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Beneficial Role of Ascorbic Acid against Lead Toxicity – A Mini Review

Ibrahim Abdulwaliyu[1*], Shefiat Olayemi Arekemase[2], Musa Latayo Batari1 , Amina Ibrahim Madugu[2], Olanipekun Oladele Idowu[1] , Aliyu Muhammad[3] , Oladipo Sunday Aribido[1], Oluwayinka Olufunmilayo Owolabi[4], Yakubu Sani[5], Musa Halidu Mahmud[1], and Suleiman Abdullahi[6]

[1]Department of Scientific and Industrial Research, National Research Institute for Chemical Technology, Basawa, Zaria, Nigeria
[2]Department of Environmental and Industrial Technology, National Research Institute for Chemical Technology, Basawa, Zaria, Nigeria
[3]Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria
[4]Bioresources Development Centre, National Biotechnology Development Agency, Lugbe, Abuja, Nigeria
[5]Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria
[6]Directorate of Research and Development, Nigerian Institute of Science and Leather Technology, Zaria, Nigeria

Review Article

***Corresponding author**
Ibrahim Abdulwaliyu

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Abstract: Environmental lead pollution is a continuous public health concern in Nigeria and the world at large. Exposure to lead results in toxicological complications, which range from brain disorders, decreased organ functions, and increased risk of chronic diseases especially in the elderly. Oxidative stress is the chief pathophysiologic mechanism by which lead impairs health integrity in humans and animals. So far, amongst the exogenous antioxidants, ascorbic acid is perhaps the most comprehensively studied antioxidant with respect to lead intoxication. It is capable of donating reducing equivalent to quench free radicals, and also facilitates lead excretion from the body. However, the bulk of the research on the role of ascorbic acid on lead toxicity was based on pre-treatment using animal models, while post treatment appears to be neglected. More so, despite enormous information on the role of ascorbic acid on lead toxicity, information on human clinical trials is still relatively scarce. This review provides a summary of toxicities associated with lead, and some benefits of ascorbic acid supplementation with respect to lead intoxication.
Keywords: Vitamin C, Lead, Toxicity, Antioxidants, Oxidative stress.

Lead

Lead is a soft, grey-blue heavy metal found ubiquitously in nature, though at low concentration. It is widely dispersed into the environment, particularly as a result of human activities, an event that poses very serious clinical issues [1]. Such activities are common in areas where metals are mined, processed and used industrially [2].

Lead has been mined and smelted for at least 8000 years [3], and its toxic attributes have been recognized for more than 2000 years [4]. To date, lead still remains a critical environmental toxicant, despite concerted effort at tackling lead pollution.

Once introduced into the environment, it accumulates and persists [5], a scenario synonymously related to its pathophysiologic effects. Its persistent and non-biodegradable nature poses serious threats to human life [6], irrespective of age and gender. Sources of lead exposure include water, soil, dust, paints, batteries, leaded gasoline, food etc. [7, 8].

ABBREVIATIONS

ALA: aminolevulinate; ALAD: aminolevulinate dehydratase; ASC: ascorbic acid; $CaNa_2EDTA$: calcium disodium ethylenediamine tetra acetic acid; CAT: catalase; CNS: central nervous system; DMSA: dimercaptosuccinic acid; FSH: follicle stimulating hormone; GIT: gastrointestinal tract; GSH: reduced glutathione; GSHpx: glutathione peroxidase; GSSG: oxidized glutathione; H_2O_2: hydrogen peroxide; L: fatty acid radical; LDL: low density lipoprotein cholesterol; LH: fatty acid; $LOO^{\bullet}$: peroxyl radical; LOOH: hydroperoxide; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: reduced nicotinamide adenine dinucleotide phosphate; MPO: myeloperoxidase; O^{-}_2: superoxide anion; OX-LDL: oxidized low density lipoprotein cholesterol; Pb: lead; PBG: porphobilinogen; PUFA: polyunsaturated

fatty acid; RDA: recommended dietary allowance; ROS: reactive oxygen species; SH: sulfhydryl; SOD: superoxide dismutase; $SVCT_1$: sodium dependent vitamin C transport type 1; TC: total cholesterol; USA: United States of America; VLDLC: very low density lipoprotein cholesterol.

