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REVIEW ARTICLE **OPEN ACCESS**

Role of Medicinal Plants Against Lead Toxicity: An Updated Review

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ABSTRACT
Lead (Pb), one of the most toxic metal pollutants, is a global concern when it comes to occupational and environmental exposure. Many years ago, it was thought that lead toxicity was one of the oldest toxins and most common environmental contaminants. One of the primary causes of Pb's hepatotoxic effects is ingestion. It can enter the body through flatware, lead-based paint, dust, water, soil, and medications for society. The majority of lead-related diseases, including hepatotoxicity, nephrotoxicity, and neurotoxicity, are brought on by ingestion. Lead acts by triggering oxidative stress as a result of glutathione replenishment waste. Due to lipid peroxidation disruption of the cell layer, lead can also cause hemolytic anaemia. Therefore, Lead toxicity was found to be a significant and safe way to reduce lead exposure and combat health issues in the general population. The primary objective of this review article is to provide a summary of lead poisoning identification, sources, and mechanism in light of various toxicological effects on human health. Further, this review demonstrates the effects of lead toxicity on the blood, soft tissues, metabolic activities, and antioxidant defense system, as well as provides an overview of the most recent information on lead toxicity, which harms the health of adults and children alike. It also focuses on the detection and treatment of lead poisoning.
Keywords: *Lead toxicity, antioxidants, hepatotoxicity, nephrotoxicity, blood lead level, medicinal plant.*

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INTRODUCTION

Lead (Pb) is a well-known pollutant and heavy metal that causes harm to live things as well as the environment and is found in the crust of the Earth. Although lead is present in small amounts in the Earth's crust, its widespread use is primarily due to activities like mining, the manufacturing of lead batteries, the utilization of unleaded gasoline, the production of plumbing materials, and the production of paints. [1] The majority of people who are exposed to this toxic metal do so through food, water, toys, paint, tap pipes, and air. The gastrointestinal and respiratory systems are the primary routes by which lead is ingested. Soft tissues absorb lead regardless of whether it is inhaled, or ingested. According to WHO (2010), lead-exposed humans have liver tissue as the primary and largest soft tissue repository (33%) of lead (Pb), followed by kidney cortex and medulla. [2] According to Chen et al., lead toxicity is the most significant health issue, accounting for only 0.7% of all toxic diseases worldwide, and it is becoming more prevalent each year, potentially increasing the global burden of diseases. [3] It is well known that lead poisoning disrupts a variety of body functions, such as reducing hemoglobin synthesis, reducing RBC production, and limiting erythrocyte morphology production.[4] Lead poisoning can also cause damage to cells. Lead-bound erythrocytes make up about 99% of human blood and also have an impact on an individual's physical, chemical, and physiological state. The most affected individuals by the exposure are infants and young children. [5]

Occurrence of Lead

Lead is a naturally occurring soft, ductile, and highly malleable heavy metal with a lustrous color bluish-white. Native lead is a poor electrical conductor and is uncommon in nature. It is a pollutant that is found in a lot of places all over the world and has a lot of physiological effects on the body and the environment. Lead can be found in a variety of forms, including lead acetate, lead nitrate, lead monoxide, lead sulfate,

lead chloride, lead iodide, lead oxide, lead carbonate, and lead tetrafluoride and fluoride. Lead is typically found in the oxidation states of divalent (+2) and tetravalent (+4). [6] The element is absorbed into the bloodstream and distributed to other tissues. It accumulates in the blood, soft tissues, and bone after being absorbed.

Lead Poisoning

In developing nations like India, lead exposure in the workplace and in the environment is a major concern. Lead poisoning occurs when lead accumulates in the body's tissues or bones for several months or years. Even if only a small amount of lead is ingested, lead poisoning can result in a variety of health issues. Lead-based paint, dust, water, soil, and medications can all carry it into the body. The Himalayan population in India had elevated levels of Pb in their blood (0.78 to 3.2 g/dL). [7] Lead poisoning is more common in children under the age of 5, affecting both their physical and mental health and it can be fatal in high concentrations (https://www.mayoclinic.org/diseases-conditions/leadpoisoning). [8] There are many factors which are involved in Lead poisoning such as a variety of industrial products, including gasoline, batteries, pipes, paints, solders, and some cosmetic products etc. Other sources of lead contamination that release lead particles into the environment include the dust of old buildings, lead-based paints, soil, air, water, canned goods, cosmetics, lead-soldered copper pipes, metal toys, pottery, and brass plumbing fixtures. [9] The symptoms of lead toxicity can be difficult to spot in a healthy person even it has high blood lead levels. The symptoms become evident once lead deposition reaches an extreme level. Constipation, abdominal pain, difficulty learning, and fatigue are all symptoms of lead poisoning, which can also affect weight, brain development, and intelligence. Early birth, premature birth, and slowed growth are the symptoms in newborn infants. [10] According to numerous studies, metal toxicity and carcinogenicity have been linked to the normal biological functioning of cells in both humans and animals. Zinc, copper, magnesium, lead, selenium, arsenic, iron, and a number of other essential metals will participate in metabolic activities through control mechanisms and signaling pathways. Lead poisoning is a threat from the environment that damages the body's oxidative system by accumulating free radicals. [11] Human symptoms of lead poisoning include headache, abdominal pain, joint pain, high blood pressure, low sperm count, abnormal sperm, and miscarriage etc. The most serious side effect of lead exposure may leads to brain tissue damage, which can be irreversible. Lead poisoning can cause kidney, liver, and brain damage in children and adults, as well as death in some cases. [12]

Detection of Lead Poisoning

A finger-prick blood test determines the amount of lead in the blood to screen for lead poisoning. X-rays can be used to identify changes in children's bones. Lead poisoning in blood cells can be detected using a variety of methods. The normal values of lead in blood is 10µg/dl for adults and 5µg/dl for children, respectively. [13] Children are more helpless against lead poisoning because they are still in the development stage. Regular examinations and blood lead levels must be set in any area where contamination is possible.

