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Review Article

DETRIMENTAL EFFECTS OF LEAD ON HUMAN HEALTH AND PROTECTIVE EFFECT BY NATURAL POLYPHENOLS: A REVIEW

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ABSTRACT

Lead is having wide application in day to day life such as building materials, ceramics, glass, water pipes, paints, protective coatings, acid storage batteries, gasoline additives, solder, ammunition, jewelry, toys, cosmetics and traditional medicines. Different edibles like medicinal plants, vegetables, fruits, fodder plants, grains, and sea fish are also commonly intoxicated by lead. Direct or edible exposure of lead is the very common cause of lead toxicity. Chronic toxicity associated with lead is more hazardous compared to acute toxicity. Young children are especially vulnerable to the harmful effects of lead and can suffer from permanent adverse health effects, particularly affecting the brain and nervous system development. Lead causes long-term toxicity in adults, including increased risk of hypertension and kidney damage. Exposure to high lead in pregnant women levels can cause miscarriage, stillbirth, premature birth, low birth weight and minor malformations. Lead is responsible for generation of free radicals which induces a broad range of physiological, biochemical and behavioral dysfunctions. Lead exposure is having detrimental effects on almost all the major organ system which is a major contributory factor for incremental mortality and morbidity. Beneficial effects of polyphenol in lead induced toxicity have been noticed. The probable reason by which it may show the protection is scavenging of reactive oxygen species, generated by lead. Moreover, it is reported that they are also responsible for detoxification by removal of accumulated heavy metals from major organs.

Key-words: lead; lead toxicity; organ toxicity, Polyphenol

INTRODUCTION

Lead is one of the earliest heavy metals discovered by human. Due to its unique properties like low melting point, softness, malleability, ductility, and resistance to corrosion it is used widely in different industries such as paint, ceramics, automobiles, plastics, *etc*. Human being has used lead for the last 5000 years in a wide range of applications. This in turn has led to manifold rise in the occurrence of free lead in biological systems and the inert environment.[1-3] It is also assumed that in the eighteenth and early nineteenth century lead was illegally added to wine both as a sweetener and to make it appear fresh. Its prolonged use was considered to have caused dementia to many Roman emperors. [4]

In modern era also use of lead is very common. Lead is used in a variety of products, primarily in lead car batteries. Other uses of lead include leaded gasoline, toys, paints, ceramics, ammunition, water pipes, solders, cosmetics, hair dye, farm equipment, airplanes, shielding for x-ray machines, and in the manufacture of corrosion and acid resistant materials used in the building industry. [5]

Exposure can also occur due to high lead levels in dust and soil in residential areas near high-density traffic, smelters or refineries, and the consumption of vegetable, fruit and grains grown on high lead soils or near sources of lead emissions containing lead in excess as a result of direct deposition of lead onto plant surfaces apart from plant uptake of lead from soils. Gunshot wounds received through bullet injury either accidentally or due to reasons of crime act as long-term sources.[6]

Lead exposure can be responsible for various organ toxicities such as liver, kidneys, hematopoietic system as well as nervous system. [7] It has been seen that a low level lead exposure is responsible for cardiovascular disease and hypertension (Fig 1). [8] Lead is very much harmful for small children and they can suffer from various long term hazardous effects of lead, mainly the brain and nervous system development is affected. Lead increases chances of getting hypertension and kidney damage in adults. High lead levels can cause miscarriage, stillbirth, premature birth, low birth weight and minor malformations if it is exposed to pregnant women. [9, 10]

CHEMICAL FORM AND PROPERTIES OF LEAD

Lead bears the symbol Pb, have atomic number 82 and atomic mass 207.2 amu. Lead is having Melting Point of 327.5 °C and boiling Point of 1740.0 °C. Lead contains 82 Number of Protons/Electrons and 125 Neutrons. Cubic crystals of lead is bluish in colour and density of 11.34 g/cm^3. [11]

It begins to tarnish on contact with air, thereby forming a complex mixture of compounds. [12] Metallic lead is resistant to corrosion, because, when it is exposed to air or water, thin films of lead compounds (oxides and carbonates) are formed and protect this metal from further attacks. It has been widely used for centuries because it is readily shaped, molded, and resistant to corrosion. Lead can exist in three forms: metallic, inorganic, and organic. Lead in the environment rarely occurs in its elemental state, but rather in its oxidation state (Pb^{2+}) in various ores throughout the earth. [2]

