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Invited Review Article

Lead toxicity in livestock and poultry: Illuminating the molecular pathomechanism, bioaccumulation and effective mitigation strategies

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Abstract

Lead (Pb) is a hazardous heavy metal and an environmental pollutant, which is continuously released in the environment due to various anthropogenic activities including urbanization, industrial establishments, and mining. Consequently, air, soil, and water in the vicinity of these areas become frequently contaminated with Pb. Due to inquisitive feeding habits of livestock and poultry, they are often exposed to this toxic heavy metal that elicits metabolic, structural, and functional alterations of different organs of all animals. Bioaccumulation of Pb in visceral organs causes disturbances in systemic functions including neurotoxicity, nephrotoxicity, and hepatotoxicity. Due to the constant exposure, Pb accumulates in various organs, primarily the liver, kidney, lungs, and reproductive organs in livestock and poultry. Intake of Pb decreases the productive performances and pathophysiological alterations of farm animals. Continuous Pb exposure produces increased oxidative stress because of the excessive creation of reactive oxygen species and depletion of antioxidant molecules at cellular levels. Damage of nucleic acid, lipid and other crucial molecules results in apoptosis, cell death, degenerative changes and altered gene expression profile. To combat the detrimental effects of Pb toxicity in animals, several antioxidants in the form of vitamin molecules, minerals or herbal additives individually or in combination have been used in feeds. Present review discusses toxic effects of Pb, histopathological changes, their biochemical and molecular mechanism, bioaccumulation and different ameliorating strategies to vanquish Pb toxicity in livestock and poultry.

Key words: Amelioration, Bioaccumulation, DNA damage, Lead toxicity, Oxidative stress

Highlights

- Content of lead (Pb) in animal products is rising in practically every country as a result of urbanization and industrialization.
- Pb-toxicity in livestock and poultry causes disorders of different physiological systems due to disruption of diverse cellular activities.
- Bioaccumulation of Pb in livestock and poultry can reduce production efficiency.
- Antioxidant herbs and minerals competitive to Pb can reduce Pb-toxicity in food animals and incorporation of Pb in human food chains.

INTRODUCTION

Earth's crust naturally contains heavy metals as components of the soil. Due to their stability and inability to degrade, they continually accumulate in the environment and transfer to animal bodies. This accumulation is expanding quickly as a result of rapid industrialization, widespread anthropogenic activities such as mining, electroplating, and leather tanning, and changes to the natural marine and terrestrial environments (Meagher, 2000; Swarup *et al*., 2005, 2006; Kar and Patra, 2021). A recent survey indicates that industrial effluents that contain traces of heavy metals are used to water about 20 million hectares of agricultural land globally (Khalid *et al*., 2018). The content of

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heavy metals in soil can range from 1 to 100,000 mg/kg depending on their geological origin in the soil or human and industrial contamination (Blaylock and Huang, 2005). These radical changes in the environment caused by man-made activities have outweighed the inherent adaptability of the life processes in this planet, and livestock species are no longer an exception to this fact. Essential nutrients, in true sense, are indispensable for the physio-biochemical and cellular metabolic processes and livestock species heavily rely on soil environment for uptake of these trace elements. During consumption of the essential nutrients from the soil and other environmental sources, animals are frequently exposed to several heavy metals including lead (Pb), a highly noxious element disrupting cellular processes.

Lead, a soft, malleable, ductile metal with relatively low electrical conductivity, is dispersed in this planet, even in the Antarctic snow and oceanic basin (Rosman *et al*., 1994; Angelidis *et al*., 2011). With the booming population all over the world its environmental concentration has increased more than 1,000 times over the past three centuries, with the highest increase occurring between 1950 and 2000. Pb levels are rising in practically every country as a result of its nonbiodegradable nature and ongoing application of items related to it, posing major risks to food security (Hu *et al*., 2017). Due to presence of richest zinc-lead ore deposits in Europe (the Silesian Uplands and Kraków-Czêstochowa Uplands) Pb-toxicity is a major public health issue in Poland (Charkiewicz and Backstrand, 2020). Livestock is no longer an exception to be exposed to Pb-toxicity. A recent report from Uruguay states the occurrence of an outbreak of lead arsenate poisoning in beef cattle exhibited by symptoms like diarrhea, paresis, ataxia, recumbency, and/or seizures (Schild *et al*., 2019). In India, Kar *et al*. (2015) reported presence of Pb and other heavy metals in soil, water, and forages in an industrial area of West Bengal. Analysis of visceral organs, milk and faeces of the goat population reared in the study area showed significantly higher concentration of Pb and other toxic heavy metals. With the growing popularity of poultry egg and meat, this sector is one of the most important agricultural industries feeding the global human population. Moreover, popular practice of backyard poultry rearing in urban agriculture sector has made the poultry a vulnerable livestock species for Pb poisoning. Pb contamination in soil, water, and feeds in areas near industrial sites in India have been reported in several research findings, and this heavy metal has also been found in the organs and bones of chicken (Kar *et al*., 2018; Raghavan *et al*., 2021). Therefore, the challenges of elevated levels of environmental Pb and associated health hazards in poultry and human must be addressed.

