

Research Article

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Effect of Livolin Forte on Cognitive Impairment Caused by Sub-Chronic Lead Acetate Administration in Wistar Rats

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Abstract

Several nutraceuticals have been used to alleviate the toxic effects of chemicals in living organisms. Lead acetate as one of the environmental pollutants causes threats to life of living creatures in many ways. The treatment of lead poisoning is classically by chelation therapy. However, there are documented reports of side effects accompanying the use of synthetic chelators, thus, necessitating the search for safer alternative treatments. Therefore, the aim of this study was to evaluate both pretreatment and post-treatment effects of Livolin Forte[®] on cognition following sub-chronic lead acetate administration in male Wistar rats. Thirty-six (36) male adult Wistar rats weighing 150 to 200 g were divided into six groups of six rats each using simple randomization. Group I rats were given 2 mL/kg body weight of distilled water, Group II rats were given 2 mL/kg of propylene glycol, Group III rats were given Livolin Forte[®] (5.2 mg/kg body weight) only, Group IV rats were given Lead acetate (Based on the reported oral LD₅₀ of lead acetate which is 600 mg/kg body weight for Wistar rats (14), 1/10th of the LD₅₀, i.e. 60 mg of Lead acetate per kg body weight), and in Group V rats, were dosed LF[®] (5.2 mg/kg) then Lead acetate (60 mg/kg) after 1hr (pretreatment). While Group VI rats were given Lead acetate (60 mg/kg) followed by Livolin forte[®] (5.2 mg/kg) after 1hr (post-treatment). The regimen was given orally once a day for seven weeks. During this period, the rats were monitored for signs of toxicity. At the end of the treatment period, the survived rats were taken for cognition studies. Significantly, ($P \leq 0.05$) higher time it takes to step down in short-term memory evaluation (68.8 ± 15.5 sec) was recorded in lead acetate exposed group when compared to other groups. From the result, it was concluded that LF had no pretreatment and post-treatment effects on sub chronic lead acetate induced cognitive impairment in adult male Wistar rats.

Keywords: lead acetate; Sub-chronic; cognition; Livolin forte; toxicity

Introduction

Technological advancements and the necessity to meet man's basic requirements, a rising number of chemicals are being purposely released into the environment. These substances interact with one another and with the environment, resulting in negative health and environmental effects (Ravi *et al.*, 2021). As a result of its vast industrial and residential applications, lead is the most common heavy metal pollutant (Patrick, 2006a). Lead (Pb) poisoning has a negative impact on both human and animal health. It is utilized in industry and in houses, and found in soil, where it poses numerous threats to humans and animals (US EPA, 2006). Known as the major polluter of the environment, and its remains have been found in children's toys, domestic kitchen products, watering cans, and pipelines (Ravi *et al.*, 2021).

Plants are typically exposed to Pb through water absorption, while animals are exposed to it through

the ingestion of plants carrying Pb residues (Hedayati and Darabitarab, 2017). It can also enter the body through drinking water and inhaling airborne polluted dust. Once absorbed, Pb rapidly diffuses through the bloodstream to numerous organs such as the brain, liver, and kidney, as well as highly calcified tissues such as teeth and bone (Alya *et al.*, 2015).

Lead poisoning (also known as plumbism, *Colica pictorum*, saturnism, Devon colic, or painter's colic) is a medical illness caused by an excessive amount of lead in the body. Developing nations are particularly at high risk of lead poisoning and carry the highest burden of this hazard (Samuel *et al.*, 2017). In Nigeria, a suspected case of Pb poisoning occurred at Unguwan Magiro and Unguwan Kawo communities in Rafi Local Government Area of Niger state in which 48 persons mostly children, (with BLL between 171.5- 224 µg/dL) including 14 deaths were reported in May15, 2015 (WHO, 2015). In March, 2010, Medecins Sans Frontieres, MSF/ doctors without Borders, an international, independent, medical humanitarian

organization was alerted to a high number of child fatalities in Zamfara state, northern Nigeria, with an estimate of 400 children died. Laboratory testing confirmed high levels of lead in the blood of surviving children in that incidence. The root cause of the lead poisoning crisis was unsafe mining and ore processing (MSF, 2012).

