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Full Length Research Article

EXPRESSION OF IFN-γ AND MPO IN BENZENE-INDUCED BONE MARROW TOXICITY IN ALBINO RATS TREATED WITH A BI-HERBAL MIXTURE OF *PICRALIMA NITIDA* AND *CYMBOPOGON CITRATUS*

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ABSTRACT
Benzene is a common environmental pollutant and industrial chemical that poses serious health risks. Its toxicity is partly mediated through the activation of inflammatory and oxidative pathways. This study aimed to determine the effects of a dual-blend formula of *P. nitida* and *C. citratus* aqueous leaf extracts on IFN-γ and MPO gene expression in bone marrow-induced toxicity in Albino Wistar rats. Sixty Wistar rats were assigned to groups A (control), B (benzene), C (cyclophosphamide), D (100mg/kg of extract), E (200mg/kg of extract), and F (400mg/kg of extract). Bone marrow samples were collected, and mRNA levels of IFN-γ and MPO were assessed using PCR. The resulting data were analysed with GraphPad Prism software. The results indicated that group B had a higher expression of IFN-γ when compared to the control group ($p<0.05$). Treatment groups significantly and progressively reduced the expression of IFN-γ, with the lowest expression observed in the highest concentration of the extract ($p<0.05$). Group B had a significantly higher expression of MPO when compared to the control group ($p<0.05$). Treatment groups had no significant change in MPO expression when compared to group B ($p>0.05$). Conclusively, benzene increased IFN-γ and MPO, and the extract reduced IFN-γ expression with no changes in MPO expression.

Keywords: Aqueous, Benzene, Bone marrow, Expression, Inflammatory, Oxidative.

INTRODUCTION

Benzene is a common industrial chemical, commonly employed in the manufacture of plastics, resins, rubber, and petroleum products, among others (Choi *et al*., 2019). Beyond its industrial applications, benzene also has a high affinity with the environment as a pollutant. Benzene is released into the environment in exhaust from motor vehicles and cigarette smoke, among others (Ekpenyong and Asuquo, 2017). Despite its presence in the environment and industries, benzene has been widely recognised as a toxic and carcinogenic compound (Loomis *et al*., 2017). High exposure or chronic exposure to benzene has been observed to have negative effects on the bone and peripheral blood cells in the environment. The exposure has been associated with a reduction in the level of red blood cells (RBCs) and platelets and an increase in white blood cells (WBCs) (Elkhalifa *et al*., 2025). The toxicity of benzene arises primarily from its metabolic activation in the liver. Once ingested or inhaled, benzene is converted into reactive intermediates such as benzene oxide, phenol, hydroquinone, and catechol. These metabolites are then transported to the bone marrow, where they interfere with hematopoietic stem cells and progenitor cells (Qin *et al*., 2025). Interaction between benzene metabolites and cellular macromolecules leads to the generation of reactive oxygen species (ROS), lipid peroxidation, and DNA damage (D'Souza *et al*., 2024). ROS are highly reactive molecules capable of oxidising proteins, lipids, and nucleic acids, thereby disrupting normal cellular function and triggering programmed cell death or necrosis (Juan *et al*., 2021). The accumulation of oxidative damage is important to the toxic effects of benzene, showing the role of oxidative stress as a key mediator in the impairment of blood cell production (Martínez-Rodríguez *et al*., 2018).

