Research Article
Lead Organ and Tissue Toxicity: Roles of Mitigating Agents (Part 1)

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Abstract: Lead is one of the metals whose toxicological effect in humans and animals is of clinical concerned as reported by researchers. Quite a number of chemical agents have been reported to ameliorate lead associated toxicological effects especially in animal studies. This literary study reviewed reported toxicological effect of lead on the liver, kidney and brain with emphasis on the roles of mitigating chemical agents. In this review it was observed that his to patho logical changes in lead associated he patotoxicity include hepatomegaly with necrosis, formation of hyper plastic nodules and presence of in tranu clear inclusion bodies within hepatocytes. In the kidney reports revealed various degenerative changes with focal tubular necrosis invaded by inflammatory cells in cortical renal tubules, diminution in the amount of filtration slits, apoptosis in epithelial cells of the glomeruli, increase in lysosomal structures, pinocytic vesicles and large mitochondria in proximal tubule cells. Lead altered mRNA levels of the following apoptotic and neurotrophic factors: caspase 2 and 3 and brain-derived neurotrophic factor in the brain. Histopathological changes occurred in gray matter, anterior cingulate cortex, hippocampus and cerebellum of treated animals. Lead exposure altered biomarkers of liver, kidney and brain function with increased lipid peroxidation and decrease antioxidants function. Lead induced toxicities were observed to be mitigated by vitamin C, vitamin E, calcium, magnesium dimercaptosuccinic acid, calcium disodium ethyl diaminetetra acetic acid and selenium. Extracts of plant origin and chemical substances of animal origin were also reported to mitigate these toxicities. One of the commonly reported mechanisms associated with lead toxicological effect is the generation of Reactive Oxygen Species in organs and tissues this may be supported by the mitigating effect of some antioxidants on lead toxicological effects.

Keywords: Animals, human, lead, mitigation, organs, tissue, toxicity

INTRODUCTION

Inorganic lead is one of the oldest occupational toxins and evidence of lead poisoning can be traced to Roman times. Lead production started at least 5000 years ago and outbreaks of lead poisoning occurred from this time (Gidlow, 2004). Lead which is a soft, grey-blue heavy metal is a common cause of poisoning in domestic animals throughout the world (Khan *et al*., 2008). Lead is a poisonous metal, which exist in both organic (Tetraethyl lead) and inorganic (lead acetate, lead chloride) forms in the environment (Shalan *et al*., 2005). It has been used in medicines, paintings, pipes, ammunition and in more recent times in alloys for welding storage materials for chemical reagents (Garaza *et al*., 2006). Exposure to lead mainly occurs through the respiratory and gastrointestinal systems. Absorbed 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. This affects many biological activities at the molecular, cellular and intercellular levels, which may result in morphological alterations that can remain even after lead level has fallen (Sidhu and Nehru, 2004; Taib *et al*., 2004; Flora *et al*., 2006; Ibrahim *et al*., 2012).

Autopsy studies of lead exposed animals indicated that liver tissue is the largest repository (33%) of lead among soft tissues followed by kidney cortex and medulla. Environmental exposures to lead have caused nephrotoxicity in humans and animals (Diamond, 2005). Bio makers of kidney functions have been reported to be impaired by lead in humans and animals (Gurer-Orhan *et al*., 2004; Ahmed *et al.*, 2008; Weaver *et al*., 2005).

Lead induced hepatotoxicity was reported to be associated with the impairments of liver structure and function (Aziz *et al*., 2012). In the brain exposure of animals to lead caused cerebellar edema, cerebral satellitosis and encephalomalacia (El-Neweshy and El-Sayed, 2011). Impairments in cortex, hippocampus and

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cerebellum were also reported. Lead intoxication in humans can be seen from the recent report of high number of children fatalities in Nigeria, an estimated 400 children died. Laboratory testing later confirmed high levels of lead in the blood of the surviving children (MSF, 2012).

Researches using animal models have shown that lead toxicity could be associated with oxidative stress via the generation of reactive oxygen species and can be mitigated by some antioxidants, materials of animal origin and extracts of plant origin. Due to reported cases of lead associated toxicity, in this study (Part one) we reviewed literature on lead induced nephrotoxicity, hepatotoxicity and neurotoxicity in animals. Reported chemical agents that could mitigate lead associated nephrotoxicity, hepatotoxicity and neurotoxicity in experimental animal studies were also evaluated.

LEAD TOXICITY AND MITIGATION BY CHEMICAL AGENTS

Liver: The liver is the major organ of drug metabolism and is highly exposed to both indigenous and exogenous chemical substances. Studies have shown that the liver is one of the primary targets in lead associated toxicity. There are also reports from some quarters on lead induced liver damage which was mitigated by some chemical substances. In this section we critical examine literature on the mitigating effects of some chemical agents on lead associated liver damage. Researchers have shown that some extracts of plant and substances of animal origin have ameliorated lead impaired liver damage in experimental animal studies. Some synthetic chemical substances with known antioxidant properties were also reported to mitigate hepatotoxicity associated with lead. The hepatotoxicity of lead and the roles of mitigating chemical substances can be seen from the study performed by Koriem, 2009. He and colleagues administered 0.5 mg/g concentration of lead acetate to rats in diet for 60 days and observed significant increase in lipid peroxidation and transaminases while SOD, GPx and other biochemical parameters were decreased. These impaired biochemical parameters were normalized when 8 mg/100 g of rat bwt of methanol extract of *C. sempervirens*, 0.3 mg/100 g of quercetin and 0.1 mg/100 g of rat bwt of rutin were administered prior to lead acetate administration.