Lead buildup in the body has an impact on the neurological, cardiovascular, and reproductive systems of mammals and birds (Patoèka and Èerný, 2003). Chickens, especially those that are young, are vulnerable to as little as 1.0 mg Pb/kg feed (Bakalli *et al*., 1995). Pb exposure affects the process of digestion in the digestive tract. Additionally, Pb exposure causes liver damage as indicated by elevated levels of liver enzymes and histological changes of liver parenchyma (Ashrafizadeh *et al*., 2018). Acute form of Pb poisoning shows general symptoms like sudden onset of muscle weakness, loss of appetite, marked weight loss, ataxia, drop in egg production and severe anaemia (Salisbury *et al*., 1958). However, chronic exposure results in demyelination of the vagus and other nerves, which results in decreased gastrointestinal motility secondary to blockage of nerve conduction, bruxism, hyperesthesia, and incoordination (Baker, 1987). In this review, we have discussed the molecular mechanism of Pb toxicity, bioaccumulation in different organs, histopathological changes and effective management practices for remediation of this hazard in livestock and poultry.

Lead - A noxious heavy metal

Lead is a non-reactive metallic element that

can cause a variety of physiological, biochemical, behavioural, and neurological issues in both people and animals (Suradkar *et al*., 2009). There are two types of Pb: organic and inorganic. Dust, soil, old paint, and other consumer products all contain the inorganic form of Pb, whereas leaded gasoline uses the organic form of Pb (tetra-ethyl Pb). Because organic Pb is absorbed through the skin and are far more toxic to the respiratory, renal, and neurological systems than inorganic Pb; organic Pb complexes are extremely dangerous in biological systems (WHO, 2010).

Sources of Pb toxicity in livestock and poultry

Fig. 1 depicts different anthropogenic sources of Pb-toxicity in livestock and poultry. Livestock and poultry are most at danger of contracting Pb poisoning, especially during scarcity of feeds during droughts and pica. The ingestion of non-food objects also increases Pb toxicity risk. Low grass cover could make it more likely for livestock to come upon hazardous Pb-containing substances. Lead acid batteries are the most common source of Pb poisoning in livestock and poultry. Both domestic and wild birds may become poisoned by Pb shots. Waterfowl, ducks and geese, which ingest Pb shot and fisherman's sinkers from the bottom of lakes and ponds, are the most common animals to exhibit it (Siddiqui and Rajurkar, 2008). Moreover, contaminated feeds or soil from Pb-based paint, solder, shot, grease, discarded asphalt, crankcase oil, and food packages are the potential sources of poisoning in urban or semi-urban areas. In wild birds, Pb-containing hunting ammunition is a well-documented source of Pb poisoning (Fisher *et al*., 2006).

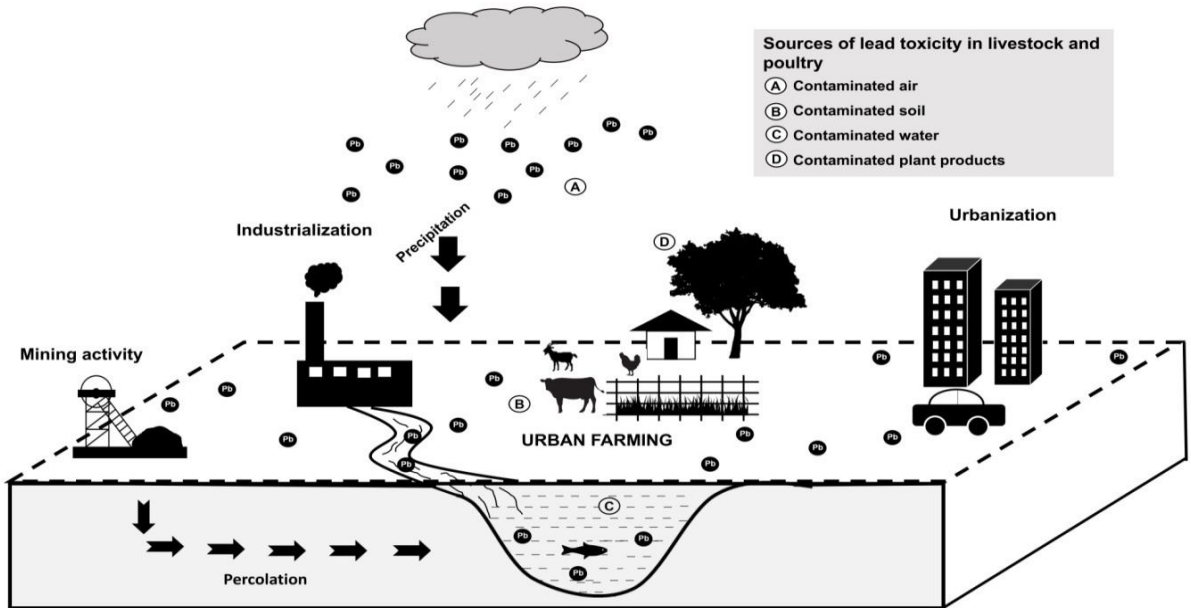

Fig. 1. Different sources of lead toxicity in livestock and poultry. A) Inhalation of air contaminated with lead conjugates causes toxicity, B) Soil contaminated with lead due to anthropogenic activities, including industrialization, urbanization or mining activities is a major source of lead exposure for livestock and poultry, C) Drinking water contaminated with lead-containing industrial effluents also cause toxicity with this heavy metal, D) Ingestion of various parts of plants accumulated with lead is also a source of lead toxicity in the grazing animals