ETIOPATHOLOGY

The non-biodegradable nature of lead is the reason for its prolonged persistence in the soil, air, and drinking water. The use of lead in pipes, paints, and gasoline additives resulted in large amounts of lead entering the environment. It is a multimedia pollutant, since the human exposure occurs via inhaled air, dust, food and drinking water (Fig 2). [4, 13, 14]

Lead contaminated food and water are the direct culprit of lead toxicity. It has been observed that fruits and vegetables contaminated with high lead levels from the soils where they were grown. The soil accumulates lead levels generally from pipes, lead paint and residual emissions from leaded gasoline. [15]

Adults absorb 35 to 50% of lead through drinking water and the absorption rate for children may be greater than 50%. Lead absorption is influenced by factors such as age and physiological status. In the human body, the greatest percentage of lead is taken into the kidney, followed by the liver and the other soft tissues such as heart and brain, however, the lead in the skeleton represents the major body fraction. The nervous system is the most vulnerable target of lead poisoning. Headache, poor attention spam, irritability, loss of memory and dullness are the early symptoms of the effects of lead exposure on the central nervous system. [3]

Lead poisoning remains one of the most common paediatric health problems throughout the glove today. Exposure to lead is of special concern among women particularly during pregnancy. Lead absorbed by the pregnant mother is readily transferred to the developing foetus. Human evidence corroborates animal findings, linking prenatal exposure to lead with reduced birth weight and preterm delivery, and with neuro-developmental abnormalities in offspring. [16]

Though its widespread use has discontinued in many countries of the world, it is still used in many industries like car repair, battery manufacturing and recycling, refining, smelting, *etc.* [4]

In chronic exposure of lead, it used to accumulate majorly in bone, with clearance half times of approximately two to three decades. Lead level in major bone such as cortical bone (e.g., tibia), gives an impression of lifetime retained cumulative dose of lead. Whereas blood lead level indicates new external exposure by lead and estimate the effect of recent dose. [12, 13]

Since the late 1970's, lead exposure has decreased significantly as a result of multiple efforts including the elimination of lead in gasoline, and the reduction of lead levels in residential paints, food and drink cans, and plumbing systems. Several federal programs implemented by state and local health governments have not only focused on banning lead in gasoline, paint and soldered cans, but have also supported screening programs for lead poisoning in children and lead abatement in housing. Despite the progress in these programs, human exposure to lead remains a serious health problem. [15]

