La Prensa Medica Argentina

Research Article

# Immunomodulatory and Antioxidant Protective Effect of *Zingiber officinale*, in Lead Intoxicated Rat

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**Rec date:** Oct 04, 2014 **Acc date:** Nov 27, 2014 **Pub date:** Dec 01, 2014

## Abstract

**Background and Aim:** *Zingiber officinale* (ZO) is commonly used as one of natural food additives. This study was designed to evaluate immunomodulatory and antioxidant effect of *Zingiber officinale* extract (ZO) against lead toxicity in rats.

**Material and Methods:** Forty eight male albino rats were divided into 6 equal groups and treated daily for 21 days. Group I; normal control, Group II treated with lead acetate in drinking water at a dose of 1000 ppm. Groups III and IV received 1000 ppm of lead and administrated orally ZO ethanol extract at 200 and 400 mg/kg bw doses, respectively. Groups V and VI, were administrated orally ZO extract at doses 200 and 400 mg /kg bw daily, respectively. At the end of the treatment period, blood samples were collected from all groups to assess some selective humoral immunological and biochemical parameters.

**Results:** In the lead exposed group, Tumor necrosis factor–α (TNF α), Interleukin-1β (IL-1 β), Interleukin 6 (IL-6), Interleukin 10 (IL-10) and malnodiladhyide (MDA) were significantly increased compared with the control group, while gamma interferon (IFN-γ), glutathione (GSH), superoxide dismutase (SOD), total antioxidant (TAC),were decreased. Regarding, liver and renal markers, in lead treatment group, there were significantly increased in the activities of amino transferases (ALT, AST) urea; creatinine and phosphorous, while total plasma proteins, albumin and calcium were significantly decreased. The ZO extract alone at the two tested doses did not induce any significant changes in hepatorenal markers, while the antioxidant markers were significant increase. ZO extract in combination with cadmium significantly reduced the elevation of serum IL-1, IL-6, TNF, IL-10 and MDA, in addition to augmenting the antioxidant enzyme activities. Moreover, ZO ameliorate lead induced hepatorenal damage.

**Conclusion:** It could be concluded that the ZO extract has a potential immunomodulatory, antioxidant activity and a protective effect against lead toxicity.

**Keywords** *Zingiber officinale* (ZO); Immunomodulatory; Antioxidants; Lead acetate; Rats

## Introduction

Lead is considered as one of the most important non-essential heavy metal contaminants in the environment. Lead is a highly toxic substance, exposure to which can produce a wide range of adverse health effects. Although different ages can suffer from the effects of lead, young ages are, in general, most susceptible to lead poisoning because their brains and central nervous systems are still developing. Exposure to lead can occur through different means such as deteriorating paint, household dust, bare soil, contaminated air, food and drinking water [1].Lead poisoning usually occurs from repeated exposure to small amounts of lead [2].

The pathogenesis of lead toxicity is multifactorial, as lead directly interrupts enzyme activation, competitively inhibits trace mineral absorption, interrupting the structural protein synthesis, as well as, mimics biologically helpful minerals such as calcium, iron and zinc[3].Lead is toxic to many organs and tissues, including nephrotxiciy, hepatoxicity, oxidative stress and depletion of antioxidant system. In addition, the immunosuppressive effect has been decoumnted with lead toxicity [3,4].

Natural products, and their active ingredients, as sources for new drug discovery and treatment of diseases have attracted attention in recent years. Ginger, the rhizome of *Zingiber officinale*, is one of the most widely used species of the ginger family (Zingiberaceae) and is primarily used to treat nausea, but it is also used as an anti-inflammatory, a pain remedy, a warming remedy, antioxidant and a cholesterol-lowering herb [5].The major strong compounds in ginger, from studies of the lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone and paradol [6]. The compound gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products. Gingerol is formed in the plant from phenylalanine, malonate and hexonate [6].The main pharmacological actions of ginger and compounds isolated there from, include immuno-modulatory, anti-tumorigenic, anti-inflammatory, anti-apoptotic, anti-hyperglycemic, anti-lipidemic and anti-emetic actions [7,8]. It is considered a safe herbal medicine with only few and insignificant adverse/side effects [9].

