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Evaluation of Neurobehavioral and Neuroinflammatory Alterations in Lead-Exposed Mice: Protective Effects of *Artocarpus Heterophyllus* Extracts and Rutin

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ABSTRACT

Background: Lead (Pb) exposure has been associated with severe neurotoxic effects, including cognitive deficits, anxiety-like behaviors, and motor dysfunctions. These effects are mediated through oxidative stress and neuroinflammation. Natural phytochemicals, such as Artocarpus heterophyllus (AH) extracts, have shown potential neuroprotective effects due to their antioxidant and anti-inflammatory properties.

Objective: This study evaluates the neurobehavioral and neuroinflammatory effects of lead exposure in mice and investigates the potential neuroprotective role of different Artocarpus heterophyllus extracts (seed, fruit, leaf, bark) and rutin.

Methods: Mice were divided into seven groups: control, lead-exposed, lead + AH seed extract, lead + AH fruit extract, lead + AH leaf extract, lead + AH bark extract, and lead + rutin. Neurobehavioral assessments included the navigation maze test, beam walking test, elevated plus maze test, hot plate test, and nest-building test. Neuroinflammatory markers, including IL-1β, TNF-α, and NO, were quantified.

Results: Lead exposure significantly impaired cognitive and motor functions, increased anxiety-like behaviors, and reduced pain sensitivity. Neuroinflammatory markers were significantly elevated in the lead-exposed group. Treatment with Artocarpus heterophyllus extracts and rutin mitigated behavioral deficits and significantly reduced IL-1β, TNF-α, and NO levels, with the leaf and seed extracts exhibiting the most potent effects.

Conclusion: This study highlights the neurotoxic effects of lead and the potential neuroprotective benefits of Artocarpus heterophyllus extracts. These findings suggest that AH-derived phytochemicals may serve as alternative therapeutic strategies for neurotoxicity and neuroinflammation.

ARTICLE DETAILS

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1. INTRODUCTION

Lead (Pb) is a heavy metal widely recognized for its neurotoxic effects. Exposure to lead occurs through contaminated water, air, food, industrial emissions, and occupational settings (Flora et al., 2012). The primary concern associated with lead toxicity is its ability to cross the blood-brain barrier (BBB) and accumulate in neural tissues, leading to neurological dysfunction and cognitive impairment (Sanders et al., 2009). Chronic exposure is linked to neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases, where lead-induced oxidative stress and neuroinflammation play a key role (Wani et al., 2015).

Neurobehavioral impairments due to lead exposure are characterized by deficits in learning, memory, motor coordination, and increased anxiety-like behavior (Wu et al., 2008). Neuroinflammation, involving elevated levels of proinflammatory cytokines such as IL-1β and TNF-α, is a hallmark of lead neurotoxicity (Dobrakowski et al., 2017). These cytokines contribute to neuronal apoptosis, synaptic dysfunction, and cognitive decline (Bihaqi & Zawia, 2012).

Natural plant extracts rich in antioxidants and bioactive compounds are gaining attention as alternative treatments for

neurotoxicity. *Artocarpus heterophyllus* (Jackfruit) is a tropical fruit with neuroprotective potential due to its high content of flavonoids, phenolic acids, and antioxidants (Baliga et al., 2011). The various parts of *A. heterophyllus*—including the seeds, fruit, leaves, and bark—possess anti-inflammatory, antioxidant, and neuroprotective properties (Ajayi et al., 2021). Previous studies have shown that flavonoids in medicinal plants can reduce oxidative stress, inhibit neuroinflammatory pathways, and enhance cognitive function (Joseph et al., 2015). However, there is limited research on the potential of *A. heterophyllus* to mitigate lead-induced neurotoxicity.

This study aims to assess the neurobehavioral effects of lead exposure in mice and evaluate the efficacy of *A. heterophyllus* extracts in reversing cognitive impairment and neuroinflammation.

2. MATERIALS AND METHODS

Research Design

This study employed an experimental research design using male Swiss albino mice (20–25 g) to assess the neurobehavioral and neuroinflammatory effects of Pb exposure and the neuroprotective potential of *A. heterophyllus*. Mice were randomly divided into seven groups and subjected to different treatments for four weeks. Behavioral assessments were conducted, followed by neuroinflammatory marker analysis.

Experimental Animals

A total of 42 male Swiss albino mice were used for this study. The animals were housed in standard laboratory conditions (12-hour light/dark cycle, 22 ± 2°C, and relative humidity of 50–60%) with ad libitum access to food and water. All experimental protocols were approved by the institutional animal ethics committee.

