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Review Article

CURCUMIN ATTENUATES LEAD (Pb)–INDUCED NEUROBEHAVIORL AND NEUROBIOCHEMICAL DYSFUNCTION: A REVIEW

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ABSTRACT

Lead is one of the common chemical elements that is assigned the symbol Pb which came from the Latin Plumbum. Pb is widely used in the field of coating, refine and glaze ceramics and pottery. It is still used in the production of products like water pipes, cooking utensils and cooking utensils. In addition it is also used in insulation of building ceilings, cable coverage and military industries. Lead enter the environment from those uses and from the environment it enter into the living organisms. Lead accumulates in many humanorgans, but the brain is the target organ of lead accumulation. Neurotoxicity of lead is, one of lead toxicity, caused many symptoms. There are many behavioral and biochemical modifications induced by lead toxicity like learning and memory deficits, anxiety disorders, social and sexual behavior modifications and neurotransmitter system deficits. Curcumin is a bioactive natural phytochemical phenolic compound (diferuloylmethane) extracted from the rhizome of *Curcuma longa*. Most studies indicated the role of curcumin in reducing the damage of lead toxicity. In the current review, emphasis was based on the toxicity of lead and its effect on behavior and some neurotransmitters related to behavior. The effect of curcumin is improving the neurotoxicity and behavioral toxicity of lead.

Keywords: Lead neurotoxity, Curcumin, Neurobehavior, Antioxidant

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INTRODUCTION

Lead is one of the earliest metals known by humans, before more than 7,000 y. It coincides with the dead civilizations, such as The Egyptian, The Romans, The Chinese, Civilizations of India, The Phoenicians and The Greeks respectively [1]. Pb is used during those civilizations in coating, refining and glazing ceramics and pottery. It is widely used in the manufacture of food and wine storage, water channels and water containers and in the production of women's jewelry. Lead is introduced in many modern industries, including the manufacture of water pipes, cooking utensils and cooking utensils. It is used in the printing and printing inks for plastic as well as in the industries of paints and cosmetics. Lead is also involved in the manufacture of dangerous radiation shields, insulation of building ceilings, cable coverage and military sectors. It also includes toys [2]. Lead attacked various body functions and also affecting hematopoietic, central nervous system, renal and hepatic system producing various disorders [3]. Acute level of lead toxicity is not common, however chronic toxicity about 40–60 ug/dL level in human blood may cause lethargy, encephalopathy, convulsions, coma and delirium [4]. Lead at the concentration of>60 µg/dL cause renal dysfunction but damage at ~10 µg/dL was also reported. Renal malfunction is classified as chronic nephropathy and acute nephropathy. Chronic nephropathy is mainly characterized by tubulointerstitial and glomerular changes, finally breakdown of renal, hyperuricemia and hypertension. Acute nephropathy is mainly characterized by degenerative changes in the tubular epithelium, an impaired tubular transport mechanism with the presence of lead protein. Lead toxicity causes abnormal excretion of glucose, amino acids, phosphates and cause Fanconi's syndrome [5].

Physical and chemical characters of lead

Lead is assigned the symbol Pb (from the Latin *Plumbum*), and the atomic weight 207.19, atomic number 82, is a bluish or silvery-gray metal with a specific gravity of 11.34, a melting point of 327.5 °C and the boiling point of 1740 °C (fig. 1) [6]. Lead is present in the form of lead acetate, lead nitrate, lead oxide, lead chromate and lead chloride. Lead compounds vary in solubility from soluble to insoluble in water and pure lead is insoluble in water.

Fig. 1: Curcumin plant [1]

Sources and environmental exposure of lead

Lead is mainly used in the production of batteries, ceramic glazes and paints. It is a highly toxic element causing a variety of effects at low dose-levels [7]. The important source of lead in the atmosphere has been mainly from leaded gasoline combustion, coal, combustion of solid waste, tobacco smoke, emissions from lead smelters and iron arid steer production and oils. Also, exposure to lead can occur from soil and foods [2]. Children are specific risk group to lead exposure because they use toys and other lead containing items. Also, lead paint is another important source of lead exposure and the primary source of lead toxicity in this group [8]. Lead contamination in drinking water is mainly due to the presence of lead in pipes and fixtures. The industries and work stations such as, lead refining and melting industries, gasoline stations, iron and steel factories and battery manufacturing plants. Inorganic lead occurs in work places of smelters and coal mines as well as battery plants and welding of lead painted metals. Moderate or low exposure of lead may also take place in the glass manufacturing units. High levels of emissions of lead in atmospheric air may pollute areas near coal fired TPPs and

lead mines. These lead can be deposited in water and on soil, thus entering humans via the food web [8].