Blood Lead Level

Blood lead level (BLL) can be elaborated as the total blood lead measurement i.e. the total amount of lead present in the blood. The major portion up to 99% is attached with red blood cells and the remaining 1% remains in blood plasma. [14] There are three assays to detect the BLL that are currently available i.e. Atomic absorption Spectroscopy (AAS), Anodic Stripping Voltammetry (ASV) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS). ICP-MS technique is very specific, selective and sensitive that can detect other toxic metals and the isotope ratios of lead in the small samples. BLL testing demonstrate about how much amount of lead (micrograms) is present per decilitre (dl) of blood and indicated as micrograms per decilitre (µg/dl). [15] According to the Centers for Disease Control and Prevention (CDC), the recommended public health action level is more than or equal to 5µg/dl and at risk of lead, poisoning is more than or equal to 10µg/dl (CDC, 2012). The categorization of the BLL level in children can be done as represented in Table 1.

Table1: An overview of Blood Lead Level (BLL) in children.

CDC Class level	BLL (µg/dl)	Abbreviated comments
I	5-9.9	Not considered as lead poisoned; treat an iron deficiency as it increases lead absorption
II A	10-14.9	Community action recommended if many children found; Rescreen
II B	15-19.9	Nutritional and educational intervention; Rescreen
III	20-44.9	Environmental remediation and Medical evaluation needed; Rescreen
IV	45-69.9	Environmental intervention: Chelation therapy; Rescreen
V	≥70	A medical emergency; Begins intervention immediately; Rescreen

(Source: CDC, 2012)

Effects of Lead Toxicity

Lead has no significant effects on the body's physiological processes. The cell membrane is harmed by reactive radicals produced by lead. Lead prevents red blood cell formation, alters collagen synthesis, and hinders the body's ability to form teeth and bones. It also prevents vitamin D synthesis and interferes with the DNA transcription enzyme process. Children exposed to lead produce a variety of inflammatory protein factors. Lead also prevents ferrochelatase, which aids in the formation of heme, from being produced. Lead can induce various abnormal conditions such as encephalopathy, nephrotoxicity, hepatotoxicity, cardiovascular toxicity, intestinal inflammation etc.

Lead Encephalopathy Caused by Lead

Lead encephalopathy condition is caused by exposure to an excessive amount of lead (Pb) that causes the brain's tissues to expand. Swelling of the brain tissue causes damage by putting more pressure on the skull, which can cause severe pain, paralysis, visual impairment or even death. Lead has an effect on the cerebral cortex of children's developing brains, facilitating the formation of the synapse. Lead also inhibits neurochemicals like neurotransmitters, the loss of the neuron myelin sheath, the number of neurons, and some association of particle channels. [16]

Nephrotoxicity Causes by Lead

Lead toxicity can have negative effects on the kidney by causing tissue damage and preventing renal function through the formation of free radicals. There are three stages that can be used to check the effects of lead on the kidney. Alterations in mitochondrial function and dysfunction of proximal tubules can be seen during the initial stage of acute exposure. Tubular atrophy, interstitial fibrosis, and glomerular filtration are all signs of the second stage, while renal tubular neoplasia is a sign of the third stage. [17] The harmful effects of lead (Pb) on traffic police by demonstrating nephrotoxicity caused by inhaling toxic air from transport vehicles. [18] Antioxidant activities like Malonaldehyde (MDA) play a crucial role in lead-induced nephrotoxicity by preventing the formation of free radicals like superoxide ions, nitrogen oxide ions, and hydroxyl radicals. [19] The MDA level is an easy way to check for free radical-induced tissue damage. Catechin, catechol, quercetin, curcumin, and other phytochemical compounds found in a variety of medicinal plants have antioxidant properties that help reduce free radicals, thereby preventing DNA and tissue damage. [20] The toxicity of lead, which causes nephrotoxicity in factory workers, followed by occupational exposure. [21]

Cardiovascular Toxicity causes by Lead

Heart and vascular damage, including hypertension and cardiovascular disease, can result from acute and chronic lead poisoning, both of which can be fatal. Low levels of lead openness can exacerbate hypertension in both animals and humans. [22] According to Rossi (2008) Ischemic coronary heart disease, injuries to the cerebrovascular system, and infections of the peripheral vascular system are additional significant issue. Although evidence of a causal relationship between lead openness and hypertension was found, it only applies to the cardiovascular effects of lead poisoning. [23]

Hepatotoxicity caused by Lead

The liver is crucial to the body's performance, maintenance, and regulation of homeostasis. It interacts with nearly every biochemical pathway involved in the development, disease prevention, nutrient supply, energy organization, and reproduction. Digesting carbohydrates, proteins, and fats, performing detoxification, producing bile, and storing nutrients are the major functions of the liver. Chemical-induced liver damage is suggested by hepatotoxicity. [24] Hepatotoxins are chemicals that harm the liver. Additionally, more than 900 medications have been linked to liver damage; it is the most well-known reason why a medication is taken off the market. Subclinical liver injury caused by chemical compounds frequently manifests as abnormal liver enzyme tests. Half of all severe liver failures and 5% of all medical clinic affirmations are caused by drug-induced liver injury. Over 75% of idiosyncratic drug reactions result in liver transplantation or death. [25] According to Sandhar and Gill (1995), lead poisoning can damage the liver by causing oxidative stress in the blood and other soft tissues. [26] It was hypothesized that lead toxicity might damage tissue by disrupting antioxidants. The autopsy studies of the patients indicate that the liver tissue of lead-exposed patients is the largest repository organ (33%) of all the body's soft tissues. [27] Lead toxicity causes cell damage, through the production of reactive oxygen species (ROS) during cell metabolism. After any internal metabolic response, supplements are assimilated first by the liver's portal vein. New insights into lead-induced hepatotoxicity are provided by the available literature on lead-induced hepatic hyperplasia, heme metabolism, cholesterol metabolism, and liver cell proliferation.

Intestinal Inflammation due to Lead Toxicity

The histological changes in the intestine and the increased levels of inflammatory factors indicate that Pb exposure generally causes oxidative reactions as a result of Pb-induced inflammation. When bees were fed lead oxide (0.65 mg/ml) for nine days, the cells' irregular distribution of nuclear chromatin showed that

the intestinal epithelial cells had been destroyed; dissolution and swelling of mitochondria; and rough expansion, fragmentation, and vesiculation of the endoplasmic reticulum. [28]

Gut Permeability and Lead Toxicity

Due to low-dose chronic or high-dose acute Pb toxicity, an analysis of mouse serum using 4,000-Da fluorescein isothiocyanate-conjugated dextran revealed a significant increase in intestinal permeability. The integrity of gut barriers, such as the mucus layer, enterocytes, and tight junction proteins that link enterocytes together, is crucial to gut permeability. [29]

MECHANISM OF LEAD POISONING

The generation of reactive oxygen species (ROS) and production of oxidative stress is the mechanism for lead toxicity. Mechanism can be like oxidative stress and their mode of actions, Heme metabolism, cholesterol metabolism, hepatic injury etc.

