
REVIEW ARTICLE**Treating Lead Toxicity: Possibilities beyond Synthetic Chelation***Venkatesh Thuppil¹*, Shambhavi Tannir¹**¹National Referral Centre for Lead Projects in India, Bangalore-560034, (Karnataka) India*

Abstract:

Lead, a ubiquitous metal, is one of the most abundant elements present on earth. Its easy availability and cost effectiveness made it an extremely popular component in the industrial revolution. However, its hazardous health effects were not considered at the time. Over the last few decades, with the adverse effects of lead coming to the forefront, nations across the world have started to recognize and treat lead toxicity. The most reliable and used method until now has been chelation therapy. Recent research has suggested the use of natural products and sources to treat lead poisoning with minimal or no side effects. This review has tried to summarize a few of the natural products/sources being investigated by various groups.

Key words:

Oxidative stress, antioxidants, side effects of chelation, coriander, tea, garlic, turmeric, ginger, amla, ascorbic acid, allicin, flavonoids, catechins.

Introduction:

Lead is a soft and malleable metal with a bluish, white colour. It is used in building construction, lead acid batteries, in paints and ceramic glazes, in solder, radiation shielding and sound proofing. The use of lead by humans dates back to thousands of years to the times of Romans, Egyptians and Babylonians. This heavy metal was used extensively in the plumbing systems

of ancient Rome. They used lead compounds to glaze containers used for food and water [1]. They also used to boil and condense grape juice in lead pots for preserving and sweetening of wine [2]. The main sources of environmental lead are from leaded gasoline, lead shots or bullets, soil, dust, toys, lead acid batteries, cosmetics and paints. The United States began to phase out leaded gasoline in 1970 and it took 20 years to nearly completely eliminate it. Since 1975, many countries have introduced unleaded gasoline, including Japan, Canada, Mexico, Central and South America, all of Western Europe, Korea, Australia, China, Thailand, Vietnam, the Philippines and Taiwan [3, 4]. In 2000, India banned the use of leaded petrol and by 2008 all but 16 countries phased out the use of leaded gasoline [5]. Children are more vulnerable to the toxic effects of lead, especially infants, as their organs systems are still developing. Children have frequent hand to mouth activity increasing the possibility of ingestion of lead [6-8]. The most obvious effect in children is that of lowered nervous system response, lowered IQ, and gastro-intestinal effects [7, 9]. Lead is a toxicant for virtually all organs of the body and has significant debilitating effects on the nervous, renal, hepatic and hematopoietic systems. Lead toxicity is extremely dangerous in children as their bodies are still developing and are the most susceptible to the adverse effects. Although, the CDC has issued a statement that 10 µg/dL of lead in

blood is the minimum threshold level, there is no safe level of lead in the human body [10]. Inhalation and ingestion are the two most common routes of entry of lead into the body. Although ingestion is more common source, inhalation is the most significant as pulmonary absorption is efficient. Lead is absorbed in the blood plasma where it equilibrates with the extracellular fluid, crosses membranes such as the blood brain barrier and placenta, and accumulates in soft tissues and bones. Lead that is stored in bones can have a half life of up to 28 years and can be mobilized intermittently at times of stress, lactation or hormonal imbalances [11]. Gastrointestinal ingestion is the most important source of lead intake in the body as lead does not have a feedback mechanism to inhibit its uptake [12]. Furthermore, dietary components, such as, sodium citrate, ascorbic acid, amino acids, vitamin D, proteins, fat and lactose can bind to lead and thus enhance the absorption of lead [13]. Lead has the ability to mimic Ca^{2+} ions and can therefore easily traverse membranes. It preferentially binds to sulfhydryl groups in proteins and enzymes causing errors in their action [14]. Lead is found to increase oxidative stress by the production of free radicals and decreasing antioxidant capacity resulting in cell apoptosis. The major method of treatment is chelation therapy. However, in recent years, a lot of new research has shown the chelating and antioxidant capacity of natural products.

Effect of Lead on Hematological System:

Lead toxicity usually manifests itself as anemia due to destruction of red blood cells and lowered production of the same [15]. Lead

inhibits certain enzymes necessary for heme production like delta-aminolevulinic acid (ALAD), coproporphyrinogen and ferrochelatase. The inhibitory effect is most significant in ALAD [16]. Crystal studies of PBGS proteins show all ALADs to be homo-octamers that purify with 8 Zn (II), of which 4 have sulfur ligands. In the presence of Pb (II), strong binding interaction is seen preferentially between these sites and lead [16]. ALAD catalyses the asymmetric addition of 2 molecules of ALA to form porphobilinogen, which is the second step in heme synthesis [16]. Lead has the ability to displace zinc at the metal binding site resulting in an increase in the ALA levels in blood and plasma which can be detected in urine and blood at blood lead levels less than $10 \mu\text{g/litre}$ [10, 14, 17]. A variety of studies have suggested that chronic exposure to lead leads to a decrease in erythrocyte membrane permeability which is due to a decrease in membrane transfer protein [18,19]. As lead displaces zinc from its position, an increase in the amount of zinc protoporphyrin in blood is also a biological marker for lead poisoning [20].

