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Research Article

Lead Organ and Tissue Toxicity: Roles of Mitigating Agents (Part 2)

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Abstract: Lead is a heavy metal which is reported to have toxicological effects on various organs in humans and animals. Due to its toxicological effects this study reviews current literature on the toxicological profile of lead on the testis, bone, blood and lungs and the possible roles of mitigating agents. In this study reports showed that in the brain lead induced cerebellar edema, cerebral satellitosis and encephalomalacia with impairments in cortex, hippocampus and cerebellum. Lead impairment of haematological parameters manifested as decrease in packed cell volume, haematoglobin, red blood cell count and total erythrocyte count. Anemia, leucopenia, neutropenia, lymphopenia and monocytopenia were also reported. Lead treated testis was characterized by reduction in the weight of sex glands, testicular sperm counts, daily sperm production, sperm density, sperm viability, sex hormones with increase in sperm abnormalities. Histopathological study of lead treated testis revealed loss of germ cells with pyknotic nuclei and vacuolated cytoplasm. Apoptosis of sertoli cells, leydig cells and mitochondria degeneration were reported. Lead treated lungs were characterized by mononuclear cell proliferation, mononuclear cell invasion, collagen fibre accumulation in the interalveolar septa and pneumonia. The antioxidants status of these organs were impaired making these organs vulnerable to lead induced oxidative stress. This laid credence to the generation of reactive oxygen species as one of the mechanisms of lead induced toxicological effects in various organs. In this study it was also observed that the toxicological effects of lead were mitigated by vitamin C, vitamin E, selenium, zinc and calcium. Chemical agents like melanin, casein, DMSA and CaNa2-EDTA also mitigated lead induced toxicity. Some extracts of plant origin also ameliorated the toxicological effects of lead. Some of these mitigating agents may require further evaluation if they could be of clinical application.

Keywords: Lead, mitigating agents, organ, tissue, toxicity

INTRODUCTION

Lead a soft, grey-blue heavy metal found ubiquitously, it is poisonous to domestic animals and humans throughout the world (Khan *et al*., 2008). Lead is a poisonous metal, which occurs in both organic (tetraethyl lead) and inorganic (lead acetate, lead chloride) forms in the environment (Shalan *et al*., 2005). Information on lead's poisonous ability can be traced back to the second century B.C., when Nikander, a Greek physician, explained the colic and paralysis associated with lead ingestion. The early reported cases of lead toxicity occurred in lead miners and wine drinkers. Workers in the metals trade remain an important risk group; lead exposure remains one of the leading causes of workplace illness. In the United States, more than 320,000 American workers are occupationally exposed to lead (Needleman, 2004).

Lead is a persistent metal that is still present in the environment water, brass plumbing fixtures, paints, soil, dust and imported products manufactured with lead (Patrick, 2006; Garaza *et al*., 2006). Exposure to lead mainly occurs through the respiratory and gastrointestinal systems. Absorbed lead (whether inhaled or ingested) is stored in soft tissues. Lead is conjugated in the liver and passed to the kidney, where a small quantity is excreted in urine and the rest accumulates in various body organs, affecting many biological activities at the molecular, cellular and intercellular levels, which may result in morphological alterations that can remain even after lead levels have fallen (Sidhu and Nehru, 2004; Taib *et al*., 2004; Flora *et al*., 2006). Lead toxicity is closely related to it accumulation in various tissues and it interference with the bioelements that hamper several physiological processes (Berrahal *et al*., 2007). Evaluation of lead exposed humans revealed that liver tissue is the largest reservoir of lead with respect to other evaluated organs and tissues. Lead was also found to accumulate in the kidney cortex and medulla of treated animals. Environmental exposures to lead have increased it toxic effects on various organ of the body. Research in

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humans and animals have shown that lead has toxicological effect on the liver, bone, blood, kidney, lung, heart, brain and testis, (Diamond, 2005, Aziz *et al*., 2012; El-Neweshy and El-Sayed, 2011; Payal *et al*., 2009; Bomfim *et al*., 2012; Garu *et al*., 2011; Moussa and Bashandy, 2008) Lead mediated toxicities have been reported to include the induction of oxidative stress in tissues and organs which can lead to oxidative damage in two separate but related pathways.

The first pathway is the generation of ROS and the second pathway is the depletion of antioxidants reserve through the generation of reactive oxygen species. Lead is reported to in activate glutathione an antioxidant by binding to its sulfhydryl moiety. Glutathione is a cysteine-based molecule whose antioxidant property includes quenching of free radical and is associated with drug and toxin metabolism in the liver (Ercal *et al*., 2001; Sharma *et al*., 2011; Lyn Patrick, 2006). Lead has also been shown to inactive enzymes containing sulfhydryl moiety like delta-aminolevunic acid dehydratase and glutathione reductase as seen in lead exposed animals (Ahamed *et al*., 2005; Gurer-Orhan *et al*., 2004).

Due to reported cases of lead toxicity, the first part of this work "lead organ and tissue toxicity and roles of mitigating agents" reviewed literature on the toxicity of lead on the liver, kidney and brain and possible roles of mitigating agents. In this second part we reviewed toxicity of lead on the blood, lung, bone and testis and possible roles of mitigating lead toxicity by natural and synthetic chemical agents.

LEAD TOXICITY AND MITIGATION BY CHEMICAL AGENTS

Toxicological effect of lead on blood: Researchers have shown that blood is one of the components in animal and humans that is not spared from damage on exposure to lead. The blood is composed of blood cells suspended in plasma. Blood has many functions; one of its primary functions is the supply of substances such as nutrients, oxygen to cells and the removal of metabolic product from cells. Scientists were able to describe on concrete terms the destructive effect of lead on the blood. Mugahi *et al*. (2003) is one of the researchers who in a study evaluated the effects of chronic lead acetate intoxication on blood indices of animals by exposing male adult rats to 1% lead acetate in 0.4% acetic acid. He and others reported decrease in red blood cell count and increase in leukocyte count. Monocytosis, eosinopenia, neutrophilia and thrombocytosis were also observed in lead treated animals (Mugahi *et al*., 2003).