Similar observation was reported by Waggas (2012), when he injected rats (i.p.) with subacute dose (100 mg/kg bwt/day) of lead acetate and documented significant increase in serum glutamate oxaloacetate, transaminases, serum glutamate pyruvate transaminase and lactate dehydrogenase level. Pretreatment with Grape seed extract (*Vitisvinifera*) (100 mg/kg bwt/day) normalized these biochemical parameters. Liver enzymes were elevated while antioxidant enzymes were

decreased and histopathological changes in the liver were noted when rats were exposed to lead acetate (0.2%) in drinking water for 4 weeks. Pretreatment with 1.5 ml/kg of natural honey orally for 4 weeks alleviated these lead induced changes (Halawa *et al.*, 2009).

Aziz *et al.* (2012) also reported the protective effect of 1:50 diluted latex/kg bwt of Ficus latex against 500 mg/L of lead acetate induced impairments of biomarkers of liver function and alterations in liver architecture of rats. Similar observation was reported by Falah, 2012 on the hepatoprotective effect of *Ficus carica* L in animal studies. The protective effect of the methanolic extract of *Pongamia pinnata* flowers was studied in rats with lead acetate induced hepatotoxicity. Administration of 160 mg/kg bwt/day of lead acetate for 90 days to male albino rats resulted in significant elevation of transaminases and lipid peroxidation. These changes were ameliorated by 150 mg/kg bwt/day of methanolic extract of *Pongamia pinnata* flowers administered for 90 days (Anuradha and Krishnamoorthy, 2012).

Ginger extract has been shown to mitigate lead induced hepatotoxicity. This was well documented by Khaki and Khaki who reported that treatment of rats with 100 mg/kg of ginger for 10 weeks prevented lead impairments of antioxidant functions and lipid peroxidation (Khaki and Khaki, 2010). Similar observations using ginger to mitigate lead induced toxicity were also reported (Badiei *et al.*, 2006). Studies have shown that *Tinospora cordifolia* stem and leaves extracts have protective property against lead nitrate induced toxicity in albino male mice. Oral treatment with 400 mg/kg body weight of aqueous stem extract and 400 mg/kg body weight of aqueous leaves extract for 30 days restored functions of transaminases, antioxidants system and architecture of the liver of lead exposed rats (Sharma and Pandey, 2010).

Coadministeration of various doses of lead and cadmium to rats synergistically and significantly impaired liver enzymes and cellular integrity of the liver. Treatment of rats with various doses of calcium and magnesium restored the function of liver enzymes and cellular integrity of the liver (Dabak *et al.*, 2009). Green tea extract (GTE) is observed to have hepatoprotective property on lead induced toxicity in Sprague-Dawley rats. Exposure of rats to 0.4% lead acetate in distilled water for 2 weeks was found to impair antioxidant function in the liver of treated rats, which was however mitigated when supplemented with (1.5%, w/v) of green tea extract. Histopathological study of liver showed that supplementation with green tea extract resulted in mild degeneration and decongestion of the blood vessels and enhanced regenerative capacity (Mehana *et al.*, 2010).

Lead treatment in rats was reported to impair significantly the liver functions of SOD, catalase and GSH. Liver functions of these parameters were restored

when W. *somnifera extract* (250 mg/kg bwt) was administered orally to mice for 7 days before intraperitoneal injection of lead nitrate (Khanam and Devi, 2005). Flaxseed Lignans administered by gavage at a dose of 300 mg/kg bwt attenuated lead acetate (200 mg/l) induced hepatotoxicity in rats (Abdou and Newairy, 2006).

Rats exposed to 75 mg/kg bwt/ day of lead acetate solution orally for 2 months exhibited hepatomegaly with necrosis, formation of hyper plastic nodules and presence of intranuclear inclusion bodies within hepatocytes. Treatment with 200 mg/kg bwt of cysteine and 500 mg/kg bwt/day of calcium gluconate reduced the toxic effect of lead acetate and improved the his topathological lesions with respect to lead treated rats (Al-Naimi *et al*., 2011). Lead acetate at a dose of 15 mg/kg body weight administered intraperitonealy to rats for seven days induced hepatic injury. Damage to liver architecture was also observed but these changes were mitigated by pre treatment with freshly prepared aqueous garlic extract (Kansal *et al*., 2011). Similar observation was reported by Jarad (2012). Ethanolic extract of *Tagetes eracta* (100 mg/kg bwt) normalized levels of enzymatic and non enzymatic antioxidants and decreased lipid peroxidation in lead (160 mg/kg bwt) intoxicated rats.

In addition to extracts of plant origin and chemical substances of animal origin, some chemical agents have been reported by scholars to confer protection against lead induced hepatotoxicity. Among these scholars are Yedjou and Tchounwou (2007) reported significant elevations in malondialdehyde (MDA) levels after10 weeks of rat exposure to lead acetate (0.1 mg/L of drinking water) with respect to the control group. Pre treatment with melatonin (60 mg/kg diet), vitamin C (1 mg/L drinking in water) and vitamin E. (1000 I.U /kg diet) caused significant reduction in lead induced lipid peroxidation. Significant synergistic effect was produced when melatonin-vitamin E were coadministered (Aziz *et al*., 2012). Exposure of the human hepatocellular carcinoma (HepG2) cell to lead nitrate was reported to decrease cell viability and increase lipid peroxidation. These toxic effects were mitigated by various doses of N-acetylcysteine.

Suleiman *et al.* (2013), showed that lead acetate (250 mg/kg bwt) administered to rats impaired liver function but pre treatment with vitamin C was observed to restore liver function status. This agreed with the study performed by Amballi *et al.* (2011) who showed that pre treatment with 100 m/kg of vitamin C ameliorated the toxicological effect of co administered chlorphyrifos (4.25 mg/kg) and lead (225 mg/kg) in rats.