Effect of Lead on the Renal System:

Acute lead toxicity can result in proximal tubular damage and manifests as glycosuria and aminoaciduria. Chronic exposure to lead can cause severe renal problems including decline in glomerular filtration rate, hypertension, hyperurecemia, gout and renal failure [21, 22]. Hyperurecemia is an effect of impaired tubular function and altered purine metabolism [23]. Short term exposure is typically seen with lead-induced nuclear inclusion bodies in the proximal tubular lining cells whereas longer period

of exposure to lead can show diffuse interstitial or peritubular fibrosis [24]. Proximal tubule cell mitochondria are significant targets for lead. Lead impairs renal function and decreases activities involved with heme synthesis as many of the enzymes involved are present in the mitochondria [25]. Studies have shown that lead nephropathy also includes reduced production of prostaglandins, reduced excretion of certain vasodilators and an increased excretion of the vasoconstrictor thromboxane [21, 22].

Effect of Lead on the Hepatic System:

Liver is the highest repository (33%) of lead in soft tissues followed by kidney [26]. Lead binds to form a stable complex with mitochondria in both the liver and kidneys [27]. Chronic ingestion of lead leads to a significant decrease in liver glutathione synthase (GSH) levels [28]. Other studies have indicated that an increase in reactive oxygen species (ROS) in the liver [29]. ROS play an important role in inducing apoptosis under physiological and pathological conditions and leads to a significant increase in DNA damage and apoptosis. Studies have shown the mitochondria to be the source and target of ROS [28]. Animal studies show a decrease in CYP450 levels (required for catalysis of organic substrates) as well as estradiol-17 beta enzyme levels (important hormone involved in female reproduction and sexual development of organs) [26]. And studies on Wistar rats have shown that a single dose of lead nitrate can cause a significant proliferation of liver cells by an increase in the number of cells entering mitosis [30]. This adds to the theory of lead being a potent teratogenic agent. A study on chicken liver indicates that the exposure to

lead causes severe periportal inflammation which suggests a similar effect in humans which will lead to liver damage [12]. Lead toxicity also leads to impaired haeme synthesis in the liver which results in impaired metabolism of endogenous antagonists. This further leads to altered metabolism of tryptophan and consequently elevated brain levels of tryptophan, serotonin and 5-Hydroxyindoleacetic acid (HIAA) which results in disturbed indoleamine neurotransmitter function [31].

Effect of Lead on the Nervous System:

One of the main targets of lead poisoning is the central nervous system (CNS) especially the developing nervous system. This makes children more susceptible to intellectual, psychological and neurological effects of lead. Lead has the ability to mimic Ca^{2+} and readily crosses the blood brain barrier. Its induction in calcium mediated cellular processes causes various debilitating effects on the development and function of the brain [32, 33]. Chronic exposure to lead can show problems in neurological functioning in adults and a lowered brain volume in adults including portions of the prefrontal cortex, insula, total gray matter, parietal white matter [34]. Studies on cognitive tests taken by workers occupationally exposed to lead showed deficits in various aspects are seen when blood lead levels are 37-52 $\mu\text{g}/\text{dl}$ [35]. Children show a variety of symptoms and effects associated with lead poisoning, specifically by way of behavioral changes, lowered IQs, underdeveloped motor skills, hand eye coordination, hyperactivity and distinctly low reaction time and concentration abilities [32, 36, 37]. Blood lead concentrations, even those

below 10µg/dl, have been shown to have an inversely proportional relationship with IQ levels [36]. The neurotoxic effect of lead in workers appears to be initiated at a level lower than 18µg/dl whereas this threshold is much lower for children at 5 µg/dl (9). A major effect of lead on the brain is the induction of oxidative stress where the neurotransmitter glutamate is the main effectors. Excess levels of glutamate and aspartate can lead to neuronal damage and death. NMDA or N-methyl-D-aspartate is most sensitive to excitatory amino acids and its activation leads to an increase in lipid peroxidation in the hippocampus region [38]. This and other neuro-excitatory amino acids are metabolized to produce oxidative species [39]. A constant generation of oxygen radicals by the mitochondria is a lifelong source of ROS in the brain [38]. Lead also results in the lowering of antioxidant activity, especially glutathione with respect to the brain. In rat brain lead was shown to increase glial fibrillary acidic protein as well as inflammatory protein levels such as cytokines, interleukin 1-beta, tumor necrosis factor- alpha and TNS-Alpha [40]. Apart from oxidative stress, membrane biophysics alterations, deregulation of cell signaling, and impairment of neurotransmissions are key aspects of lead toxicity on the nervous system [32]. Lead is an environmental toxicant and developmental exposure can remain unnoticed or silent for several years. Recent studies on Alzheimer's Disease have shown that the delayed over expression of Amyloid Precursor Protein (APP) in old age, long after Pb exposure has ceased, suggests that developmental exposure to Pb had reprogrammed the respon-

siveness of the *APP* gene [41].