In addition, ginger is a strong anti-oxidant substance and may either mitigate or prevent generation of free radicals[10].Several studies have documented the antioxidant effect of ZO, in rats fed on a high-fat diet, in arsenic induced rat, and in paracetamol-induced hepatotoxicity rats, and in rats treated with radiation[11-14]respectively. These studies have revealed that treatment with Zingiber has significantly increased the SOD and GSH levels in liver homogenate. In light of the activity profile of ZO, the aim of the present study was to investigate the immunomodulatory,

antioxidant as well as hepatic and renal protective effects of *Zingiber officinale*'s extract against lead toxicity in rats.

## Material and Methods

### Materials

#### Experimental Animals

Forty eight male albino rats of body weight 150 ± 20 g were used in this study. The animals were kept in metal cages under strict hygienic conditions. The animals were ensured free from any infection. The rats were maintained on a standard laboratory diet and fresh water ad libitum.

#### *Zingiber officinale*

The root of ZO was purchased from a local market. They were identified by morphological and microscopic comparison, according to different standard texts by Botany Department, Mansoura University, Egypt.

### Methods

#### *Zingiber officinale* ethanol extraction

The ethanolic extract of ZO was obtained according to the procedure outlined by Mirsa et al. [15]. In brief, the dried and finely powdered of ZO powder (500 g) was mixed with one liter of 99.9 % ethanol. The mixture was kept at 37ºC for two days with occasional shaking. The mixture was then centrifuged at 2000 rpm for 10 min and the supernatant was collected. The solvent in the pooled supernatant was evaporated at room temperature, and then frozen. The residue obtained (8.75 g) was suspended in 175mL of distilled water

#### Experimental Design

Forty eight rats were randomly divided into six equal groups.

Group I: normal control, Group II received lead acetate 1000 ppm in drinking water for 21 days according to Suradkar et al. [16].Groups III and IV were treated with ZO ethanol extract at doses of 200 and 400 mg/kg b wt, respectively, and were given lead acetate daily for 21 days. Groups V and VI were administrated, orally, ZO ethanolic extract at doses of 200 and 400 mg/kg b wt, respectively. At the end of experiment period, blood samples were obtained from all groups and serum samples were separated for estimation of some selective immunological and serum biochemical parameters. All samples were analyzed in duplicate.

#### Some selective humoral immunological parameters

The humoral immunological parameters (Tumor necrosis factor– α (TNF α), Interleukin 1β (IL-1 β), Interleukin 6 (IL-6), Interleukin 10 (IL-10), and gamma interferon (IFN-γ.) were measured by means of an Enzyme Amplified Sensitivity Immunoassay (EASIA, R & D Systems, Minneapolis, MN, USA) according to an enclosed pamphlet (Aushon Searchlight Biosystem; Billerica, MA). The lower detection limits of measurements were 1.5 pg/mL for IL-1β, 6.3 pg/mL for IL-6, 5.4 pg/mL for IL-10, 3.1 pg/mL for TNFα, and 6.2 pg/mL for IFN-γ. The data are presented as pg cytokine/mL serum.

#### Serum biochemical analysis

Antioxidant markers, malondialdehyde (MDA), reduce glutathione (GSH), superoxide dismutase (SOD), were determined from undiluted serum samples, using commercially available ELISA Kits (Cayman Chemical Co. USA). The plates were read at 450 nm and a correction wavelength of 550 nm was measured on a computerized automated microplate ELISA reader. ALT, AST, Alkaline phosphatase, total protein, albumin, uric acid, urea, creatinine, calcium and phosphorous (Cresent Diagnostic Co. KSA) were estimated spectrophotometeically (BM- Germany-5010) according to a standard procedure (enclosed pamphlet).