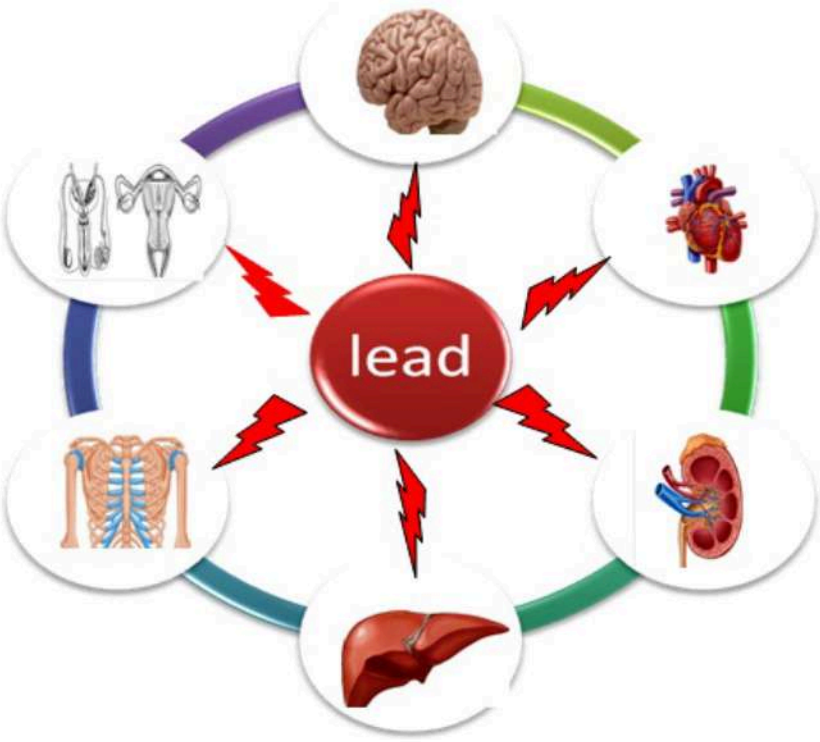

Fig 1: Systems affected by lead toxicity

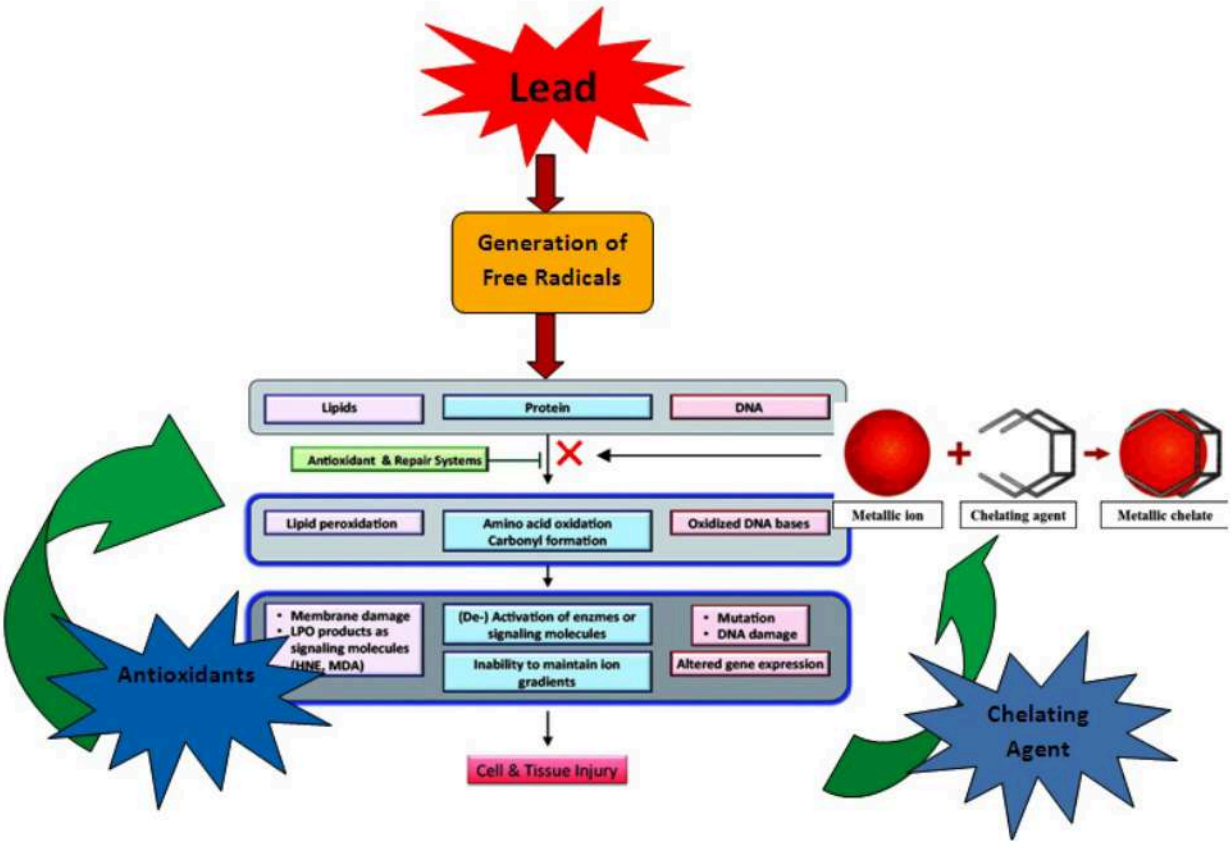

Fig 2: Mechanism of lead toxicity

EFFECT ON CARDIOVASCULAR SYSTEM

Different studies throughout the glove demonstrated a link between lead exposure and subsequent development of hypertension and cardiovascular disease. Lead exposure is associated with severe cardiovascular manifestation such as coronary heart disease, stroke, and peripheral arterial disease, left ventricular hypertrophy and alterations in cardiac rhythm.[16]

Lead is readily absorbed; distributed in the blood, bone, and soft tissues. A large number of blood lead approximately 99% is bound to red blood cells; only 1% is present in the plasma and is available for exchange with lead contained in the other tissues. For a normal person the half-life of lead in the blood is 30 days where as it's still more in individuals with renal insufficiency. Over 95% of the total body lead content resides in the bone, where the half-life of lead is decades long. Consequently, bone serves as the principal repository of this element in the body. [17,18]