Effect of Lead on the cardiovascular system:

The toxic effect of lead is well established in the cardiovascular system. Studies done on hypertensive patients showed a positive relation between associated blood levels and blood pressure [42-45]. Some studies have shown this associative relationship to be present at blood lead levels below 5 µg/dL [46]. Several animal data are available that show specific effects of lead on the heart. A study in 1965 by Kuzminskaya, showed increased atherosclerosis when rabbits were fed with cholesterol and lead rather than only cholesterol. Myocarditis, arteriosclerosis, altered heart rate activity and increased risk for ischemic heart disease are among the reported cardiovascular abnormalities associated with lead [47-49]. Using animal data, it has been shown that oxidative stress, impaired NO (nitric oxide) system, inflammation, dysregulation of vasoactive hormones, and aberrations in cellular Ca²⁺ transport and intracellular Ca²⁺ distribution [48, 50]. A study on 775 men who participated in the Normative Age Study (average age 68, range 48-93), showed that increased bone lead levels are associated with prolonged heart rate corrected QT and QRS intervals in terms of the heart's electrical cycle and with increased risk of intraventricular and atrioventricular (AV) conduction defect. Increased risk of intraventricular defect and prolonged QT and QRS intervals were seen more commonly in men below the age of 65 whereas AV conduction defect was seen for older men [51]. The burden of cardiovascular

diseases related to lead exposure amounts to 3.1 million disability-adjusted life years (DALY - sum of the years of life lost due to death and years of life with disability, where each condition is attributed a defined severity weight), which is about 2% of the total cardiovascular disease burden [52].

Effect of Lead on Reproductive System:

Lead poisoning diminishes fertility in both men and women. In a study on male battery workers it was found to cause testicular atrophy, lowered testosterone levels and hypospermia [53]. Exposure to inorganic lead at levels more than 40 µg/dl, results in impaired male reproductive function [54]. In humans, protamines protect sperm DNA. Zinc is required for sperm chromatin stability and binds to protamine P2. As lead can replace zinc, it reduces the HP2-DNA interaction leading to alterations in sperm chromatin condensation thus reducing fertility [55]. Animal studies indicate that lead levels between 30-40 µg/dl causes impairment in spermatogenesis and reduced concentrations of androgens [54]. In women the effect of lead also manifests as irregular estrus, decreased gestational period and abnormalities in the offspring [56, 57]. In some cases, spontaneous abortion has been reported [58, 59]. Animal studies on female specimens have shown that postnatal exposure to lead during the critical hypothalamic development stage alters the development and function of reproductive system [60].

Lead and Oxidative Stress:

One of the most significant effects of lead poisoning is the induction of oxidative stress via the production of free radicals and lowering of

antioxidant system. Free radicals are produced from endogenous (mitochondria, cytp450 mechanism, peroxisomes) as well as exogenous sources (xenobiotics, chemical reactions) [61, 62]. Presence of the antioxidant system makes sure that the prooxidant/antioxidant balance is not disturbed. However the presence of xenobiotics, such as lead, will lead to aberrations in the prooxidant/antioxidant balance. This results in the overproduction of free radicals resulting in oxidative stress [63, 64]. Oxidative stress is a precursor of damage to the organs of the body. Although reactive oxygen species (ROS) are important in signaling processes, excessive production leads to cellular and tissue damage. ROS attack lipid membranes, proteins and nucleic acids [61, 65]. Mitochondria utilize O_2 to produce H_2O , however, at the same time it produces radicals such as superoxide (O_2^-), H_2O_2 and hydroxyl (OH) radicals. The enzymatic reaction of nitric oxide synthase leads to the formation of superoxide radicals. Nitrous oxide synthase (NOS) also produces NO which exists as nitrosonium (NO^+) or even peroxy nitrite ($ONOO^-$) by reaction with superoxide radical. This is a potent neurotoxicant as it can interact with thiol groups as well as decomposition to OH radicals [66]. ALA, at a pH range of 7.0-8.0 also produces OH and superoxide radicals via autooxidation (via the Haber Weissman reaction) [64, 67, 68]. When tested on phosphatidyl choline: cardiolipin liposomes, it indicates its involvement in lipid peroxidation. The formation of thiobarbituric reactive substances (TBARS) and its subsequent inhibition by alpha-tocopherol showed that OH radicals are indeed formed and promote lipid permeability

[61, 67]. The highly reactive OH radical abstracts a hydrogen ion from a fatty acid which results in the formation of a fatty acid radical. This initializes the chain of reactions involving the removal of a H ion from another fatty acid and so on and so forth. The cumulative effect of this is the weakening of membrane integrity of cells leading to cellular damage [69].

Lead exists as a divalent cation and has electron sharing abilities resulting in covalent attachments with sulhydryl groups of proteins [63]. Lead has the ability to bind to enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and glucose-6-phosphate dehydrogenase (G6PD) [71]. GPx, SOD and CAT are especially susceptible to lead toxicity as their function is dependent on the presence of trace metals, particularly zinc, copper and selenium. Selenium is an essential constituent of GPx, which detoxifies H_2O_2 to water and lipid peroxides to their respective alcohols at the expense of reduced glutathione (GSH). The oxidized form, glutathione disulphide (GSSG) is regenerated by glutathione reductase which utilizes NADPH as the redox equivalent provided by pentose phosphate shuttle [72, 73]. In the presence of lead (Pb^{2+}) selenium is displaced leading to the inactivity of GPx which increases the amount of H_2O_2 consequently increasing the amount of free radicals [68]. SOD catalyses the formation of H_2O_2 from superoxide radicals and hydrogen ions [74, 75]. In humans 3 types of SODs are found, SOD1 in cytoplasm i.e. Cu/Zn-SOD, SOD2 in the mitochondria i.e. Mn-SOD and SOD3 in the extracellular region or EC-SOD [75, 76]. SOD3 is the major antioxidant enzyme with activity against O_2 radicals.