Ascorbic acid

Ascorbic acid is traditionally known as vitamin C, and structurally related to glucose [9]. It is well absorbed from the gastrointestinal tract (GIT), and the absorption takes place mainly in the distal intestine via ascorbate transportation, known as the sodium-dependent vitamin C transport type 1 ($SVCT_1$). The absorbed ascorbic acid attains a plasma level of 50-60µm for a well-nourished, healthy non-smoker [10]. The recommended dietary allowance (RDA) of ascorbic acid for women and children is about 90mg/day and 45mg/day respectively [11]. Reduced intake of this vitamin is associated with scurvy development, anaemia, muscle degeneration, atherosclerotic plaques and infectious diseases [12]. Ascorbic acid is widely distributed in nature, especially in green leafy vegetables and fruits [13-15]. One of its biochemical roles is the modulation of collagen synthesis (it serves as a co-factor in the hydroxylation of proline and lysine residues) [16], and this makes it essential for wound healing [17, 18]. It is also important for carnithine and neurotransmitter biosynthesis [19]. Ascorbic acid also participates in metal catalysed reactions such that it reduces oxides of iron (Fe^{3+}) and copper (Cu^{2+}) respectively [20]. It helps to regenerate some antioxidants such as Vitamin E and β-carotene [21-24] both of which possess anti-oxidative stress properties. Ascorbic acid has both industrial and medicinal values. It prevents loss of flavour and aroma, extends shelf life and enhances nutrient content of processed foods [25]. Its medicinal attributes include anti-atherogenic, anti-cancer, anti-inflammatory properties; it helps (mega doses) in the prevention and treatment of cataracts, glaucoma, stroke, diabetes etc. [26-30].

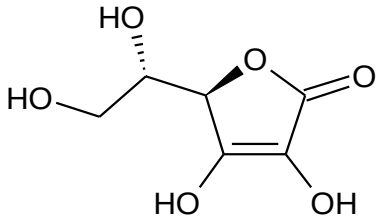

Fig-1: Structure ascorbic acid. $C_6H_8O_6$

The relationship between ascorbic acid and lead toxicity is beyond recent time. Ascorbic acid has the ability to modulate lead induced toxicity, though preventive measures have remained the best solution to curbing the menace associated with lead toxicity. But despite efforts made to tackling the threat, both occupational and environmental lead exposure remain a serious threat, particularly in developing nations, where uncontrolled mining activities still take place. More so, the multifaceted effects of lead on biochemical processes, and overall pathophysiologic ill nature of lead remain a big challenge. Therefore, this review focus on the role of ascorbic acid on toxicities associated with lead.

Benefits of ascorbic acid on lead induced oxidative Stress

Lead induced oxidative stress

Lead induced oxidative stress has been postulated as the basic mechanism by which lead exerts toxic effects [31-35]. Oxidative stress represents an imbalance between free radical production, resulting in various degree of body injury, and inability of the body's system to repair the damage. It is associated with drastic increase in the malonyldialdehyde (a measure of lipid peroxidation) content, and decrease in the activities of endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) etc. [36, 37].