Mechanism of lead induced cardiotoxicity

Oxidative stress

During normal physiology also due to different biochemical reactions a huge amount of reactive oxygen species (ROS), such as superoxide (O_2^-) and H_2O_2, are normally produced in the course of oxygen metabolism. But those ROS are effective neutralized by the antioxidant defense system. But during pathophysiological conditions such as lead exposure result in enormous increase production of ROS and/or impaired antioxidant capacity, which culminate in oxidative stress. [19]

Effect on decreased guanylate cyclase, nitic oxide and cGMP

Lead exposure is responsible for generation of huge amount of free radicals which is responsible for development of oxidative stress. This leads to reduction in nitric oxide production and inhibition. Moreover it causes down regulation of soluble guanylate cyclase responsible for reduction in cGMP production. As a consequence it results in increases cytosolic Ca^{2+} concentration in vascular smooth muscle cells. All these etiological factors are responsible for increased systemic vascular resistance and rise in arterial pressure.[20]
Generation of free radicals by lead can promote inflammation, fibrosis, and apoptosis by activating NF-κB, which is the general transcription factor for numerous proinflammatory cytokines, chemokines, and adhesion molecules. [20]

Effect of lead exposure on adrenergic system

Lead is having profound effect on adrenergic system. Lead exposure is responsible for elevated plasma norepinephrine but normal plasma dopamine and epinephrine levels.[21]

Effect of lead on vascular reactivity

It has been observed that lead exposure is responsible for increased Protein kinase C (PKC) activity. PKC is associated with vasoconstriction.[16]

Effect of lead exposure on prostaglandins

Lead exposure is responsible for significant increase in vasoconstrictive prostaglandin, thromboxane. Apart from that lead promotes in vitro release of arachidonic acid by vascular smooth cells via activation of phospholipase A_2.[18]

Lead induced cardiovascular manifestation

Lead exposure is responsible for different cardiac manifestation such as atherosclerosis, prolonged AV node and His bundle conduction times, reduced coronary blood flow, lowered heart rate and altered cardiac energy metabolism which are accused of increased mortality rate.[16]

EFFECT ON NERVOUS SYSTEM

The nervous system is the most sufferer organ being principal target of number of metals. The alkyl derivatives of certain metals such as lead, mercury and tin are specially neuro-toxic.[22]

The symptoms associated with acute lead exposure often involves rapid onset of nausea, headaches, cognitive changes, and emotional disruptions. In chronic exposure, fatigue, decreased processing speed, fine and gross motor deficits, and generally decreased cognitive functioning, neuro-degeneration and psychiatric manifestations like increased depression, anxiety, and irritability are more prevalent.[23]

It has been observed that immature organisms are particularly susceptible to the adverse neurological effects of chronic lead exposure. As compared to adults, lead is absorbed and retained more readily perinatally, and the developing nervous system appears to be much more sensitive to the toxic effects of low-level lead exposure, it is responsible for intellectual and behavioral deficits in children, including hyperactivity; deficits in fine motor function, hand-eye coordination, reaction time; and lowered performance on intelligence tests.[24,4]

Mechanism of lead induced neurotoxicity

Continued research on toxic effect of lead on nervous system revealed that multiple mechanisms are involved in lead toxicity. Majorly it is of two types; first one is neuro-developmental toxicity, possibly involving interference with cell adhesion molecules, resulting in miswiring of the central nervous system during early development and possibly permanent dysfunction; and another one is neuropharmacological toxicity, which might involve interactions between lead and calcium; and lead and zinc, resulting in interference with neurotransmission at the synapse and this may be reversible.[25]

Neuro-developmental toxicity may be due to improper synapse formation, reduced in neuronal sialic acid production, premature differentiation of glial cells. Exposure of lead in neuron is responsible for alteration in the release of neurotransmitter from presynaptic nerve endings and spontaneous release of neurotransmitter is enhanced and evoked release is inhibited. The former may be due to activation of protein kinases in the nerve endings and the latter due to blockade of voltage-dependent calcium channels. This disruption of neuronal activity may, in turn, alter the developmental processes of synapse formation and result in a less efficient brain with cognitive deficits. In addition to a direct toxic effect upon the endothelial cells, lead may alter indirectly the microvasculature by damaging the astrocytes that provide signals for the maintenance of blood-brain barrier integrity.[23]

