Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-020-07654-2

REVIEW ARTICLE

Therapeutic role of garlic and vitamins C and E against toxicity induced by lead on various organs

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Received: 25 October 2019 / Accepted: 7 January 2020

Abstract

Due to industrial and urban sewage, the metal contaminations in aquatic and terrestrial environments are increasing day by day, especially in developing countries. Despite the study of several years, we are inert far away from an actual medication for prolonged toxicity of heavy metals such as mercury, lead, cadmium etc. Lead is one of the most common heavy metals that possess toxicological effects on numerous tissues of animals as well as humans. Several toxic effects of lead on reproductive organs, renal system, central nervous system, liver, lungs, blood parameters, and bones have been reported. On the other hand, several reports depicted that garlic is operative in declining the absorption of lead in bones as well as soft tissues. A combination of vitamin C and vitamin E enhances the biological recovery induced by lead and mobilize the heavy metal such as lead from intra-cellular positions. This review provides therapeutic approaches such as vitamin C, vitamin E, and extract of garlic to treat the detrimental effects caused after the exposure of lead. These therapeutic strategies are beneficial for both the prevention and alleviation of lead noxiousness.

Keywords Vitamin E (α-tocopherol · Garlic (*Allium sativum L.*) · Ascorbic acid (vitamin C) · Lead · Oxidative stress · Toxicity

Introduction

Lead

Heavy metals are persistent and uninterrupted ecological pollutants that are capable to cause numerous dysfunctions in target tissues of exposed animals as well as humans (Das and Saha 2010). Cadmium (Cd), copper (Cu), lead (Pb), nickel (Ni), chromium (Cr), zinc (Zn), arsenic (As), and mercury (Hg) are considered the main heavy metals. Metallic components arrive into the animal or human body then become stored mainly in the liver, brain, kidneys, adrenal gland, lungs, hair, and skin. Heavy metals cannot be broken down in the human body. They inhibit the normal functions of cells and tissues in numerous ways after communications with macromolecules such as hormone proteins and enzymes. They can freely form stable covalent complexes with tissue and proteins (Mudgal et al. 2010). Lead is deliberated as one of the most common global and industrial contaminants which cause toxicity at a low level as well as capable to damage numerous tissues. The latest studies proposed that lead induces the oxidative stress through the formation of free radicals and interrupts reliably or ultimately the balance of antioxidants resulting in cell apoptosis (Amadi et al. 2019).

Sources of lead

Humans are exposed to lead and its compounds, via numerous ways such as drinking water or food polluted through lead and inhalation through lead-containing dust particles that are present in the air (Karrari et al. 2012). On other hand, disclosure of lead can occur through various occupational sources such as lead-based painting, battery recycling, the printing of books, coal combustion, smelting of lead, boat building, industrial

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processes, leaded gasoline, grids, and bearings, *etc* (Veta et al. 2015).

Harmful effects of lead

Lead, a strong industrial toxicant due to its extensive use that has the capability to cause adverse health effects in humans as well as in animals (Nelson et al. 2011; Adikwu et al. 2013). Acute disclosure of lead can cause hypertension, abdominal pain, glomerular dysfunction, lethargy, loss of appetite, hallucinations, headache, sleeplessness, and pain in joints, whereas prolonged exposure is characterized by birth defects, intellectual disability, hyperactivity, allergies, paralysis, dyslexia, weight loss, muscular weakness, CNS damage, and renal dysfunction producing serious disorders (Neal and Guilarte 2010). Lead induces conspicuous testicular injuriousness, interference of serum gonad/pituitary hormone levels such as follicle-stimulating hormone (FSH), testosterone as well as luteinizing hormone (LH). Lead also decreases the action of glutathione (GSH), superoxide dismutase (SOD), and catalase in cells (Al-Masri 2015).

Mechanism action of lead toxicity

Lead poisoning causes the oxidative stress through depletion of the antioxidant defense system and enhanced formation of free radicals such as singlet oxygen, hydroperoxides ($HO_2\cdot$), and hydrogen peroxide (H_2O_2) or ROS which result in cellular impairment occurs as shown in Fig. 1 (Flora 2011). Antioxidant enzymes including SOD, GPx, and CAT are the main targets to lead toxicity (Kim et al. 2015). Lead is also able to replace bivalent cations such as Mg2+, Fe2+, and Ca2+ and the monovalent cations such as Na+, which act as a cofactor for these antioxidant enzymes to achieve the enzymatic reclamation of ROS (Lidsky Schneider 2006). The most vital antioxidant enzyme found in mammalian tissues is GSH