Vitamin E was also reported to have hepatoprotective effect against lead induced hepatic damage which was supported by the work of Ebuehi *et al.* (2012). He and co researchers exposed rats to lead acetate 60 mg/kg for 7 days, they observed elevated levels of serum transaminases which were restored after pre treatment with 40 mg/kg bwt of vitamin E. Co administration of vitamin E and selenium (100 mg and 0.25 mg/kg bwt) and (200 mg and 0.25 mg/kg bwt) respectively produced synergistic hepatoprotective effect against lead (0.5, 1, 1.5%) induced hepatotoxicity (Al-bideri, 2011). In experimental animal studies humic acid was reported to decrease the accumulated levels of lead acetate in the liver of lead intoxicated rats (Zralý *et al*., 2008).

Combine administration of garlic oil and vitamin E was reported to mitigate lead acetate induced hepatotoxicity in animal models (Sajitha *et al*., 2010). Calcium and magnesium were reported to inhibit cadmium and lead synergistically induced hepatotoxicity (Dadak *et al*., 2009).

Kidney: The kidney is the major organ of drug excretion and is also one of the organs of primary target during lead toxicity. There are reports from some quarters on lead induced kidney damage in experimental animal studies and humans. Among reported studies on lead toxicity is the work of Missoun *et al*. (2009) who exposed rats to 1000 ppm of lead acetate in drinking water for 8 weeks. He and friends documented increase in phosphaturia and calcium level. Decrease in level of creatinine, urea and presence of calcium oxalate dihydrate crystals observed in samples of urine of exposed rats was also reported. All lead-treated rats showed intranuclear inclusion bodies in kidney proximal tubular. Some scholars also reported similar changes when they exposed animals to lead (Mohamed and Saleh, 2010).

Deveci *et al*. (2011) in a study to investigate the ultrastructural effects of lead on the kidney cortex of rats, exposed rats to drinking water containing 500 ppm lead acetate for a period of 2 months. Histopathological examination of the kidney revealed various degenerative changes with focal tubular necrosis invaded by inflammatory cells in cortical renal tubules. The ultrastructural alterations found in lead acetate-treated rats were diminution in the amount of filtration slits, increased fusion of foot processes in epithelial cells of the glomeruli, increase in lysosomal structures and pinocytic vesicles as well as large mitochondria in proximal tubule cells.

Oral administration of lead acetate (10 mg/kg) to pregnant mice was reported to significantly decrease fetuses' cortical thickness. Moderate cortical tubular atrophy showing thickening of endothelial basement membrane in glomeruli, desquamated epithelium with degenerated nuclei in proximal and distal tubules was observed in lead treated rats (Jabeen *et al*., 2010).

Ponce-Canchihuamán *et al*. (2010) administered 25 mg/0.5 mL of lead acetate intraperitoneally to rats weekly. It was found that activities of SOD, CAT and GSH in rat kidney were significantly ($p < 0.05$)

decreased while level of MDA was significantly ($p<0.05$) increased with respect to the control.

Berrahal and colleagues investigated the effects of chronic exposure to lead (50 mg/L) on kidneys of two different age groups of male rats from delivery until puberty period (40 days) and post puberty period (65 days). Results clearly showed that administration of lead produced oxidative damage in kidney, as strongly suggested by the significant increase in TBARS, decrease in total SH, the alteration of SOD activity and impairments of some kidney function parameters. In young lead-exposed animals, lead-induced perturbations on the synthetic function of the kidney were more pronounced. However, nephropathy is evident for adult lead-exposed animals (Berrahal *et al.*, 2011). A number of studies have laid credence to the renal toxicity of lead, also quite a number of studies have reported the abilities of some chemical agents to mitigate lead induce impairments in renal function and structure. The abilities of some chemical agents to mitigate lead associated renal impairment were reported by Abdel-Aal and Hussein (2008). They administered lead acetate (0.2%) in drinking water for 5 weeks to rats and observed impairment in renal function. But treatment with 20 mg/kg body weight/day of (i.p) dimercaptosuccinic with 25 mg/kg body weight/day i.p. of lipoic acid restored renal function in lead treated rats.

Similar renal function impairment was reported by Ashour *et al.* (2007) in lead (1000 or 2000 ppm) treated rats. Garlic or olive oil (1 ml/kg body weight/day), DMSA (50 mg/kg body weight/day) and CaNa2-EDTA (100 mg/kg body weight/day) restored renal function in lead treated rats. Ishiaq *et al.* (2011) reported the protective effect of lycopene (an active constituent of tomatoes) as a natural antioxidant against lead induced renal toxicity and its attendant reduction of reduced glutathione (GSH) levels in lead poisoned kidney of wistar rats. They recommended that lycopene-rich tomatoes can be used as regular diets to improve reduced glutathione activity especially in subjects occupationally exposed to lead as an intervention mechanism against lead nephrotoxicity. Exposure of rats to 20 mg/kg lead acetate by Abdel-Moniem *et al.* (2011) impaired functions of renal biomarkers, antioxidant status and increased lipid peroxidation. It is quite outstanding to know that pretreatment with flax oil normalized these lead induced changes and restored renal function. Abnormal histopathological changes were also observed in the kidney of treated rats but were also normalised by flaxseed oil treatment. Melatonin, (60 mg of melatonin/kg diet) vitamin C (1mg of vitamin C/l of drinking of water) and vitamin E (1000 I.U of vitamin E /kg diet) were reported to mitigate lead acetate (0.1 mg/L drinking water) induced kidney injury by decreasing oxidative stress and restoring antioxidant function (Aziz *et al.*, 2012; Al-Attar, 2011).

Alpha lipoic acid (40 mg/kg body weight) and vitamin E (20 mg/kg body weight) respectively reduced lead levels in serum and tissues as well as restored renal function in lead (0.2 mg/kg bwt) intoxicated rats (Osfor *et al.*, 2010). Melatonin was reported to reduce lipid peroxidation and restore antioxidant function. Morphological changes in the kidney of lead treated rats were also mitigated by melatonin (El-Sokkary *et al.*, 2005). Ambali *et al.* (2011) reported the protective effect of vitamin C against lead induced renal damage. He and co researchers showed that pre treatment with 100 m/kg of vitamin C ameliorated the toxicological effect of co administered chlorphyrifos (4.25 mg/kg) and lead (225 mg/kg) in rats.