Several fascinating theories about the mechanism of lead-induced neuropharmacological toxicity have been proposed. Lead is having profound effect on calcium metabolism and transport which inhibit the release of acetylcholine. Moreover Lead is well known to disrupt heme synthesis. The loss of heme containing enzymes is associated with mitochondrial function producing adverse effects on energy metabolism. Lead may affect neurotransmission by interference with neurotransmitters. In fact, aminolevulinic acid, produced as a result of lead action on heme synthesis, has a similar chemical structure to γ-amino-isobutyric acid. Action on the GABA system might produce signs of neurotoxicity similar to those seen in severe lead poisoning.[26]

Apart from that lead exposure is associated with some of the indirect effects on the nervous system result from interference with other body systems that support nervous system function. Lead exposure in the body is responsible for some of the pathological conditions such as hypertension, impaired renal function, impaired thyroid function, vitamin D deficiency, and preterm birth which are having very detrimental effect on nervous system.[27]

EFFECT ON RENAL SYSTEM

The kidney is the critical organ after long-term occupational or environmental exposure to lead. Excessive exposure to lead may cause acute or chronic nephrotoxic effects. Two types of nephropathy, acute and chronic nephropathy have been observed in humans. Acute lead induced nephropathy is characterized functionally by a generalized deficit of tubular transport mechanisms (Fanconi syndrome) and morphologically by the appearance of degenerative changes in the tubular epithelium and the nuclear inclusion bodies containing lead protein complexes. These effects, which are usually reversible with chelation therapy, have been reported mainly in children manifested by glycosuria and aminoaciduria. Chronic occupational exposure to lead has also been linked to a high incidence of renal dysfunction, which is characterized by glomerular and tubulointerstitial changes, resulting in chronic renal failure, hypertension and hyperuricemia. Chronic lead nephropathy is an irreversible renal disease that develops over months or years of excessive exposure.[28,29]

Mechanism of lead induced nephrotoxicity

Lead exposure is responsible for occurrence of acute and chronic nephrotoxicity. In case of acute toxicity exposure to lead results in accumulation in proximal renal tubular lining cells in the form of morphologically discernible inclusion bodies which are lead-protein complexes. Intracellular lead is associated with specific high affinity proteins and can also bind to metallothionein. Acute nephrotoxicity consists of proximal tubular dysfunction development of a glycosuria, aminoaciduria, phosphaturia, collectively representing the Fanconi-type syndrome, alterations in mitochondrial structure and can be reversed by treatment with chelating agents. These functional changes may be due to effect of lead on mitochondrial respiration and phosphorylation. Recent studies have shown that lead can directly inhibit the function of rBAT, a protein involved in the high affinity transport of neutral and dibasic amino acids across renal and intestinal brush borders. Acute lead intoxication is also capable of reducing 1,25-dihydroxyvitamin D synthesis, prolonged hyperphosphaturia and hypophosphatemia in children could result in bone demineralization and rickets. The renal manifestations of acute lead poisoning are usually reversible after chelation therapy and cessation of lead exposure.[30,31]

Chronic lead nephropathy is irreversible and is typically accompanied by interstitial fibrosis, both hyperplasia and atrophy of the tubules, glomerulonephritis and ultimately, renal failure. In addition, lead produces renal neoplasms, interstitial fibrosis and progressive nephron loss, azotaemia and renal failure. Chronic lead exposure is also implicated in the development of saturnine

gout and hypertension. The metal interacts with renal membranes and enzymes and disrupts energy production, calcium metabolism, glucose homeostasis, ion transport processes and the renin-angiotensin system. [32,29]

EFFECT OF LEAD ON REPRODUCTIVE SYSTEM:

Infertility is a reproductive health problem worldwide which affects many couples especially in developing countries. Lead is ubiquitous and persistent heavy metal which has detrimental effects on almost all the major organs.[33] Male and female reproductive systems are one of the major target sites of lead induced toxicities.[34]

Effect on Male reproductive system

The deterioration of male reproductive health is one of the major manifestations of occupational and environmental lead exposure.[35] It has been reported that acute or chronic exposure to lead is responsible for alteration of testicular functions in humans and even wild life. [36] It has been documented that the presence of higher amounts of lead in the blood of exposed workers compared to control workers (about 3.5 times) is associated with reduced volume of ejaculation, semen density, total sperm number and motility, and increased percentage of pathological spermatozoa.[37] Some of the other effects of high levels of blood lead includes reduced libido, abnormal spermatogenesis, chromosomal damage, infertility and changes in serum testosterone. In one study, it was observed that high levels of lead in semen reduce the sperm count, contributing to its infertility. [38]