SOD2 requires manganese for catalytic activity. SOD3 and SOD1 require copper and zinc for catalytic activity to scavenge O_2 radical by reduction and subsequent oxidation of copper at the active site of the enzyme [77]. As with the inhibition of GPx, the presence of lead displaces copper leading to lowered activity of SOD. Catalase is a heme containing tetrameric enzyme that has antioxidant role and is negatively affected by lead. It is involved in the degradation of hydrogen peroxide to water [78-80]. As it is known that lead is an inhibitor of heme synthesis, it consequently results in the lowered production and activity of catalase [81]. The disturbed pro-oxidant/antioxidant balance results in the excessive formation of ROS. ROS results in oxidative damage on heart, liver, brain, kidneys, reproductive system and erythrocytes [68]. Animal studies have shown that atherosclerotic plaques produce ROS. Lipid peroxidation products lead to lesion formation. Studies suggest that O_2 and H_2O_2 contribute to hypertension by different mechanisms: O_2 by inactivating NO and H_2O_2 by altering vascular remodeling [75, 82]. In humans, ROS activity in the vessel walls can cause the formation of oxidized low density lipoprotein (LDL) leading to atherosclerosis. ROS also play a role in tissue necrosis and reperfusion injury, cardiac hypertrophy, altering the functioning of ion channels and calcium flux biologically important for heart muscle. An excess of superoxide radical inhibits action of NO leading to significant effects on cardiac function [82, 83]. ROS have also been cited in several neurodegenerative disorders such as Alzheimer's and Parkinson's disease [38, 39]. ROS leads to lipid peroxidation and subsequent

cytotoxicity in hepatocytes, erythrocytes and neurons [75]. Some studies have shown that ROS reduces sperm motility and production [84].

Chelation Therapy and Its Side Effects:

Lead poisoning has classically been treated by chelation. Commonly used lead chelators include succimer (meso-DMSA), DMSA, CaNa₂EDTA, Dimercaprol (BAL), Unithiol (DMPS) and D- penicillamine (DPA) [85-87]. However, synthetic chelators also show some side effects.

Side effects of succimer usage including gastrointestinal symptoms, rash and transient elevations of serum aminotransferase levels, although occurrence is uncommon. The most common adverse effects reported in clinical trials of succimer in children and adults were nausea, vomiting, diarrhea, appetite loss, and loose stools; these effects may be related to the drug's unpleasant mercaptan odor [88]. A significant number of individuals treated with BAL experience unpleasant side effects, including nausea, vomiting, sweating, high fever, hypertension, and tachycardia [86, 89]. Most commonly to affect the compliance with the

medication are gastrointestinal side effects with acute and chronic use of DMSA. Dermatologic reactions such as papular rash, pruritis and mucocutaneous reactions have occurred during clinical trials [86, 89]. Common adverse reactions that have occurred in patients treated for heavy metal poisoning include nausea, vomiting, headache, fatigue, rash, and pruritis [89]. One report describes three deaths associated with chelation-therapy-related hypocalcemia that resulted in cardiac arrest [90]. Early studies of penicillamine in the treatment of Wilson's disease resulted in adverse reactions that were attributable to zinc deficiency such as skin lesions on pressure points, desquamations, delayed wound healing, alopecia and sometimes glossitis, and stomatitis. In a study of 84 patients treated with penicillamine, an adverse reaction occurred in 33% of patients and included transient leucopenia, transient thrombocytopenia, rash, enuresis, and abdominal pain [89]. Animal studies have shown that provocative chelation therapy can lead to mobilization of lead towards the nervous system [91, 92]. Repeated chelation therapy could result in renal impairment as the kidney is the eliminatory route of the mobilized lead.

Table 1 – Side effects of Chelation Therapy

Chelator	Organ	Effects
EDTA	Kidneys, Heart	Renal Toxicity, Cardiac problems due to hypocalcemia
Succimer	Gastrointestinal tract, Skin	Nausea, Vomiting, Diarrhoea, skin rash
DMSA	Gastrointestinal tract, Skin	Nausea, Vomiting, Papular rash, Pruritis
Penicillamine	Gastrointestinal tract, Skin, Hemotological system, kidney	Abdominal pain, skin lesions, alopecia, stomatitis, glossitis, leucopenia, thrombocytopenia, enuresis

Recent Trends: The Use of Antioxidants -

With the observance of side effects in using chelators being recognized, the last few decades have seen an increase in the studies directed on antioxidants as an option of treatment. Antioxidants used in monotherapy or in conjunction with chelators have been shown to result in alleviated symptoms of lead poisoning along with the diminished side effects. Antioxidants can be enzymatic (SOD, GPx, CAT) or non-enzymatic (Vitamin C and E, carotenoids, thiol antioxidants, flavonoids) [93]. Vitamin C is known to have radical scavenging abilities in aqueous phase of cells and from circulatory system. Studies as far back as the mid 19th Century have shown administration of Vitamin C in workers exposed to toxic levels of lead resulted in the lowered levels of lead in urine excretion [94, 95]. Vitamin C acts as a potent reducing agent, reducing, oxygen-, nitrogen-, and sulfur- centered radicals [95]. It acts in a synergistic manner with tocopherol as Vitamin C cannot scavenge lipophilic radicals within the lipid region of the membranes and proteins. It also helps in regenerating the antioxidant vitamin E by reducing the tocopherol radical that is generated when vitamin E scavenges a peroxy radical [95-97]. Studies on lead treated rats have shown lowered levels of iron leading to impaired haeme formation. However, treatment with Vitamin C restored the levels of iron [98].

