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Expression of AKT and PTEN genes in benzene-induced haematotoxicity bearing wistar rats treated with a dual-mixture of *Picralima nitida* and *Cymbopogon citratus* extract

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ABSTRACT

***Background*:** Recognizing the anti-inflammatory, antioxidant, and blood-boosting properties of *Picralima nitida* and *Cymbopogon citratus*, this study investigated if their combined aqueous extract could mitigate benzene-induced blood toxicity in rats. The study specifically analyzed changes in AKT and PTEN gene expression, which are key regulators of inflammatory and oxidative pathways, to understand the mechanism of potential protection.

***Methods*:** The study involved 60 male Wistar rats, divided into six groups, to evaluate the effect of a *Picralima nitida* and *Cymbopogon citratus* leaf extract blend on GSK3β and AMPK mRNA levels. The groups were: control (A), benzene (B), cyclophosphamide (C), and benzene with 100 mg/kg (D), 200 mg/kg (E), or 400 mg/kg (F) of the extract. PCR was used to measure gene expression, and GraphPad Prism was used for data analysis.

Results: Compared to group A, groups B, C, D, and E showed significantly higher levels of both AKT and PTEN mRNA. PTEN expression was also notably decreased in group F compared to group C, with group D exhibiting the highest PTEN expression overall ($p<0.05$).

Conclusion: The study revealed that the treatment significantly altered AKT and PTEN expression. To fully understand the therapeutic potential of this plant mixture in treating blood toxicity, long-term studies and clinical trials are necessary.

Keywords: Benzene, Cymbopogon citratus, Phosphatase tensin homolog gene, Picralima nitida, Protein kinase-B gene

1. INTRODUCTION

For centuries, various cultures have relied on herbal medicines for their therapeutic effects in treating numerous ailments, including blood disorders [1]. Historical records and ethnobotanical research emphasize the widespread use of plant-based treatments in traditional medicine, especially in regions with limited access to modern pharmaceuticals [2]. In recent years, interest in herbal remedies has resurged, largely due to increasing recognition of their potential health benefits and the perception that they have fewer side effects than synthetic drugs [3]. This renewed focus is particularly notable in the management of haematological conditions, where herbal extracts are being investigated for their role in promoting blood health and counteracting the toxic effects of environmental pollutants [2, 4]. Picralima nitida, a specie of the Picralima genus within the Apocynaceae family, is a tropical plant native to West Africa. It has been an integral part of traditional African medicine for centuries, with its seeds, bark, leaves, and roots utilized for various medicinal purposes. Traditionally, it has been used to treat fever, malaria, pain, and skin infections [5]. The plant is also recognized for its role in managing infections and gastrointestinal disorders, while its antioxidant properties help counteract oxidative stress associated with chronic diseases. Additionally, some studies suggest it may have anticancer potential by inhibiting cancer cell growth and promoting apoptosis. Ongoing research continues to validate these traditional applications, highlighting the cultural and therapeutic importance of *Picralima nitida* [6]. *Cymbopogon citratus*, commonly known as