#### Statistical Analysis

Serum biochemical parameters were analyzed by analysis of variance, one way (ANOVA) using SPSS statistical software. The mean and standard deviation were calculated for each variable. The Pearson omnibus normality test was used to assess the normality of data distribution. Data were normally distributed, therefore, post hoc LSD multiple comparison was used to assess statistical differences among different groups. For all statistical examinations, the results were considered significant at $p < 0.05$

## Results

### Cytokines Parameters

The serum cytokines IL-1β, TNF α, IL-6 and IL-10 were significantly higher in lead-treated group, while the serum level of IFN-γ, was significantly decreased when compared with the control. ZO treated groups rats showed a significant decreasedIL-10 at high dose 400mg/ Kg bw when compared with control rats, while other cytokines (IL-1β, TNF α, IL-6, IFN-γ) showed no significant changes. Lead and ZO administrated groups no significant changes were observed in the (IL-1β, TNF α, IFN-γ, IL-10) cytokine serum level, while IL-6 showed a significant increase when compared with the control group as shown in (Table 1).

| Group | TNF α Pg/mL | IL-1β Pg/ml | IL-6 Pg/mL | IFN-γ Pg/mL | IL-10 Pg/mL |
|---|---|---|---|---|---|
| Gr-1 | 21.67 ± 1.3$^{b}$ | 34.15± 2.8$^{c}$ | 26.82± 4.8$^{c}$ | 40.36± 4.1$^{a}$ | 9.55± 0.61$^{b}$ |
| Gr-2 | 38.19±4.5$^{a}$ | 51.15± 4.6$^{a}$ | 34.12 ± 5.2$^{a}$ | 32.04 ± 4.3$^{b}$ | 13.21 ± 0.42$^{a}$ |
| Gr-3 | 24.26± 1.4$^{b}$ | 48.18± 4.4$^{b}$ | 33.85± 4.2$^{ab}$ | 34.71± 3.9$^{b}$ | 12.65 ± 0.64$^{a}$ |

| Gr-4 | 23.75 ± 1.9$^{b}$ | 38.85± 4.5$^{c}$ | 30.18 ± 3.2$^{ab}$ | 44.82 ± 5.7$^{a}$ | 9.25± 0.52$^{b}$ |
|---|---|---|---|---|---|
| Gr-5 | 20.94± 1.2$^{b}$ | 35.25 ± 3.7$^{c}$ | 24.85± 4.8$^{c}$ | 42.74 ± 3.7$^{a}$ | 9.12 ± 1.4$^{b}$ |
| Gr-6 | 22.68± 2.1$^{b}$ | 31.19 ± 3.4$^{c}$ | 27.92± 4.6$^{c}$ | 44.38 ± 4.6$^{a}$ | 7.02 ± 1.3$^{c}$ |

**Table 1:** The effect of lead and *Zingiber officinale* extract on selective cytokine markers (mean ± SE) 21 days post treatment. Gr-1: Control, Gr-2: Lead 1000 ppm; Gr-3: Lead & ZO 200 mg; Gr-4: Lead & ZO 400 mg; Gr-5: ZO 200 mg; Gr-6: ZO 400 mg. Means in the same column not followed by the same letter differ significantly ($P < 0.05$)

## Antioxidant markers and lipid peroxidation

The antioxidant markers, GSH, SOD and TAC were significantly decreased in the lead-treated group as compared to the control group. In addition, lipid peroxidation (MDA) was significantly higher in the lead-treated group when compared with the control group. On the other hand, treatment with ZO extract alone at a dose 400 mg/ Kg bw caused a significant increase in GSH and TAC as compared to the control group. The antioxidant markers, GSH, SOD and TAC as well as lipid peroxidation (MDA), in the lead and ZO at higher dose did not significantly differ from those of the control group as displayed in (Table-2).

