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Expression of P13K And STAT3 Genes in Benzene Bone Marrow-Induced Toxicity in Wistar Rats Treated with A Dual-Blend Formula of *Picralima nitida* And *Cymbopogon citratus* Aqueous Leaf Extracts

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ABSTRACT

Background: Considering the well-established antioxidant and anti-inflammatory activities of *Picralima nitida* and *Cymbopogon citratus*, and the emerging interest in plant-based modulation of cellular signaling pathways, this study investigates the effect of a dual-blend aqueous leaves extract of these plants on the expression of PI3K and STAT3 genes in Wistar rats exposed to benzene bone marrow-induced toxicity.
Materials and Methods: The study involved 60 male Wistar rats, divided into six groups, to evaluate the ef fect 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 in bone marrow aspirates, and Graph Pad Prism was used for data analysis.
Results: Groups B (Benzene) had significantly higher expression of PI3K when compared to group A (Control). There was no significant change in expression observed in groups C (Benzene + Cyclophosphamide), D (Benzene + 100mg/kg of extract), E (Benzene + 200mg/kg of extract) and F when compared to group B (Benzene) ($P<0.05$). Group B (Benzene) had higher expression of STAT3 when compared to the control group although this was not statistically significant. Groups E (Benzene + 200mg/kg of extract) and F (Benzene + 400mg/kg of extract) had significantly higher expression of STAT3 compared to group A (Control) and B (benzene) ($P<0.05$).
Conclusion: This study revealed that while PI3K expression remained largely unaffected by the treatment, alterations in STAT3 expression point to a potential immunomodulatory role of the extract.

Keywords: PI3K, STAT3, *Picralima nitida* leaves, *Cymbopogon citratus* leaves, Benzene.

INTRODUCTION

Benzene, a flammable, aromatic hydrocarbon, is an occupational and environmental contaminant widely utilized in the production of plastics, resins, synthetic fibres, pesticides, and detergents (1). Chronic exposure to benzene, particularly by inhalation or dermal absorption, is of great public health concern globally due to its established haematotoxic, genotoxic, and carcinogenic properties (2). Having been designated as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), benzene has been largely linked to haematopoietic malignancies such as acute myeloid leukaemia (AML), aplastic anaemia, and myelodysplastic syndromes (3). The toxic effect of benzene is primarily mediated by its biotransformation to reactive metabolites such as benzene oxide, hydroquinone, and benzoquinone that induce oxidative stress, DNA damage, and disruption of cellular signalling pathways in hematopoietic stem and progenitor cells (4).

Among the cell signalling pathways impacted by benzene toxicity, the phosphoinositide 3-kinase (PI3K) pathway plays a role in regulating aspects of haematopoietic physiology. PI3K is a family of lipid kinases that phosphorylate phosphatidylinositol lipids, initiating a signalling cascade that activates downstream effectors such as AKT (Protein Kinase B) and mTOR. The pathway controls basic cellular processes such as cell proliferation, survival, differentiation, metabolism, and angiogenesis (5). In haematopoietic tissues, the PI3K/AKT pathway controls the functions of haematopoietic stem cells (HSCs) and also controls oxidative stress responses (6). PI3K signalling dysregulation (through hyperactivation or inhibition) has been involved in haematological diseases, including leukemogenesis and bone marrow failure syndromes. Inhibition of PI3K gene expression by benzene is reported to cause haematopoietic

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dysfunction through the defective survival of progenitor cells and by promoting apoptosis (7).

Signal Transducer and Activator of Transcription 3 (STAT3) is a transcription factor in the JAK/STAT signalling pathway that is involved in cytokine-induced hematopoiesis and immune homeostasis. Phosphorylated STAT3 translocates to the nucleus upon cytokine or growth factor stimulation where it comes into contact with DNA and regulates gene transcription for cell survival, proliferation, and inflammation (8). STAT3 is important in induction of G-CSF-dependent production of neutrophils in haematopoietic tissues and regulation of pro- vs. anti-inflammatory reactions (9). STAT3 dysregulation has been implicated in immune-mediated cytopenias and myeloproliferative neoplasms (10). Benzene and its metabolites can down-regulate or inhibit STAT3 signalling, hence interfering with immune function and hematopoietic homeostasis. Thus, the measurement of PI3K and STAT3 gene expression levels provides a molecular window for evaluating the haematotoxic effects of benzene (11).