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lemongrass, is a perennial plant from the Poaceae family, widely valued for its culinary, medicinal, and aromatic applications, especially in tropical regions [7]. Originally native to Southeast Asia, it is now globally recognized for its health benefits in both traditional and modern medicine [8]. Lemongrass is rich in bioactive compounds, including citral, limonene, myrcene, geraniol, and flavonoids such as luteolin and quercetin, which contribute to its diverse therapeutic properties [9]. Its phytochemical composition provides numerous medicinal benefits, including antimicrobial, anticancer, anti-inflammatory, and antioxidant effects, as well as analgesic properties, protection against cellular damage and oxidative stress, antifungal and antibacterial activities, and calming effects [10, 11]. The AKT gene, also referred to as Protein Kinase B (PKB), encodes a serine/threonine kinase that plays a crucial role in various cellular functions, including metabolism, growth, proliferation, survival, and angiogenesis [12]. Its activation is initiated through receptor tyrosine kinases (RTKs) or G protein-coupled receptors (GPCRs), which stimulate phosphoinositide 3-kinase (PI3K) to generate phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This process facilitates AKT recruitment to the plasma membrane, where phosphorylation occurs, triggering key cellular activities such as cell growth via mTOR regulation and enhanced cell survival through apoptosis inhibition [12]. In haematopoiesis, AKT signaling is essential for the survival of hematopoietic stem cells (HSCs) and the differentiation of progenitor cells into various blood cell lineages. AKT dysregulation has been linked to haematological disorders, including leukemia, making it a promising target for therapeutic interventions [13]. Additionally, benzene-induced haematotoxicity has been associated with altered gene expression, highlighting the need for further research on AKT's involvement in haematotoxicity. Investigating AKT's role, particularly in response to toxic agents like benzene, may uncover novel treatment strategies, including the potential of herbal extracts to support HSC survival and recovery from haematotoxic damage [14, 15]. The PTEN gene, a well-known tumor suppressor, encodes a phosphatase that plays a crucial role in regulating cellular processes such as growth, proliferation, and survival. It achieves this by dephosphorylating phosphoinositides, particularly phosphatidylinositol (3,4,5)-trisphosphate (PIP3), thereby counteracting the PI3K/AKT signaling pathway and preventing AKT activation [16]. This regulatory function is essential for maintaining normal cellular activity and preventing unchecked cell proliferation, which could lead to cancer [16]. PTEN mutations or loss are linked to various cancers, as they result in heightened AKT signaling and promote tumorigenesis [17]. In haematopoiesis, PTEN is integral to balancing hematopoietic stem cell (HSC) self-renewal and differentiation. Research indicates that PTEN depletion leads to increased HSC proliferation but disrupts proper differentiation, highlighting its critical role in maintaining hematopoietic homeostasis [18]. Benzene-induced haematotoxicity refers to the detrimental impact of benzene exposure on blood and bone marrow, leading to significant disruptions in haematopoiesis. As a widely used industrial solvent, benzene undergoes metabolic conversion into reactive metabolites that trigger oxidative stress and damage hematopoietic stem cells [19]. This damage results in reduced production of red and white blood cells as well as platelets, increasing the risk of various haematological disorders and potentially progressing to malignancies affecting the blood and blood-forming organs [20]. Investigating the genetic factors involved in haematotoxicity can aid in the development of therapeutic approaches using plant-based compounds to regulate cell signaling and mitigate the harmful effects of benzene-induced haematotoxicity [21]. Benzene is a toxic environmental pollutant known to cause severe haematotoxicity, leading to conditions such as anaemia, leukopenia, and leukaemia. Despite its widespread presence in industrial emissions, vehicle exhaust, and tobacco smoke, effective therapeutic interventions remain limited. While herbal remedies have been traditionally used to treat blood disorders, their molecular effects on gene expression in benzene toxicity remain largely unexplored. The protein kinase (AKT) and phosphatase and tensin homolog (PTEN) genes, which regulate cell survival and apoptosis, are key targets in understanding benzene-induced haematotoxicity. However, there is limited research on how bi-herbal formulations can modulate these genes to mitigate blood toxicity. Hence, this study is to determine the effect of the dual-mixture of *Picralima nitida* and *Cymbopogon citratus* aqueous leaf extract on protein kinase B gene (AKT) and phosphatase and tensin homolog gene (PTEN) gene expressions in benzene-induced haematotoxicity in albino *Wistar* rats and to explore the potential of the dual-mixture as a natural remedy to alleviate benzene-induced Haematotoxicity, thereby addressing a critical public health concern.

2. MATERIALS AND METHODS

2.1 Materials

2.2.1. Biological Materials

Cymbopogon citratus leaves, *Picralima nitida* leaves and albino rats.

2.1.2 Reagents and equipment

Sorvall biofuge, Hisense Microwave, Trizol, ZymoDNA extraction kit, TBE bufferystem, Electrophoresis system, UV-visible, Loading dye, Eppendorf Containers, EZ-Vision, Agarose, Germany eppendor mastercycler, Nuclease Free Water [22].