Inflammatory processes also play a role in the response to benzene exposure. Benzene stimulates the production of pro-inflammatory cytokines, which act as signalling molecules to coordinate immune responses. Among these cytokines, Interferon-gamma (IFN-γ) has been noted as a key mediator of immune activation and inflammation (Guo *et al*., 2021). IFN-γ is primarily secreted by T-helper 1 (Th1) cells, cytotoxic CD8+ T cells, and natural killer (NK) cells. It regulates the activation and proliferation of macrophages and other immune cells, enhancing their pathogen-killing capacity (Rodrigues *et al*., 2021). While IFN-γ is essential for host defence under normal circumstances, its overproduction in response to toxic agents like benzene can amplify inflammatory reactions, worsen bone marrow suppression, and compromise haematopoiesis (De Benedetti *et al*., 2021). Closely associated with the inflammatory response is Myeloperoxidase (MPO), an enzyme abundantly present in neutrophils and monocytes. MPO catalyses the conversion of hydrogen peroxide and chloride ions into hypochlorous acid, a potent reactive oxidant. This enzyme is necessary for killing microbes and innate immunity (Andres *et al*., 2022). However, excessive MPO activity contributes to oxidative stress, increasing tissue injury and inflammation (Chen *et al*., 2020). In toxicology, MPO is commonly measured as a biomarker to evaluate oxidative damage and inflammatory activation in various tissues, including the bone marrow (Khan *et al*., 2018). The relationship between inflammation and oxidative stress is important in getting a proper understanding of benzene toxicity. IFN-γ-driven immune activation recruits and stimulates neutrophils, which then release MPO, generating reactive oxygen species that can damage haematopoietic cells (Imran *et al*., 2025).

Given the adverse effects of benzene, there is growing interest in discovering treatments that can reduce oxidative stress and inflammatory responses. Medicinal plants with antioxidant, anti-inflammatory, and immunomodulatory properties have been identified as suitable for protective or therapeutic use (Nwozo *et al*., 2023). *Picralima nitida*, commonly known as "Akuamma," is a tropical plant traditionally used in West African medicine for managing pain, fever, inflammation, and gastrointestinal disorders (Araloyin *et al*., 2022). Phytochemical investigations of *P. nitida* have revealed a rich composition of bioactive compounds, including indole alkaloids, flavonoids, saponins, tannins, and phenolic acids. These constituents are known to cause antioxidant effects by scavenging free radicals, reducing lipid peroxidation, and enhancing endogenous antioxidant enzyme activities (Ilenowa *et al*., 2024). Also, *P. nitida* exhibits cytoprotective properties, helping to stabilise cellular membranes and reduce tissue injury (Obazelu and Williams, 2024). Previous studies have demonstrated that extracts from various parts of the plant, such as the seeds, bark, and leaves, can modulate oxidative stress and inflammation (Ajayi *et al*., 2021; Ngozika *et al*., 2024). Similarly, *Cymbopogon citratus*, commonly referred to as lemongrass, is a widely studied aromatic plant known for its diverse pharmacological activities (Oladeji *et al*., 2019). Traditionally used as a cooking herb and herbal remedy, *C. citratus* has shown anti-inflammatory, antioxidant and antimicrobial properties. The plant's leaves are rich in bioactive compounds such as citral, limonene, flavonoids, and phenolic acids, which contribute to its ability to reduce oxidative stress and modulate immune responses (Aćimović *et al*., 2019; Onyedikachi *et al*., 2021). Although these plants have demonstrated antioxidant, anti-inflammatory, and immune-modulating properties, their combined effects on MPO and IFN-γ are not well established.

MATERIALS AND METHODS

Plant Identification

The foliage from both plants was harvested on August 23, 2024, in a community located within the Ovia Northeast region. The identification and authentication of the leaves were carried out by Dr A.O. Akinnibosun from the Department of Plant Biology and Biotechnology at the University of Benin.

Plant Processing

The process started with stripping off damaged leaves from the batch. After that, they got washed well, then drained out. For better grinding, the leaves sat shaded to dry in open air for two weeks straight. Then, a hot air oven dried them further at 50°C for one full day. This made sure the leaves got dry enough before being ground. Grinding was done using a fast-spinning grinder, specifically a 1000A model.

Extract Preparation

One and a half kilos of ground plant material were combined with fifteen litres of clean water, left to soak while being stirred consistently for a full day. After that, the liquid was pushed through a fine filter (Whatman type Nitro cellulose 45, hole size 0.45 micrometres) to trap solids. Once filtered, the fluid was concentrated by heating gently in a water bath held at 37ºC. Then, it was stored in a tightly sealed jar, kept cool in the fridge till needed.