Clinical signs, hematobiochemical profile and histological changes of Pb toxicity

The detailed descriptions of the clinical symptoms or postmortem findings of Pb poisoning in hens are limited in the literature due to relative tolerance of fowl to Pb toxicity compared to other bird species (Gwaltney-Brant, 2004). A dose of 100 mg/kg of feed can be consumed by poultry without causing any symptoms. Serious poisoning was reported at a dose of 500 mg/kg (Siddiqui and Rajurkar, 2008). Clinical indications have been reported in waterfowls and these include anorexia, lethargy, green diarrhoea, stained vent feathers, muscular weakness, crop impaction, and the inability to fly or walk (Locke and Thomas, 1996). In a recent investigation on backyard poultry in California, Sobhakumari *et al*. (2019) reported neurologic signs, such as head wobbling, incoordination, swollen crop, or inability to walk. Kar *et al*. (2018) reported the alteration in haemoglobin percentage, packed cell volume, lymphocyte count and hepatic enzymes in poultry exposed to heavy metals (copper, Pb and cadmium) in an industrial area of West Bengal, India. Histological changes included necrotic lesions and tubulitis in the kidney, degeneration and necrosis in liver parenchyma, peribronchiolitis, periarteriolitis, and the presence of hemosiderin pigments in the lung of chickens in the exposed site (Kar *et al*., 2018).

Molecular patho-mechanisms of Pb toxicity

Toxicological manifestations of Pb-toxicity occur due to various cellular, intracellular and molecular mechanisms (Fig. 2).

Oxidative stress: Oxidative stress is the major mechanism behind Pb-induced toxicity. Upon

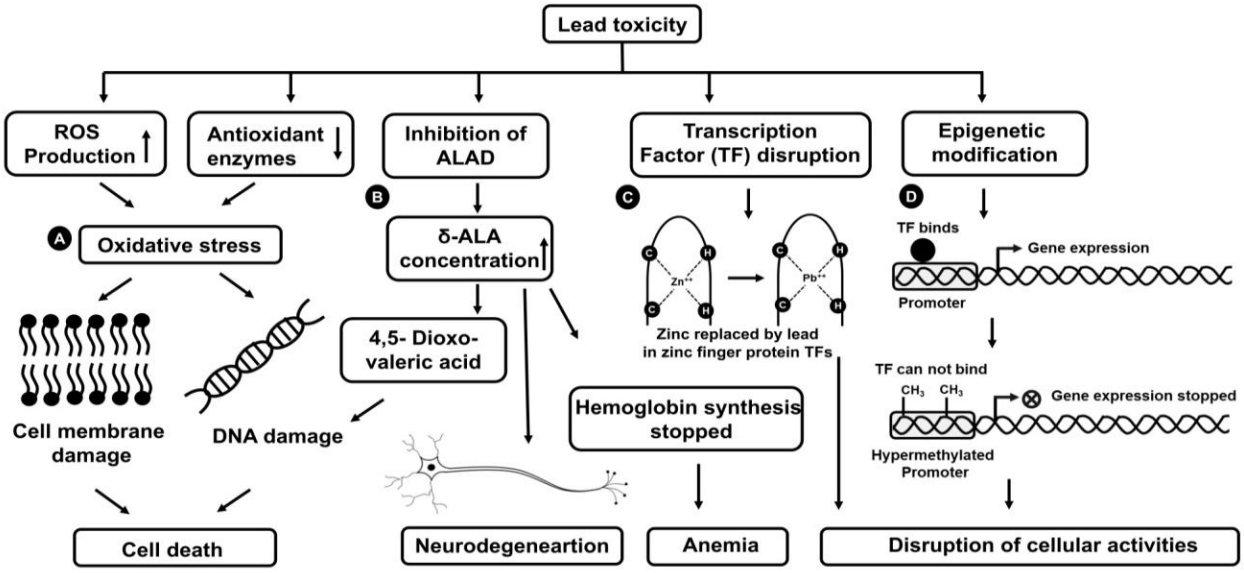

Fig. 2. Major molecular-biochemical mechanism of lead toxicity as revealed in different *in vivo* or *in vitro* model studies. A) Pb toxicity causes oxidative stress by reactive oxygen species (ROS) production and depletion of antioxidant enzymes. B) Pb causes inactivation of δ-aminolevulinic acid dehydratase (ALAD). As a result, δ-aminolevulinic acid (δ-ALA) accumulates, and oxidation product of this causes DNA damage. Also, heme synthesis is disrupted resulting in anaemia. δ-ALA also causes neurodegeneration. C) Pb replaces zinc (Zn) in zinc finger protein transcription factors leading to altered gene expression. D) Epigenetic modification of promoter sites of essential genes results in hindrance in transcription process

