INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY
Volume: 2: Issue-3: July-Sept -2011 IJABPT ISSN 0976-4550

PROTECTIVE ROLE OF CORIANDRUM SATIVUM (CORIANDER) EXTRACTS AGAINST LEAD NITRATE INDUCED OXIDATIVE STRESS AND TISSUE DAMAGE IN THE LIVER AND KIDNEY IN MALE MICE.

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ABSTRACT : The present study describes antioxidant effect of *Coriandrum sativum* against lead nitrate induced toxicity in mice. Oxidative stress was induced in mice by a daily dose of lead nitrate (40 mg/kg body weight by oral gavage) for seven days. From day eight, after lead nitrate treatment, experimental animals received an oral dose of coriander extracts (aqueous extract - 300 mg/kg body weight and 600 mg/kg body weight; ethanolic extract - 250 mg/kg body weight and 500 mg/kg body weight) daily. The effect of these treatments in influencing the lead induced changes on hepatic and renal oxidative stress and biochemical changes along with histopathological alterations in soft tissues was studied. The data showed significant increase in liver and kidney LPO levels in animals treated with lead nitrate while the effect was attenuated by the plant extracts. Also, lead caused a significant decrease in antioxidant enzyme activity and this effect was reversed in groups treated with plant extract. Treatment with coriander significantly reduced the adverse effects related to most of biochemical parameters altered in animals treated with lead, related to hepatic and renal oxidative stress. Oral administration of Coriander to lead treated mice attenuated the deranged histopathological changes to some extent. It can be concluded from these results that *Coriandrum sativum* protects against lead toxicity and warrants the identification and isolation of active compounds responsible for its antioxidant effects.
Keywords: Oxidative stress, Lead nitrate, Hepatic, Kidney, *Coriandrum sativum*, Biochemical parameters

INTRODUCTION

Lead is known to induce a broad range of physiological, biochemical, and behavioural dysfunctions in laboratory animals and humans (Flora et al., 2006), including central and peripheral nervous systems (Bressler et al., 1999), haemopoietic system (Lanphear et al., 2000), cardiovascular system (Khalil-Manesh et al., 1993), kidneys (Poprawa and Kapusta, 2004), hepatic (Patra et al., 2001) and male (Lancranjan et al., 1975) and female reproductive systems (Ronis et al., 1998).

One of the major mechanisms behind heavy metal toxicity has been attributed to oxidative stress. Toxic metals increase production of free radicals and decrease availability of antioxidant reserves to respond to the resultant damage. A growing amount of data provide evidence that metals are capable of interacting with nuclear proteins and DNA causing oxidative deterioration of biological macromolecules (Leonard, 2004).

Considering that lead toxicity is currently one of the serious problem world wide, there is still no specific, reliable and safe treatment. Several metal chelators ($CaNa_2EDTA$ and DMSA) have been used to manage lead toxicity in the event of exposure but none are suitable in reducing lead body burden (Osweiler, 1999). Moreover these chelators in turn are potentially toxic (Gilman, 1991) and often fail to remove Pb burden from all body tissues (Cory-Slechta et al., 1987).

Thus, there has been an increased interest in the therapeutic potential of plant products or medicinal plants having antioxidant properties in reducing free radical-induced tissue injury (Gupta & Flora, 2005).

Coriandrum sativum (Common name: Coriander), belonging to family Umbelliferae, is a herb that is widely cultivated in India and is recognized for its carminative and cooling properties (Sairam, 1998). It was shown that coriander extracts have phenolic compounds and flavonoides, suggesting that these compounds contribute to the antioxidative activity (Helle Wangensteen, 2004). Phenolic substances such as flavonoids, cumarins, cinnamic acid and caffeic acids are believed to have antioxidant properties, which may play an important role in protecting cells and any organ from oxidative degeneration (Wiseman et al., 2000). Coriander suppresses the deposition of lead by chelating the metal (Aga, 2001). A sorbent prepared from coriander was found to have good efficiency in removing organic and methyl mercury from aqueous solutions (Karunasagar et al., 2005).

Coriander has been reported to exhibit several pharmacological effects such as as antifertility (Al-Said et al., 1987), antihyperglycemic (Eidi et al., 2009), anti-hyperlipidemic (Chithra & Leelamma, 1999), antiproliferative (Nakano et al., 1998), hypotensive (Burdock & Carabin, 2008) and digestive stimulant (Platel & Srinivasan, 2000).

In the light of aforementioned medical properties of coriander, this study was carried out to investigate the possible protective properties of coriander extracts on various oxidative stress and toxicity related biochemical parameters in liver and kidney of lead intoxicated mice.

MATERIALS AND METHODS

Experimental Plant Material

The plant *Coriandrum sativum* (seeds) was collected from Krishi Vigyan Kendra, Banasthali University, Rajasthan, India and was identified as a RCR 435 variety

Preparation of aqueous extract of *Coriandrum sativum*

Dried coriander seeds were ground to a fine powder, of which 100 g were added to 500 ml distilled water. After 24 h maceration was done at room temperature (37 ^{0}C), the mixture was then heated for 30 min in the water bath at 65 ^{0}C. The extract was filtered, concentrated by heating over the water bath (65 ^{0}C) and dried under vacuum (Gray & Flatt, 1999) with the yield of 5.9 % (w/ w). The extract was stored at 4 ^{0}C and used to treat animals as needed.

Preparation of alcoholic (ethanolic) extraction of *Coriandrum sativum*

The dried and powered seeds (200 g) were extracted successively with ethanol (800 ml) in a soxhlet extractor for 48 hours at 60 ^{0}C. After extraction, the solvent was evaporated to dryness at 50-55 ^{0}C by using a rotary evaporator and the extract left behind (yield was 9.8 %) was stored at 4 ^{0}C. It was dissolved in distilled water whenever needed for experiments.

Animals

Male Swiss albino mice weighing approximately 15-30 g (2 to 2.5 months) were obtained from Haryana Agricultural University, Hissar, India for experimental purpose. The Animal Ethics Committee of Banasthali University, Banasthali, India has approved the experimental protocol. All experiments were conducted on adult male albino mice (*Mus musculus* L.) weighing 25-35 g (3-4 month old). They were housed in polypropylene cages in an air conditioned room with temperature maintained at 25 °C ± 3 °C, relative humidity of 50 % ± 5 % and 12 h alternating light and dark cycles. The mice were provided with a nutritionally adequate chow diet (Hindustan lever Limited, India) and drinking water *ad libitum* throughout the study.

Chemicals

Lead nitrate was purchased from Central Drug House (India). All other chemicals used in the study were of analytical reagent and obtained from Sisco Research Laboratories (India), Qualigens (India/ Germany), SD fine chemicals (India), HIMEDIA (India) and Central Drug House (India).

Experimental design

Adult Swiss albino male mice were divided into 6 groups of 12 mice each and treated by oral gavage as follows:

Group I- Control (normal, untreated), received distilled water;

Group II- Lead nitrate treated group, received freshly dissolved $Pb(NO_3)_2$ in 1 ml distilled water at a dose of 40 mg/ kg body weight/ day;

Group III and Group IV were administered with aqueous coriander extract at a dose of 300 mg/ kg body weight and 600 mg/ kg body weight, respectively, by oral gavage once daily for 33 days from 8 day after beginning of lead nitrate exposure to the end of the experiment.

Group V and Group VI were administered with ethanolic coriander extract at a dose of 250 mg/ kg body weight and 500 mg/ kg body weight, respectively, by oral gavage once daily for 33 days from 8 day after beginning of lead nitrate exposure to the end of the experiment.

The dose for lead nitrate was decided on the basis of experiments conducted in the laboratory and the concentration of lead nitrate used in the experiment was 1/ 56 of LD_{50} (Plastunov & Zub, 2008). The plant doses were selected on the basis of experiments conducted in our own laboratory and on the basis of earlier published reports (Sushruta et al., 2006). After the administration of last dose, the animals were given a one-day rest and were killed under light chloroform anaesthesia. The hepatic and renal tissues were excised and divided into two parts; one part was fixed in 10% formalin for histological studies and the second part was homogenized in ice-cold buffer and utilized for various oxidative stress and biochemical analysis.

Oxidative stress and biochemical analysis

Liver and kidney were minced and homogenized (10 % w/ v) in ice-cold 0.1 M sodium phosphate buffer (pH-7.4). The homogenate was centrifuged at 10,000 rpm for 15-20 min at 4 °C twice to get enzyme fraction. The resultant supernatant was used for various biochemical assays.

LPO was estimated by thiobarbituric acid (TBA) reaction with malondialdehyde (MDA), a product formed due to the peroxidation of membrane lipids (Nwanjo & Ojiako, 2005). SOD activity was assessed according to the method of Marklund and Marklund (1974). CAT activity was assayed following the method of Aebi (1983). GSH content was determined according to the method of Ellman (1959). Activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assayed by the method of Reitman and Frankel (1957). Activities of acid phosphatase (ACP) and alkaline phosphatase (ALP) were determined according to the protocol described in laboratory practical manual (Sadashivam & Manickam, 1996). Total protein content was estimated by the method of Lowry et al. (1951) using bovine serum albumin as standard. The cholesterol level was determined by using cholesterol as a standard by the method of Zak's (1977).