One of the known major mechanisms of associated illnesses is oxidative damage caused by oxidative stress (Alya *et al.*, 2015). Oxidative damage is caused by an imbalance between the synthesis and manifestation of reactive oxygen species (ROS) and the ability of a biological system to readily detoxify the reactive intermediates or repair the ensuing changes (El-Erain *et al.*, 2015).

Livolin forte® (LF) is a relatively new medicine that is used in hospitals around the world to treat and control liver disease (Olaoluwa *et al.*, 2014). It mostly comprises polyunsaturated phosphatidylcholine (300mg), vitamin B₁ (thiamine, 10mg), vitamin B₂ (riboflavin, 6mg), vitamin B₆ (pyridoxine, 10mg), vitamin B₁₂ (cyanocobalamin, 10g), nicotinamide (30mg), and vitamin E (alpha tocopherol, 10mg) (Olaoluwa *et al.*, 2014).

Lead (Pb) is one of the metallic xenobiotics found as a contaminant in air, water, and food (Onyem *et al.*, 2021). It is a toxin that affects almost all organs and has major detrimental effects on the neurological, renal, hepatic, reproductive, cardiovascular, and hematological systems (Patra *et al.*, 2011). In Nigeria, an epidemic of lead poisoning has been documented, and sublethal exposure with chelating agents such as (dimercaptosuccinic) remains the most common therapy (Onyem *et al.*, 2021).

Although chelation therapy is traditionally used to treat Pb poisoning, there is documented evidence of the side effects of synthetic chelators (Thuppil and Tannir, 2013). Commonly used chelators include dimercaptosuccinic acid (DMSA), calcium disodium versenate (CaNa₂EDTA), dimercaprol (BAL), Unithiol (DMPS), and D- penicillamine (DPA). Ethylenediaminetetraacetic acid (EDTA) has been linked to renal toxicity and cardiac problems caused by hypocalcaemia; penicillamine has been linked to abdominal pain, skin lesions, alopecia, stomatitis, glossitis, leucopenia, thrombocytopenia, and enuresis; succimer has been linked to nausea, vomiting, diarrhoea, and skin rash; and DMSA has been linked to nausea, vomiting (Thuppil and Tannir, 2013).

Despite substantial study on heavy metal toxicity, little or no attention has been made to the moderating effects of naturally occurring antioxidants and their potential nutritional values in humans and animals during heavy metal exposure.

Materials and methods

Location of Experiment

The experiment was carried out at the Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria.

Experimental Animals

Thirty- six (36) adult male (150-200 g) Wistar strain Albino rats served as subjects. They were obtained from the Laboratory animal house of the Department of Veterinary Pharmacology and Toxicology. The rats were kept in the Department's animal holding facility. The Ahmadu Bello University committee on Animal Use and Care guidelines were strictly adhered to, in order to minimize unwanted stress or discomfort to the animals during experimental procedures by ensuring minimal handling. The rats were given free access to standard commercially prepared rat chow and water.

Ethical Clearance

The Ahmadu Bello University committee on Animal Use and Care provided ethical approval for the use of Wistar Rats in this study, with clearance approval number: ABUCAUC//2023/023

Chemical Acquisition and Preparation

Lead acetate was purchased from Sigma Aldrich (St. Louis, MO, USA). It was reconstituted in distilled water to make a stock solution. Livolin forte® (500 mg LF per capsule) was purchased from a reputable pharmaceutical store in Kaduna state, Nigeria. According to (Olaoluwa *et al.*, 2014), one capsule of 500 mg was dissolved in 20 mL of propylene glycol to make a 25 mg/mL suspension daily before administration.