Moussa and Bashandy also exposed wistar male rats to 2% lead acetate in drinking water and reported increase in the electrical conductivity and relaxation time of hemoglobin with respect to the control. This was attributed to increased reactive oxygen species induced by lead therefore leading to an increase in the surface charge density of hemoglobin macromolecule (Moussa and Bashandy, 2008).

Mice exposed to two different concentrations of lead nitrate 50 ppm/kg and 100 ppm/kg for two exposure periods, acute (10 days) and chronic (20 days) showed decrease in hemoglobin concentration and percentage neutrophils. Increases in total white blood cell count, basophils, eosinophils and lymphocytes were also reported. Impairments of these hematological parameters were reported to be higher during chronic exposure (Kadhim and Abdula, 2007).

Okediran and co researchers were able to evaluate the toxic effect of lead on blood cells in animal study. They administered lead 0.5, 1.0, 1.5, 2.0 mg/kg bwt to rats for 14 days and reported higher blood lead concentration, decreased packed cell volume, decreased haematoglobin concentration and decreased red blood cell count. Leukocytosis, monocytosis and neutrophilia were observed at higher doses of administered lead (Okediran *et al*., 2010). Similar observation was reported by some scholars with respect to the toxicological effect of lead on blood (Drugut *et al*., 2008; Ibrahim *et al*., 2011; Alghazal *et al*., 2008; Nashwa *et al*., 2006; Ayla *et al*., 2005; Banu *et al*., 2007).

In an experiment to study the hemato-biochemical alterations induced by lead acetate, wistar rats were exposed to lead acetate 1 PPM, 100 PPM and 1000 PPM, in drinking water for 28 days. Dose dependant significant reductions in total erythrocyte count, hemoglobin, pack cell volume and total lymphocyte count were observed. No significant changes were observed in neutrophil, eosinophil, basophil and monocyte count, whereas lymphocyte count decreased significantly (Suradkar *et al*., 2009).

They implication of lead ingestion on the blood during gestation and lactation in animals was elucidated by Barber and co researchers. In their study to evaluate lead induced alterations in blood cell counts and hemoglobin during gestation and lactation they treated Swiss albino mice with lead (266.66, 533.33, 1066.66 mg/kg bwt) orally from day 10 of gestation to 3rd week of lactation. Hemoglobin content and blood cell counts were examined on 17th day of gestation and on 1st, 7th, 14th and 21st day after birth. It was observed that lead intoxicated pregnant females mice exhibited decrease hemoglobin content and red blood cell counts while white blood cells count increased. They further reported that lead induced hematological alteration observed might be due to the effect of lead on the activity of Aminolevulinic Acid Dehydratase (ALAD), a key enzyme in heme synthesis (Barber *et al*., 2011). One of the factors that could be responsible for decreased in hematoglobin content is lead inhibition of the conversion of coproporphyrinogen III to protoporphyrin

IX leading to reduction in haemoglobin production and shortened life span of erythrocytes (Klassen, 2001). Progressive destruction of RBCs due to binding of lead compounds to RBCs, leading to increase fragility and destruction; could be another reason for decrease in haematological values (Rous, 2000). Anemia, leucopenia, neutropenia, lymphopenia and monocytopenia were recorded with oral administration of lead acetate at various doses (Hashem and El-Sharkawy, 2009). Administration of different doses of lead acetate (1/20, 1/40 and 1/60 of LD50) to rats significantly decreased, total hemoglobin, red blood cell count and white blood cell count (Ibrahim *et al*., 2012).

Anuradha (2007) found that lead induced anaemia, resulted from shortening of erythrocyte life span and inhibition of haemoglobin synthesis. Lead acts on heme synthesis via it inhibitory effect on Aminolevulinic Acid Dehydratase (ALAD), the enzyme involved in the final step of heme synthetic pathway. Many authors have also reported toxicity of lead on the blood (Ambali *et al*., 2011; Ashour *et al*., 2007; Basha *et al*., 2012; Golalipour *et al*., 2007; Mahdy *et al*., 2012a; Sharma *et al*., 2011).

Mitigating the toxicological effect of lead on blood: Due to the ravaging effect of lead on the blood, researchers were able to demonstrate that some chemical agents could mitigate the toxic effects of lead on the blood. Experimental animal studies have shown that antioxidants like vitamin C ameliorated the toxicological effect of lead on the blood. This fact can be seen from the work of Ambali and colleagues who co-administered CPF (4.25 mg/kg) and lead (250 mg/kg) to rats and reported alterations in pack cell volume, erythrocyte indices and concentrations of hemoglobin. But these changes were abrogated by vitamin C (100 mg/kg) (Ambali *et al*., 2011).

Ashour and others reported the abilities of DMSA or CaNa2-EDTA to ameliorate the toxic effect of lead on the blood in animal studies. They orally administered 1000 or 2000 ppm of lead acetate to rats for 20, 40 and 60 days and reported significant decrease in red blood cell count, hemoglobin level and hematocrit value. Administration of Garlic or olive oil (1 mL/kg body weight/day, each) alleviated previous reported changes in the blood, whereas DMSA (50 mg/kg body weight/day) or CaNa2-EDTA (100 mg/kg body weight/day) reversed such changes to near the control levels (Ashour *et al*., 2007).

Casein is a protein fraction from bovine milk and it has been shown to be effective in mitigating the toxic effect of lead on blood. This can be seen from the work of Azo and Raafat who reported the efficacy of casein and charcoal against lead toxicity in rats. They treated rats with lead (0.5 g/100 mL) in drinking water for 2 months and observed significant decrease in red blood cells count, blood haemoglobin concentration and packed cell volume. Cytogenetically increase in the percent of multinucleated polychromatic erythrocytes as well as significant increase in the polychromatic-erythrocytes and normochromatic erythrocyte ratio was observed. They further reported that supplementation with charcoal and casein provided protective effect against lead induced toxicity on the above mentioned parameters (Azoz and Raafat, 2012)

Supplements containing iron, calcium and zinc could be of clinical importance in preventing lead toxicities as reported by Basha *et al*. (2012). He and colleagues exposed male albino rats lactationally to 0.2% lead-acetate in drinking water of the mother from postnatal day 1 to postnatal day 21. In addition to other results they documented significant alteration in hematological parameters following lead exposure. Administration of (0.02%) of nutrient metal mixture containing iron, calcium and zinc in drinking water significantly reversed these changes. Rats treated with lead acetate 20 mg/kg bwt for 28 days showed decreased total erythrocyte count, total leukocyte count, hemoglobin content and packed cell volume. These changes were ameliorated when the rats were pretreated with sodium selenite and vitamin B6 (Ali *et al*., 2010).