Oxidative Stress and Mode of Action

Substances that prevent the oxidation of the substrate (when present in a lower proportion than the oxidizable substrate) and repair damage caused by the body's formation of free radicals are known as antioxidants. When a cell experiences oxidative stress in the human body due to the accumulation of free radicals it will lead to toxicity in the body (Figure 1). Oxidative stress and cell death are brought on by an increased number of free radicals and an overpowering antioxidant system. According to Flora and Gupta (2012) the production of reactive oxygen species (ROS) and oxidative stress is the main mechanism for lead toxicity. [30] The body is generally protected by antioxidants, which also eliminate the produced reactive oxygen species (ROS). The most important enzyme is glutathione (GSH), which is made by a tripeptide sulfhydryl group. It is present in smaller amounts in the tissues of mammals and it is a major free radical scavenging enzyme. [31] With the assistance of the chemical enzyme glutathione disulfide reductase, ROS are stabilized by GSH, which transforms into glutathione disulfide reductase (GSSG). GSH is returned to GSSG. Lead binds to the sulfhydryl group of GSH, which makes GSH inactive and makes oxidative stress worse. Lead reduces GSH levels and inhibits the activity of the enzymes aminolevulinic corrosive dehydratase (ALAD), glutathione reductase, glutathione peroxidase, and glutathione S transferase. Lipid peroxidation damages the cell membrane when lead is consumed at a significant level in the human body. [32] Lead's neurotoxicity is caused by an ionic mechanism that allows calcium particles to cross the blood-brain barrier (BBB). Toxicity to lead also affects sodium-ion concentration; in this manner, preventing communication between cells and the absorption of neurotransmitters. [33] Indeed, it has the potential to influence protein kinase C, which is responsible for delayed neural excitation and memory storage, even in extremely small quantities. [34] Lead acts by triggering oxidative stress as a result of glutathione replenishment waste. Due to lipid per oxidation's disruption of the cell layer, lead can also cause hemolytic anaemia. An expansion in ROS improves lipid peroxidation; Oxidative stress causes cellular protein oxidation and significant damage to cell structures. [35] Through the inhibition of antioxidant enzymes and the consumption of glutathione, lead exposure can cause oxidative stress in the cells. [36] Additionally, it inhibits the enzyme δ-aminolevulinic acid dehydrase, which promotes the accumulation of δ-aminolevulinic acid (ALA) and the production of reactive oxygen species (ROS) through auto-oxidation of accumulated ALA. [37] Lead poisoning increases DNA damage, lipid peroxidation, and protein sulfhydryl group oxidation. [38] Lead also binds to the sulfhydryl groups in antioxidant enzymes, which lowers glutathione levels by inactivating antioxidant enzymes related to glutathione. Additionally, it decreases superoxide dismutase and the enzyme inactive catalase. [39] According to Pietta (2000), oxidative stress is a disproportion between the biological system's capacity and the number of free radicals produced. [40]

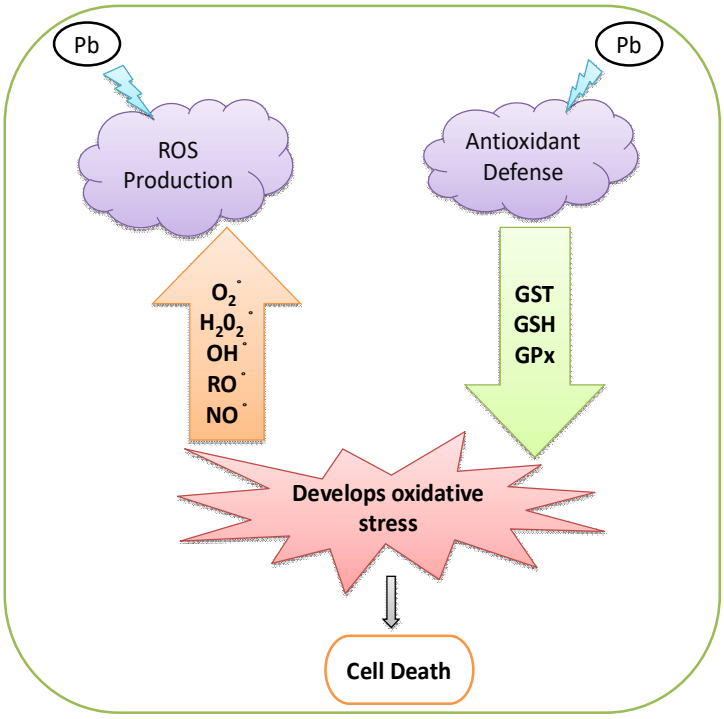

Figure 1: Lead-induced oxidative stress.

Human Hepatic Injury and Cytochrome P450

It has been discovered that exposure to lead concentrations greater than >70 µg/dl leads to make changes in a process of P450 expression and increases phase II enzyme activity. It has been observed that lactate dehydrogenase and alkaline phosphatase levels were found to be significantly elevated in construction, printing, garage, and gas station workers. The workers' average blood lead level was 78µg/dl. [41] Epidemiological studies determined that lead exposure had a greater impact on hepatic cytochrome P450 in children than in adults estimating the levels of P450 metabolite in the urine. [42]

Heme Metabolism and Lead Toxicity

The metabolism of heme is crucial to the health of the liver. In liver tissues, the Cytochrome P450 is involved in cellular redox processes and detoxification pathways. The final phase of heme production is carried out by the ALA dehydrogenase enzyme, which is inhibited by lead (Pb). [43] Heme, which is created in the human body in the liver in amounts of 15–16%, is crucial for the creation of RBCs. Lead has been shown to block ALAD pathways in the liver both in vitro and in vivo, according to Lake and Gercheson's investigations. [44]

Cholesterol Metabolism

The lead (Pb) toxicity alters cholesterol metabolism by raising liver cholesterol levels. [45] The cholesterol biosynthetic enzymes are also activated by lead toxicity, which results in liver hyperplasia. An increase in the concentration of lead in liver tissue is caused by the suppression of enzymes such as 3-hydroxy-3-methylglutaryl CoA reductase (HMGR), farnesyl pyrophosphate synthase (FPPS), squalene synthase (SQS), and lanosterol 14α demethylase (CYP51). Additionally, the suppression of cholesterol 7-α-hydroxylase (CYP7A1). [46] Figure 2 shows the cholesterol biochemical pathway caused by lead interactions.