Alpha-tocopherol is a sterically hindered phenol, a chain breaking antioxidant and a free radical scavenger of peroxy radicals. It competes for the peroxy radical much faster than polyunsaturated fatty acids [99, 100]. However as it is consumed in the process, alpha-tocopherol

needs to be regenerated, for example, via the tocopheroxyl radical (formed by supplying a hydrogen ion to a peroxy radical) by vitamin C [100]. Vitamin E, especially alpha-tocopherol, is a major lipid-phase antioxidant [101, 102]. Some animal studies have shown that Vitamin E deficiency increases the risk of lead poisoning [103, 104].

Alpha-lipoic acid is an antioxidant formed in the body that is both fat-soluble and water-soluble and has therapeutic properties where oxidative stress is involved [105, 106]. It is a hydroxyl radical scavenger. It has potential ameliorative effects against lead poisoning when used in conjunction with a chelating agent [106]. Lipoic acid, along with its reduced form dihydrolipoic acid (DHLA), has antioxidant potential and the ability to regenerate vitamin C and E, as well as chelating abilities [106].

Dietary excess of zinc can lead to lowered toxic effects of lead, possibly by competing with lead by binding to a metallothionein-like protein in the gastro-intestinal tract [107, 108]. A case study on 39 storage battery workers showed that a 24-week regimen of Zn and vitamin C resulted in a significant reduction in blood lead levels. As Zn is required for heme synthesis, its inactivation by lead can be overcome by both in vitro and in vivo zinc administration [109].

Recent Developments:**Turning towards Nature –****Use of *Coriandrum sativum* to treat Lead Toxicity:**

Coriandrum sativum, commonly known as coriander or cilantro is a spice crop known for its fragrance. It is used in Mediterranean, In-

dian and other South Asian cuisine. Coriander has various medicinal properties including being a carmitive and a diuretic. Coriander is well known for its antioxidant properties and contains compounds that are free radical scavengers [110]. Coriander contains the active phenolic acid compounds like caffeic acid, chlorogenic acid, vanillic acid, p-coumaric acid, ferulic acid (cis and trans form) [110, 111]. The research of Dr. Yoshiaki Omura showed that consumption of cilantro lowered the level of mercury in patients probably via a chelation mechanism [112]. The flavonoids in coriander leaves have been identified as quercetin (an important free radical scavenger), kaempferol and acacetin [110, 111, 113].

Recent animal studies have shown that cilantro can be used to ameliorate the detrimental effects of lead toxicity on different organs. Supplementation of coriander in lead affected animals (experimental) resulted in lowered blood lead levels and improved parameters of lead toxicity. The lowered RBC, WBC count and hemoglobin concentration was improved with treatment with coriander (the effect was more pronounced with ethanolic extract). The increased levels of aminotransferases namely serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT), cholesterol and creatinine due to hepatotoxicity, are decreased on treatment with coriander extract. Serum testosterone level and sperm density are suppressed in lead-treated group compared with the control. Treatment with *Coriandrum sativum* extract shown to restore these levels [114-116]. Cholesterol has been levels are possibly reduced due to increased rate of its degradation to bile acids and

neutral sterols [117]. Coriander's antioxidant properties are seen as treatment with the extract has shown increased SOD, CAT and GPx levels in tissues (liver and kidney) [116]. Treatment of lead affected group also has shown lowered lipid peroxidation in the tissues [116]. Studies on the exact active compound responsible for this ameliorating effect and the mechanism are being researched upon presently.

Use of *Curcuma longa* to treat lead toxicity:

Curcumin {1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione} (diferuloyl methane), is a yellow colored, bioactive component of turmeric or *Curcuma longa* [118]. Turmeric is largely used as a spice and food coloring agent in India, China and South East Asia. In India turmeric is used for its medicinal properties and as a household remedy for colds, biliary disorders, sinusitis, diabetic wounds and hepatic disorders [119]. Curcumin has several pharmaceutical applications owing to its potent antioxidant and anti-inflammatory properties [118, 120, 121]. Curcumin prevents the formation of ROS like superoxide anions and nitrile radicals [119]. It is also known to protect lipid membranes from peroxidation due to its ability to scavenge free radicals. It is a unique antioxidant in that it has several functional groups (not just phenolic or beta-diketo group), including carbon-carbon double bonds and phenyl rings containing different amounts of hydroxyl and methoxy substituents [118, 121]. One possible mechanism of antioxidant activity was proposed by Masuda et al. using linoleate as an oxidizable polyunsaturated lipid and proposed that the mechanism involves oxidative coupling reaction at the 3' position of

curcumin followed by an intramolecular Diels-Alder reaction [119]. Recent studies have also shown that curcumin can be used in cancer treatment as a chemopreventive in conjunction with chemotherapy [122].