D-penicillamine which is reported to be use in the treatment of lead induced toxicity couldn't inhibit the toxicological effect of lead in animal studies as reported by Golalipour and others. He and colleagues treated rats with lead for seven days and observed increase in red blood cell count, decrease in hemoglobin and hematocrite. Also mean corpuscular volume and mean corpuscular hemoglobin were significantly decreased. Red blood cell distribution width, platelet distribution width and mean platelet volume were significantly higher in lead exposed rats. However treatment of rats with 25-35 mg/kg-b-wt/day of oral D-penicillamine couldn't mitigate lead induced hematological changes (Golalipour *et al*., 2007).

Experimental animal studies have also shown that extracts of plant origin could mitigate toxicological effect of lead on blood. Khan and others reported the ability of *Rubia cordifolia* extract in preventing lead toxicity. How? He and colleagues exposed rats to lead nitrate 40 mg/kg body weight/day dissolved in distilled water by oral gavage for 40 days and documented insignificant decrease in total lymphocytes count and neutrophil count. Significant decrease in haemoglobin, lymphocyte and monocytes count was observed with respect to the control. However co-administration of *Rubia cordifolia* at 50 and 100 mg/kg body weight with lead nitrate 40 mg/kg body weight/day increased total lymphocytes count, hemoglobin and monocyte count (Khan *et al*., 2008). Similar observation was reported by Lodia and Kansala (2012) when they administered 40 mg/kg bwt of lead nitrate to rats. They observed decrease in white blood count, red blood cell count and hemoglobin level. These changes were mitigated when extract of *Rubia cordifolia* was administered (Lodia and Kansala, 2012).

Significant increases in mean cell volume, mean cell hemoglobin, concentration and other hematologic parameters were reported when rats were administered 1000 mg/kg of lead acetate by gavage daily for 7 days. These changes were ameliorated by treatment with 1000 mg/kg of *Moringa oleifera* or 1000 mg/kg of activated charcoal (Mahdy *et al*., 2012b).

Coriandrum sativum is a plant with numerous local medicinal uses, if fully elucidated it could be of clinical importance in ameliorating toxicity induced by lead with respect to the work of Sharma and friends. He and colleagues treated mice with lead nitrate 40 mg/kg bwt for 40 days and documented significant decrease in red blood cell, white blood cell and hemoglobin levels. However oral administration of *Coriandrum sativum* (aqueous extract of 300, 600 mg/kg and ethanolic extract 250, 500 mg/kg) to lead treated mice led to significant improvement in hematological parameters (Sharma *et al*., 2011).

Intraperitoneal lead acetate (100 µmol Pb/kg body weight) administered to rats daily for seven days, showed significant reduction in the levels of hemoglobin, packed cell volume and concentration of erythrocyte protoporphyrin. However garlic supplemented diet (200 g minced garlic/kg diet) and vitamin C (500 mg/kg body weight) daily ameliorated these biochemical alterations (Adeniyi *et al*., 2012). Rahman *et al*. (2012) reported alteration in hematological parameters on day 14 and 28 of treatment with lead acetate 20 mg/kg body weight, but administration of *Spirulina* extract 1500 mg/kg and 2000 mg/kg bwt restored these hematological parameters.

Extract of *Garcinia* kola was reported to terminate lead associated toxicity by Nwokocha and others. They administered lead acetate solution orally at a concentration of 100 ppm to rats and observed decrease in red blood cell, haemoglobin, haematocrit with increase in white blood cells, Platelet and lymphocytes. However these hematological changes were ameliorated in rats pretreated with 5% by mass of *Garcinia kola* and lead acetate solution at concentration of 100 ppm (Nwokocha *et al*., 2011).

Mice treated with lead acetate 100 mg/kg bwt exhibited significant reduction in total erythrocyte count, total leukocyte count, haemoglobin content and packed cell volume. However these changes were not observed in mice treated with lead acetate along with Garlic extract 1mL/mice bwt and vitamin B-complex 40 mg body weight. This showed the ability of B complex and Garlic in inhibiting lead induced hematological toxicity (Khan *et al*., 2008). Extract of fruits of *Phyllanthus emblica* at the concentration of 50 g/kg (w/w) along with lead acetate at 1000 mg/kg feed daily ameliorated lead induced hematological changes in rats (Jaiswal and Qureshi, 2004).

Toxicological effect of lead on bone: Bone is one of the vital components of the mammalian system, there are four general categories of bones they are long bones, short bones, flat bones and irregular bones. The bones of the skeleton provide structural support for the rest of the body, permit movement by providing levers for the muscles. Bones protect vital internal organs, structures and provide maintenance of mineral homeostasis and acid-base balance. Bones also serve as a reservoir of growth factors, cytokines and provide the environment for hematopoiesis within the marrow spaces (Clarke, 2008). Recent reports have solidly showed that continuous exposure of bones to lead could retard their functions. In adult human it was reported that high concentration of ingested lead (more than 95%) accumulates in the bone with its half-life being in the order of decades. Bone lead can remain elevated despite a decline in environmental exposure. Available data suggests that there is a close relationship between bone pathology and lead exposure (Moussa and Bashandy, 2008; Oliveira *et al*., 2002).