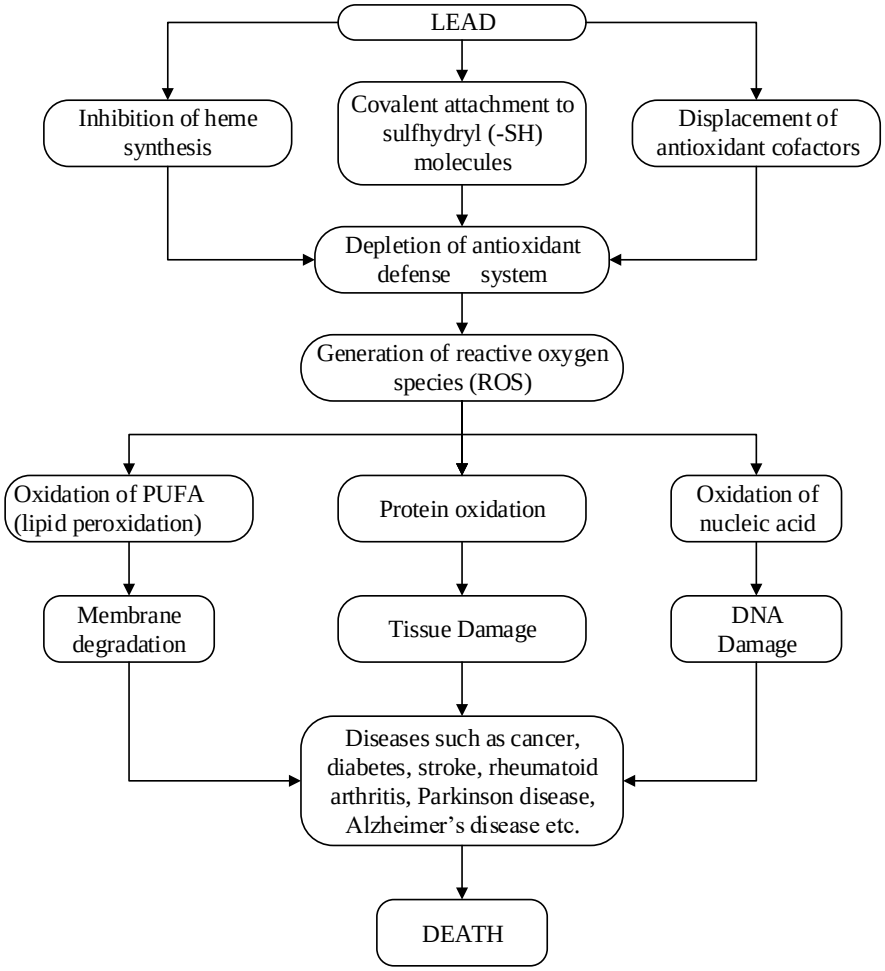

Fig-2: Proposed mechanism of lead induced toxicity. In ideal physiological condition, free radicals generated during oxygen metabolic process exist as nontoxic substances as their levels are being regulated by endogenous enzymes, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSHpx). However, exposure to lead decreased the activities of the aforementioned antioxidants, thereby leading to generation of reactive oxygen species (ROS), molecules capable of inducing various degrees of body injuries.

Oxygen consumption is vital especially in aerobic metabolic process, where it is reduced to water. Lead amongst other factor interferes with the process via three mechanistic approach; (1) the displacement of antioxidants co-factors [38, 39], (2) inhibition of the heme synthesis pathway, (3) covalent attachment to sulfhydryl (-SH) containing molecules (Figure 1).

Lead and superoxide dismutase (SOD) activity

Under aerobic condition, oxygen is converted to superoxide by NADPH oxidase, using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as substrate. The NADPH transfers electron to the molecular oxygen (O_2) to produce superoxide anion (O^-_2), a reactive free radical.

