DOI: 10.7860/JCDR/2020/45615.14345

Review Article

Public Health Section

Human Exposure to Lead, Mechanism of Toxicity and Treatment Strategy- A Review

KS SRIDEVI SANGEETHA[1], S UMAMAHESWARI[2]

ABSTRACT

Lead is one of the earliest metals discovered by humans. It has a number of unique properties such as softness, high malleability, ductility, low melting point, resistance to corrosion and low cost. This has made its widespread usage in different industrial sectors, which in turn has led to its manifold occurrence in free form in biological systems and the inert environment. Over the last few decades, with the adverse effects of lead coming to the forefront, nations across the world have started to recognise lead toxicity. This review covers the history behind the usage of lead, sources of lead exposure, absorption, distribution and excretion of lead, toxic signs and symptoms of lead toxicity and methods to evaluate the lead levels and the current treatment regimen. This also covers the details of current research work going on in the area of herbal remedies against lead induced liver damage.

Keywords: Chelator, Environment, Heavy metal, Oxidative stress, Pollutant, Symptoms

INTRODUCTION

Contamination of heavy metals in the environment is a major global concern, because of toxicity and threat to the human life and ecosystem. The levels of metals and its toxicity is increasing in all states of environments including air, water and soil. Metal contaminated environments pose serious threat to health and ecosystems. One of the earliest metals discovered by the human population is Lead (Pb). It has a number of unique properties such as low melting point, ductility, high malleability, resistance to corrosion and low cost. This has made its widespread usage in different industrial sectors, which in turn has led to its manifold occurrence in free form in the environment. During that time hazardous effects of lead was not considered, but recent years the side effects of lead toxicity become worst. At the same time, because of its non biodegradable nature, it is considered as potent hazardous toxins and causes serious health issues to people. There are a number of reports evidencing this aspect. One such report is the incidence of childhood lead poisoning, it is mainly due to drinking contaminated water in West Bengal and Bangladesh [1]. The use of lead and its toxicity in the urban and rural areas has become a national calamity when compared to its occurrence in Himalayan population with no industrial lead exposure.

HISTORY BEHIND USAGE OF LEAD

The use of lead by humans dates back to thousands of years to the times of Romans, Egyptians and Babylonians for making statues, coins, water pipes and weights. It was not used for ornamental usage because of its soft nature. They used lead compounds to glaze containers used for food and water, boil and condense grape juice in lead pots for pre serving and sweetening of wine [2]. One of the major sources of lead exposure are from lead acid batteries, cosmetics, leaded gasoline and paints. The usage of leaded gasoline was banned in US from 1970, followed by 1975 many countries including Western Europe, Korea, Thailand, Australia, China, Vietnam, the Philippines, Japan, Canada, Mexico, Central and South America stopped using this of leaded gasoline [3]. India banned the use of leaded petrol by 2000.

SOURCES OF LEAD EXPOSURE

Domestic Environment

Lead is ubiquitous in the environment, the contribution sources includes both natural and human activities. Human activity includes smelting, refining and mining, this may results in lead concentration in the environment.

Food: Lead present in the environment may get deposited in the growing plant or food processing and results in lead contamination, few reasons are given below:

- Lead present in the pesticide, fertilizer or soil may taken up into a root and gets deposited in leaf.
- Lead from industrial origin may get deposited in the plant.
- Canned foods are the source of lead which is leached from the solder in the seams of can.
- Leaching of lead from vessels like lead glazed ceramic or porcelain pots.

Drinking water: Usage of water pipes which are made up of lead may contaminate the drinking water and increases the blood lead level who consumes it.

Air: Lead in the air comes from various sources. Largest contribution through leaded gasoline. Highest concentration observed near smelters.

Lead based paint: Lead has been used as a pigment and drying agent in primers, paints and resigns. Its usage was banned in 1970's. The usage of lead paints was banned for residential purpose, but still older building that were already painted with leaded paint may cause lead exposure in young children [4].

Occupational Environment

Occupational and environmental exposure [Table/Fig-1] to lead may resulting in serious health issues in developing countries [5].