Histopathology/ Histological Analysis

Liver and Kidneys were removed, washed in saline were fixed in buffered 10 %) formalin at room temperature for 72 h. After fixing the tissue, it was thoroughly washed under running water and dehydrated in ascending grades of ethyl alcohol, cleared and then embedded in soft paraffin. Tissue sections of about 6 µm were obtained, stained by Haematoxylin and Eosin and examined under light microscope.

Statistical analysis

Data are expressed as the Mean ± SEM. The data was analyzed using the Statistical Package for Social Science program (S.P.S.S. 11). Statistical analysis was done using analysis of variance (ANOVA) followed by Tukey test and the level of significance was set at $p < 0.05$.

RESULTS

Hepatic oxidative stress and antioxidant defense variables

Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on LPO and antioxidant related parameters in liver of various groups were assessed and are presented in Table 1.

Table (1): Antioxidant potential of Coriandrum sativum extracts on lipid peroxidation and antioxidant related variables in hepatic tissue of lead nitrate exposed mice.

Parameters	Group I Distilled water	Group II Lead nitrate (40 mg/ kg body weight)	Group III Lead nitrate (40 mg/ kg body weight) + aqueous coriander extract, low dose (300 mg/ kg body weight)	Group IV Lead nitrate (40 mg/ kg body weight) + aqueous Coriander extract, high dose (600 mg/ kg body weight)	Group V Lead nitrate (40 mg/ kg body weight) + ethanolic Coriander extract, low dose (250 mg/ kg body weight)	Group VI Lead nitrate (40 mg/ kg body weight) + ethanolic coriander extract, high dose (500 mg/ kg body weight)
LPO (nmole of MDA formed/ g of tissue)	111.58 ± 3.23	181.66 ± 0.69* (+62.80 %)	132.40 ± 0.71[a] (-27.11 %)	128.85 ± 0.46[a] (-29.07 %)	124.16 ± 0.64[a] (-31.65 %)	122.01 ± 0.47[a] (-32.83 %)
SOD (unit/ ml of tissue homogenate)	1.13 ± 0.04	0.72 ± 0.007* (-36.28 %)	0.90 ± 0.005[a] (+25 %)	0.94 ± 0.007[a] (+30.55 %)	0.97 ± 0.006[a] (+34.72 %)	1.02 ± 0.02[a] (+41.66 %)
CAT (µM of H2O2 degraded/ min/mg protein)	32.22± 0.47	21.14 ± 0.41* (-34.38 %)	21.12 ± 0.40 (+0.09 %)	24.50 ± 0.31[a] (+15.89 %)	25.75 ± 0.43[a] (+20.52 %)	25.27 ± 0.41[a] (+19.53 %)
GSH (mg/ g of tissue)	7.62 ± 0.14	1.80 ± 0.12* (-76.37 %)	3.40 ± 0.14[a] (+88.88 %)	3.57 ± 0.13[a] (+98.33 %)	4.33 ± 0.09[a] (+140.55 %)	4.94 ± 0.06[a] (+174.44 %)

Values are Mean ± S.E.M.; n= 12.
*P< 0.001 compared to normal animals.
[a]P< 0.001 compared to lead nitrate exposed animals.
[b]P< 0.01 compared to lead exposed animals.
[d]P< 0.05 compared to lead exposed animals.

Lead nitrate at a dose of 40 mg/kg body weight caused significant ($p < 0.001$) increase in the level of TBA-reactive product in liver and significant decrease in SOD and CAT activity, and GSH content, in comparison to control group (group I).
However, treatment with aqueous coriander extract along with lead nitrate caused a significant reduction ($p<0.001$for both low and high dose) in LPO level when compared with lead induced group. A significant increase ($p<0.001$ for both low and high dose) in the activity of SOD, CAT and GSH were observed after the treatment with aqueous coriander extract, in comparison to lead nitrate exposed group II.
Supplementation of ethanolic extract of coriander offered significant reduction in lipid peroxidation level in both groups, compared to group II ($p<0.001$for both low and high dose) while administration of the same dose significantly elevated the SOD, CAT and GSH activity in group V and VI, compared to lead group ($p<0.001$ for both low and high dose).

Renal oxidative stress and antioxidant defense variables
Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on LPO and antioxidant related parameters in kidney of various groups were assessed and are presented in Table 2.

Table (2): Antioxidant potential of Coriandrum sativum extracts on lipid peroxidation and antioxidant related variables in renal tissue of lead nitrate exposed mice.

Parameters	Group I Distilled water	Group II Lead nitrate (40 mg/ kg body weight)	Group III Lead nitrate (40 mg/ kg body weight) + aqueous coriander extract, low dose (300 mg/ kg body weight)	Group IV Lead nitrate (40 mg/ kg body weight) + aqueous Coriander extract, high dose (600 mg/ kg body weight)	Group V Lead nitrate (40 mg/ kg body weight) + ethanolic Coriander extract, low dose (250 mg/ kg body weight)	Group VI Lead nitrate (40 mg/ kg body weight) + ethanolic coriander extract, high dose (500 mg/ kg body weight)
LPO (nmole of MDA formed/ g of tissue)	99.80±2.66	138.60±0.93* (+38.87 %)	122.26±0.65[a] (-11.78 %)	123.57±0.70[a] (-10.84 %)	117.42±0.61[a] (-15.28 %)	112.53±0.66[a] (-18.80 %)
SOD (unit/ ml of tissue homogenate)	1.08±0.08	0.65±0.01* (-39.81 %)	0.70±0.008 (+7.69 %)	0.87±0.012[b] (+33.84 %)	0.92±0.01[a] (+41.53 %)	0.95±0.01[a] (+46.15 %)
CAT (µM of H2O2 degraded/ min/mg protein)	30.43±0.97	14.18±0.31* (+53.40 %)	16.48±0.28[d] (-16.22 %)	18.05±0.31[a] (-27.29 %)	23.55±0.36[a] (-66.07 %)	26.30±0.32[a] (-85.47 %)
GSH (mg/ g of tissue)	6.86± 0.15	2.18±0.04* (-68.22 %)	2.69±0.08[b] (+23.39 %)	2.95±0.04[a] (+35.32 %)	3.89±0.05[a] (+78 .44 %)	4.34±0.07[a] (+99.08 %)

Values are Mean ± S.E.M.; n= 12.
*P< 0.001 compared to normal animals.
[a]P< 0.001 compared to lead nitrate exposed animals.
[b]P< 0.01 compared to lead exposed animals.
[d]P< 0.05 compared to lead exposed animals.

The level of lipid peroxidation was significantly higher ($p<0.001$) in lead-treated animals (group II) than that of normal untreated mice. Whereas, significant decrease ($p<0.001$) in renal SOD, CAT activity, and GSH content of mice were observed in lead nitrate treated animals as compared with control group. After the treatment with aqueous coriander extract at a dose of 300mg/kg body weight and 600mg/ kg body weight, showed significant decrease ($p<0.001$) in the level of LPO was observed in comparison to lead nitrate-treated group. While the administration of same dose significantly elevated GSH content ($p<0.01$ and $p<0.001$ respectively), compared to lead nitrate treated animal (group II). In comparison to lead nitrate exposed animals (group II), SOD and CAT activity increased significantly in group IV but insignificantly in group III treated animals.
Supplementation of ethanolic coriander extract in animals registered a significant decrease ($p<0.001$for both low and high dose) in LPO, in both plant treated group, compared with lead treated group. Moreover, low and high dose of ethanolic *Coriandrum sativum* extract treatment led to significant ($p < 0.001$) elevation in the SOD, CAT and GSH content, when compared with group II animals.

Hepatic biochemical variables
Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on some hepatic biochemical variables in liver of various groups were assessed and are presented in Table 3.

Table (3): Antioxidant potential of Coriandrum sativum extracts on some hepatic biochemical variables in lead nitrate exposed mice.

