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Immunomodulatory and Anti-Inflammatory Effects of *Aframomum Melegueta* on Lead-Induced TNF- α and IL-10 Imbalance in Wistar Rats

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Abstract

Lead (Pb) exposure is a persistent global health concern, particularly in developing countries, causing multi-organ toxicity through oxidative stress, immune dysregulation, and inflammatory responses. Dysregulation of cytokines, including elevated tumor necrosis factor-alpha (TNF- α) and suppressed interleukin-10 (IL-10), represents a key mechanism of lead-induced immunotoxicity. Natural agents with antioxidant and immunomodulatory properties, such as *Aframomum melegueta* (alligator pepper), may offer protective benefits. This study evaluated the immunomodulatory and anti-inflammatory effects of ethanolic extract of *A. melegueta* on lead-induced TNF- α and IL-10 dysregulation in Wistar rats, compared with standard chelation therapy (EDTA). Thirty-five adult Wistar rats were randomly assigned to five groups, including normal control, lead-exposed untreated, lead-exposed treated with low (200 mg/kg), high (400 mg/kg) doses of *A. melegueta*, EDTA-treated. Lead acetate (100 mg/kg) was administered by gastric gavage for 14 days, followed by 14 and 5 days of treatment for extract and Standard chelator respectively. Serum TNF- α and IL-10 levels were measured via ELISA. Data were expressed as mean \pm SEM and analyzed using student t- test ($p < 0.05$). Lead exposure significantly elevated TNF- α and suppressed IL-10, indicating pronounced inflammatory and immunosuppressive effects. Treatment with *A. melegueta* extract, particularly at 400 mg/kg, significantly reduced TNF- α and restored IL-10 levels, comparable to calcium disodium EDTA treatment.

Keywords: *A. melegueta*, immunotoxicity, TNF- α , IL-10, immunomodulatory, calcium disodium EDTA

Introduction

Lead exposure continues to pose a critical global health challenge, particularly in developing countries where industrial emissions, contaminated water, and consumer products contribute significantly to environmental and occupational exposure (WHO, 2023). Lead is a persistent heavy metal that exerts toxic effects on nearly every organ system in the body, owing to its ability to bioaccumulate and interfere with essential physiological processes (ATSDR, 2022). Among its numerous toxic effects, the dysregulation of immune and inflammatory responses represents one of the most deleterious yet underexplored aspects of lead-induced toxicity (Fortier *et al.*, 2008; Fenga *et al.*, 2017).

The immune system is exceptionally sensitive to heavy metal stress. Lead exposure exerts dual immunotoxic effects, displaying both immunosuppressive and immunostimulatory properties depending on dose and duration (Fortier *et al.*, 2008). It disrupts both innate and adaptive immune responses, resulting in increased vulnerability to infections and a heightened risk of autoimmune and inflammatory disorders (Bahrami & Hassanzadeh Makoui, 2025). Mechanistically, lead interferes with the differentiation and activation of T cells, impairs cytokine secretion, and alters the balance between T-helper 1 (Th1) and T-helper 2 (Th2) immune pathways, thereby promoting immune imbalance (Fenga *et al.*, 2017; Couper *et al.*, 2022).

A central feature of this immune dysregulation is the disturbance in cytokine homeostasis, particularly between pro-inflammatory and anti-inflammatory mediators. Tumor necrosis factor- α (TNF- α), a key pro-inflammatory cytokine produced primarily by macrophages and monocytes, mediates host defense responses but can induce cytotoxicity, apoptosis, and chronic inflammation when excessively expressed (Singh *et al.*, 2018; Zhang *et al.*, 2023). Elevated TNF- α levels during lead exposure contribute to oxidative stress, hepatocellular injury, renal dysfunction, and systemic inflammation (Allameh *et al.*, 2023).

Conversely, interleukin-10 (IL-10), a potent anti-inflammatory cytokine secreted by regulatory T cells (Tregs), monocytes, and macrophages, plays a crucial role in maintaining immune tolerance and suppressing overactive inflammatory responses (Couper *et al.*, 2022; Smith *et al.*, 2022). IL-10 inhibits the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, thereby protecting tissues from immune-mediated injury. However, lead exposure has been reported to suppress IL-10 expression, disrupt its signaling through oxidative stress and epigenetic modulation, and consequently aggravate inflammation (Gupta & Sharma, 2022; Chen *et al.*, 2023; Martinez *et al.*, 2023). Imbalances between TNF- α and IL-10 thus represent a hallmark of lead-induced immunotoxicity, leading to persistent inflammation, organ dysfunction, and tissue degeneration.