Major occupations and industries associated with lead over exposure	
❖ Battery manufacturing	❖ Pigment manufacturing
❖ Construction workers	❖ Pipe fitters
❖ Demolition workers	❖ Plastics industry
❖ Foundry workers	❖ Pottery workers
❖ Gas-station attendants	❖ Radiator repair
❖ Gasoline additives	❖ Rubber industry
❖ Lead miners	❖ Soldering of lead products
❖ Lead smelters and refiners	❖ Welders

[Table/Fig-1]: Industries and occupation associated with lead exposure.

ABSORPTION, DISTRIBUTION AND EXCRETION OF LEAD

Absorption

Routes of absorption of Lead (Pb) is through ingestion, inhalation or through skin. Exposure to lead occurs mainly through gastrointestinal (GI) tracts and respiratory system [6]. Absorption is through respiratory

system mainly dependents on size of the particle. It is estimated that be 30-40% of inhaled lead reaches the bloodstream [7]. Absorption rate through GI tract also depends on the age and nutritional status of the exposed individual. The average percentage of lead absorption in adults is 10 to 15% of the ingested quantity whereas it increases upto 50% in infants, young children and pregnant women. The percentage of lead absorption increases in fasting state and in the deficiency of calcium, iron, phosphorus or zinc [8]. Iron leads to defective absorption of lead, hence, Iron deficiency leads to increased concentration of blood lead in children [9]. Researchers demonstrated that increased intake of calcium supplementation in infants and children results in decreased absorption of lead [10]. High intake of magnesium, phosphate and dietary fat leads to decrease gastrointestinal absorption of lead [11]. Lead absorption occurs through both passive and facilitated diffusion [12]. Some studies evidences the hypothesis that divalent metal transporter 1 (DMT1) is responsible for lead transport [13].

Inorganic form of Pb from food, water, paint, vinyl products and tetraethyl lead from leaded gasoline are absorbed through the skin [14]. Incase of lead absorption through skin, it is first transported into the plasma and rapidly concentrated into the extra cellular fluid pool like sweat and saliva without significant uptake by erythrocytes.

Distribution of Lead

After absorption lead gets accumulate in blood, soft tissues and bone. Approximately 99% of the absorbed lead is found in the erythrocytes, 1% is left in plasma and serum. The kinetics of lead transfer from blood to soft tissues which tends to be low and takes approximately 4 to 6 weeks. Because of the short half-life of 35 days in the blood, this blood lead level cannot be used to diagnose the lead exposure happened 6 weeks before [15]. Higher percentage of lead is taken up by the kidney followed by liver and other soft tissues [16]. Half life of lead in various organis varies, in blood the half-life is 35 days in blood [17]. In soft tissues half-life was found to be 40 days and in bones it was 20 to 30 years [18].

Lead distribution in various organs depends on the blood flow to the tissues. It can crosses the blood brain barrier [19]. Various studies revealed that oral intake of inorganic lead affect the immune system.