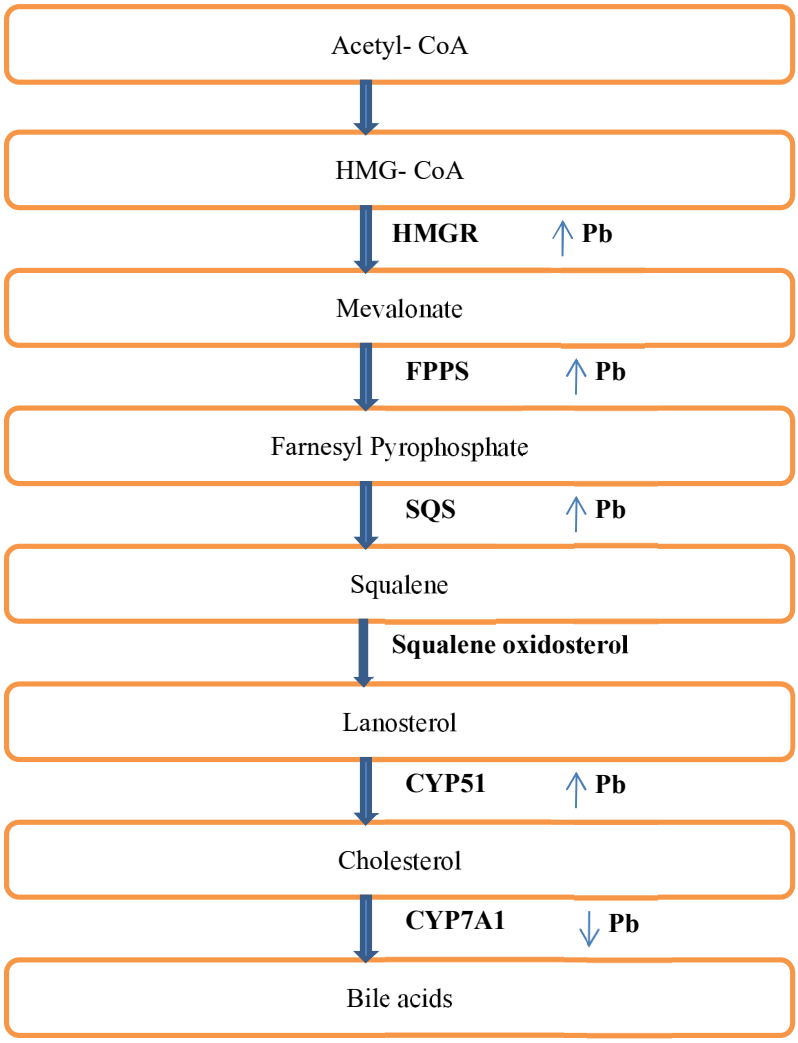

Figure 2. Lead mediated events in the cholesterol synthesis pathway.

Plants and Their Role in Lead Toxicity

Natural products, vegetables, and other edible plants are important sources of essential minerals and nutrients in the diet. Supplementing with sufficient amounts of edible plants can raise the body's levels of essential nutrients and metals, lowering the risk associated with lead toxicity. Table 2 provides a comprehensive list of the various plants studied for their protective effects against lead poisoning. In addition, edible plants supply a wide range of supplements, including phytochemicals and dietary protein, which have been shown to protect against Pb toxicity. From one region of the world to the next, garlic, ginger, and onion are utilized as ingredients for flavor, aroma, and taste enhancement throughout the world. Garlic decreased the Pb burden and recovered immunological parameters in the blood and tissues. [47] Additionally, garlic is a well-known healing plant. In rats, Pb-induced brain, hepatic, renal, and hemolytic toxicity is reduced by garlic extract. Supplementing with these food fixings protected against Pb-induced renal and developmental harm because they have similar cell-strengthening properties to garlic.

Tomato (*Lycopersicon esculentum*) is one of the most well-known natural antioxidants and can prevent renal poisoning in rodents caused by Pb openness. When exposed to heavy metal particles, tomatoes have also been shown to produce metal-chelating proteins and phytochelatins. In point of fact, it has been demonstrated that taking tomatoes orally reduces the accumulation of heavy metals in rats' livers. Tomato intake recovered renal function and prevented the alterations of antioxidant enzymes activities in blood plasma. [48] Green tea is a common ingredient in Asian cuisine and has a number of known health benefits, including lowering oxidative stress, which is linked to diabetes. Green tea recovered hepatic function and alleviated histological changes in the liver. [49] Neem (*Azadirachta indica*), Torch ginger (*Etlingera elatior*), European columbine (*Aquilegia vulgaris*), and Tossa jute (*Corchorus olitorius*) are just a few of the plants