Furthermore some extracts of plant and chemical substances of animal origin have been reported to confer protection against lead impairment of kidney function and structure. There are reports from some quarters on the protective effect of natural honey against lead induced toxicities which can be attested to by the work of Halawa *et al.* (2009). He and colleagues showed that administration of 1.5 ml/kg of natural honey orally for 4 weeks improved liver function and architecture in lead treated rats. Elmenofi (2012) reported similar observation when he administered 200mg/kg of lead to animals and observed impairment in biomarkers of renal function and renal architectural damage. Administration of honey significantly ameliorated these lead induced changes.

The protective effect of *Coriandrum sativum* against lead nitrate induced toxicity was observed 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. Increase in lipid peroxidation, decrease in antioxidant system and impairment in kidney architecture was observed. Treatment with aqueous coriander extract 300 mg/kg body weight and 600 mg/kg body and ethanolic extract 250 and 500 mg/kg bwt inhibited lipid peroxidation, restored antioxidant status and kidney architectures (Kensal *et al.*, 2011). One of the plant extracts that have been shown to improve renal function in lead treated animals is *Nigela sativa* extract. It was reported that treatment of lead exposed animals with *Nigela sativa* led to marked improvement in biochemical and histopathological alterations with respect to lead treated rats (Farag *et al.*, 2007).

Similar observation was reported by Abdel-Moniem *et al.* (2011), they reported impairment in antioxidant status, increase lipid peroxidation in lead treated rats. These changes were significantly normalized after treatment with 1000 mg/kg of flax seed. Intraperitoneal injection of lead acetate (20 mg/kg bwt) to rats was observed to impair renal biochemical parameters and induced histopathological damage to kidney of treated rats. These changes were mitigated by artichoke extract (Ghanem *et al.*, 2008).

Brain: They brain is an essential organ of the body which is reported to be impaired on exposure to lead with respect to time. A good number of researches have reported lead impairment in brain architecture and function on exposure to lead. One of these researches was performed by Xu *et al*. (2009), he and colleagues exposed rats to 0.2% lead acetate during gestation and lactation. Following necessary evaluations they observed higher concentration of lead in hippocampus of the lead-exposed rats. They further explained that exposure to lead before and after birth can damage short-term and long-term memory ability of young rats and hippocampal ultrastructure. However, their study could not provide evidence that the expression of rat hippocampal *mGluR*3 and *mGluR*7 can be altered by systemic administration of lead during gestation and lactation. Similar finding was reported by other scholars (Ha *et al*., 2010).

The work of Cecil *et al*. (2008) further reported the relationship between childhood lead exposure and adult brain volume using magnetic resonance imaging. They documented that exposure to lead significantly decreased brain volume in association with childhood blood lead concentrations. Approximately 1.2% of the total gray matter was significantly and inversely associated with mean childhood blood lead concentration. The most affected regions are frontal gray matter and the anterior cingulate cortex. Areas of lead-associated gray matter volume loss were much larger and more significant in men than women. This study found that fine motor factor scores positively correlated with gray matter volume in the cerebellar hemispheres with respect to blood lead concentrations. Berkowitz and Tarrago (2006), reported a case of lead toxicity involving a 4-year-old who presented with vomiting, low-grade fever and dehydration that were thought to be caused by viral gastroenteritis. He later developed brain herniation leading to brain death. The ultimate cause of death was found to be acute lead intoxication from a swallowed foreign body.

The work of Chao *et al*. (2007), also supported the fact that lead exposure is detrimental to brain function. He and co researchers exposed timed-pregnant rats to 0.2% of lead acetate in drinking water 24 h following birth at postnatal day one. Dams and pups were also exposed to lead through the drinking water of the dam until post natal day 20. They observed that postnatal exposure in the pups resulted in altered mRNA levels of the following apoptotic and neurotrophic factors: caspase 2, caspase 3 and brain-derived neurotrophic factor. Their reports suggested a brain region and time-specific response following lead acetate exposure. The region most vulnerable to alterations is the hippocampus. Furthermore high concentration of lead was significantly observed in hippocampus and cerebellum.

Adonaylo and Oteiza (1999) added credence to the toxicological effect of lead on the brain by chronically exposing the brain to 1 g of lead acetate/l of drinking water for 8 weeks. They reported elevated levels of thiobarbituric acid reactive substances (TBARS), glutathione reductase and glutathione peroxidase while ubiquinol level was decrease in the brain. Some researchers reported similar effect of lead on the brain (Bennet *et al*., 2007). Further studies have shown that exposure to lead could lead to neurochemical and neurobehavioral changes (Bijoor *et al*., 2012; Hassan and Jassim, 2010). Lead exposure may have the ability to induce memory loss and impair spatial learning (Soodi *et al*., 2008). The toxicological effects of lead in the brain of animals were also reported by some authors (Nakao *et al*., 2010; Aziz *et al*., 2012; Kumar *et al*., 2009).

In the light of lead associated brain toxicity; researches have also reported cases of lead induced brain toxicities that were mitigated by some chemical agents. One of these researches is the role of exogenous hydrogen peroxide (H_2O_2) in inducing mouse tolerance to lead exposure. Administration of lead was found to significantly ($p < 0.05$) inhibit SOD and CAT activities in the brain. Application of 1.2 micro grams H_2O_2 per kg body weight efficiently decrease lead induced injury as revealed by decreased growth suppression, increased antioxidative enzyme activity, reduced lipid peroxidation and protection of nuclear DNA integrity (Li *et al*., 2009).