exposure to Pb, two different mechanisms vis-à-vis generation of reactive oxygen species (ROS) and depletion of antioxidant reserve become simultaneously operative in cellular milieu (Fig. 2A). ROS generated due to oxidative stress are scavenged by the antioxidant defense mechanism of the body. Glutathione, a tripeptide antioxidant molecule with sulfhydryl group, is a significant antioxidant used for this purpose in physiological system (Mates, 2000). Glutathione is present in both reduced (GSH) and oxidized form (GSSG). GSH detoxifies ROS by donating its reducing equivalents ($H^+ + e^-$) from its thiol groups present in cysteine residues. The GSH condenses with another molecule of glutathione to form glutathione disulfide (GSSG) by the action of the enzyme glutathione peroxidase (GP_X). GSH is regenerated by the enzyme glutathione reductase.

Pb has the ability to share electrons, which leads to the development of covalent bonds between the sulfhydryl groups of antioxidant enzymes and the Pb moiety resulting in inactivation of antioxidant enzymes. Pb also inactivates glutathione by binding with its sulphhydryl group. Pb depletes glutathione levels by inactivating enzymes including glutathione reductase, GPx, and glutathione-S-transferase (Ahamed and Siddiqui, 2007). Some other antioxidant enzymes like superoxide dismutase and catalase are also inactivated by Pb moiety. This causes impairment in removal of superoxide radical (O_2^-). Pb also removes zinc ion, an important cofactor of antioxidant enzymes, thereby inactivates them (Flora *et al*., 2007).

Ionic mechanism of Pb toxicity: Pb can substitute other bivalent cations including Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations such as Na^+ which are essential for various physiological processes of the body (Lidsky and Schneider, 2003). As a consequence, several biological processes, e.g., cell adhesion, protein folding and maturation, cascade of cell signaling events, apoptosis, ionic transportation, enzyme regulation, neurotransmission are hampered. Pb can cross the blood brain barrier and accumulates in astroglial cells. Destruction of immature astroglial cells and impairment of myelin sheath formation cause neurodegenerative disorders associated with Pb toxicity. Replacement of Ca^{2+} by Pb causes disruption of neurotransmission (Flora *et al*., 2012).

Binding interactions with proteins: The most common target of Pb in animal and plant species is the enzyme δ-aminolevulinic acid dehydratase (ALAD) or porphobilinogen synthase. Inactivation of ALAD results in elevated concentration of its substrate - the δ-aminolevulinic acid (δ-ALA). The increased concentration of δ-ALA in cellular environment induces production of free radicals, e.g., superoxide anion (Bechara, 1996). 4,5-Dioxovaleric acid, the final product of δ-ALA oxidation, is an alkylating factor that can modify guanines, thus results in DNA damage (DiMascio *et al*., 2000). Due to its structural resemblance to gamma-aminobutyric acid (GABA), δ-ALA can bind to GABA receptors in the nervous system and is likely to contribute to their oxidative degradation (Adhikari *et al*., 2006), which may partially explain neurotoxic effects of Pb toxicity (Fig. 2B).

Pb can affect the function of calmodulin (CaM), a second messenger protein. Depending upon the intracellular calcium levels CaM can interact with hundreds of proteins and modulates different biological processes. Compared to calcium ions, Pb has a greater affinity for both the N- and C-terminal domains of CaM. Pb^{2+} binds to the calcium-binding sites at low concentrations, which may cause calmodulin to become activated (Ouyang and Vogel, 1998). On the contrary, at higher concentration, Pb^{2+} binds to the linker region of CaM domains, displaces Ca^{2+} from two of its binding sites. Thus, the structure of CaM is distorted, and interactions with CaM target proteins are stalled (Kirberger *et al*., 2013).

Pb^{2+} ions can also bind with high affinity to osteocalcin, a protein involved in bone mineralization and resorption. The altered dynamics of bone mineralization is responsible for Pb-toxicity induced abnormalities of osteogenic development (Dowd *et al*., 1994). Pb can also bind with zinc finger proteins which are crucial parts of gene regulatory networks and contribute in the transcriptional activation of various crucial genes involved in a variety of processes (Klug, 1999; Laity *et al*., 2001). Pb^{2+}, due to its affinity for thiol groups, can effectively compete with Zn^{2+} for binding sites within cysteine-rich zinc finger motifs. Several transcription factors of the gene regulatory network are zing finger protein. Substitution of Zn^{2+} with Pb^{2+} thus results in disruption or alteration of its transcriptional activity and expression of corresponding genes (Fig. 2C).