that have been shown to protect against Pb poisoning. Tossa jute, which is used as a vegetable and food fixing by people of Eastern Asia and Africa, it significantly restore the biochemical and haematological parameters and/or by preventing bioaccumulation of Pb within the tissues. [50] Torch ginger, which is used in Malaysian neighbourhood dishes, are two examples of these plants that are well-known dietary components in particular regions. The increasing of enzymes levels in the oxidative biomarkers and histology of bone marrow was observed in the recent study. [51] Curcumin could be therapeutically used to chelate toxic metals. It potentially reduced their neurotoxicity and prevent tissue damage. [52] Spirulina and chlorella, two types of algae, can reduce Pb toxicity in animals' brain, kidneys, and liver. However, others of these plants are frequently used in drinks and confections (like liquorice). As a result, populations that are at risk of heavy metal exposure and who regularly consume these plants may benefit from their inclusion as dietary enhancements for the purpose of reducing and even eliminating symptoms of heavy metal intoxication. *Saraca indica* (SI) belongs to the family Caesalpinaceae and is a crucial supporting plant with traditional importance. *Saraca indica* (SI) is important for uterine/ovarian fibroids, diseases, menorrhagia, uterine prolapse, and provocative conditions. It is primarily used for uterus prosperity. It is crucial for preventing unsuccessful labor beginning in the second trimester. The climate and human health are both significantly impacted by *S. indica*. *Saraca indica* is an excellent source of natural antioxidants and their antioxidant activity may be due to phenolic and flavonoid content in different extracts like aqueous and ethanolic extract of *S. indica.* [53] The present study revealed that the various phytochemical components such as carbohydrates, flavonoids, saponins, phenols, tannins, glycosides, and steroids, are present in the leaves, bark, and flower of *S. indica.* Recent studies have suggested that *Saraca indica* extracts (aqueous and ethanolic) may have potential in preventing initial damage caused by lead acetate toxicity in liver and kidney cells. HepG2 and HEK293 cells co-exposed to both compounds (lead acetate and *S. indica* extract) resulted in a significant ($p<0.05$) increase of cell growth and proliferation. These findings clearly showed evidence that *S. indica* extracts (aqueous and ethanolic) acts as a potential chelator of heavy metal that attenuates lead acetate induced toxicity in HepG2 and HEK293 cells. [54]

Table2: Studies on the protective effects of various plants against Pb toxicity.

Plant	Dose	Animal model	Duration (days)	Target sites	Protective effects	References
Garlic (*Allium sativum*)	250 or 500 mg/kg b.wt. garlic extract orally	Male rats exposed to 100 mg/L lead nitrate in drinking water	30	Kidney brain	Garlic decreased the Pb burden and recovered immunological parameters in the blood and tissues	[24]
Ginger (*Zingiber officinale*)	150 mg/kg b.wt. ginger extract by orally	Male rats exposed to 300 mg/kg b.wt. Pb-nitrate by oral gavage	21	Kidney	Ginger recovered the activity of antioxidant enzymes, GSH level and alleviated renal histological changes	[13]
Tomato (*Lycopersicon esculentum)*	1.5 mL tomato paste orally	Male rats exposed to 1% Pb-acetate in drinking water	56	Kidney	Tomato intake recovered renal function and prevented the alterations of antioxidant enzymes activities in blood plasma	[48]
European columbine *(Aquilegia vulgaris*)	100ppm ethanol European columbine extract orally	Male rats exposed to 20ppm lead acetate orally	28	Liver kidney	improved the histological pictures of liver and kidney and the biochemical parameters	[47]
Green tea (*Camillia sinensis*)	1.5% w/v green tea extract in drinking water	Male rats exposed to 0.4% Pb-acetate in drinking water	56	Liver	Green tea recovered hepatic function and alleviated histological changes in the liver.	[49]
Neem (*Azadirachta indica*)	200mg/kg b.wt. neem extract orally	Pregnant rabbits exposed to 1% lead acetate b.wt.	14	Brain	Neem extract recovered hepatic function and alleviated histological changes in the liver, kidney and lungs.	[29]
Turmeric (curcumin)	30mg/kg b.wt turmeric extract given i.p	Male wistar rats exposed to 20mg/kg lead acetate i.p	14	Brain	Curcumin could be used therapeutically to chelate toxic metals.	[34]

					It potentially reduced their neurotoxicity and tissue damage.	
Torch ginger (*Etlingera elatior*)	100mg/kg b.wt. torch ginger extract orally	Male Sprague–Dawley rat exposed to 500 ppm lead acetate in drinking water	14	Bone marrow	changes in the oxidative biomarkers and histology of bone marrow was observed.	[51]
Tossa Jute (*Corchorus olitorius)*	25,50&100 mg/kg b.wt. jute extract	Male Wistar rat given 5mg/kg lead acetate in drinking water	7	blood, liver, kidney, brain and heart	significantly restore the biochemical and haematological parameters and/or by preventing bioaccumulation of Pb within the tissues	[50]
Chlorella *(Chlorella vulgaris)*	2,5and 10% CV extract orally	Male Sprague–Dawley rat exposed to 200mg/L lead acetate in drinking water	28	Brain	Inhibits oxidation process in lipids and in the cellular components.	[28]

Despite the fact that plants do not require it as a supplement, lead is consumed by them through their roots and leaves. The compound can disrupt the plant's ability to absorb nutrients and water by affecting its chemical activity and hormonal status. The plant will encourage undesirable effects like stunted growth, chlorosis, and darkening of the roots. Lead harmfulness in plants, like some other types of pressure, will affect the photosynthetic rate and, ultimately, yield efficiency. Additionally, eating food that has spoiled with lead can result in serious health problems for individuals. A few plants can treat diseases with their medicinal properties. Figure 3 depicts the human body's lead toxicity mechanism and the protective effects of medicinal plants against lead toxicity.