Reckziegel *et al*., 2011 reported the protective effect of garlic in lead induced brain damage. He and colleagues exposed rats to 50 mg/kg of lead intraperitoneally once daily for 5 days and observed decreased locomotor, exploratory activities with increase in lipid peroxidation and protein carbonyl. Administration of 13.5 mg/kg of garlic acid orally mitigated these toxic effects of lead in the brain. Both garlic acid and EDTA reduced accumulated level of lead in brain tissues. The protective effects of some chemical agents (Vitamin C and E) against lead induced brain damage were also evaluated by Hassan and Jassim (2010). They administered 10 mg/kg, of lead acetate to female lactating rats orally in distilled water and reported significant increase in open field activity test which include olfactory discrimination test. A significant decrease in glutathione brain tissue and high density lipoproteins in their pups was also observed. Administration of 600 mg/kg diet of vitamin E, 100 mg/kg, of vitamin C orally normalized the above reported lead associated changes.

Hernandez and friends reported similar observation of brain protection offered by Vitamin C and E when they intoxicated pregnant wistar rats throughout gestation with solutions containing either 320 or 160 ppm of lead. The pups were treated after birth in the same way until 45 days of age. They observed that lead

accumulated preferentially in the parietal cortex, striatum and thalamus as compared to the control group, while lipid fluorescence products were significantly increased in the striatum, thalamus and hippocampus of the treated animals (Hernandez *et al.*, 2001).

El-Neweshy and El-Sayed, 2011, further showed that vitamin C, 20 mg/kg bwt mitigated lead acetate (20 mg/kg bwt) induced cerebellar edema, cerebral satellitosis and encephalomalacia in the brain of six weeks old rats. Propolis pre treatment before lead intoxication showed recommendable brain protection against lead intoxication. Propolis was reported to inhibit lead induced neurological toxicity as indicated by normalization of acetylcholine activity, inhibition of brain lipid peroxidation and protein carbonyl formation. In addition, propolis protected the mitochondrial NADH-cytochrome C reductase, succinate dehydrogenase and cytochrome C activities from lead induced damage. Propolis also increased brain vitamin C, vitamin E and sulphhydryl proteins levels in rat's brain (El-Masry *et al.*, 2011). Recently, propolis has been reported to be a powerful scavenger of Reactive Oxygen Species (ROS) (Ozguner *et al.*, 2005).

Fan *et al.* (2009) reported learning and memory impairment in rats' exposed to lead. They observed that optimum combinations of nutrients containing methionine, taurine, zinc, ascorbic acid and glycine prevented lead associated learning and memory impairment. Taurine and thiamine appeared to be the effective agents for reversing lead neurotoxicity as observed in this study. These nutrients prevented lead induced learning and memory impairment by decreasing prolonged escape latency, normalising SOD, nitric oxide synthase (NOS) activities and nitric oxide (NO) levels in the hippocampus (Fan *et al.*, 2009). Post administration of NAC (160 mg/kg body wt/d) for a period of 3 wks was reported to normalized antioxidant status and decreased lipid peroxidation in the brain of lead (20 mg/kg body wt/d) intoxicated rats (Nehru and Kanwar, 2004).

Rats exposed to 750 ppm of lead acetate in drinking water for 11 weeks manifested significant increase in thiobarbituric acid reactive substances (TBARS), decreased acetyl cholinesterase and monoamine oxidase in the brain. Behavioral test indicated a significant hyperactivity in lead exposed rats. But treatment with aqueous wormwood extract (200 mg/kg body weight), ameliorated lead associated toxicological effect in the brain (Kharoubi *et al.*, 2011).

Wang *et al.*, 2007 documented the ability of iron (Fe) supplement to restore brain function in lead intoxicated rats. He and co researchers observed significant inter nucleosomal DNA fragmentation, increased caspase-3 activity and a significant decrease in Fe concentration in the cortex of rats administered 400 mg/mL lead of acetate in drinking water. Supplementation with two doses of Fe (20 mg/kg and 40 mg/kg FeSO4 solution) appeared to restore brain Fe level and mitigated lead induced neurological changes in the brain.

Mice given lead (1 g/l) in drinking water for 8 weeks developed learning deficit, memory loss and increased activity of the cell death marker enzyme caspase-3 was observed. Co-treatment with aqueous *Thunbergia laurifolia* leaf extract at 100 mg/kg or 200 mg/kg body weight was found to alleviate adverse effects of lead on learning deficit and memory loss. The increased activity of the cell death marker enzyme caspase-3 observed in the brain of mice treated with lead suggested that the memory loss could be caused by lead-induced loss of neurons in the brain. Co-treatment with aqueous *Thunbergia laurifolia* leaf extract at 100 mg/kg or 200 mg/kg body weight was found to restore the level of caspase-3 activity and maintain total anti-oxidant capacity and anti-oxidant enzymes in the brain. The mitigation of lead induced brain damage was attributed to the anti-oxidant activities of the *Thunbergia laurifolia* leaf extract (Tangponga and Satarug, 2010). Yun *et al.* (2011) also showed that extract of *Chlorella vulgaris* ameliorated lead induced brain damage in rats.

Administration of lead acetate to the female lactating rats caused significant increase in open field activity test including (the number of squares crossed and rearing test within 3 min), olfactory discrimination test, triglycerides and malondialdehyde brain tissue. A significant decrease in glutathione brain tissue and high density lipoproteins in their pups was also observed. Treatment with vitamin C and E was observed to ameliorate these lead induced changes (Hassan and Jassim, 2010).

CONCLUSION

Toxicities due to lead exposure have been attributed to the ability of lead to induce oxidative stress through the generation of reactive oxygen species (ROS). The ability of lead to induce reactive oxygen species could be supported by the fact that lead induced toxicities were found to be mitigated by chemical agents like vitamin C, vitamin E, N- acetyl cysteine dimercaptosuccinic acid, calcium disodium ethyldiaminetetra acetic acid, melatonin and selenium which have antioxidant properties. Plant extracts and materials of animal origin were also observed to protect against lead induced toxicity in experimental animals. The abilities of these extracts to mitigate these toxicities were attributed to the antioxidant properties of principles contained in these extracts. Some of these mitigating agents may need more evaluation if they could be of clinical application.