Benzene Preparation

A benzene solution was prepared by mixing distilled water, 2-propanol, and benzene in a 1:5:5 ratio. This means that for every 1-part benzene, 5 parts 2-propanol and 5 parts distilled water were used.

Preparation of Cyclophosphamide

To make the cyclophosphamide solution, 500 mg of the powdered drug was dissolved in 25 ml of distilled water.

Experimental Animals

Sixty grown male rats, all in good health, were obtained and then moved into their on-site animal house. These animals stayed inside a properly aired section within the anatomy department facility. Food and water were available nonstop under a daily cycle of 12 hours lit, followed by 12 hours of darkness. Before testing, they spent fourteen days adjusting to the surroundings.

Ethical approval

Ethical clearance for the use of animals in this study was obtained from the Committee on Animal Research Ethics under the Ministry of Health, Benin City, Edo State. The official approval, reference number HA/737/24/D/0708328, was issued on July 31, 2024.

Research Design

For the 28-day experiment, rats were divided into six groups with different treatments. The control group, Group A, was given only food and water. Groups B through E all received a 0.2 ml dose of benzene solution every 48 hours via intraperitoneal injection. Group B was the benzene-only group, while Group C also received a 0.3 ml dose of a cyclophosphamide solution every 48 hours. In contrast, Groups D and E were treated daily with a dual blend of the extract. Group D received a low dose of 0.15 ml (100 mg/kg), while Group E received a higher dose of 0.3 ml (200 mg/kg), both administered orally using a gavage tube. Finally, Group F was administered 0.2 ml of benzene intraperitoneally every 48 hours for 28 days and received 0.6 ml of a 400 mg/kg dose of the leaf extract combination orally each day via gavage.

Sacrifice of Animals and Collection of Samples

Rats underwent a thorough physical examination. To ensure minimal pain, chloroform was used to induce anaesthesia. Carefully, the thigh bone was sliced open along its entire span, exposing the inner marrow cavity. Using clean forceps, the soft marrow material was pulled out slowly and steadily, then dropped into Eppendorf tubes filled with Trizol to preserve it for later genetic testing.

Molecular Analysis

Total RNA was isolated from rat bone marrow samples using the Quick-RNA MiniPrep™ Kit (Zymo Research), and residual DNA contaminants were removed through DNase I (NEB, Cat: M0303S) treatment. The RNA concentration and purity were determined spectrophotometrically at 260 nm and 280 nm using an A&E Spectrophotometer (A&E Lab, UK). One microgram (1 µg) of DNA-free RNA was reverse-transcribed into complementary DNA (cDNA) using the ProtoScript II First-Strand cDNA Synthesis Kit (New England BioLabs) following a three-step thermal protocol: 65 °C for 5 min, 42 °C for 1 h, and 80 °C for 5 min. Polymerase Chain Reaction (PCR) amplification of IFN-γ and MPO genes was carried out using OneTaq® 2X Master Mix (NEB) in a total reaction volume of 25 µl containing cDNA, gene-specific forward and reverse primers, and Ready Mix Taq PCR master mix. The PCR conditions consisted of an initial denaturation at 95 °C for 5 min, followed by 30 cycles of denaturation at 95 °C for 30 s, annealing for 30 s, and

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extension at 72 °C for 60 s, with a final extension at 72 °C for 10 min. Amplified products were separated on a 1.0% agarose gel, and the relative expression levels were normalised using Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) as the housekeeping gene. Band intensities were quantified using *ImageJ* software (Elekofehinti *et al*., 2020). The primer sequences used were as follows:

IFN-γ
Forward: GTGAACAACCCACAGATCCA
Reverse: GAATCAGCACCGACTCCTTT
MPO
Forward: GGCATCACTACCGTGTCTAAG
Reverse: CCAGGAAGCCAGATTCAGTT
GAPDH
Forward: AGACAGCCGCATCTTCTTGT
Reverse: CTTGCCGTGGGTAGAGTCAT

Statistical Analysis
GraphPad Prism software was used to analyse the data and generate bar charts depicting mRNA gene expression. The result was presented in mean and standard deviation. Statistical significance was represented with * when p<0.05, ** when p<0.01 and *** when p<0.001.