There is growing interest in plant natural products from medicinal plants as a means of controlling chemical-induced haematotoxicity. *Picralima nitida*, commonly known as "*akuamma*," is a long-traditioned indigenous West African tree. *P. nitida* contains a variety of indole alkaloids, including *akuammine*, *akuammidine*, and *pseudo-akuammigine*, which have been found to display significant analgesic, anti-inflammatory, antimicrobial, and antioxidant effects (12). Recent studies have demonstrated that these alkaloids can modulate significant enzymatic and receptor-mediated processes, suggesting potential protective mechanisms against oxidative and cytotoxic damage in mammalian systems (13). *Cymbopogon citratus* or lemongrass is yet another highly studied medicinal plant with a broad spectrum of pharmacological activities. It is native to tropical and subtropical regions and has bioactive compounds such as citral, geraniol, limonene, and flavonoids. These phytochemicals have potent antioxidant, anti-inflammatory, antimicrobial, and cytoprotective activities (14). Lemongrass extracts have also been shown to scavenge reactive oxygen species and regulate pro-inflammatory mediators such as TNF-α and IL-6 (15).

While the therapeutic value of each of *Picralima nitida* and *Cymbopogon citratus* is individually known, their synergistic or concurrent action most significantly in benzene-induced haematotoxicity remains poorly studied. Also, how this two-blend extract can modulate critical haematopoietic gene expression such as PI3K and STAT3 remains unknown. The current research therefore seeks to evaluate the haematoprotective effectiveness of a binary-blend aqueous extract of *Picralima nitida* and *Cymbopogon citratus* in benzene-induced haematotoxicity in Wistar rats. By gaining insight into the mechanism of action of plant therapies in modulating molecular reactions to environmental toxins, the research seeks to contribute to the development of alternative and complementary methods to the prevention or alleviation of haematotoxicity.

MATERIALS AND METHODS

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.

Identification of *Cymbopogon citratus and Picralima nitida* LeavesThe leaves of both plants used in this study (*P. nitida* and *C citratus*) were gathered from Oluku 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; ID Number: UBH-C451 and UBH-P424 for *Cymbopogon citratus and Picralima nitida* leaves respectively.

Processing of Plant 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, the leaves were air-dried under shade for duration of 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.

Preparation of Plants Extract

About 2.5 litres of distilled water were mixed with 250 grammes (250g) of the pulverized plant. After that, the combination was left to stay for a full day under carefully monitored storage conditions. Following the soaking time, the mixture was filtered with Whatman's (Nitro cellulose 45; 0.45µm pore size) 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.

Preparation of Benzene Solution

Distilled water, 2-propanol, and benzene were combined in a 1:5:5 ratios 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 between 150g- 200g received a dosage of 0.2 ml of this solution every 48 hours (16).

Preparation 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, between 150g- 200g in weight, received a dose of 0.3ml (40mg/kg.bw) of this solution orally. The administration was carried out every 48 hours for duration of 28 days (17).

Experimental Animals

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

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 acclimatize for two weeks.

Research Design

The sixty (60) Wistar rats 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.

Administered Doses of Dual-blend of *C. citratus* and *P. 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 (40mg/kg.bw) 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.bw 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.bw 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.bw of *C. citratus* and *P. nitida* leaves extract orally on a daily basis through a gavage tube (17).

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.

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 (18). The primers used for amplification were as follows:

PI3K – Forward: AACACAGAAGACCAATACTC
Reverse: TTCGCCATCTACCACTAC

STAT 3 – Forward: CACCCATAGTGAGCCCTTGGA
Reverse: TGAGTGCAGTGACCAGGACAGA

GAPDH – Forward: AGACAGCCGCATCTTCTTGT
Reverse: CTTGCCGTGGGTAGAGTCAT

Statistical Analysis

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

RESULTS

Figure 1 shows the expression levels of PI3K in all the groups studied, with each group's PI3K expression represented by a specific bar on the bar chart. Groups B (Benzene) had significantly higher expression of PI3K when compared to group A (Control). There was no significant change in expression observed in groups C (Benzene +

Cyclophosphamide), D (Benzene + 100mg/kg of *P. nitida* and *C. citratus* leaves extract), E (Benzene + 200mg/kg of *P. nitida* and *C. citratus* leaves extract) and F when compared to group B (Benzene) (P<0.05).