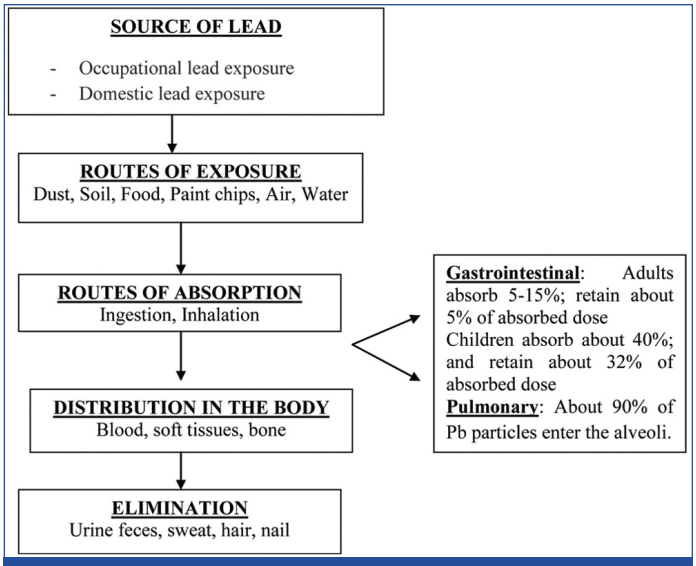
Excretion of Lead

Inorganic lead does not metabolised in our body, which is excreted unchanged in urine. The mechanisms by which the absorbed lead excreted appear unclear. Lead Excreted by many ways which includes secretion into the bile, gastric fluid, and saliva [20]. Alkyl lead like tetraethyl and tetramethyl lead on oxidative dealkylation form a highly neurotoxic compounds [21]. This reaction is catalysed by cytochrome p450-dependent monooxygenase enzyme present in liver [22]. Other routes of excretion of lead includes nails and sweat [23,24]. On the whole, lead is excreted very slow and tends to accumulate in the body with biological half-life of 10 years. Lead is also excreted in milk in concentrations of upto 12 µg/L.

Children are more vulnerable to lead toxicity due to the following reasons:

1. Frequent hand to mouth activity.
2. Children absorb 40 to 50% of dietary lead whereas adult absorb only 10%.
3. Nervous systems are rapidly developing in children.
4. Lead in kidney interfere with vitamin D 1,2 dihydroxy cholecalciferol.
5. Lead interferes with the formation of active vitamin D, thereby interfere with calcium absorption.

The absorption, distribution and excretion of lead is presented in [Table/Fig-2].



[Table/Fig-2]: Diagrammatic representation showing the source of exposure, absorptions, distribution and excretion of lead.

BIOCHEMICAL INDICATORS OF LEAD TOXICITY

Generally Blood Lead Level (BLL), Blood δ Amino Levulinic Acid Dehydratase (ALAD) activity, Urinary Amino Levulinic Acid (ALA), Eythrocyte Protoporphyrin level and creatinine levels are measured to evaluate lead toxicity.

TOXIC SIGNS AND SYMPTOMS OF LEAD TOXICITY

Blood Lead Level (BLL) of 60 µg/dL was considered safe during 1960s. In 1985, the acceptable level was reduced to 25 µg/dL and it was further reduced to 10 µg/dL in 1991 [25,26,27]. The World Health Organisation (WHO) lead guidelines recommended tolerable lead intake level based from review of the scientific evidence conducted in 2010, the Joint Food and Agriculture Organisation of the United Nations estimated the safer weekly intake 25 µg/kg body weight.

The following [Table/Fig-3] describes the toxic effect of lead in various organs in adults and children.

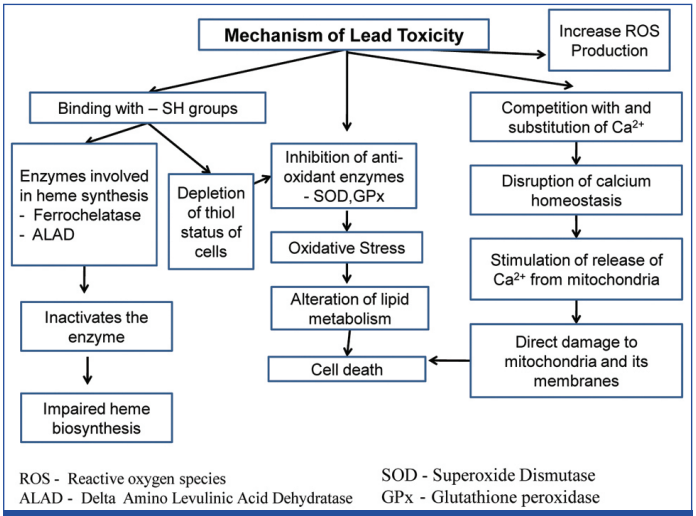
Toxic effects of lead in adults	
Toxic effects	**Blood Pb level (in pb/dL)**
Nervous system: Overt clinical encephalopathy	100-120
Kidney: Atrophy and interstitial nephritis	40-100
Gastrointestinal: Colic	40-60
Blood cells: Anemia	50
Nervous system: Learning/IQ disruption, sensory system deficits	40
Heart and blood vessels: Hypertension	<7
Biochemical: Enzymes changes	3-30
Toxic effects of lead in children	
Toxic effects	**Blood Pb level (in pb/dL)**
Kidney: Atrophy and interstitial nephritis	80-120
Nervous system: Clinical encephalopathy	80-100
Gastrointestinal: Colic	60-100
Blood cells: Anaemia	20-40
Biochemical changes: Enzymes level altered	<10
Nervous system: IQ disruption, sensory system deficits	<10

[Table/Fig-3]: Toxic effects of lead in different organs in children and adults.