$$NADPH + 2O_2 \overset{Oxidase}{\longleftrightarrow} NADP^+ + 2O_2^- + H^+$$

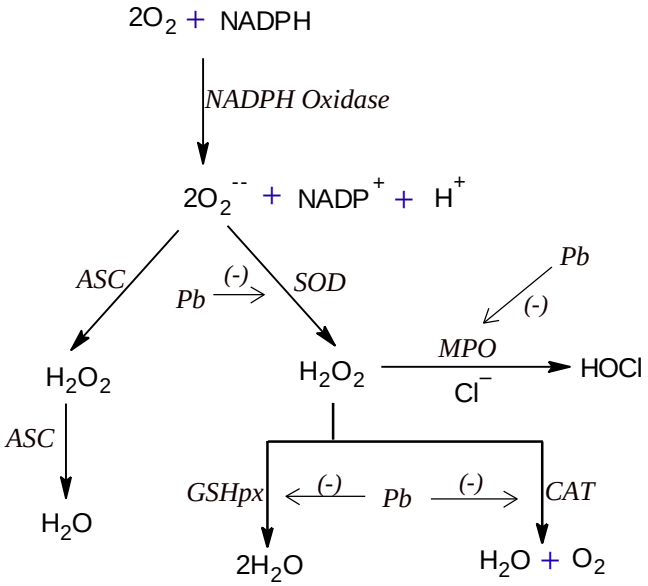

Fig-3: Proposed mechanism of lead induced oxidative stress, and role of ascorbic acid. CAT- catalase, GSHpx-glutathione peroxidase, H_2O_2-hydrogen peroxide, NADP-nicotinamide adenine dinucleotide phosphate, NADPH-reduced nicotinamide adenine dinucleotide phosphate, MPO-myeloperoxidase, O^{-}_2-superoxide anion, Pb-lead, SOD-superoxide dismutase. H_20- water, HOCL- hypochlorous acid, ASC- ascorbic acid, (-) inhibition.

The O^{-}_2 generated, is a primary byproduct of oxygen metabolism [40], which progresses to the formation of hydrogen peroxide (H_2O_2) by SOD. This enzyme contains copper and zinc as co-factors. Both are important for the functionality and stability of SOD. However, the functionality and stability could be impaired in the presence of lead, thereby rendering the enzyme less active or inactive, so the conversion of O^{-}_2 to H_2O_2 is impeded.

$$Cu^{2+} - SOD + O_2^- \rightarrow Cu^{+} - SOD + O_2$$
$$Cu^{+} - SOD + O_2^- + 2H^+ \rightarrow Cu^{2+} - SOD + H_2O_2$$

Lead and catalase (CAT) activity

Lead has also shown to impair the activity of catalase (CAT), the enzyme that catalyses the conversion of H_2O_2 to metabolic water (H_2O) and molecular oxygen (O_2). It impairs CAT function via inhibition of heme biosynthesis [39]. It inhibits δ-aminolevulinate synthase, the enzyme that catalyses the condensation of glycine (a non-essential amino acid), and succinyl Co-A (intermediate of the TCA cycle) to δ-aminolevulinate (ALA). Lead also inhibits the activities of δ-aminolevulinate dehydratase (ALAD), an enzyme that condenses two molecules of δ-aminolevulinate to porphobilinogen (PBG). It either binds to the sulfhydryl (-SH) component of the enzyme (ALAD), or displaces the enzyme co-factor (zinc) [41], thereby rendering the enzyme inactive. More so, lead inhibits the activities of ferrous chelatase (ferrous synthetase), the enzyme responsible for the insertion of ferrous iron (Fe^{2+}) into the central cavity of protoporphyrin IX, a metabolic event that leads to the formation of heme. Heme groups are very important for the functionality of CAT.

$$2H_2O_2 \xrightarrow{catalase} 2H_2O + O_2$$
$$H_2O_2 + Fe^{3+} - CAT \rightarrow H_2O + O = Fe^{4+} - CAT(\bullet+)$$
$$H_2O_2 + O = Fe^{4+} - CAT(\bullet+) \rightarrow H_2O + Fe^{3+} - CAT + O_2$$

The reaction takes place via the interaction of H_2O_2 with asparagine and histidine of the amino acids sequence of CAT, and allows the transfer of a proton (hydrogen ion) between the oxygen atoms. The oxygen atom co-ordinates with the iron, and frees the water molecule. The heme containing enzyme then reacts with another H_2O_2 molecules to reform the Fe^{3+}-CAT, H_2O and O_2 respectively. It's worthy to note that the Fe^{3+} represent the iron containing heme, attached to the enzyme. The Fe^{4+} formed is not relatively stable, so it receives stabilizing electron (a radical cation (●+) to stabilize itself. So, the overall effect of lead on heme synthesis consequently impairs the conversion of H_2O_2 to H_2O and O_2. This implies that there will be more of H_2O_2 generation than it decomposition.