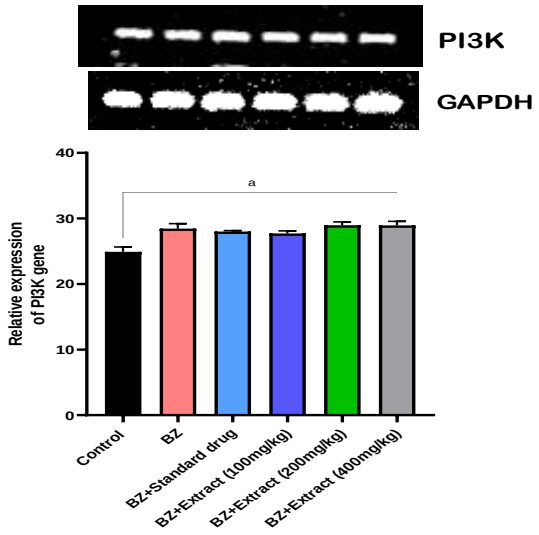


Figure 1 shows the mRNA expression of PI3K in the studied groups, with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letter a, indicates significant differences from the control group.

Figure 2 shows the expression levels of STAT3 in all the groups studied, with each group's STAT3 expression represented by a specific bar on the bar chart. Group B (Benzene) had higher expression of STAT3 when compared to the control group although this was not statistically significant. Groups E (Benzene + 200mg/kg of *P. nitida* and *C. citratus* leaves extract) and F had significantly higher expression of STAT3 compared to group B (Benzene) (P<0.05).

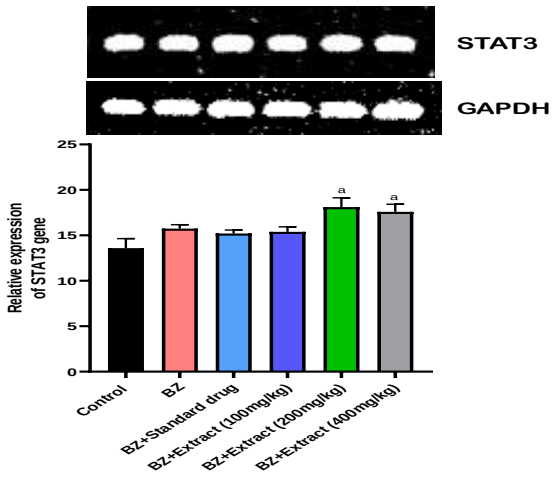


Figure 2 shows the mRNA expression of STAT3 in the studied groups, with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letter a, indicates significant differences from the control group.

DISCUSSION

Benzene, a well-known haematotoxic agent, has been extensively studied for its deleterious effects on bone marrow function and its ability to induce haematological malignancies through mechanisms involving oxidative stress, immune dysregulation, and genotoxicity (3). One of the central pathways implicated in benzene-induced hematotoxicity involves the aberrant activation of signaling molecules such as phosphoinositide 3-kinase (PI3K) and signal transducer and activator of transcription 3 (STAT3), which are closely associated with cell survival, proliferation, and inflammation. Dysregulation of these genes can lead to impaired hematopoiesis and increased susceptibility to myelotoxic conditions (7, 10).

In recent years, attention has turned toward exploring the therapeutic potential of phytochemicals in mitigating benzene toxicity. Natural plant extracts, known for their antioxidant and anti-inflammatory properties, offer promising avenues for intervention (19). In this study, we investigated the expression of PI3K and STAT3 genes in Wistar rats exposed to benzene and subsequently treated with a dual-blend formula of *Picralima nitida* and *Cymbopogon citratus* extracts. These plants have been individually reported to possess bioactive compounds capable of modulating oxidative stress pathways and supporting immune function. However, the combined effect of their phytochemical constituents on some molecular markers of haematotoxicity has not been comprehensively examined.

This study revealed a significant upregulation of PI3K in all the groups administered benzene-exposed groups when compared to the control group. This suggest that benzene exposure stimulates the activation of the PI3K signaling pathway. This finding aligns with earlier reports suggesting that benzene metabolites induce oxidative stress and inflammatory responses, which in turn activate the PI3K/Akt signaling cascade as a cellular adaptive mechanism to maintain survival and counteract apoptosis (20, 21).

The group administered cyclophosphamide and benzene, also showed significantly elevated PI3K expression relative to the control. Cyclophosphamide is known for its cytotoxic and immunosuppressive properties and its administration may have compounded the oxidative insult initiated by benzene, further amplifying PI3K activation (22). This is consistent with findings from Rosario *et al.* (23), who stated that cyclophosphamide can upregulates PI3K signalling.