| Group | GSH μmol/L | SOD U/ml | Total Antioxidant μmol/L | Malnoaldihyide mmol/dl |
|---|---|---|---|---|
| Gr-1 | 9.85± 0.41$^{b}$ | 5.42 ± 0.15$^{a}$ | 4.38 ± 0.16$^{b}$ | 17.15 ± 0.82$^{b}$ |
| Gr-2 | 5.91± 0.24$^{d}$ | 3.12 ± 0.24$^{b}$ | 3.01 ± 0.21$^{c}$ | 22.85 ± 1.10$^{a}$ |
| Gr-3 | 7.10±0.13$^{c}$ | 3.78 ± 0.22$^{b}$ | 3.12 ± 0.29$^{c}$ | 17.91 ± 1.43$^{b}$ |
| Gr-4 | 9.31± 0.31$^{b}$ | 5.09 ± 0.32$^{a}$ | 4.12 ± 0.18$^{b}$ | 17.82 ± 0.84$^{b}$ |
| Gr-5 | 10.15± 0.38$^{b}$ | 5.51 ± 0.26$^{a}$ | 4.42 ± 0.15$^{b}$ | 17.01 ± 1.02$^{b}$ |
| Gr-6 | 12.11 ± 0.37$^{a}$ | 5.85 ± 0.36$^{a}$ | 6.01 ± 0.20$^{a}$ | 17.12 ± 1.05$^{b}$ |

**Table 2:** Some selective antioxidant markers (mean ± SE) 21 days post treatment with lead and *Zingiber officinale*. Gr-1: Control, Gr-2: Lead 1000 ppm; Gr-3: Lead & ZO 200 mg; Gr-4: Lead & ZO 400 mg; Gr-5: ZO 200 mg; Gr-6: ZO 400 mg. Means in the same column not followed by the same letter differ significantly ($P < 0.05$)

## Hepatic Markers

Results presented in Table 3 showed a significant increase in the ALT and AST serum activities, significant decrease in total protein and albumin, and a non-significant change in alkaline phosphatase in the lead-treated group when compared with the control group. All tested parameters were none significantly changed in ZO treated group alone, as well as in lead and ZO treated group (400 mg/ Kg bw) when compared with the control group as shown in (Table 3).

| Group | ALT IU/L | AST IU/L | ALP IU/L | T. Protein g/dl | Albumin g/dl |
|---|---|---|---|---|---|
| Gr-1 | 38.6 ± 3.51$^{c}$ | 41.1 ± 3.52$^{c}$ | 121.9 ± 9.25$^{a}$ | 7.51 ± 0.61$^{a}$ | 3.74 ± 0.34$^{a}$ |
| Gr-2 | 60.5 ± 4.21$^{a}$ | 72.1 ± 4.12$^{a}$ | 136.4 ± 9.16$^{a}$ | 6.02 ± 0.35$^{b}$ | 2.61 ± 0.26$^{b}$ |
| Gr-3 | 47.9 ± 4.24$^{b}$ | 58.8 ± 5.24$^{b}$ | 126.1 ± 8.46$^{a}$ | 7.22 ± 0.36$^{a}$ | 3.54 ± 0.31$^{a}$ |
| Gr-4 | 44.1 ± 5.22$^{bc}$ | 46.1 ± 4.21$^{bc}$ | 123.5 ± 8.65$^{a}$ | 7.31 ± 0.30$^{a}$ | 3.64 ± 0.25$^{a}$ |
| Gr-5 | 37.81 ± 3.12$^{c}$ | 42.9 ± 3.02$^{c}$ | 118.5 ± 8.05$^{a}$ | 7.49 ± 0.42$^{a}$ | 3.75 ± 0.31$^{a}$ |
| Gr-6 | 39.21 ± 4.14$^{c}$ | 44.1 ± 3.65$^{c}$ | 122.6 ± 7.91$^{a}$ | 7.54 ± 0.39$^{a}$ | 3.91 ± 0.35$^{a}$ |

**Table 3:** Some selective liver markers (mean ± SE) 21 days post treatment with lead acetate and *Zingiber officinalis*. Gr-1: Control, Gr-2: Lead 1000 ppm; Gr-3: Lead &ZO 200 mg; Gr-4: Lead & ZO 400 mg; Gr-5: ZO 200 mg; Gr-6: ZO 400 mg. Means in the same column not followed by the same letter differ significantly ($P < 0.05$)

### Renal Markers

(Table-4) display, renal function test, revealed that urea, creatinine and phosphorous levels were higher in groups administrated with lead in comparison with the control group, while the calcium serum level was significantly decreased. Uric acid, however, did not significantly change in the lead treated group when compared with the control group. There were none significant changed in renal markers in ZO treated group alone, as compared to the control group. Results also indicated that urea, uric acid and phosphorous levels of lead and ZO at higher doses treated groups, did not significantly change when compared with the control group.