DNA damage induced by Pb toxicity: The ROS produced by Pb exposure can cause oxidation of the nucleobases in DNA producing several oxidized products including 8-oxo-guanine, 8-oxo-adenine, thymine glycol, and 5-hydroxyuracil (Marnett, 2000). These altered base adducts are highly mutagenic in nature (Wang *et al*., 1998). Banu *et al*. (2012) reported that Pb is an important catalyst in the oxidation of guanine to produce 8-oxo-dG, which can produce G→T and A→ C transversions (Cheng *et al*., 1992; McCulloch *et al*., 2009). The ROS also oxidizes deoxyribose moiety of DNA at its 5' carbon to produce furfural. Furfural derivative combines with the amino group of adenine to produce kinetin (N6-furfuryladenine), which is highly mutagenic in nature (Barciszewski *et al*., 1997). All these base analogs and adducts can cause replication error due to misincorporation of nucleotide at their proximity (Wyszko *et al*., 2003) (Fig. 2A).

Telomere instability: Several *in vitro* studies with mammalian cell line have shown that Pb-exposure causes telomere shortening and instability of telomere. Addition of Pb nitrate to human endothelial cell line culture resulted in the quick formation of γH2Ax foci in the chromosome which is an indicator of double-strand breaking DNA (Gastaldo *et al*., 2007). Subsequent experimentation by Pottier *et al*. (2013) revealed that Pb-induced γH2Ax foci or double-strand break are concentrated in the telomeric regions of the chromosome causing telomere instability and shortened telomere in the cells. The molecular reason behind the Pb-induced telomeric instability was revealed in a study by Liu *et al*. (2011). According to the study, the stabilization of the G-quadruplexes in telomere by Pb^{2+} ions causes this instability. Telomere possesses G-quadruplex structures consisting of stacked G-tetrad planes connected by Hoogsteen hydrogen bonds. This structure is stabilized by monovalent cations (e.g., Na^{+} or K^{+}). Thermal stability study of G-quadruplexes showed that Pb^{2+} ion helps to create structures that are more compact and much more stable than those that rely on monovalent Na^{+} or K^{+} ions for stabilisation. Due to higher stability of G-quadruplex of chromosomal telomere in Pb-exposed cells, helicase enzyme cannot access and unwind the structure. This results in incomplete telomere replication and loss of stability (Webb *et al*., 2013).

Incorrect epigenetic modification: Accurate methylation patterns are essential for the development, establishment, and maintenance of cell identity (Koh and Rao, 2013). The epigenetic changes of the chromatin have a significant impact on gene expressions (Fig. 2D). Methylation of cytosines results in 5-methylcytosine (m^5C), one of the important epigenetic markers, in the DNA. Several investigations have reported the link between exposure to Pb and other heavy metals to a changed DNA methylation status (Sciandrello *et al*., 2004; Jirtle and Skinner, 2007; Reichard *et al*., 2007). Exposure of Pb and the degree of DNA methylation have a significant negative correlation, according to an examination of long interspersed nuclear elements-1 repetitive elements in cultured cells and workers exposed

to Pb at the battery plant (Li *et al*., 2013). Pb-induced decreased expression of ALAD enzyme has also been associated with increased methylation at CpG island of promoter site of the gene (Li *et al*., 2011).

Bioaccumulation of lead in livestock and poultry

Several investigations across the globe have reported bioaccumulation of this hazardous heavy metal in the food products obtained from livestock and poultry, especially from areas with industrialization, mining, and mechanization of agriculture.

Secretion in milk: Multitudes of reports from regions at the vicinity of industrial areas in different countries have reported the presence of Pb in raw milk at concentrations sometimes crossing the carcinogenic limit especially in children. A recent report from the dairy basin of the Mantaro River located in the centre of Peru has revealed Pb concentrations at 15±2.6 µg/kg in fresh milk of dairy cows reared in the area (Chirinos-Peinado *et al*., 2022). Analysis of heavy metals in raw milk sample from Machachi, Pichincha Province, Ecuador reported the Pb concentration of 0.208 mg/kg. Hasan *et al*. (2022) recently determined target carcinogenic risk value in children consuming raw milk or pasteurized milk containing Pb (13±4 µg/kg) and other heavy metals in different districts of Bangladesh. The study showed that children milk consumers are vulnerable to carcinogenic health risk.