MECHANISM OF LEAD-INDUCED TOXICITY

Though various mechanisms postulated about lead induced toxicity, the mechanism represented in [Table/Fig-4] was considered to be most important mechanism which involves oxidative stress.

Enormous number of evidences have shown that lead induced generation of reactive oxygen species resulted in oxidative stress and weakens the cells defense mechanism [28].



[Table/Fig-4]: Schematic representation of various mechanisms of lead toxicity.

There is an important indirect mechanism also which involves the depletion of cells' major sulfhydryl resulting in oxidative stress [29]. When Glutathione (GSH) is depleted in the body by lead, the body starts making more GSH from cysteine. This antioxidant defense mechanism may be protected by many enzymes. The cofactors like selenium, zinc, copper of many enzymes may be replaced by lead, and thereby, resulting in enzyme inactivation. Various studies in lead-exposed animals reported to have either elevated lipid peroxidation or decreased intrinsic antioxidant defense in various tissues.

Oxidative Stress

Superoxide Dismutase (SOD), a free radical scavenger and metalloenzyme (zinc/copper) [30]. Various research revealed that lead exposure significantly decreased the level of SOD. This may be due to an increase in lead concentration in these tissues and their possible reaction with this enzyme thereby, reducing the disposal of superoxide radicals. Catalase is an efficient decomposer of H_2O_2 and known to be susceptible to lead toxicity. Lead induced decrease in brain Glutathione Peroxidase (GPx) activity may arise as a consequence of impaired functional groups such as GSH and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) or selenium mediated detoxification of toxic metals. While antioxidant enzyme Glutathione S-transferase (GST) is known to provide protection against oxidative stress [31].

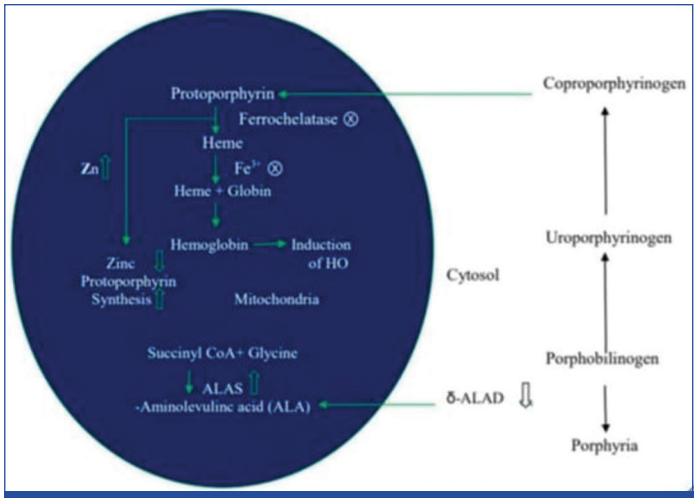
Lead reaction with oxyhaemoglobin results in superoxide radical formation. 5-ALAD is involved in the formation of heme precursor (porphobilinogen) by the condensation of two S-aminolevulinic acid (ALA). Hence, the ALAD inhibition results in the impairment of heme synthesis, and resulting in accumulation of ALA [Table/Fig-5]. Accumulation of ALA undergo metal catalysed autooxidisation, resulting in the conversion of oxyhaemoglobin to methemoglobin. This conversion results in the formation of ROS like superoxide and hydroperoxides.