Lead metabolism in the body

It was estimated that the human body contains 120 mg lead. The intestines alone contain nearly 10-20% of lead. Also, it was noted that lungs absorb approximately 50% of inhaled inorganic lead. Children absorb the copious amount of lead per unit body weight than adults (up to 40%). Women are highly susceptible to the poisoning of lead than men. And, children are highly susceptible to lead poisoning than the adult group. The symptoms of lead poisoning include concentration disorder, behavioral changes and lower IQs. Lead is also accumulated by leg tissues and encephalopathy is the severe type of lead poisoning [9]. In general, adults absorb 10 to 15% of lead from the food, whereas children absorb up to 50% lead through the gastrointestinal tract. In the human body, the absorbed lead binds with erythrocytes and eliminated through urine, however, the elimination process is much slower. Lead is also accumulated in the skeleton of the body and is very slowly released from the body part. In the skeleton, the half-life of the lead is 20 to 30 y and in the blood is approximately one month [10]. Lead is mainly excreted in faeces and the urine. However, it also appears in nails, hair, saliva, sweat and breast milk. As the body accumulates lead over many years and releases into urine only slowly, even small can at times leads to intoxication (fig. 2) [8].

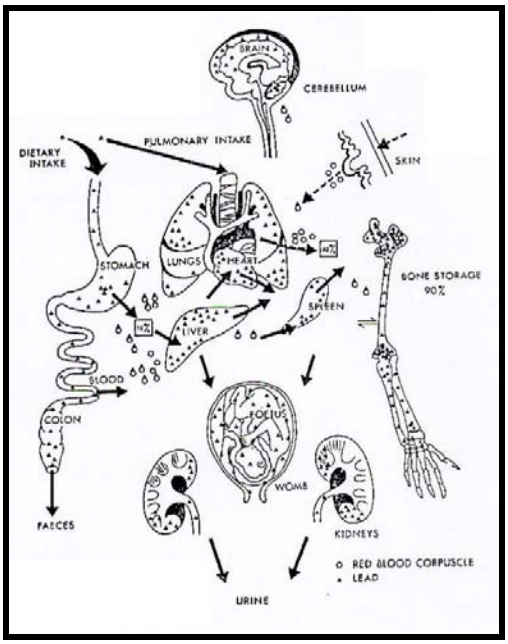

Fig. 2: Lead distribution in the body and its elimination [4]

Mechanism of lead action

The entry of lead into the body and its accumulation in the body's various organs leads to the emergence of many symptoms of diseases. The substantial affinity of Pb^{+2} for phosphate and thiol (-SH) containing legends mainly inhibits the biosynthesis of heme and thereby strongly affects the permeability of membrane in liver, kidney and brain cells. These results in either complete breakdown of these tissues since Pb is a cumulative poison or malfunction of these organs [11]. Lead accumulation in the tissue affects its structure and function, such as the production of neurotransmitters, secretion of hormones, malfunctioning in their function and the receptors of these enzymes and neurotransmitters [10]. It was reported that the lead causes severe oxidative stress by involving the release of hydrogen peroxide, hydroxyl radicals, lipid peroxides and superoxide radicals [12]. The molecular mechanism involved in lead toxicity is because of oxidative stress (OS), which is a result of an unbalance between antioxidant systems and oxidative agents. Fig. 3 summarize the mechanisms of lead poisoning.

Fig. 3: Mechanics of lead poisoning [12]

Possible disorders of lead

Lead induces biochemical, physiological and behavioural changes in animals and humans. It was well reported as one to the insidious and dangerous poisons. Its continuous occupational and environmental exposure contributes to nervous, renal, haematological, hepatic and infertility in animals and human (fig. 4) [2].