There are numerous studies that have attested to the detrimental effect of lead on bone. In order to buttress this point we will have a relative overview of reported studies on the toxicological harassments of lead on bones. We will open up this discussion by looking at the work of Haleagrahara and co workers. In their study, they evaluated the toxic effect of lead on bone marrow oxidative biomarkers in sprague-dawley rats. Rats were given three different doses (200, 400 and 600 ppm) of lead acetate in drinking water for 21 days. Results showed significant increase in lipid hydroperoxides and protein carbonyl contents of bone marrow. Significant decreases in bone marrow total antioxidants, superoxide dismutase, glutathione peroxidase and catalase enzyme levels were observed. Significant increase in lipid peroxidation and decreases in antioxidant enzymes levels were recorded with 600 ppm dose of lead. Also a significant level of perturbation in bone marrow antioxidant enzyme levels was observed in lead treated rats (Haleagrahara *et al*., 2011).

Payal and colleagues monitor the biochemical and antioxidant status of bone of 30 and 80 days old male wistar rats treated with lead acetate 250 mg/mL in drinking water for 5 weeks. It was observed that lead treatment increased the production of malondialdehyde and reduced activities of catalase, glutathione S-transferase and superoxide dismutase, indicating lead induced oxidative stress. Also lead significantly reduced nucleic acid content and the activity of alkaline phosphatase, which are considered as biomarkers of osteoblast function and bone development. Moreover the concentrations of copper, zinc, iron and sodium were reduced in the evaluated bones (Payal *et al*., 2009).

Gangoso *et al*. (2009) reported the susceptibility of birds to lead accumulation which is higher in males than females. This bone lead concentration increased with age, reflecting a bioaccumulation effect. Bone composition was significantly altered by increase in lead accumulation. Mineralization degree decreased as lead concentration levels increased. Their reports added credence to the long term accumulation and toxicological effect of lead on bones.

To further buttress the toxic effect of lead on the bone Syarif *et al*. (2008), reported a case of lead induced chromosomal aberration in animal bone marrow when they exposed rats to lead acetate (0, 1008, 1327, 1747, 2299 and 3025 mg/kg bwt). The chromosomal aberration identified were Stickiness, broken fragment, fragment chromosome, gap chromosome, acentric chromosome, triradials chromosome, ring chromosome, double point chromosome and numeric aberration with respect to normal chromosome.

The toxicological effect of lead on bone was further supported by the work of Brandini *et al*. (2011). He and co researchers treated pregnant rats with a single intraperitoneal injection of 2.5 mg of lead acetate/100 g body weight on the 10^{th} day of pregnancy. Evaluation of lead treated animals revealed smaller volume density of Meckel's cartilage of fetuses with decrease in size of the lacunae, as well as modification of the lacunae shape. Moreover, the number density of lacunae and the volume density of the matrix increased significantly in the Meckel's cartilage in treated group fetuses.

Furthermore Sharifi *et al*. (2011) reported the toxicological effect of lead on mesenchymal stem cells. In their study they revealed that lead acetate induced cell death in a dose-dependent manner in mesenchymal stem cells. Significant over-expression of pro-apoptotic proteins, including Bax, caspases-9, -3, was obtained in lead-treated cells. There was a significant increase in DNA fragmentation in treated mesenchymal stem cells with respect to the control using flow-cytometry.

Also in a study to identify possible direct and indirect mechanisms underlying the effects of lead on skeletal growth, 3 studies were conducted by Roni *et al*. (2001). In their first study, a male and female pups, were exposed to 0, 825, or 2475 ppm lead acetate in drinking water from gestational day 4 to euthanasia on day 55. Tibial strength was tested by bending and plasma levels of vitamin D metabolites were measured. A dose-dependent decrease of the load to failure was observed only in male pups. No observed differences in plasma levels of vitamin D metabolites. The second study was conducted to test the possible role of sex steroid on the growth suppression and skeletal effects produced by developmental lead exposure during the peripubertal period. This led to the exposure of male and female pups to 2475 ppm of lead acetate and then, from 30-60 days of age, male animals received L-dopa and testosterone while female animals received estradiol. Lead exposure significantly reduced somatic growth, longitudinal bone growth and bone strength during the pubertal period. Sex steroid and L-dopa replacement did not restore skeletal parameters in lead exposed rats. The third study showed that osteogenesis gap, x-ray density and proximal new endosteal bone formation were decreased in lead-treated animals. There are many reports that have authenticated the toxicological effect of lead on bone function and architecture (Haleagrahara *et al*., 2010; Pourjafar *et al*., 2007; Owolabi *et al*., 2012; Sujatha *et al*., 2012; Al-Naimi *et al*., 2011; Lee *et al*., 2008; Shih *et al*., 2007). Bone marrow damage by lead acetate was reported to be associated with oxidative stress (Vinodhini and Narayanan, 2009; El-Ashmawy *et al*., 2005). Other reports too have shown strong relationship between oxidative stress and bone loss (Sánchez-Rodríguez *et al*., 2007; Liu *et al*., 2008; Shen *et al*., 2008; Smith *et al*., 2008).

Mitigating the toxicological effect of lead on bone: Due to the toxicological effects of lead in humans and animals, quite a number of chemical agents have been screened for their mitigating properties on the toxicological effects of lead. Interestingly a number of agents have shown outstanding protective effect against lead toxic effect on bones. Among these agents are some extracts of plant origin which have been reported to ameliorate lead induced toxicological effect on bones. One of these plants is *Carica papaya* whose extract was reported to mitigate lead induced bone toxicity in animals by Tham *et al*. (2013). He and co researchers administered 50 mg/kg body weight of lead acetate to rats for 14 days and observed significant increase in protein carbonyl content and a significant decrease in glutathione content in lead treated rats. There was strong evidence of fibrosis, focal areas of sclerosis, marrow hypoplasia and coarse reticulin fibres with minimal cells. They further reported that pre and post treatment with *Carica papaya* extract (50 mg and 200 mg) produced significant reduction in the protein carbonyl content activity and significantly increased the glutathione content in the bone marrow. *Carica papaya* also improved the histology of bone marrow compared with that of the lead acetate treated group.