CURRENT TREATMENT STRATEGY FOR LEAD TOXICITY

Chelation Treatment [32]

Some common chelating agents used against lead poisoning are given below:

1. Calcium disodium ethylene diamine tetraacetic acid ($CaNa_2EDTA$)
2. D-penicillamine
3. Meso 2,3-dimercaptosuccinic acid (DMSA)
4. Sodium 2,3-dimercaptopropane-1-sulphonate (DMPS)



[Table/Fig-5]: Lead effects in haemoglobin synthesis pathway.
ALAD: Amino levulinic acid dehydratase

Limitations of Current Chelating Agents

Treatment with DMSA and DMPS has got lesser adverse effects given in [Table/Fig-6]. Most of the conventional have side effects like reducing essential element level in the body. The Centers for Disease Control and Prevention (CDC) recommend chelating agent only when the blood lead level goes beyond 45 µg/dL. So, there is always a need for an alternative treatment with no side effects.

Chelating agents	Limiting factors
$CaNa_2EDTA$	Cannot pass through cellular membrane, use is restricted to ECF
	Produce renal toxicity
	Diuresis of endogenous zinc, hence monitoring is essential
D-penicillamine	Cause anaphylactic reaction in patient allergic to penicillin
	In children-monitoring with blood count, urinanalysis

[Table/Fig-6]: Limitations of current chelating agents.
$CaNa_2EDTA$: Calcium disodium ethylene diamine tetraacetic acid; ECF: Extracellular fluid

NEWER RESEARCH APPROACH AGAINST LEAD TOXICITY

Role of Antioxidant in Lead Toxicity Treatment [33]

In recent days, attention on usage of herbal drugs is increasing. Many plant products are rich source of antioxidant and can be used to prevent oxidative stress. As number of synthetic antioxidants has shown to have side effects, thus there has been increasing interest in using plant extract. Crude extracts of many plants observed to modify the toxic effect of lead, it is mainly due to antioxidant properties of flavonoids present in plants. Currently, antioxidants are reported to have vital role in the treatment of lead poisoning in humans as lead induces toxicity in various organs like brain, kidney and Liver.

Lead induced Liver Toxicity

Environmental exposure to pollutant like lead will affect and produce damage to the liver by various mechanism, mainly due to oxidative stress. Considering the mechanisms have been explicitly defined, oxidative stress was found to be one of the important mechanisms involved in toxic effects of lead. Hepatotoxicity is the injury to the liver that results in the impaired function of liver caused by the exposure to a drug or environmental xenobiotics. It may be due to lipid peroxidation, reduced glutathione and overproduction of ROS [34].

Role of Herbal Extracts in Lead induced Hepatic Damages [35-49]

Numerous studies have been done to find the effect herbal product against lead induced damages. The literature below [Table/Fig-7] shows the protective effect of various plant extract against lead

Plant name	Inducing agent and dosing	References
Cayratia carnosa	Lead acetate - 20 mg/Kg/b.wt/i.p for one day	Suganthi V et al., 2013 [35]
Tinospora cordifolia	Lead nitrate - 5 mg/kg/B.W/oral for 30 days	Sharma V and Pandey D, 2010 [36]
Asparagus racemosus	Lead nitrate - 20 mg/Kg body weight/oral for 45 days	Sharma VE et al., 2012 [37]
Leucas aspera	Lead acetate - 50 mg/kg/ b.wt/oral for 21 days	Thenmozhi M et al., 2013 [38]
Zingiber officinale Roscoe	Lead acetate -500 ppm by oral 50 for days	Attia AM et al., 2013 [39]
Spirulina	Lead acetate - 1.89 mg/kg for 7 days	Hemalatha K et al., 2012 [40]
Coriandrum sativum	Lead nitrate - 40 mg/kg/b.wt/oral for 7 days	Kansal L et al., 2011 [41]
Ocimum sanctum linn	Lead acetate - 2.10 mg/150 g/b.wt/oral for 3 days	Akilavalli N et al., 2011 [42]
Vitis vinifera	Lead acetate - 100 mg/kg/b.wt/ip - 7 days	Abeer M, 2012 [43]
Turmeric and myrrh	Lead acetate - 0.5% oral- 8 weeks	El-Ashmawy IM et al., 2006 [44]
Curcuma longa	Lead acetate - 1000 mg/kg/b.wt/oral for 28 days	Baxla SL et al., 2013 [45]
Morocco carob honey	Lead acetate - 2 g/kg.b.wt/oral for 24 days	Fihri AF et al., 2016 [46]
Green tea	Lead acetate - 0.4% oral for 8 weeks	Mehana EE et al., 2012 [47]
Murraya koenigii	Lead acetate - 15 mg/kg/b.et/i.p for 7 days	Ghosh DE et al., 2013 [48]
Moringa oleifera	Lead acetate - 2000 ppm for 2 weeks after that 7 days drug treatment	Velaga MK et al., 2014 [49]

[Table/Fig-7]: Herbal research on lead induced heapatic damage [35-49].

induced hepatic damages. The hepatoprotective effects produced by these plants are may be due to the presence of secondary metabolites, polyphenolic compound flavonoids.