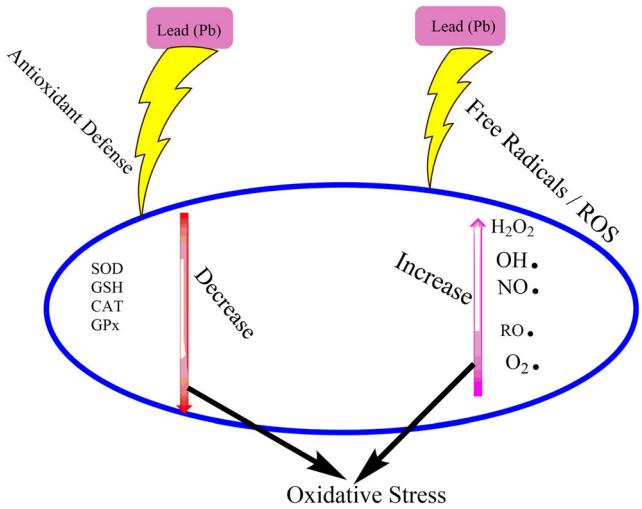

Fig. 1 Mechanism of lead (Pb) toxicity

which works to destroy or neutralize the production of free radicals or ROS. Lead inactivates the GSH level via binding to the sulfhydryl group of glutathione and also hindering the function of enzymes like glutathione peroxidase, glutathione reductase (GR), glutathione S-transferase, δ-aminolevulinic acid dehydratase, SOD, and CAT which result in oxidative stress increase (Kim et al. 2015). Reduced concentration of CAT and SOD impairs the clearance of superoxide radical ($O2^{-}$) scavenging activity (Flora et al. 2007). Important processes of the cell have been considerably affected by the above-mentioned mechanism of lead such as ionic transportation, intra, and intercellular signaling, cell adhesion, enzyme regulation, protein folding and its maturation, cell death, and discharge of neurochemicals (Patocka and Kuca 2016). At a significant rate, it is capable to cross the blood-brain barrier (BBB) after the replacement of calcium ions. Protein kinase C which is key neurotransmitters that regulate the memory storage and long-term neural excitation might be affected via replacement of Ca^{2+} via lead as picomole concentration. Lead also impairs the concentration of sodium ion that is responsible for uptake of neurotransmitters (dopamine and choline) and uptake retention and regulation of calcium by synaptosomes (Assi et al. 2016). A significant molecular mechanism induced by lead is increased production of ROS, which damage the cellular components and affect the regular metabolism due to its ability to have more than one unpaired electrons which make it extremely responsive with new molecules. ROS can impair the function of macromolecules such as oxidation of protein, disintegration of plasma membrane through lipid peroxidation, alteration of permeability, integrity and oxidation of RNA and DNA which can cause cancer as shown in Fig. 2 (Birben et al. 2012). Overproduction of free radicals due to exposure of lead starts from mitochondria then reach to all tissue and cellular components then cause oxidative stress which results in apoptosis of cell (González Rendón et al. 2018).

Effect of lead on liver

Lead poisoning causes focal hepatic necrosis, congestion of sinusoids, hyperchromatic hepatocytes with occasional vacuolations, and interruption of the normal anatomical organization of hepatic lobules (Omotoso et al. 2015). In soft tissues, the liver is the highest depositor (33%) organ of lead tracked via the kidney (Gargouri et al. 2016). Impairment of liver due to lead mostly occurs via lipid peroxidation and generation of ROS which disturb the antioxidant balance (Riethmüller et al. 2015). Oxidative stress made by lead in the liver is related with the elevation of malondialdehyde (MDA) level and LPO that causes the modification of fatty acid composition and membrane integrity as shown in Fig. 3 (Omobowale et al. 2014). Available literatures stated that when lead acetate (15 mg/kg body weight) was supplemented to the mice for

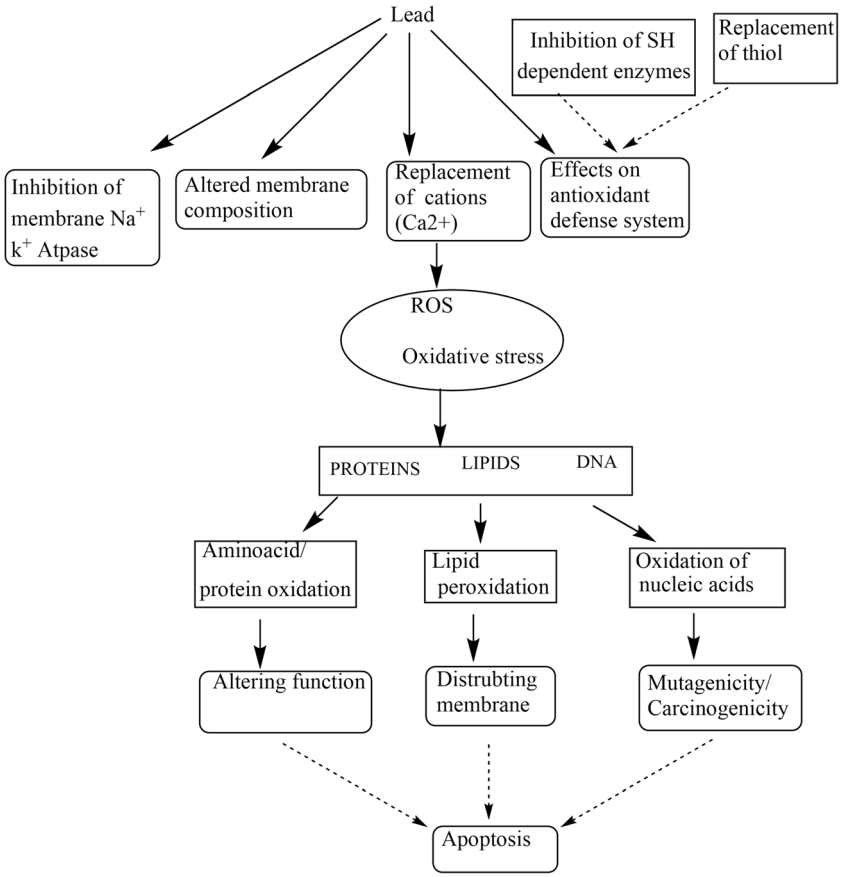

Fig. 2 Mechanism and targets for increase and oxidative stress via introduction of lead (Pb)