Etlingera elatior extract was reported to improve lead-induced changes in oxidative biomarkers and histology of bone marrow of rats as studied by Haleagrahara *et al*. (2010). He and colleagues exposed rats to 500 ppm of lead acetate in drinking water for 14 days. They observed significant increase in lipid hydroperoxide, protein carbonyl content and a significant decrease in total antioxidants, superoxide dismutase, glutathione peroxidase and glutathione--S-transferase in bone marrow after lead acetate exposure.

Oral treatment with *Etlingera elatior* extract (100 mg/kg body weight) in combination with, or after lead acetate treatment decreased lipid hydroperoxides, protein carbonyl contents and significantly increased total antioxidants and antioxidant enzymes. Treatments with *E. elatior* extract also reduced, lead-induced histopathological damage in bone marrow.

Extracts of garlic have been reported to ameliorate lead impairment of bone; this can be seen from the work of Pourjafar. He administered 5 mg/kg of lead acetate and reported accumulation of lead acetate in organs including bones. But treatment with 125, 250 and 500 mg/kg of garlic extract decreased lead levels in bones and other organs (Pourjafar *et al*., 2007).

A study evaluated the healing and prophylactic effects of *Moringa oleifera* leaf extract on lead induced damage to hematological and bone marrow elements in adult wistar rat. Results showed that the extract of *Moringa oleifera* ameliorated lead induced histopathological changes in the bone marrow of adult wistar rats and normalized hematological changes in lead treated rats (Owolabi *et al*., 2012).

Sujatha and others were able to show that extract of *Ocimum santum* mitigated lead induced genotoxicity in adult wistar albino rats. They treated rats with lead 60 mg and 30 mg/kg bwt and observed a dose dependant increase in the number of micronuclei in polychromatophilic erythrocytes of bone marrow. These effects were ameliorated by 400 mg/kg bwt of *Ocimum santum* (Sujatha *et al*., 2012).

Protective effect of *Withania somnifera* against the formation of micronuclei induced by lead nitrate in bone marrow cells of mice was evaluated by Khanam and Devi (2005). They administered lead nitrate (40 mg/kg bwt) which induced significant micronuclei formation in mouse bone marrow. The rate of formation of micronucleated cells in bone marrow was significantly reduced when methanolic extract of *W. somnifera* (250 mg/kg b.w) was pre administered orally to mice before intraperitoneal injection of lead nitrate (Khanam and Devi, 2005).

Other agents like melatonin, vitamin E, cysteine and calcium have been reported to mitigate lead toxicities. Melatonin is shown to ameliorate the toxic effect of lead on bones as seen from the work performed by Othman and colleagues. They examined the bone marrow of lead treated rats for 7 days and reported erythroid hyperplasia with a sign of dyserythropoiesis and ringed sideroblasts in varying proportions. Daily pretreatment with melatonin (30 mg/kg) intragastricaly for 7 days significantly mitigated the changes induced by lead. In addition, melatonin administration ameliorated the toxicological effect of lead on erythroid cell count in the bone marrow. Less dyserythropoiesis and megaloblastic changes were observed in bone marrow film when melatonin was concurrently administered with lead. In the same animals, iron staining of the bone marrow cells showed absence of ringed sideroblasts (Othman *et al*., 2004). This is contrary to the report of Baranowka-Bosiacka and others who chronically exposed rats to lead during their fast developmental period (from birth until reaching sexual maturity). They reported significant increase in lead concentration in the bones; melatonin supplementation did not cause any significant decrease in lead concentration in bones of lead treated animals (Baranowska-Bosiacka *et al*., 2008).

Cysteine and calcium were reported to mitigate lead induced toxicological effect in rats by Al-Naimi and others. They observed that cysteine and calcium administered to lead intoxicated rats ameliorated lead induced hyperplasia of hemopoietic tissue, delay calcification and osteoporosis in rats' bone marrow (Al-Naimi *et al*., 2011). Mesenchymal stem cells are bone marrow population of cells with the ability to differentiate into various cell types, particularly osteocytes and chondrocytes. Ascorbic acid supplementation at graded levels of 50; 100; 150 and 200 mg/kg in feed couldn't decrease accumulated levels of lead 200 mg/kg bwt in selected organs of animals including bone but rather increase the concentration of lead. An increase in tissue lead retention might be due to an increase in lead absorption caused by ascorbic acid administration. Ascorbic acid has been known with the ability to bind lead *in vitro* and thus maintains lead in a physical state that makes it more available for absorption in the duodenum as reported by Patra *et al*. (2001), Veda *et al*. (2003) and Ibitoye *et al*. (2012).

Toxicological effect of lead on testis: Testis is the major organ for male sexual development and fertility. It secretes hormones to promote male-specific traits and produces sperm for reproduction. The key structural components in a testis are seminiferous tubules, which provide physical barriers and nutrient supplies for the survival and maturation of sperm. Leydig cells of the testis are responsible for the biosynthesis and secretion of androgens, critical for developmental and reproductive function in the male. Sertoli cells provide support, protection and, apparently nutrition until the spermatids are transformed into mature spermatozoa during spermatogenesis. In addition sertoli cells control the entry and exit of nutrients and hormones (Sharma and Garu, 2011).

The testis is one of the organs of target during lead toxicity; researches have implicated lead in the impairment of testicular function and structure. One of these researches is the work of Ait Hamadouche *et al*. (2009). He and colleagues exposed animals to mineral water containing lead acetate (250 mg/L and 500 mg/L) by oral gavage for 90 days. They reported reduction in the weight of sex glands, pituitary and alteration of the normal histological structure of testes. Reduction in epididymal, testicular sperm counts and daily sperm production was also reported. Moreover, lead obviously affected sperm density, sperm viability with a significant increase in sperm abnormalities in lead

exposed rats. Sex hormones (testosterone, follicle-stimulating hormone and luteinizing hormone) were also impaired in lead treated rats. Lead acetate treatment in rats was reported to decrease the weight of reproductive organs. This was shown by Biswas and Ghosh (2004), when they treated rats with lead acetate at a dose of 8 mg/kg body weight for 14 days and reported decrease in weights of testes and accessory sex organs. Serum levels of follicle- stimulating hormone, luteinizing hormone and testosterone were also decreased.