Keeping these facts in mind, the possibility of curcumin being used to treat heavy metal toxicity has been studied in animal experimental groups of late [123, 124]. Cadmium leads to nephrotoxicity manifesting as increased lipid peroxidation and lowered GSH levels which could be reversed and alleviated by supplementing the animal group with curcumin [125]. Based on animal studies curcumin has been suggested to reduce lead induced neurotoxicity, hepatotoxicity and cardiotoxicity [126-128]. Treatment with curcumin has raised the lowered SOD, GSH and CAT levels and has reduced the level of lipid peroxidation in 4 regions of the rat brain [126, 128]. Lead also causes oxidative stress in bones. A recent study on supplementing curcumin with lead in animal groups has shown an alleviated level of regional bone mineral density in of femur and tibial bones [129]. Lead induced genotoxicity, due to its interaction with DNA and proteins causing single and double strand breaks and DNA-protein cross-linking, is lowered with treatment with curcumin. One study has shown a lowered number of aberrant cells on treatment with 5% and 1% turmeric powder [128]. Apart from curcumin being a free radical scavenger; it has been previously proposed that turmeric is a potent inhibitor of eicosonoid generation and lipid peroxidation via the inhibition of the lipoxygenase and cyclooxygenase pathways of archidonate metabolism [128]. Another mode of mechanism that has been proposed recently is that of curcumin being a natural chelator for

heavy metals. Electrochemical studies, IR and UV analysis suggest a strong ligand interaction for Pb^{2+} and Cd^{2+} and curcumin. This animal study showed that Cd^{2+} and curcumin could be bound in a ratio of 1:1 whereas due to Pb^{2+} having a larger ionic ratio, the metal-curcumin complex was formed at a larger ratio [124]. Hence curcumin, used so liberally in many countries, could be a potent heavy metal chelator with little or no side effects.

Effect of Tea (Black and Green) on Lead toxicity:

Tea is one of the most popular beverages around the world and its various varieties, especially green, black and Oolong are produced and consumed in significant quantities. Tea has been known for centuries to contain compounds that are good for health and have antioxidant behavior [130-133]. The major green tea polyphenols are (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC), (+)-gallocatechin (GC), and (+)-catechin [130, 133]. Catechins are free radical scavengers and can scavenge both hydroxyl and superoxide radicals as well as lipid free radicals and peroxy radicals [133]. Catechins also have the ability to chelate metals such as Cu^{2+} and Fe^{3+} due to their catechol structure, and form inactive complexes [133, 134]. Literature has documented that the potency of catechins' free radical scavenging abilities is related to the structure especially the gallate moiety esterified at the 3 position of the C ring, the catechol group in the B ring and hydroxyl groups at 5 and 7 positions in the A ring [131, 133, 135]. Catechins also increase the level of endogenous antioxidants adding to their ability to protect against oxidative damage and lipid peroxidation which

accounts for some of their cyto-protective action. EGCG has the highest antioxidant activity due to the presence of gallate moiety on the C ring and has been proven to have potent neuroprotective abilities against Parkinson's disease, in animal studies [132, 133, 136]. Polyphenols in black tea, the flavins and the rubins also have antioxidant properties [131]. Tea extracts have ameliorating effects on lead induced toxicity. Recent animal studies and in vitro and in vivo studies have shown this to be true. Studies on animal groups have shown that treatment with lead resulted in oxidative stress induced necrosis of hepatocytes as well as biliary hyperplasia, edema and mild fibrosis. Liver injury has been by the increased levels of Aminotransferases, Alanine transaminase (ALT) and Alkaline phosphatase (ALP). Treatment with green tea extract reduced oxidative stress and regulating the deregulated prooxidant/antioxidant ratio [137]. In vitro studies with HepG2 cells decreased cell viability and stimulated lipid peroxidation by exposure to Pb^{2+} . Electron Spin Resonance (ESR) studies showed that lead could decrease the fluidity in polar surfaces of cells. Treatment with green tea extract increased cell viability, decreased lipid peroxidation and maintained cell fluidity [134]. Similar results were obtained when PC12 cells were used for the study. Mitochondrial dysfunction is improved and rapid elevation of Ca^{2+} on exposure to lead has been shown to decrease when treated with catechins [135]. Lead induced toxicity in blood and brain (due to lowered levels of SOD and GST and increased lipid peroxidation) has been reduced on treatment with green tea extract and blood lead levels have been shown to decrease [138]. Along with its free radical scavenging ability and regulation of pro-oxidant/antioxidant status, tea com-

pounds having the possibility of metal chelation show great promise for the treatment of lead toxicity.

Effect of *Allium sativum* on Lead toxicity:

Allium sativum, or garlic, is a pungent plant bulb closely related to onions, shallots and leeks. It has been used for centuries for both culinary and medicinal purposes throughout the Middle East, Central Asia, South Asia and many parts of Africa. Traditionally garlic has been used as a remedy for dog bites, intestinal disorders, flatulence, skin diseases and wounds. Garlic and its bioactive components although used for centuries, the last few decades have seen in depth studies being done on the medicinal potency of garlic. Garlic's medicinal properties have been attributed to its organosulfur compounds. Garlic contains three α -glutamyl peptides, that is, α -L-glutamyl-S-(2-propenyl)-L-cysteine (GSAC), α -L-glutamyl-S-(trans-1-propenyl)-L-cysteine (GSPC), and α -L-glutamyl-S-methyl-L-cysteine (GSMC); their corresponding sulfoxide derivatives, that is, (+)-S-(2-propenyl)-L-cysteine sulfoxide (alliin), (+)-S-(trans-1-propenyl)-L-cysteine sulfoxide (isoalliin), and (+)-S-methyl-L-cysteine sulfoxide (methiin), respectively; and (1S,3R,5S)-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide (cycloalliin) [139, 140]. Allicin occurs abundantly in garlic with $0.76 \pm 0.40\%$ in fresh weight. Crushed garlic cloves contain allicin, an oil-soluble oxygenated sulfur compound that has potent antimicrobial effects [139, 141, 142]. Allicin and other sulfur compounds are responsible for the characteristic odor of garlic [139, 142]. In addition, garlic is one of the vegetables that contain elevated levels of selenium which plays a key role in maintaining the body's antioxidant