In addition to cytokine alterations, lead-induced inflammation often occurs concurrently with oxidative stress, mitochondrial damage, and apoptotic signaling, amplifying tissue injury and impairing immune competence (Sanders *et al.*, 2009). The interplay between oxidative and inflammatory mechanisms underscores the need for therapeutic agents capable of restoring cytokine equilibrium while attenuating oxidative damage. While chelation therapy with ethylenediaminetetraacetic acid (EDTA) remains a cornerstone of lead detoxification, its limitations—including depletion of essential trace elements and lack of immunorestorative capacity—highlight the importance of natural

alternatives with immunomodulatory potential (WHO, 2023).

Aframomum melegueta (alligator pepper), a member of the Zingiberaceae family, has gained increasing scientific attention due to its diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and immunoregulatory activities (Oladimeji *et al.*, 2022; Adegbite *et al.*, 2023). Rich in bioactive compounds such as flavonoids, alkaloids, tannins, and terpenoids, and containing pungent principles like 6-paradol, 6-gingerol, and 6-shogaol, *A. melegueta* exhibits free radical scavenging and cytokine-modulating properties (Adebayo *et al.*, 2023; Mensah *et al.*, 2023). These phytochemicals have been shown to suppress pro-inflammatory mediators (TNF- α , IL-6), enhance anti-inflammatory signaling, and protect cellular membranes from oxidative insult (Adegboye *et al.*, 2022; Olatunji *et al.*, 2023).

Emerging evidence indicates that *A. melegueta* not only mitigates inflammation but may also restore cytokine balance and immune cell function disrupted by toxic exposures (Okonkwo *et al.*, 2021; Sharma *et al.*, 2023). Its combined antioxidant and anti-inflammatory activities suggest a dual therapeutic mechanism capable of both neutralizing oxidative radicals and regulating cytokine networks. Nevertheless, scientific data on its immunomodulatory efficacy specifically in the context of lead-induced cytokine dysregulation remain sparse.

Therefore, this study investigates the immunomodulatory and anti-inflammatory effects of ethanolic extract of *Aframomum melegueta* on lead-induced dysregulation of TNF- α and IL-10 in Wistar rats. By comparing its effects with those of the standard chelator drug like calcium disodium EDTA, this study aims to elucidate the plant's capacity to modulate immune responses, restore cytokine balance, and protect vital organs against lead-induced inflammatory injury. Findings from this work are expected to contribute valuable insights into the development of phytotherapeutic agents for heavy metal-induced immune dysfunction.

Materials and Methods

Chemicals and Reagents

Lead acetate trihydrate ($\text{Pb}(\text{CH}_3\text{COO})_2 \cdot 3\text{H}_2\text{O}$), disodium edetate (EDTA), methanol, and all other analytical-grade reagents were purchased from Sigma-Aldrich (USA). ELISA kits for tumor necrosis factor-alpha (TNF- α) and interleukin-10 (IL-10) were obtained from Elabscience Biotechnology Co., Ltd. (USA). All solutions were freshly prepared using double-distilled water, and glassware was acid-washed before use to prevent trace metal contamination.

Experimental Animals

A total of Thirty-five (35) healthy adult Wistar rats, weighing 150–200 g, were used for this study. The animals were procured from Bashir Research Laboratory, Ilorin, Nigeria, and acclimatized for 7 days under controlled environmental conditions (temperature 22 ± 2 °C; relative humidity $55 \pm 5\%$; 12-h light/dark cycle). Rats were housed in standard plastic cages with stainless-steel covers and provided ad libitum access to commercial rat pellets and clean water.

All experimental procedures complied with international standards for laboratory animal care. Ethical clearance was obtained from the Kwara State University Centre for Research and Development Ethics Committee, with reference number KWASU/CR&D/REA/2025/0121. All efforts were made to minimize pain and distress throughout the study.

Plant Material and Extract Preparation

Fresh pods of *Aframomum melegueta* (alligator pepper) were purchased from Oja Oba Market, Ilorin, Kwara State, Nigeria. Botanical authentication was conducted at the Department of Plant Biology, University of Ilorin, where a voucher specimen was deposited under the number UILH/001/1854/2025.