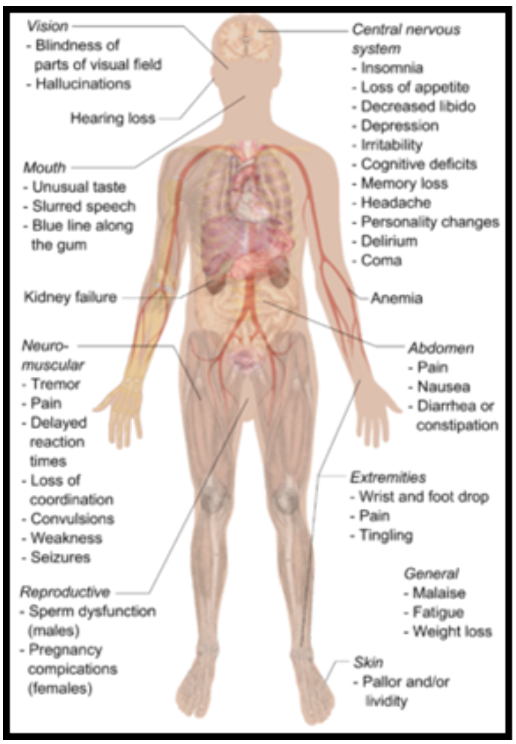

Fig. 4: Possible lead poisoning in human [2]

Disorders in nervous system

This system is very sensitive and lead easily target for lead-induced toxicity compared to the other organ system [13]. Both the peripheral nervous system and the central nervous system become severely affected by lead toxicity. In children, the central nervous system is prominently affected and in adults, the peripheral nervous system is severely affected [13]. Lead exposure cause encephalopathy in individuals. It is a direct consequence of lead exposure and the symptoms include irritability, headache, and loss of memory, hallucinations, muscular tremor, poor attention span and dullness. Very severe manifestations occur at very high exposures of lead and include paralysis, lack of coordination, delirium, coma, ataxia and convulsions [13]. Young children and features are highly vulnerable to the neurological effects of lead as the developing nervous system absorbs a high quantity of lead. The proportion of systemically circulating lead and absorbing access to the brain of young children is much higher as compared to adults. In children, higher lead levels may be severely affected with delayed growth, hearing loss and short-term memory. At extreme levels, the lead may cause brain damage and may cause death [14]. Repercussions of exposure of lead on the peripheral nervous system have been observed in the form of peripheral neuropathy in adults, involving motor activity reduction due to loss of myelin sheath which covers the nerves, thus severely causing weakness, impairing the transduction of nerve impulses, lack of muscular coordination especially of the exterior muscles and fatigues [15].

Neurobehavioral disorders

Behaviour is a set of coordinated movements that lead to a function so that the owner has access to a goal or a physical or moral purpose. Behavioural science seeks to identify the inherited and quoted traits in living organisms according to their interaction with the environment, and the whole behaviour of the brain and nervous system and the body contains hormones or chemicals active in the behaviour patterns and mechanisms of the body. Exposure to lead affects behaviour, especially if the exposure is during pregnancy and/or during the first days after birth.

Learning behaviour and memory retention

Many of the studies pointed out that the lead exposure caused learning and memory retention deficits. Few reports claimed that the exposure of males and female mice offspring to lead during gestation and lactation induced many alterations in behaviour like cognitive, emotional, motor functions and gene expression. Lead and manganese-exposed rats, individually and in combination, in the period of early development throw their dams drinking water solutions. The treatment started in the first day of gestation and continued until weaning period. The results in the Morris water maze, locomotor activity and anxiety showed that the exposure of lead and manganese affected cognitive and memory behaviour [16]. It was also reported that the exposure of lead acetate with or without xanthene throw oral drinking water in mice for 38 d [16]. They also found that Pb induced memory deficit and AChE dysfunction in a dose-dependent manner. The neurobehavioral defect indicators were found in the Morris water maze and forced swimming tests [17]. Step-through passive avoidance test tested learning/memory. The results indicated that Pb consumption caused deficits in mice memory or learning ability.