Animal Grouping

Thirty-six (36) male adult Wistar rats were divided into six groups of six rats each using simple randomization (Table 1). Group I rat were given 2 mL/kg body weight of distilled water, Group II rats were given 2 mL/kg of propylene glycol, Group III rats were given LF (5.2 mg/kg) only, Group IV rats were given Pb (Based on the reported oral LD₅₀ of Pb which is 600 mg/kg body weight for Wistar rats (14),

1/10th of the LD₅₀, i.e., 60 mg of Pb per kg body weight). Group V rats were given LF (5.2 mg/kg) followed by Pb (60 mg/kg) after 1hr. While, Group VI rats were given Pb (60 mg/kg) followed by LF (5.2

mg/kg) after 1hr. The regimens were administered by gavage, once daily for seven weeks. During this time, the rats were monitored for signs of toxicity.

Table 1: Dosing protocol showing various treatments in rats

Group	Treatment	Dosage regimen
I	Distilled water	2 ml/kg
II	Propylene glycol	2 ml/kg
III	Livolin Forte®	5.2 mg/kg
IV	Lead acetate	60 mg/kg
V	Livolin Forte® then Lead acetate after 1hr	5.2 mg/kg + 60 mg/kg
VI	Lead Acetate then Livolin Forte® after 1hr	60 mg/kg + 5.2 mg/kg

Evaluation of Neurobehavioral Changes

Evaluation of learning

The effect of lead on learning task in rats and the possible ameliorative effect of antioxidant vitamin (ascorbic acid) was assessed 48 hours to the termination of the study using the step-down inhibitory avoidance learning task as described by (Zhu *et al.*, 2001). The apparatus used for the learning test was a 40 × 25 × 25 cm acrylic chamber, consisting of a floor made of parallel 2-mm calibre stainless steel bars spaced 1cm apart. An electric shock was administered through the floor bars. A 2.5-cm-high, 8 × 25 cm wooden platform was placed on the left extreme of the chamber. Each animal was gently placed on the platform. Upon stepping down, the rat immediately received a single 80-volt foot-shock. If the animal did not return to the platform, the foot-shock was repeated every 5 seconds. A rat was considered to have learned the avoidance task, if it remained on the platform for more than 2 minutes. The number of foot-shocks applied before the animal learned the avoidance task was recorded as an index of learning acquisition.

Evaluation of short-term memory

Short-term memory was assessed in individual rat from each group using the stepdown avoidance inhibitory task as described by (Zhu *et al.*, 2001). The apparatus used for the memory test consisted of 40 × 25 × 25 cm acrylic chamber with floor made of parallel 2-mm-calibre stainless steel bars spaced 1 cm apart. A 2.5-cm-high, 8 × 25 cm wooden platform was placed on the left extreme of the chamber. In this case, the rat was again placed gently on the platform 24 hours after performing the learning task. The time an animal remained on the platform was recorded as an index of memory retention. Staying on the platform

for 2 minutes was counted as maximum memory retention (ceiling response).

Data Analysis

Data obtained were expressed as Mean ± standard error of the mean (SEM) and subjected to one-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* multiple comparison test. Graph pad prism version 5, San Diego, California, USA (www.graphpad.com) was used to analyse all the data. Values of $p \leq 0.05$ were considered significant.

Results

Sub-chronic Toxicological Studies

Clinical Signs

There were no toxicity signs in the control animals that were given distilled water alone and those that were given Propylene glycol alone, and the group that were dosed with Livolin forte® alone. However, toxicity signs such as spasms, weight loss, weakness, decrease in feed intake, and rough hair coat were observed in the Pb -treated animals, the pretreatment group as well as the post-treatment group.

Effect of Livolin forte® and Lead acetate on Cognition

Effect of livolin forte and lead acetate on learning

There was no significant difference ($P \geq 0.05$) in learning test across the groups (Figure 1).

Effect of livolin forte® and lead acetate on short-term memory

There was a significant increased ($P \leq 0.05$) time it takes to step down in the lead acetate exposed rats (68.8 ± 15.5 sec) when compared to the other groups DW (47.4 ± 3.4 sec), PG (52.6 ± 5.6 sec), LF (54.4 ± 6.1 sec), LF+Pb1hr (51.8 ± 5.3 sec), and Pb+LF1hr (59.4 ± 6.3 sec) (Figure 2).