The seeds were manually separated, washed, and air-dried at ambient temperature before being pulverized into fine powder. Extraction was performed via cold maceration: 500 g of the powder was soaked in 70% methanol (1:5 w/v) for 72 h with intermittent agitation. The filtrate obtained through Whatman No. 1 paper was

concentrated using a rotary evaporator at 45 °C and air-dried to a semi-solid residue. The extract was preserved in airtight containers at 4 °C until use.

For dosing, the extract was freshly reconstituted in olive oil to obtain concentrations of 200 mg/kg (low dose) and 400 mg/kg (high dose) body weight. All oral administrations were performed using a calibrated gastric gavage cannula.

Experimental Design

The study employed a randomized, controlled experimental design lasting 14 days of lead exposure followed by 14 days of treatment (subacute phase). Thirty-Five (35) rats were randomly assigned into eight groups (n=7) as follows:

Group 1 (Normal Control): Received distilled water orally for 28 consecutive days and served as the untreated baseline control.

Group 2 (Untreated Lead-Exposed): Received lead acetate at a dose of 100 mg/kg body weight daily through gastric gavage for 14 days without any therapeutic intervention (Momodu and Idemudia, 2024). This dose and duration are well established, which was also confirmed in one of the pilot studies I conducted to significantly elevate hepatic and renal biomarkers, trigger oxidative stress, inflammatory cytokines, and induce notable histoarchitectural lesions in liver and kidney tissues.

Group 3 Lead acetate induced rats received methanolic extract of *A. melegueta* (200mg/kg/bwt) for 14 days (Mohamed *et al.*, 2020; Morakinyo *et al.*, 2020).

Group 4 Lead acetate induced rats received methanolic extract of *A. melegueta* (400mg/kg/bwt) (Mohamed *et al.*, 2020; Morakinyo *et al.*, 2020).

Group 5 Lead acetate induced rats received calcium disodium ethylene diamine tetra acetic acid (50 mg/kg/d) for 5 days (Sánchez-Fructuoso *et al.*, 2002).

Body weights and clinical behaviors were monitored daily. At the end of the experimental period, animals were anesthetized, blood was collected via cardiac for analysis.

Cytokine Determination

Serum concentrations of TNF- α and IL-10 were determined using sandwich ELISA kits (Elabscience Biotechnology Co., USA), following the manufacturer's protocol. Optical density was measured at 450 nm using a microplate reader (Bio-Rad, USA). Cytokine concentrations (pg/mL) were calculated from standard calibration curves generated for each assay. All samples and standards were analyzed

in duplicate to ensure reproducibility. Results were expressed as mean \pm SEM.

Statistical Analysis

All data were presented as mean \pm standard error of mean (SEM). Statistical differences between groups were compared using student's t-test followed by Tukey's post hoc for multiple comparisons. Statistical significance was accepted at $p < 0.05$.

Table 1: Quantitative phytochemical composition of *Aframomum melegueta* seeds (Mean \pm SEM, n = 3)

ELEMENT	CONCENTRATION (PPM)
GLYCOSIDES	73.36 \pm 0.1
TANNIN	3.09 \pm 0.1
STEROIDS	21.15 \pm 0.1
TRITEPENOIDS	11.63 \pm 0.4
SAPONIN	108.8 \pm 1.6

Values are expressed as mean \pm standard error of the mean (SEM), based on triplicate determinations (n = 3). ppm = parts per million.

Table 2: Proximate composition of *Aframomum melegueta* seeds (Mean \pm SEM, n = 2)

PARAMETER	CONCENTRATION
% CRUDE PROTEIN	3.45 \pm 0.16
% CRUDE LIPID	11.93 \pm 0.07
% MOISTURE CONTENT	13.55 \pm 0.08
% TOTAL ASH	2.22 \pm 0.23
% CRUDE FIBRE	34.48 \pm 0.05
% CARBOHYDRATE	34.42 \pm 0.02

Values are expressed as mean \pm standard error of the mean (SEM), based on triplicate determinations (n = 3). ppm = parts per million.

Table 3: Elemental composition of *Aframomum melegueta* seeds (Mean ± SEM, n = 3)

ELEMENT	CONCENTRATION (cmol/kg)
Sodium (Na)	2.36±0.22
Magnesium (Mg)	5.80±0.13
Nickel (Ni)	0.05±0.01
Calcium (Ca)	0.59±0.02
Iron (Fe)	0.32±0.18
Zinc (Zn)	0.16±0.00
Potassium (K)	6.85±0.13
Copper (Cu)	0.08±0.02
Manganese (Mn)	0.17±0.03

Values are expressed as mean ± standard error of the mean (SEM), based on triplicate determinations (n = 3). cmol/kg = centimole per kilogram.