The groups that were co-treated with benzene and the dual-extract blend of *Picralima nitida* and *Cymbopogon citratus* demonstrated significantly elevated PI3K expression compared to the control and benzene groups. This consistent upregulation across the groups suggests that the phytochemical constituents of the dual formula may modulate the PI3K pathway in a compensatory or cytoprotective manner, rather

than simply inhibiting it. In both *Picralima nitida* and *Cymbopogon citratus*, certain bioactive flavonoids and polyphenolic compounds may contribute to the modulation of the PI3K pathway. For instance, *Picralima nitida* contains alkaloids like *picralimines*, as well as flavonoids such as *quercetin* and *kaempferol*. *Cymbopogon citratus*, on the other hand, is rich in flavonoids like *apigenin* and *kaempferol* (12). These plant-derived compounds are known for their antioxidant, anti-inflammatory, and anticancer activities, which can potentially influence signaling pathways like PI3K/Akt/mTOR (24). In this study, the observed elevation of PI3K expression in the groups co-treated with the dual-extract blend and benzene can be compared to previous studies that have shown the ability of flavonoids, such as quercetin and kaempferol, to activate PI3K/Akt pathways under stress conditions. For example, quercetin has been reported enhance cell survival by modulating key survival pathways like PI3K/Akt (25, 26, 27). However, in contrast to this study, kaempferol, present in both plants, is known to inhibit the PI3K/Akt/mTOR pathway in various cancer models which was not the case as observed in this present study since there was no definite inhibition of PI3K. This disparity however can be due to the dosage administered (28). Furthermore, *Cymbopogon citratus*' *apigenin* has demonstrated anticancer potential through its interaction with PI3K/Akt, promoting apoptosis in liver cancer cells (24). The modulation of this pathway is consistent with the idea that the phytochemicals in the dual-extract blend could be mediating an adaptive response, promoting cellular resilience and enhancing haematopoiesis, even in the presence of toxic insults like benzene. The upregulation of PI3K in the extract-treated groups could therefore be a result of a fine-tuned interaction between the bioactive compounds and the PI3K signaling cascade. This interaction is not simply about inhibition but may reflect a balance between cytoprotective and regenerative processes, facilitating cellular survival and immune modulation while combating oxidative stress.

In this study, the groups treated with the higher dose of the dual-extract blend of *Picralima nitida* and *Cymbopogon citratus* had significantly higher STAT3 expression compared to the other groups, including the control. The increased STAT3 expression in these groups could be attributed to the bioactive compounds present in *P. nitida* and *C. citratus*, rather than any direct impact of benzene exposure. Benzene itself, as observed in this study, did not induce any significant changes in STAT3 expression, which is in contrast to the study of Duval *et al*. (29) who observed that benzoquinone, a leukemogenic metabolite of benzene, catalytically inhibits STAT signaling. Another study has also identified benzobis (a relative of benzene) as a STAT3 signal inhibitor with antitumor activity (21).

Previous studies have highlighted that certain plant-derived compounds, particularly flavonoids found in *P. nitida* and *C. citratus*, can activate STAT3 as part of their cellular protective effects (30, 31). A study carried out by Hämäläinen *et al*. (32) has also shown that flavonoids like quercetin and kaempferol in these plants have been shown to inhibit the activation of other signal transducers like STAT1 which can activate STAT3 depending on the context (33). In this study, the extracts could be enhancing STAT3 expression as a part of a stress-response mechanism, particularly under conditions where cellular protection or immune modulation is needed, but not necessarily due to the toxic effects of benzene. STAT3 activation may serve as a cellular defense mechanism, as STAT3 is known to regulate the expression of genes involved in anti-apoptosis, cell survival, and immune response (34). The higher doses of the dual-extract blend might have been more effective in activating this pathway, potentially due to synergistic effects of the bioactive compounds. This suggests that the increased STAT3 expression in these groups reflects an adaptive response to the administration of the extracts rather than a response to benzene toxicity.

Conclusion: This study demonstrates that the dual-blend aqueous extract of *Picralima nitida* and *Cymbopogon citratus* may modulate gene expression in benzene-induced bone marrow toxicity in Wistar rats. While PI3K expression remained largely unaffected by the treatment, alterations in STAT3 expression point to a potential immunomodulatory role of the extract.

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