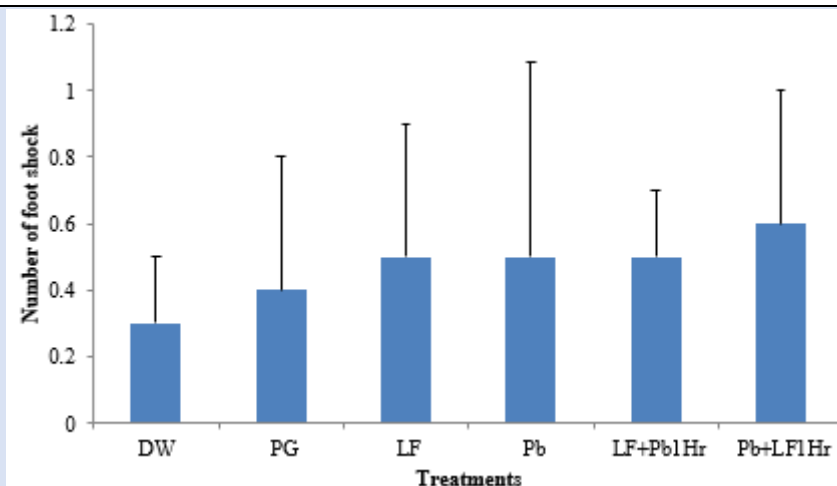


Figure 1: Effect of sub-chronic administration of LF and Pb on learning. Values are presented as Mean±SEM, ($P>0.05$), $n=6$.

Key: DW: Distilled Water (2 ml/kg); Pg: Propylene glycol (2 ml/kg); Pb: Lead acetate (60 mg/kg); LF: Livolin forte® (5.2 mg/kg); LF+Pb1Hr: Livolin forte® (5.2 mg/kg) then Lead acetate (60 mg/kg) after 1hr, Pb+LF1Hr: Lead acetate (60 mg/kg) then Livolin forte® (5.2 mg/kg) after 1hr.

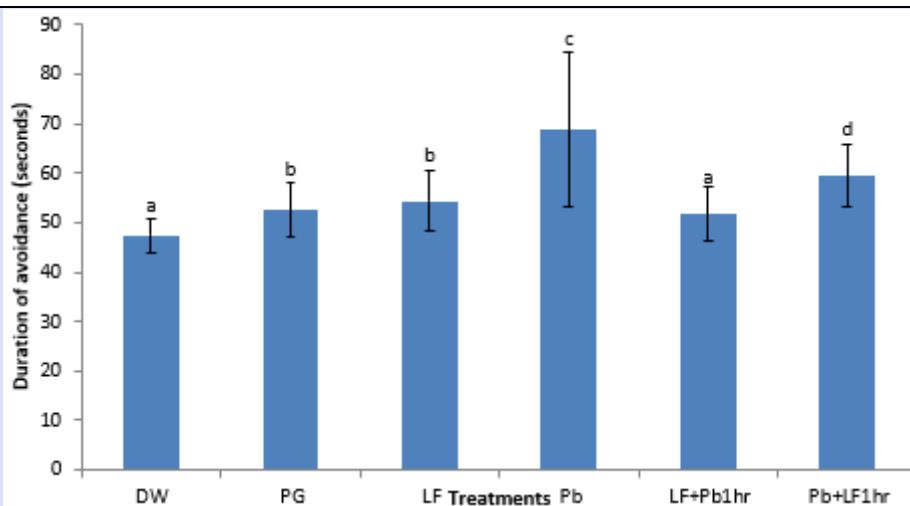


Figure 2: Effect of sub-chronic administration of LF and Pb on memory. Values are presented as Mean ± SEM. Values with different letters (a, b, c, d) are significantly different ($P \leq 0.05$), $n = 6$.

Key: DW: Distilled Water (2 ml/kg); Pg: Propylene glycol (2 ml/kg); Pb: Lead acetate (60 mg/kg); LF: Livolin forte® (5.2 mg/kg); LF+Pb1Hr: Livolin forte® (5.2 mg/kg) then Lead acetate (60 mg/kg) after 1hr, Pb+LF1Hr: Lead acetate (60 mg/kg) then Livolin forte® (5.2 mg/kg) after 1hr.