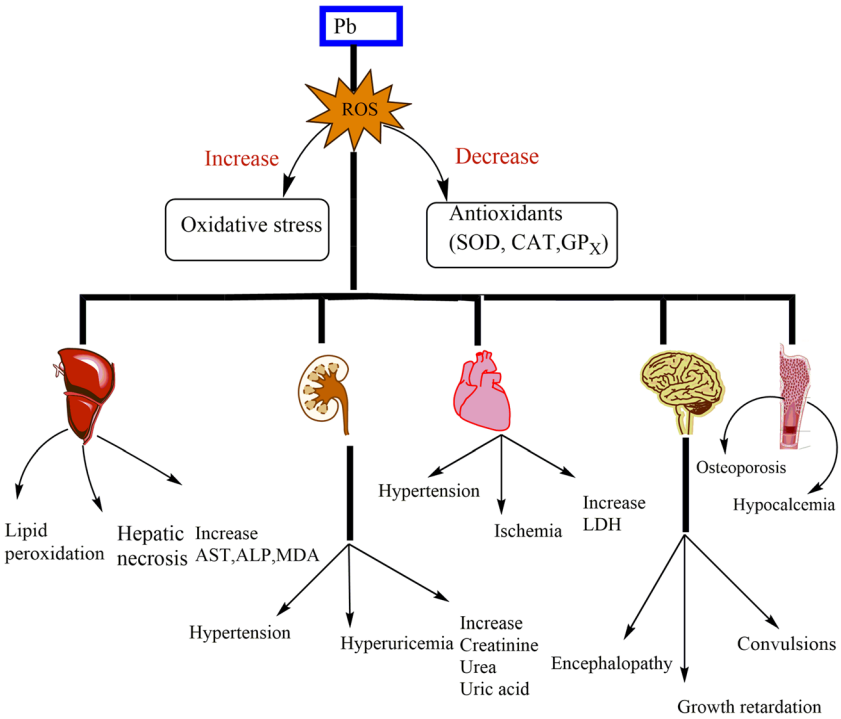

Fig. 3 Effect of lead (Pb) toxicity on various organs

1 week consecutive, then it revealed that 62% activity of ALP was considerably elevated as compared to untreated animals, while level of bilirubin was 38% substantial rise in serum with respect to control group (Nadia 2013).

Effect of lead on the renal system

Kidney dysfunction commonly occurs at high levels of Pb disclosure (> 60 μg/dL); however, impairment to minor levels (~ 10 μg/dL) has also been described (Carocci et al. 2016). Histopathological examination of the renal system of mice disclosure to lead toxicity indicated a degeneration in kidney cells, inflammation, and tubule lumen dilatation (Aziz et al. 2012). Renal functional aberrations induced by lead are of two types: prolonged and acute nephropathy. Acute nephropathy gives rise to the presence of deteriorating modifications in the tubular epithelium along with the manifestation of nuclear inclusion bodies which form the complex with lead. Renal tubular impairment with aminoaciduria and glucosuria is a consequence of exposure of lead at a high level. Prolonged nephropathy is described as tubulointerstitial and glomerular fluctuations such as hyperuricemia renal failure as well as hypertension (Flora et al. 2012). The exposure of lead acetate revealed a substantial ($p < 0.05$) elevation in the absorption of creatinine and urea in mice with respect to the untreated group (Salim 2015).

Cardiovascular toxicity

Exposure of lead causes cardiovascular disorders through altering the rennin-angiotensin system, increasing endothelial production, damaging nitric oxide signaling, limiting nitric oxide availability, promoting inflammation, raising vasoconstrictor prostaglandins, ischemia, disturbing vascular smooth muscle Ca2+, and reduced the endothelial cell growth (Inneh and Ebeigbe 2016). Prolonged and severe exposure of lead causes cardiac and vascular impairment such as raises the rate of hypertension and cardiovascular illnesses which can cause death (Weisskopf et al. 2010). Other research showed that oxidative stress is a mechanism of high blood pressure at a low level of exposure to lead, which might be directly affected by the vascular smooth muscle through constraining the Na-K-ATPase activity, which is associated with intracellular elevation of calcium level (Dobrakowski et al. 2016).

Toxicity of lead on testis

Testes are one of the target organs for the toxicity of lead. Dorostghoal et al. (2011) observed that oral administration of lead acetate to animals affected the daily assembly of semen, the weightiness of sex glands and modification in the common structure of testes. Reproductive hormones such as luteinizing hormone LH, FSH, and testosterone were damaged in rats by exposure of lead (Dorostghoal et al. 2011). It was observed that exposure of lead altered the morphology of spermatozoa, histology of testis, as well as suppressed the hypothalamic-pituitary-testicular axis in mice. When lead-exposed men were mated with non-exposed women, the fertility rate was reduced in exposed males (Assi et al. 2017).