Social and anxiety behaviour

Social behaviour is a set of movements such as the nose, attend, groom, sniff, follow, investigate, crouch, push-under, crawl-over and push past. Lead ingestion in the early stage of mice has led to the dispersion of social behaviour. Social investigation was increased after 7-8 w, however, exploratory behaviour was decreased considerably. After 34 w social investigation and exploratory behaviour were increased and immobility was decreased in animals of both sexes treated with lead. In mice, at 15-16 w non-social activity was decreased in females and increased in males, however sexual and social investigation was not affected in these female-male encounters. At age of 17-18 w, lead-treated males showed very shorter latencies to aggression towards unfamiliar males than that of control groups. The effect of lead on prenatal conditions in the mice offspring was carried out. The level of alkaline and acid phosphatases in the liver, and acetyl cholinesterase level changes were determined in the brain tissues of the developing offspring. Increase in various parameters of 'locomotory test', and a decrease in attacking behaviour and abnormal in the acts and postural behavior changes in the 'Standard Opponent Test' was reported in the Pb exposed offspring of adult males. The 'tube restraint test' was carried out and a significant change in the latency to the first bite and in the number of targets biting by the Pb treated female offspring. Recently other report suggested that the aggressive behaviour of mice was increased after exposing to lead acetate in their drinking water [18]. Anxiety is generally described as a physiological, behavioural and psychological state induced in humans and animals by a threat to well-being, potential or either actual. It is mainly characterized by expectancy, increased arousal, neuroendocrine activation, autonomic and unique behaviour patterns [19]. The results found that Pb consumption could cause anxiety and deficits on fear in mice. It was also reported that lead acetate enhanced anxiety behaviour in the mice than that of the control groups.

Neuro-biochemical disorders

Neurotransmitter like Noradrenaline (NAd) or Norepinephrine (NE), Adrenaline (Ad) or Epinephrine (Epi), Serotonin (5-HT), Acetyl cholinesterase (AChE) and Dopamine (DA) are excreted in the peripheral and central nervous system. One of its most important functions is to assist in the neural conduction process. They associated in control some behaviours. One of lead neurotoxicity mechanism is believed to exert its neuro-toxic effects significantly through causing changes in various neurotransmitter systems [20].

Monoamenes

Monoamine neurotransmitters are called neurotransmitters and neuromodulators. All monoamines are mainly derived from aromatic amino acids such as, tryptophan, phenylalanine and tyrosine by the action of aromatic amino acid decarboxylase. It was found that the exposure of lead affects the function and composition of monoamine neurotransmitters. Lead exposure also caused decreased the activity of mitochondrial MAO in almost all the brain regions in a dose-dependent manner. The young mice are highly vulnerable to neurotoxicity induced by lead. The effects of developmental stress induced by lead and rise on blood Pb level were reported [21]. Lead exposure at the prenatal stage alters postnatal aminergic and cholinergic system in rat brain. Experiments done on various postnatal days of rats showed a decrease in synaptosomal AChE and mitochondrial MAO activities and dopamine, epinephrine and Ach level increased in the hippocampus and in the cerebellum of rats exposed with lead. These results showed the Pb-exposure at a prenatal stage severely affect the expression of D2R in brain region in a specific manner. The behavioral changes by the exposure of lead are significantly accompanied by cholinergic and serotonergic modifications were studied previously. The level of acetylcholinesterase (AChE) and dopamine activity were increased while serotonin level was considerably decreased. In anothor study, brain monoamines levels, DOPAC (dihydroxyphenylacetic acid), DA, NE, 5-HT and 5-HIAA (5 hydroxyindoleacetic acid) and HVA (homovanillic acid) from the right hemisphere of nucleus accumbens, frontal cortex, hypothalamus, striatum, midbrain, hippocampus and olfactory bulb in rats were evaluated using HPLC with electrochemical detection. The findings indicated that all monoamines were significantly decreased in all regions of experimental animals [22]. A recent report claimed that the protective role of essential elements like iron, zinc and calcium against lead-induced effect in rats. They found increased levels of norepinephrine, serotonin, epinephrine and synaptosomal dopamine. Also, in lead-exposed rats, at these age groups (PND 45, 4, 12 and 18 mo), mitochondrial monoamine oxidase level was significantly decreased. The variations were found to be greater in the hippocampus region than cerebellum and cortex. Ashafaq *et al.* (2016) analyzed the impact of tannic acid on neurochemical variation and oxidative stress markers induced by lead acetate treatment [23, 24]. The level of oxidative stress markers

such as protein carbonyl and lipid peroxidation observed in LA treated rats were increased, whereas the activity of enzymatic antioxidants, non-enzymatic antioxidants and neurotoxicity biomarker were strongly depleted. Developmental stress induced by the accumulation of lead was studied previously [25-30].