Bioaccumulation in meat and meat products: Meat of food animals has been found to be contaminated with Pb, arsenic and cadmium. In an Iranian city, bioaccumulation of Pb was reported at an excessive concentration in sheep, beef, turkey and ostrich (Raeeszadeh *et al*., 2021). The concentration of Pb in the muscle of goats reared near the mining polluted area (Mejia, West Bengal, India)) did not exceed the permissible, but was greater in the polluted area (Kar *et al*., 2015). In the northwestern region of Iran, 25 of the 30 buffalo meat samples (or 80.33%) were contaminated with Pb, and the concentration of Pb in 3.33% of the contaminated samples was higher than the permissible limit (0.1 mg/kg) recommended by the European Commission (Mahmoudi *et al*., 2018). Badis *et al*. (2014) analysed fresh meat of sheep, chicken, beef and camel from a slaughterhouse of Algeria and observed presence of Pb along with other heavy metals, and the concentrations of Pb in these meat samples were more than the permissible limit suggested by FAO (0.5 mg/kg). In addition to raw meat samples, presence of Pb has been reported in processed beef or pork salami (Lukáěová *et al*., 2014). In Saudi Arabia, some processed meat, meat products and fish products also contained Pb exceeding the recommended maximum acceptable levels proposed by the Joint FAO/WHO and EC Committees (Alturiqi *et al*., 2012). From all these reported studies of Pb contamination in raw as well as processed meat samples of different livestock and poultry species, it is clear that Pb is one of the hazardous heavy metals present in the food chain. Their concentration only differs in the meat and meat products depending on mobility of the animals or eatables or environmental conditions.

Concentration in eggs: 'Urban farming' of fruits, vegetables and eggs is becoming a popular practice in different parts of the world due to increased food prices and consumers' desire for chemical-free food products. Residential backyards, however, may contain residual contaminants from the past or due to human activities around. Normally, chickens forage for seeds and insects in the soil. When foraging or preening, earth particles can accidentally get ingested by them if they are stuck to feeds. Contaminated soil has been observed as a major source of Pb in poultry eggs (Waegeneers *et al*., 2009). Ovalbumin and phosvitin, two nutritional components of eggs, have the ability to bind a wide range of metals, significantly raising the risk of heavy metal buildup in eggs (Castellani *et al*., 2004;

Dobrzañski *et al*., 2017). An earlier study showed that Pb might affect calcium metabolism in poultry, making it simpler for Pb to be integrated into eggshells (Scheuhammer, 1987). In a study by Grace and MacFarlane (2016), significant correlation between the Pb level in eggs and the Pb level in soil accessible to chickens was observed in urban areas of Australia. In a recent study, Yazdanparast *et al*. (2022) analysed samples from 69 domestic chickens from 55 Sydney urban gardens and concluded that soil Pb level should be less than 117 mg/kg to retain egg Pb level below 0.1 mg/kg (i.e., a food safety benchmark value).

Bioaccumulation in bone: Maximum bioaccumulation of Pb occurs in the bones of both mammals and birds (Berglund *et al*., 2000). Deposition of Pb is greater in laying birds compared to non-layers (Finley and Dieter, 1978). This may be attributed to the elevated Ca mobilization of bones during laying period (Wang *et al*., 2019). Studies on birds have revealed a substantial reduction in the degree of mineralization as bone Pb content increases. This might result in bone thinning and osteoporosis (Álvarez-Lloret *et al*., 2017). The function of osteoblasts and osteoclasts may be affected by Pb, which may also raise the risk of fractures or osteoporosis (Berglund *et al*., 2000; Pounds *et al*., 1991). A recent study showed the high deposition (13-53 mg/kg) of Pb in skeletons of cattle in the Silesian-Cracovian region of Southern Poland (Cabala *et al*., 2022). Use of artificial scaffold or collagen protein from bone for therapeutic purpose and commercial application in cosmetics preparation are quite common. Bone as a natural sink for Pb deposition therefore, increases the risk of Pb-exposure in human through these bone byproducts.

Bioaccumulation in visceral organs: Organs have a very specific affinity for metals, which varies depending on the chemical characteristics of the metals and the physiological characteristics of the organs (Storelli *et al*., 2006). As the kidney concentrates Pb by glomerular filtration, it contains the greatest quantity of Pb (Goyer, 1989). Pb concentrations in kidney, liver, lung and spleen in goats were greater in the polluted (Mejia, West Bengal, India) than the unpolluted (Vatar, West Bengal, India) site (Kar *et al*., 2015). The organ with the highest Pb concentration was the kidney, followed by the liver, lung, spleen, and muscle, and Pb concentrations are greater in older animals than in young ones (Kar *et al*., 2015). A significant amount of glutathione is found in the liver, where it binds to Pb and facilitates its excretion through urine (McGowan and Donaldson, 1986). Wang *et al*. (2021) reported high concentration of Pb in kidney and liver of poultry (2.34 and 0.51 mg/kg, respectively). Retrospective studies of Pb deposition in different visceral organs of cattle have been performed in Canada, the United States, and the United Kingdom (Hoff *et al*., 1998; Sharpe and Livesey, 2006; Payne and Livesey, 2010). One such study carried out on 438 calves (6-10 months old) and 56 cows (2-16 years old) slaughtered in Spain revealed mean Pb concentration of 0.053, 0.052 mg/kg in liver and kidney, respectively (Alonso *et al*., 2000). Accumulation of Pb in liver and kidney of cattle reared in the proximity to metal smelting (37–39) areas has been demonstrated in India, Kazakhstan, and other locations globally (Farmer and Farmer, 2000; Dwivedi *et al*., 2001, Swarup *et al*., 2005).