Lead and glutathione peroxidase activity

Glutathione peroxidase (GSHpx), another endogenous enzyme has the ability to convert H_2O_2 to H_2O, using glutathione (GSH) as substrate. However, exposure to lead could impede the activities of GSHpx via the displacement of

selenium, a key co-factor of the enzyme, thereby making the enzyme inactive. More so, it covalently attaches itself to the sulfhydryl groups of the substrate, which eventually get degenerated [39].

$$2G - SH + H_2O_2 \quad \rightarrow \quad GS - SG + 2H_2O$$

Thus, the metabolic arrest of GSHpx and CAT by lead hampers the decomposition of H_2O_2 to H_2O, and the H_2O_2 instead progresses to hydroxyl radical ($^{\bullet}OH$) formation.

$$Fe^{2+} + H_2O_2 \quad \rightarrow \quad Fe^{3+} + HO^{\bullet} + OH^{-}$$
$$Fe^{3+} + H_2O_2 \quad \rightarrow \quad Fe^{2+} + HOO^{\bullet} + H^{+}$$

The hydroxyl radical can initiate a sequence of reactions that could lead to membrane degradation.

$$LH + HO^{\bullet} \quad \rightarrow \quad L^{\bullet} + H_2O$$

The $^{\bullet}OH$ is chemically unstable. It removes hydrogen atom (H) from the vulnerable site (double bond) of polyunsaturated fatty acids (PUFA), represented as LH, thereby producing fatty acid radical ($L^{\bullet}$). Under aerobic conditions, the $L^{\bullet}$ takes up oxygen to produce peroxyl radical ($LOO^{\bullet}$). The $LOO^{\bullet}$ can also attract hydrogen atom to form hydroperoxide (LOOH), and these reactions continues in series, leading to oxidation of PUFA.

$$L^{\bullet} + O_2 \quad \rightarrow \quad LOO^{\bullet}$$
$$LOO^{\bullet} + LH \quad \rightarrow \quad LOOH + L^{\bullet}$$

Role of ascorbic acid on oxidative stress

Ascorbic acid has the ability to normalize alteration of oxidative stress biomarkers initiated by lead [42-45]. Its ability to quench free radicals and chelate heavy metals makes it a unique antioxidant [46], and this led to the presumption that supplementation of ascorbic acid could be the best chelation therapy for lead intoxication [47]. This was further strengthened in studies by Wang *et al*. [37], and Seven *et al*. [48] that lead intoxication was shown to reduce the level of endogenous antioxidants which was normalized upon ascorbic acid supplementation. Ascorbic acid does not only reduce or reverse oxidative stress, but also helps to replenish and improve ascorbic acid level [49], which is vital for maximum health integrity.

Depletion of antioxidants by lead leads to proliferation of reactive oxygen species (ROS) (O^{-}_2, H_2O_2, $^{\bullet}OH$) [50], most of which could be scavenged by ascorbic acid supplementation [12] directly or indirectly. Ascorbic acid directly scavenges free radicals, either generated by lead or by other factors [51, 52], and protects the cells from oxidative damage [53, 54]. The hydrogen atoms of ascorbic acid pairs up with unpaired electron of the free radicals, converting them to non-free radicals.

$$2O_2^{-} + 2H + ascorbate \quad \rightarrow \quad 2H_2O_2 + dehdroascorbate$$
$$H_2O_2 + 2ascorbate \quad \rightarrow \quad 2H_2O + 2monodehydroascorbate$$

Ascorbic acid indirectly quenches free radicals by virtue of regenerating some important antioxidants such as GSH, and vitamin E [52]. The latter is capable of terminating lipid peroxidation chain reactions [55].

$$ASCH_2 + GS - SG \quad \rightarrow \quad ASC + 2GSH$$
$$LOO^{\bullet} + \alpha - tocopherol - OH \quad \rightarrow \quad LOOH + \alpha - tocopherol - O$$

Table-1: List of ROS [55].