Lead was also reported to impair testicular function of pulps of female treated rats as reported by Dorostghoal and coresearchers. They exposed female rats to 20, 100 and 300 mg/kg/day of lead acetate via drinking water from day 2 to day 21 of lactation, at 7, 14, 21, 28, 60, 90 and 120 days after birth. They observed that testis weight and volume of offspring decreased significantly in a dose-related manner. Dose-dependent significant reductions were seen in seminiferous tubules diameter and germinal epithelium height during neonatal, prepubertal and postpubertal periods. Sperm density and testosterone levels were also decreased (Dorostghoal *et al*., 2011).

Similar observation was reported by Garu and co workers who treated pregnant mice with (532 mg/kg/bwt) of lead orally from GD 10 day to PND 21. They evaluated pulps from lead exposed mice and reported impairment in testicular morphology and histological alterations in the various components of the testis (Garu *et al*., 2011). The above report agrees with the work of Al-Ani and friends who injected female rats with lead (25, 50 and 100) mg/Kg during gestation. They reported that increased number of injections and/or dose of lead acetate injected to the mothers during gestation cause an elevation in the percentage of abnormal morphology of both epididymal and testicular spermatozoa of the male mice offspring (Al-Ani *et al*., 2009). Similar testicular damage induced by lead was reported by some Scholars (Marchlewicz *et al*., 2007; Allouche *et al*., 2009; El-Sayeda and El-Neweshy, 2010).

Previous studies showed that lead exposure suppressed the hypothalamic-pituitary-testicular axis, thus altered the histology of testis, the morphology of spermatozoa and the relationship of cell types in the testes. Mating of lead-treated males with non-treated females confirmed the reduction of fertility in the exposed males (Sharma and Garu, 2011). There are reports that lead toxicological effect on male reproductive function could be mediated through impairment of hypothalamic-pituitary axis. This was demonstrated by Lamia and friends when they intoxicated rats with tap water containing 0.3% lead acetate for two months. They reported impairment of hypothalamic-pituitary axis and decrease in plasma testosterone, follicle stimulating hormone and luteinizing hormone. The secretion of testosterone by the leydig cells decreased and epididymal sperm count also decreased. Histopathological examination showed lead deposits in the walls of the seminiferous tubules (Lamia *et al*., 2008). Similar observation was reported when rats were exposed to 50 and 100 mg/kg lead acetate orally for 28 days and significant decrease in testosterone hormone level and impairment in behavioral activity was reported (Mokhtari and Zanboori, 2011).

Mitigating the toxicological effect of lead on testis: Despite the fact that many researchers have proved the toxicological effect of lead on testicular function and structure as discussed above, also quite a number of researches have reported the mitigating effect of some chemical agents on lead testicular impairment. Among these chemical agents are antioxidants which have shown great mitigating effects in lead intoxicated animals. Vitamin C which is one of the water soluble antioxidants was reported to ameliorate lead induced testicular toxicity in animal studies. This was demonstrated by EL-Tohamy and El-Nattat (2010) who exposed rats to lead acetate (10.8 and 15 mg/kg bwt) and observed impairment of male reproductive function via reduction in the sperm count, sperm volume, sperm density, sperm motility and increase in sperm abnormality. These effects were ameliorated by vitamin C 1 g/L in drinking water every day (EL-Tohamy and El-Nattat, 2010). Similar observation was reported by El Neweshy and El-Sayed who treated rats with lead acetate 20 mg/kg bwt and reported spermatogenesis arrest and interstitial edema. But co administration of lead 20 mg/kgbwt plus vitamin C, 20 mg/kg bwt ameliorated lead induced testicular damage (El Neweshy and El-Sayed, 2011).

Vitamin E which is a lipid soluble antioxidant was also reported to ameliorate impairment of male reproductive function in animal exposed to lead. This can be seen from the work of Makhlouf and colleagues. They intraperitoneally injected lead acetate to rats at a dose of 10 mg/kg for one, two and three months, respectively. They reported shrinkage in seminiferous tubules and loss of germ cells with pyknotic nuclei and vacuolated cytoplasm. These changes increased with the duration of lead acetate treatment. Ultra structurally, the most characteristic features observed were the apoptosis of the germ cells, sertoli cells, leydig cells and also degenerative changes especially in mitochondria. They further observed that pre treatment with vitamin E (100 mg/kg bwt) twelve hours before lead treatment exhibited marked improvement in most of the previously mentioned lead induced changes (Makhlouf *et al*., 2008).

Similar observation was reported when intraperitoneal injection of lead acetate (10 mg/kg bwt)

was administered to rats. This stimulated testicular lipid peroxidation indicated by a significant increase in malondialdehyde and generation of noxious Reactive Oxygen Species (ROS). Zinc is one of the metallic antioxidants that have ameliorated lead induced toxicity. Its antioxidant property has been reported by some researchers. Piao and colleagues evaluated the gonadal protective effect of zinc in lead treated rats by administering 25 mg/kg of lead acetate to rats. They reported lead impaired male reproductive function which was alleviated when coadministered with 4 mg/kg of Zn acetate (Piao *et al*., 2007).

The above report is in agreement with the work of Fadda and colleagues who exposed rats to lead and reported significant impairment in the testis of off springs at all age groups. Lead treatment also affected the process of spermatogenesis. In early ages, lead impaired development of germinal epithelial with vacuolization of the cytoplasm of the cells in the seminiferous tubules. In older ages, it decreased stratification with distortion of the lining epithelium with germinal epithelium showing apoptotic changes. However administration of zinc to lead exposed animals normalized spermatogenic process with few apoptotic changes (Fadda *et al*., 2008).

The above report is consistent with the work of Batra *et al*. (1998) who administered lead acetate (50 mg/kg bwt) daily for 3 months to male rats. Their observations include lead accumulation in various body organs as well as in the reproductive system. A significant decrease in testicular enzymes superoxide dismutase and delta-aminolevulinic acid dehydratase with histopathological changes in the testes were observed. Coadministration of zinc prevented or mitigated these lead induced abnormal changes (Batra *et al*., 1998).