Parameters	Group I Distilled water	Group II Lead nitrate (40 mg/ kg body weight)	Group III Lead nitrate (40 mg/ kg body weight) + aqueous coriander extract, low dose (300 mg/ kg body weight)	Group IV Lead nitrate (40 mg/ kg body weight) + aqueous Coriander extract, high dose (600 mg/ kg body weight)	Group V Lead nitrate (40 mg/ kg body weight) + ethanolic Coriander extract, low dose (250 mg/ kg body weight)	Group VI Lead nitrate (40 mg/ kg body weight) + ethanolic coriander extract, high dose (500 mg/ kg body weight)
AST (IU/ L)	32.08 ± 0.24	66.72 ± 1.0* (+107.98 %)	53.21 ± 0.99 [a] (-20.24 %)	49.57 ± 0.52 [a] (+25.70 %)	40.75 ± 0.66 [a] (+38.92 %)	38.84 ± 0.85 [a] (+41.78 %)
ALT (IU/ L)	48.46 ± 0.34	71.62 ± 0.95* (+47.79 %)	58.00 ± 0.79 [a] (-19.01 %)	55.42 ± 0.44 [a] (-22.61 %)	54.61 ± 0.41 [a] (-23.75 %)	52.27 ± 0.46 [a] (-27.01 %)
ACP (µM of PNP formed/min/g tissue)	12.62 ± 0.14	36.13 ± 0.05* (+186.29 %)	28.36 ± 0.13 [a] (-21.50 %)	20.41 ± 0.11 [a] (-43.50 %)	23.05 ± 0.02 [a] (-36.20 %)	20.97 ± 0.17 [b] (-34.8 %)
ALP (µM of PNP formed/min/g tissue)	17.03 ± 0.02	45.44 ± 0.13* (+ 166.82 %)	37.33 ± 0.12 [a] (-17.84 %)	30.69 ± 0.12 [a] (-32.46 %)	34.96 ± 0.06 [a] (-23.06%)	27.43 ± 0.13 [a] (-39.63 %)
Protein (g/ dl)	8.25 ± 0.26	5.75 ± 0.03* (-32.51 %)	5.87 ± 0.05 (+2.08%)	6.24 ± 0.07 (+8.52 %)	6.45 ± 0.10 [b] (+12.17 %)	6.80 ± 0.06 [a] (+18.26 %)
Cholesterol (mg/g of tissue)	24.48 ± 0.39	51.70 ± 0.30* (+111.19 %)	38.49 ± 0.52 [a] (-25.55 %)	36.27 ± 0.45 [a] (-29.84 %)	31.55 ± 0.35 [a] (-38.97 %)	29.74 ± 0.23 [a] (-42.47 %)

Abbreviations- AST: Aspartate transaminase (IU/ L); ALT: Alanine transaminase (IU/ L); ACP: Acid phosphatase (µM of PNP formed/min/g tissue); ALP: Alkaline phosphatase (µM of PNP formed/min/g tissue); Total protein (g/ dl); Total cholesterol (mg/ g of tissue)
Values are Mean ± S.E.M.; n= 12.
*P< 0.001 compared to normal animals.
[a]P< 0.001 compared to lead nitrate exposed animals.

It is clear from the results that treatment with lead nitrate showed a significant elevation in some biochemical parameters which include AST, ALT, ACP, ALP and total cholesterol as compared to control group animals ($p<0.001$). The mean value of total protein was significantly decreased by lead nitrate intake when compared with control ($p<0.001$).
The AST, ALT, ACP, ALP and total cholesterol levels in liver homogenate were significantly reduced by administration of aqueous coriander extract at a dose of 300 and 600 mg/kg body weight ($p < 0.001$ vs. lead nitrate intoxicated mice). In comparison to lead nitrate exposed animals (group II), total protein increased insignificantly in groups III and IV.
Compared with the lead nitrate control (group II), administration of ethanolic *Coriandrum sativum* extract at a dose of 250 and 500 mg/kg body weight resulted in significant decrease
($p < 0.001$) of hepatic AST, ALT, ACP, ALP and total cholesterol levels. The total protein content in groups V and VI significantly ($p<0.01$ and $p < 0.001$ respectively) increased in hepatic tissues, when compared with lead control values (group II).

Renal biochemical variables
Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on some renal biochemical variables in kidney of various groups were assessed and are presented in Table 4.

Table (4): Antioxidant potential of Coriandrum sativum extracts on some renal biochemical variables in lead nitrate exposed mice.

Parameters	Group I Distilled water	Group II Lead nitrate (40 mg/ kg body weight)	Group III Lead nitrate (40 mg/ kg body weight) + aqueous coriander extract, low dose (300 mg/ kg body weight)	Group IV Lead nitrate (40 mg/ kg body weight) + aqueous Coriander extract, high dose (600 mg/ kg body weight)	Group V Lead nitrate (40 mg/ kg body weight) + ethanolic Coriander extract, low dose (250 mg/ kg body weight)	Group VI Lead nitrate (40 mg/ kg body weight) + ethanolic coriander extract, high dose (500 mg/ kg body weight)
AST (IU/ L)	22.01±0.30	52.67±0.93* (+139.30 %)	41.34±0.96[a] (-21.51 %)	37.74±0.71[a] (-28.34 %)	37.00±0.60[a] (-29.75 %)	31.20±0.66[a] (-40.76 %)
ALT (IU/ L)	17.72±0.30	45.43±1.16* (+ 156.37 %)	32.20±0.67[a] (-29.12 %)	34.18±0.51[a] (-24.76 %)	28.06±0.54[a] (-38.23 %)	25.95±0.28[a] (-42.87 %)
ACP (µM of PNP formed/min/g tissue)	13.20±0.07	35.22±0.16* (+166.81 %)	24.50±0.15[a] (-30.43 %)	19.95±0.06[a] (-43.35 %)	21.45±0.15[a] (-39.09 %)	17.55±0.14[a] (-50.17 %)
ALP (µM of PNP formed/min/g tissue)	17.17±0.08	49.26±0.12* (+186.89 %)	40.62±0.13[a] (-17.53 %)	28.46±0.15[a] (-42.22 %)	38.47±0.14[a] (-21.90 %)	26.08±0.08[a] (-47.05 %)
Protein (g/ dl)	5.75±0.26	2.93±0.12* (-49.04 %)	2.97±0.04 (+1.36 %)	3.01±0.03 (-2.73 %)	3.87±0.05[a] (-32.08 %)	4.02±0.02[a] (-37.20 %)
Cholesterol (mg/g of tissue)	18.38±0.21	45.29±0.33* (+ 146.40 %)	34.45±0.49[a] (-23.93 %)	32.62±0.44[a] (-27.97 %)	28.21±0.43[a] (-37.71 %)	24.36±0.44[a] (-46.21 %)

Values are Mean ± S.E.M.; n= 12.
*P< 0.001 compared to normal animals.
[a]P< 0.001 compared to lead nitrate exposed animals.

In comparison to normal control mice, a significant ($p < 0.001$) increase in the total cholesterol level and activities of marker enzymes such as AST, ALT, ACP and ALP were recorded in lead nitrate exposed mice. A significant ($p < 0.001$) decrease in total protein level followed by lead nitrate exposure was also noticed in group II, as compared to control animals (group I).

Treatment with low and high dose of aqueous coriander extract significantly ($p < 0.001$) reduced lead nitrate induced increase in the levels of total cholesterol, AST, ALT, ACP and ALP, as compared to lead nitrate treated animals (group II). On the other hand, lead nitrate-induced depletion in protein content was insignificantly prevented by treatment with aqueous coriander extract at a dose of 300 mg/kg body weight and 600 mg/kg body weight, when compared with lead treated group II animals.

Administration of ethanolic coriander extract at 250 and 500 mg/kg body weight significantly ($p < 0.001$) suppressed the increased levels of total cholesterol, AST, ALT, ACP and ALP, when compared with lead nitrate treated animals (group II). Total protein level recovered significantly ($p < 0.001$) in response to 250 and 500 mg/kg body weight of ethanolic coriander extract, in comparison to lead intoxicated mice (group II).

Histological examination

Histology of hepatic tissue

Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on hepatic histologic images of experimental mice of various groups were examined (Figure 1-6).

Group I (Control, Untreated, Normal animals)

The histological examination showed normal architecture of liver of the group I animals (Fig. 1). Control mice showed normal hexagonadal or pentagonadal lobules with central veins and peripheral hepatic triads or tetrads embedded in connective tissue. Hepatocytes were arranged in trabecules running radiantly from the central vein and were separated by sinusoids containing Kupffer cells. They are regular and contained a large spheroidal nucleus Control mice showed radially arranged hepatic cords around the Central vein and Sinusoids were evident.

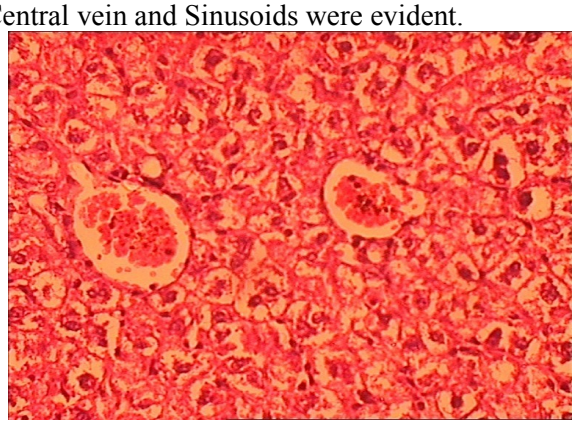

Figure (1): T.S. of liver of the control mice.