| Group | Urea mg/dL | Creatinine mg/dL | Uric Acid mg/dL | Calcium mg/dL | Phosphorous mg/dL |
|---|---|---|---|---|---|
| Gr-1 | 36.1 ± 3.15$^{b}$ | 0.46 ± 0.05$^{d}$ | 0.96 ± 0.17$^{a}$ | 9.1 ± 0.82$^{a}$ | 4.24 ± 0.32$^{b}$ |
| Gr-2 | 59.2 ± 5.11$^{a}$ | 0.85 ± 0.09$^{a}$ | 1.19 ± 0.22$^{a}$ | 7.4 ± 0.65$^{b}$ | 5.82 ± 0.27$^{a}$ |
| Gr-3 | 54.1 ± 4.38$^{a}$ | 0.61 ± 0.07$^{b}$ | 1.15 ± 0.14$^{a}$ | 8.6 ± 0.97$^{b}$ | 4.41 ± 0.17$^{b}$ |
| Gr-4 | 41.1 ± 4.78$^{b}$ | 0.54 ± 0.06$^{c}$ | 1.12 ± 0.15$^{a}$ | 8.9 ± 0.67$^{b}$ | 4.31 ± 0.25$^{b}$ |
| Gr-5 | 38.2 ± 3.52$^{b}$ | 0.45 ± 0.06$^{d}$ | 0.99 ± 0.18$^{a}$ | 9.3 ± 0.88$^{a}$ | 4.38 ± 0.28$^{b}$ |
| Gr-6 | 39.4 ± 4.08$^{b}$ | 0.49 ± 0.05$^{d}$ | 1.04 ± 0.20$^{a}$ | 9.05 ± 0.85$^{a}$ | 4.19 ± 0.34$^{b}$ |

**Table 4:** Some selective renal markers (mean ± SE) 21 days post treatment with lead acetate and *Zingiber officinale* Gr-1: Control, Gr-2: Lead 1000 ppm; Gr-3: Lead & ZO 200 mg; Gr-4: Lead & ZO 400 mg; Gr-5: ZO 200 mg; Gr-6: ZO 400 mg. Means in the same column not followed by the same letter differ significantly ($P < 0.05$)

## Discussion

Many cytokines contribute to the inflammatory process by activating leukocytes. Interleukin, IL-1β, and IFN-γ, together with TNF-α, play an important role in the onset of inflammatory processes that regulate the expression of other cytokines and chemokines. IL-1β, IL-6 and TNF- α help in the acute phase response by acting on a variety of cells [17]. In addition, IL-6 a very important pro-inflammatory cytokine, known as a traditional marker of inflammation, not only promotes the induction of acute phase proteins, but may also be involved in the regulation of the transition from acute to chronic inflammation and stimulation of T- and B-lymphocytes [17].The results of the present study revealed a significant increase in IL-1β, IFN-γ, TNF-α, IL- 6, while IL-10 was significantly decreased in the lead-treated group compared with the control group. Elevation pro-inflammatory cytokines after exposure to heavy metals has been reported by different research groups [17-21].In the lead and *Zingiber officinale* treated groups, the above interleukin levels were reduced towards the control level, especially in the ZO high dose group. ZO inhibits production of TNF-α, IL-1β, and nitric oxide from LPS-stimulated Macrophages [22].

Interleukin (IL)-10 is a pleiotropic, immunoregulatory cytokine that is important in protecting the host from infection-associated immunopathology, autoimmunity, and allergy. IL-10 was initially characterized as a T helper $(TH)_2$ specific cytokine [23].It is now known that almost all cells of both the innate and adaptive arms of the immune system can express IL-10 [24]. In this work, IL-10 showed a significant decrease in lead exposed group compared with the control. IL-10-deficient mice develop prolonged and exacerbated fever in response to lipopolysaccharide (LPS) [25]. IL-10-deficiency also aggravates the autoimmune pathology in a range of experimental models, including rheumatoid arthritis [26] and experimental systemic lupus erythematosus[27]. In the lead-treated group with *ZO* extracts, the IL-10 was significantly increased compared to lead group, however, the increase was not significant when compared with the control group. The immunomodulatory effect of ZO has been recently documented [8].

