prevention of Pb toxicity. From the present findings, the possible mechanism of JPLE attributed to its antioxidant roles which evaluated by GSH and SOD levels. The petroleum ether fraction of *J. procera* showed significant activity as hepatoprotective when investigated against carbon tetrachloride (CCl_4) induced liver injury in Wistar male rats [45]. Al-Attar *et al*. [46] studied the influence of JPLE on thioacetamide (TAA)-induced hepatic cirrhosis in male mice. JPLE shown pharmacological influence against the histopathological and physiological alterations induced by TAA. The authors suggested that the supplementation of JPLE may act as antioxidant agents and could be an excellent adjuvant support in the therapy of hepatic cirrhosis induced by TAA. The ethyl acetate fraction of juniper leaves was investigated for its hepatoprotective effect in paracetamol induced hepatic damage in rats. This fraction treated hepatotoxic rats exhibited remarkably decrease in the elevated levels of

serum ALT, AST, ALP and bilirubin as compared to untreated hepatotoxic rats [47]. Al-Khedaide [48] investigated the anti-inflammatory effect of JPLE on rats exposed to cytotoxicity caused experimentally by streptozotocin (STZ). STZ induced inflammation within hepatic tissues which clearly reduced in hepatic tissues of both insulin and JPLE cotreated groups.

In conclusion, the present study demonstrated that the administration of Pb has a potential hepatotoxic effect in male rats. The biomarkers of liver injury (ALT, AST, ALP and total bilirubin) and oxidative stress markers (GSH and SOD) alterations induced by exposure to Pb were improved under the treatment effect of JPLE. The hepatoprotective effect of JPLE was attributed to the antioxidant activity. This study therefore suggests that JPLE is a useful preventive agent against the effect of Pb due to its antioxidant properties. Further investigations are required to study the effects of different concentrations and doses of JPLE against Pb toxicity and to explore exactly the mechanism action of JPLE against Pb induced physiological and biochemical disturbances.

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