Effect of lead on bone

Bones are one of the foremost sites for storage of lead. Lead can be deposited in cortical aspect of the bone or at the surface of bone. Lead enhances the threat of osteoporosis in adults through reducing bone density (Khalil et al. 2014). The deposition of lead occurs in both hard tissues (bone) and soft (brain, liver, heart kidneys, and muscle). Bone matrix is the main target for lead because of its capacity to substitute the divalent cations (Fe^{2+}, Ca^{2+}, and Mg^{2+}) and monovalent cations (Na^{+}) in the body. Lead disturbs the mineral metabolism of phosphorus and calcium through hindering the 1-α-hydroxylase enzyme of the kidney that is responsible for the production of 1,25-dihydroxy-vit D_3 which results in hypophosphatemia and hypocalcemia occurs (Dongre et al. 2013). Lead-exposed animals showed that accumulation of Pb in the body has harmful outcomes on the bone such as decreasing bone density and cortical width, delayed cartilage formation, maturation, and delayed fracture healing (Carmouche et al. 2005). In vitro research showed that lead reduced the activity of ALP in osteoblasts and reduced the production of osteocalcin. During chondrocyte maturation, lead altered the growth factors and second messenger signaling reactions as well as inhibited type II and type X collagen manifestation in osteoblast. Detrimental effects on bones of young animals due to lead poisoning such as increased bone resorption prevent the production of matrix and interruption of mineralization and inhibit the development of axial bone showed by various in vivo studies (Holz et al. 2012).

Effect of lead on brain

The brain is most susceptible to the noxiousness of lead about the period. The central nervous system (CNS) is mostly influenced by youngsters, while the peripheral nervous system (PNS) is mostly influenced in grown-ups (Wani et al. 2015). Severe toxicity of lead in the CNS that causes encephalopathy, convulsions, delirium, or coma occurs as shown in Fig. 3. Exposure of high level of lead can cause a decline in the intelligence, hindered growth, loss of hearing, and short-term memory in children. A higher concentration of lead may be a reason for long-lasting impairment of the brain and cause death (Cleveland et al. 2008).

Solutions to avoid the harmful effects of lead

Preventive approaches to lead toxicity are preferred over the treatment commands because when lead arrives into the body, it is not possible to eliminate it from the body (Eneh and Agunwamba 2011). Three preventive methods toward lead toxicity are including preventive medicine strategy, individual intervention, and public health strategy. Public health approach actions at a community level to decrease the exposure of lead from inhabitable areas.

Several preventive approaches for monitoring lead have been recommended by public health services. These approaches included completely prohibit the usage of lead wherever applicable vacant is accessible and banning of setting up industries distributing lead near to inhabitable regions (Patra et al. 2011). Some studies showed that usage of various nutrients, e.g., vitamins, flavonoids, and mineral elements, can offer defense from the Pb already existent in the body as well as from the environment (Patra et al. 2011).

Garlic (*Allium sativum* L.)

Garlic is used as foodstuff and medical herb (Chen et al. 2013). It has numerous essential nutritious and antioxidant ingredients such as sulfur compounds, selenium, and flavonoids (Bozin et al. 2008). Garlic increments are commercially available in different forms such as garlic oils (capsule), aged garlic extracts (tablets, capsules, and liquid), garlic powder (tablets). Garlic supplements are different in the organosulfur compound profile (Fujisawa et al. 2009). Highly odorous and unstable compounds are converted into more odorless and stable compounds, during the aging of garlic. Consequently, aged garlic (up and about 20 months) gives the better-known garlic preparations and more capable for the therapeutic purpose. Various studies specified that the ingestion of garlic extract as a nutritional supplement reinforces the antioxidant capacity and declines the levels of oxidants in blood (Ried et al. 2013). Garlic can enhance the antioxidant defense mechanism as well as diminish the oxidation of lipids in animals and humans (higher radical scavenging and reducing capability have been found in garlic than onion (Kikelomo et al. 2008)).

It acts as an anti-carcinogenic, antibacterial, hypoglycemic, antioxidant, antifungal, and anti-atherosclerotic (Hassan et al. 2009). Usually, garlic has been used as a medicine for intestinal ailments, dog bites, flatulence, wounds, and skin diseases. Garlic oil is capable of scavenging free radicals and form complexes with metal ions. Garlic is recommended as an active antioxidant against heavy metal-induced toxicities (Johnson 2012). It might act as a lead chelator and enhance the excretion of lead and other heavy metals from the body (Sharma et al. 2010). Natural chelating ability of allicin and sulfhydryl groups which are present in garlic makes it strong antioxidant for treatment of toxicity induced by lead, particularly prolonged toxicity of lead (Sajitha et al. 2010).

Components of garlic (*Allium sativum* L.)

Garlic possesses many medical and pharmacological applications. Several advantageous health assets of garlic are recognized to organosulfur compounds, especially to sulfur-bearing compounds viz. allin, allicin, myrosinase, peroxidase ajone, S-allyl-cysteines, diallyl-di-sulfide, and diallyl-sulfide. It maintains the antioxidant defense system of the body due to presence of high level of selenium that can prevent the cancer. Allicin (diallylthiosulfinateor allyl-2 propenethiosulfinate) is a bioactive component of garlic present in raw garlic homogenate or aqueous extract of garlic and is to some extent soluble in alcohol and water due to (OH) group (Amagase et al. 2006). Allicin is produced when garlic is crushed or chopped; then, allinase is activated and actions on alliin (S-allylcysteinesulfoxide) (Lawson et al. 2005). This reaction can take place due to enzyme 'alliinase' which depresses the activation energy. Allicin possesses the antioxidant effects by inhibiting lipid peroxidation, blood sugar lowering action, and scavenging free radicals as shown in Fig. 4. The bioactive element of garlic (Allicin) has the capability in decreasing the levels of lead from blood and various such as liver and kidneys (Baghishani et al. 2011).