Discussion

Lead is a common heavy metal that pollutes the environment and accumulates in human and animal body through absorption, bioavailability, bioconcentration, and biomagnification disrupts the neurological, skeletal, reproductive, haematopoietic, renal, and cardiovascular systems (Collin *et al.*, 2022). The results of the present study showed that sub-chronic exposure of Wistar rats to lead acetate had no significant effect on learning in rats. The group exposed to Pb had an increase in learning, when compared to the other groups. It has been shown that Pb in toxic quantity have no significant effect on learning in rats (Susan *et al.*, 2013). This could be the

reason why the learning in the Pb treated group was not affected.

The current results on short-term memory demonstrated a decrease in the cognitive function of rats exposed to repeated low-dose lead, indicating a reduction in the index of short-term memory retention of the experimental animals. Several studies have demonstrated the effect of lead on short-term memory in animals (Aldridge *et al.*, 2005; Haider *et al.*, 2005; Azzaoui *et al.*, 2009). The exposed rats spent less time on the platform in the step-down avoidance inhibitory apparatus, compared to rats in other treatment groups. This fact, apparently, showed that lead impairs cognitive function in rats. Several

mechanisms of altered cognitive function following lead exposure have been proposed. One is the alterations in glutamate release from the hippocampus (Wisden *et al.*, 2000). The hippocampus is a brain area which is rich in glutamate receptors. Appropriate glutamate activity is critical for the development of the central nervous system, including the ontogeny of learning and memory (Adams *et al.*, 2009). The effects of glutamate are often mediated through the N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) and kainate receptors (Frerking *et al.*, 2001; Bortolotto *et al.*, 2005; Adams *et al.*, 2009). Infact, NMDA receptors are important in their role in long-term potentiation (Rison and Stanton, 1995; MacDonald *et al.*, 2006), which is a form of synaptic plasticity often used as a model system for the study of cognitive functions (Porterfield and Hendrick, 1993; Laroche *et al.*, 2000; O'Mara *et al.*, 2000). The memory process is based on the creation and remodeling of synapses and the toxic effect of lead on 112 this process suggests that lead specifically damages synaptic functions (Bradbury and Deane, 1993; Lasley and Gilbert, 2000; Bouton *et al.*, 2001). Damage to the hippocampus has been reported to cause severe impairments in memory (Eichenbaum *et al.*, 1990; McDonald and White, 1995; Grigorenko *et al.*, 1997), but this damage was found not to affect spatial information (Gilbert *et al.*, 2005). Another mechanism is via decrements in the activities of acetylcholinesterase. Sub chronic exposure to lead has resulted in a decrease in activity of acetylcholinesterase in rats (Nehru and Sidhu, 2002; Reddy *et al.*, 2003; Saxena and Flora, 2004). Similarly, the central cholinergic system has been linked to synaptic plasticity and memory processes in several studies (Sachdev *et al.*, 1998; Reddy *et al.*, 2007). A decrease in brain serotonin (5-hydroxytryptamine) levels has also been implicated as a cause of impaired cognitive function in lead-treated rats (Haider *et al.*, 2005). In addition, rat brain neurotoxicity has been demonstrated to occur via the induction of oxidative stress as a result of the accumulation of delta-aminolevulinic acid during lead exposure (Tandon *et al.*, 2002; Patrick, 2006b; Wang *et al.*, 2006). The result of the present study demonstrated a beneficial effect of pre-treatment and post-treatment with Lf, as short-term memory of lead-exposed rats was slightly improved. In addition, agents that inhibit generation of reactive oxygen species in

the brain may block tissue damage resulting from excitotoxicity from glutamate and loss of cellular calcium (Bose *et al.*, 1992; Siesjo, 1993). This mechanism involved in the pathogenesis of neuronal damage resulting in impaired cognition, further confirms the beneficial role of Lf in improving memory in rats.