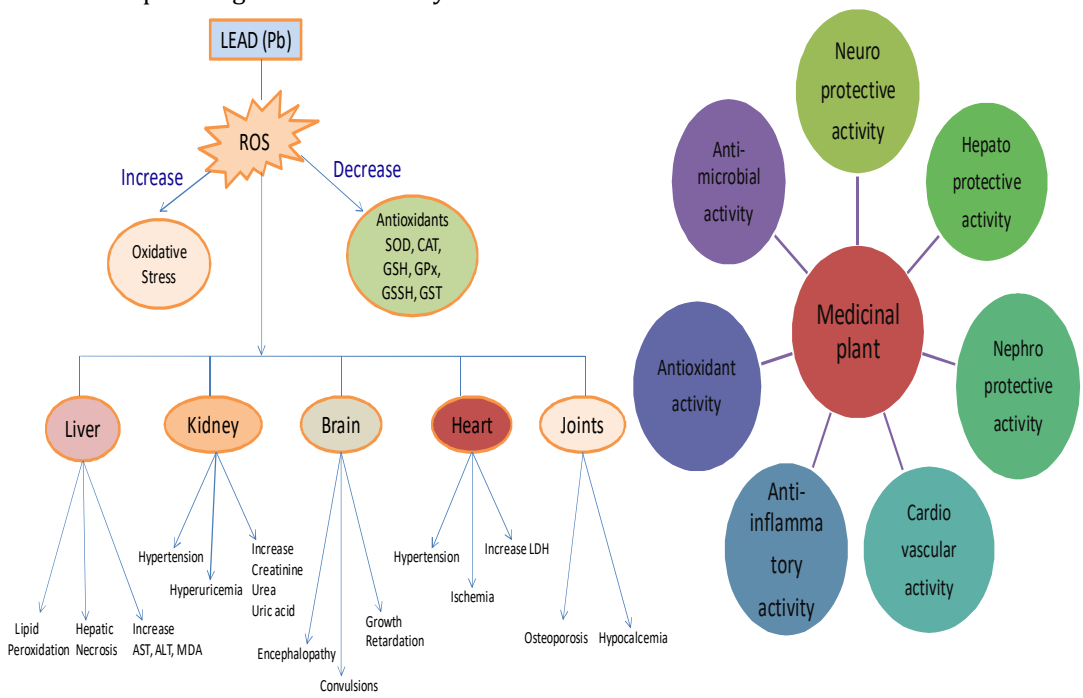

Figure 3. Lead toxicity in body and protective effects of medicinal plants against toxicity.

Prevention and Treatment of Lead Toxicity

Lead poisoning is a serious problem, but it can absolutely be avoided. Avoiding contact with lead in any way is the best way to prevent lead poisoning. [55] It's important to stay away from toxic materials with a lot of lead in them. Frequently washing the hands of children and replacing lead-containing household pipes to prevent water contamination. Chelating agents like Dimercaprol, succimer, a disodium salt of ethylene-diamine-tetraacetic acid (EDTA), and N-acetylcysteine (NAC) can be used to treat lead poisoning by lowering blood lead levels. [56] Antioxidants like curcumin, puerarin, and beta-carotene, such as nanoencapsulation, are currently being used to treat lead poisoning. In tissue culture models, garlic extract

protects against Pb-induced mitochondrial injury and apoptosis and alleviates Pb-induced neural, hepatic, renal, and hemodynamic toxicity in rats. According to these studies, first, organosulfur compounds like diallyl tetrasulfide provide garlic with its antioxidative ability, which protects it from Pb toxicity. Second, its ability to chelate, which is made possible by compounds with free carboxyl and amino groups and amino acids that contain sulfur; this helps the body get rid of Pb; and, thirdly, the inhibition of Pb's intestinal absorption by its sulfur-containing amino acids, such as S-allyl mercaptocysteine and cysteine. According to a recent study, the administration of plant-derived beta-carotene led to a significant drop in homocysteine levels. [57] Supplementing with ginger and onion, which have similar antioxidant properties to garlic, protected against Pb-induced renal and developmental toxicity. One of the most potent natural antioxidants, tomatoes can protect rats' kidneys from Pb-induced renal toxicity. The consumption of tomato significantly reduces heavy metal accumulation. A recent study on groups of workers who were exposed to lead (Pb) in the workplace found that those treated with NAC had lower blood lead levels. As a result, it was decided that NAC could be used as a modification therapy to treat lead toxicity in humans. [58]

CONCLUSION

Lead (Pb) is one of the most common metals that pollute the natural environment due to man's anthropogenic activities. As Pb cannot be degraded, it accumulates in the atmosphere, water, foods, and in organisms living in contaminated areas. Environmental accumulation of Pb has accelerated due to its dose relationship to industrialization and its wide usage in paints and gasoline. It is a widespread environmental pollutant that is known to induce a wide range of biochemical and physiological dysfunctions in humans and laboratory animals. The persistence of Pb in the animals and humans and the associated health risk is a topic of current concern. Lead appears to be the most prevalent heavy metal poisoning. Numerous restorative plants play a significant role in treating lead damage. India is a rich source of numerous medicinal plants with many pharmacological properties. Herbal extracts rather than pure substances are used in the Ayurvedic medical system. One of the most appreciated and historic tree is Ashoka. Ashoka has numerous medicinal applications and is a nontoxic traditional medicinal herb, extract used to treat a variety of ailments. Based on their *in vitro* and *in vivo* experiments, the researchers looked at a variety of study methods that show lead exposure causes hepatotoxicity, nephrotoxicity, and neurotoxicity. Overall, these various pieces of evidence suggest that lead (Pb) exposure has negative effects on living cells, including neurotoxicity, hepatotoxicity, and nephrotoxicity. Children are more vulnerable, especially at work sites close to where they play. To avoid lead-related risks, children of the worker should have their blood lead levels checked frequently. In a developing nation, the global impact on public health is very significant, which helps reduce the effects of lead and makes their exposure very important. However, there are currently a few methods for treating lead poisoning. Nano-epitome and N-acetylcysteine (NAC) are the most distinctive of the few methods for lead treatment chelation. The best way to avoid lead exposure is to avoid it. Chelation is used to treat blood lead toxicity when the level is 45 µg/dl or higher. By overseeing continuous clinical end, prosperity careful and appropriate clinical treatment can reduce lead toxicity, associated ghastliness, and mortality.

ABBREVIATIONS

Pb - Lead
WHO - World Health Organisation
RBC - Red Blood Corpuscle
BLL - Blood Lead Level
AAS - Atomic absorption Spectroscopy
ASV - Anodic Stripping Voltammetry
ICP-MS - Inductively Coupled Plasma Mass Spectrometry
CDC - Centers for Disease Control and Prevention
DNA - Deoxyribose Nucleic Acid
MDA - Malondialdehyde
ROS - Reactive Oxygen Species
GSH - Reduced Glutathione
GSSG - Glutathione Disulfide Reductase
ALAD - δ- Aminolevulinic Acid Dehydratase
BBB - Blood Brain Barrier
ALA - δ- Aminolevulinic Acid
RBC – Red Blood Corpuscle

HMGR - 3-hydroxy-3-methylglutaryl CoA reductase
FPPS - Farnesyl Pyrophosphate Synthase
SQS -Squalene Synthase
CYP450 - Cytochrome P450
PPM - Parts Per Million
EDTA - Ethylene Diamine Tetra Acetic Acid
NAC - N Acetyl Cysteine

DECLARATION OF INTERESTS

Authors declare that they have no known competing for financial interests or personal relationships.