Allicin possesses 1% of the effectiveness of penicillin. The therapeutic property of garlic may be recognized due to its antioxidant capability that is provided by organosulfur compounds (thiol). It also possesses isoleucine, glutamine, and methionine which defend the cells from the production of ROS (Reddy et al. 2011).

Garlic (allicin) is capable to improve anemia, thrombocytopenia, and leucopenia by enhancing the activity of bone marrow. Allicin is instinctively degraded into ajoene which has a potent antiviral, antithrombotic agent, anti trypanosomal, and antimalarial activities. It has also inhibitory effect on platelet aggregation and adhesion as well as shows inhibitory effect on synthesis of cholesterol (Singh 2017).

Vitamin E (α-tochopherol)

Vitamin E is a primary liposoluble and possesses numerous organic activities. It acts as an anti-oxidant and inhibits the lipid peroxidation via hindering the response of free radical chain (Rendon-Ramirez et al. 2007). Vitamin E deactivates the generated ROS through eliminating the free radical chain reaction, inhibiting the further production of ROS by chelating and maintains the Pb ion in a redox state (Garcia and Gonzalez 2008).

During oxidative reactions, vitamin E donates the electrons to ROS and becomes oxidized in the process by scavenging

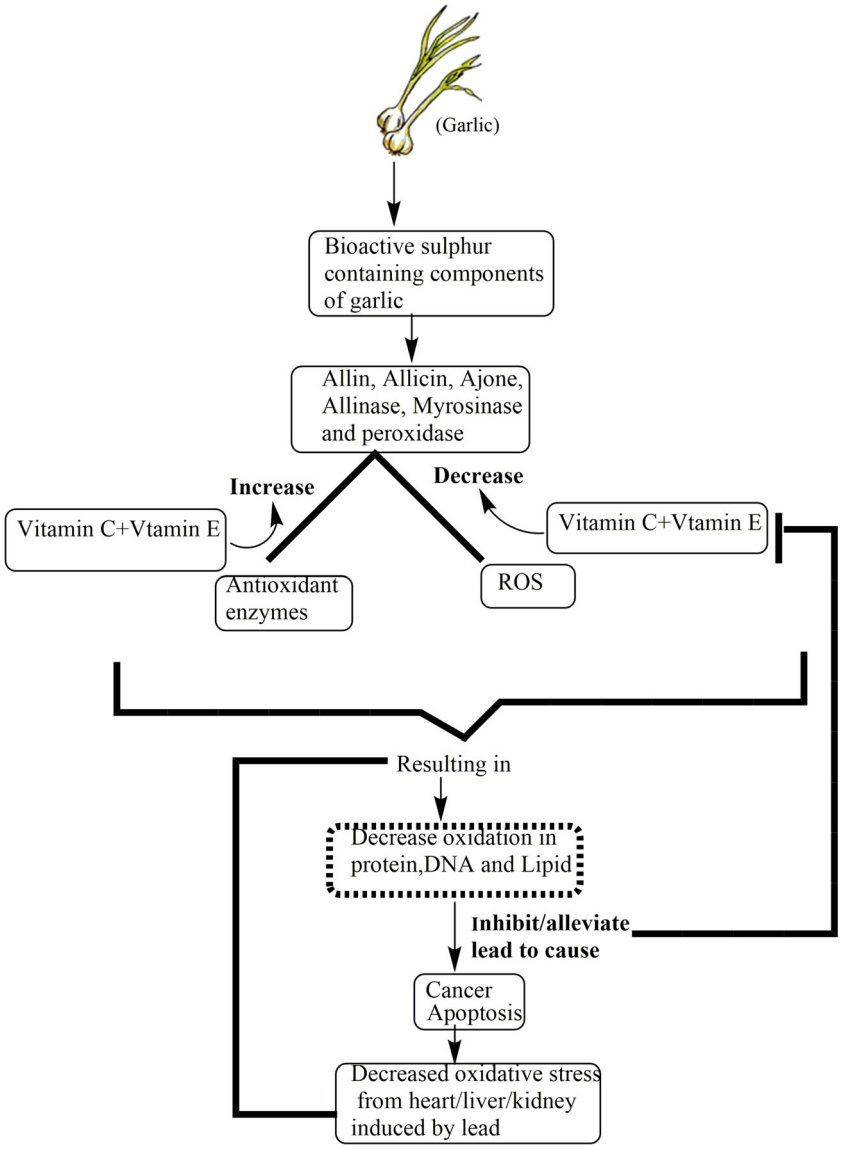

Fig. 4 Mechanism for alleviation of lead toxicity through garlic and vitamins

the ROS. It reduces the oxidative stress and lipid peroxidation in tissues (Obianime and Aprioku 2009). Vitamin E capable to improve the intellectual loss triggered by aged. It is capable to inhibit the oxidative stress and stabilize the harmful effects of lead (Pb) through penetrating free radicals (Fig. 4). Lead inhibits the ALAD in the red blood cells, while elevation in (RBCs) was found via usage of vitamin E (Rendon-Ramirez et al. 2007). Proper treating with vitamin E has been suggested as good for inhibiting the complications related to health induced by lead (Khodamoradi et al. 2015). Vitamin E can be useful to defend the membrane lipids by preventing the oxidation of protein produced by lead (Sharma 2013). Bera et al. (2010) have been reported that supplementation of vitamin E individual or in combination with other chelators can decline the level of lipid peroxide in hepatic and nervous system of lead-exposed mice. Supplementation of α-tocopherol and ascorbic acid has been known to modify the extent of RNA impairment through prohibiting the stimulation of caspase cascade and decreasing the level of tumor necrosis factor alpha (TNF-α) because co-administration of vitamins showed synergistic effects (Bera et al. 2010).