Group II (Lead nitrate exposed animals)

Examination of liver mice treated with lead (group II) showed that the normal structural organization of the hepatic lobules was impaired and the characteristic cord-like arrangement of the normal liver cells was lost. The central and portal veins were congested. Considerable number of hepatic cells were damaged and lost their characteristic appearance while others showed marked cytoic plasmic vacuolization which was so extensive in some cells to the extent that only slight remnants of the cytoplasmic mass cells – frequently forming a narrow peripheral rim was left. The nuclei of these cells were pyknotic. Central vein and sinusoids between hepatocyts were dilated. Some leucocyte infiltration and fatty deposition was also evident (Fig. 2).

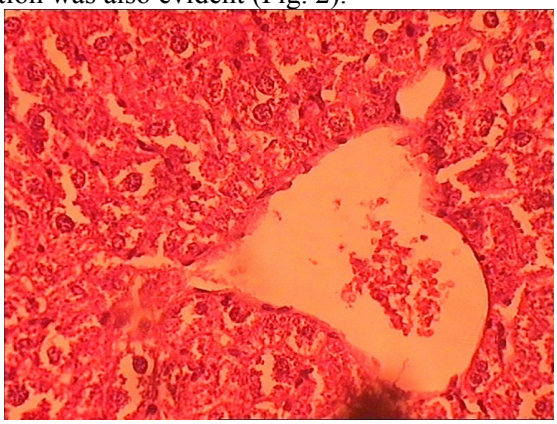

Figure (2): T. S. of liver of mice treated with lead nitrate.

Group III, IV (Lead nitrate + Aqueous extract of Coriander) and Group V and VI (Lead nitrate + Ethanolic extract of Coriander)

Animals treated with lead and coriander extracts showed that most of these histopathological changes were diminished but some hepatocytes appeared with vacuolized cytoplasm and Kupffer cells were activated in low doses groups (Fig. 3 and 5).

In high doses groups, the liver tissue restored most of its normal structure and was able to diminish the fibrosis, congestion, incidence of inflammatory cells infiltration, centrilobular hepatocytes swelling, hepatocytes vacuolization, fatty changes and hemorrhagic clots (Fig. 4 and 6).

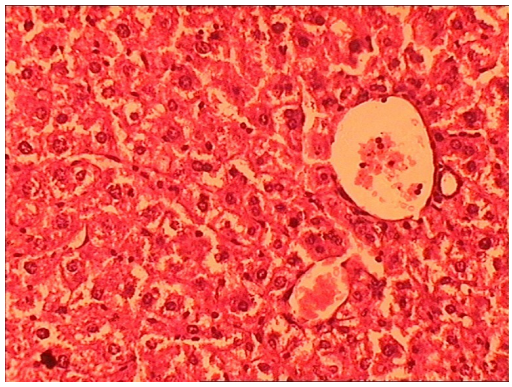

Figure (3): T.S. of liver obtained from mice treated with lead nitrate along with aqueous coriander extract (low dose).

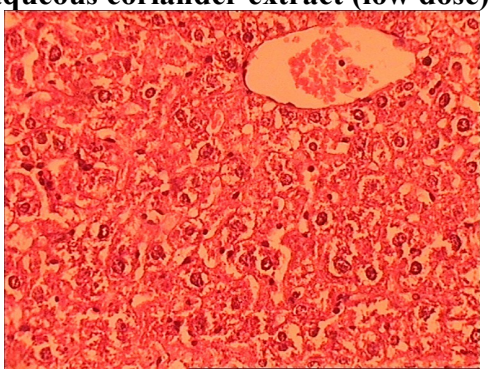

Figure (4): T.S. of liver section obtained from mice after treatment with lead nitrate and Coriandrum sativum aqueous extract (high dose).

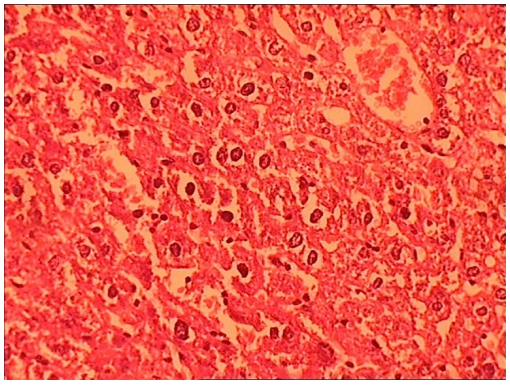

Figure (5): T.S. of liver obtained from mice treated with lead nitrate along with ethanolic extract of coriander (low dose).

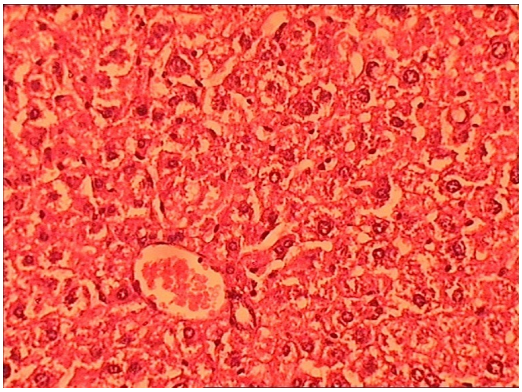

Figure (6): T.S. of liver section obtained from mice after treatment with lead nitrate and Coriandrum sativum ethanolic extract (high dose).

3.5.2. Histology of renal tissues

Effect of lead nitrate alone and ameliorating effect of *Coriandrum sativum* extracts individually during lead nitrate exposure on renal histological images of experimental mice of various groups were examined (Fig. 7-12).

Group I (Control, Untreated, Normal animals)

A section of the control mice showed normal structure of both the renal corpuscles and tubules. Control mice showed normal rounded glomeruli and did not show any signs of damage. Renal tubules are lined with typical thick cubic epithelium. The tubules had a relatively regular distinct lumen. The tubules were well arranged and uniformly stained (Fig. 7).

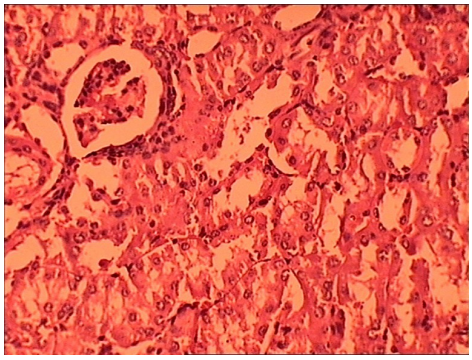

Figure (7): T. S. of renal cortex of control mice

Group II (Lead nitrate exposed animals)

The pattern which emerges in the lead nitrate exposed mice is that of dilation of tubules; sloughing of epithelium indicated advanced disintegration of tubules. At places, casts (dead tubule's remains) was also seen. Glomeruli showed shrinkage, widened urinary space of the Bowman's capsule; however, at places they showed complete disintegration. A few proximal convoluted tubule cells were vacuolated and swollen. Inflammatory cells were observed in the intertubular spaces. Most of the cells of the convoluted tubules were highly swollen and their lumens were nearly obliterated. Some blood sinusoids appeared to be filled with erythrocytes (Fig. 8).

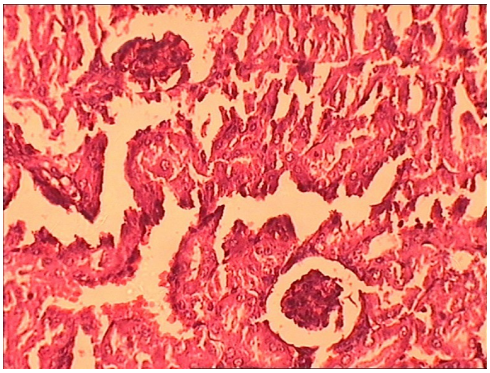

Figure (8): T. S. of renal cortex of lead nitrate treated group (II).

Group III, IV (Lead nitrate + Aqueous extract of Coriander) and Group V and VI (Lead nitrate + Ethanolic extract of Coriander)

Glomeruli appeared normal. They do not show damage at any spot. Casts are absent. Tubules were compact, rounded and at places thin-walled but neither dilated nor damaged. No inclusion of blood cells was evident (Fig. 9 and 11). However, in Group III and V slight oedema and vacuolation of the tubular cells appeared (Fig. 10 and 12). These findings also suggest that the coriander extracts were helpful in bringing about functional improvement of mesangial cells. The remedial effect of coriander extracts was also confirmed by histological observations.

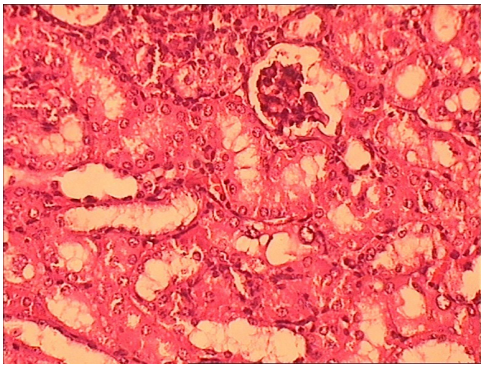

Figure (9): T. S. of Kidney of mice ingested to lead nitrate plus aqueous extract of Coriandrum sativum (low dose).