REFERENCES

1. Patrick L. (2006): Lead toxicity part II: the role of free radical damage and the use of antioxidants in the pathology and treatment of lead toxicity. Altern Med Rev; 11:114.
2. Organization WH. (2010): Childhood lead poisoning. 908
3. Chen H and Pan SS (2005): Bioremediation potential of spirulina: toxicity and biosorption studies of lead. J Zhejiang Univ Sci B 6: 171-174.
4. El-Nekeety, A. A., El-Kady, A. A., Soliman, M. S., Hassan, N. S., & Abdel-Wahhab, M. A. (2009). Protective effect of Aquilegia vulgaris (L.) against lead acetate-induced oxidative stress in rats. Food and chemical toxicology, 47(9), 2209-2215.
5. Vigeh M, Saito Hand Sawada S (2011): Lead exposure in female workers who are pregnant or of childbearing age. Ind Health 49: 255-261.
6. Bradman A, Eskenazi B, Sutton P, Athanasoulis M and Goldman LR(2001): Iron deficiency associated with higher blood lead in children living in contaminated environments. Environ Health Perspective 109: 1079-1084.
7. Flora G, Gupta D, Tiwari A. (2012): Toxicity of lead: A review with recent updates. Interdiscip Toxicol ;5 (2):47-58.
8. https://www.mayoclinic.org/diseases-conditions/leadpoisoning/symptoms-causes/syc-20354717 3/9.
9. Mielke HW and Reagan PL (1998): Soil is an important pathway of human lead exposure. Environ Health Perspect 106 Suppl 1: 217-229.
10. Flora SJS, Flora G, Saxena G. (2006): Environmental occurrence, health effects and management of lead poisoning" In Cascas SB, Sordo J, editors. Lead chemistry, analytical aspects, environmental impacts and health effects. Netherlands: Elsevier Publication; p. 158-228.
11. Massage AM, Al-Safi SA, Momani IF, Alomary AA, Jaradat QM and AlKofahi AS (2007): Garlic (Allium sativum L.) as a potential antidote for cadmium and lead intoxication: cadmium and lead distribution and analysis in different mice organs. Biol Trace Elem Res 120: 227-234.
12. Rader JI, Peeler JT and Mahaffey KR (1981): Comparative toxicity and tissue distribution of lead acetate in weanling and adult rats. Environ Health Perspect 42: 187-195.
13. Reddy, Y.A.; Chalamaiah, M.; Ramesh, B.; Balaji, G.; Indira, P. (2011): Ameliorating activity of ginger (Zingiber officinale) extract against lead induced renal toxicity in male rats. J. Food Sci. Technol., 1, 1–7.
14. Sheffield, S.R., Sawicka-Kapusta, K., Cohen, J.B., Rattner, B.A., (2001):. Rodentia and Lagomorpha. In: Shore, R.F., Rattner, B.A. (Eds.), Ecotoxicology of Wild Mammals. Wiley, Chichester. New York, Weinheim, Brisbane, Singapore, Toronto, pp. 215–314.
15. Lyn P. (2006): Lead toxicity, a review of the literature. Part I: exposure, evaluation and treatment. Altern Med Rev; 11: 2-22.
16. Casaret LJ, Klaassen CD, Doull J, editors (2007): Casarett and Doull's Toxicology: The Basic Science of Poisons. 7th ed. McGraw Hill Professional;
17. Sudjarwo SA, Eraiko K, Wardani Sudjarwo GW, Koerniasari (2017): Protective effects of piperine on lead acetate induced-nephrotoxicity in rats. Iran J Basic Med Sci; 20:1227-1231. doi: 10.22038 /IJBMS. 2017.9487.
18. Mortada WI, Sobh MA, El-Defrawy MM, Farahat SE (2001): Study of Lead exposure from automobile exhaust as a Risk for Nephrotoxicity among traffic policemen. Am J Nephrol; 21: 274–279.
19. Mervat HG, Nabela IE, Mohamed MAH, Gihan GM (2012): Efficacy of Curcumin on Lead Induced Nephrotoxicity in Female Albino Rats. J Am Sci; 8:78-82.
20. Xu J, Lian LJ, Wu C, Wang XF, Fu WY (2008): Lead induces oxidative stress, DNA damageand alteration of p53, Baxand Bcl-2 expressions in mice. Food Chem Toxicol 46:1488-1494.
21. Hond CD, Hanson IB, Lerner S, Hammond PB, Pesce AJ. (2008): Occupational exposure of lead: Effects on renal function. Kidney Int; 489-494.
22. Rossi E. (2008). Low-level environmental lead exposure – A Continuing Challenge. Clin Biochem Rev 29: 63–70.
23. Agency for Toxic Substances and Disease Registry (ATSDR). (2005) Toxicological profi le for lead. (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; pp.43–59.
24. Sharma A., Chakraborti K.K., Handa S.S. (1991): Anti-hepatotoxic activity of some Indian herbal formulations as compared to silymarin. Fitoterapia.; 62: 229-235.
25. Ostapowicz G., Fontana R.J., Schiodt F.V., Larson A., Davron J.T., Steven H.B., Timothy M., Reish J. (2002): Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. ; 137: 947–954.