Ascorbic acid (vitamin C)

Vitamin C or ascorbic acid is major hydro soluble and structurally related to glucose. It is an indispensable dietary nutrient and is one of the naturally occurring antioxidants in nature for a wide range of biological functions (Farris 2005). Vitamin C mostly occurs in ascorbate anion form at biological pH states. Natural sources of vitamin C are citrus fruits, strawberries, fresh fruits papaya, chili pepper or parsley, guava, rosehip, and broccoli and green leafy vegetables (Farris and Krol 2015). Absorption of vitamin C mostly takes place in gastrointestinal tract (GIT) or the distal intestine through sodium-

dependent vitamin C transporters (SVCTs), which are present all over the physique and responsible for transportation into further soft tissues (Figueroa-Méndez and Rivas-Arancibia 2015). It possesses the potential to quench the peroxyl radicals, hydrogen peroxide, hypochloride, superoxide, and hydroxyl radicals as well as renovate the antioxidant assets of vitamin E (Mccallum et al. 2011).

Mechanism action of vitamin C

Vitamin C (ascorbic acid) is a non-enzymatic antioxidant that has potential to decline the metabolism of lipid as well as tramp the free radicals. It has also the capability to chelate the metal ions (Fe^{++}) due to the presence of OH groups on an adjacent side of carbon atoms. It acts as a free radical scavenger and quench the free radicals of oxygen O^{-2} and donate hydrogen to an oxidizing system and prevent oxidation (Brewer 2011). It has the potential to defend the essential biomolecules, e.g., DNA, RNA, lipids, proteins, and carbohydrates from disclosure to pollutants and toxins such as cigarette smoke. It also defends from impairment by oxidants which are produced during normal metabolism of the cell (Griffiths et al. 2016). Vitamin C acts as a free radical searcher that can defend the cell from oxidative stress produced through ROS via a process of electron donation or transfer. Ascorbic acid converts the free radicals into non-free radicals because paired hydrogen atoms of ascorbic acid form the complex with unpaired electrons of free radicals and convert them into non free radicals.

$$\text{Ascorbate} + 2H + 2O_2 \rightarrow \text{dehydroascorbate} + 2H_2O_2$$

$$2\text{Ascorbate} + H_2O_2 \rightarrow 2\ \text{monascorbate} + 2H_2O$$

It can also defend the antioxidant enzymes of a cell for example glutathione peroxidase, catalase, and superoxide dismutase (Jagetia et al. 2003; Downie et al. 2018).

It possesses protecting properties against toxicity of lead in the hepatic system, CNS, renal system, and reproductive system as shown in Fig. 4 (El-Sokkary and Awadalla 2011). Vitamin C is capable of reducing the oxidative stress produced by lead (Das and Saha 2010). Moreover, it is found to be effective in the reduction of lead and elevated the action of ALAD in blood. It has been also found in the treatment and prevention of diabetes, glaucoma cataracts, stroke, aging, and inflammation etc. (Walingo 2005). According to Ommati et al. (2018), co-administration of vitamin C and vitamin E has synergetic effects in animals and humans ().

Therapeutic role of garlic and vitamins against toxicity of lead on bone

Pourjafar and his colleagues supplemented 5 mg/kg body weight of lead acetate in mice and described that it accumulated in bones and other organs. However, 125, 250, and 500 mg/kg extract of garlic declined the levels of lead in bones as well as in soft tissues (Pourjafar et al. 2007). When rats were treated with different doses of lead acetate (200, 400, and 600 ppm) for 3 weeks, a significant elevation in protein carbonyl contents and lipid hydroperoxides of bone marrow was observed while a reduction in glutathione peroxidase, superoxide dismutase, and catalase enzyme was observed (Haleagrahara et al. 2011). Literature data showed that supplementation of lead acetate for 20 and 40 days at a dose rate of 75 mg/kg B.W. produced a mild hyperplasia while supplementation of garlic juice and vitamin C in pregnant mice exposed to lead acetate have preventive effects on malformation of bones of mice neonates (Reddy et al. 2012). Ascorbic acid or vitamin C possesses a particular role in the formation of collagen, and deficiency of vitamin C results in disrupted endochondral ossification as well as an abnormal extracellular matrix of the bone. According to Mohamed et al. (2012), supplementation of vitamin E in mice showed a vital function in increasing the density of bone as well as a protective role against osteoporosis through scavenging the free radicals (Mohamed et al. 2012).

Therapeutic role of garlic and vitamins against toxicity of lead on cardiovascular system

Literature data indicated that when rats were treated with lead acetate for 1 week revealed a substantial elevation in the levels of catalase LDH as well as glutamate oxaloacetate transaminase was observed in heart with respect to the level measured in control but when lead intoxicated mice were treated with garlic and vitamin C for 1 week, significant reduction in activity of these enzymes was observed (Kilikdar et al. 2013).