CONCLUSION(S)

Lead is an environmental pollutant. It reaches environment through the deterioation from lead based paints, batteries and business that involves lead. When blood lead level reaches more than 10 microgram/dL, it produces toxicity. The signs and symptoms varies depends upon the dose of exposure. It affects the Nervous system, Renal system, Endocrine glands, Blood, Gastrointestinal tract, Cardiovascular system and Reproductive system. The major mechanism for lead toxicity is due to increased production of reactive oxygen species and inhibition of enzyme action (Lead binds to enzymes with sulphydryl group). Chelating agents like DMSA-2,3 dimercapto succinic acid and monoisoamyl DMSA can be used against lead toxicity. But, the main disadvantage of chelators is that, they are toxic in nature and it cannot completely remove lead from all tissues. Newer trend in treating lead toxicity is by using natural antioxidants. Antioxidant potential of herbal products can have beneficial effect on treating lead induced toxicity. This review will help young researchers to start more works on lead related toxicity study.

REFERENCES

[1] Kalia K, Flora SJ. Strategies for safe and effective therapeutic measures for chronic arsenic and lead poisoning. Journal of Occupational Health. 2005;47(1):01-21.
[2] Patrick L. Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment. Altern Med Rev 2006;11:02-22.
[3] Tzanakakis GN, Tsatsakis AM. Lead toxicity update. A brief review. Med Sci Monit. 2005;11(10):RA329-36.
[4] Dixon SL, Wilson JW, Clark CS, Galke WA, Succop PA, Chen M. Effectiveness of lead-hazard control interventions on dust lead loadings: Findings from the evaluation of the HUD lead-based paint hazard control grant program. Environmental Research. 2005;98(3):303.
[5] Yucebilgic G, Bilgin R, Tamer L, Tükel S. Effects of lead on Na+-K+ ATPase and Ca+ 2 ATPase activities and lipid peroxidation in blood of workers. International Journal of Toxicology. 2003;22(2):95-97.
[6] Wani AL, Ara A, Usmani JA. Lead Toxicity- A review. Interdiscip Toxicol. 2015;8(2):55-64.
[7] Rabinowitz MB, Kopple JD, Wetherill GW. Effect of food intake and fasting on gastrointestinal lead absorption in humans. The American Journal of Clinical Nutrition. 1980;33(8):1784-88.
[8] Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. Absorption and retention of lead by infants. Pediatric Research. 1978;12(1):29-33.
[9] Bogden JD, Gertner SB, Christakos S, Kemp FW, Yang Z, Katz SR, Chu C. Dietary calcium modifies concentrations of lead and other metals and renal calbindin in rats. The Journal of Nutrition. 1992;122(7):1351.
[10] Mahaffey KR, Gartside PS, Glueck CJ. Blood lead levels and dietary calcium intake in 1-to 11-year-old children: The Second National Health and Nutrition Examination Survey, 1976 to 1980. Pediatrics. 1986;78(2):257-62.
[11] Barltrop D, Meek F. Effect of particle size on lead absorption from the gut. Archives of Environmental Health: An International Journal. 1979;34(4):280-85.
[12] Aungst BJ, Fung HL. Kinetic characterization of in vitro lead transport across the rat small intestine: Mechanism of intestinal lead transport. Toxicology and Applied Pharmacology. 1981;61(1):39-47.
[13] Bressler JP, Olivi L, Cheong JH, Kim Y, Bannona D. Divalent metal transporter 1 in lead and cadmium transport. Annals of the New York Academy of Sciences. 2004;1012(1):142-52.