Table 4: Comparison of TNF- and IL-10 between Negative control group and group exposed with 100mg/kg bw of Pb

Parameters	Negative control	Pb-untreated	p-values
TNF-α (µg/L)	58.53 ± 3.82	95.29 ± 4.17	0.000*
IL-10 (µg/L)	45.88 ± 1.18	28.63 ± 2.72	0.000*

The values are mean ± standard deviation, Student t-test was used to compare the means and value of significance was set and p = 0.005. *=significant, Pb=Lead

Table 5: Comparison of TNF- and IL-10 between 100mg/kg bw of Pb and group exposed with 100mg/kg bw of Pb + treated with 200mg/kg bw *A.Melegueta*

Parameters	Pb-untreated	Pb+ 200mg/kg <i>A.Melegueta</i>	p-value
TNF-α (µg/L)	95.29 ± 4.17	61.57 ± 3.57	0.000
IL-10 (µg/L)	28.63 ± 2.72	49.80 ± 3.57	0.000

The values are mean ± standard deviation, Student t-test was used to compare the means and value of significance was set at p = 0.005. *=significant, Pb=Lead

Table 6: Comparison of TNF- and IL-10 between 100mg/kg bw of Pb and group exposed with 100mg/kg bw of Pb + treated with 400mg/kg bw *A.Melegueta*

Parameters	Pb-untreated	Pb+ 400mg/kg <i>A.Melegueta</i>	p-value
TNF- α ($\mu\text{g/L}$)	95.29 \pm 4.17	53.82 \pm 2.06	0.000
IL-10 ($\mu\text{g/L}$)	28.63 \pm 2.72	47.84 \pm 2.64	0.000

The values are mean \pm standard deviation, Student t-test was used to compare the means and value of significance was set at p = 0.005,

Table 7: Comparison of TNF- and IL-10 between 100mg/kg bw of Pb and group exposed with 100mg/kg bw of Pb + treated with 50mg/kg bw Calcium disodium EDTA

Parameters	Pb-untreated	Pb +Calcium disodium EDTA	P-value
TNF- α ($\mu\text{g/L}$)	95.29 \pm 4.17	73.53 \pm 0.00	0.000
IL-10 ($\mu\text{g/L}$)	28.63 \pm 2.72	27.45 \pm 2.18	0.000

The values are mean \pm standard deviation, Student t-test was used to compare the means and value of significance was set at p = 0.005,

Table 8: Comparison of TNF- and IL-10 between Pb + treated with 50mg/kg bw Calcium disodium EDTA and Pb + 400mg/kg *A.Melegueta*

Parameters	Pb +Calcium disodium EDTA	Pb+ 400mg/kg <i>A.Melegueta</i>	P-value
TNF- α ($\mu\text{g/L}$)	73.53 \pm 0.00	53.82 \pm 2.06	0.000*
IL-10 ($\mu\text{g/L}$)	27.45 \pm 2.18	47.84 \pm 2.64	0.000*

The values are mean \pm standard deviation, Student t-test was used to compare the means and value of significance was set at p = 0.005.

Table 9: Comparison of TNF- and IL-10 between Pb + treated with 50mg/kg bw Calcium disodium EDTA and Pb + 200mg/kg *A.Melegueta*

Parameters	Pb+ calcium disodium EDTA	Pb+ 200mg/kg <i>A.Melegueta</i>	p-values
TNF- α ($\mu\text{g/L}$)	73.53 \pm 0.00	61.57 \pm 3.57	0.002
IL-10 ($\mu\text{g/L}$)	27.45 \pm 2.18	49.80 \pm 3.57	0.000

The values are mean \pm standard deviation, Student t-test was used to compare the means and value of significance was set at p = 0.005

Results and Discussion

The phytochemical analysis of *Aframomum melegueta* seeds revealed the presence of glycosides (73.36 ± 0.1 ppm), steroids (21.15 ± 0.1 ppm), triterpenoids (11.63 ± 0.4 ppm), saponins (108.8 ± 1.6 ppm), and tannins (3.09 ± 0.1 ppm) (Table 1). These bioactive compounds, particularly saponins, glycosides, and triterpenoids, are known for their antioxidant, anti-inflammatory, and immunomodulatory properties and may contribute to the plant's therapeutic potential (Adegboye *et al.*, 2022; Mensah *et al.*, 2023).