Several reports suggest that workers exposed to lead suffered with oligospermia and asthenozoospermia [39], with altered sperm morphology. [40] It is also seen that lead toxicity can even extend to epididymis and results in altered sperm maturity. [41] Lead is also considered as endocrine disruptor modifying hormonal metabolism by altering synthesis and breakdown of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH). [42] So, it appears that, lead burden disturbs hormone-mediated spermatogenesis and steroidogenesis of male reproduction. [43]

Effect of lead on Female reproductive System

In women the effect of lead also noticeable as irregular estrus, decreased gestational period and abnormalities in the offspring. In some cases, spontaneous abortion has been reported. [34] It has been demonstrated that women with severe lead intoxication are more susceptible to prolonged and abnormal menstruations, stillbirth, abortion, premature membrane rupture, pregnancy hypertension, infertility, miscarriage, premature delivery and infant mortality. [44] Besides, direct influence of lead on the various stages of development in foetus has also been reported during pregnancy. [45] Moreover, placental transfer of lead into the mother milk makes the blood lead levels of the mothers and infants usually similar. [46]

In experimental animals, chronic lead exposure may cause inhibition of menstruation, ovulation and follicular growth in monkeys, delay in vaginal opening in pubertal rats and decrease in frequency of implanted ova and of pregnancies in mice. Lead damages endometrium, myometrium and perimetrium, along with reduction in uterine gland and decrease in height of columnar cells in mice. [47]

EFFECT OF LEAD ON HEPATIC SYSTEM

The liver is composed of highly active metabolic tissue containing a huge complement of detoxification machinery referred to as phase I and phase II enzyme systems that ideally serve to guard other physiological systems from the toxic effects of xenobiotic compounds. Through portal vein liver is exposed to nutrients and other xenobiotics. In different studies it has been observed that acute and chronic intoxication of lead is responsible for alterations in hepatic xenobiotic metabolism, cholesterol metabolism, liver cell proliferation and DNA synthesis. It has been reported that after lead exposure a huge amount approximately 33% accumulated in soft tissue like liver. Lead exposure is responsible for detrimental effect on hepatic microsomal cytochrome P-450 and associated enzymatic activities in rat liver. Lead induced toxicity is associated with decrease in ALA dehydratase, benzo pyrene hydroxylase, ethylmorphine N-demethylase activities. [48]

Mechanism of lead induced hepatotoxicity

Hepatic drug metabolism

Lead exposure is responsible for inhibition of hepatic microsomal enzymes. The inhibition of hepatic CYP450s mediated by two different mechanisms:

(i) the inhibitory effects of Pb at the level of transcription
(ii) the decreased synthesis of heme and the subsequent decrease in heme saturation. [49]

Cholesterol metabolism

Lead intoxication is responsible for impaired hepatic cholesterol metabolism that results in simultaneous increase in both liver and serum total cholesterol levels. Exposure of lead involves the activation of cholesterol biosynthetic enzymes (*i.e.*, 3-hydroxy-3methyglutaryl-CoA reductase, farnesyl diphosphate synthase, squalene synthase, CYP51) and the inhibition of cholesterol-catabolic enzymes such as 7a-hydroxylase. Both this reactions collectively resulted in increased cholesterol level. [50]

Heme Synthesis

Lead is associated with synthesis of fifteen percent of heme production. Lead intoxication is responsible for inhibition of ALA dehydrogenase enzyme involved in final step of heme synthesis. Impaired heme synthesis leads to lead induced anaemia. [51]

Oxidative stress

Lead exposure generates lipoperoxide, other oxidants, induce expression of cytokine mediators, including TNF-a. These mediators contribute to decline in intracellular ATP, oxidative DNA damage and the apoptosis of hepatocytes. [52]

SYMPTOMS OF LEAD TOXICITY

Lead poisoning causes a variety of symptoms, including abnormal behaviour, and here time of exposure plays an important role. [53]

In chronic exposure, manifestations build up more severe as the weeks to months passes, but in acute exposure, suddenly strong symptoms appear from short time intense exposures. [44]

Organic lead is highly lipid soluble compared to inorganic lead, so its highly toxic and its symptoms are mainly associated with the central nervous system; cognition problems, insomnia, delirium, and tremors are mostly seen. [54, 55]

The symptoms in adults are memory loss, renal failure, headache, stomach pain, sexual dysfunction and reduced sensation in the limbs.