Acetylcholine (ACH) and acetyl cholinesterase (AChE)

Liu *et al.* (2013) evaluated the impact of puerarin and its protective effect on mice lead-induced cognitive impairment by modifying the enzyme activities, including, nitric oxide synthase, monoamine oxidase, and acetyl cholinesterase [25]. The activity of AChE was decreased considerably in lead-exposed mice brain. Puerarin increased activities of monoamine oxidase (MAO) and AChE in the brain of Pb-treated mice. Few researchers reported the effects of lead acetate exposure with xanthone on acetylcholinesterase (AChE) levels through drinking water orally in mice for 38 d [31, 32]. Results revealed that lead inhibited the enzyme activity of acetyl cholinesterase (AChE). In another study, the experimental mice were fed with lead acetate in drinking water. AChE activity was further determined using a colourimeter, and MDA and GSH levels were determined using a fluorometer in the whole cerebral cortex, striatum, cerebellum, brain minus cerebellum, midbrain and hippocampus. Lead exposure decreased GSH levels and increased lipid peroxidation in almost all tested parts of the brain [33].

Reproductive health effects

Toxicity of lead in the human body causes various adverse effects on the reproductive system. The effects include abnormal spermato-genesis, severe chromosomal damage, abnormal prostatic function, infertility, changes in serum testosterone and reduced libido in male individuals. In the other hand, lead toxicity causes miscarriage, infertility; pre-eclampsia, premature delivery, pregnancy hypertension and premature membrane rupture in females [34].

Prevention and control of lead-induced toxicity

Prevention of toxic exposure of lead is more important than treatment, because of its irreparable toxic effect. It is almost impossible to eliminate the lead from the body system, once it enters. It is also highly impossible to repair the lead toxicity in the human body. There are many ways suggested to prevent lead-induced toxicity in human, including, public health strategy, preventive medicine strategy and individual intervention. Prevention of lead toxicity mainly involved in the screening of blood lead level in children. Medical intervention is also recommended if lead content is very high in the blood mainly to control blood poisoning [35-38]. Many preventive measures have been suggested to control lead exposure. These measures include: not permitting industries dealing with manufacturing lead related products and banning the application of lead, once the suitable replacement is found. The phytochemicals such as, flavonoids and vitamins provide good protection against the environmental pollution caused by lead and accumulated lead in the body. The mechanisms of action by these nutrient factors restore the oxidant/pro-oxidant ratio is not very clear, however, findings suggested a constructive role of these phytochemicals against the poisoning of lead [39, 40].

Role of antioxidants and its protecting effect in lead-induced oxidative stress

Antioxidants play a critical role in preventing oxidative stress in the human body. The accumulated lead mainly stimulated oxidative stress that results in lipid peroxidation to cancer [41-43]. The antioxidant can prevent toxicity caused by lead in three different. These include inactivation of generated ROS and terminating chain breaking, prevention of formation of ROS by chelating lead ions, maintaining the lead in a redox state, by chelating lead. Antioxidants are generally classified into primary and secondary antioxidants. The antioxidants such as tocopherol, flavonoids and ascorbic acid are primary antioxidants [44].

