Nig. J. Anim. Prod. 2023, 50(3):86 - 97 https://doi.org/10.51791.njap.v50i3.3916 Nigerian Journal of Animal Production

Synergistic ameliorative effect of ascorbic acid and *Moringa oleifera* in lead-induced toxicity: a review

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Abstract

This review is aimed at discussing the synergism between Moringa oleifera and ascorbic acid in lead poisoning. Lead is one of the heavy metals that is ubiquitous in nature and has various industrial applications. This is because of its advantageous physical properties. Although its use has been phased out in some industrial applications such as paints in developed countries, it remains a widely used heavy metal in the developing world. Lead toxicity accounts for thousands of deaths annually. Children are mostly affected by serious outcomes such as permanent neurocognitive damage. A literature search was conducted using ScienceDirect, PubMed, MDPI, Wiley, and Springer. Keywords used for search include "Moringa oleifera" "Ascorbic acid" "Lead toxicity" "Medicinal preparations" "Nutraceuticals" and "Chinese herbal medicine". Oxidative stress was the major mechanism underlying Pb toxicity. Oxidative stress causes the depletion of endogenous antioxidant systems. Both Moringa oleifera and ascorbic acid have antioxidant properties. This has made it possible for these two agents to be used for treating various ailments, including Pb toxicity. Previous findings have shown a probable synergism between Moringa oleifera and ascorbic acid in ameliorating Pb-induced toxicity. This study indicates that a combined treatment approach comprising of Moringa oleifera and ascorbic acid could provide the best solution for managing Pb-induced toxicity. The classical management for Pb toxicity is chelation therapy, which is usually accompanied by serious side effects. Hence, there is a need for the deployment of nutraceuticals and other plant-derived substances for the better management of Pb toxicity.

Keywords; Lead, *Moringa oleifera*, Ascorbic acid, Synergism

Effet améliorateur synergique de l'acide ascorbique et du *Moringa oleifera* sur la toxicité induite par le plomb: une revue

Résumé

Cette revue vise à discuter de la synergie entre le Moringa oleifera et l'acide ascorbique dans le saturnisme. Le plomb est l'un des métaux lourds omniprésent dans la nature et qui a diverses applications industrielles. Cela est dû à ses propriétés physiques avantageuses.

Bien que son utilisation ait été progressivement abandonnée dans certaines applications industrielles telles que les peintures dans les pays développés, il reste un métal lourd largement utilisé dans les pays en développement. La toxicité du plomb est responsable de milliers de décès chaque année. Les enfants sont principalement touchés par des conséquences graves telles que des dommages neurocognitifs permanents. Une recherche documentaire a été menée à l'aide de ScienceDirect, PubMed, MDPI, Wiley et Springer. Les mots clés utilisés pour la recherche incluent « Moringa oleifera », « Acide ascorbique », « Toxicité au plomb », « Préparations médicinales », « Produits nutraceutiques » et « Plantes médicinales chinoises ». Le stress oxydatif était le principal mécanisme sous-jacent à la toxicité du plomb. Le stress oxydatif entraîne l'épuisement des systèmes antioxydants endogènes. Le Moringa oleifera et l'acide ascorbique ont tous deux des propriétés antioxydantes. Cela a permis à ces deux agents d'être utilisés pour traiter diverses affections, notamment la toxicité du plomb. Des découvertes antérieures ont montré une synergie probable entre le Moringa oleifera et l'acide ascorbique pour améliorer la toxicité induite par le Pb. Cette étude indique qu'une approche thérapeutique combinée comprenant du Moringa oleifera et de l'acide ascorbique pourrait constituer la meilleure solution pour gérer la toxicité induite par le Pb. La prise en charge classique de la toxicité du Pb est la thérapie par chélation, qui s'accompagne généralement d'effets secondaires graves. Il est donc nécessaire de déployer des nutraceutiques et d'autres substances d'origine végétale pour une meilleure gestion de la toxicité du plomb.