2.2 Methods

2.2.1. Study Population

Sixty healthy rats were obtained from the Anatomy department at the University of Benin in Benin City, Nigeria, and subsequently housed in their animal facility.

2.2.2. Identification of Cymbopogon citratus and Picralima nitida leaves

The leaves of both plants used in this study (*P. nitida* and *C citratus*) were gathered from a local community located in Ovia Northeast area on August 23, 2024. 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.

2.2.3. Processing of Cymbopogon citratus and Picralima nitida leaves

Leaves were first inspected, and any damaged or unhealthy ones were discarded. Following this, the leaves were washed thoroughly and allowed to drain. To prepare them for grinding, they were left open to dry for two weeks. Subsequently, the process of drying was moved to a hot air oven at 50°C (24 hours) to ensure complete dryness. Once dried, the leaves were ground using an industrial 1000A high-speed grinder. A precise weight of 250 grams from each leaf type was then measured for further use [22].

2.2.4. Preparation of Plants Extract

2.5 litres of distilled water were mixed with 250 grammes (250g) of the pulverised plant powder. After that, the combination was left to steep for a full day under carefully monitored storage conditions. Following the soaking time, the mixture was filtered with filter paper and any leftover residue was disposed of. After filtering, the liquid was made into a paste-like consistency using a water bath that was heated to 45°C. To create the necessary concentrations for administration, the resultant paste was precisely weighed and then dissolved in distilled water [22].

2.2.5. Animal Care

The rats were kept in a well-ventilated area within the University of Benin, Benin City's Department of Anatomy's animal holding facility. They were given food and water continuously during a 12-hour light/dark cycle. Before the experiment started, the rats were allowed to acclimatise for two weeks [22].

2.2.6. Ethical Consideration

The research received ethical clearance from the Ministry of Health's Committee Overseeing Animal Research Ethics in Benin City, Edo State. The July 31, 2024, approval reference number was HA/737/24/D/0708328.

2.2.7. Preparation of Benzene and Cyclophosphamide Drug Solution

2.2.7.1. Benzene solution

Distilled water, 2-propanol, and benzene were combined in a 1:5:5 ratio to create the benzene solution. This indicates that 5 parts distilled water, 5 parts 2-propanol, and 1 component benzene were combined. Over the course of 28 days, each animal weighing around 150g received a dosage of 0.2 ml of this solution every 48 hours [20].

2.2.7.2. Cyclophosphamide Drug Solution

To prepare the cyclophosphamide solution, 500 mg of the drug in powdered form was dissolved in 25 ml of water (distilled). Each rat in Group C, averaging 150 g in weight, received a dose of 0.3ml of this solution orally. The administration was carried out every 48 hours for a duration of 28 days [20].

2.2.8. Research Design

This study involved the use of sixty (60) mature Wistar rats, each weighing between 150-200 g, which were assigned into six groups (10 rats per group). Group A was the control group and that was given standardized feed and clean water only. Group B was exposed solely to benzene administered intraperitoneally. Group C received intraperitoneal benzene along with treatment using the standard drug solution, cyclophosphamide. Group D was administered intraperitoneal benzene and treated orally with a low dose of *C. citratus* and *P. nitida* leaves extract. Similarly, Group E received intraperitoneal benzene but was treated orally with a higher dose of the herbal formulation, while Group F was exposed to intraperitoneal benzene and received the highest dosage of the herbal preparation [20].