REFERENCES

Abdel-Aal, K.M. and M.R. Hussein, 2008. Therapeutic efficacy of alpha lipoic acid in combination with succimer against lead-induced oxidative stress, hepatotoxicity and nephrotoxicity in rats. Ass. Univ. Bull. Environ. Res., 11(2): 87-99.

Abdel-Moneim, A.E., M.A. Dkhil and S. Al-Quraishy, 2011. The protective effect of flaxseed oil on lead acetate-induced renal toxicity in rats. J. Hazard Mater., 30(194): 250-5.

Abdou, H.M and A.A. Newairy, 2006. Hepatic and reproductive toxicity of lead in female rats and attenuation by flaxseed lignans. JMRI., 27(4): 295-302.

Adonaylo, V.N and I. P. Oteiza, 1999. Lead intoxication defenses and oxidative damage in rat brain. Toxicology, 135: 77-85.

Ahmed, K., G. Ayana and E. Engidawork, 2008. Lead exposure study among workers in lead acid battery repair units of transport service enterprises, Addis Ababa, Ethiopia: A cross-sectional study. J. Occupat. Med. Toxicol., 3(30): 1-8.

Al-Attar, M.A., 2011. Antioxidant effect of vitamin E treatment on some heavy metals-induced renal and testicular injuries in male mice. Saudi J. Biol. Sci., 18: 63-72.

Al-Bideri, A.W., 2011. Histopathological study on the effect of antioxidants (vitamin E and selenium) in hepatotoxicity induced by lead acetate in rats. Q. M. J., 7(12): 142-155.

Al-Naimi, R.A., D. Abdul-Hadi, O.S. Zahroon and E.H. Al-Taae, 2011. Toxicopathological study of lead acetate poisoning in growing rats and the protective effect of cysteine or calcium. Al-Anbar J. Vet. Sci., 4: 26-39.

Ambali, S.F., M.I. Angani, A.O. Adole, M.U. Kawu and M. Shittu, 2011. Protective effect of vitamin C on biochemical alterations induced by subchronic co-administration of chlorpyrifos and lead in wistar rats. Environ. Anal. Toxicol., 1(3): 1-7.

Anuradha, R. and P. Krishnamoorthy, 2012. Impact of pongamia pinnata extract on lead acetate mediated toxicity in rat liver. Int. J. Pharm. Tech. Res., 4(2): 878-882.

Ashour, A.A., M.M. Yassin, N.M. Abu Aasi and R.M. Ali, 2007. Blood, serum glucose and renal parameters in lead-loaded albino rats and treatment with some chelating agents and natural oils. Turk J. Biol., 31: 25-34.

Aziz, F.M., I. M.Maulood and M.A.H. Chawsheen, 2012. Effects of melatonin, vitamin C and E alone or in combination on lead-induced injury in liver and kidney organs of rats. IOSR J. Pharmacy, 2(5): 13-18.

Badiei, K., K. Mostaghni, A. Nowroozias and A.T. Naeini, 2006. Ameliorated effects of allium sativum on subclinical lead toxicity in goats. Pak. Vet. J., 26(4): 184-186.

Bennet, C., R. Bettaiya, S. Rajanna, L. Baker, P.R. Yallapragada, J.J. Brice, S.L. White and K.K. Bokara, 2007. Region specific increase in the antioxidant enzymes and lipid peroxidation products in the brain of rats exposed to lead. Free Radic. Res., 41(3): 267-273.

Berkowitz, S. and R. Tarrago, 2006. Acute brain herniation from lead toxicity. Pediatrics, 118(2548): 2548-2551.

Berrahal, A.A., M. Lasram, N. El-Elj, A. Kerkeni, N. Gharbi and S. El-Fazâa, 2011. Effect of age-dependent exposure to lead on hepatotoxicity and nephrotoxicity in male rats. J. Environ. Toxicol., 26(1): 68-78.

Bijoor, A.R., S. Sudha and T. Venkatesh, 2012. Neurochemical and neurobehavioral effects of low lead exposure on the developing brain. Ind. J. Clin. Biochem., 27(2): 147-151.

Cecil, K.M., C.J. Brubaker, C.M. Adler and K.N. Dietrich, 2008. Decreased brain volume in adults with childhood lead exposure. PLoS Med., 5(5): 741-750.

Chao, S.L., J.M. Moss and G.J. Harry, 2007. Lead-induced alterations of apoptosis and neurotrophic factor, mrna in the developing rat cortex, hippocampus and cerebellum. J. Biochem. Mol. Toxicol., 21(5): 265-272.

Dadak, J.B., S.Y. Gazuwa and G.A. Ubon, 2009. Hepatoprotective potential of calcium and magnesium against cadmium and lead induced hepatotoxicity in wistar rats. Asian J. Biotecnol., 1(1): 12-19.

Deveci, E., S. Söker, O. Baran, S. Tunik and E. Ayaz, 2011. Ultrastructural changes in the kidney cortex of rats treated with lead acetate. Int. J. Morphol., 29(3): 1058-1061.

Diamond, G.L., 2005. Risk Assessment of Nephrotoxic Metals. In: Tarloff, J. and L. Lash (Eds.), the Toxicology of the Kidney. CRC Press, London, pp: 1099-1132.

Ebuehi, O.A., R.A. Ogedegbe and O.M. Ebuehi, 2012. Oral administration of vitamin C and vitamin E ameliorates lead-induced hepatotoxicity and oxidative stress in the rat brain. Nig. Q. J. Hosp. Med., 22(2): 85-90.