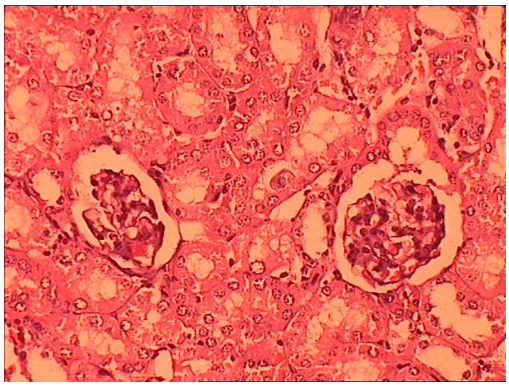

Figure (10): T. S. of Kidney of mice ingested to lead nitrate plus aqueous extract of Coriandrum sativum (High dose).

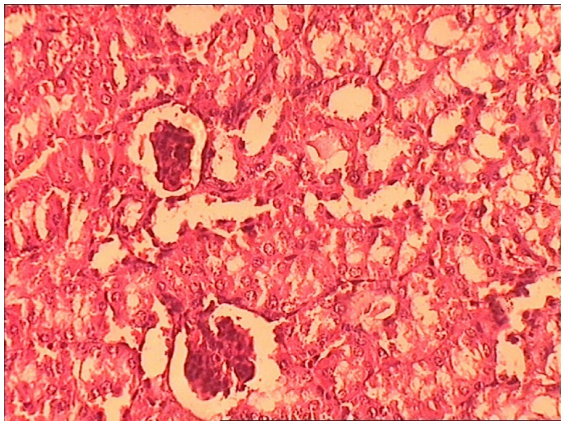

Figure (11): T. S. of Kidney of mice ingested to lead nitrate plus Coriandrum sativum ethanolic extract (low dose).

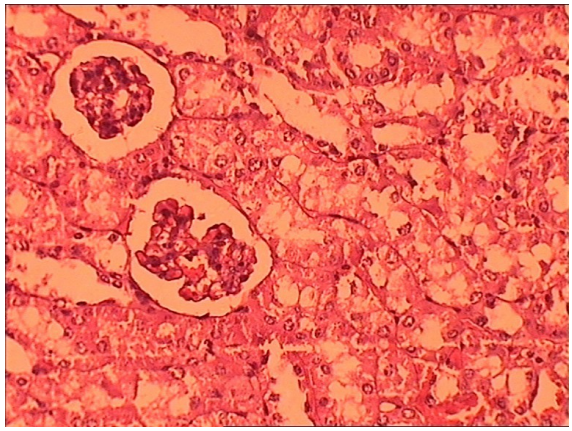

Figure (12) T. S. of Kidney of mice ingested to lead nitrate plus Coriandrum sativum ethanolic extract (High dose).

DISCUSSION

Lead (Pb) is an ubiquitous environmental toxicant that induces a broad range of dysfunctions. Although the exact mechanism of lead nitrate induced toxicity is not completely cleared but cumulative data showed that oxidative stress plays an essential role in its toxicity. Lead administration induces overproduction of reactive oxygen species (ROS) and depletes the cellular antioxidant capacity.

The present study has investigated the efficacy of *Coriandrum sativum* which is considered both a traditional natural medicine and an edible vegetable, against the toxicological disorders induced by lead nitrate using a mice model. It is evident from the results of the present investigation that supplementation of *Coriandrum sativum* aqueous and ethanolic extract with lead nitrate protected animals from toxic effects of lead in general and oxidative stress in particular, besides there was depletion of lead from blood and tissues. This study is in confirmation with the earlier report that suggests the preventive effects of *Coriandrum sativum* (Chinese parsley) on localized lead deposition in male ICR mice (Aga et al., 2001).

Mice administered with *Coriandrum sativum* restored the altered levels to some extent suggest that the active ingredients in the coriander possess antioxidant properties and protects against lead induced oxidative stress. Typically such an aqueous and alcoholic extract of coriander contains linalool and glucosides, such as various β-D- glucopyranosides.

Long chain (C_6-C_{10}) alcohols and aldehydes are common and they also contain phospholipids, phytosterols, flavonoids and active phenols (Henry et al., 2003). Such an extract can function as a primary or secondary chelator for mercury, as well as be used to prepare a primary chelator blend. Positive correlations were already found between total phenolic content in the extracts and antioxidant activity (Helle Wangensteen et al., 2004). Phytonutrients, flavonoids and active phenolic acid compounds of coriander help to control blood sugar, lower cholesterol and fight inflammation and free radicals **(**Drumweaver, 2009).

Effect on oxidative and biochemical related parameters in liver and kidney tissues

Lipid peroxidation, a basic cellular deteriorative change, is one of the primary effects induced by oxidative stress and occurs readily in the tissues due to presence of membrane rich in polyunsaturated highly oxidizable fatty acids (Cini et al., 1994).

Although the source of prooxidant during lead induced oxidative stress is not known, it is suggested that autooxidation of excessively accumulated amino levulinic acid due to inhibition of amino levulinic acid dehydratase, may result in formation of highly reactive cytotoxic compounds like oxidative free radicals like superoxide and hydrogen peroxide (Gurer et al., 1999). The most abundant oxidative free radicals generated in living cells are superoxide anions and derivatives, particularly the highly reactive and damaging hydroxyl radical which induces peroxidation of cell membrane lipids (Bhattacharya et al., 1999). Gibanananda & Hussain (2002) observed that the improper balance between reactive oxygen metabolites and antioxidant defense results in "oxidative stress". Participation of iron in Fenton reaction *in vivo*, leading to production of more reactive hydroxyl radicals from superoxide radicals and H_2O_2 (Halliwell, 1994) results in increased lipid peroxidation. This might be one of the reasons for significant alteration in LPO and significant changes in the activity of antioxidant enzymes, observed in the present study.

CAT and SOD are metalloproteins and accomplish their antioxidant functions by enzymatically detoxifying the peroxides (OH, H_2O_2) and superoxide anion. CAT decomposes H_2O_2 to H_2O and O_2 whereas superoxide dismutase dismutates superoxide into H_2O_2, and needs copper and zinc for its activity.

Superoxide anions (O_2-) itself directly affects the activity of catalase and peroxidase by affecting intracellular enzymes (Ghosh & Myers, 1998), creatine phosphokinase (Lee et al., 1998). Superoxide dismutase (SOD) was found to be decreased in the treated animal's tissues particularly in liver and kidney. Similar results were achieved in our previous study (Sharma et al., 2010). Decreased activity of Cu-Zn SOD, observed may be caused by the interaction between Pb and Cu, a metal necessary for the proper functioning of the SOD cytosol enzyme. A decrease in SOD was explained by direct blocking action of the metal on -SH group of the enzyme (Kasperczyk et al., 2004).

However, a few studies show that superoxide radicals can also inhibit the catalase (CAT) activity and the increase in H_2O_2 levels resulting from CAT inhibition could finally inhibit the SOD activity.

CAT activity in tissues (liver and kidney) of lead treated mice showed a dip compared to the control group. This may be due to the inhibitory action of Pb on CAT (Gurer et al., 1999).

New findings showed that GSH reduction is another essential mechanism of lead toxicity. Glutathione (GSH) is a multifunctional intracellular non-enzymatic antioxidant. It is considered to be the major thiol-disulfide redox buffer of the cell (Masella et al., 2005). Glutathione is highly abundant in the cytosol, nuclei and mitochondria, and is the major soluble antioxidant in these cell compartments. Generally, the antioxidant capacity of thiol

compounds is due to the sulfur atom which can easily accommodate the loss of a single electron. Lead binds to the –SH group of GSH, and interfere with the antioxidant activity of GSH thus decreases its level (Bechara, 2004).

Administration of *Coriandrum sativum* caused increase in SOD, CAT activity and GSH content and decrease in LPO level in lead treated mice tissues (liver and kidney), supporting the antioxidant effect of both aqueous and ethanolic plant extracts.

In the current study, it is reported that coriander extract treatment decreases the LPO level in liver and kidney of experimental animals. Thus it appears that the orally administered aqueous and ethanolic extract of *Coriandrum sativum* protects against lead nitrate induced toxicity possibly through the inhibition of increased LPO level in tissues. In contrast, plant extracts treatment was found to be beneficial in improving SOD enzyme activity which could explain the decrease in LPO levels. Increase in SOD activity should accelerate the removal of the ROS. A previous study has shown that the formation of lipid peroxides declined whereas activities of antioxidant enzymes (catalase, glutathione peroxidase) increased in rats treated by *Coriandrum sativum* (Chithra & Leelamma, 1999). The antioxidative property of coriander seed is related to the large amounts of tocopherols, carotenoids and phospholipids (Ramadan et al., 2004), which act through different mechanisms. Carotenoids act as primary antioxidants by trapping free radicals and as secondary antioxidants by quenching singlet oxygen (Reische et al., 2002). Tocopherols and sterols interact with oil surfaces and release hydrogen, inhibiting the propagation step of radical reactions (Reische et al., 2002). Synergetic effects were evidenced with combinations of carotenoids and tocopherols (Reische et al., 2002). Although the exact mechanism of antioxidative action of phospholipids is not still fully established, these substances would synergistically act with tocopherols, would form barrier for O_2 between air/oil interfaces, would favor formation of Mallard like compounds with oxidation products or would chelate pro-oxidant metals with phosphate groups (Haila et al., 1996).