Oxidative stress is defined as an imbalance between local reactive oxygen species (ROS) production and anti-oxidative mechanisms [28].To avoid redox imbalance and oxidative damage; aerobic organisms possess efficient biochemical defense systems such as superoxide dismutase (SOD), catalase (CAT), total antioxidant (TAC), and glutathione peroxidase (GPx). Antioxidants have been shown to protect hepatocytes against lipid peroxidation or inflammation; therefore, they prevent the occurrence of hepatic necrosis. SOD and GSH are the major antioxidants involved in the defense mechanism against lipid peroxidation in biological systems and convert active oxygen molecules into non-toxic compounds [29].

The antioxidant activity of ZO have been previously investigated and reported to be variable[11,13,14].Results from this investigation demonstrated that treatment with *Zingiber officinale* significantly increase GSH, SOD and TAC(Tables 1).Numerous reports dealing with the antioxidative and free radical scavenging potential of *Zingiber officinale* extracts as well as their particular components, i.e., gingerol, acid resins, vitamin C compounds, folic acid, inositol, chlorine, pathothenic acid, sesquiterpene, vitamin B3 & B6, volatile oils and bio trace elements have been published [10].These bioactive components with antioxidative and antiproliferative activities are also constituents of the ZO extract used in the present study. The antioxidant barriers of the ZO extracts plays a role in the inhibition of ROS generation, ROS neutralization, or the induction of endogenous antioxidants as recently obtained [12,13].

The, lipid peroxidation plays an important role in carcinogenesis and may lead to the formation of several toxic products, such as malondialdehyde [30]. In the present study, malondialdehyde level showed significant increase in lead treatment groups and reduced in ZO treated group (400 mg/ Kg. b wt) compared to the control. This result is in agreement with results obtained by other researchers [31], who found that there was a significant decrease in lipid peroxidation

groups treated with ZO when compared to animals treated with lead alone. The observed reductions in the level of lipid perioxidation in ZO treated animals were presumably due to its ability to scavenge the hydroxyl and peroxyl radicals. Moreover, it was confirmed that, the ginger extract is a powerful free hydroxyl (OH.) scavenger, resulting in inhibiting lipid peroxidation in the linoleic acid model system [32].

In the present study, the antioxidant system, reduced glutathione, total antioxidant and superoxide dismutase activities were significantly decreased in the serum of lead exposed rats while there was an increase in malnoaldihyide in accordance with previous studies [33-35].Additionally, others have concluded a high correlation between decreased superoxide dismutase and decreased copper concentrations in the blood of animals [36]. Lead induced copper deficiency has been recorded by Adler and colleagues [37], where the authors indicated that this effect of lead decreased scavenging of ROS resulted in oxidative damage [38].

In the present investigation(Tables 1-3), it was found that lead treated group with ZO extract , showed significant increase in the reduced levels of GSH, SOD and TAC while malnoaldihyide level was reduced. Previous reports in the literature have indicated that ZO has an antioxidant potential, inhibited the non-enzymatic lipid peroxidation and free radical scavenging effects, thereby it may protect cellular components against free radical induced damage [11-14].

Liver enzymes, such as AST, ALT, and ALP are markers for liver's function and integrity. These enzymes are usually elevated in hepatotoxicity or mild hepato-cellular injury [38]. Results from this study revealed that, administration of lead acetate to rats led to liver damage; this is manifested by a significant rise in AST and ALT activities, and conversely a decrease in total protein and albumin levels. These results are in agreement with those obtained by others [39,40,41],who reported elevated liver enzyme activities in rats intoxicated with lead. The oxidative stress contributes an important generating factor in the pathogenesis of acute and chronic liver diseases [42-44]. Moreover, the increased levels of AST and ALT could be attributed to the damaged structural integrity of the liver. Lead causes cell lysis by affecting the $K^{+-}$ $Ca^{2+}$ channels; cytoskeleton alterations induce increased susceptibility to lysis [45].