El-Masry, T., A.M. Emara and N.A. El-Shitany, 2011. Possible protective effect of propolis against lead-induced neurotoxicity in animal model. J. Evolut. Biol. Res., 3(1): 4-11.

Elmenofi, G.A.M., 2012. Bee honey dose-dependently ameliorates lead acetate- mediated hepatorenal toxicity in rats. Life Sci. J., 9(4): 780-788.

El-Neweshy, M. and Y. El-Sayed, 2011. Influence of vitamin C supplementation on lead-induced histopathological alterations in male rats. Exp. Toxicol. Pathol., 63(3): 221-227.

El-Sokkary, G.H., G.H. Abdel-Rahman and E.S. Kamel, 2005. Melatonin protects against lead-induced hepatic and renal toxicity in male rats. Toxicology, 213(1-2): 25-33.

Falah, A.M., 2012. Protective effects of latex of *Ficus carica L.* against lead acetate-induced hepatotoxicity in rats. J. J. Biol. Sci., 5(3): 175.

Fan, G., C. Feng, Y. Li, C. Wang and J. Yan, 2009. Selection of nutrients for prevention or amelioration of lead-induced learning and memory impairment in rats. Ann. Occup. Hyg., 53(4): 341-351.

Farag, A.H., A.K. Mandy, G.H. Abdel-Rahaman and M.M. Osofor, 2007. Protective effect of *Nigella Sativum* seeds against lead induced hepatorenal damage in males rats. J. Biol. Sci., 10(17): 2809-2816.

Flora, S.J.S., G. Flora and G. Saxena, 2006. Environmental Occurrence, Health Effects and Management of Lead Poisoning. In: Casas, S.B. and J. Sordo (Eds.), Lead: Chemistry, Analytical Aspects, Environmental Impact and Health Effects. Elsevier, the Nethlands, pp: 158-228.

Garaza, A., R. Vega and E. Soto, 2006. Cellular mechanisms of lead neuro toxicity. Med. Sci. Monitor., 12(3): 57-65.

Ghanem, K.Z., M.M. Ramadan, A.H. Farrag and H.Z. Ghanem, 2008. Egyptian artichoke volatile compounds: Protect against lead-induced hepatic and renal toxicity inmale rats. JASMR, 3(2): 193-203.

Gidlow, D.A., 2004. Lead toxicity. Occup. Med., 54: 76-81.

Gurer-Orhan, H., H.U. Sabır and H. Ozgune, 2004. Correlation between clinical indicators of lead poisoning and oxidative stress parameters in controls and lead-exposed workers. Toxicology, 195: 147-154.

Halawa, H.M., N.E. El-Nefiawy, N.A. Makhlouf and A.M. Awatef, 2009. Evaluation of honey protective effect on lead induced oxidative stress in rats. JASMR, 4(2): 197-209.

Hassan, A.A. and H.M. Jassim, 2010. Effect of treating lactating rats with lead acetate and its interaction with vitamin E or C on neurobehavior, development and some biochemical parameters in their pups. Iraqi J. Vet. Sci., 24(1): 45-52.

Ha, X., Q. Yin, T. Lü, B. Liu and Y. Xu, 2010. Lead acetate in drinking water is toxic to hippocampal tissue. Neural Regen Res., 5(7): 519-524.

Ibrahim, N.M., E.A. Eweis, H.S. El-Beltagi and E. Yasmin, 2012. Effect of lead acetate toxicity on experimental male albino rat. Asian Pac. J. Trop. Biomed., 2(1): 41-46.

Ishiaq, O., A.G. Adeagbo and H. Nta, 2011. Effect of a natural antioxidant fruit-tomatoes (Lycoperscion esculentium) as a potent nephroprotective agent in lead induced nephrotoxicity in rat. J. Pharmacog. Phytotherap., 3(5): 63-66.

Jabeen, R., M. Tahir and S. Waqas, 2010. Teratogenic effects of lead acetate on kidney. J. Ayub Med. Coll. Abbottabad, 22(1): 76-79.

Jarad, A.S., 2012. Protective effect of garlic against lead acetate toxicity in some biochemical and histopathological parameters in rats. Al-Anbar. J. Vet. Sci., 5(1): 108-114.

Kansal, L., V. Sharma, A. Sharma, S. Lodi and S.H. Sharma, 2011. Protective role of *Coriandrum sativum* (coriander) extracts against lead nitrate induced oxidative stress and tissue damage in the liver and kidney in male mice. Int. J. Appl. Biol. Pharm. Technol., 2(3): 65-83.

Khaki, A. and A. Khaki, 2010. Antioxidant effect of ginger to prevents lead-induced liver tissue apoptosis in rat. J. Med. Plants Res., 4(14): 1492-1495.

Khan, M.S.H., M.S. Mostafa, M.A. Hossain and M.A. Sayed, 2008. Effect of garlic and vita-min B-complex in lead acetate induced toxicities in mice. Bang. J. Vet. Med., 6(2): 203-210.

Khanam, S. and K. Devi, 2005. Effect of withania somnifera root extract on lead-induced DNA damage. J. Food, Agric. Environ., 3(1): 31-33.

Kharoubi, O., M. Slimani and A. Aoues, 2011. Neuroprotective effect of wormwood against lead exposure. J. Emerg. Trauma. Shock., 4: 82-8.

Koriem, K.M., 2009. Lead toxicity and the protective role of *Cupressus sempervirens* seeds growing in Egypt. Rev. Latinoamer. Quím., 37(3): 230-242.

Kumar, K.B., Y.R. Prabhakara, T. Noble, K. Weddington, V.P. McDowell, S. Rajanna and R. Bettaiya, 2009. Lead-induced alteration of apoptotic proteins in different regions of adult rat brain. Toxicol. Lett., 184(1): 56-60.