Symbol	Name
$^1O_2$	Singlet oxygen
$O_2^{\bullet -}$	Super anion radical
$^{\bullet}OH$	Hydroxyl radical
$RO^{\bullet}$	Alkoxyl radical
$ROO^{\bullet}$	Peroxyl radical
H_2O_2	Hydrogen peroxide
LOOH	Hydroperoxide

Consequences of oxidative stress

Under normal physiological conditions, the aforementioned reactive species are not harmful to the body. However, when the production of ROS exceeds the cellular antioxidant capacity, it becomes harmful to the host. ROS destroys biomolecules (lipids, proteins, nucleic acids), and predisposes the host to health complications such as neurodegenerative diseases (Alzheimer's disease, Parkinson's disease etc.) [56-59], cancer [60-62], and diabetes [63-65].

Ascorbic acid and cancer

The antioxidant role of ascorbic acid is vital to processes associated with cancer [66], although the relationship between ascorbic acid and cancer development are controversially related. Late stage cancer patients usually have ascorbic acid deficiencies [67], hence the need from exogenous source becomes inevitable, as it plays a vital role in improving quality of health [68]. Controversially, Gonzalez *et al.* [16] explicitly stated that many scientists failed to reproduce the scientific basis that was earlier presented that ascorbic acid can be used as a therapeutic agent in the treatment of cancer.

Table-2: Some symptoms and health issues associated with lead exposure

Lead toxicity	Children	Adults
Acute toxicity	Headache [69], abdominal pain, vomiting, muscle pain, irritability, attention deficit, constipation, seizure etc.	High blood pressure, headache [69], vomiting, muscle pain, abdominal pain [70].
Chronic toxicity	Anemia (haemolytic anemia and frank anemia) [39], hearing loss, development delay, stunted growth.	Neuronal problem, reduced sperm count, repeated miscarriage [71], still birth, diabetes, cancer, stroke, arthritis, Organs (kidney, brain etc.) damage [72].

Ascorbic acid and diabetes

The displacement of some essential metals by lead, could in part explain the pathophysiologic mechanism by which lead induces diabetes or processes associated with diabetes. Most essential metals, though not produced by the body, are necessary for maximum health integrity. For example, chromium (Cr^{3+}), which performs insulin like functions [73], and zinc are important for the optimal activity of insulin, in terms of secretion and regulation of blood glucose levels. Since lead exhibits the ability to displace the aforementioned essential metals, then insulin secretion and function could be impaired. More so, the onset of oxidative stress may decrease the activity of insulin gene promoter and mRNA expression in pancreatic islet cells [74]. The impairment of insulin secretion and function shoots blood glucose level, which may probably exceed normal range of 126mg/dl, and persistent increase could lead to chronic hyperglycaemia [75]. The onset of hyperglycaemia exacerbates ascorbic acid deficiency, as it competitively inhibits glucose transport system [76], also responsible for the transport of oxidized form of ascorbic acid to cells. This inhibition may contribute to oxidative stress and consequently increase risk of cardiovascular diseases [76].

Ascorbic acid and cardiovascular disease risk

Oxidation of low density lipoprotein cholesterol (OX-LDLC), may partly explain oxidative stress induced cardiovascular diseases [77-81]. OX-LDLC, being that it is a target molecule for scavenging receptors, could easily be incorporated in to plaque formation [82]. A scenario that contributes to narrowing of arterial blood vessels, thereby contributing to cardiovascular health risk. However, ascorbic acid has shown to prevent the oxidation of LDLC, and decrease the risk of cardiovascular health issues [83].