However, when lead intoxicated mice were treated with vitamin E 200 mg/kg body weight, significant reductions in level of AST and LDH were observed (El Sheikh et al. 2014). Garlic (*Alium sativum*), as well as extracts of garlic, has valuable properties for inhibition of heart disorders and prophylactic usage of vitamin C is moderately operative during intoxication of lead (Rahman and Lowe 2006). Vitamin C protects the living system by increasing GSH level of blood and sulfhydryl groups. Vitamin C (ascorbic acid) has a depressing conclusion on hypertension particularly on high blood pressure than a low blood pressure. Low level of vitamin C in plasma associated with stroke. Increased intake of vitamin C raises the ascorbic level in serum and might decline the possibility of mortality due to stroke (Hesta et al. 2009).

Therapeutic role of vitamins and garlic against toxicity of lead on liver

Besides blood, main target of lead is the liver to induce the oxidative stress. Toxicity in liver through lead is associated

with modifications in metabolism of hepatic cholesterol and elevation in the levels of hepatic enzymes in plasma such as ASAT, ALP, and ALAT (Omobowale et al. 2014). Sharma et al. (2010) found that methanolic extracts of garlic play an essential function in declining the irregularly high levels of lipid peroxidation as well as aminotransferases which were enhanced in lead-treated groups. Abdou and Hassan (2014) stated that exposure of lead-acetate 15 mg/kg B.W intraperitoneally for 7 days caused a reduction in CAT, GPx, and SOD activity. When animals were treated with lead acetate .25, 0.5, and 1.0 mg/mL for 1 week, substantial rise in level of hepatic enzymes ASAT, ALP, and ALAT was observed while reduction in the content of GSH and antioxidant enzymes (GPx, SOD, CAT) was observed after treatment with lead acetate (Abdou and Hassan 2014). It is reported that post-treatment of the lead-exposed rats with ascorbic acid and garlic indicated a huge decline in the levels of serum ALP plus ALT. On the other hand, when lead-exposed rats treated with vitamin C elevation in an antioxidant enzyme such as SOD was observed (Ajayi et al. 2009; Fox 1975), syndicate administration of vitamin E and garlic oil alleviated the lead acetate toxicity in liver of animal models. High levels of transaminases in serum were repaired after pretreatment with vitamin E (Al-Bideri 2011). Vitamin C diminishes the hepatic poisonousness by enhancing the urinary excretion of lead and protects the hepatic cells from oxidative stress (El-Neweshy and El-Sayed 2011). Co-administration of vitamin C and vitamin E provides a synergistic effect to protect the hepatic cells against oxidative injury induced by lead (Samir and Bashandy 2006).

Protective role of garlic and vitamins against toxicity of lead on testis

When mice treated with lead acetate 2–25 mg/kg body weight for 1-week reduction in sperm viability, sperm volume motility sperm count, testosterone, and LH were observed, however, administration of 420 mg/kg vitamin C in mice improved these abnormal changes induced by lead (Falana and Oyeyipo 2012). Previous studies showed that lead affects the motility of sperm by disturbing the role of mitochondria, while usage of the extract of garlic recovering the motility of sperm approximately to normal levels (Ouarda and Abdennour 2011). Acharya and his co-researcher informed that vitamin E (100 mg/kg body weight) deliberates the same gonadal protecting effects in lead-treated rats like vitamin C (Ascorbic acid); however, co-administration of vitamin E and vitamin C has synergistic effects. Ommati et al. (2018) and Sajitha et al. (2010) have stated that oral supplementation of ripened garlic extract enhances the spermatogenesis in lead nitrate-exposed mice as well as in humans.

Therapeutic role of garlic and vitamins against toxicity of lead on brain

Available data suggest that vitamin C (ascorbic acid) diminished the lead acetate-influenced changes in the brain of mice such as cerebral satellitosis, encephalomalacia as well as cerebellar edema (El-Masry et al. 2011). Garlic possesses the potential to defend the brain against ROS produced through lead (Simagol et al. 2017). Oral administration 13.5 mg/kg of garlic declined the poisonous properties of lead in the brain of rats. Hassan and his co-researcher administered lead acetate (10 mg/kg) orally to female lactating mice which result in high-density lipoproteins, and significant reduction in glutathione in their puppies was perceived. Oral administration of 100 mg/kg vitamin C and vitamin E (600 mg/kg) stabilized the changes related to lead acetate as shown in Table 1 (Hassan and Jassim 2010). The supplementation of vitamin E to lead-exposed rats showed significant reductions in nitrogen oxide concentrations and malondialdehyde in the cerebral cortex of mice while a significant elevation in activities of

Table 1 Designated studies on therapeutic effects of antioxidants (garlic and vitamins) against toxicity of lead

Antioxidant	Administered form	Animal model	Duration	Target sites	Therapeutic effects	References
Garlic	500 mg/kg b.w. orally administration of garlic extract	Male rats exposed to 50 mg/kg b.w. lead nitrate by oral gavage	30 days	kidneys, brain and blood	Garlic declined the lead and improved the immunological parameters from tissues and stimulated defecation of Pb from the tissues	Simagol et al. (2017)
Vitamin C	20 mg/kg b.w. orally vitamin C	Rats exposed to 20 mg/kg b.w. lead acetate by oral gavage	90 days	Testes	Vitamin C ameliorates lead induced testicular damage and spermatogenic process.	Shaban El-Neweshy and Said El-Sayed (2011)
Vitamin E	600 mg/kg b.w. orally administration of vitamin E	Female lactating mice exposed to (10 mg/kg) b.w. lead acetate orally	5 days	Brain	Normalized the glutathione brain tissue and HDL proteins.	Hassan and Jassim (2010)

Table 2 List of abbreviations

Abbreviations	Full name
Pb	Lead
mg	Milligram
kg	Kilogram
B.w.	Body weight
HDL	High-density lipoprotein
CAT	Catalase
GSH	Glutathione
ALAD	Aminolevulinic acid dehydratase
TNF	Tumor necrosis factor
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASAT	Aspartate amino transferase
CNS	Central nervous system
SOD	Superoxide dismutase
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
ROS	Reactive oxygen species
Ni	Nickel
Cu	Copper
Hg	Mercury
BBB	Blood-brain barrier

CAT, GSH levels, and SOD was observed in the brain of rats (Ebuehi et al. 2012) (Table 2).