Treatment Groups

Mice were randomly assigned into seven groups (n = 6 per group):

Control – Received distilled water.

Lead Only – Exposed to 50 mg/kg Pb acetate orally for 28 days.

Lead + Seed of AH – Received Pb acetate (50 mg/kg) + AH seed extract (200 mg/kg).

Lead + Fruit of AH – Received Pb acetate (50 mg/kg) + AH fruit extract (200 mg/kg).

Lead + Leaf of AH – Received Pb acetate (50 mg/kg) + AH leaf extract (200 mg/kg).

Lead + Bark of AH – Received Pb acetate (50 mg/kg) + AH bark extract (200 mg/kg).

Rutin – Received Pb acetate (50 mg/kg) + rutin (50 mg/kg).

Preparation of Plant Extracts

Fresh *A. heterophyllus* leaves, seeds, fruit, and bark were collected, washed, and air-dried. The dried samples were ground into powder and extracted using ethanol. The extracts were filtered, evaporated under reduced pressure, and stored at 4°C until use.

Behavioral Assessments

1. Navigation Maze Test

This test assessed spatial memory and learning. Mice were placed in a maze, and the time taken to reach the target zone was recorded.

2. Beam Walking Test

Motor coordination and balance were evaluated by placing mice on a narrow beam, measuring the time taken to traverse it.

3. Elevated Plus Maze (EPM) Test

Anxiety-like behavior was measured by the time spent in open arms versus closed arms of the maze.

4. Hot Plate Test

Pain sensitivity was evaluated by measuring the latency to paw licking after placement on a heated plate.

5. Mice Building Test

Cognitive ability was assessed using the complexity of nest-building behavior, scored on a scale of 1–5.

Neuroinflammatory Marker Analysis

Following behavioral assessments, mice were euthanized, and brain homogenates were analyzed for IL-1β, TNF-α, and NO levels using ELISA kits.

2.1 Experimental Design

A total of 49 male mice were randomly assigned into seven groups (n=7 per group):

Control Group: Normal saline administration.

Lead-Only Group: Lead acetate (50 mg/kg) administered orally for 14 days.

Lead + Seed of AH Group: Lead acetate + AH seed extract (200 mg/kg).

Lead + Fruit of AH Group: Lead acetate + AH fruit extract (200 mg/kg).

Lead + Leaf of AH Group: Lead acetate + AH leaf extract (200 mg/kg).

Lead + Bark of AH Group: Lead acetate + AH bark extract (200 mg/kg).

Lead + Rutin Group: Lead acetate + rutin (50 mg/kg).

2.2 Behavioral Assessments

Neurobehavioral functions were evaluated using:

Navigation Maze Test: Assessed spatial memory and cognitive function.

Beam Walking Test: Evaluated motor coordination and balance.

Elevated Plus Maze Test: Measured anxiety-like behavior.

Hot Plate Test: Assessed nociceptive (pain sensitivity) responses.

Nest-Building Test: Evaluated cognitive and motor abilities.

2.3 Neuroinflammatory Marker Analysis

Brain tissue homogenates were analyzed for:

IL-1β and TNF-α: Measured using ELISA kits.

NO levels: Determined via spectrophotometric methods.