defense system as well as prevention of cancers [143-145]. Garlic has been shown to prevent cancer, especially stomach and colon cancer. Multiple case studies indicate that the intake of raw and/or cooked garlic has a preventive effect on many ailments [146,147]. Garlic has been recognized to prevent and cure cardiovascular diseases as well as other metabolic diseases such as thrombosis and atherosclerosis. Garlic shows a lipid lowering effect, it inhibits platelet aggregation and lowers blood pressure [148]. A study on 410 patients aged between 49-58 years, suffering from elevated cholesterol levels has shown that intake of garlic or supplementation with garlic (diet, powder, capsules) could lower the cholesterol levels by approximately 9% [149]. Garlic also boosts immunity and along with its other health benefits, it has been used for centuries to retard or slow down aging [150, 151]. *Allium* sps. has also been known to have antioxidant properties. Garlic is a free radical scavenger, inhibits lipid peroxidation and increases the levels of endogenous antioxidants [151-154]. Aged garlic extract (10 to 20 months) modifies unstable molecules (allicin) with antioxidant capacity and increases stable bioavailable water soluble compounds, S-allylcysteine and S-allylmercaptosysteine. Aged garlic extract (AGE) contains phytochemicals – water and lipid soluble organosulfur compounds and flavonoids (allicin and selenium) – that have antioxidant properties [155]. Garlic has higher radical scavenging ability than onion as well as reducing capacity and hydrogen peroxide scavenging ability [153].

The strong antioxidant potential and the natural chelating ability of allicin and sulfhydryl groups, make it a strong candidate for the

therapeutic treatment of lead toxicity, especially chronic lead poisoning [153, 156, 157]. Animal studies have shown garlic and its main bioactive component, allicin, to be effective in lowering lead levels in soft tissues and blood [158, 159]. Allicin and its antioxidant properties have ameliorated the oxidative stress induced damage to various organs such as the liver, kidneys, brain and reproductive organs by lowering lipid peroxidation, scavenging free radicals and renewing the levels of endogenous antioxidant enzymes [157-163]. Studies conducted have used various forms of garlic, such as crushed garlic lobes, dried garlic powder, raw garlic, aqueous and ethanolic or methanolic extracts of garlic [157, 160, 161, 163]. Liver damage has included a sharp increase in liver aminotransferases, cholesterol and lipid peroxidation in lead treated groups. In addition, there has been a significantly lowered level of antioxidant enzyme (SOD, CAT and GPx) levels. Treatment with aqueous and methanolic extracts of garlic has helped stabilize the enzyme levels and has lowered the abnormally high levels of aminotransferases and lipid peroxidation (160). A significant effect on the CNS of animal groups has been seen as a lowered acetylcholine esterase (AChE) levels in different regions of the brain causing disturbances in CNS function. Treatment with crushed garlic extract has shown a marked improvement in these levels indicating its high prophylactic efficacy [161]. One effect of lead on the reproductive system is lowering sperm motility possibly by interfering with mitochondrial function leading to lowered amount of available energy. Treatment with garlic juice has been shown to return the sperm motility to almost normal levels [163].

Garlic, being a natural source, has minimal or

no side effects and many studies have shown its therapeutic effect when used as monotherapy or in conjunction with vitamins or chelating agents. Garlic oil when used with Vitamin E or Vitamin C has shown a reversal in the deleterious effects of lead on various organ systems. Vitamin C and E have strong antioxidant properties and can scavenge free radicals. Garlic oil has these same properties along with the ability to form metal complexes. Hence when used together, the disrupted parameters are brought back to normal levels [162, 164]. A study on 117 battery workers has shown that treatment with garlic returned systolic pressure to normal whereas treatment with penicillamine-D has shown no such effect. Blood lead levels are lowered with both treatments without much difference in the reduced levels. However, treatment with garlic resulted in no side effects which were seen with treatment with penicillamine D [165].

Treatment with garlic and Dimercaptosuccinic acid (DMSA) in mice affected by lead poisoning has shown return to healthy state without any side effects [158]. Other active components in garlic and other *Allium* species are being studied to understand their efficacy in treating lead poisoning. The present animal data and human data promise that garlic is a potent inhibitor and curative source for lead toxicity.

The effect of *Zingiber officinale* (Ginger) on lead toxicity:

Ginger is a common household spice used widely in India, China and South East Asia as an ingredient in the cuisines as well as for its medicinal value. Historically, ginger has been used to treat arthritis, common colds, sore throats, fever, cramps constipation and other unrelated problems [166]. Recent interest in identifying

and isolating the specific active chemical constituents resulting in the medicinal effect of ginger has led to several studies. From these studies it has been found that ginger has profound antimicrobial, anti-inflammatory, antiemetic, cyto-protective and antioxidant properties [166-170]. The most potent and important chemical constituents include monoterpenoids, gingerols, polyphenols, flavonoids and tannins [171]. Monoterpenoids such as phellandrene, cineole, (+)-camphene, citral, borneol and curcumene, are responsible for the smell. The pungency is due to a homologous series of phenols known as gingerols, the most potent of which is Gingerol-[6]. The antioxidant activity is related to the phenolic and flavonoid composition [166-168, 171].