26. Sandhir, R., Gill, K.D., (1995): Effect of lead on lipid peroxidation in the liver of rats. Biol. Trace Elem. Res. 48, 91–97.
27. Pande, M., Mehta, A., Pant, B.P., Flora, S.J.S., 2001. Combined administration of a chelating agent and an antioxidant in the prevention and treatment of acute lead intoxication in rats. Environ. Toxicol. Pharmacol. 9, 173–184.
28. Yun, H., Kim, I., Kwon, S. H., Kang, J. S., & Om, A. S. (2011). Protective effect of Chlorella vulgaris against lead-induced oxidative stress in rat brains. Journal of Health Science, 57(3), 245-254.
29. Bamidele, F.P. (2013). A Study of Some Effects of Aqueous Extract of Neem (Azadirachta Indica) Leaves on the Lead Acetate Induced Neurotoxicity in the Superficial Layers of Superior Colliculus of Adult Wistar Rats (Rattus norvegicus). British journal of pharmaceutical research, 3, 217-231.
30. Flora G, Gupta D, Tiwari A. (2012): Toxicity of lead: A review with recent updates. Interdiscip Toxicol ;5 (2):47-58.
31. Nemsadze K, Sanikidze T, Ratiani L, Gabunia L, Sharashenidze T. (2009): Mechanisms of lead-induced poisoning. Georgian Med News; 172-173:92-6.
32. Kim HC, Jang TW, Chae HJ, Choi WJ, Ha MN, Ye BJ, et al. (2015): Evaluation and management of lead exposure. Ann Occup Environ Med; 27:30.
33. Tobwala S, Wang HJ, Carey JW, Banks WA, Ercal N. (2014): Effects of lead and cadmium on brain endothelial cell survival, monolayer permeability and crucial oxidative stress markers in an in vitro model of the blood-brain barrier. Toxics; 2:258-75.
34. Neal AP, Guilarte TR. (2012): Mechanisms of heavy metal neurotoxicity: Lead and manganese. J Drug Metab Toxicol; S5:1-13. [Doi: 10.4172/2157-7609.S5-002].
35. Ercal N, Gurer-Orhan H, Aykin-Burns N. (2001): Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem; 1:529-39.
36. Ahamed M, Siddiqui MKJ. (2007): Low-level lead exposure and oxidative stress: current opinions. Clin Chim Acta, ; 383:57–64.
37. Hultberg Bandersson A, Isaksson A. (2001): Interaction of metals and thiols in cell damage and glutathione distribution: potentiation of mercury toxicity by dithiothreitol. Toxicology,; 156:93–100.
38. Kalia K, Flora SJ. (2005): Strategies for safe and effective therapeutic measures for chronic arsenic and lead poisoning. J Occup Health; 47:1–21.
39. Blokhina O, Virolainen E, Fagerstedt KV. (2003): Antioxidants, oxidative damage and oxygen deprivation stress: review. Ann Bot,; 91:179–94.
40. Pietta PG. (2000): Flavonoids as antioxidants. J Nat Prod, ; 63:1035–42.
41. Al-Neamy FR, Almehidi AM, Alwash R, Pasha MA, Ibrahim A, Bener A. (2001): Occupational lead exposure and amino acid profiles and liver function tests in industrial workers. Int J Environ Health Res ; 11: 181-8.
42. Hsiao CY, Wu HD, Lai JS, Kuo HW. (2001): A longitudinal study of the effects of long-term exposure to lead among lead battery factory workers in Taiwan (1989-1999). Sci Total Environ; 279: 151-8.
43. Jover R, Lindberg RLP, Meyer UA. (1996): Role of heme in cytochrome P450 transcription and function in mice treated with lead acetate. Mol Pharmacol; 50: 474-81.
44. Lake L, Gershenson LE, (1978): Cellular and molecular toxicology of lead. III. Effect of lead on heme synthesis. J Toxicol Environ Health; 4: 527-40.
45. Gupta S. (2005): Effect of gestational and lactational exposure to lead and/or cadmium on reproductive performance and hepatic oestradiol metabolizing enzymes. Toxicol Lett; 155: 179-86.
46. Kojima M, Nemoto K, Murai U, Yoshimura N, Ayabe Y, Degawa M. (2002): Altered gene expression of hepatic lanosterol 14xdemethylase (CYP51) in lead nitrate-treated rats. Arch Toxicol; 76 : 398-403.
47. Sharma, V.; Sharma, A.; Kansal, L. (2010): The effect of oral administration of Allium sativum extracts on lead nitrate induced toxicity in male mice. Food Chem. Toxicol. 48, 928–936.
48. Salawu, E.O.; Adeleke, A.A.; Oyewo, O.O.; Ashamu, E.A.; Ishola, O.O.; Afolabi, A.O.; Adesanya, T.A. (2009): Prevention of renal toxicity from lead exposure by oral administration of Lycopersicon esculentum. J. Toxicol. Environ. Health Sci. : 1, 22–27.
49. Mehana, E.; Meki, A.R.; Fazili, K.M. (2012): Ameliorated effects of green tea extract on lead induced liver toxicity in rats. Exp. Toxicol. Pathol. 64, 291–295.
50. Dewanjee, S., Sahu, R., Karmakar, S., & Gangopadhyay, M. (2013). Toxic effects of lead exposure in Wistar rats: involvement of oxidative stress and the beneficial role of edible jute (Corchorus olitorius) leaves. Food and chemical toxicology, 55, 78-91.
51. Haleagrahara, N., Jackie, T., Chakravarthi, S., Rao, M., & Pasupathi, T. (2010). Protective effects of Etlingera elatior extract on lead acetate-induced changes in oxidative biomarkers in bone marrow of rats. Food and Chemical Toxicology, 48(10), 2688-2694.
52. Daniel, S., Limson, J. L., Dairam, A., Watkins, G. M., & Daya, S. (2004). Through metal binding, curcumin protects against lead-and cadmium-induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain. Journal of inorganic biochemistry, 98(2), 266-275.
53. Shivhare B, Rani R, Pandey M and Kumar R. Antioxidant capacity and metabolic characterization of aqueous and ethanolic extract of *Saraca indica*, Journal of Pharmacognosy and Phytochemistry, Vol. 12, Issue 1, pp 44-51.
54. Shivhare B, Pandey M and Kumar R. Antioxidant potential and *in vitro* cytotoxicity study of *Saraca indica* extract on lead-induced toxicity in HepG2 and HEK293 cell lines, Indian Journal of Natural Products and Resources, Vol. 14(1), pp 67-74.

55. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. (2007). Lead exposure and cardiovascular disease--a systematic review. Environ Health Perspect 115: 472–482.
56. Park SK, O'Neill MS, Vokonas PS, Sparrow D, Wright RO, Coull B, Nie H, Hu H, Schwartz J. (2008). Air Pollution and Heart Rate Variability: Effect Modification by Chronic Lead Exposure. Epidemiology 19: 111–120.
57. Dobrakowski M, Kasperczyk J, Romuk E, Prokopowicz A, Birkner E. (2014). The influence of beta-carotene on homocysteine level and oxidative stress in lead-exposed workers. Med Pr 65: 309–16.
58. Kasperczyk S, Dobrakowski M, Kasperczyk A, Romuk E, RykaczewskaCzerwińska M, Pawlas N, Birkner E. (2015). Effect of N-acetylcysteine administration on homocysteine level, oxidative damage to proteins and levels of iron (Fe) and Fe-related proteins in lead-exposed workers. Toxicol Ind Health. 32(9):1607-18. doi: 10.1177/0748233715571152.

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