[14] Papanikolaou NC, Hatzidaki EG, Belivanis S, Tzanakakis GN, Tsatsakis AM. Lead toxicity update. A brief review. Medical Science Monitor. 2005;11(10):329-36.
[15] Al-Modhefer AJ, Bradbury MW, Simons TJ. Observations on the chemical nature of lead in human blood serum. Clinical Science. 1991;81(6):823-29.
[16] Rabinowitz MB. Toxicokinetics of bone lead. Environmental Health Perspectives. 1991;91:33.
[17] Roberts JR, Roberts J, Reigart JR, Ebeling M, Hulsey TC. Time required for blood lead levels to decline in nonchelated children. Journal of Toxicology: Clinical Toxicology. 2001;39(2):153-60.
[18] Rabinowitz MB, Wetherill GW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. J Clin Invest. 1976;58:260-70.
[19] Sanders T, Liu Y, Buchner V, Tchounwou PB. Neurotoxic effects and biomarkers of lead exposure: A review. Rev Environ Health. 2009;24(1):15-45.
[20] Rabinowitz MB, Wetherill GW, Kopple of lead metabolism in healthy humans. Journal of Clinical Investigation. 1976;58(2):260.
[21] Bolanowska W. Distribution and excretion of triethyllead in rats. Br J Ind Med. 1968;25:203-08.
[22] Kimmel EC, Fish RH, Casida JE. Bioorganotin chemistry. Bioorganotin chemistry. Metabolism of organotin compounds in microsomal monooxygenase systems and in mammals. J Agric Food Chem. 1977; 25(1):01-09.
[23] Omokhodion FO, Crockford GW. Lead in sweat and its relationship to salivary and urinary levels in normal healthy subjects. Sci Total Environ. 1991;103:113-22.
[24] Hohnadel DC, Sunderman FW Jr, Nechay MW, McNeely MD. Atomic absorption spectrometry of in microsomal monooxygenase systems and in mammals. J Agric Food Chem. 1977;25:01-09.
[25] CDC. Centre for disease control and prevention. Preventing lead poisoning in young children. A statement by the CDC. Atlanta GA: US Dept. of Health and Human Services; 1991.
[26] Canfield RL, Henderson CRJ, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microgram per deciliter. N Engl J Med. 2003;348:1517-26.
[27] Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol. 2004;26:359-71.
[28] Flora SJ. Nutritional components modify metal absorption, toxic response and chelation therapy. Journal of nutritional & environmental medicine. 2002;12(1):53-67.
[29] Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress part I: Mechanisms involved in metal-induced oxidative damage. Current Topics in Medicinal Chemistry. 2001;1(6):529-39.
[30] Saxena G, Flora SJ. Lead-induced oxidative stress and hematological alterations and their response to combined administration of calcium disodium EDTA with a thiol chelator in rats. Journal of Biochemical and Molecular Toxicology. 2004;18(4):221-33.
[31] Magos L, Webb M, Clarkson TW. The interactions of selenium with cadmium and mercury. CRC Critical Reviews in Toxicology. 1980;8(1):1.
[32] Flora SJ. Metal poisoning: Threat and management. Al Ameen J Med Sci. 2009;2(2):04-26.
[33] Flora SJ, Pachauri V. Chelation in metal intoxication. International Journal of Environmental Research and Public Health. 2010;7(7):2745-88.
[34] Saalu LC, Ajayi GO, Adeneye AA, Imosemi IO, Osinubi AA. Ethanolic seed extract of grapefruit (Citrus paradisi Macfad). Int J Cancer Res. 2009;5:44-52.
[35] Suganthi V, Gowri S, Gurusamy K. Hepatoprotective activity of Cayratia carnosa on liver damage caused by lead acetate in rats. J Nat Prod Plant Resour. 2013;3(2):76-79.