The potent antioxidant behaviour exhibited by both fresh and dry ginger, has been used to study its ability to treat lead toxicity. In addition, few recent studies have indicated a possible chelating property in ginger [169, 172]. Animal studies here shown that effects of lead on the liver lead to apoptosis, increased malondialdehyde (MDA) levels, lowered SOD levels and reduction in liver weight. Treatment with ginger has shown to increase the plasma SOD levels and lower lipid peroxidation and cell apoptosis [173]. Another study has shown ginger extract's ability to enhance renal levels of SOD, CAT and GPx in lead treated male rats [174]. The ameliorating effects of ginger on lead poisoning have been studied in developmental toxicity. Supplementation with ginger has been shown to lower the number of fetal deaths, growth retardation and fetal length and increase the fetal weight [175]. Although a relatively recent consideration, ginger has the potential to be a serious treatment or preventive source in lead poisoning.

Effect of *Emblica officinalis* Gaertn, or *Phyllanthus emblica* Linn, (Indian gooseberry or Amla) on lead toxicity:

The Indian gooseberry is a popular fruit consumed in several countries in Asia especially in its pickled form in India. For centuries, it has been used to treat various conditions such as flatulence, colic, dyspepsia, anemia, jaundice, dental problems, diabetes, cough, inflammations and even cardiac disorders [176]. Its large range of medicinal properties include protection against chromosomal damage, anti-inflammatory action, antimicrobial properties, stomachic and gastro-protective action, neuron-protective action, hepato and reno-protective properties and cyto-protective properties [176-182]. A most important property of *E. officinalis* is its antioxidant and free radical scavenging property. Recognized decades ago, this property has gained importance in the last few decades as free radicals and oxidative stress have been found to be a source of degenerative diseases and tissue damage [181-184]. The antioxidant action may be attributed to a combination of phenolic compounds (such as geranin), tannins (such as emblicanin A and B), flavonoids (such as quercetin and kaempferol) and vitamin C. Amla is reputed to have the highest ascorbic acid content amongst fruits and vegetables. It is also a good source of minerals and amino acids such as lysine, alanine, proline and aspartic acid [181, 182, 185, 186]. In addition to this, ascorbic acid has known chelating properties making amla a useful method for treating heavy metal poisoning [187]. The ameliorating effect of this fruit has been studied in animals with cadmium, mercury and cesium chloride poisoning [188-190]. Cesium chloride is a known clastogen and treatment with *E. officinalis* decreased the total number of chromosomal aberrations [188]. Mercury induced

oxidative stress in rat erythrocytes marked by increased lipid peroxidation and lowered levels of SOD, CAT and GPx were reversed on treatment with amla [189]. Animal studies on cadmium and radiation induced nervous system damage has indicated by decline in protein content in the brain, glycogen accumulation, increased cholesterol levels, cellular damage and reduced antioxidant enzyme levels has shown improvement after treatment with amla. Improvement in all the above mentioned parameters could be explained by its protective mechanism including antioxidant activity, binding to mutagens, increasing GSH levels, and free radical scavenging ability [190].

Apart from those already mentioned, several other animal studies have shown *E. officinalis* to have similar ameliorating and protective effect in lead induced toxicity. Animal studies have shown that treatment with lead has led to lipid peroxidation and significant changes in levels of SOD, CAT and GPx in blood, liver, kidney and brain leading to severe oxidative stress. Treatment with amla extract has been shown to maintain the levels of endogenous antioxidant enzymes and lower the lipid peroxidation probably due to its free radical scavenging ability [189, 192]. The protective effect of amla against clastogenicity induced by lead has been seen by the lowered number of sperm head abnormalities and sister chromatid exchanges formed in lead induced genotoxicity [191, 193, 194]. Apart from its medical value, its easy availability makes amla a very important source of protection and therapy for lead induced toxicity.

Other sources recently being studied:

There are several other natural sources being investigated for their therapeutic effects against lead poisoning. They all have high anti-

oxidant potential and some possess the possibility of chelation. These include *Tinospora cordifolia* (*Guduchi*), *Thurnbergia laurofolia* (*Laurel clock vine or Blue trumpet vine*), *Artemisia absinthium* (*Green Ginger or Grand wormwood*), *Azadirachta indica* (*Neem*), *Lycopersicon* sps (*tomato, love apple*). and several others [196-201]. The extraction, isolation and identification of the active compounds are presently being studied as these could lead to novel lead compounds for the treatment.

Conclusion:

Over the last several years, lead has been labeled as not only an environmental pollutant but also a serious health hazard. Having been used liberally in various industries due to its cost effectiveness and stability, lead has managed to infiltrate most areas around us. Unfortunately, lead is readily taken up by living beings and directly interacts with, and hence disturbs, the normal functioning of the body. Development of chelating agents to combat the increasing rate of lead poisoning cases has led to a drastic decrease in the same. However, being that these agents are of a synthetic nature, they do come with their own sets of side effects.

This article has highlighted a few of natural sources currently being researched which can be used to substitute the use of synthetic chelators. Usage of these natural sources have virtually no side effects or minimal at best. Another key aspect in this is the easy availability and cost effectiveness of these plants. In developing and developed countries, medication often least being costly and sometimes unaffordable, is not sought after. More so for diseases like lead poisoning, where the symptoms are not as obvious and many times go undiagnosed. A dietary inclusion or consumption

of these afore mentioned plants is a simple way of treating the disease. While the threat of lead poisoning is still prevalent in these countries, knowledge and awareness of such natural sources as a substitute for chelating agents will prove to be beneficial for the various populations facing this problem.

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