Advantages of ascorbic over conventional chelating therapy

Ascorbic acid is probably the most extensively studied antioxidant with respect to lead induced oxidative stress [39], metabolic event proposed to be the main factor responsible for organ damage [36]. It has advantages over conventional chelating agents (DMSA, $CaNa_2EDTA$). The conventional chelating agents are mostly used in the removal of lead from the body, especially in acute lead exposure, but ineffective in reversing metabolic injuries associated with lead induced oxidative stress. They have deleterious side effects [47], including disrupting essential micronutrient balance and enhancing the redistribution of lead from the stored site (bone) to other regions (brain, liver, testes, kidney etc.) of the body [36]. Such redistribution may further aggravate organ dysfunction, especially in pre-existing cases of organ malfunction. Moreso, conventional chelating agents may also not be useful in instances of chronic lead exposure, where people are exposed to the toxic metal over a long period of time. Such exposure (chronic) usually manifests irreversible health complications, which could be managed by ascorbic acid supplementation, as it could easily be excreted from the body, and poses little or no health risk.

However, continuous use of mega doses of ascorbic acid may put the kidney at risk. It contributes to oxalic acid formation, the end product of ascorbic acid oxidation that has the potential to crystallise as calcium oxalate in the urinary space [84] thereby increasing the risk of kidney stone formation [85, 86]. It may also serve as a pro-oxidant (in mega doses), and heighten oxidative stress rather than mitigating it. As a pro-oxidant, ascorbic acid interacts with transition metal ions and promotes their reduction, accompanied by increased H_2O_2 production and consequently $^{\bullet}OH$ formation [87].

Benefit of ascorbic acid on lead induced hepatotoxicity

The liver, being the primary metabolic organ of the body, is highly vulnerable to lead intoxication [88-92]. However, ascorbic acid supplementation has been shown to mitigate lead induced hepatic damage [3, 93-95], chiefly in animal models.

Benefit of ascorbic acid on lead induced infertility

The toxic insult of lead to the reproductive system is one of the fastest growing research interests in toxicological discipline. Maternal lead exposure during neonatal period has dose-related and long term effects on postnatal development of testes as seen in offspring of Wister rats [96], and this maybe the possible cause of infertility seen in adulthood. Sometimes male infertility of unknown aetiology may be attributed to various environmental and occupational exposures to toxic substances, such as lead [97]. Other complications associated with maternal lead exposure include decreased birth weight, morphological abnormalities in the head and limbs, [38, 98, 99], spontaneous abortions, stillbirth and miscarriage [99, 100]. Exposure to lead could also cause reduction in the serum levels of gonadotropins such as the follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone [101], reduction of spermatogenic cells, and reduction of the size and diameter of seminiferous tubules [102, 103], all of which are vital for the maintenance of testicular activity.

Lead induced testicular damage is a function of ROS generation [104-106], that has been linked to decreased sperm integrity [107], germ cell death, low sperm synthesis (hypospermatogenesis) and, above all, testicular damage [108]. However, ascorbic acid is an antioxidant with long known fertility importance. It has been shown to improve sperm quality [109], human fertility [110], increase spermatogenesis and maintain the volume of testes of lead intoxicated Wister rats [111]. A study by [112] showed that lead treated mice exhibit deformations of sperm morphology and testicular injury, while daily supplementation of ascorbic acid improves the sperm morphology. More so, ascorbic acid supplementation has been shown to modulate toxicity associated with prolonged lead exposure [113]. Similarly, Ayinde *et al*. [31] verified the influence of ascorbic acid on testicular zinc content and testicular damage in lead exposed albino rats. Their findings revealed that lead intoxication was responsible for histological damage and disturbances of male reproductive organs. However, ameliorative effects were observed upon vitamin C and/or vitamin E supplementation. Supplemented ascorbic acid concentrates appreciably in the seminal plasma of living species [114], where it protects the testes [115], and maintains the genetic architecture of the sperm cells [116]. Thus, decrease in the concentration of testicular ascorbic acid content may predispose the testes to toxic injury.

Despite the described, significant role of ascorbic acid on the maintenance of the reproductive integrity, excessive intake has been linked to reproductive failure, while deficiency decline reproductive performance in Wister rats [114]. This implies that both deficiency and excessive intake of ascorbic acid affect reproductive performance. However, low dosage of ascorbic acid, co-supplemented with other vitamins has been shown to be more effectual. Wang *et al*. [117] explored the impact of combined administration of ascorbic acid and thiamine (at different levels) on the apoptosis of lead exposed mice testes. The impaired testicular tissues were ameliorated by the lower doses of ascorbic acid and thiamine, while the highest dose of the co-supplementation promotes testicular cell death.