Mots-clés; Plomb, *Moringa oleifera*, Acide ascorbique, Synergie

Introduction

Exposure of animals to Lead (Pb) affects the anatomy and physiology of different body organs and also causes reproductive anomalies such as fetal malformations, abortion and low weight at birth, especially if exposure occurs during pregnancy (Agyemang *et al*., 2020). Lead has harmful effects on human health, and exposure to these metals has been increased by industrial and anthropogenic activities and modern industrialization. Millions of people around the world are affected by exposure to drinking water and air which have been contaminated with heavy metals. Contamination of food by heavy metals is an issue of concern for both human and animal health. Animals easily get exposed to Pb because it is a ubiquitous environmental toxicant. (Hedayati and Darabitabar 2017). Lead has been identified as an environmental toxicant with detriment to human and animal. Lead is the most important environmental toxicant. Exposure to Pb is primarily through air and surfaces (Aliyu and Musa, 2021). Humans are mainly exposed to Pb through occupational settings and as such, working populations are most prone to Pb poisoning. Lead has greater detriment in children, where it has been found to affect brain and nervous system development with consequent cognitive impairment (Fiham *et al*., 2022). Lead poisoning in childrenis still an important issue of public health concern worldwide. There was a lead poisoning epidemic in Zamfara State, Northern Nigeria in 2010 where more than 400 children under the age of five lost their lives, many more were reported poisoned with risks of permanent neurocognitive damage and blood level greater than 149 µg/dL (Tirima *et al.,* 2016). Lead binds to proteins via competition with calcium, zinc, and other metals at ionic binding sites as well as to accessible sulfhydryl, amine, phosphate, and carboxyl groups (Markowitz, 2021). Lead causes more than a million deaths around the world annually (ATSDR, 2020). Lead is one of the most pervasive heavy metals which affects all biological systems and it builds up gradually in the body, especially in the bones (Charkiewicz and Backstrand 2020). *Moringa oleifera* belongs to the order capparales and classified in the moringaceae family (Abdelazim *et al.,* 2024). *Moringa oleifera* is a wonder tree because of its numerous uses and adaptability. All parts of the plant are used for traditional medicines in many developing countries (Magaji *et al*., 2020). The leaves of *Moringa oleifera* contain a good amount of selenium, calcium, zinc, Vitamins, A, B and C (Momin and Memis, 2023). *Moringa oleifera* boosts enzymatic antioxidant levels alongside enhancement of detoxification (Hasan *et al*., 2019). The natural antioxidants present in *Moringa oleifera* function in the same way as synthetic antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole (Siddhuraju *et al*., 2003). Phenolic compounds, fatty acids, alkaloids, glucosinolates, isothiocyanates, folates, tannins, saponins, and carotenoids are the most important bioactive compounds present in *Moringa oleifera* (Kashyap *et al*., 2022). Hydroxyl groups are responsible for the antioxidant activities of *Moringa oleifera* leaves (Zhao *et al*., 2019). Ascorbic acid is a potent antioxidant that combats free radicals through neutralizing hydroxyl and superoxide radicals (Santosh and David, 2017). It serves as a reducing cofactor for many enzymes (Du *et al*., 2012). The use of ascorbic acid has been indicated as a dietary supplement in the management of Pb toxicity (Zhai *et al*., 2015).

This review aims at highlighting the potential synergistic ameliorative effects of *Moringa oleifera* and ascorbic acid in cases of Pb toxicity.

Lead uses

Lead is one of the earliest metals discovered by humans (Flora *et al*., 2012). The environmental accumulation of Pb is difficult to curb due to its valuable physical properties, including its softness, malleability, ductility, resistance to corrosion, and low conductivity (Wani *et al*., 2015). Lead has several recent industrial applications including coating of photo-thermographic paper, rodenticides and as a heat stabilizer in nylon and polyester (Arrad, 2019). Lead is used in metal products such as alloys, solders, pipes and ammunitions as well as batteries, cosmetics and paints (Vijay, 2022). Lead is a highly toxic substance, which has resulted in its use being significantly limited, especially in paints and gasoline (Vijay, 2022). However, it still has applications in fertilizers, pesticides, and the octane rating of gasoline (Hernberg, 2000). The low density of Pb and its resistance to corrosion have made it useful in sailboat keels as ballast and sheath for submerged cables (Parker, 2005; Jensen, 2013). The Chinese use Pb in oral herbal medicine (Ming-Ling *et al*., 2013).