Higher Pb concentrations in animals and human beings have been reported from various parts of India, particularly in urban areas, which are mainly due to intake of feeds contaminated with Pb as well as inhalation of Pb particles (Swarup *et al*., 2006; Kumar *et al*., 2007; Kar *et al*., 2015). The concentrations of Pb in blood and milk were reported to be greater around the polluted area in lactating cows, which was attributed to intake through contaminated feeds (Swarup *et al*., 2005). Pb concentrations in fodder and soil around Pb–zinc smelter were 29.1 and 233 mg/kg, respectively compared

with the control (2.1 and 28.7 mg/kg) area (Swarup *et al*., 2006). Chicken samples collected from the markets in district city of Bareilly had mean Pb concentration (positive samples) of 1.18 (93%), 0.95 (70%) and 0.41 (53%) mg/kg in kidney, liver and muscle, respectively (Kumar *et al*., 2007). Most of the Pb emitting from various emissions enters into air and is deposited on nearby vegetation and thus human and animals are exposed to excess Pb by inhalation of contaminated air and/or ingestion of contaminated feeds in urban and industrial areas (Kumar *et al*., 2007; Kar *et al*., 2015). In India, vehicular pollution still accounts for more than 2/3 of total air pollution (Lal, 1996). Higher Pb concentration in different tissues of goats slaughtered in Chennai in India was reported, which was attributed to air pollution. Shaposhikov and Prisnyi (2001) reported Pb concentration of 0.11 mg/kg in blood of pigs reared around polluted localities.

Amelioration of Pb-toxicity in livestock and poultry

Pb causes oxidative stress and tissue damage in the affected livestock and poultry species. Therefore, to combat the adverse effects of Pb toxicity various attempts have been made to supplement the diets with various antioxidant herbal substances used in traditional medicine, vitamins and trace minerals (Table 1).

Herbal additives: *Coriandrum sativum* (coriander) -The primary components of coriander are coriandrin and isocoumarines with powerful antioxidant property of coriander (Taniguchi *et al*., 1996). Coriander ameliorated the increased oxidative status in male rats experimentally exposed to overdose of Pb (Sharma *et al*., 2010). Treatment with the hydroalcoholic seed extract of *C. sativum* improved Pb-induced oxidative stress in certain tissues. Administration of methanolic extract of coriander also resulted in a reduction in Pb concentration and extent of histopathologically damaged liver tissues in rats (Téllez-López *et al*., 2017).

Allium sativum (garlic) - The potential beneficial effects of garlic on biological effects are due to the presence of high amounts of water-soluble organic sulfur compounds, lipid soluble compounds, and S-allylcysteine (Mikaili *et al*., 2013). Garlic can effectively detoxify various heavy metals including Pb, cadmium, methyl mercury, phenyl mercury, and arsenic by reducing mitochondrial damage and apoptosis in tissue culture models and attenuating Pb-induced brain, renal, hepatic, and haematological toxicity in rats (Sharma *et al*., 2010; Lawal and Ellis, 2011). The protective role of garlic against Pb has been reported in several investigations in broiler chickens (Hanafy *et al*., 1994; Hossain *et al*., 2014a, 2014b) and rabbit (Shehata, 2011). Garlic supplementation at different concentrations (1, 2 and 4%) reversed the alterations of reduced growth performance (Hossain *et al*., 2014a) and improved the values of blood variables (Hossain *et al*., 2014b) induced by Pb poisoning (100 mg/kg) in broiler chickens.

Yucca schidigera (yucca) - *Yucca schidigera* has been reported to exhibit modulatory effects toward the Pb-induced inhibitory effect on the productive and reproductive features of Japanese quails and rabbits (Alagawany *et al*., 2018; Farag *et al*., 2018; Taha *et al*., 2019). According to the authors, *Yucca* treatment, specifically at a dose of 200 mg/kg diet, was effective in reversing Pb-induced alterations as well as enhanced immunohistochemical and histomorphometrical alterations, which is likely due to antioxidant ability (Alagawany *et al*., 2018; Farag *et al*., 2018; Taha *et al*., 2019) and decreasing levels of inflammatory indicators like nitric oxide, vascular endothelial growth factor, and tumour necrosis factor alpha.

Vitamin molecules: Ascorbic acid (vitamin C) is recognized to have well-known antioxidant capabilities against heavy metals (Kumar *et al*., 2009). According to a recent study, broiler chicks purposely exposed to high concentrations of Pb-acetate had their blood and egg Pb levels reduced when given sub-chronic

Table 1. Amelioration impacts of phytogenic plants, vitamins and trace minerals against lead-induced toxicities