Benefit of ascorbic acid on lead induced dyslipidaemia

Exposure to lead has been shown to induce lipid abnormalities, and increase risk of atherosclerosis [118-121]. Atherosclerosis is a condition in which plaque (made up of fat, cholesterol, calcium and other substance found in the blood) builds up inside the arteries (blood vessels that carries oxygen rich blood to heart and away from the heart), thereby impeding blood flow. Any obstruction in the blood flow could lead to health problems such as heart attack, stroke, or even death. Lead induced hyperlipidaemia is a potential, though modifiable risk factor for coronary artery disease, the leading cause of death in developed countries (e.g. USA) [122-124]. However, curbing such effects has been promising using various chelating agents such as ascorbic acid. Ugbaja *et al*. [125] investigated the comparative effect of ascorbic acid and conventional chelation therapy on lead induced dyslipidaemia. They revealed that ascorbic acid may not be more efficacious than other chelating agents but could be a cheaper and more convenient therapy for lead toxicity. It possesses the ability to lower total cholesterol (TC) level, very low density lipoprotein cholesterol (VLDLC) and low density lipoprotein cholesterol (LDLC) [126]. More so, ascorbic acid deficiency is an inevitable contributing factor for cardiovascular disease and of course a risk factor for cardiovascular related morbidity [127].

Benefit of ascorbic acid on lead induced alterations of haematological indices

Exposure to lead, especially during the first few days, impairs the hematopoietic system [4, 128-130]. Lead acetate of environmentally comparable concentrations induced haematological changes, of which significant reduction in pack cell volume, haemoglobin concentration and a significant increase in total leukocyte counts in albino rats were noteworthy [2]. Among the haematological parameters, the erythrocytes exhibited a high affinity for lead, thus making them more vulnerable than other haematological indices [131]. The implication of lead on haematological architecture includes anaemia, and decreased immune working capacity. However, ascorbic acid could efficiently enhance the

working capacity of the immune system by a mechanism that involves the combination of humoral, immune competence, and cell mediated defence reaction [132]. The cell mediated immunity of the ascorbate is a function of increased ascorbate contents of the leukocytes [133].

Benefit of ascorbic acid on lead induced brain damage

The brain exhibits high degree of vulnerability to lead intoxication, especially in children with neurological challenges [134]. The chief target of lead toxicity is the central nervous system (CNS), where it causes permanent intellectual deficit, such as behavioural and learning abnormalities, cognitive impairment, memory loss etc. [135-139]. Exposure to lead especially during pregnancy and lactation could be responsible for behavioural and cognitive impairment in infants [140]. However, ascorbic acid has shown to be an important antioxidant in the protection of the brain cells, especially in oxidative brain damage [141, 142]. Salehi *et al*. [143] investigated the detrimental role of lead on learning and memory loss, and the possible preventive role of ascorbic acid. Their findings revealed that lead treatment impairs learning and memory, while ascorbic supplementation improves learning and reduces memory deficit pre and post exposure to lead. More so, Musa *et al*. [144] examined the protective role of ascorbic acid on the cerebellum of lead intoxicated adult Wister rats. Their findings clearly revealed that lead exposure causes significant cerebellum degeneration in the brain of the experimental rats, and supplementation of ascorbic acid counteracts the damage.

CONCLUSION

Lead is a serious environmental toxicant that affects almost every living creature. The role of vitamin C in lead intoxication is well documented across the globe. However, research so far has primarily focused on the protective and ameliorative effect of ascorbic acid on lead intoxication. More so, studies on human clinical trials are relatively scarce. In light of these, we suggest that increased focus should be placed on explorations of other areas, including tandem action of ascorbic acid with other chelating agents or effects of ascorbic acid on sequestered heavy metals. These may open up new avenues for the treatment of chronically lead intoxicated patients.

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