There is another class of bioactive substances called phthalides, which have anticarcinogenic potential. They are found in umbelliferous plants like celery, parsley, cumin, dill, fennel, and coriander. The phthalides are known to increase the glutathione-S-transferase level (Wildman, 2000). This could thus be attributed to the possibility that coriander might be providing some recovery in GSH level.

In current findings, administrations of lead showed elevation in tissue AST, ALT, ACP, ALP activities and cholesterol level and conversely decreased protein level.

Liver enzymes such as ALT, AST, ACP and ALP are marker enzymes for liver function and integrity (Adaramoye et al., 2008). These enzymes are usually raised in acute hepatotoxicity or mild hepatic cellular injury, but tend to decrease with prolonged intoxication due to damage to the liver (Jens & Hanne, 2002). The present available data suggest that lead exerts possible toxic effects as the increase in ALT, AST, ACP and ALP suggest tissue damage. Lead is known to bind to the sulfydryl groups of enzymes containing cysteine, and found to form complexes with amino acids and protein. Since ALT is liver enzyme, lead will alter the level of ALT activity in the tissues by disrupting their membrane. Consequently, there will be discharge of the cell content into the blood stream and ALT activity is known to increase only in heavy metal poisoning, toxic hepatosis, and muscular dystrophy (Nduka, 1999).

Administration of lead nitrate also caused assimilation of fat in the liver leading to the increased ACP activity. This may be also due to the lysosomal imbalance resulting in the destruction of the intact membranes (Abraham & Wilfred, 2000). Alkaline phosphatase (ALP) is a ‘marker’ enzyme of damage for the plasma membrane and endoplasmic reticulum (Shahjahan et al., 2004). It is frequently used to assess the integrity of the plasma membrane (Akanji MA, Olagoke, 1993) and required in certain amounts for proper functioning of organs (Brain & Kay, 1927). The increase in ALP activity following lead exposure suggests disruption of the ordered lipid-bilayer of the membrane structure of the affected organs.

Rich sources of alkaline phosphatase are the bile canaliculli of the liver, osteoblasts in the bone, proximal tubules in the kidney and mucosal cells of the small intestine (Verley, 1967). Damage to any of these organs or tissues would lead to elevated activity of its isoform of ALP in the serum (Ngaha et al., 1989). Moderate exposure to lead is known to cause the leakage of IALP. The significantly high alkaline phosphatase activity detected from the renal tissues enumerated above, which are established target organs of heavy metal toxicity (Ahn and Park, 1995).

It seems, therefore, that lead induces the biosynthesis of alkaline phosphatase in the bone and kidney before the disruption of cellular integrity, if any, and this usually occurs by way of lipid peroxidation (Sarkar et al., 1995). Moreover, the increased activity of testicular acid phosphatase and alkaline phosphatase in lead nitrate treated mice reflects testicular degeneration, which may likely be a consequence of suppressed testosterone and indicative of lytic activity (Kaur et al., 1999).

Total protein level is a rough measure of protein status but reflects major functional changes in kidney and liver functions. One of the main targets of lead poisoning is the kidney. Chronic poisoning can lead to kidney failure, and acute poisoning to tubulopathy with Toni-Debre-Fanconi syndrome. β-2-microglobinuria and enzymuria were reported in lead toxicity in children (Gourrier et al., 1991). Proteinuria due to kidney impairment in lead toxicity may be a cause of protein loss among these animals because inhibitory role of lead in protein synthesis is not yet reported. Protein loss in lead toxicity might decrease the level of specific proteins such as albumin, hormones, hormone and metal binding proteins, drug binding proteins, enzymes etc. and thereby disturb the homeostasis and rate of metabolic activities.

Moreover, Pb^{+2} disturbs intracellular Ca^{+2} homeostasis (Simons, 1993) and damage the endoplasmic reticulum, which results in decrease in protein synthesis. The increase concentration of cholesterol could result in relative molecular ordering of residual phospholipids resulting in a decrease in membrane fluidity (Kumari et al., 1990).

The coriander mediated suppression of the increased AST, ALT, ALP and ACP activities and cholesterol level suggests the possibility of the extract to give protection against hepatic, renal and testicular injury upon lead induction. Co-administration of aqueous and alcoholic coriander extracts significantly increased total protein content. The efficiency of Coriander was due to presence of several pharmacological effects such as as antifertility (Al-Said et al., 1987), antihyperglycemic (Eidi et al., 2009), anti-hyperlipidemic (Chithra & Leelamma 1999), antiproliferative (Nakano et al., 1998), hypotensive (Burdock & Carabin, 2008) and digestive stimulant (Platel & Srinivasan, 2000).

Thus the present study with coriander suggests that plant is capable of scavenging lead induced free radical generation ((Drumweaver, 2009).

Effect on histology of hepatic tissue

The effect of lead nitrate on liver cells has been widely studied by the group of Columbano both at the histological and the ultrastructural level. In those studies only alterations in hepatocytes were reported while no attention was paid to eventual alterations in sinusoidal liver cells. In the present investigation, lead exposure produced pronounced hepatic histopathology evidenced by histological alternations in liver include focal necrosis with hepatocyte vacuolation dilation of central vein and sinusoids. These findings are in support with Shalan et al. (2005). In accordance with present finding El Sokkary et al. (2005) showed that liver of lead treated rats revealed remarkable degenerative alterations. Lead hepatotoxicity lead to vacuolization of the cells, polymorphism of the nuclei and a decrease in glycogen content of the hepatocytes (Pereira et al., 2001).

In general, lead is well known to induce hepatic injury. Also the pathological changes may lead to impaired liver function, which interferes with the secretion of plasma proteins (Lapeyre et al., 2006). This leads to decreased blood osmotic pressure, with subsequent decreased drainage of tissue fluids, which explains the oedema and congestion observed in the different tissue. Zhang and Wang (1984) suggested that the cytoplasmic vacuolation is mainly a consequence of considerable disturbance in lipid inclusions and fat metabolism occurring during pathological changes. Also, vacuolar degeneration has been regarded by Durham et al. (1990) to be an alteration produced to collect the injurious substances in the cells. Results also showed a remarkable cellular infiltration in the hepatic tissue. This supports El-Banhawy et al. (1993) whose studies suggested that abundance of leucocytes, in general, and lymphocytes, in particular, are a prominent response of body tissues facing any injurious impacts.

These pathological changes were prevented to moderate extent in *Coriandrum sativum* extracts treated groups. This might be due to the presence of flavonoids and ascorbic acid. Antioxidant property is claimed to be one of the mechanism of hepatoprotective drugs. Further Flavonoids and ascorbic acid have been suggested to act as antioxidants by free radical scavenging. Some reports suggest that Flavanoids are hepatoprotectives (Wegner & Fintelmann, 1999). Thus the hepatoprotective activity of *Coriandrum sativum* may be attributed to the presence of flavonoids and ascorbic acid.

Effect on histology of renal tissue

From the results of current study, lead exposure produced marked histological alternations in kidney include dilation of tubules; sloughing of epithelium indicates advanced disintegration of tubules. The results of the some previous investigation showed that subtoxic chronic lead exposure resulted in progressive tubular, glomerular and interstitial alterations. Some of these findings are in agreement with some results of previous investigations (Lin et al., 1993). Fowler et al. (1980) found that rats exposed to low doses of lead (0.005 % and 0.025 %) for nine months developed proximal tubular changes consisting of intranuclear inclusion bodies, swollen dysfunctional mitochondria, and numerous electrondense lysosomes, but no interstitial fibrosis.

These results suggest that the kidney may be a major target organ of lead toxicity, and that the epithelial cells of proximal convoluted tubules and Bowman's capsule seem to be more sensitive to lead induced nephrotoxicity. Many recent studies have provided experimental evidences that lead exposure can result in the generation of ROS and cause cell damage or death through the ROS signaling pathway (Honglian et al., 2004). The results of the present work showed that the tubular damages were more prominent in the proximal convoluted tubules in comparison to that in the distal ones. This could be due to the fact that the proximal convoluted tubules are the primary sites of reabsorption and active transport leading to higher concentration of lead in the epithelial lining of these tubules.

Tubular vacuolization, necrosis and dilation found in the present studies due to lead intoxication were reported by other workers (Karmakar et al., 1986). These tubular alterations due to lead toxicity might be a result of a hydrolic changes in the renal tissue and suggest that lead intoxication yields to a partial failure in the ion pump transport of tubules cells which in turn produces tubular swelling and causes necrosis and vacuolization of the tubules. Also, these changes might indicate incapability of the renal cells to deal with the accumulated residues resulting from metabolic and structural disturbances caused by lead. The presence of hyaline casts in the lumen of the damaged tubules might be an indication of glomerulonephritis and or partial failure of tubular reabsorption due to lead intoxication.