Ameliorative agent	Species	Dose	Effect	References
Allium sativum (Garlic)	Rat	250 and 500 mg/kg body weight	• Antioxidant • Prevention of intestinal absorption of lead, due to presence of amino acids containing sulfur group • Reduce mitochondrial damage	Sharma *et al.*, 2010
Garcinia kola Heckel (bitter cola)	Rat	At the ratio of 12 g/0.002 g feed to bitter cola powder	• Attenuate the chronic lead acetate poisoning	Osemwegie *et al.*, 2017
Coriandrum sativum	Mouse	0.25% in drinking water	• Antioxidants • Reduce stomach ulcers	Nishio *et al.*, 2019
Yucca schidigera	Quail	100 and 200 mg/kg diet	• Potential modulatory function towards the Pb-induced inhibitory impacts on the productive and reproductive traits of Japanese quails • Decreasing levels of inflammatory indicators including nitric oxide, vascular endothelial growth factor, tumor necrosis factor alpha and transforming growth factor-β1	Alagawany *et al.*, 2018; Farag *et al.*, 2018; Taha *et al.*, 2019
Ascorbic acid	Layer hen	500 mg/kg body weight/day	• Reduction in lead levels in egg-yolk, egg-albumen, and egg-shell samples	Shawahna *et al.*, 2016; Shawahna *et al.*, 2020
	Broiler chicken	200 mg/kg basal diet	• Reversal of Pb-induced alteration in serum biochemical variables such as ALT, AST, creatinine level and albumin-globulin ratio	Jaiswal *et al.*, 2017
	Broiler chicken	100 mg/kg diet	• Reduction in the plasma malondialdehyde levels induced by lead and neutralization of inhibitory effect of lead on growth	Erdoðan *et al.*, 2005
Vitamin E	Broiler chicken	100 mg/kg basal diet	• Ameliorated Pb-induced alteration in serum ALT, AST, creatinine level and albumin-globulin ratio	Jaiswal *et al.*, 2017
Selenium	Broiler chicken	0.1 mg/kg basal diet	• Decreased of Pb-induced alteration in serum ALT, AST, creatinine level and albumin-globulin ratio	Jaiswal *et al.*, 2017
	Laying hen	0.4 mg/kg feed	• Ameliorated oxidative stress, improved laying performance and hepatic function	Wu *et al.*, 2022
Zinc	Wistar rat	71 mg/L drinking water	• Mitigation of Pb-induced oxidative stress and restoration of spermatogenesis and steroidogenesis	Anjum *et al.*, 2017

ALT, alanine aminotransferase; AST, aspertate amino transferase

treatment with high doses of ascorbic acid (Shawahna *et al*., 2016; Shawahna *et al*., 2020). In a similar study, Jaiswal *et al*. (2017) observed that feeding of Pb-contaminated feed for 42 days to broiler chickens led to alterations in biochemical profile of serum and ascorbic acid (200 mg/kg basal diet), vitamin E (100 mg/kg basal diet) can reverse the biochemical parameters towards the normal range. Thus, these studies show that antioxidant vitamins may have favorable impact to ameliorate Pb-toxicity induced changes in poultry.

Minerals: Several essential trace minerals have ameliorating effect on heavy metal toxicity including Pb in animals (Kar and Patra, 2021). Zinc is an element which is an active component of several enzymes and participates in different metabolic reactions. Pb-exposure in Wistar rats have been found to cause spermatogenic impairment and several pathological conditions of testis. Supplementation of Zn at the concentration of 71 mg/L of drinking water recovered suppressed spermatogenesis, steroidogenesis, elevated oxidative status, and histological damage in the testis (Anjum *et al*., 2017). According to a recent study that examined the toxic effects of various heavy metals (cadmium, Pb, mercury, and chromium) along with their deposition and ion homeostasis in the reproductive organs and eggs of laying hens, selenized-yeast (containing 0.2% selenium) at 0.4 mg/kg in feeds significantly reduced the negative effects of heavy metals (Wu *et al*., 2022).

Conclusion

Numerous investigations have reported incidences of Pb exposure in livestock and poultry reared in the vicinity of industrial zones from different parts of the world. Experiments performed with *in vivo* animal models as well as *in vitro* cell culture models have unraveled the biochemical and molecular mechanisms associated with detrimental impact of Pb toxicity in biological systems. Bioaccumulation of Pb in the liver, kidney, brain and other visceral organs cause gross and histopathological changes in these organs and hemato-biochemical alterations in livestock. This results in oxidative stress induced apoptosis or cell death, telomere instability, and alteration in expression of genes crucial for cellular physiology. All these changes in the context of livestock and poultry biological system hamper production performances. The ameliorative efficacy of several antioxidant substances has been proved in animals or poultry birds experimentally exposed to Pb. Biological remediation, such as use of herbal additives and their extracts in diet has also been tried to avoid or decrease Pb toxicity. However, ameliorative effects of these substances are scanty in domestic mammals. Protein engineering of cellular Pb-transporter molecules that control import and export by cells is also a viable approach. Genetic manipulation of plants and microbes that can efficiently destroy or drain the heavy metal from environment is an alternative approach to reduce the toxicity in Pb-contaminated zone.

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Author's contribution: AM, IK, AKP: Conceptualized the manuscript and prepared the draft of this manuscript; AKP: Reviewed and edited the manuscript. All authors read and approved the manuscript.

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