Toxicity of exposure of lead in animals

The toxicity of Pb can cause irreversible health problems. Lead exerts its toxic effects through the mechanism of oxidative stress (Ayinde *et* al., 2012). This oxidative stress is associated with rapid increase in malondialdehyde (a marker of lipid peroxidation) concentration and decrease in the activities of endogenous enzymatic antioxidants, such as catalase, glutathione peroxidase and superoxide dismutase (Ebuehi *et al*., 2012). High levels of exposure to Pb results in poor performance, poisoning and death in animals (Seven *et al*., 2021). Lead causes oxidative damage to the brain, kidneys, reproductive organs, heart and liver, the mechanism of this toxicity is through effects on the cell membrane, DNA and antioxidant system (Seven *et al*., 2021). The oxidative stress disrupts calcium homeostasis and depletes the antioxidant defence system by causing excessive production of free radicals (Dabrowska *et al.*, 2015). Lead also induces inflammatory responses (Balali-Mood *et al*., 2021). Lead sulphide nano particles have reportedly caused significant body and liver weight changes as well as changes in triglycerides, protein, albumin, glucose, lipids and blood (Aleksiichuk *et al*., 2018). Following absorption, Pb is distributed to the blood, soft tissues and bone (Jallad *et al*., 2021). Most of the absorbed Pb is found in bone because it persists in bone for decades, where it is increasingly mobilised during stress, pregnancy and lactation (Gulson *et al*., 2003). The accumulation of Pb is a good biomarker of toxicity and its presence in blood indicates a recent exposure (Jan *et al*., 2015). In the blood, Pb exerts its detrimental effect by interfering with the biosynthesis of haeme. Having high affinity for thiol (–SH) groups, it affects the functioning of δ-aminolevulinic acid dehydratase (δ-ALAD), catalyzing the conversion of two molecules of δ-aminolevulinic acid (δ-ALA) to porphobilinogen (Skoczynska, 2008). Lead disrupts the synthesis of haemoglobin. Even in minute quantities, Pb causes chronic renal malfunction (Barbier *et al*., 2005).

Management of lead toxicity

Lead is toxic and has no physiological applications in the body, as such, it needs to be eliminated completely. Lead toxicity causes serious health effects which are preventable. Thus, the best approach is to avoid exposure (Kosnett, 2007). To ameliorate the effects of lead, various regimen and methods have been used including chelation therapy which are either ineffective or accompanied with side effects (Ezejiofor and Orisakwe, 2019; Mumtaz et al., 2020). Since Pb is known to have no physiological function in the body and it displaces Ca^{2+}, removal of Pb can be facilitated by replacing it with Ca^{2+}. The seeds of *Moringa oleifera* have been shown to chelate Pb (Velaga *et al*., 2014) and found to have protective effects against toxicants such as arsenic (Sheikh *et* al., 2014). *Moringa oleifera* was originally from India but it has spread across Africa (Padayachee and Baijnath, 2012). The classical treatment of Pb is by chelation therapy. The commonly used lead chelators include dimercapto succinic acid (DMSA), D-penicillamine and calcium disodium ethylene diamine tetra acetic acid (Ca-EDTa) (Kim *et al*., 2015). However, the use of these chelators is accompanied with serious side effects such as stomatitis, alopecia, abdominal pain, diarrhoea and vomiting (Thuppil and Tannir, 2013). The accompanying side effects associated with the use of chelators and their inability to satisfactorily ameliorate Pb toxicity has been an issue of great concern (Ajayi *et al*., 2009), hence the need to find better alternatives for the amelioration of Pb toxicity.

Antioxidants therapy for lead toxicity

Different bioactive substances that are obtained from plants have huge therapeutic and minimal side effects, making them important raw materials for pharmaceutical industries (Calixto, 2019). The importance of natural substances in arresting heavy metal toxicity is on the rise (Ilesanmi *et al*., 2022). Antioxidants can be used as good antidotes to Pb toxicity since the major mechanism of Pb toxicity is oxidative stress. Natural products containing compounds with known antioxidant activities have been used as hepatoprotective agents against Pb poisoning (Adli *et al*., 2020). Antioxidants protect cells of the body from oxidative stress through enzymatic and nonenzymatic processes. Due to the untoward effect of the use of chelating agents, there is need to explore better alternatives in form of naturally occurring substances that have both antioxidant and chelating effects during Pb exposure in both humans and animals. Antioxidants have the ability to mitigate the effects of reactive oxygen species (ROS) (Owoeye and Onwuka, 2016). Over the years, many plants with antioxidant properties have been harnessed in ameliorating the toxic effects of Pb and other heavy metals. *Physalis Peruviana* fruit extracts have been used by Fatma *et al*. (2022) to ameliorate the toxic effects of Pb on liver and kidneys of Wistar rats. *Citrus sinensis* peel extract has also shown antioxidant and chelating effects on Pb and cadmium toxicity (Ekhator *et al*., 2022). The organic flowers extract of *Pongamia pinnata* have exhibited hepatoprotective effect against Pb toxicity by increasing the levels of protein, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transferase (Singh *et al*., 2018). Salem and Salem, 2016 reported decreased Pb, malondialdehyde and superoxide anion concentrations and correspondent increase in the serum activities of endogenous antioxidants (superoxide dismutase and catalase), following pre-supplementation with garlic in adult male rats.