RESULTS
Figure 1 illustrates the mRNA expression of the interferon gamma (IFN-γ) gene across six experimental groups. An internal control gene, glyceraldehyde-3-phosphate dehydrogenase (GADPH), was used to ensure accurate comparisons between samples. The study included a control group (A) and five treatment groups: one exposed to benzene only (B), another to benzene plus cyclophosphamide (C), and three groups (D, E, and F) treated with benzene and increasing doses (100, 200, and 400 mg/kg) of a dual-blend extract from *Picralima nitida* and *Cymbopogon citratus*. The results show that groups B and C had a higher expression of IFN-γ when compared to the control group (p<0.05). Groups D, E and F significantly and progressively reduced the expression of IFN-γ, with the lowest expression observed in the highest concentration of the extract (p<0.05).

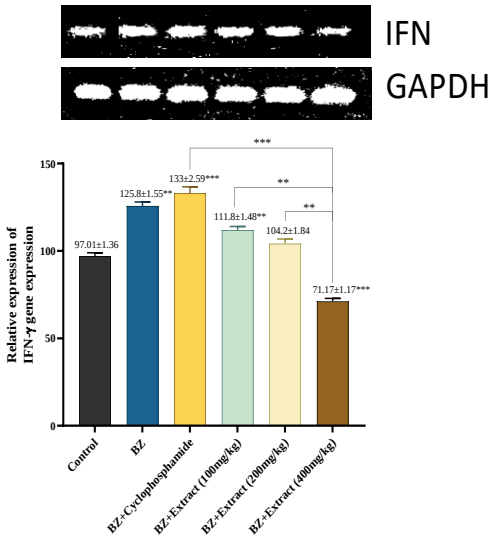

Figure 1: mRNA expression of the interferon gamma (IFN-γ) gene. Figure 1 displays the mRNA expression levels of interferon gamma (IFN-γ) for all experimental groups. The error bars on the graph represent the standard error of the mean (mean ± SEM). Statistical significance represented by (*p<0.05, **p<0.01, ***p<0.001). The group treated with benzene is labelled as BZ.

Figure 2 illustrates the mRNA expression of the myeloperoxidase (MPO) gene across six experimental groups. An internal control gene, glyceraldehyde-3-phosphate dehydrogenase (GADPH), was used to ensure accurate comparisons between samples. The study included a control group (A) and five treatment groups: one exposed to benzene only (B), another to benzene plus cyclophosphamide (C), and three groups (D, E, and F) treated with benzene and increasing doses (100, 200, and 400 mg/kg) of a dual-blend extract from *Picralima nitida* and *Cymbopogon citratus*. The results show that groups B and C had a significantly higher expression of MPO when compared to the control group (p<0.05). Groups D, E and F had no significant change in MPO expression when compared to group B (p>0.05).

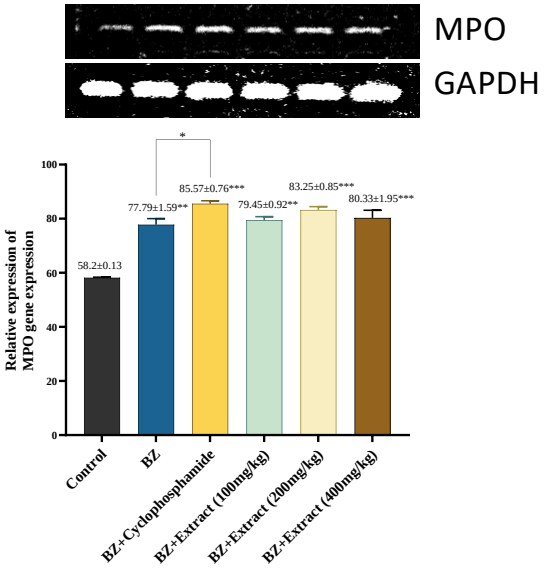

Figure 2 displays the mRNA expression levels of myeloperoxidase (MPO) for all experimental groups. The error bars on the graph represent the standard error of the mean (mean ± SEM). Statistical significance represented by (*p<0.05, **p<0.01, ***p<0.001). The group treated with benzene is labelled as BZ.