Li, R.G., T.T. Li, L. Hao and X. Xu, 2009. Hydrogen peroxide reduces lead-induced oxidative stress to mouse brain and liver. Bull. Environ. Contam. Toxicol., 82: 419-422.

Mehana, E.E., M.A. Meki and K.M. Fazili, 2010. Ameliorated effects of green tea extract on lead induced liver toxicity in rats. Exp. Toxicol. Pathol., 645(4): 291-5.

Missoun, F., M. Slimani and A. Aoues, 2009. Toxic effect of lead on kidney function in rat Wistar African. J. Biochem. Res., 4(2): 21-27.

Mohamed, N.A. and S.M. Saleh, 2010. Effect of pre and postnatal exposure to lead acetate on the kidney of male albino rat: A light and electron microscopic study. Egypt. J. Histol., 33(2): 365-379.

MSF (Medecins Sans Frontieres), 2012. Lead poisoining crisis in Zamfara Northern Nigeria. Briefing Paper May.

Nakao, K., K. Kibayashi, T. Taki and H. Koyama, 2010. Changes in the brain after intracerebral implantation of a lead pellet in the rat. J. Neurotrauma, 27(10): 1925-1934.

Nehru, B.S. and S. Kanwar, 2004. N-acetylcysteine exposure on lead-induced lipid peroxidative damage and oxidative defense system in brain regions of rats. Biol. Trace Elem. Res., 101(3): 257-264.

Osfor, M.H., H.S. Ibrahim, Y.A. Mohamed and S.M. Ahmed, 2010. Effect of alpha lipoic acid and vitamin E on heavy metals intoxication in male albino rats. J. Am. Sci., 6(8): 56-63.

Ozguner, F., A. Armagan, A. Koyu, S. Calıskan and H. Koylu, 2005. A novel antioxidant agent Caffeic Acid Phenethyl Ester (CAPE) prevents shock wave-induced renal tubular oxidative stress. Urol. Res., 33: 239-243.

Ponce-Canchihuamán, J.C., O. Pérez-Méndez, R. Hernández-Muñoz and P.V. Torres-Durán, 2010. Protective effects of Spirulina maxima on hyperlipidemia and oxidative-stress induced by lead acetate in the liver and kidney. Lipids Health Dis., 9: 35.

Reckziegel, P., V.T. Dias, D. Benvegnú and N. Boufleur, 2011. Locomotor damage and brain oxidative stress induced by lead exposure are attenuated by gallic acid treatment. Toxicol. Lett., 203: 74-81.

Sajitha, G.R., R. Jose, A. Andrews, K.G. Ajantha, P. Augustine and K.T. Augusti, 2010. Garlic oil and vitamin e prevent the adverse effects of lead acetate and ethanol separately as well as in combination in the drinking water of rats. Indian J. Clin. Biochem., 25(3): 280-288.

Shalan, M.G., M.S. Mostafa, M.M. Hassouna, S.E. Nabi and A. Rafie, 2005. Amelioration of lead toxicity on rat liver with vitamin C and silymarin supplements. Toxicology, 206: 1-15.

Sidhu, P. and B. Nehru, 2004. Lead intoxication: Histological and oxidative damage in rat cerebrum and cerebellum. J. Trace Elem. Exp. Med., 17(1): 45-53.

Soodi, M., N. Naghdia and M. Sharifzadeh, 2008. Effect of lead (Pb^{2+}) exposure in female pregnant rats and their offspring on spatial learning and memory in morris water maze. Iran. J. Pharm. Res., 7(1): 43-51.

Suleiman, J.B., E.D. Eze, I.J. Momoh, W. Usman and N.C. Hedima, 2013. Ameliorative effect of vitamin C on serum liver enzymes in lead-induced toxicity in Wistar rats. J. Sci., 3(1): 188-192.

Taib, N.T., B.M. Jarrar and M. Mubarak, 2004. Ultrastructural alterations in hepatic tissues of white rats (Rattus norvegicus) induced by lead experimental toxicity. Saudi J. Biol. Sci., 11(1): 11-20.

Tangponga, J. and S. Satarug, 2010. Alleviation of lead poisoning in the brain with aqueous leaf extract of the *Thunbergia laurifolia* (*Linn.*). Toxicol. Lett., 198: 83-88.

Waggas, A.M., 2012. Grape seed extract (*Vitisvinifera*) alleviate neurotoxicity and hepatotoxicity induced by lead acetate in male albino rats. J. Behav. Brain Sci., 2: 176-184.

Wang, C., J. Liang, C. Zhang, Y. Bi, X. Shi and Q. Shi, 2007. Effect of ascorbic Acid and thiamine supplementation at different concentrations on lead toxicity in liver. Ann. Occup. Hyg., 51(6): 563-9.

Weaver, V.M., B.G. Jaar, B.S. Schwartz and A.C. Todd, 2005. Associations among lead dose biomarkers, uric acid and renal function in Korean leadworkers. Environ. Health Perspect., 113(1): 36-42.

Xu, J., H.C. Yan, B. Yang, L.S. Tong and Y.X. Zou, 2009. Effects of lead exposure on hippocampal metabotropic glutamate receptor subtype 3 and 7 in developmental rats. J. Negative Results BioMed., 8(5): 1-8.

Yedjou, C.G. and P.B. Tchounwou, 2007. N-Acetyl-L-Cysteine affords protection against lead-induced cytotoxicity and oxidative stress in human liver carcinoma (HepG2) cells international. J. Environ. Res. Pub. Health, 4(2): 132-137.

Yun, H., I. Kim, S. Kwon and J.S. Kang, 2011. Protective effect of *Chlorella vulgaris* against lead induced in rats brain. J. Health Sci., 57(3): 245-204.

Zralý, Z., B. Písaříková, M. Trčková and M. Navrátilová, 2008. Effect of humic acids on lead accumulation in chicken organs and muscles. Acta Vet., 77: 439-445.