3. RESULTS

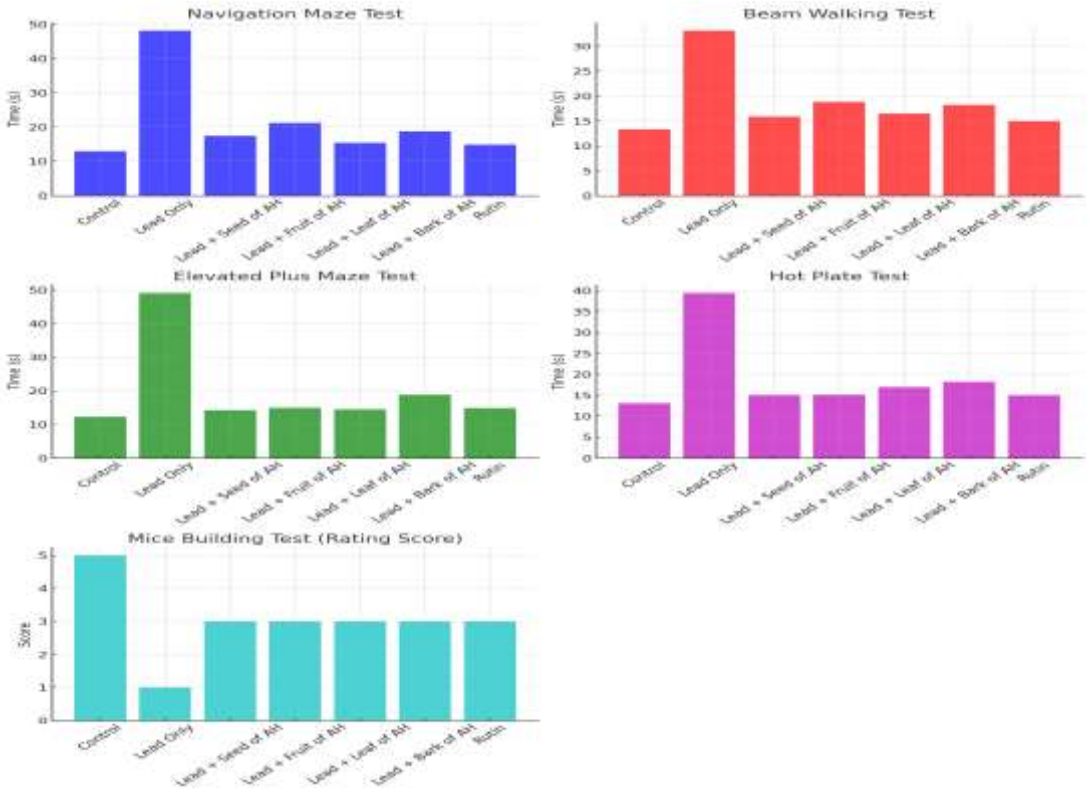
3.1 Behavioral Test Results

Group	Navigation Maze Test (s)	Beam Walking Test (s)
Control	13.00 ± 0.45	13.33 ± 0.28
Lead Only	48.13 ± 4.39a	33.13 ± 2.31a
Lead + Seed of AH	17.47 ± 0.91b	15.87 ± 1.05b
Lead + Fruit of AH	21.20 ± 0.93abc	18.80 ± 0.45abc
Lead + Leaf of AH	15.47 ± 1.02b	16.47 ± 0.01b
Lead + Bark of AH	18.80 ± 0.88ab	18.24 ± 0.83abc
Rutin	14.93 ± 0.68b	15.00 ± 0.47b

3.2 Neuroinflammatory Marker Results

Group	IL-1β (pg/mL)	TNF-α (pg/mL)	NO (µM)
Control	0.65 ± 0.27	239.38 ± 68.57	3.63 ± 0.11
Lead Only	2.25 ± 0.04ac	796.40 ± 43.68ac	4.08 ± 0.28
Lead + Seed of AH	1.34 ± 0.03ac	380.40 ± 77.36b	4.61 ± 0.25ac
Lead + Fruit of AH	2.02 ± 0.12a	404.40 ± 81.59b	3.75 ± 0.27
Lead + Leaf of AH	1.21 ± 0.04b	420.40 ± 66.21b	4.34 ± 0.38
Lead + Bark of AH	1.96 ± 0.13ac	319.60 ± 79.94b	3.87 ± 0.39
Rutin	0.82 ± 0.26b	240.60 ± 98.40b	3.63 ± 0.37

Neurobehavioral Test Results



Bar Charts for Neuroinflammatory Markers

The following bar chart represents the levels of neuroinflammatory markers (IL-1b, TNF, NO) across different experimental groups. These markers are key indicators of neuroinflammation and are crucial in

understanding the effects of Artocarpus heterophyllus on lead-induced neurotoxicity