DISCUSSION
Myeloperoxidase (MPO) and interferon-gamma (IFN-γ) are important biomarkers that reflect inflammatory and immune responses associated with such toxicity (Khan *et al*., 2018; Abdel Aziz *et al*., 2021). Assessing their expression provides insight into the mechanisms of benzene-induced damage and the possible protective effects of therapeutic agents. Exposure to benzene alone significantly increased the mRNA expression of interferon gamma (IFN-γ) compared to the control group, which points towards the fact that benzene triggers a strong inflammatory response. IFN-γ is a key cytokine produced by activated T cells and natural killer cells (Mah and Cooper, 2016), and its upregulation

suggests activation of the immune system in response to cellular stress and damage caused by benzene. Benzene and some of its metabolites are known to generate reactive oxygen species (ROS) in the bone marrow, causing oxidative stress, DNA damage, and apoptosis in haematopoietic cells (Elsayed, 2015). These injuries can stimulate immune cells to release IFN-γ as part of a compensatory response to tissue damage (Minciullo *et al*., 2014). This finding is in agreement with several studies that have reported an increased serum level of proinflammatory cytokines interleukin (IL-6, IL-8, tumour necrosis factor (TNF)-α, interferon (IFN)-γ, and IFNB1) or increased expression in their corresponding genes, even at low levels of benzene exposure. These proinflammatory cytokines induce blood vessels to become more permeable, recruit other immune cells such as neutrophils, basophils and T-cells to sites of inflammation, and raise the temperature in infected tissue (Dutta *et al*., 2013; Elango *et al*., 2013; Moro *et al*., 2015; Jørgensen *et al*., 2018; Guo *et al*., 2019; Samadi *et al*., 2019). In the cyclophosphamide-treated group, IFN-γ expression was even higher than in the group treated with only benzene. Cyclophosphamide has been proven to be a cytotoxic agent that suppresses bone marrow function and kills rapidly dividing cells, which can enhance tissue injury and trigger strong immune activation (Ahlmann and Hempel, 2016). The combined effect of benzene and cyclophosphamide likely caused an amplified and possibly synergistic inflammatory response, explaining the increased IFN-γ expression. However, the study by Kim *et al*. (2021) showed that cyclophosphamide reduced IFN-γ in mice. Treatment with the dual herbal extract of *Picralima nitida* and *Cymbopogon citratus* significantly reduced IFN-γ expression in a manner that was indirectly proportional to each other, with the lowest levels of IFN-γ observed at the highest dose of the extract. This suggests that the herbal formulation has strong anti-inflammatory and immunomodulatory effects (Otu-Boakye *et al*., 2024; Iwo *et al*., 2025). The phytochemicals found in *Picralima nitida*, such as alkaloids, can inhibit inflammatory signaling pathways (Li *et al*., 2020; Liu *et al*., 2020). Similarly, *Cymbopogon citratus* contains flavonoids and essential oils that are known to suppress pro-inflammatory cytokine release and reduce ROS production (Katsukawa *et al*., 2010). By lowering oxidative stress, these compounds may prevent the overactivation of immune cells and reduce IFN-γ expression. The dose-dependent decrease in IFN-γ suggests that higher concentrations of the extract provided greater protective effects, possibly by both reducing benzene-induced oxidative damage and directly modulating immune cell activity. These findings are consistent with previous studies showing that medicinal plant extracts can reduce inflammatory molecules in models of chemical-induced toxicity (Obazelu and Faluyi, 2023).