2.2.9. Administered Doses of bi herbal formulation of Cymbopogon citratus and Picralima nitida Leaves Extract

For the 28-day study, rats were assigned to three treatments. The control group (A) was provided with standard feed and water. The benzene group (B) received 0.2 ml of benzene solution through intraperitoneal injections

every 48 hours. The cyclophosphamide group (C) was given 0.2 ml benzene and 0.3 ml of 6 mg/ml cyclophosphamide, both via intraperitoneal injections every 48 hours. Group D was given 0.2 ml benzene solution by intraperitoneal administration at 48-hour interval for 4 weeks and subsequently treated orally with 0.15 ml of a 100 mg/kg of *C. citratus* and *P. nitida* leaf extracts, administered daily using a gavage tube. Group E was treated with 0.2 ml benzene solution by intraperitoneal administration at 48-hour interval for 4 weeks and given 0.3 ml of a 200 mg/kg of *C. citratus* and *P. nitida* leaf extracts orally each day via a gavage tube. Lastly, Group F received 0.2 ml benzene solution intraperitoneally at 48-hour intervals for 28 days and was administered 0.6 ml of a 400 mg/kg of *C. citratus* and *P. nitida* leaves extract orally on a daily basis through a gavage tube.

2.2.10. Sacrifice of Animals and Collection of Samples

Rats were carefully evaluated for their general physical condition. Anaesthetic induction was performed using chloroform to ensure minimal distress. The femur was then carefully accessed and opened along its length to expose the marrow cavity. Bone marrow was gently extracted using sterile forceps and transferred into Eppendorf tubes containing Trizol reagent to preserve the sample for subsequent molecular analysis.

2.2.11. Laboratory Analysis

Total RNA extraction from tissue samples was done using the Quick-RNA MiniPrep™ Kit. To eliminate DNA contamination, the samples underwent treatment with DNase I. RNA concentration was determined using spectrophotometry at 260 nm, and purity was assessed by the 260/280 nm ratio. To create cDNA, 1 µg of RNA was used with a cDNA synthesis kit based on ProtoScript II technology. This involved heating the RNA at 65°C for 5 minutes, then at 42°C for 1 hour, and finally at 80°C for 5 minutes. PCR was used to determine gene expression levels. Reactions were set up with a OneTaqR2X master mix and primers from Inqaba Biotec. The PCR protocol included an initial denaturation step, followed by 30 amplification cycles of denaturation, annealing, and extension. Amplified DNA was visualized on an agarose gel, and gene expression was normalized to GAPDH. The intensity of the bands on the gel was quantified using ImageJ software [23]. The primers used for amplification were as follows: AKT (Forward: AACACAGAAGACCAATACTC, Reverse: TTCGCCATCTACCACTAC), PTEN (Forward: CCCACCACAGCTAGAACTTATC, Reverse: CGTCCTTTCCCAGCTTTACA), and GAPDH (Forward: AGACAGCCGCATCTTCTTGT, Reverse: CTTGCCGTGGGTAGAGTCAT).

2.3. Statistical Analysis

GraphPad Prism software was used to analyze the data and generate bar charts depicting mRNA gene expression. Statistical significance was defined as a p-value below 0.05.

3. RESULTS

Figure 1 illustrates expression levels of AKT in all the groups studied, with each group's AKT expression represented by a specific bar on the bar chart. Groups A (Control) showed significantly lower expression of AKT compared to groups B (Benzene), C (Cyclophosphamide), D (Benzene + 100mg/kg of *P. nitida* and *C. citratus* leaves extract) and E (Benzene + 200mg/kg of *P. nitida* and *C. citratus* leaves extract) ($p<0.05$). Groups E (Benzene + 200mg/kg of *P. nitida* and *C. citratus* leaves extract) and F (Benzene + 400mg/kg of *P. nitida* and *C. citratus* leaves extract) had lower AKT levels when compared to group C (Cyclophosphamide) and D (Benzene + 100mg/kg of *P. nitida* and *C. citratus* leaves extract) ($p<0.05$).