Naturally available antioxidants

Antioxidants have effectively involved in curing and preventing oxidative stress. These antioxidants are mainly grouped into two types (non-enzymatic and enzymatic). The antioxidants such as, GPX, CAT, SOD are the enzymatic type, whereas minerals, vitamins, carotenoids, flavonoids are non-enzymatic type [31]. The exogenous antioxidants prevent many deleterious effects, like inflammation, toxicity due to heavy metals, cardiovascular disorder, brain disorders and cancer. The vitamins such as vitamin B, C and E have a significant ability to fight lead poisoning. Vitamin B6 is a moderate chelator and signalling the production of GSH. Ascorbic acid significantly involved in the prevention of oxidative stress induced by lead and is the potential lead detoxifying agent. The fat-soluble vitamin E (α-tocopherol) has numerous health benefits and possesses potent anti-oxidant properties [45]. Flavonoids are the important naturally available polyphenolic compounds and fruits and vegetables are the important sources of flavonoids. These anti-oxidants prevent or cure oxidative stress by terminating the free radical chain reaction and chelating redox-active metal ions.

Curcumin and its antioxidant properties

Curcumin (Cur) is a bioactive natural phytochemical compound rich in phenol (diferuloylmethane) found as abundant in the rhizome of turmeric plant. It is belonging to the family *Zingiberaceae* [33]. Curcumin possesses numerous health benefits and is highly effective to treat various diseases, including anorexia, coryza, cough, hepatic diseases and sinusitis. Curcumin has potential prophylactic, and therapeutic use, as antifungal, anticarcinogenic, antiviral, antimutagen, anti-infectious, antiparasitic, anti-inflammatory and antioxidant compound. The neuroprotective effects have been observed from Curcumin and are effective to treat age-related neurodegenerative diseases. Many studies revealed that Cur exhibits various antioxidant properties. In general, commercially available curcumin contains approximately 3% bisdemethoxycurcumin, 17% de-desmethoxycurcumin and 77% curcumin [34].

Curcumin attenuates lead toxicity

Curcumin plays a protective role in rats against neurotoxicity induced by lead. In curcumin treated rats, CAT, SOD and reduced glutathione (GSH) activities were increased and these investigations suggested the preventive role of curcumin in lead-induced neurotoxicity. Recently, Saad (2013) evaluated the anti-oxidative activities and the protective role of curcumin against some heavy metals induced testicular and renal injuries in male rats [2, 35, 36]. The results revealed that a mixture of heavy metals leads to an increase in the level of plasma creatinine, uric acid and urea, meanwhile, a significant decrease in serum testosterone concentration. Glutathione content and superoxide dismutase activities in kidney and testis tissues were significantly decreased by using a mixture of heavy metals. But groups administrated with curcumin before administrated with a mixture of heavy metals, exerted noticeable amelioration against their damage in most of the biochemical and histological tested parameters [46-48]. The prospect of curcumin has been used to care for heavy metal toxicity. Based on animal studies curcumin has been suggested to reduce lead-induced neurotoxicity, hepato-toxicity and cardiotoxicity. Treatment with curcumin has raised the lowered SOD, GSH and CAT levels and has reduced the level of lipid peroxidation. Lead also causes oxidative stress in the bones. Lead induced genotoxicity, due to its interaction with DNA and proteins causing double and single-strand breaks and DNA-protein cross-linking, is reduced with management with curcumin. Apart from curcumin being a free radical scavenger; it has been previously proposed that turmeric is an efficient inhibitor of lipid peroxidation via the inhibition of the lipoxygenase and cyclooxygenase pathways of archidonate metabolism. Another mode of mechanism that has been proposed recently is that of curcumin being a natural chelator for heavy metals. Hence curcumin, used so copiously in many countries, could be a strong heavy metal chelator with little or no side effects. Curcumin, like other anti-oxidants, has a great ability to bind elements such as lead and other toxic elements and help to minimize the damage that can cause the survival of the element in the body [35, 49-50].

CONCLUSION

In conclusion, our and other studies had shown that the dangers of exposure to lead (Pb) direct and indirect on the animals and humans. Pb exposure affects all body systems. Pb accumulates in the

brain and induces neurotoxicity and neurobehavioral disorders like cognition and memory retention deficits. Curcumin has an anti-oxidant property that ameliorates lead neurotoxicity and neurobehavioral toxicity. The curcumin amelioration effects need more studies to clarify the effects of curcumin on other problems can induce by lead exposure.

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AUTHOR CONTRIBUTION

Gasem Mohammad Abu-Taweel designed the rewiew and collected the informations from various sources. Gasem Mohammad Abu-Taweel drafted the manuscript

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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