Myeloperoxidase (MPO) expression was significantly increased at the mRNA level in the group exposed to benzene alone compared to the control, suggesting activation of neutrophil-driven oxidative pathways in response to chemical-induced toxicity. MPO is an enzyme released by activated neutrophils and helps in generating reactive oxygen species (ROS) to combat pathogens and damaged cells (Aratani, 2018). The upregulation of MPO suggests that benzene exposure induced oxidative stress in the bone marrow, promoting neutrophil activation and inflammatory responses. These findings are consistent with earlier reports on benzene metabolism, which indicate that benzene is initially activated in the liver by phase I enzymes, particularly cytochrome P450 2E1 (CYP2E1), to form intermediate metabolites such as phenol, hydroquinone, catechol, and 1,2,4-benzenetriol (Dougherty *et al*., 2008). These metabolites can go to peripheral tissues and even reach the bone marrow, where MPO catalyses their conversion into highly reactive quinones like 1,4-benzoquinone, which can generate excessive ROS (Zhang *et al*., 2007). The increased MPO expression observed in this study therefore supports the established role of MPO in the bioactivation of benzene metabolites and the amplification of oxidative damage in haematopoietic tissues. Furthermore, previous studies have demonstrated that genetic variations in enzymes involved in benzene metabolism, including polymorphisms in CYP2E1 and MPO genes, can influence enzyme activity and susceptibility to benzene-induced toxicity (Qu *et al*., 2005; Dougherty *et al*., 2008). In particular, the MPO 463G>A polymorphism has been associated with reduced MPO activity and a lower risk of acute leukaemia due to diminished activation of toxic benzene metabolites (Kiyohara *et al*., 2005; Zhang *et al*., 2007). In contrast, the increased MPO expression observed in the present study suggests enhanced enzymatic activity and greater conversion of benzene metabolites into reactive intermediates, thereby promoting oxidative stress and inflammatory responses in the bone marrow. In the cyclophosphamide-treated group, MPO expression was also significantly elevated, reflecting the cytotoxic effects of cyclophosphamide on haematopoietic cells. Cyclophosphamide induces DNA damage and apoptosis in rapidly dividing bone marrow cells (Ahlmann and Hempel, 2016), which can stimulate neutrophil activation and further increase MPO expression as part of the body's response to tissue injury and cellular stress. This finding is in line with the study of Arafa (2009), who also noted that cyclophosphamide can cause an elevation in MPO activity. The combined exposure to benzene and cyclophosphamide likely amplified oxidative stress, accounting for the highest MPO expression observed in these groups. Treatment with the dual herbal extract of *Picralima nitida* and *Cymbopogon citratus* did not significantly alter MPO expression compared to the benzene-only group. This suggests that while the extract effectively modulated inflammatory cytokines such as IFN-γ, it may have limited direct impact on neutrophil-derived MPO activity under the conditions of this study. The phytochemicals in the herbal blend, including alkaloids and flavonoids, are known for antioxidant and anti-inflammatory properties, but the persistence of MPO upregulation could indicate that neutrophil activation and oxidative stress induced by benzene were not fully suppressed by the extract at the tested doses. The lack of a significant reduction in MPO expression with the herbal treatment suggests that additional or longer-term interventions may be required to fully mitigate oxidative stress.

Public Health Implications

The increase in IFN-γ and MPO following benzene administration shows the ability of benzene to induce inflammatory and immune dysregulation. This shows the need to monitor benzene as a compound in occupational and environmental settings. Also, the combined plant extract was able to reverse the effect of benzene on IFN-γ revealed potential for plant-based immunomodulatory agents that could reverse the inflammatory effects of toxic exposures in low and middle-income countries.

Limitation of Study

1. Studies on animal models may not fully show the complexity of benzene exposure and immune

responses in humans, thereby limiting direct generalisation of the findings to human populations.

2. Only IFN-γ and MPO gene expression were evaluated, which may not show the full inflammatory and immunotoxic effects induced by benzene exposure.

Conclusion

Benzene exposure in albino rats significantly increased the expression of inflammatory genes IFN-γ and MPO, indicating activation of immune and oxidative pathways. The bi-herbal mixture of *Picralima nitida* and *Cymbopogon citratus* effectively reduced IFN-γ expression in a dose-dependent manner, demonstrating anti-inflammatory effects, but had no significant effect on MPO.

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