Protective role of garlic and vitamins against toxicity of lead on kidney

Literature data showed that exposure of lead acetate to mice showed a substantial elevation in the level of uric acid, urea, and creatinine to an untreated group while supplementation of garlic to lead-intoxicated mice brought back the level of uric acid, urea, and creatinine close to control group (Salem and Salem 2016).

It was reported that vitamin E, vitamin C, and garlic extract diminished the impairment of kidney due to toxicity of the lead acetate through reducing the oxidative stress as well as repairing function of antioxidant (Al-Attar 2011). Vitamin C elevated the level of CAT in the renal system of lead-exposed mice (Khan et al. 2008). Lead-intoxicated mice treated with garlic revealed that a substantial decline in lead bioaccumulation and substantial rise in SOD, CAT, and GSH in the kidney of mice was observed as compared to individual administration of lead (Salem and Salem 2016).

Supplementations of lead acetate (15 mg/kg) to mice for 2 weeks cause oxidative damage through enhancing the LPO and inhibition of antioxidant enzymes (El Sheikh et al. 2014). Garlic shows a vital function in the prohibition of lipid peroxidation, decrease creatinine levels as well as urea and elevation of antioxidant enzymes in lead-exposed mice (Marsoul et al. 2016). Sary et al. (2015) stated that simultaneous use of vitamin E and vitamin C in lead-exposed mice for 6 weeks showed the normal histological structure of renal medulla.

Conclusions

Exposure of lead stimulates the contaminated effects on various organs through production of reactive oxygen species, diminishing their structures, prohibition of the roles of antioxidants. Pre-treatment with antioxidant like vitamin C and vitamin E and extract of a plant such as garlic decreases the oxidative stress, inhibits progressive fluctuations convinced through lead, repaired the biochemical alterations rising in the testis, liver, brain, kidneys, and bone to almost nearby the standard assemblage. Several scholars revealed and inspected that treatment with vitamins and garlic not only

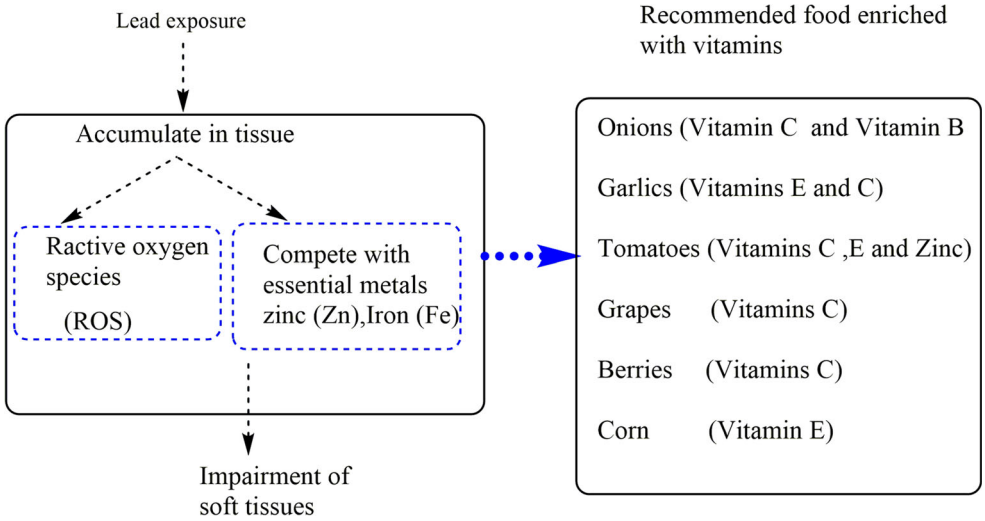

Fig. 5 Recommended food scheme against toxicity of lead

deliberate defense contrary to toxicity of lead, but it may also accomplish the therapeutical character contrary to noxiousness of any heavy metal and xenobiotics.

Future perceptions

We recommend that individuals who have high possibility of introduction to toxic metals should abundantly intake the fruits and vegetables on a regular basis which are enriched with essential elements and vitamins such as berries, grapes (enriched in vitamin C and anthocyanin), tomatoes (possessed calcium, iron, zinc, selenium, vitamin C, and vitamin B), garlic (enriched in sulfur-containing compounds, vitamins E, vitamin C (ascorbic acid)), and onions (quercetin, selenium, and vitamins B and vitamin C), which possess significant concern as natural competitors to noxiousness of lead and other heavy metals (Fig. 5). These nutritive complements have fewer side effects than chelation treatment as well as cost-effective for billions of individuals in the world who have unintentionally treated for exposure to contaminated metals regularly. Eatable animals that are affected by the toxicity of heavy metals, e.g., lead, might be an indirect source of poisonousness in humans. So, nutrient supplements that are enriched with natural antioxidants should be provided the cattle and cultivated fishes.

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