Lead and ZO extract treated groups, showed significant reduction in ALT and AST levels compared with lead treated group (Tables 1, Table 2, and Table 3). In the same manner, it was noted that the hepatoprotective effect of the aqueous ethanol extract of ZO against acetaminophen-induced acute toxicity is mediated either by enhancing hepatic antioxidant (GSH and SOD) or due to its direct radical scavenging capacity. Debrupet al.[12] reported that treatment of arsenic intoxicated rats with gingerol, showed less accumulation of ROS and a significant increase in cell viability of hepatocyteets. Asmah et al. and Ghada et al. [13,14]documented hepatoprotective effect of ZO in rat intoxicated with paracetamol and radiation respectively. They concluded that generally reduced the oxidative stress as revealed from the increased activity of antioxidant biomarkers like CAT, SOD, GPx and GSH.

The results also demonstrated that the total plasma proteins and albumin levels were reduced in lead treated rats as a result of decreased hepatic capacity to synthesize protein (Tables 1, Table 2, and Table 3). The total protein level, including albumin level, will be depressed in hepatotoxic conditions due to defective protein biosynthesis in liver [46]. The hypoproteinemia and hypoalbuminemia in the present work is in agreement with results obtained by other researchers [33],who reported hypoproteinemia and hypoalbuminemia in rats received lead nitrate (5 mg/Kg bw) intraperitoneal daily for 30 days. Similarly, others [47], found a decrease in rat's hepatic total protein content in response to lead intoxication. The inhibitory role of lead in protein synthesis may be due to its damaging effect on DNA and RNA [41].Lead is associated with DNA damage through base pair mutation, deletion, or oxygen radical attack on DNA. Moreover, $Pb^{2+}$ disturbs intracellular $Ca^{2+}$ homeostasis and damages the endoplasmic reticulum, which in turn results in a reduction of protein synthesis [48].

With respect to the renal function, the present study shows that administration of lead acetate led to an increase in the serum creatinine, urea, phosphorous and decreased calcium levels. An elevation in serum urea, uric acid, and creatinine was observed by others in lead treated albino rats [49,50].In addition, hypocalcemia and hypephosphatemia were also reported[38]. On other hand Liua et al. [51], concluded that the chief mechanism of lead-induced nephrotoxicity was the enhancement of ROS generation and inhibition of the antioxidant enzyme system. Serum creatinine, urea, and phosphorous were significantly decreased in rats subjected to ZO, as compared to lead exposed rats. These findings indicate that ZO ameliorating nephrotoxic effect of lead by increased antioxidant markers in lead poisoning rats. The antioxidant effect of ZO has been documented by several authors [12]. Likewise, the liver markers (ALT, AST, and ALP) as well as renal markers (urea, creatnine and uric acid) were not significantly changed in ZO treated group. The ZO extracts are harmless on the liver and other tissues [33].

SOD, GSH, GPx and TAC are the major antioxidants involved in the defense mechanism against lipid peroxidation in biological systems; they convert active oxygen molecules into non-toxic compounds. They have been shown to protect hepatocytes against lipid peroxidation or inflammation; therefore, they prevent the occurrence of hepatic necrosis [43].In the present study, the hepato-protective and reno-protection of ZO extracts against lead toxicity is supported by a decrease in ALT and AST activities as well as creatinine and urea serum levels l, compared to lead exposed rats. Treatment of animals with ZO extracts alleviated such toxic effects of lead. The assumption of oxidative stress as a mechanism of lead toxicity suggests that the antioxidant action of ZO might play a role in the treatment of lead poisoning [12].

## Conclusion

In conclusion, we have demonstrated through this investigation that lead acetate can cause marked, immunosuppressive, oxidative damage in addition to inhibiting the activities of antioxidant enzymes. *Zingiber officinale* extract can be given as a dietary supplement and can provide protection against environmental toxic effects caused by lead without being substantially harmful itself.

## Competing Interests

The authors declare that they have no competing interests.

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