In early stage of lead exposure, non-specific symptoms may exhibit, such as depression, nausea, muscle weakness, sensory abnormalities, occasionally brain inflammation, diarrhea, reduced appetite, stomach pain, and constipation. [55, 56]

Neuropsychological problems such as delayed reaction time, reduced concentration, reduced neurotransmitter speed, and headaches first appear at blood lead levels from 25 and 60 µg/dL, anaemia appears at blood lead levels higher than 50 µg/dL, colic with paroxysms of pain in cases of higher than 80 µg/dL, whereas very severe symptoms of increased intracranial pressure, delirium, coma, seizures can be seen when blood lead levels exceed 100 µg/dL, along with wrist drop, foot drop, and encephalopathy. In case of children, these symptoms can be seen to at a blood lead levels exceeding 70 µg/Dl. [53,57]

Intense exposure is responsible for Central nervous system and neuromuscular manifestations, but longer exposure is responsible for gastrointestinal symptoms. [58]

In chronic exposure symptoms are loss of short-term memory, lack of concentration, Fatigue, insomnia, headaches, slurred speech, anaemia, depression, nausea, vomiting, abdominal pain, loss of coordination, and numbness and tingling in the extremities. [59,56] There may be green coloration of skin and bluish gums- called as Burton line. [60]

If a foetus is exposed to lead in uterus, it is responsible to increase the chance of low birth weight and premature birth. Babies crawl on the floor and suck on various objects, because of that they are exposed to lead more commonly. Common symptoms in children are loss of appetite, stomach pain, vomiting, learning problem, behavioural disorders, and anemia; whereas in too much high levels of lead exposure, leukonychia striata symptoms are reported. [61,62]

EFFECT OF POLYPHENOLS AGAINST LEAD INTOXICATION

Polyphenolic compounds have many phenolic groups, are widely present in different plants, fruits and vegetables. Their beneficial effect against many diseased conditions affecting different major organs already has been well established. [63, 64]

Polyphenols can be divided into different classes according to specific biological properties. Polyphenols can be extracted from different natural sources like plants, fruits and vegetables. They have remarkable health benefits which include antioxidant, anti-inflammatory, cardio-protective, nephro-protective, hepato-protective, anti-diabetic, antimicrobial and tumor preventive activities. [65-67]

Beneficial effects of polyphenol in lead toxicity have already been noticed. Polyphenols were also reported for detoxification and removal of lead. [68]

Effect of polyphenol against lead induced neurotoxicity

Rich polyphenolic components present in pomegranate juice caused beneficial effect on behavioural impairments and histopathological changes against chronic intoxication with lead acetate for 3 months. [69]

Polyphenols present in methanolic extract of *Indigofera oblongifolia* leaf significantly protected the neuronal damage which was induced by five days intra gastric administration of lead acetate through oral route. [70]

Treatment with tertiary butylhydroquinone which a phenolic organic compound is reflected decrease in MDA level and increase in SOD and GSH content, in the hippocampus and frontal cortex of rat.[71]

Puerarin, a natural polyphenolic flavonoid showed significant protection against lead induced neurotoxicity. [72]

Quercetin treatment for three months reported significant neuro-protective effect against intra-gastral administration of lead acetate due to significant decrease in brain lead content. [73]

Selenite treatment improved locomotion behaviors, decrease in intracellular reactive oxygen species and protection in sensory neurons with against lead-induced neurotoxicity. [74]

Green tea treatment demonstrated significant protection against lead induced loss of body weight, decreased concentration of reduced glutathione and SOD activity in brain tissues, high DNA fragmentation and pathological changes. [75]

Effect of polyphenol against Lead induced nephrotoxicity

Phenolic compounds present in *Mangosteen pericarp* protects against lead acetate induced nephrotoxicity in male mice. Treatment significantly improves Creatinine, Blood Urea Nitrogen, Malondialdehyde, Superoxide Dismutase and Glutathione Peroxidase.[76]

Terminalia catappa leaves possess protective effect against lead induced nephrotoxicity by restoring levels of marker enzymes and transaminases and phosphatases. [77]