Moringa oleifera and ascorbic acid in traditional Chinese medicine (TCM)

Traditional Chinese Medicine (TCM) is an ancient system of healing that is characterized by unique sets of theories and philosophies (Yang *et al.,* 2023). About 400 plant species are used in traditional Chinese Medicine or drug manufacturing units in China (Liu *et al*., 2017). *Moringa oleifera* is found in the Chinese herbal medicine dictionary, although, it is not noted in the TCM classical herbal books (Meireles *et al*., 2020). There has been large importation of *Moringa oleifera* in the Hainan province since 1998, with focus on the development of leaves and pods which are sold to Wuhan, Beijing, Guangzhou, Shanghai, Shenzhen and Hangzhou (Liu *et al.,* 2018). The Chinese Ministry of Public Health granted permission in 2012 for *Moringa oleifera* to be considered as a new resource food (Liu *et al.,* 2018). Tian *et al*., 2015 reported that Chinese researchers have reported high quality draft genome sequence of *Moringa oleifera* which can improve its application in China. Moringa industry association was formed in 2016 to promote *Moringa oleifera* industry in China. According to TCM, *Moringa oleifera* leaves have anti-anaemic and immune-stimulant effects (Brown, 2002). Moringa also acts in maintaining blood vessels through astringent action, guiding the muscles and useful in memory level (Liu *et al*., 2003). Previous studies have established the positive effects of TCM and ascorbic acid combination for treatment of different ailments. Findings from the studies of Yang *et al*., 2022 reported that a combination treatment comprising of western medicine, TCM and high doses of ascorbic acid resulted in the most effective outcome in the treatment of COVID-19. Idiopathic thrombocytopenic purpura was successfully treated with a combination of ascorbic acid and TCM (Hirano *et al*., 2007).

Synergism between Moringa oleifera and ascorbic acid against Pb toxicity

Since ancient times, use of plants such as *Moringa oleifera* as remedies has been a common traditional practice and this has created a lot of interest due to their lower side effects and relatively lower cost. *Moringa oleifera* prevents formation of free radicals due to its antioxidant properties (Ogbunugafor *et al*., 2011). Ascorbic acid has been reported to have antioxidant and ani-inflammatory properties (Moores, 2013). Ascorbic acid supports cellular glutathione levels by acting as a reducing agent, thus preventing the oxidation of -SH group to non-functional disulphide groups. *Moringa oleifera* has been demonstrated to facilitate the removal of Pb from the liver and kidneys by catalyzing its chelation and biotransformation (Albasher *et al*., 2020). *Moringa oleifera* and ascorbic acid have antioxidant functions that are beneficial to health (Reheem *et al*., 2019). Usman *et al*., 2022 suggested a probable synergism between *Moringa oleifera* and ascorbic acid in amelioration of Pb induced haematological and histopathological toxicity. Lead elicits various physiological, biochemical and behavioural anomalies as a toxin (Singh *et al*., 2018). Administration of *Moringa oleifera* and ascorbic acid to rats subjected to Pb poisoning proffered better amelioration of the negative biochemical effects when compared to administration of either *Moringa oleifera* or ascorbic acid alone (Usman *et al*., 2022). The properties of ascorbic acid such as radical scavenging ability, prevention of oxidation of protein, lipid and nuclear materials as well as redox potentials are what make it a potent antioxidant (Chakraborthy *et al*., 2014). Among the Moringaceae family, *Moringa oleifera* is the most widely known, used and studied species (Anwar *et al*., 2005). Ascorbic acid, commonly known as Vitamin C, is composed of six carbons and related to the C_6 sugars. It is an essential micronutrient that plays a vital role in the maintenance of normal metabolic processes and homeostasis (Yin *et al*., 2022). Ascorbic acid is one of the most important antioxidants in the body and plays a key role in ameliorating Pb induced toxicity (Ayoubi *et al*., 2015; Flora *et al*., 2012). *Moringa oleifera* binds with and chelate toxic metal ions (Flora and Pachauri, 2010). In oxidative brain damage, ascorbic acid has been reported to protect the cerebellum in brains of lead intoxicated Wistar rats (Musa *et al*., 2014).

Conclusion

Lead poisoning is still an issue of concern especially in developing countries. Due to the serious side effects posed by the classical management regimen-chelation therapy, efforts are been made to explore natural products for more effective management of lead toxicity. Antioxidant potentials of plant constituents are been harnessed to deal with the oxidative stress caused by lead poisoning. A combination of *Moringa oleifera* and ascorbic acid could serve as a viable management option for lead induced toxicity.

Recommendations

There should be sustained research efforts to wholly uncover the potentials of other nutraceuticals and plant materials for effective treatment of lead toxicity. Studies should be carried out to uncover the molecular basis of *Moringa oleifera* and ascorbic acid synergism.

Limitation of the study

Paucity of information to reveal the importance of ascorbic acid in traditional Chinese medicine (TCM) alone, not in a combination therapy

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Date received: 28th December, 2023
Date accepted: 5th February, 2024