Kidney of mice ingested to lead plus *Coriandrum sativum* extracts shows the tubules appear more or less normal. Thus coriander extract produced protective effects in renal tissue against lead toxicity.

CONCLUSION

In conclusion the current study suggests that aqueous and ethanolic extracts of *Coriandrum sativum* can prevent or slow down the oxidative damage induced by lead in mice. The effect of lead on LPO level, GSH concentration, antioxidant enzyme activity and some biochemical variables were reversed by treatment with plant extracts. Further studies are needed to evaluate its pharmacokinetics and toxicity profile to determine its clinical dose and isolation and characterization of bioactive components.

CONFLICT OF INTEREST

No.

ACKNOWLEDGMENTS

The authors are thankful to the authorities of Banasthali University for providing support to the study.

REFERENCES

1. Abraham, P., Wilfred, G. (2000). Lysosomal enzymes in the pathogenesis of carbontet-rachloride induced injury to the testis and the rat. Ind. J. Pharmacol; 32: 250−251.
2. Adaramoye, O.A., Osaimoje, D.O., Akinsanya, M.A., Nneji, C.M., Fafunso, M.A., Ademowo, O.G. (2008). Changes in antioxidant status and biochemical indices after acute administration of artemether, artemether-lumefantrine and halofantrine in rats. Authors J. Compilation: *Basic Clin. Pharmacol. Toxicol; 102:* 412-418.
3. Aebi, H. (1983). Catalase, In: Methods in enzymatic analysis. Bergmeyer H. Ed. New York. *Academic Press;. 2,* 76-80.

4. Aga, M. (2001). Preventive effect of *Coriandrum sativum* (Chinese parsley) on localized lead deposition in ICR mice. *J. Ethnopharmacol; (2-3):* 203-8.
5. Ahn, D.W., Park, Y.S. (1995). Transport of inorganic phosphate in renal cortical brush-border membrane vesicles of cadmium intoxicated rats. *Toxicol. Appl. Pharmacol; 133(2):* 239-243.
6. Akanji, M.A., Olagoke, O.A., Oloyede, O.B. (1993). Effect of chronic consumption of metabisulphite on the integrity of the kidney cellular system. *Toxicol; 81:* 173-179.
7. Al-Said, M.S., Al-Khamis, K.I., Islam, M.W., Parmar, N.S., Tariq, M., Ageel, A.M. (1987). Post-coital antifertility activity of the seeds of Coriandrum sativum in rats. *J. Ethnopharmacol; 21:* 165-73.
8. Bechara, E.J.H. (2004). Lead poisoning and oxidative stress. *Free Radic. Biol. Med; 36(Suppl 1):* S22.
9. Bhattacharya, A., Chatterjee, A., Ghosal, S., Bhattacharya, S.K. (1999). Antioxidant activity of active tannoid principles of Emblica officinalis (amla). *Ind. J. Exp. Biol;* 37: 676–680.
10. Brain, R.I., Kay, K.O. (1927). Kidney phosphatase II: The enzyme in disease. *Biochem. J; 21:* 1104-1103.
11. Bressler, J., Kim, K.A., Chakraborti, T., Goldstein, G. (1999). Molecular mechanisms of lead neurotoxicity. *Neurochem. Res; 24:* 595-600.
12. Burdock, G.A., Carabin, I.G. (2008). Safety assessment of coriander (Coriandrum sativum L.) essential oil as a food ingredient. *Food Chem. Toxicol; 47:* 22-34.
13. Chithra, V., Leelamma, S. (1999). *Coriandrum sativum* changes the levels of lipid peroxides and activity of antioxidant enzymes in experimental animals. *Ind. J. Biochem. Biophys; 36:* 59-61.
14. Cini, M., Fariello, R.Y., Bianchettei, A., Morettei, A. (1994). Studies on lipid peroxidation in the rat brain. *Neurochem. Res; 19:* 283.
15. Coryslechta, D.A., Weiss, B., Cox, C. (1987). Mobilization and redistriobution of lead over the course of calcium disodium ethylenediamine tetraacetae chelation therapy. J. Pharmacol. *Exp. Ther; 243:* 804-813.
16. Damek-Poprawa, M., Sawicka-Kapusta, K. (2004). Histopathological changes in the liver, kidneys, and testes of bank voles environmentally exposed to heavy metal emissions from the steelworks and zinc smelter in Poland. *Environ. Res; 96:* 72-8.
17. Drumweaver (2009). Coriander chelates heavy metals and toxins from your body. Available from hubpages.com/hub/cilantro-chelates.
18. Durham, S.K., Brouwer, A., Barelds, R.J., Comparative endotoxin-induced hepatic injury in young and aged rats. *J. Pathol; 162:* 341-349.
19. Eidi, M., Eidi, A., Saeidi, A., Molanaei, S., Sadeghipour, A., Bahar, M., Bahar, K. (2009). Effect of Coriander seed (Coriandrum sativum L.) ethanol extract on insulin release from pancreatic beta cells in Streptozotocin induced diabetic rats. *Phytother. Res; 23(3):* 404-6.
20. El Sokkary, G.H., Abdel-Rahman, G.H., Kamel, E.S. (2005). Melatonin protects against lead induced hepatic and renal toxicity in male rats. *Toxicol; 231:* 25-33.
21. El-Banhawy, M.A., Sanad, S.M., Sakr, S.A., El- Elaimy, I.A., Mahran, H.A. (1993). Histopathological studies on the effect of the anticoagulant rodenticide "Brodifacoum" on the liver of rat. *J. Egypt. Ger. Soc. Zool. 12(C);* 185-227.
22. Ellman, G.C. (1959). Tissue sulfhydryl groups. *Arch. Biochem. Biophys; 82:* 70-77.
23. Flora, S.J.S., Flora, G., Saxena, G. (2006). Environmental occurrence, health effects and management of lead poisoning" In: Cascas SB, Sordo J, editors. Lead chemistry, analytical aspects, environmental impacts and health effects. Netherlands: Elsevier Publication. p. 158-228.
24. Fowler, B.A., Kimmel, C.A., Woods, J.S., McConnel, E.E., Grant, L.D. (1980). Chronic low-level lead toxicity in the rat: III. An integrated assessment of long-term toxicity with special reference to the kidney. *Toxicol. Appl. Pharmacol; 56:* 59–77.
25. Ghosh, J., Myers, E. (1998). Inhibition of arachidonate 5-lipoxyenase triggers massive apoptosis in human prostate cancer cells. Proceeding of National Academic Science, USA. 95: 13-182.
26. Gibanananda, R., Hussain, S.A. (2002). Oxidants. *Ind. J. Exp. Biol; 40:* 1213-1232.
27. Gilman, A.G., Rall, T.W., Nies, A.S., Taylor, P. (1991). Goodman and Gilman's. The Pharmacology basis of therapeutics. Pergamon: New York.