Methanolic extract of *Leucas aspera (*100 mg/kg) exhibits protection against lead acetate induced (160 mg/kg) nephrotoxicities. Significant protection was marked by reduction in haemorrhages, atrophic glomerular tufts degenerative changes in the tubular epithelial cells.[78]

Thymoquinone (5 mg/kg/day, per oral), a phenolic compound active ingredient of the volatile oil of *Nigella sativa* seeds, improved affected antioxidant parameters by increase in reduced glutathione level, superoxide dismutase, glutathione peroxidase, catalase, and glutathione reductase activities in the renal tissue. [79]

Curcumin mitigate the nephrotoxic, oxidative, histopathological and residual impacts of lead acetate exposure. [80]

Nephro protective effects of *Berberis vulgaris* against lead acetate induced nephrotoxicity in mice have been observed. [81]

Effect of polyphenol against Lead induced reproductive toxicity

Punicalagin the major polyphenol of *Punica granatum* can protect against lead-induced testicular damage in mice. [82]

It has been found that polyphenolic compounds present in *Momordica charantia* extracts show significant effect on lead-induced male reproductive toxicity. [83]

It has been reported phenolic compounds present in *Fumaria parviflora* leaves demonstrated significant protection against lead induced testicular oxidative stress in rats. [84]

Cinnamon polyphenols witnessed significant protection against lead acetate induced reproductive toxicities in male rats. [85]

Rich phenolic compounds present in *Tribulus terrestris* root extract and vitamin C have preventive role against lead acetate induced testicular toxicity in mice. [86]

Phenolic compounds of *Nigella sativa* reported improvement against lead induced reproduction toxicity. [87]

Effect of polyphenol against Lead induced hepatotoxicity

It has been observed that polyphenols present in *Nigella saliva* seeds produced significant hepatoprotective effect against lead intoxication. [88]

Berberine a polyphenol reported protection against aqueous solution of lead acetate induced oxidative stress, elevated levels of enzymes, liver damage, indicated by necrosis and inflammatory cell infiltration. [89]

It has been investigated Silymarin (200-mg/kg silymarin, orally) and D-penicillamine (100-mg/kg D-penicillamine, intraperitoneally) alone and their combinations showed significant protection against lead induced toxicity. [90]

Polyphenol rich *Indigofera oblongifolia* (100 mg/kg, orally) leaf extract reported for hepatoprotective activity which was co-administered with lead exposure (20mg/kg). [91]

Proanthocyanidins (100 mg/kg, oral gavage), are a class of polyphenol showed significant hepatoprotective activity against water containing 0.2% lead acetate intoxication in mice. Proanthocyanidins witnessed beneficial effects due to retrieval of liver function parameters, decrease in lead level, lipid peroxidation, inhibition of antioxidant enzyme and histological alterations. [92]

Effect of polyphenol against Lead induced cardiotoxicity

Nigella sativa oil showed protection against lead induced cardio toxicity in rat. [93]

Polyphenolic compounds present in aqueous leaf extract of *Murraya koenigii* showed significant protection against lead induced oxidative damage in cardiac tissue of rats. [94]

Cardioprotective effects of curcumin on lead acetate induced myocardial damage on rats have been documented. [95]

Resveratrol the major polyphenolic compound of grapes witnessed significant cardioprotection against lead induced myocardial toxicity. [96]

Tannic acid is responsible for reduction in lead accumulation in rat heart. [97]

CONCLUSION

Lead is used widely since ancient times because of its unique physicochemical properties. Even though its toxicities have been evident and well documented, still it is in use all over the globe and modernization has increased the use of lead overall. Acute and chronic exposure of lead is responsible for various major organ toxicities, mainly affecting the central nervous system; followed by cardiovascular, haemopoietic, hepatic, renal and reproductive systems. Occupational lead poisoning is common and the children are exposed more. Areas with high lead level are necessary to be detected in order to prevent from unwanted lead toxicity. Natural polyphenolic compounds are able to detoxify lead from major organs and can revert the detrimental effects of lead. The probable reason by which it may show the protection is scavenging of reactive oxygen species, generated by lead and other heavy metals. Moreover, it is reported that they are also responsible for detoxification by removal of accumulated heavy metals from major organs. Apart from that, Polyphenols attenuated ROS-mediated inflammatory cytokines secretion through ERK/JNK/p38 pathways which is responsible for protection against lead induced inflammatory reactions.

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