The proximate composition indicated high carbohydrate ($34.42 \pm 0.02\%$) and crude fiber ($34.48 \pm 0.05\%$) content, moderate lipid levels ($11.93 \pm 0.07\%$), and low protein content ($3.45 \pm 0.16\%$) (Table 2). Moisture content was $13.55 \pm 0.08\%$, while total ash content was $2.22 \pm 0.23\%$, indicating the presence of minerals. High fiber and carbohydrate contents suggest a potential role in nutritional supplementation and metabolic regulation.

Elemental analysis revealed measurable concentrations of essential minerals, including potassium (6.85 ± 0.13 cmol/kg), magnesium (5.80 ± 0.13 cmol/kg), sodium (2.36 ± 0.22 cmol/kg), calcium (0.59 ± 0.02 cmol/kg), iron (0.32 ± 0.18 cmol/kg), and zinc (0.16 ± 0.00 cmol/kg) (Table 3). These minerals are critical for enzymatic function, antioxidant defense, and hematopoietic activity, which may underlie the observed protective effects against lead-induced toxicity.

Lead exposure (100 mg/kg bw) induced a marked inflammatory response, as evidenced by a significant increase in TNF- α (95.29 ± 4.17 $\mu\text{g/L}$) compared to negative control (58.53 ± 3.82 $\mu\text{g/L}$, $p = 0.000$) and a concomitant decrease in IL-10 (28.63 ± 2.72 $\mu\text{g/L}$ vs 45.88 ± 1.18 $\mu\text{g/L}$, $p = 0.000$) (Table 4). These results confirm that lead induces systemic inflammation and suppresses anti-inflammatory cytokine signaling, consistent with previous reports (Fenga *et al.*, 2017; Allameh *et al.*, 2023).

Administration of *A. melegueta* extract at both 200 mg/kg bw and 400 mg/kg bw significantly mitigated lead-induced cytokine dysregulation.

Treatment with 200 mg/kg bw resulted in a decrease in TNF- α to 61.57 ± 3.57 $\mu\text{g/L}$ and an increase in IL-10 to 49.80 ± 3.57 $\mu\text{g/L}$ ($p = 0.000$ for both) (Table 5). A higher dose of 400 mg/kg bw further reduced TNF- α to 53.82 ± 2.06 $\mu\text{g/L}$ and increased IL-10 to 47.84 ± 2.64 $\mu\text{g/L}$ ($p = 0.000$ for both) (Table 6). These findings suggest a dose-dependent immunomodulatory effect, with the high dose exerting slightly stronger TNF- α suppression.

Treatment with 50 mg/kg bw calcium disodium EDTA significantly reduced TNF- α (73.53 ± 0.00 $\mu\text{g/L}$) but failed to restore IL-10 levels (27.45 ± 2.18 $\mu\text{g/L}$) (Table 7), highlighting that chelation therapy effectively removes lead but does not correct the inflammatory imbalance. When compared directly with the high-dose extract, *A. melegueta* produced significantly lower TNF- α and higher IL-10 than EDTA ($p = 0.000$) (Table 8). Similarly, at the 200 mg/kg dose, the extract achieved better IL-10 restoration ($p = 0.000$) and TNF- α reduction ($p = 0.002$) than EDTA (Table 9).

These observations indicate that *A. melegueta* not only attenuates pro-inflammatory cytokine expression but also enhances anti-inflammatory responses, providing a dual mechanism of protection that chelation therapy alone lacks.

Conclusion

This study demonstrates that lead exposure induces a profound inflammatory and immunosuppressive state in Wistar rats, as evidenced by increased TNF- α and reduced IL-10 concentrations. Administration of *Aframomum melegueta* extract significantly mitigated these immune alterations, with the 400 mg/kg dose showing the greatest therapeutic benefit. The extract effectively attenuated pro-inflammatory cytokine elevation while enhancing anti-inflammatory cytokine activity, producing outcomes comparable to standard chelation with calcium disodium EDTA. These findings highlight the potential of *A. melegueta* as a complementary therapeutic agent for managing lead-induced immunotoxicity.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Authors' Contributions

WOG conceived and designed the study, carried out the analysis and manuscript writing. AAI supervised the work. MOB and AA carried out statistical analysis and manuscript writing

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