28. Gourrier, E., Lamour, C., Feldmann, D., Bensman, A. (1991). Early tubular involvements in lead poisoning in children. *Arch. Fr. Pediatr; 48:* 685-689.
29. Gray, A.M., Flatt, P.R. (1999). Insulin-releasing and insulin-like activity of the traditional anti-diebetic plant *Coriandrum sativum* (coriander). *Br. J. Nutr; 81:* 203-9.
30. Gupta, R., Flora, S.J.S. (2005). Protective value of *Aloe vera* against some toxic effects of Arsenic in rats. *Phytother. Res; 19:* 23-28.
31. Gurer, H., Ozgunes, H., Oztezcan, S., Ercal, N. (1999). Antioxidant role of alpha lipoic acid in lead toxicity. *Free Radic. Biol. Med; 27:* 75.
32. Haila, K.M., Lievonon, S.M., Heinonen, M.I. (1996). Effects of lutein, lycopene, annatto, and γ-tocopherol on autoxidation of triglycerides. *J. Agric. Food Chem; 44:* 20096-2100.
33. Halliwell, B. (1994a). Free radicals, antioxidants and human disease: curiosity, cause and cosequence? *Lancet; 344:* 721.
34. Helle Wangensteen, Anne Berit Samuelsen, Karl Egil Malterud (2004). Antioxidant activity in extracts from coriander. *Food Chem; 88:* 293-297.
35. Henry DC, Neil RS, William JS (2003). Dietary supplement for promoting removal of heavy metals from the body. Available from: www.freepatentsonline.com/y2003/0194453.html.
36. Honglian, S., Xianglin, S., Ke, J.L. (2004). Oxidative mechanism of arsenic toxicity and carcinogenesis. *Mol. Cell. Biochem; 255:* 67-78.
37. Jens, J.J., Hanne, H. (2002). A Review on liver Function Test. The Danish Hepatitis. C: website http://home3.inet.tele.dk/omni/hemochromatosis_iron.htm
38. Karmakar, N., Saxena, R., Anand, R. (1986). Histopathological changes induced in rat tissues by oral intake of lead acetate. *Environ. Res; 41(1):* 23-8.
39. Karunasagar, D., Krishna, M.V., Rao, S.V., Arunachalam, J. (2005). Removal and preconcentration of inorganic and methyl mercury from aqueous media using a sorbent prepared from the plant *Coriandrum sativum*. *J. Hazard Mater; 14(1-3):* 133-9.
40. Kasperczyk, S., Birkner, E., Kasperczyk, A., Zalejska-Fiolka, J. (2004). Activity of superoxide dismutase and catalase in people protractedly exposed to lead compounds. *Ann. Agric. Environ. Med; 11:* 291-296.
41. Kaur, R., Dhanuju, C.K., Kaur, K. (1999). Effect of dietary selenium on biochemical composition in rat testis. *Ind. J. Exp. Biol; 37:* 509-511.
42. Khalil-Manesh, F., Gonick, H.C., Weiler, E.W., Prins, B., Weber, M.A., Purdy, R.E. (1993). Lead-induced hypertension: possible role of endothelial factors. *Am J Hypertens; 6:* 723-9.
43. Kumari, S.S., Verghese, A., Muraleedharan, D., Menon, U.P. (1990). Protective action of aspirin in experimental myocardial infarction induced by isoproterenol in rats and its effect on lipid peroxidation. *Ind. J. Exp. Biol; 28:* 480-5.
44. Lancranjan, I., Popescu, H.I., Gavanescu, O., Klepsch, I., Serbanescu, M. (1975). Reproductive ability of workmen occupationally exposed to lead. *Arch. Environ. Health; 39:* 431-440.
45. Lanphear, B.P., Dietrich, K., Auinger, P., Cox, C. (2000). Cognitive defcits associated with blood lead concentrations <10 µg/ dl in US children and adolescents. *Public Health Rep; 115:* 521-9.
46. Lapeyre-Mestre, M., De Castro, A.M., Bareille, M.P. (2006). Non-steroidal antiinflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. *Fundam. Clin. Pharmacol; 20(4):* 391-395.
47. Lee, Y.J., Galoforo, S.S., Berns, C.M. (1998). Glucose deprivation induced cytotoxicity and alteration in mitogen activated protein kinase activation are mediated by oxidative stress in multi drug resistant human breast carcinoma cells. *J. Biol. Chem; 243:* 52-94.
48. Leonard, S.S., Harris, G.K., Shi, X.L. (2004). Metal-induced oxidative stress and signal transduction. *Free Rad Biol Med; 37:* 1921-42.
49. Lin, J.L., Yeh, K.H., Tseng, H.C., Chen, W.Y., Lai, H.H., Lin, Y.C. (1993). Urinary N-acetyl-glucosaminidase excretion and environmental lead exposure. *Am. J. Nephrol; 13:* 442- 447.
50. Lowry, O.H., Rosenbrough, N.J., Farr, A.L. (1951). Protein measurements with the folin phenol reagent. *J. Biol. Chem; 193:* 265-275.
51. Marklund, S., Marklund, G. (1974). Involvement of Superoxide anion radical in the autooxidation of pyrogallol and convenient assay for SOD. *Eur. J. Biochem; 47:* 469-74.
52. Masella, R., Benedetto, R.D., Vari, R., Filesi, C., Giovannini, C. (2005). Novel mechanisms of natural antioxidant compounds in biological systems: involvement of glutathione and glutathione-related enzymes. *J. Nutr. Biochem; 16:* 577–586.

53. Nakano, Y., Matsunaga, H., Saita, T., Mori, M., Katano, M., Okabe, H. (1998). Antiproliferative constituents in Umbelliferae plants II. Screening for polyacetylenes in some Umbelliferae plants, and isolation of panaxynol and falcarindiol from the root of *Heracleum Moellendorffii*. *Biol. Pharm. Bull; 21:* 257-61.
54. Nduka, N. (1999). Clinical Biochemistry for Students of Pathology. Longman. Nigerian. Plc: pp. 1-236.
55. Ngaha, E.O., Akanji, M.A., Madusuolumo, M.A. (1989). Studies on correlation between chloroquine - induced tissue damage and serum enzyme changes in the rat. *Experientia; 45:* 143-146.
56. Nwanjo, H.U., Ojiako, O.A. (2005). Effect of vitamins E and C on exercise induced oxidative stress. Global J. Pure Appl. Sci; 12: 199-202.
57. Osweiler, G.D. (1999). Williams and Wilkins Philadelphia. Veterinary Toxicology.
58. Patra, R.C., Swarup, D., Dwidedi, S.K. (2001). Antioxidant effects of α-tocopherol, ascorbic acid and L-methionine on lead-induced oxidative stress of the liver, kidney and brain in rats. *Toxicol; 162:* 81-8.
59. Pereira, R., Pereira, M.L., Ribeiro, R., Goncalves, F. (2001). Wildlife animals as sentinels to human health due to wnvironmental exposure to heavy metals. In: Abstarct Book. In: Proceeding of the 11th Annual meeting, SETAC Europe, 6-10 May, Soc. Environ. Toxicol. Chem. Madrid.
60. Plastunov, B., Zub, S. (2008). Lipid peroxidation processes and antioxidant defense under lead intoxication and iodine-deficient in experiment. Anales Universitatis mariae curie skłodowska Lublin–polonia. 21: 215-217.
61. Platel, K., Srinivasan, K. (2000). Stimulatory influence of select spices on bile secretion in rats. *Nutr. Res; 20(10):* 1439-1503.
62. Ramadan, M.F., Mörsel, J.T. (2004). Oil goldenberry (Physalis peruviana L.). *J Agric. Food Chem; 51:* 969−974.
63. Reische, D.W., Lillard, D.A., Eitenmiller, R.R. (2002). Antioxidants in: Food lipids, second edition. Eds. Akoh CC, Min DB, Marcel Dekker NY (USA). 489-516.
64. Reitman, S., Frankel, A.S. (1957). A colorimetric method for the determination of serum Glutamic oxaloacetic and Glutamic pyruvic transaminase. *Am. J. Clin. Path; 28:* 53-6.
65. Ronis, M.J.J., Bedger, T.M., Shema, S.J. (1998). Endocrine mechanism underlying the growth effects of developmental lead exposure in rat. *J. Toxicol. Environ. Health; 54:* 101-20.
66. Sadashivam, S., Manickam, A. (1996). Biochemical methods. 2nd edition. India; 121-124.
67. Sairam, T.V. (1998). Home remedies; a hand book of herbal cures for common ailments. (Penguin Books, India), 75.
68. Sarkar, S., Yadav, P., Trivedi, R., Bansel, A.K., Bhatnagar, D. (1995). Cadmium-induced lipid peroxidation and the status of the antioxidant system in rat tissues. *J. Trace Elem. Med. Biol; 9(3):* 144-149.
69. Shalan, M.G., Mostafa, M.S., Hassouna, M.M., Hassab, S.E., El-Nabi, A., Elrafaie (2005). Amelioration of lead toxicity on rat liver with vitamin C and silymarin supplements. *Toxicology; 206:* 1–15.
70. Sharma V, Sharma A, Kansal L (2010). The effect of oral administration of Allium sativum extracts on lead nitrate induced toxicity in male mice. *Food and Chemical Toxicology; 48:* 928-936.
71. Simons, T. (1993). Lead-calcium interactions in cellular lead toxicity. *Neurotoxicol; 14:* 77-86.
72. Sushruta, K., Satyanarayana, S., Srinivas, N., Raja Sekhar, J. (2006). Evaluation of the blood-glucose reducing effects of aqueous extracts of the selected Umbelliferous fruits used in culinary practices. Trop. J. Pharma. Res; 5(2): 613-617.
73. Verley, H. (1967). Heinemann Medical Books Ltd and New York Interscience Books, Inc, New York. Practical Clinical Biochemistry 4th edition, pp. 891–921.
74. Wegner, T., Fintelmann, V. (1999). Flavonoids and bioactivity. *Wien. Med. Wochenschr; 149:* 241–247.
75. Wildman, R.E.C. (2000). Handbook of Nutraceuticals and Functional Foods. London, New York, Washington D.C.: CRC Press, p. 16.
76. Wiseman, H., Okeilly, J.D., Aldlercreutz, H., Mallet, A.J., Bowery, E.A., Sanders, A.B. (2000). Isoflavones phytoestrogen consumed in soya decrease F2-isoprostane concentrations and increase resistance of low density lipoprotein to oxidation in humans. *Am. J. Clin. Nutr; 72:* 397-400.
77. Zak, B. (1977). Cholesterol methodologies: *A review. Clin. Chem; 23:* 1201-14.
78. Zhang, L.Y., Wang, C.X. (1984). Histopathological and histochemical studies on toxic effect of brodifacoum in mouse liver. *Acta. Acad. Med. Sci; 6(5):* 386-388.