Similar observation was reported by Falana and Oyeyipo who exposed rats to 2-25 mg/kg bwt of lead acetate for 3 days and reported decrease in sperm count, sperm viability, sperm volume motility, serum luteinizing hormone and testosterone. They further reported that coadministeration of selenium and zinc attenuated lead induced changes (Falana and Oyeyipo, 2012).

Combinations of antioxidants have been reported to produce better gonadal protection in lead treated rats than individual antioxidants. This can be attributed to the synergistic effect of these antioxidants when coadministered. One of the researches which showed antioxidants synergism is the work of Wang and colleagues who exposed animals to 0.2% lead acetate in drinking water and documented DNA damage in testicular cells, increased levels of TGFbeta1 and caspase-3. It is interesting to know that pretreatment of animals with ascorbic acid (140, 420, 1260 mg/kg) and thiamine (10, 30, 90 mg/kg) by oral gavage daily ameliorated lead induced changes. However, simultaneous supplementation with ascorbic acid and thiamine at the highest dose promoted testicular cell apoptosis via increased expressions of TGFbeta1 and caspase-3 (Wang *et al*., 2006).

Similar observation was reported by Shan *et al*. (2009) who administered 20 mg/kg of lead to rats daily for 6 weeks and reported significant decrease in epididymal sperm count and motility. Increase in apoptosis of germinal cells, capase 3 and Fas/Fas-L was also observed. However coadministeration with ascorbic acid 420 mg/kg and thiamine 30 mg/kg ameliorated these lead induced abnormal changes. Vitamin E and C have exhibited synergism in the amelioration of lead induced changes in testicular function and structure. This can be substantiated by the research performed by Ayinde *et al*. (2012). He and colleagues treated rats with Lead (60 mg/kg body weight) and observed decline in the reproductive function of male rats via induction of oxidative stress, inhibition of enzymes and depletion of testicular zinc contents. However administration of 40 mg/kg bwt and 150 mg/kg bwt of vitamin C and vitamin E attenuated these deleterious impacts of lead on the reproductive system.

Similar synergistic effect was reported when vitamin C and vitamin E were administered to lead treated rats. Mishra and Acharya reported that vitamin E (100 mg/kg bwt) treatment of lead-injected mice produced similar gonadal protective effect as vitamin C but synergistic effect was observed when vitamin C and E were coadministered (Mishra and Acharya, 2004)

Furthermore it was observed that supplementation with testosterone inhibited lead impairment of testicular function in rats. This was noted when rats were treated with lead, significant decrease in the fertility index and mating index in females was observed in females exposed to lead treated male rats. Pre- and post implantation loss was increased significantly in females mated with lead exposed males. Supplementations with testosterone (4.16 mg/kg bwt) in lead exposed male rats restored lead induced changes in reproductive parameters (Anjum and Reddy, 2012).

Extracts of plant and materials of animal origin have been reported to have shown good results in mitigating lead induced testicular damage in animals. Extract of *Coriandrum sativum* inhibited lead induced reproductive damage in animals. This was shown by Sharma who treated rats with lead acetate and observed significant decrease in testicular SOD, CAT, GSH, total protein, serum testosterone level and sperm density. These lead induced changes were prevented by concurrent daily administration of *Coriandrum sativum* (Sharma *et al*., 2010). Exposure of rats to lead acetate showed a significant decrease in epididymal weight, sperm count, sperm motility and testosterone level. Significant increase in abnormal structure of spermatozoa was also observed. These lead induced

changes were however, prevented in rats treated with aqueous extract of *Juglans nigra* (Alhassan *et al*., 2010).

Extract of *Zingiber officinale* (ginger) was also reported to ameliorate lead induced reproductive toxicity in animals by Riaz and coresearchers. They treated rats with 0.3% lead acetate in drinking water for 2, 4 and 6weeks and observed significant decrease in testicular function via decrease in serum testosterone levels. This lead induced effect was ameliorated when 0.5 gm/kg body weight and 1 gm/kg body weight of *Zingiber officinale* (ginger) was administered (Riaz *et al*., 2011). Similar observation was reported by Zhang *et al*. (2006).

Administration of *Punica granatum* (pomegranate) extract or ascorbic acid ameliorated lead induced testicular impairment. These lead induced changes include, inhibition of spermatogenesis by reducing the length of the stages related to spermiation and onset of mitosis. Lead treated rats also showed a reduction in epididymal sperm number and daily sperm production. These changes were inhibited by extract of *Punica granatum* (Leiva *et al*., 2011).

Salawu *et al*. (2009) reported the protective effect of *lycopersicon esculentum* against lead induced testicular toxicity. He and colleagues exposed rats to 1% lead acetate in drinking water and documented significant reduction in testicular weight, sperm count, sperm motility, testicular SOD and CAT. However treatment of animals with 1.5 mL of *lycopersicon esculentum* ameliorated these changes.

EL-Nager (2010) reported the significance of plant oil as protective agent against lead induced toxicity in animals. He carried out this investigation by administering 20 mg/kg bwt of lead acetate to mice. He reported abnormal testicular architecture which manifested as degeneration, necrosis of seminiferous tubules and interstitial tissue. More results showed small spermatogonia and few numbers of spermatocytes. Lumen was filled with cell remnants, distorted spermatids and rarely mature sperm cells. These changes could be summarized as lead induced atrophy of testicular cells. However oral administration of 1000 mg/kg corn oil, 1000 mg/kg flaxseed oil and 1000 mg/kg black seed oil ameliorated these abnormal histopathological changes induced by lead (EL-Nager, 2010).

Abdel Moniem and coworkers also reported similar observation when the treated animals with lead acetate (20 mg/kg). They observed alterations in testes histology as well as enhanced lipid peroxidation and nitric oxide production in both serum and testes. Concomitant reductions in superoxide dismutase, glutathione reductase, glutathione-S-transferase, glutathione peroxidase and DNA fragmentation were also observed in the testes of lead treated rats. Treatment with flaxseed oil (1000 mg/kg) resulted in marked improvement in lead induced changes in the testis (Abdel-Moniem *et al*., 2010).