The World Health Organization (WHO) report of 31st August, 2022, stated that the neurological and behavioural effects of lead are believed to be irreversible (WHO, 2022). This may be due to the inhibition of δ -ALAD in the plasma. Excess of δ -ALA (gamma aminolevulinic acid) causes severe neurological effects (Dehari-Zeka *et al.*, 2020). This could be the reason why Lf could not modulate the toxic effect of lead on memory. Exposure to lead element, and thus its toxicity, has increased around the world as industries have developed. The central nervous system is the most vulnerable to lead intoxication. Lead-induced neurotoxicity (Saeedeh *et al.*, 2016) results in behavioral, morphological, and electrophysiological changes (Sharfi *et al.*, 2002).

The current study found that continuous lead exposure had a negative impact on rat memory. The findings are consistent with experimental and clinical research that has shown that lead exposure disrupts cognitive functioning and damages processes in humans and animals (Finkelstein *et al.*, 1998). A number of mechanisms have been proposed to explain lead neurotoxicity. The increase of reactive oxygen species triggers lipid peroxidation and oxidative stress processes, which is one of the most critical pathways in lead-induced neurotoxicity (Kuhlmann *et al.*, 1997). Furthermore, lead binds to the thiol groups of biological macromolecules such as glutathione, reducing their reductive potency and antioxidant activity (Marchetti, 2003). Other pathways involved in lead neurotoxicity have been documented to include the activation of the apoptotic cascade, an increase in inflammatory mediators, changes in glutamate-induced neuroplasticity, and abnormalities in calcium homeostasis (Xu *et al.*, 2006). Many vitamins have been discovered to help reduce the neurotoxic consequences of lead exposure. One of the most critical supplements required for the regular functioning of neurons in the neurological system is vitamin B12, which is included in Lf. As a cofactor, it regulates CNS enzyme activity and ensures proper metabolic function (Saeedeh *et al.*, 2016).

The higher number of steps down in Pb-exposed rats in this study implies that Pb induces memory loss,

which is consistent with the work of (Daniela *et al.*, 2021). This reduction in cognitive ability could be due to oxidative damage to brain tissue, particularly the hippocampus, which is important for learning and memory (Nathaniel and Gabriel, 2020).

During the development of industries in the world, exposure to lead element and consequently its toxicity has been increased worldwide. Central nervous system is the most important target for the lead toxicity. Lead induced neurotoxicity include behavioral, morphological, and electrophysiological disruptions (Sharfi *et al.*, 2002).

Several mechanisms have been proposed to explain the neurotoxicity of Pb^{2+} . One of the most important mechanisms in lead-induced neurotoxicity is the triggering of lipid peroxidation and oxidative stress processes by accumulation of reactive oxygen species [58]. In addition, lead binds to the thiol groups of biologic macromolecules like glutathione and decreases their reductive potencies and antioxidant activities (Marchetti, 2003). It has been reported that the initiating of apoptosis cascade, increasing inflammatory mediators, alteration in glutamate-induced neuroplasticity and changes in calcium homeostasis are some of other mechanisms involved in lead neurotoxicity [60].

One of the most important disorders following lead exposure is neurotoxicity [55]. Neurotoxicity is a popular disorder from lead exposure which involves both central and peripheral nervous system. Lead induced neurotoxicity triggers a wide range of structural and behavioral changes in the nervous system [56].

Conclusion

In summary, the present study shows that livolin forte had both pretreatment and post-treatment effects on memory impairment induced by lead element.

This study supports the role of oxidative stress in the pathophysiology of low-level lead poisoning. The beneficial effects of LF were not observed on cognition in rats.

Declarations

Authors' Contributions

E.M. conceived and planned the experiments. E.M. carried out the experiments. E.M. planned and carried out the simulations. E.M. contributed to sample preparation. M.M. and S.M. contributed to the interpretation of the results. E.M. took the lead in writing the manuscript. All authors provided critical

feedback and helped shape the research, analysis and manuscript.

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Competing Interests

The authors declare that there is no conflict of interest.

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