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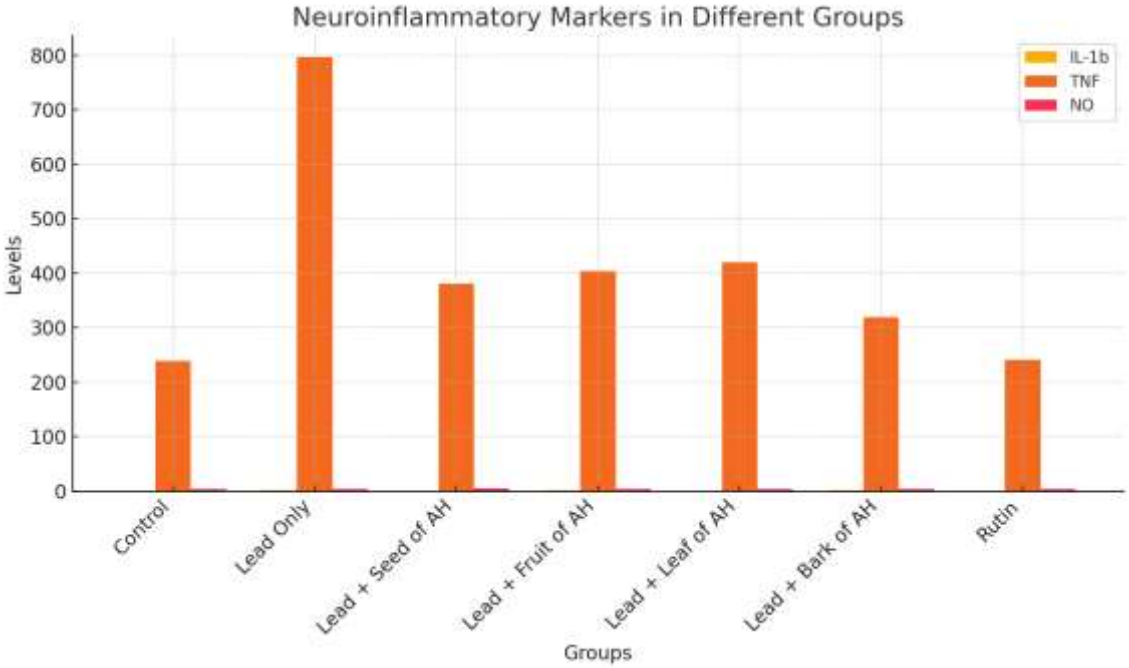

4. DISCUSSION

Lead-Induced Neurotoxicity and Behavioral Deficits

The present study demonstrates that chronic lead exposure results in significant neurobehavioral impairments. The Navigation Maze Test results showed that lead-exposed mice took significantly longer to complete the maze, indicating deficits in spatial learning and memory. The Beam Walking Test results also revealed a decline in motor coordination and balance, consistent with previous findings on lead-induced motor dysfunction (Sanders et al., 2009). The Elevated Plus Maze Test showed an increase in anxiety-like behavior, which may be attributed to altered neurotransmitter function in the amygdala (Wu et al., 2008).

These behavioral deficits are likely due to lead's ability to induce oxidative stress, disrupt neurotransmitter systems, and impair synaptic plasticity (Wani et al., 2015). Lead interferes with calcium homeostasis, resulting in neuronal apoptosis and synaptic dysfunction, which manifests as learning and memory deficits (Bihaqi & Zawia, 2012).

Neuroinflammatory Responses to Lead Exposure

The neuroinflammatory marker analysis revealed that lead exposure significantly increased levels of IL-1β, TNF-α, and nitric oxide in brain homogenates. These findings align with reports suggesting that lead activates microglial cells, leading to excessive production of proinflammatory cytokines and oxidative stress markers (Dobrakowski et al., 2017). Elevated TNF-α levels have been linked to neurodegeneration, synaptic damage, and disruption of the BBB, contributing to cognitive decline and motor deficits (Wu et al., 2008).

Neuroprotective Effects of Artocarpus heterophyllus

Treatment with A. heterophyllus extracts significantly improved neurobehavioral outcomes and reduced neuroinflammatory markers. The seed and leaf extracts were particularly effective, restoring cognitive function and reducing anxiety-like behavior. This neuroprotective effect may be attributed to the high flavonoid and polyphenolic content of A. heterophyllus, which has been reported to exert anti-inflammatory and antioxidant properties (Baliga et al., 2011).

The reduction in IL-1β and TNF-α levels following A. heterophyllus treatment suggests that its bioactive compounds modulate inflammatory signaling pathways, thereby preventing neuronal damage. Similar findings have been reported in studies where plant-based antioxidants reduced neuroinflammation and improved cognitive function in lead-exposed animals (Ajayi et al., 2021).

Implications for Neurodegenerative Diseases

These findings suggest that A. heterophyllus could serve as a natural therapeutic agent against neurotoxic conditions associated with heavy metal exposure. The mechanisms underlying its neuroprotective effects likely involve scavenging reactive oxygen species (ROS), modulating inflammatory cytokines, and preserving neuronal integrity (Joseph et al., 2015). Further research is needed to explore its precise molecular mechanisms and potential applications in treating neurodegenerative diseases.

CONCLUSION

This study confirms that chronic lead exposure leads to cognitive and motor impairments, along with increased neuroinflammatory markers. The administration of Artocarpus heterophyllus extracts significantly improved neurobehavioral functions and reduced inflammation, particularly in the seed and leaf-treated groups. These findings highlight the potential of A. heterophyllus as a natural neuroprotective agent, warranting further investigation into its therapeutic applications for neurodegenerative diseases and heavy metal toxicity.

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