[36] Sharma V, Pandey D. Protective role of Tinospora cordifolia against lead-induced hepatotoxicity. Toxicology International. 2010; 17(1):12.
[37] Sharma VE, Verma RB, Sharma SH. Preliminary evaluation of the hepatic protection by pharmacological properties of the aqueous extract of Asparagus racemosus in lead loaded Swiss albino mice. Int J Pharm Pharm Sci. 2012;4(1):55-62.
[38] Thenmozhi M, Dhanalakshmi M, Devi KM, Sushila K, Thenmozhi S. Evaluation of hepatoprotective activity of Leucas aspera hydroalcoholic leaf extract during exposure to lead acetate in male albino Wistar rats. Asian J Pharm Clin Res. 2013;6(1):78-81.
[39] Attia AM, Ibrahim FA, Nabil GM, Aziz SW. Antioxidant effects of ginger (Zingiber officinale Roscoe) against lead acetate-induced hepatotoxicity in rats. African Journal of Pharmacy and Pharmacology. 2013;7(20):1213-19.
[40] Hemalatha K, Pugazhendy K, Jayachandran K, Jayanthi C, Meenambal M. Studies on the protective efficacy of Spirulina against lead acetate induced hepatotoxicity in Rattus norvegicus. Group. 2012;2(3.17):0-15.
[41] Kansal L, Sharma V, Sharma A, Lodi S, Sharma SH. Protective role of coriandrum sativum (coriander) extracts against lead nitrate induced oxidative stress and tissue damage in the liver and kidney in male mice. International Journal of Applied Biology and Pharmaceutical Technology. 2011;2(3):65-83.
[42] Akilavalli N, Radhika J, Brindha P. Hepatoprotective activity of Ocimum sanctum Linn. Against lead induced toxicity in albino rats. Asian Journal of Pharmaceutical and Clinical Research. 2011;4(2):84-87.
[43] Abeer M. Grape seed extract (Vitisvinifera) alleviate neurotoxicity and hepatotoxicity induced by lead acetate in male albino rats. Journal of Behavioral and Brain Science. 2012;2(1):12-19.
[44] El-Ashmawy IM, Ashry KM, El-Nahas AF, Salama OM. Protection by turmeric and myrrh against liver oxidative damage and genotoxicity induced by lead acetate in mice. Basic & Clinical Pharmacology & Toxicology. 2006;98(1):32-37.
[45] Baxla SL, Gora RH, Kerketta P, Kumar N, Roy BK, Patra PH. Hepatoprotective effect of Curcuma longa against lead induced toxicity in Wistar rats. Vet World. 2013;6(9):664-67.
[46] Fihri AF, Al-Waili NS, El-Haskoury R, Bakour M, Amarti A, Ansari MJ, Lyoussi B. Protective Effect of Morocco Carob Honey Against Lead-Induced Anemia and Hepato-Renal Toxicity. Cellular Physiology and Biochemistry. 2016;39(1):115-22.
[47] Mehana EE, Meki AR, Fazili KM. Ameliorated effects of green tea extract on lead induced liver toxicity in rats. Experimental and Toxicologic Pathology. 2012; 64(4):291-95.
[48] Ghosh DE, Firdaus SB, Mitra EL, Dey MO, Chattopadhyay AI, Pattari SK, Dutta SA, Jana KU, Bandyopadhyay DE. Hepatoprotective activity of aqueous leaf extract of Murraya koenigii against lead-induced hepatotoxicity in male wistar rat. Int J Pharm Pharm Sci. 2013;5(1):285-95.
[49] Velaga MK, Daughtry LK, Jones AC, Yallapragada PR, Rajanna S, Rajanna B. Attenuation of lead-induced oxidative stress in rat brain, liver, kidney and blood of male wistar rats by Moringa oleifera seed powder. Journal of Environmental Pathology, Toxicology and Oncology. 2014; 33(4).

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Faculty of Allied Health Sciences, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu, India.
2. Professor and Head, Department of Pharmacology, Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
KS Sridevi Sangeetha,
No 4A/7, Ponniamman Koil Street, Kottur, Chennai-600084, Tamil Nadu, India.
E-mail: sangeethsb@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 26, 2020
- Manual Googling: Sep 15, 2020
- iThenticate Software: Dec 02, 2020 (17%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 25, 2020**
Date of Peer Review: **Aug 21, 2020**
Date of Acceptance: **Sep 18, 2020**
Date of Publishing: **Dec 15, 2020**