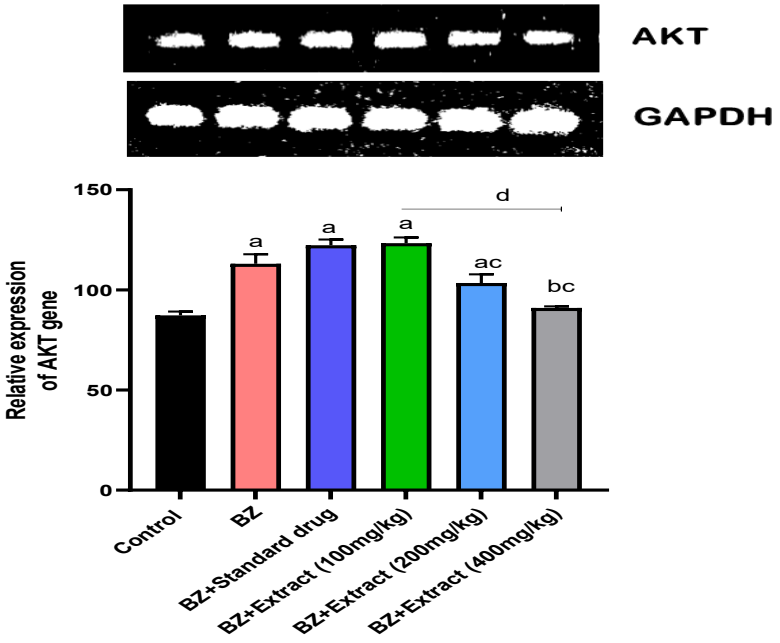

Figure 1: The mRNA expression of AKT in the studied groups, with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letters a, b, c, d, e and f indicate significant differences when compared to groups A, B, C, D, E and F, respectively.

Figure 2 illustrates expression levels of PTEN in all the groups studied, with each group's PTEN expression represented by a specific bar on the bar chart. Groups A (Control) showed significantly lower expression of PTEN compared to groups B (Benzene), C (Cyclophosphamide), D (Benzene + 100mg/kg of *P. nitida* and *C. citratus* leaves extract) and E (Benzene + 200mg/kg of *P. nitida* and *C. citratus* leaves extract) ($p<0.05$). Groups F (Benzene + 400mg/kg of *P. nitida* and *C. citratus* leaves extract) had lower PTEN levels when compared to group C (Cyclophosphamide) ($p<0.05$).

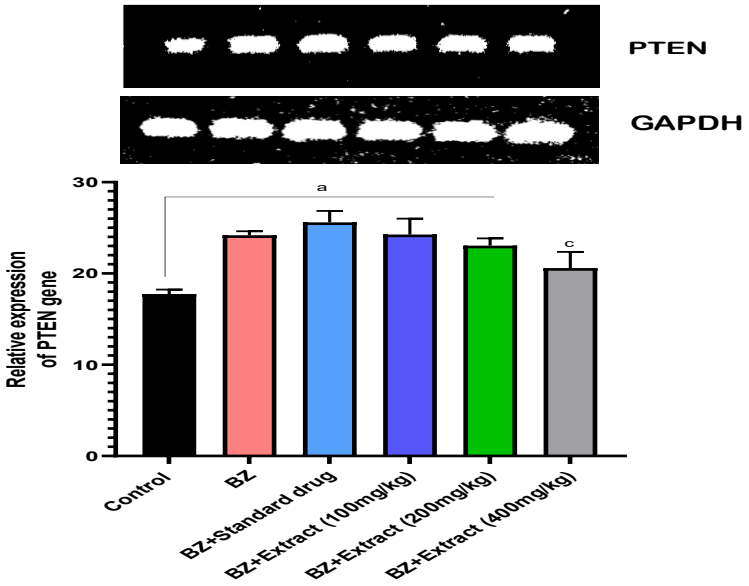

Figure 2: The mRNA expression of PTEN in the studied groups, with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letters a, b, c, d, e and f indicate significant differences when compared to groups A, B, C, D, E and F, respectively.