Exposure of animals to lead acetate 500 pmm via drinking water for 14 days impaired antioxidant status of the testes, testosterone levels and architecture of the testes. Coadministration and post treatment with extracts of *Etlingera elatior (*100 mg/kg body weight/day*)* ameliorated these changes (Haw *et al*., 2012). Extracts of *Etlingera species* were proven to have high anti-oxidant and anti-bacterial activity (Chan *et al.*, 2007; Mohamad *et al*., 2005).

Toxicological effect of lead on lungs: Healthy human lungs are spectacularly designed to take in life-sustaining oxygen and get rid of unwanted carbon dioxide. They are also equipped to defend themselves and the whole body against inhaled disease-producing insults and to maintain the partnership between the distribution of incoming fresh air and incoming poorly oxygenated mixed venous blood, thus preserving essential gas exchange (Murray, 2010). Due to the importance of the lungs to humans and animals the toxicological insult by lead on the lung can't be overemphasize. There are many reports that have shown that exposure of lungs to lead could be detrimental. One of these reports is the work of Samarghandian and co researchers who exposed rats to lead acetate (250, 500 and 1000 ppm) in drinking water for 14 days. They reported significant dose-dependent increase in BALF supernatant and lung homogenate levels of MDA and NO. Decrease in GSH level and SOD activities were observed in the lead-treated groups with respect to the control. Thus, lead acetate may contribute to respiratory disorders via increased oxidative stress (Samarghandian *et al*., 2013).

Animals exposed to 500 mg/0.1 mls/day of lead for one and two weeks showed mononuclear cell proliferation, mononuclear cell invasion and collagen fibre accumulation in the interalveolar septa and pneumonia. The structural organization of the alveoli was disturbed and the interalveolar septa was thickened. These findings may indicate that lung tissues had undergone fibrosis (Onarlioglu *et al*., 1999).

Similar observation was reported in a study of heavy metal poisoning, in which morphological analysis of bronchoalveolar lavage demonstrated pneumonia, multinuclear cell accumulation and fibrosis in lung tissues. In addition, investigation of the alveolar wall in the same samples revealed intensive macrophage accumulation and cell exfoliation into the alveolar lumen (Davison *et al*., 1983, Ferin, 1982). Previous histopathological studies of heavy metal poisoning have suggested fibrosis along with hyperplastic alveolar epithelium in the lung tissue, as well as asthma and pneumonia (Haslam *et al*., 1980).

In rats exposed to 1000, 2000, 3000 ppm of lead acetate for six months, histopathological evaluation

showed compensatory alveolar emphysema, peribronchitis with septal proliferation and pulmonary edema in the lungs of treated rats (Muselin *et al*., 2010). In a study to evaluate the distribution of lead in selected organs and tissues of albino rats exposed to acute lead, Babalola and others were able to expose rats to various concentrations (1000, 1500 and 2000 ppm of lead solution) for 7 consecutive days. The reported significant concentration of lead in various organ including lungs (Babalola *et al*., 2010). In a toxicological study, the lungs of 20 fetuses from female rats that were previously treated with 12.5, 25.0 and 50.0 mg/kg of body weight of lead acetate were evaluated. The lesions found in the lungs revealed restructuring of the parenchyma, impregnation with fluids, reduction lead acetate, formation of fibrosis, extravasation of vascular fluids, reduction of the alveolar spaces and formation of alveolar edema (Bomfim *et al*., 2012).

Pulmonary toxicity caused by lead was studied in rats after an intraperitoneal administration of lead acetate at a dose of 25 mg/kg for 3 days. Lead was reported to accumulate in the lungs of the treated animals at a concentration of 9.62 µg/g w.w. with respect to the control. Histopathological examination showed accumulation of aggregated platelets, leucocytic elements and monocytes within capillaries. Interstitium revealed substantial number of collagen, elastin filaments and lipofibroblasts. Pulmonary alveoli were filled with macrophages and the extracellular lining layer of lung alveoli was partially destroyed (Kaczynska *et al*., 2011).

Most lead exposures in humans were reported to be associated with chest tightness, wheezing, cough, production of sputum and higher lead concentration in urine and serum (Khazdair *et al*., 2012). In addition, experimental studies in animal models exposed to lead showed morphological changes in the respiratory system as well as increased tracheal responsiveness. These observations may demonstrate the role of lead in the pathogenesis of asthma disease (Salovsky *et al*., 1994).

The effect of lead acetate on tracheal smooth muscles of dog pups was investigated by Sopi *et al*. (2009). In vitro administration of lead acetate in increasing concentrations induced concentration-dependent contraction of tracheal smooth muscles which was inhibited by the presence of bradykinin (BK, 0.4 mM). This study suggests that subacute exposure to lead induces epithelium dependent contraction of airway smooth muscle probably via modulation of nitric oxide release.

Lead can form toxicological synergy with other metals like arsenic. This was reported by Odunola and others who treated rats with sodium arsenite 25 mg/kg bwt and lead acetate 14 mg/kgbwt. Among other observations, they reported mild infiltrative haemorrhage in the lungs of treated rats (Odunola *et al*., 2007). Furthermore rats treated with lead acetate 1, 100 and 1000 ppm in drinking water for 21 days revealed lesions in the lungs which were characterized by congestion, haemorrhage, emphysema and infiltration of MNC (Suradkar *et al*., 2010).

CONCLUSION

This review ascertained the toxicological effects of lead on bone, blood, lung and testis via impairment of their structures, functions and antioxidant status. One of the mechanisms that could be involved in the toxicological effect of lead is the induction of oxidative stress via the generation of reactive oxygen species in these organs as reported by researchers (Anurdha, 2007). In these organs antioxidants and antioxidants enzymes were impaired leaving the organs at the mercy of oxidative stress. A number of agents (vitamin C, vitamin E, thiamine, testosterone, melatonin, cysteine, calcium, zinc) including extracts of plant origin were observed to ameliorate lead induced toxicities. These agents might be of clinical importance if fully evaluated.

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