4. DISCUSSION

The regulation of hematopoiesis is intricately linked to cell signaling pathways, particularly those involving AKT (Protein Kinase B) and PTEN (Phosphatase and Tensin Homolog). The interplay between AKT and PTEN is crucial for maintaining hematopoietic balance under normal and pathological conditions, including haematotoxicity. Dysregulation of these pathways due to benzene exposure often results in aberrant cell survival and apoptosis, further worsening hematopoietic dysfunction [24]. In the study, Control group demonstrated baseline AKT expression levels, reflective of normal cellular homeostasis. Benzene exposure significantly up regulated AKT mRNA expression; a response consistent with benzene's ability to induce oxidative stress and dysregulate AKT expression [25]. Cyclophosphamide-treated rats also showed elevated AKT expression, albeit slightly lower than in the benzene-only group. Cyclophosphamide's pro-apoptotic effects likely resulted in reduced activation of the PI3K/AKT pathway, as observed in prior studies by Albayrak *et al*. [26]. The groups administered the extract showed a dose-dependent modulation of AKT expression. The group administered 100 mg/kg exhibited the highest AKT expression indicating a possible stimulatory effect of the herbal formulation on the PI3K/AKT pathway. This result suggests that moderate doses of *Picralima nitida* and *Cymbopogon citratus* may enhance cellular survival and repair mechanisms through AKT activation, consistent with findings by Xu *et al*. [27] stating that terpenoids activate the AKT pathway. However, higher doses resulted in a marked reduction in AKT expression, with the group administered 400mg/kg showing AKT levels comparable to the control group. This suggests that at higher doses, the bi-herbal mixture may suppress excessive AKT activation, thereby restoring balance to cellular signaling pathways. This observation is corroborated by Paul *et al*. [28], who made mention of the possibility of phytochemical modulation of signaling pathways. The results suggest that the bi-herbal mixture can regulate AKT expression in a dose-dependent manner, offering a promising therapeutic strategy for managing benzene-induced haematotoxicity. Its ability to modulate AKT expression aligns with its anti-oxidative and anti-inflammatory properties, as demonstrated in other studies on *Picralima nitida* and *Cymbopogon citratus*. However, further research is needed to elucidate the precise molecular mechanisms underlying these effects, particularly at higher doses. It was also revealed in this study that the control group exhibited baseline PTEN expression, reflecting normal cellular homeostasis. Benzene exposure led to a significant upregulation of PTEN mRNA expression compared to the control. This increase is consistent with findings by Nosiri *et al*. [29], who observed elevated PTEN expression as a cellular response to counteract the hyperactivation of survival pathways such as PI3K/AKT. Benzene-induced oxidative stress and DNA damage likely triggered this compensatory mechanism, as PTEN activation plays a role in promoting apoptosis to eliminate damaged cells [30]. Cyclophosphamide treatment resulted in the highest PTEN expression among all groups, indicating its strong pro-apoptotic effect. Cyclophosphamide is particularly effective in enhancing tumor cell autophagy and activates anti-tumor immune responses in cancer patients as corroborated by [31]. The groups administered the extract also demonstrated a dose-dependent modulation of PTEN expression. At a moderate dose (100 mg/kg), PTEN expression was slightly elevated compared to the control, indicating its role in preventing excessive cell survival without inducing apoptosis. However, higher doses (200 mg/kg and 400 mg/kg) resulted in a significant decrease in PTEN expression, with the group administered 400mg/kg showing levels comparable to the control. These results suggest that at higher doses, the dual-mixture effectively suppresses excessive PTEN activation, which might otherwise hinder hematopoietic recovery. This finding is consistent with work by Sari *et al*. [32], which showed that *Cymbopogon citratus* possesses anti-oxidant activity facilitating cell survival and recovery.

5. CONCLUSION

Data from this study revealed that the mRNA expression of AKT and PTEN showed significant up-regulation in response to the benzene-induced haematotoxicity however, their expression reduced to normal levels in a dose-dependent manner with the highest dose causing the most near normal levels and the dual- mixture outperformed cyclophosphamide in treating haematotoxicity. These findings highlight the dual- mixture as a promising phyto-therapeutic agent for haematotoxicity. However, further studies are recommended to evaluate the long-term effects of the dual-mixture and its potential for clinical application in managing haematotoxicity.

Declarations

Acknowledgement

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Conflict of Interest

The Authors declare no conflict of interest

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Progress A. Obazelu: Conceptualization and Manuscript writing
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